EFFECTS OF LIGAND TUNING ON DINUCLEAR INDIUM CATALYSTS FOR THE
POLYMERIZATION OF LACTIDE

by

Kimberly Marie Osten

B.Sc., The University of Victoria, 2009

A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF
THE REQUIREMENTS FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

in

THE FACULTY OF GRADUATE AND POSTDOCTORAL STUDIES
(Chemistry)

THE UNIVERSITY OF BRITISH COLUMBIA
(Vancouver)

December 2014

© Kimberly Marie Osten, 2014
Abstract

We are interested in the biodegradable polymer poly(lactic acid) (PLA) formed from the ring-opening polymerization of lactide. Our promising results on the polymerization of racemic lactide to form isotactically enriched PLA by a dinuclear indium catalyst bearing a chiral diaminophenolate ligand prompted us to investigate several ligand modifications in order to establish detailed structure-activity relationships within these complexes. Modifications to the terminal amine substituents, the central amine donors and the phenolate substituents of our tridentate ligands were undertaken. The factors affecting the stereoselectivity and activity of these indium catalysts were investigated in detail. Finally, pentadentate dinucleating ligands were used to synthesize dinuclear indium complexes with the goal of producing more stereoselective and/or active catalysts.

Modifications to our tridentate ligand system led to complications in their coordination to indium, possibly due to flexibility of the ligands leading to aggregation. It was found that bulkier substituents on the terminal amine position of these ligands led to a lowering of the isoselectivity of the resulting indium complexes due to dissociation of the dimers during the polymerization of lactide.

Changing the central amine donors from secondary to tertiary amines led to a profound decrease in polymerization rate. The contributions of intramolecular hydrogen bonding in these dimers on their resulting polymerization activity was explored. However, the nature of the amine, not hydrogen bonding, was found to be the determining factor in their activity towards lactide polymerization.

Increasing the steric bulk of the phenolate substituents was found to influence the structure of indium dichloride complexes made with these ligands in solution and the solid state.
However, these modifications were found to have only minor impact on the lactide polymerization activity and stereoselectivity of the related dinculear indium ethoxide complexes. A family of pentadentate proligands was utilized for the formation of dinuclear indium ethoxide complexes for the polymerization of racemic lactide. However, only one dinuclear indium ethoxide complex could be isolated cleanly. It was found to have low activity in the polymerization of racemic lactide, requiring weeks to reach full conversion. However, the complex was highly stereoselective producing over 90% heterotactic PLA.
Preface

Chapter 2

Contributions towards developing a synthetic methodology for the proligands investigated in this chapter were made by Dr. Christopher J. Wallis. Work towards the initial synthesis and characterization of these proligands was completed in part by previous undergraduate students in our group Joey C.-C. Yu, Paraskevi O. Lagaditis and Lucy Yuan. Optimization of the synthesis and purification of these proligands as well as full characterization data for some proligands was completed by myself. Work towards the synthesis of metal complexes with proligands H(NMesH_N^+O^+_Bu) (L-5) and H(N_NpH_N^+O^+_Bu) (L-6) was first investigated by former undergraduate student Ian R. Duffy and completed by myself. I completed all other metal chemistry and polymerization studies. The crystals structures presented in this chapter were run and solved by Insun Yu and the crystals were obtained by Ian R. Duffy (complex 5) and myself (all other structures). The majority of this work has been previously published in *Dalton Transactions*\(^1\). The bulk of the manuscript was written by myself with significant contributions from Prof. Parisa Mehrkhodavandi and contributions to work that will be discussed in Chapter 4 written by Insun Yu (see below).

Chapter 3

The synthesis and characterization of metal complexes using proligand H(NMe_2NMeO^+_Bu) (L-3) was completed by myself. The synthesis of metal complexes using proligand H(LMe) (L-1) was completed by Insun Yu and has been previously published in *Dalton Transactions*\(^1\) and her doctoral dissertation and will be discussed here only as it relates to the work completed by myself for this chapter. The synthesis and characterization of proligand H(L_H) (L-8) and the synthesis of metal complexes using this proligand was completed by myself, with assistance
from former undergraduate student Molly Sung. The crystal structures presented in this chapter
were run and solved by Insun Yu, Dinesh Aluthge and Dr. Brian Patrick and the crystals were
obtained by myself. DFT studies were completed and analysed by Dinesh Aluthge. The
polymerization studies presented in this chapter were completed solely by myself with the
exception of data presented for complex 11, which was completed by Insun Yu and has been
previously published in *Dalton Transactions* as discussed above.\(^1\) This work has been recently
published in *Inorganic Chemistry*.\(^2\) The majority of the manuscript was written by myself with
significant contributions from Prof. Parisa Mehrkhodavandi and the discussion of the DFT
studies written by Dinesh Aluthge.

**Chapter 4**

Contributions towards the design of proligands H(N\(_{\text{Me}_2}\)N\(_{\text{H}}\)O\(_{\text{SiPh}_3}\)) \((L-9)\), H(N\(_{\text{Me}_2}\)N\(_{\text{H}}\)O\(_{\text{Ad}}\)) \((L-10)\) and H(N\(_{\text{Me}_2}\)N\(_{\text{H}}\)O\(_{\text{Cm}}\)) \((L-11)\) were made by Dinesh Aluthge and myself. The work
presented in this chapter was completed solely by myself, with some assistance towards the
synthesis, purification and full characterization of H(N\(_{\text{Me}_2}\)N\(_{\text{H}}\)O\(_{\text{SiPh}_3}\)) \((L-9)\) being provided by
former undergraduate student Molly Sung and some assistance towards the synthesis of
salicylaldehyde starting materials being provided by Dinesh Aluthge. This work has not been
previously published. This chapter was written entirely by myself, with contributions from Prof.
Parisa Mehrkhodavandi.

**Chapter 5**

The synthesis of proligand HO\(_{\text{Bu}}(L_{\text{Me}})_2\) \((L-12)\) was first completed by Insun Yu in our
group. I subsequently repeated and optimized the synthesis and purification and fully
characterized this proligand. The synthesis, purification and characterization of HO\(_{\text{Bu}}(L)_2\) \((L-13)\)
and HO\(_{\text{Bu}}(L_{\text{H}})_2\) \((L-14)\) was completed by myself. The synthesis of chiral proligands
HO_{Bu}(NNMe_2) (L-15) and HO_{Bu}(NHMe_2) (L-16) was completed by myself with assistance from former undergraduate student Alex Gatien. The synthesis of metal complexes with proligand HO_{Bu}(LMe)_2 (L-12) was first completed by Insun Yu, and I subsequently repeated and optimized the synthesis and fully characterized these complexes. All other metal chemistry presented in this chapter was completed solely by myself. Crystals of complex 26 were obtained by myself and the structure was run and solved by Dinesh Aluthge. The crystal structure of complex 27 was obtained and solved by Insun Yu. Polymerization studies were completed by myself, with the exception of the long-term polymerization of lactide by complex 26, which was completed by Insun Yu. This work has not been previously published. This chapter was written entirely by myself, with contributions from Prof. Parisa Mehrkhodavandi.
Table of Contents

Abstract ........................................................................................................................................... ii

Preface ........................................................................................................................................... iv

Table of Contents ........................................................................................................................ v

List of Tables .................................................................................................................................. xi

List of Figures ............................................................................................................................... xii

List of Schemes ............................................................................................................................ xx

List of Abbreviations and Symbols ............................................................................................. xxii

Acknowledgements ....................................................................................................................... xxix

Dedication ....................................................................................................................................... xxx

Chapter 1: General introduction ................................................................................................... 1

1.1 Introduction to poly(lactic acid) ............................................................................................ 1

1.2 Industrial synthesis of PLA ................................................................................................. 3

1.3 Mechanism of the ROP of lactide using metal catalysts .................................................... 6

1.4 Tacticity of PLA .................................................................................................................. 8

1.5 Quantification of the tacticity of PLA ................................................................................ 12

1.6 Defined metal catalysts for the ROP of lactide .................................................................... 17

1.6.1 Tripodal homo and heteroscorpionate ligands ............................................................... 18

1.6.2 Tridentate diamidoamino and related ligands ............................................................... 25

1.6.3 Tridentate diamidoether and linked bis(phenolate) ligands ........................................ 28

1.6.4 Ketiminate ligands ........................................................................................................ 32

1.6.5 Iminophenolates and related ligands ............................................................................ 34
1.6.6 Diaminophenolate ligands ..............................................................................39
1.7 Project goals .......................................................................................................42

Chapter 2: Effects of varying terminal amine substituents ........................................44
2.1 Introduction ........................................................................................................44
2.2 Results ................................................................................................................48
  2.2.1 Synthesis and characterization of proligands ..............................................48
  2.2.2 Synthesis and characterization of indium dichloride complexes ..............51
  2.2.3 Synthesis and characterization of dinuclear indium alkoxide complexes ......57
  2.2.4 Polymerization studies ................................................................................66
2.3 Discussion and conclusions ..............................................................................68
2.4 Experimental .....................................................................................................70

Chapter 3: Effects of secondary versus tertiary amine donors ...................................88
3.1 Introduction ........................................................................................................88
3.2 Results ...............................................................................................................91
  3.2.1 Synthesis and characterization of indium complexes ..................................91
  3.2.2 Synthesis and characterization of deuterated indium complexes ..................96
  3.2.3 Examination of hydrogen bonding parameters in the solid-state .............101
  3.2.4 Polymerization studies ...............................................................................106
3.3 Discussion and conclusions .............................................................................114
3.4 Experimental ....................................................................................................115

Chapter 4: Effects of varying phenolate substituents ..................................................125
4.1 Introduction .......................................................................................................125
4.2 Results and discussion .....................................................................................127
4.2.1 Synthesis and characterization of proligands ..................................................127
4.2.2 Synthesis and characterization of indium dichloride complexes ....................128
4.2.3 Synthesis and characterization of dinuclear indium ethoxide complexes ..........138
4.2.4 Polymerization studies .....................................................................................142
4.3 Discussion and conclusions ................................................................................146
4.4 Experimental .......................................................................................................150

Chapter 5: Indium complexes with pentadentate dinucleating ligands ....................170

5.1 Introduction ........................................................................................................170
5.2 Results and discussion .......................................................................................173
  5.2.1 Synthesis and characterization of achiral pentadentate proligands ...............173
  5.2.2 Synthesis and characterization of chiral pentadentate proligands .................175
  5.2.3 Synthesis and characterization of indium complexes ....................................181
  5.2.4 Polymerization studies ...................................................................................187
5.3 Discussion and conclusions ...............................................................................189
5.4 Experimental ......................................................................................................193

Chapter 6: Conclusions and future work ..................................................................202

References .................................................................................................................206

Appendices ...............................................................................................................215

Appendix A ...............................................................................................................215
  A.1 Characterization of compounds in solution ....................................................215
  A.2 Characterization of compounds in the solid-state ..........................................222
Appendix B ...............................................................................................................223
  B.1 Characterization of compounds in solution ....................................................223
<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>B.2 Characterization of compounds in the solid-state</td>
<td>227</td>
</tr>
<tr>
<td>B.3 DFT studies</td>
<td>228</td>
</tr>
<tr>
<td>Appendix C</td>
<td>229</td>
</tr>
<tr>
<td>C.1 Characterization of compounds in solution</td>
<td>229</td>
</tr>
<tr>
<td>C.2 Characterization of compounds in the solid-state</td>
<td>237</td>
</tr>
<tr>
<td>C.3 Kinetic data for the polymerization of lactide</td>
<td>238</td>
</tr>
<tr>
<td>Appendix D</td>
<td>241</td>
</tr>
<tr>
<td>D.1 Characterization of compounds in solution</td>
<td>241</td>
</tr>
<tr>
<td>D.2 Characterization of compounds in the solid-state</td>
<td>247</td>
</tr>
</tbody>
</table>
List of Tables

Table 1.1. Tetrad probabilities and equations for calculating the tactility of PLA. ...............15
Table 2.1. Selected bond distances, angles and $\tau$ values for related indium dichloride complexes. ..........................................................................................................................56
Table 2.2. Selected bond lengths and angles for complexes 9 and 10..................................64
Table 2.3. Results for the polymerization of rac-LA by catalyst 7. .................................67
Table 3.1. Selected bond lengths and angles for complexes 15 and 16.........................96
Table 3.2. Selected bond lengths and angles for the (RR/RR) dimers in the previously reported solid-state structure of complex 1, new structure of complex 1 and structure of complex 17. 103
Table 3.3. Select solid-state structural data and hydrogen bonding parameters for related indium complexes. ..........................................................................................104
Table 3.4. Rates for the polymerization of rac-LA with select indium ethoxide complexes. ....106
Table 3.5. Results for the polymerization of rac-LA by catalysts 15, 16 and 17...............114
Table 4.1. Select bond lengths and angles for complexes (RR/SS)-19 and (RR/SS)-20........132
Table 4.2. Diffusion coefficients and radii for select compounds determined by PGSE NMR experiments...........................................................................................................136
Table 4.3. Select bond lengths and angles for complexes (±)-23 and (±)-24. .......................142
Table 4.4. Kinetic data for the polymerization of rac, L and D-LA by catalysts (±)- and (R,R)-22 and 23 and (±)-24. ..................................................................................................................143
Table 4.5. Results for the polymerization of rac-LA by catalysts 22-24. .........................146
Table 5.1. Selected bond lengths and angles for complexes 26 and 27..........................187
Table 5.2. Results for the polymerization of 200 eq. rac-LA by catalyst 26.....................188
List of Figures

Figure 1.1. Structures of commonly studied biodegradable polyesters, poly(lactic acid) (PLA), poly(glycolic acid) (PGA) and poly( ε-caprolactone) (PCL). .......................................................... 1

Figure 1.2. Homoleptic metal complexes used industrially for ROP of lactide. ...................... 6

Figure 1.3. Coordination-insertion mechanism for lactide ROP by metal catalysts. .............. 8

Figure 1.4. PLA microstructures resulting from ROP of enantiopure LA. ............................ 9

Figure 1.5. Microstructures of PLA that can result from the polymerization of rac-LA. .......... 10

Figure 1.6. Tetrad sequences for different tacticities of PLA resulting from rac-LA polymerization. ................................................................................................................. 13

Figure 1.7. 1H{1H} NMR spectrum (600 MHz, CDCl3, 25 °C) of an atactic PLA sample (Pm = 0.50) resulting from the polymerization of rac-LA, showing tetrad assignments of each peak according to the literature. 30-35 .................................................................................... 14

Figure 1.8. Stereoerrors and resulting tetrads in different microstructures of PLA resulting from the polymerization of rac-LA................................................................................................. 16

Figure 1.9. Landmark catalysts for rac-LA polymerization bearing mono- to pentadentate ligands. 20-21,28,35-39 ............................................................................................................. 17

Figure 1.10. Tris(pyrazolyl)borate (I-1-6) and tris(indazolyl)borate (I-7-9) complexes developed by Chisholm et al. 45-48 ................................................................................................. 19

Figure 1.11. Tris(pyrazolyl)borate and tris(pyrazolyl)methane cationic and zwitterionic Y and Ca complexes reported by Mountford et al. 50-51 .................................................................................. 21

Figure 1.12. Mg and Zn complexes bearing bis(pyrazolyl)methane ligands with amidinate pendant arms reported by Otero et al. 52,54-55 .................................................................................. 22
Figure 1.13. Enantiopure zinc complexes with bis(pyrazolyl)methane ligands bearing chiral myrtenyl substituted cyclopentadienyl and alkoxy pendant arms.\textsuperscript{56-58} .................................................................25

Figure 1.14. Aluminum complexes with tridentate triamine ligands reported by Bertrand \textit{et al.}\textsuperscript{64} ........................................................................................................................................................................26

Figure 1.15. Tridentate sulfonamide ligand supported Al\textsuperscript{66}, In\textsuperscript{68} and Ti\textsuperscript{67} complexes reported by Mountford \textit{et al}. ........................................................................................................................................................................26

Figure 1.16. Neutral and cationic zinc complexes with tridentate bis(pyrazolyl)amido ligands developed by Carpentier \textit{et al.}\textsuperscript{69} ........................................................................................................................................................................28

Figure 1.17. Al and Ga complexes bearing tridentate diamidoether ligands reported by Dagorne \textit{et al.} ........................................................................................................................................................................29

Figure 1.18. Ti and Zr complexes bearing bis(aryloxy) ligands with chalcogen and NHC bridging groups reported by Okuda \textit{et al.}\textsuperscript{73} and Dagorne \textit{et al.}\textsuperscript{74-75} .................................................................30

Figure 1.19. Group 3 complexes bearing bis(naphthoxy) and bis(phenoxy) ligands bridged by pyridine or thiophene groups reported by Carpentier \textit{et al.}\textsuperscript{76-77} ..................................................................................................31

Figure 1.20. Various metal complexes bearing tridentate ketiminate ligands reported by Lin \textit{et al.}\textsuperscript{79-83} ........................................................................................................................................................................33

Figure 1.21. Sn (II) complexes ligated by tridentate iminophenolates and tetradequate diamidophenolates with various side arm donor groups reported by Gibson \textit{et al.}\textsuperscript{84-85} ..................35

Figure 1.22. Mg and Zn complexes with Salen-like iminophenolate ligands reported by Lin \textit{et al.}\textsuperscript{86} ........................................................................................................................................................................36

Figure 1.23. Mg, Zn and Ca complexes bearing iminophenolate ligands reported by Lin \textit{et al.}\textsuperscript{87-89} and Daresbourg \textit{et al.}\textsuperscript{90-93} ........................................................................................................................................................................38
**Figure 1.24.** Highly active zinc catalyst reported by Hillmyer and Tolman for the polymerization of lactide.94

**Figure 1.25.** Achiral proligand H(L\textsubscript{Me}) (L-1) developed by Hillmyer and Tolman \textit{et al.}\textsuperscript{94} and chiral proligands H(N\textsubscript{Me2}N\textsubscript{H}O\textsubscript{Bu}) (L-2) and H(N\textsubscript{Me2}N\textsubscript{Me}O\textsubscript{Bu}) (L-3) developed by Mitchell and Finney\textsuperscript{95} and Mehrkhodavandi \textit{et al.} \textsuperscript{96,109}

**Figure 1.26.** Zinc complex (N\textsubscript{Me2}N\textsubscript{Me}O\textsubscript{Bu})Zn(OPh) and indium complex [(N\textsubscript{Me2}N\textsubscript{H}O\textsubscript{Bu})InCl\textsubscript{2}(\mu-Cl)(\mu-OEt)] (1) reported by Mehrkhodavandi \textit{et al.} for the polymerization of lactide.\textsuperscript{96,109}

**Figure 1.27.** Ligand designs discussed in each chapter of this work.

**Figure 2.1.** Possible mononuclear (A) and dinuclear (B) mechanisms for the polymerization of lactide with dinuclear catalyst 1.

**Figure 2.2.** Chemdraw and solid-state molecular structure of [(N\textsubscript{Me2}N\textsubscript{H}O\textsubscript{Bu})InCl\textsubscript{2}(\mu-Cl)(\mu-OEt)] (1) showing the small steric bulk of the NMe\textsubscript{2} groups (circled).

**Figure 2.3.** Calculation of the tau geometrical parameter (\(\tau\)).\textsuperscript{114}

**Figure 2.4.** Solid-state molecular structures of complexes 4 (top), 5 (middle) and 6 (bottom).

**Figure 2.5.** Methylene region of the \textsuperscript{1}H NMR spectrum (600 MHz, CDCl\textsubscript{3}, 25 °C) of complex 7.

**Figure 2.6.** COSY NMR spectrum (400 MHz, CDCl\textsubscript{3}, 25 °C) of complex 7.

**Figure 2.7.** Methylene region of the VT \textsuperscript{1}H NMR spectra (400 MHz, C\textsubscript{6}D\textsubscript{6}) of complex 7. Moving from the bottom to the top spectrum represents heating from 25 – 70 °C and subsequent cooling from 70 – 25 °C.

**Figure 2.8.** \textsuperscript{1}H NMR spectra (400 MHz, CDCl\textsubscript{3}, 25 °C) of (a) crystals isolated from a saturated hexane solution of the crude mixture resulting from the reaction of complex (\(\pm\)-...
(N<sub>Pr2N</sub>H<sub>O</sub>渤)InCl<sub>2</sub> (4) with 2 eq. NaOEt and (b) complex (±)-[(N<sub>Pr2N</sub>H<sub>O</sub>渤)InCl]<sub>2</sub>(μ-Cl)(μ-OEt) (7).

**Figure 2.9.** Solid-state molecular structure of complex 9. Thermal ellipsoids are shown at 50% probability and H atoms and disorder of the ethoxide group are removed for clarity.

**Figure 2.10.** Plot of the ln([LA]) vs. time for the polymerization of 200 eq. *rac*-LA (0.48 M) by catalyst 7 ([7] = 2.4 mM) with 1,3,5-trimethoxybenzene (TMB) used as an internal standard ([TMB] = 0.03 M). The reaction was monitored to 98% conversion by <sup>1</sup>H NMR spectroscopy (400 MHz, CD<sub>2</sub>Cl<sub>2</sub>, 25 °C).

**Figure 2.11.** <sup>1</sup>H NMR spectra (400 MHz, CD<sub>2</sub>Cl<sub>2</sub>, 25 °C) of (a) (±)-(N<sub>Pr2N</sub>H<sub>O</sub>渤)InCl<sub>2</sub> (4) and (b) reaction of (±)-[(N<sub>Pr2N</sub>H<sub>O</sub>渤)InCl]<sub>2</sub>(μ-Cl)(μ-OEt) (7) with 200 eq. of *rac*-LA after 5 minutes ([LA] = 0.48 M, [7] = 2.4 mM).

**Figure 3.1.** Activity and selectivity of dinuclear indium catalysts 1 and 11 bearing chiral and achiral ligands with central secondary and tertiary amine donors. 1,96,98

**Figure 3.2.** Schematic of the possible hydrogen bonding seen in dinuclear indium catalysts such as [(N<sub>Mε2N</sub>H<sub>O</sub>渤)InCl]<sub>2</sub>(μ-Cl)(μ-OEt) (1) in the solid-state.

**Figure 3.3.** Solid-state molecular structures of complexes 15 (top) and 16 (bottom). H atoms, solvent and disorder of the OEt group (for 15) are removed for clarity.

**Figure 3.4.** (a) <sup>2</sup>H NMR spectrum (400 MHz, CHCl<sub>3</sub>, 25 °C) of D(N<sub>Mε2N</sub>D<sub>O</sub>渤) used to prepare indium complexes, (b) (N<sub>Mε2N</sub>H/D<sub>O</sub>渤)InCl<sub>2</sub> formed from the
deuterated proligand and (c) \([NMe_2NH/DOBu]InCl]_2(\mu-OEt) (1) formed from the

deuterated dichloride complex..........................................................99

**Figure 3.6.** $^1$H NMR (400 MHz, CD$_2$Cl$_2$, 25 °C) of (a) D(N$_{Me_2}NH/DOBu$) used to prepare indium complexes, (b) (N$_{Me_2}NH/DOBu$)InCl$_2$ (2) formed from the deuterated proligand and (c) \([NMe_2NH/DOBu]InCl]_2(\mu-OEt) (1) formed from the deuterated dichloride complex......99

**Figure 3.7.** (a) $^2$H NMR spectrum (400 MHz, CHCl$_3$, 25 °C) of the crude product resulting from reaction of protonated complex \([NMe_2NH/DOBu]InCl]_2(\mu-OEt) (1) with EtOD overnight and $^1$H NMR spectra (400 MHz, CDCl$_3$, 25 °C) of the crude products resulting from the reactions of protonated complex \([NMe_2NH/DOBu]InCl]_2(\mu-OEt) (1) with (b) EtOD overnight, (c) EtOD for 1 hour that had been dried overnight over anhydrous Na$_2$SO$_4$ and (d) EtOD for 30 minutes that had been dried overnight over activated molecular sieves (4 Å) that had been pretreated with D$_2$O..........................................................101

**Figure 3.8.** Solid-state molecular structures of (RR/RR) dimers of complexes 1 (top) and 17 (bottom). Thermal ellipsoids are set at 50% probability. H atoms, solvent and the (SS/SS) dimers are removed for clarity. ........................................................................................................102

**Figure 3.9.** The plot of ln([LA]) vs. time for the ROP of 200 eq. of rac-LA (0.47 M) with complex 15 (2.4 mM) monitored to 97% conversion by $^1$H NMR spectroscopy (300 MHz, CD$_2$Cl$_2$, 25 °C). 1,3,5-trimethoxybenzene (0.031 M) was used as an internal standard...........107

**Figure 3.10.** The plot of ln([LA]) vs. time for the ROP of 200 eq. of rac-LA (0.50 M) with complex 16 (2.5 mM) monitored to 93% conversion by $^1$H NMR spectroscopy (400 MHz, CD$_2$Cl$_2$, 25 °C). 1,3,5-trimethoxybenzene (0.029 M) was used as an internal standard..........108
Figure 3.11. The plot of observed rate constants \( (k_{\text{obs}}) \) at different catalyst concentrations for the polymerization of rac-LA by 17, monitored to >97% conversion by \(^1\)H NMR spectroscopy (400 MHz, 25 °C, CDCl\(_3\)). \([\text{LA}] = 0.45 \, \text{M}, \quad [17] = 0.7, 0.9, 1.1, 1.6 \text{ and } 2.2 \, \text{mM} \) with 1,3,5-trimethoxybenzene (0.033 M) used as an internal standard.

Figure 3.12. \(^1\)H NMR spectra (300 MHz, CD\(_2\)Cl\(_2\), 25 °C) of (a) complex 15, (b) complex 12 and (c) polymerization of rac-LA (0.47 M) with complex 15 (2.4 mM) ~10 min after preparation of the sample.

Figure 3.13. \(^1\)H NMR spectra (400 MHz, CD\(_2\)Cl\(_2\), 25 °C) of (a) complex 16, (b) polymerization of rac-LA (0.50 M) with complex 16 (2.5 mM) ~7 min after preparation of the sample and (c) polymerization of rac-LA (0.50 M) with complex 16 (2.5 mM) ~66 min after preparation of the sample.

Figure 4.1. Examples of Al Salen catalysts with various backbones and phenolate substituents reported by Gibson et al.\(^{137}\)

Figure 4.2. Solid-state molecular structures of complexes (RR/SS)-19 (top) and (RR/SS)-20 (bottom). Ellipsoids are depicted at 50% probability and H atoms and solvent are removed for clarity.

Figure 4.3. Methylene (N-CH\(_2\)-Ar) region of the \(^1\)H NMR spectra (a-c: 600 MHz, d: 400 MHz, CD\(_2\)Cl\(_2\), 25 °C) of (±) (top) and (R,R) (bottom) (NMe\(_2\)NHOR\(_2\))InCl\(_2\) complexes (a) 19, (b) 20, (c) 21 and (d) 2.

Figure 4.4. Plot of \( \ln(I/I_0) \) vs. \( \Upsilon^2 \delta^2 G^2 [\Delta - (\delta/3)] \times 10^{10} \, \text{m}^{-2} \text{s} \) from PGSE NMR experiments (400 MHz, CD\(_2\)Cl\(_2\), 25 °C). \( I = \) intensity of the observed spin-echo, \( I_0 = \) intensity of the spin-echo in the absence of gradients, \( G = \) varied gradient strength, \( \Upsilon = \) gyromagnetic ratio (2.675 x \( 10^8 \, \text{rad s}^{-1} \text{T}^{-1} \)), \( \delta = \) length of the gradient pulse, \( \Delta = \) delay between the midpoints of the...
The hydrodynamic radius ($r_H$) of each compound was calculated by using the slopes ($D_t$) of the linear fits to this data.

Figure 4.5. Methylene region of the $^1$H NMR spectra (600 MHz, CDCl$_3$, 25°C) of (a) (±)-22, (b) (±)-23 and (c) (±)-24.

Figure 4.6. Solid-state molecular structures of complexes (±)-23 (top) and (±)-24 (bottom). Ellipsoids are depicted at 50% probability, and H atoms and solvent are removed for clarity...

Figure 4.7. $^1$H NMR spectra (400 MHz, CDCl$_3$, 25 °C) of the polymerization of rac-LA (0.48 M) at 29% (bottom) and 97% (top) conversion with racemic catalysts (2.4 mM): (a) 23 and (b) the parent catalyst 1. The blue dots mark unreacted catalyst peaks and the red dots mark the indium-polymeryl species.

Figure 4.8. $^1$H NMR spectra (400 MHz, CDCl$_3$, 25 °C) of the polymerization of rac-LA (0.48 M) at 29% (bottom) and 97% (top) conversion with racemic catalysts (2.4 mM): (a) 22 and (b) 24. The blue dots mark unreacted catalyst peaks and the red dots mark the indium-polymeryl species.

Figure 5.1. Catalysts with a pentadentate dinucleating ligand investigated by Hillmyer, Tolman and Williams et al. for the polymerization of cyclic esters.

Figure 5.2. Dinuclear zinc catalysts with pentadentate dinucleating ligands investigated by Williams et al. for the polymerization of lactide.

Figure 5.3. $^1$H NMR spectra (300 MHz, CDCl$_3$, 25 °C) of the crude product mixtures resulting from the reaction of 4-tert-butyl-2,6-diformylphenol with (a) 1 eq. (±)-NNMe$_2$ for 1 hour, (b) 2 eq. (±)-NNMe$_2$ for 3.5 days and (b) an additional 1 eq. (±)-NNMe$_2$ added to reaction (b) for 18 hours. The reactions were carried out in methanol at room temperature.
Figure 5.4. $^1$H NMR spectrum (600 MHz, CDCl$_3$, 25 °C) of crude proligand L-16 showing the aromatic and methylene regions. ..................................................................................................................................................................................180

Figure 5.5. $^1$H NMR spectra (300 MHz, CDCl$_3$, 25 °C) of (a) crude complex 25 and (b) crystals of complex 25 isolated from a saturated solution of the crude complex in THF. .........................183

Figure 5.6. Solid-state molecular structures of complexes 26 (left) and 27 (right). Thermal ellipsoids are set at 50% probability and H atoms and solvent removed for clarity. The unit cell for complex 26 contains two distinct molecules differing in the position of their ethoxide groups, only one of which is depicted here. ..................................................................................................................................................................................186
List of Schemes

Scheme 1.1. Lifecycle and synthesis of PLA from renewable resources. .......................................................... 4

Scheme 1.2. Synthesis of lactide from petrochemical feedstocks. ................................................................. 5

Scheme 2.1. Synthesis of racemic N-alkylated-trans-1,2-diaminocyclohexanes with various amine substituents ........................................................................................................................................ 48

Scheme 2.2. Synthesis of racemic proligands L-4-7 with various terminal amine substituents... 50

Scheme 2.3. Synthesis of racemic indium dichloride complexes 4-6 with various terminal amine substituents. ........................................................................................................................................ 52

Scheme 2.4. Synthesis of racemic indium ethoxide complexes with various terminal amine substituents. ........................................................................................................................................ 58

Scheme 2.5. General scheme for water reactivity of parent ethoxide bridged complexes. ............. 65

Scheme 2.6. Possible route towards the formation of complex 9. ............................................................... 65

Scheme 3.1. Synthesis of chiral and achiral indium dichloride complexes 12 and 13 with central tertiary and secondary amine donors. ........................................................................................................................................ 92

Scheme 3.2. Synthesis of chiral and achiral dinuclear indium ethoxide complexes 15 and 16 with central tertiary and secondary amine donors. ........................................................................................................................................ 93

Scheme 3.3. Synthetic routes towards deuterated compound [(NMe2NpOEtBu)InCl]2(μ-Cl)(μ- OEt)(I^D). ......................................................................................................................................................... 97

Scheme 4.1. Synthesis of racemic and enatiopure dianaminophenolate proligands (±)- and (R,R)- H(NMe2NHOR2) (L-9-11) with various phenolate substituents. ....................................................................................... 127

Scheme 4.2. Synthesis of indium dichloride complexes (±)- and (R,R)- 19-21 with various phenolate substituents ........................................................................................................................................ 128
Scheme 4.3. Synthesis of dinuclear indium ethoxide complexes (±)- or (R,R)-

\[(N_{Me2N\text{H}O\text{R}_2})\text{InCl]}_2(\mu -\text{Cl})(\mu -\text{OEt}) (22-24)\) with various phenolate substituents. ..................138

Scheme 5.1. Synthesis of achiral pentadentate proligands \(\text{HO}_{\text{Bu}}(\text{L}_{\text{Me}})_2\) (L-12) and \(\text{HO}_{\text{Bu}}(\text{L}_{\text{H}})_2\) (L-14) with central tertiary and secondary amine donors and \(\text{HO}_{\text{Bu}}(\text{L})_2\) (L-13) with central imine donors. .................................................................174

Scheme 5.2. Synthesis of chiral pentadentate ligands L-15-16 with cyclohexyldiamine backbones. ........................................................................................................................................176

Scheme 5.3. Product distributions in the synthesis of chiral imine proligand L-15. .............177

Scheme 5.4. Synthesis of chiral amine proligand L-16 from reduction of crude mixture of imine products L-15 and unreacted diamine. ..................................................................................................................................179

Scheme 5.5. Synthesis of dinuclear indium chloride complex 25 with bridging pentadentate ligands L-12-14 and L-16. ......................................................................................................................................182

Scheme 5.6. Synthesis of dinuclear indium ethoxide complex 26 bridged by an achiral pentadentate ligand. ..................................................................................................................................184
### List of Abbreviations and Symbols

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROP</td>
<td>ring-opening polymerization</td>
</tr>
<tr>
<td>PLA</td>
<td>poly(lactic acid)</td>
</tr>
<tr>
<td>PGA</td>
<td>poly(glycolic acid)</td>
</tr>
<tr>
<td>PCL</td>
<td>poly(ε-caprolactone)</td>
</tr>
<tr>
<td>LA</td>
<td>lactide</td>
</tr>
<tr>
<td>L-LA</td>
<td>(S,S)-lactide</td>
</tr>
<tr>
<td>D-LA</td>
<td>(R,R)-lactide</td>
</tr>
<tr>
<td>meso-LA</td>
<td>(R,S)-lactide</td>
</tr>
<tr>
<td>rac-LA</td>
<td>a 1:1 mixture of (S,S) and (R,R)-lactide</td>
</tr>
<tr>
<td>PLLA</td>
<td>poly(L-lactide)</td>
</tr>
<tr>
<td>PDLA</td>
<td>poly(D-lactide)</td>
</tr>
<tr>
<td>P_m</td>
<td>probability of meso linkages within a polymer chain</td>
</tr>
<tr>
<td>P_r</td>
<td>probability of racemic linkages within a polymer chain</td>
</tr>
<tr>
<td>T_g</td>
<td>glass transition temperature</td>
</tr>
<tr>
<td>T_m</td>
<td>melting temperature</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>^1H</td>
<td>proton</td>
</tr>
<tr>
<td>^2H</td>
<td>deuterium</td>
</tr>
<tr>
<td>^13C{^1H}</td>
<td>proton decoupled carbon-13</td>
</tr>
<tr>
<td>^1H{^1H}</td>
<td>homonuclear proton decoupled</td>
</tr>
<tr>
<td>^1H{^13C}</td>
<td>carbon-13 decoupled proton</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>NOESY</td>
<td>nuclear overhauser enhancement spectroscopy</td>
</tr>
<tr>
<td>COSY</td>
<td>correlation spectroscopy</td>
</tr>
<tr>
<td>PGSE</td>
<td>pulsed gradient spin-echo</td>
</tr>
<tr>
<td>VT</td>
<td>variable temperature</td>
</tr>
<tr>
<td>ppm</td>
<td>parts per million</td>
</tr>
<tr>
<td>MS</td>
<td>mass spectrometry</td>
</tr>
<tr>
<td>MALDI-TOF</td>
<td>matrix-assisted laser desorption time of flight</td>
</tr>
<tr>
<td>ESI</td>
<td>electrospray ionization</td>
</tr>
<tr>
<td>EI</td>
<td>electron ionization</td>
</tr>
<tr>
<td>GC</td>
<td>gas chromatography</td>
</tr>
<tr>
<td>HR</td>
<td>high resolution</td>
</tr>
<tr>
<td>LR</td>
<td>low resolution</td>
</tr>
<tr>
<td>DFT</td>
<td>density functional theory</td>
</tr>
<tr>
<td>GPC</td>
<td>gel-permeation chromatography</td>
</tr>
<tr>
<td>EA</td>
<td>elemental analysis</td>
</tr>
<tr>
<td>MHz</td>
<td>megahertz</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
</tr>
<tr>
<td>Et</td>
<td>ethyl</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>tBu</td>
<td>tert-butyl</td>
</tr>
<tr>
<td>nPr</td>
<td>n-propyl</td>
</tr>
<tr>
<td>iPr</td>
<td>iso-propyl</td>
</tr>
<tr>
<td>Symbol</td>
<td>Name</td>
</tr>
<tr>
<td>--------</td>
<td>------</td>
</tr>
<tr>
<td>Np</td>
<td>neopentyl</td>
</tr>
<tr>
<td>Mes</td>
<td>mesityl</td>
</tr>
<tr>
<td>Myrtenyl</td>
<td>(1R)-6,6-dimethylbicyclo[3.1.1]hept-2-ene-2-methyl</td>
</tr>
<tr>
<td>NHC</td>
<td>N-heterocyclic carbene</td>
</tr>
<tr>
<td>OMe</td>
<td>methoxide</td>
</tr>
<tr>
<td>OEt</td>
<td>ethoxide</td>
</tr>
<tr>
<td>OPh</td>
<td>phenoxide</td>
</tr>
<tr>
<td>OBn</td>
<td>benzoxide</td>
</tr>
<tr>
<td>OSiMe3</td>
<td>trimethylsiloxide</td>
</tr>
<tr>
<td>O(2,6-iPrC₆H₃)</td>
<td>2,6-iso-propylphenoxide</td>
</tr>
<tr>
<td>N(SiMe₃)₂</td>
<td>bis(trimethylsilyl)amide</td>
</tr>
<tr>
<td>BPh₄⁻</td>
<td>tetraphenylborate</td>
</tr>
<tr>
<td>SiMe₃</td>
<td>trimethylsilyl</td>
</tr>
<tr>
<td>SiPh₃</td>
<td>triphenylsilyl</td>
</tr>
<tr>
<td>Si/tBuMe₂</td>
<td>tert-butyldimethylsilyl</td>
</tr>
<tr>
<td>CH₂SiMe₃</td>
<td>(trimethylsilyl)methyl</td>
</tr>
<tr>
<td>Ad</td>
<td>adamantyl</td>
</tr>
<tr>
<td>Cm</td>
<td>cumyl (-C(CH₃)₂(C₆H₅))</td>
</tr>
<tr>
<td>MeOH</td>
<td>methanol</td>
</tr>
<tr>
<td>EtOH</td>
<td>ethanol</td>
</tr>
<tr>
<td>EtOD</td>
<td>deuterated ethanol (CH₃CH₂OD)</td>
</tr>
<tr>
<td>BnOH</td>
<td>benzylalcohol</td>
</tr>
<tr>
<td>Symbol</td>
<td>Description</td>
</tr>
<tr>
<td>--------</td>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>D$_2$O</td>
<td>deuterium oxide</td>
</tr>
<tr>
<td>C$_6$D$_6$</td>
<td>deuterated benzene</td>
</tr>
<tr>
<td>CDCl$_3$</td>
<td>deuterated chloroform</td>
</tr>
<tr>
<td>CD$_2$Cl$_2$</td>
<td>deuterated dichloromethane</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>CH$_2$Cl$_2$</td>
<td>dichloromethane</td>
</tr>
<tr>
<td>Tol.</td>
<td>toluene</td>
</tr>
<tr>
<td>KBN</td>
<td>benzyl potassium</td>
</tr>
<tr>
<td>NaO$t$Bu</td>
<td>sodium tert-butoxide</td>
</tr>
<tr>
<td>KOrBu</td>
<td>potassium tert-butoxide</td>
</tr>
<tr>
<td>NaOEt</td>
<td>sodium ethoxide</td>
</tr>
<tr>
<td>KOEt</td>
<td>potassium ethoxide</td>
</tr>
<tr>
<td>TMB</td>
<td>1,3,5-trimethoxybenzene</td>
</tr>
<tr>
<td>BINAP</td>
<td>2,2'-bis(diphenylphosphino)-1,1'-binaphthyl</td>
</tr>
<tr>
<td>Pd$_2$(dba)$_3$</td>
<td>tris(dibenzylideneacetone)dipalladium(0)</td>
</tr>
<tr>
<td>Ar</td>
<td>aryl</td>
</tr>
<tr>
<td>Ac</td>
<td>acyl</td>
</tr>
<tr>
<td>Boc</td>
<td>tert-butoxycarbonyl</td>
</tr>
<tr>
<td>DACH</td>
<td>trans-1,2-diaminocyclohexane</td>
</tr>
<tr>
<td>DACH$_{Ac}$</td>
<td>N-acetyl-trans-1,2-diaminocyclohexane</td>
</tr>
<tr>
<td>DACH$_{Boc}$</td>
<td>N-tert-butoxycarbonyl-trans-1,2-diaminocyclohexane</td>
</tr>
<tr>
<td>N$_{Me2N}$</td>
<td>N,N-dimethyl-trans-1,2-diaminocyclohexane</td>
</tr>
</tbody>
</table>
eq. equivalent(s)
vs. versus
conv. conversion
calc. calculated
anal. analytical
cat. catalyst
solv. solvent
theo. theoretical
H-bond hydrogen bond
s second(s)
min. minute(s)
h hour(s)
d day(s)
mol moles
mmol millimoles
M molar (moles per litre)
mM millimolar
mL millilitres
g grams
mg milligrams
m metres
mm millimetres
µm micrometres

temp. temperature

R.T. room temperature

Da Daltons (grams per mole)

w/w % weight to weight percentage

M<sub>n</sub> number average molecular weight

PDI polydispersity index

M<sub>LA</sub> molar mass of lactide (144.13 g/mol)

M<sub>EtOH</sub> molar mass of ethyl and hydroxy end group (46.07 g/mol)

dn/dc the rate of change in the refractive index of a polymer solution with a change in concentration

et al. and others

vide infra see below

in vacuo in vacuum

in situ in a chemical reaction

< less than

> greater than

~ approximately

± plus-minus

(±) racemic

° degrees

°C degrees Celsius

% percent
<table>
<thead>
<tr>
<th>Symbol</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>µ</td>
<td>denotes a bridging ligand</td>
</tr>
<tr>
<td>δ</td>
<td>chemical shift relative to tetramethylsilane at 0 ppm</td>
</tr>
<tr>
<td>J</td>
<td>coupling constant</td>
</tr>
<tr>
<td>τ</td>
<td>parameter used to denote the degree of square pyramidal or trigonal bipyramidal geometry in five coordinate complexes (τ = (β-α)/60°)</td>
</tr>
<tr>
<td>α</td>
<td>the second largest angle in a five coordinate crystal structure</td>
</tr>
<tr>
<td>β</td>
<td>the largest angle in a five coordinate crystal structure</td>
</tr>
<tr>
<td>Å</td>
<td>angstrom</td>
</tr>
<tr>
<td>d</td>
<td>H-X distance of an amine proton to halogen hydrogen bond</td>
</tr>
<tr>
<td>D</td>
<td>N-X distance of an amine proton to halogen hydrogen bond</td>
</tr>
<tr>
<td>θ</td>
<td>N-H-X angle of an amine proton to halogen hydrogen bond</td>
</tr>
<tr>
<td>R_{HX}</td>
<td>normalized hydrogen bond distance (d over the combined Van der Waals radii of the participating atoms)</td>
</tr>
<tr>
<td>D_t</td>
<td>translational diffusion coefficient</td>
</tr>
<tr>
<td>r_H</td>
<td>hydrodynamic radius</td>
</tr>
<tr>
<td>r_{x-ray}</td>
<td>X-ray crystallographic radius</td>
</tr>
<tr>
<td>k_{obs}</td>
<td>observed rate constant of polymerization</td>
</tr>
<tr>
<td>k_p</td>
<td>propagation rate constant of polymerization</td>
</tr>
<tr>
<td>k_{rel}</td>
<td>relative observed rate of polymerization of L-LA versus D-LA (k_L/k_D)</td>
</tr>
</tbody>
</table>
Acknowledgements

I first need to acknowledge my supervisor Dr. Parisa Mehrkhodavandi for her constant support and guidance over the past five years. I could not have done this without her, and I want to give her a huge thank you for helping me to learn and grow both professionally and personally during my time with her. I need to thank her particularly for believing in me and for pushing me to see the value in my work, even though I may not always have shown it. I also need to thank her for making me strive for success (but not always perfection), without which this thesis may never have been completed.

Secondly, I need to give a big thanks to all the staff and faculty at the UBC Chemistry department, without whose help much of this work would not have been possible. In particular Maria for all her help with NMR, Marshall for his tips about mass spec and his morning hellos and all the staff in the electronics, glass blowing and mech shops for all their help.

Thirdly, I need to give a huge thank you to all the past and present Mehr group members. In particular all the wonderful undergrad students who worked on this project with (or without) my help: Joey, Vivian, Ian, Lucy, Molly and Alex, and also all the undergrads I had the pleasure of working with over the years. A huge thank you goes to Insun for her constant help, guidance and friendship, without whom I could not have accomplished so much. I also want to thank Dinesh and Cuiling for their wonderful friendship and encouragement over the years. A big thanks goes to the rest of our current group members, Ese, Tannaz, Emiliya, Paul, Steve, Alex and Alan, for putting up with the past few months, weeks and days of me either ignoring and/or bothering them while I was writing this thesis.

Lastly, I need to thank my family for all their love and support, without which I would not be where I am today.
To Grandpa
Chapter 1: General introduction

1.1 Introduction to poly(lactic acid)

As concerns over the persistence of non-degradable plastics in the environment have grown, interest in developing biodegradable alternatives to traditional polymers, such as polyolefins, has become a large area of scientific research. To this end there has been increasing interest in the production of polyesters (Figure 1.1) both for their interesting properties, such as biodegradability and biocompatibility, and for the fact that they can be produced from renewable resources. Of particular interest is poly(lactic acid) or PLA. PLA is a biodegradable and biocompatible polyester that can be produced from lactic acid obtained from the fermentation of corn, sugar beets or other renewable resources.³

![Figure 1.1. Structures of commonly studied biodegradable polyesters, poly(lactic acid) (PLA), poly(glycolic acid) (PGA) and poly(ε-caprolactone) (PCL).](image)

In North America the largest producer of PLA is NatureWorks LLC, an independent subsidiary of Cargill started in 2002, which is now also jointly owned by Thailand’s largest chemical producer PTT Global Chemical.⁴ The company has a 300 million pound per year PLA facility in Nebraska as well as the largest lactic acid production plant in North America.

PLA is a stiff and brittle thermoplastic polymer with mechanical properties comparable to polystyrene.³⁵ PLA typically produced industrially has a glass transition temperature (T₉) of ~55 °C and a melting temperature (Tₘ) of ~175 °C.³ PLA has low thermal stability at high temperatures and therefore thermal processing of PLA often leads to degradation of the
material. In addition, PLA materials are easily deformed at low

temperatures due to their low T_g values and have low impact strength, which limits their usefulness in certain applications.

PLA degrades in the environment through a two step process. First, hydrolysis of the ester bonds occurs to lower the molecular weight to approximately 40 kDa, after which microorganisms in the environment will degrade the polymer further producing carbon dioxide, water and humus. The degradation of PLA under industrial composting conditions (elevated temperatures of up to 60 °C) will allow for the complete degradation of PLA in approximately 40 days. Under normal environmental conditions PLA will degrade over 6 months to 2 years, which is a considerable advantage over polyolefin based plastics that degrade on the order of 500 to 1000 years.

In addition to the limitations in the physical properties of PLA, its sourcing from food crops such as corn makes it less desirable than plastics and materials made from other renewable resources, such as cellulose or biomass. Future efforts will focus on moving towards the use of waste plant materials and other renewable resources as a feedstock, such as corn husks and stalks. For example, the US Department of Energy recently invested 2.5 million dollars to support NatureWorks’ ongoing research into converting renewable biomethane into lactic acid.

Despite some of the challenges associated with PLA it has found a wide variety of applications, including use in agricultural products, fibers and packaging. In addition PLA and its co-polymers with other biodegradable polymers, including PGA and PCL, have found wide applications in the medical sector. For example, these polymers can be used as resorbable sutures, bone implants, tissue engineering devices and sustained drug delivery vehicles. However, there still exists a significant opportunity to improve the properties of PLA, including its brittleness, low impact strength and low thermal stability as described above,
and expand its use into other sectors. This remains a significant challenge that has fueled expanding research in this area in both academia and industry.\textsuperscript{3,5-14}

1.2 Industrial synthesis of PLA

PLA can be produced through the direct condensation polymerization of lactic acid (Scheme 1.1, Route A), however this process produces PLA with low molecular weights and high polydispersity indices (PDIs) due to the reversibility inherent in this process. Efficient removal of the water generated during this reaction is necessary to produce PLA of high molecular weight. Although azeotropic distillation processes have been developed to achieve this, they suffer from high energetic costs and the use of solvents and therefore are not favoured industrially.\textsuperscript{8}

Alternatively, PLA can be produced in a controlled manner using a suitable catalyst for the ring-opening polymerization (ROP) of the cyclic dimer of lactic acid, lactide (LA) (Scheme 1.1, Route B). Lactide is produced industrially through a two-step process (Scheme 1.1). First, feedstocks of lactic acid are polymerized via condensation to produce low molecular weight oligomers of PLA. Then these oligomers are depolymerized using tin(II) carboxylates or alkoxides to produce the cyclic lactide monomer.\textsuperscript{8}
Scheme 1.1. Lifecycle and synthesis of PLA from renewable resources.

Lactide has three isomers: the two enantiomers L-LA and D-LA and meso-LA (Scheme 1.1). The naturally occurring isomer of lactic acid is L-lactic acid, and therefore when biologically sourced feedstocks of lactic acid are used to synthesize lactide the major isomer formed is L-LA. However, some racemization occurs during the production of LA producing D-LA and to a lesser extent meso-LA. The meso-LA produced during this process can be separated easily from the L-LA and D-LA by recrystallization or distillation, typically producing feedstocks of LA for industrial use comprised of 98-99% L-LA contaminated with 1-2% D-LA.14
Although the polymerization of meso-LA is interesting, because it is produced as a byproduct in smaller amounts than L-LA or D-LA, it is not as industrially relevant and therefore is not the focus of this work and will not be discussed in further detail.

Alternatively, lactide can be produced from petroleum resources (Scheme 1.2). In this process, acetaldehyde, produced from the oxidation of ethylene, is used as a feedstock to produce lactonitrile via reaction with hydrogen cyanide (HCN).\textsuperscript{12,15} The lactonitrile is then converted to lactic acid via hydrolysis in sulfuric acid, and the resulting racemic lactic acid mixture can be converted to lactide via the usual route.\textsuperscript{15} This process yields racemic lactide (rac-LA), a 1:1 mixture of L-LA and D-LA.

\textbf{Scheme 1.2.} Synthesis of lactide from petrochemical feedstocks.

Industrially utilized catalysts for the ROP of LA are typically simple metal alkoxide complexes, such as tin(II) octanoate and aluminum(III) isopropoxide (Figure 1.2). These complexes are highly active and produce PLA with high molecular weights, but suffer from a low degree of control, producing polymers with high polydispersity indices (PDIs) due to large amounts of transesterification during the polymerization reaction (note that the term PDI will be...
used throughout this thesis despite the recent replacement of the term polydispersity (PDI) with dispersity (D) to describe the molecular weight distribution of polymers and the reader is referred to the IUPAC recommendations on the subject for more information\(^\text{16}\). These systems are capable of producing high molecular weight, crystalline PLA from enantiopure L-LA feedstocks (no epimerization occurs), however they are not stereoselective in the polymerization of rac-LA.\(^\text{17}\) This is an important distinction, as the properties of PLA are highly dependent on the relative stereochemistry within the polymer chains. The polymerization of rac-LA allows access to PLA microstructures with improved physical properties to those produced solely from enantiopure L-LA feedstocks. As discussed in the previous section this limits the applications of PLA currently produced industrially.

![Figure 1.2. Homoleptic metal complexes used industrially for ROP of lactide.](image)

### 1.3 Mechanism of the ROP of lactide using metal catalysts

The metal catalyzed polymerization of lactide has been studied with a variety of metal catalysts.\(^\text{17-19}\) Some of the first metal catalysts studied extensively in the polymerization of lactide were simple homoleptic metal complexes such as those discussed above, tin(II) octanoate and aluminum(III) isopropoxide, which are still used for the industrial synthesis of PLA from lactide.\(^\text{20-24}\) As mentioned above, these systems can be very active, but they are not stereoselective for the polymerization of rac-LA, which has generated interest in discovering well-defined single-site catalysts of the type L\(_n\)MX (L\(_n\) = ancillary ligand, M = electropositive
metal, $X =$ initiator group, typically an alkoxide or amide) that can combine activity with high stereoselectivity for the polymerization of lactide. Although metal catalysts are the most studied types of catalysts for LA polymerization, organocatalysts for ROP of lactide are known, however these systems are typically not highly stereoselective and will not be discussed in further detail.

The polymerization of LA with metal catalysts typically occurs through a coordination-insertion mechanism (Figure 1.3), first proposed by Dittrich and Schulz in 1971. The first evidence for this mechanism was found in the polymerization of lactones with aluminum(III) isopropoxide although it is also the typical mechanism of polymerization with more well defined $L_2$MX type catalysts.

In this mechanism, coordination of a lactide monomer to the metal centre via the carbonyl oxygen is followed by attack of the initiating group, usually an alkoxide, at the carbonyl carbon. This results in a bicyclic intermediate, or transition state depending on the catalyst system, which then undergoes acyl bond cleavage resulting in the ring opening of the cyclic ester and formation of a new polymeryl alkoxide species. This polymeryl alkoxide species remains coordinated to the metal, acting as the initiator when further equivalents of lactide coordinate to the metal centre, leading to propagation of the polymer chain.
Stereoselectivity in this mechanism can be achieved in two ways: chain end control and enantiomorphic site control. In chain end control the stereochemistry of the next incorporated monomer is determined by the stereochemistry of the preceding monomer unit, and is seen most often with bulky achiral catalysts. However, in enantiomorphic site control, often encountered in systems bearing chiral ligands, the morphology of the ligand, and by extension the catalyst, dictates which monomer will be enchained. These mechanisms are not mutually exclusive and both mechanisms may be active to varying degrees in a particular catalyst system.

1.4 Tacticity of PLA

The microstructure of a PLA sample is related to its tacticity. Tacticity is defined by the relative absolute stereochemistry of each stereogenic centre along the polymer chain. A number of microstructures are possible when considering the polymerization of the two chiral enantiomers of LA, L and D-LA. The polymerization of enantiopure LA results in isotactic PLLA or PDLA when L-LA or D-LA is polymerized respectively. This results when no
racemization occurs during the polymerization, thereby ensuring that each stereogenic centre along the polymer chain has the same absolute stereochemistry (Figure 1.4).

![Diagram of polymerization and microstructures]

**Figure 1.4.** PLA microstructures resulting from ROP of enantiopure LA.

During the polymerization of *rac*-LA (a 1:1 mixture of L and D-LA) there are a number of possible microstructures that can be formed depending on the selectivity of the catalyst system being used (Figure 1.5). A non-stereoselective system will produce atactic PLA, where there is a completely random arrangement of stereogenic centres along the polymer chains. A heteroselective system will incorporate L and D-LA in an alternating fashion, producing heterotactic PLA, where there are alternating pairs of stereogenic centres with the same stereochemistry along the polymer chains.
Figure 1.5. Microstructures of PLA that can result from the polymerization of rac-LA.

When the catalyst system is isoselective, several different isotactic microstructures can be formed depending on both the mechanism and degree of isoselectivity (Figure 1.5). Chiral catalyst systems that are highly site selective, with each enantiomer of a chiral catalyst system selecting for only one enantiomer of LA, may form isotactic stereocomplex PLA, a mixture of separate PLLA and PDLA chains, when the racemic catalyst is used to polymerize rac-LA (an example of kinetic resolution). However, more commonly in site selective systems an isotactic stereoblock or stereogradient PLA microstructure is formed, where there are either two discrete blocks of isotactic PLLA and PDLA along one polymer chain (stereoblock) or a gradient forming two regions enriched in PLLA and PDLA along one polymer chain (stereogradient).
Stereoblock and stereogradient PLA can be formed from site selective catalysts that are capable of polymerizing both enantiomers of LA, albeit with one being the preferred monomer and having a faster rate of polymerization. In highly selective systems there will be a lower probability of a catalyst enchaining the non-preferred monomer (a stereoerror) and therefore the polymerization will generally proceed to ~50% conversion by incorporation of only the preferred monomer of LA, after which the catalyst will start to incorporate the other enantiomer forming a di-block structure. Stereogradient PLA can be formed in a similar manner from less selective catalysts, where the higher probability of stereoerrors will lead to a more gradual change from regions enriched in PLLA to regions enriched in PDLA or vice versa.

Alternatively, stereoblock PLA can result from racemic chiral catalyst systems through a chain exchange mechanism. This occurs when one enantiomer of catalyst enchains its undesired enantiomer of LA and then exchanges the growing PLA chain with the other enantiomer of catalyst, thereby continuing to grow PLA with its preferred monomer. This type of mechanism has been proposed to occur in highly site selective aluminum salen catalysts.\(^2^8\)

The above discussion details isotactic microstructures that can result from enantiomorphically site controlled systems, however when chain end control is the dominant selectivity mechanism isotactic multiblock PLA can be formed. Here there will be several blocks of PLLA and PDLA along the polymer chains, the number of which will depend on the degree of selectivity. This occurs due to the differences in correcting stereoerrors between site and chain end controlled systems. When the undesired enantiomer of LA is enchained, a chain end controlled isoselective system will then continue to polymerize that enantiomer of LA, as the isoselectivity comes only from the chirality of the chain end, not the catalyst itself. This will eventually form several blocks of PLLA and PDLA along the polymer chains, with lower
selectivity leading to more numerous and shorter blocks. This is in contrast to site controlled systems that will correct a stereoerror by continuing to enchain the preferred monomer of LA after the error occurs (as detailed above).

The microstructure of PLA has a large influence on the resulting physical properties of the material. For example, atactic PLA is an amorphous polymer with a glass transition temperature of \( \sim 50 \, ^\circ\text{C} \) and no observable melting temperature.\(^{29}\) This makes it unsuitable for many applications, such as molded articles and containers for example.\(^{17}\) Conversely, isotactic PLLA or PDLA is a crystalline polymer with a glass transition temperature of \( \sim 50 \, ^\circ\text{C} \) and a melting temperature of up to \( 180 \, ^\circ\text{C} \). Even higher melting temperatures of up to \( 230 \, ^\circ\text{C} \) are reached when stereocomplex or stereoblock PLA are formed, which is due to an increased degree of crystallinity arising from the co-crystallization of PLLA and PDLA regions. In contrast, heterotactic PLA has no observable glass transition temperature and has a lower melting temperature of \( 130 \, ^\circ\text{C} \), despite having a stereoregular microstructure.\(^{17-18}\) Control of PLA microstructure is therefore of great importance in producing materials with the specific physical properties needed for particular applications. As a result, the stereocontrolled polymerization of \( \text{rac-LA} \) has become a large area of research as it allows access to PLA microstructures (stereocomplex/block/gradient) not possible in the homopolymerization of L-LA or D-LA.\(^{18-19}\)

Consequently, the accurate and quantitative measurement of the tacticity of the PLA produced by a particular catalyst system is of particular importance in this field and will be detailed in the next section.

1.5 Quantification of the tacticity of PLA

The tacticity of PLA can be defined by two parameters, the \( P_m \) and \( P_r \) values, which are the probabilities of finding either a \textit{meso} or \textit{racemic} linkage within the polymer chain,
respectively. A *meso* linkage \((m)\) exists where two adjacent stereocentres have the same stereochemistry and a *racemic* linkage \((r)\) exists where they have the opposite stereochemistry (Figure 1.6). As a result, perfectly heterotactic PLA will have a \(P_r\) of 1, as the probability of forming *racemic* linkages is 100%, and perfectly isotactic PLA will have a \(P_m\) value of 1, as the probability of forming *meso* linkages is 100%. Atactic PLA therefore has a \(P_r\) value equal to \(P_m\) at 0.50.

The tacticity of PLA is measured experimentally by using NMR spectroscopy to identify and quantify particular “n”-ad sequences within the polymer chains, where \(n\) is equal to the number of adjacent stereogenic centres.\(^{30-35}\) For example, a tetrad is a unit of four adjacent stereogenic centres that is defined by the three different linkages present, either \(m\) or \(r\). In Figure 1.6, the PLA chain shown at the top is an example of an \(mrm\) tetrad sequence, which would exist in heterotactic PLA.

![Diagram of PLA tacticity](image)

**Figure 1.6.** Tetrad sequences for different tacticities of PLA resulting from *rac*-LA polymerization.

Each tetrad sequence will have a unique chemical shift in the NMR spectra of the polymer, and therefore detailed NMR spectroscopic studies have been completed to identify which peaks correspond to particular tetrad sequences, and in some cases pentad level sequences,
in both $^{13}$C and $^1$H NMR spectra of PLA. $^{30-35}$ In the polymerization of rac-LA homonuclear decoupled $^1$H NMR spectroscopy ($^1$H{ $^1$H} NMR) is particularly useful, as it provides better resolution of the tetrads and is easier to quantify than $^{13}$C NMR spectroscopy. $^{32}$ The signals of interest in the $^1$H{ $^1$H} NMR spectrum of PLA are the methine protons of the PLA backbone (5.1 – 5.3 ppm region), which are decoupled from the neighbouring methyl groups (~1.6 ppm) in order to simplify the spectrum into a series of singlets (Figure 1.7). Each peak corresponds to a particular tetrad sequence, however the rmr and mmr tetrads are indistinguishable and therefore cannot be unambiguously assigned. $^{32-35}$

**Figure 1.7.** $^1$H{ $^1$H} NMR spectrum (600 MHz, CDCl$_3$, 25 °C) of an atactic PLA sample ($P_m$ = 0.50) resulting from the polymerization of rac-LA, showing tetrad assignments of each peak according to the literature. $^{36-35}$

Bernoullian statistics provides a set of equations defining the probability of each particular tetrad sequence to occur within the polymer chain, which can be expressed in terms of $P_m$ and $P_r$ values (Table 1.1). $^{35}$ By using these equations and the total integration of the methine region peaks (Table 1.1, equation 1) to relate the integrations of the rmr ($x$) and rmr/mmrm ($y$)
peaks to their concentrations, $P_r$ (Table 1.1, equation 2) and $P_m$ (Table 1.1, equation 3) can be easily calculated from the $^1$H-$^1$H NMR spectrum of a PLA sample.

**Table 1.1.** Tetrad probabilities and equations for calculating the tacticity of PLA.\(^{35}\)

<table>
<thead>
<tr>
<th>Tetrad</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>[mmm]</td>
<td>$P_m^2 + P_rP_m/2$</td>
</tr>
<tr>
<td>[mnr]</td>
<td>$P_rP_m/2$</td>
</tr>
<tr>
<td>[rmn]</td>
<td>$P_rP_m/2$</td>
</tr>
<tr>
<td>[rmr]</td>
<td>$P_r^2/2$</td>
</tr>
<tr>
<td>[mrm]</td>
<td>$(P_r^2 + P_rP_m)/2$</td>
</tr>
</tbody>
</table>

Total integration = $\varepsilon = x + y + z$ (1)

$[rmr] = x/\varepsilon = P_r^2/2$ therefore if $x = 1$: $P_r = (2/\varepsilon)^{1/2}$ (2)

$[mnr/rmn] = y/\varepsilon = P_rP_m/2$ therefore: $P_m = yP_r$ (3)

These equations are specific to the polymerization of either *rac*-LA or *meso*-LA, as different tetrad sequences will be possible in each case.\(^{35}\) For example, in the polymerization of *rac*-LA only five tetrad sequences (*mmm, mnr, rmn, rmr* and *mrm*) are possible. The *rrr, rrm* and *mrr* tetrads are only observed in the polymerization of *meso*-LA, unless epimerization or transesterification reactions take place in the polymerization of *rac*-LA, leading to these defects.

In addition to the calculation of the tacticity of the polymer, NMR spectroscopy is useful in elucidating mechanistic differences between different catalyst systems on the basis of stereoerrors. During the stereoselective polymerization of *rac*-LA, the catalyst may make an error and incorporate the “wrong” enantiomer of LA, forming a stereoerror in the polymer chain. For example, in catalyst systems that form heterotactic PLA (chain end control) the tetrad sequences possible are the *mrm* and *rmr* sequences, however a stereoerror will allow for the *rmn, mmm* and *mnr* tetrad sequences to be present (Figure 1.8).
As mentioned above, the mechanism for isoselectivity in the polymerization of rac-LA can be either chain end control or enantiomorphic site control. A distinction between these two mechanisms can be made on the basis of stereoerrors (Figure 1.8). In chain end controlled systems the stereoselectivity is determined by the chirality of the last enchainment monomer unit. Therefore, once a stereoerror is made, meaning a LA unit of opposite stereochemistry is incorporated, the system will continue to polymerize LA of the same stereochemistry as the “new” LA unit. This means that other than the isotactic mmm tetrad sequence, the mnr, mrm and rmm tetrads will be present in a 1:1:1 ratio. In contrast, site controlled systems prefer to polymerize a single enantiomer of LA, and therefore after the stereoerror is made, the system will correct the error by continuing to polymerize the preferred enantiomer of LA. This means that in addition to the isotactic mmm tetrad, the mnm, rmm, rnr and mrm tetrads will be present.
in a 1:1:1:2 ratio. In this way NMR spectroscopy can be used to gain insight into the mechanism of stereocontrol in a particular catalyst system in addition to providing a way to quantitatively determine the tacticity of PLA. In the next section a short review of the relevant literature on metal catalyzed ROP of lactide will be provided, with an emphasis where possible on the factors affecting stereocontrol in different catalyst systems.

1.6 Defined metal catalysts for the ROP of lactide

Metal containing complexes have been the most successful catalysts for stereoselective polymerization of rac-LA. Ligand design lies at the heart of developing stereoselective catalysts for this reaction. A variety of ligand designs, ranging from monodentate to pentadentate, have been explored for control of activity and selectivity. Some landmark examples are included in Figure 1.9.

![Landmark catalysts for rac-LA polymerization bearing mono- to pentadentate ligands.](image)

*Figure 1.9. Landmark catalysts for rac-LA polymerization bearing mono- to pentadentate ligands.*
The field of metal catalyzed ROP of lactide has been extensively reviewed in the literature.\textsuperscript{17-19,40-44} Consequently, only a brief overview of the relevant literature to this project will be discussed herein. Specifically, the following sections will focus on catalysts incorporating tridentate ligands. Comparisons of the polymerization activity of these complexes are difficult to make as differences in experimental procedure (solvent, temperature, catalyst concentration and monomer loading etc.) make direct comparisons between different catalyst systems difficult. Where possible, discussions of high versus low activity are made only in relation to another catalyst system as a comparison. In fact, high stereoselectivity may be more desirable and is certainly the focus of this work, and therefore the stereoselectivity of the following catalyst systems has also been discussed in detail where possible.

1.6.1 Tripodal homo and heteroscorpionate ligands

Work in this field was pioneered by Chisholm in the late nineties, when his group published the first report on a complex bearing a scorpionate ligand that was active for the ROP of lactide.\textsuperscript{45} The reported magnesium complex, [HB(3-'Bupz)\textsubscript{3}]MgOEt (I\textsubscript{1}), featuring a bulkyl tert-butyl substituted tris(pyrazolyl)borate ligand is capable of polymerizing L-LA without any epimerization, forming isotactic PLA (Figure 1.10). It undergoes the typical coordination insertion mechanism with acyl bond cleavage, as evidenced by the presence of ester end groups in the \textsuperscript{1}H NMR spectra of the polymers. Controlled molecular weights and low PDI (~1.2) are observed up to 1000 eq. of monomer.

These promising results prompted Chisholm to investigate these ligands in more detail, and he subsequently published more thorough studies involving the synthesis and polymerization activity of magnesium\textsuperscript{46}, zinc\textsuperscript{46} and calcium\textsuperscript{47-48} complexes featuring both tris(pyrazolyl)borate
and chiral tris(indazolyl)borate ligands with a variety of alkoxide and amide initiator groups (Figure 1.10).

![Chemical structures of complexes I-1 to I-9 with notation and structural formulas.]

**Figure 1.10.** Tris(pyrazolyl)borate (I-1-6) and tris(indazolyl)borate (I-7-9) complexes developed by Chisholm et al.\(^{45-48}\)

Some general activity trends in the ROP of LA were seen with these complexes: 1) increasing activity towards LA polymerization was seen in moving from Zn to Mg to Ca complexes such that complexes with the same ligand system (I-1-3) polymerized 100 eq. of LA to over 90% conversion in 1 minute for Ca, 1 hour for Mg and 6 days for Zn\(^{47}\); 2) in Mg and Zn complexes bearing tris(pyrazolyl)borate and tris(indazolyl)borate ligands the indazolyl species (I-7-9) were more active prompting the authors to suggest that steric crowding may play a factor in enhancing the rate of polymerization\(^{46}\); 3) substitution of the pyrazolyl substituents for
electron withdrawing groups, such as in zinc complex I-5, renders the resulting complex inactive.\textsuperscript{46}

The Mg and Zn analogues are not very stereoselective in \textit{rac}-LA polymerization, with the most stereoselective complexes having chiral tris(indazolyl)borate ligands. For example, zinc complex I-8 was the most stereoselective but only showed very mild isoselectivity in the polymerization of \textit{rac}-LA.\textsuperscript{46} However, all the Mg and Zn complexes show a marked diastereoselectivity in the polymerization of mixtures of \textit{meso}-LA and \textit{rac}-LA, with all complexes showing a preference for the polymerization of \textit{meso}-LA and the chiral tris(indazolyl)borate magnesium complex I-7 showing the highest diastereoselectivity, and a mild syndioselectivity in the polymerization of \textit{meso}-LA.\textsuperscript{46}

The selectivity of the Ca complexes is higher than the related Mg or Zn analogues, with the tris(pyrazolyl)borate Ca complexes bearing either amide or alkoxide initiators (I-3-4) producing 90\% heterotactic PLA from 200 eq. of \textit{rac}-LA in under 1 min at room temperature in THF, making them the most active and selective complexes in this family.\textsuperscript{47-48} A similar selectivity is seen for the chiral tris(indazolyl)borate complex I-9, although the activity is slightly lower, with the polymerization complete in 5 minutes under similar conditions.\textsuperscript{47-48} The selectivity is completely lost in complexes without sufficient steric bulk, such as the tris(pyrazolyl)borate Ca complex bearing \textit{iso}-propyl groups on the pyrazolyl rings (I-6). In fact, Ca complexes with tris(pyrazolyl)borate ligands bearing phenyl substituents could not be synthesized, as there is not sufficient steric bulk to shut down the Schlenk equilibrium and CaL\textsubscript{2} complexes are formed exclusively.\textsuperscript{48} These systems have been reviewed extensively.\textsuperscript{49}
Inspired by the work of Chisholm in this area, Mountford et al. have published Y\textsuperscript{50} and Ca\textsuperscript{51} cationic and zwitterionic complexes bearing tris(pyrazolyl)borate and the related tris(pyrazolyl)methane ligand systems (Figure 1.11).

Figure 1.11. Tris(pyrazolyl)borate and tris(pyrazolyl)methane cationic and zwitterionic Y and Ca complexes reported by Mountford et al.\textsuperscript{50-51}

The Y dicationic complex I-\textbf{10} is active for the polymerization of rac-LA, however much less so than the related complexes reported by Chisholm \textit{et al.}, requiring elevated temperatures (70 °C in THF) to reach substantial conversion in over 12 hours, something the authors attribute to the high electrophilicity of this dication. This complex produces PLA with controlled molecular weights, but it is not selective in the polymerization of rac-LA, producing only atactic PLA.\textsuperscript{50}

The related Ca cationic complex I-\textbf{11} shows better activity, reaching high conversions of 250 eq. rac-LA at room temperature within 2 hours, forming PLA with controlled molecular weights and low PDI (1.2-1.4), albeit the molecular weights are slightly higher than the expected values. Again, as for the Y complex this catalyst is not selective, producing only atactic PLA.\textsuperscript{51}

The related formerly zwitterionic Ca complex I-\textbf{12} is more active, reaching over 90% conversion of 200 eq. rac-LA within 5 minutes at room temperature. As for I-\textbf{11}, the molecular weights were well controlled, however slightly less so for this catalyst due to its high activity. In contrast
to I-11 complex I-12 proved to be selective in the polymerization of rac-LA forming heterotactic PLA with a $P_r$ value up to 0.80 at room temperature (up to 0.90 at lower temperatures).

Significant contributions to this field have been made by the group of Otero et al., specifically in the development of new heteroscorpionate ligands based on bis(pyrazolyl)methane systems with various pendant arms for use in Mg, Zn, Al, and rare-earth metal chemistry towards LA polymerization.

Magnesium and zinc complexes active for the polymerization of cyclic esters bearing amidinate based heteroscorpionate ligands were first reported by Otero et al. in 2007. The ligands have either iso-propyl or tert-butyl/ethyl groups on the amidinate pendant arm, with either methyl or tert-butyl pyrazolyl substituents (Figure 1.12).

Figure 1.12. Mg and Zn complexes bearing bis(pyrazolyl)methane ligands with amidinate pendant arms reported by Otero et al.\cite{52,54,55,58,59,60,61,62}

Most of the complexes shown in Figure 1.12 were tested for the polymerization of L-LA, showing no epimerization and producing isotactic PLA with generally well controlled molecular
weights and low PDIs (1.04 – 1.2). As well, the polymerization of L-LA was generally faster than the polymerization of rac-LA within a particular catalyst system.\textsuperscript{52,54-55} In terms of the polymerization of rac-LA all analogues showed generally well controlled molecular weights with low PDIs (<1.2), however there were stark contrasts in the activity and selectivity of the systems based on the ligand substituents.

The magnesium analogues with the less bulkyl methyl substituted pyrazolyl groups (I-13/18) were much less active than their bulkier analogues with tert-butyl substituents (I-15/19).\textsuperscript{52,54} For example, the polymerization of rac-LA (100 eq.) with complex I-18 reaches only 42% conversion after 72 hours at 70 °C in toluene,\textsuperscript{52} whereas with complex I-19 the polymerization reaches 66% conversion in only 6 minutes at 20 °C in toluene and reaches 91% conversion in only 2 minutes at 20 °C in THF.\textsuperscript{54} The comparison between complexes I-13 and I-15 shows a similar trend, although these analogues with the bulkier tert-butyl substituted amidinate group are slightly less active.\textsuperscript{52,54}

A similar trend is not observed within the related zinc complexes (I-14/16/17). All three compounds show similar activity in the polymerization of rac-LA (100 eq.), with conversions of 65%, 71% and 63% after 48 hours at 110 °C in toluene for complexes I-14, I-16 and I-17, respectively.\textsuperscript{55}

These trends in activity were explained by means of the propensity of these systems to undergo ligand redistribution via Schlenk equilibria, thereby forming inactive ML\(_2\) sandwich complexes. The trends fit this hypothesis, as complexes that were shown to form sandwich complexes, namely the less bulky Mg analogues I-13/18 are considerably less active than either the related zinc complexes I-14/16/17 or their bulkier Mg analogues I-15/19, which do not form sandwich complexes.\textsuperscript{52,54-55}
The trends in the selectivity of these systems in the polymerization of rac-LA were similarly related to their steric bulk, with all analogues with the bulkier tert-butyl pyrazolyl substituents showing a preference for the formation of heterotactic PLA ($P_r = 0.60 – 0.79$) and all analogues with the less bulkyl methyl pyrazolyl substituents forming only atactic PLA.$^{52,54-55}$ The most active and selective analogues in this series were therefore the bulky Mg complexes I-15 and I-19, which reach high conversions in only minutes at room temperature in THF forming heterotactic PLA with $P_r$ values of $\sim$0.7. This group has also published related dinuclear and tetranuclear Mg complexes made with these amidinate ligands by reaction with excess Mg starting materials, which were also shown to be heteroselective, although they are less active and less selective than complexes I-15 and I-19.$^{53}$

Other notable examples from Otero et al. include ligands bearing cyclopentadienyl$^{53,57}$ and alkoxy$^{56,58}$ pendant arms (Figure 1.13). Of particular note are the enantiopure zinc complexes based on chiral myrtenyl substituted arms (I-20-23), with the cyclopentadienyl version (I-20) remarkably showing isoselectivity in the polymerization of rac-LA ($P_m = 0.73 - 0.77$).$^{57}$ Related dimeric zinc complexes with myrtenyl substituted alkoxy pendant arms with either alkyl (I-21) or alkoxy/thioalkoxy (I-22-23) initiators show a shift in the selectivity from heterotactic (I-21: $P_r = 0.77$) to isotactic (I-22: $P_m = 0.73$ and I-23: $P_m = 0.71$).$^{56,58}$ Complexes I-20, I-22 and I-23 are quite remarkable in that they are rare examples of zinc initiators capable of producing isotactic PLA from rac-LA.
Figure 1.13. Enantiopure zinc complexes with bis(pyrazolyl)methane ligands bearing chiral myrtenyl substituted cyclopentadienyl and alkoxy pendant arms.$^{56-58}$

1.6.2 Tridentate diamidoamino and related ligands

In 1998 Bertrand and co-workers reported a series of Al, Ga and In compounds with tridentate (N,N,N)-type triamine ligands (Figure 1.14).$^{64}$ Of the large number of compounds reported only the Al methyl (I-24) and hydride (I-25) compounds were active for the polymerization of rac-LA, converting 50 equivalents to 37% and 76% conversion in 5 and 7 days, respectively, with relatively low PDI (1.7 – 1.8). Another active complex could be formed by the activation of a cationic Al chloride complex (I-26) with propylene oxide (I-26/PO = 1/20), forming a reactive alkoxide in situ that could initiate the polymerization of rac-LA to 46% conversion in 5 days for 50 equivalents, and 85% conversion in 25 days for 500 equivalents, with relatively low PDI (1.2 – 1.4). The selectivity of these systems was not reported. Bertrand and Bourissou have also reported related Zn, Sm and Sn compounds with these ligands for the co-polymerization of lactide and glycolide, however the homopolymerization of lactide was not reported.$^{65}$

25
Recently, Mountford and co-workers have described the synthesis and polymerization activity of a series of Al\textsuperscript{66}, Ti\textsuperscript{67} and In\textsuperscript{68} complexes coordinated by a tridentate sulfonamide ligand system in addition to their work with related tetradentate ligand systems (Figure 1.15).

The Al ethyl complex (I-30) is the least active and controlled, polymerizing 100 equivalents of rac-LA (toluene, 70 °C) to only 20% conversion in 72 hours, with higher than expected molecular weights and high PDI (1.47). In comparison, the related Al alkoxide complexes I-31 and I-32 reach 81% and 76% conversion in the same time frame with controlled molecular weights and low PDI (1.12), although they produce only atactic PLA. The related indium alkyl complex (I-33) has a comparable rate under the same conditions, reaching 89%
conversion in 94 hours, but as for complex I-30 the molecular weight is not well controlled, although the PDI is lower (1.16). Both Al and In complexes are also active in melt polymerization of rac-LA, generally giving similar molecular weights albeit with slightly higher PDI values.

The related Ti alkoxide complexes I-34 and I-35 are more active than their Al or In counterparts, reaching 71% and 44% conversions in 11 and 2 hours, respectively, under similar conditions. However, although molecular weights are reasonably well controlled and PDIs are low (1.09 – 1.13) with these Ti catalysts, the catalysts become inactive at longer reaction times and high conversion of monomer cannot be reached.

Carpentier et al. have reported related zinc complexes (I-27-29) with tridentate bis(pyrazolyl)amine ligands for the polymerization of rac-LA and methylmethacrylate (Figure 1.16). All three complexes are active for the polymerization of rac-LA, reaching conversions of >90% in 30 hours (unoptimized time) at room temperature, although the ethoxide complex (I-28) is slightly more active. The ethoxide complex (I-28) is also very well controlled, with molecular weights matching well with theoretical values with low PDI (1.23 – 1.40). In contrast, the ethyl (I-27) and cationic (I-29) complexes are not well controlled, producing lower and higher molecular weights than expected, respectively, with high PDI values (1.71 – 1.97). Complex I-28 was tested for selectivity, but only atactic PLA was formed from rac-LA with this system. A related bis-ligated homoleptic Mg compound with the same ligand system was also reported and found to be highly active in the polymerization of rac-LA (full conversion in 10 min) however it too produced only atactic PLA.
Figure 1.16. Neutral and cationic zinc complexes with tridentate bis(pyrazolyl)amido ligands developed by Carpentier et al.\textsuperscript{69}

1.6.3 Tridentate diamidoether and linked bis(phenolate) ligands

Dagorne et al. have reported a series of Al and Ga complexes bearing tridentate (N,O,N) diamidoether ligands with amide and alkoxide initiators (Figure 1.17).\textsuperscript{71-72} The lithium aluminum dimeric complexes I-36-I-37 polymerize rac-LA (230 eq.) at room temperature in CH\textsubscript{2}Cl\textsubscript{2} at approximately the same rate, reaching 82% (I-36) and 85% (I-37) in 16 hours. Complex I-36 produces PLA with controlled molecular weights and low PDI (1.03 – 1.06), although MALDI-TOF mass spectrometry shows some amount of transesterification is present. This complex is moderately selective, producing heterotactic PLA with a P\textsubscript{r} = 0.65 – 0.67.\textsuperscript{71} In comparison, the related alkoxy dimer I-38 requires more forcing conditions (toluene, 80 °C) to reach high conversions, converting 100 eq. of rac-LA to only 79% conversion in 3 hours. This catalyst is also less controlled, with higher than theoretical molecular weights and relatively high PDI (1.25 – 1.32), although it is also selective, producing instead isotactic PLA with P\textsubscript{m} = 0.62.\textsuperscript{72}
The related Al (I-39) and Ga (I-40) amide complexes are more active than the alkoxide (I-38), reaching 80% conversion in 3 hours and 100% conversion in 1 hour, respectively, in toluene at 80 °C. The Ga complex is remarkably more controlled than its Al analogue, with better molecular weight control and lower PDIs (1.12 for Ga vs. 1.66 for Al). Under slightly different conditions (CH₂Cl₂ at 40 °C) complex I-40 produces isotactic PLA with a P_m = 0.70, although the Al complex I-39 can also produce isotactic PLA (P_m = 0.70) through immortal ring-opening polymerization with a suitable chain transfer reagent (BnOH, 5 eq.) in toluene at 60 °C.

In 2002 Okuda and Harada *et al.* reported several Ti complexes with bis(phenolate) ligands bridged by chalcogen donors for use in the polymerization of several cyclic esters, including lactide (Figure 1.18). Of the reported complexes, the polymerization of lactide was investigated with only the chloride complexes I-41 (Te bridged) and I-42 (S bridged). Complex I-41 was active for the polymerization of L-LA in toluene, anisole and dioxane, producing isotactic PLA (no epimerization) with controlled molecular weights and low PDIs (~1.1). In anisole the polymerization of 200 eq. of L-LA with I-41 proceeded to 97% conversion in 112 hours to produce PLA with a PDI of 1.13, whereas the related S bridged complex I-42 was not well controlled under the same conditions and produced higher than expected molecular weights.

**Figure 1.17.** Al and Ga complexes bearing tridentate diamidoether ligands reported by Dagorne *et al.*
of PLA after 80% conversion. The controlled nature of complex I-41 also allowed for the co-polymerization of L-LA and ε-caprolactone.

![Chemical structures](image)

**Figure 1.18.** Ti and Zr complexes bearing bis(aryloxy) ligands with chalcogen and NHC bridging groups reported by Okuda *et al.* and Dagorne *et al.*

Dagorne *et al.* have also reported Ti and Zr complexes with similar tridentate bis(phenolate) ligands bridged by N-heterocyclic carbenes (Figure 1.18). The Zr complex (I-44) is far superior to the Ti analogue (I-43), with each polymerizing 100 equivalents of rac-LA to 91% conversion in CH₂Cl₂ at room temperature and 89% conversion in toluene at 90 °C over 15 hours, respectively. Both show relatively controlled molecular weights with low PDIs (<1.1), however the Ti complex I-43 produces atactic PLA whereas the Zr analogue I-44 produces highly heterotactic PLA with a Pₜ > 0.95. The Zr catalyst I-44 is also able to polymerize commercial rac-LA that has not been recrystallized or purified as well as polymerize rac-LA in the melt or under immortal ring-opening polymerization conditions with BnOH with little change in performance or selectivity.
Similar group 3 complexes bearing bis(naphthoxy) and bis(phenoxo) ligands bridged by either pyridine or thiophene groups have been reported by Carpentier et al (Figure 1.19).\textsuperscript{76-78}

The related amido complexes (I-45-48) are all highly active in the polymerization of \textit{rac}-LA at room temperature and show some intriguing trends in activity and selectivity. In the series with bis(naphthoxy) ligands (I-45-47) all compounds polymerize \textit{rac}-LA to produce heterotactic PLA with controlled molecular weights and reasonably low PDIs (1.32 – 1.90) in a few hours in either toluene or THF; however, the polymerization rate is faster in toluene. The selectivity is highest in THF, such that polymers formed in toluene are atactic whereas those formed in THF have varying degrees of heterotacticticy. However, the thiophene bridged complexes (I-46) are less selective than the pyridine bridged complexes (I-45/47). As well, in complexes with Si’BuMe\textsubscript{2} groups (I-47) the selectivity increases with decreasing ionic radius of the metal centre (P\textsubscript{r} = 0.93 for Sc, 0.84 for Y and 0.50 for La). This is not observed in the related SiPh\textsubscript{3}}
complexes (I-45) where the Sc complex is the least selective ($P_r = 0.65$) and the Y and La complexes have similar selectivity ($P_r \sim 0.9$). The related bis(phenoxy) pyridine bridged Y complex (I-48) is more active than the naphthoxy complexes polymerizing \textit{rac}-LA in THF at room temperature to 70% conversion in only 15 minutes. It is also more selective than the related bis(naphthoxy) analogues (I-45/47) producing heterotactic PLA in toluene ($P_r = 0.55 – 0.60$) and THF ($P_r = 0.94 – 0.96$), although the same trend of increased selectivity in THF over toluene is also seen with this complex. 

1.6.4 Ketiminate ligands

Lin \textit{et al.} have extensively studied ketiminate ligands with a third amine donor arm for use in Mg, Zn, Al and Ca complexes for the polymerization of lactide (Figure 1.20). Mg complexes I-49-52 reveal interesting substituent effects on the polymerization of lactide. The polymerization of 200 eq. L-LA in toluene at room temperature reaches over 99% conversion with complex I-50 in 2 minutes, 89% conversion with complex I-51 in 4 minutes, 97% conversion with complex I-49 in 8 minutes and 89% conversion with complex I-52 in 10 hours. These effects were rationalized based on steric effects for complexes I-49-51, with the bulkiest complex promoting more dissociation of the dimers and therefore higher activity, and electronic effects for complex I-52, where the electron withdrawing CF$_3$ groups promote a decreased nucleophilicity of the OBn group, thereby reducing its ability to initiate polymerization.
Lin and co-workers also investigated a related ligand system derived from 4-benzoyl-3-methyl-1-phenyl-2-pyrazolin-5-one. The related Mg and Zn benzyloxy bridged complexes I-53-55 are all active for the controlled polymerization of lactide, with the Zn complex I-54 (R₁ = Me, R₂ = H) being more reactive than its Mg analogue I-53. These two complexes were also tested
for the polymerization of rac-LA, again showing higher activity for the Zn complex I-54 but lower selectivity ($P_r = 0.61$ for I-54 vs. $P_r = 0.87$ for I-53). Several analogues of the Zn complex (I-54) were made with $R_2 = \text{Me, } ^{3}\text{Bu, CF}_3$ and F however no significant substituent effects were seen with these analogues, as they all polymerize L-LA (100 eq. in CH$_2$Cl$_2$ at 0 °C) to over 90% conversion in 12 minutes with controlled molecular weights and low PDIs (<1.1). Even changing $R_1$ to a phenyl substituent from methyl (I-55) had little effect on the polymerization activity.

Similar Al dimethyl complexes (I-56) and CaL$_2$ homoleptic complexes (I-57) were investigated for the polymerization of L-LA.$^{81,83}$ Although the complexes were not active without an external initiator, they were active in the presence of benzyl alcohol, with the Al complexes (I-56) reaching high conversions of L-LA (100 eq. in toluene at 110 °C) in 14 hours and the Ca complexes (I-57) reaching high conversions of L-LA (25-500 eq. in CH$_2$Cl$_2$ at 30 °C) in 3 hours, both with reasonably controlled molecular weights and low PDIs (1.15 – 1.48), although they are considerably less active than the related Mg and Zn alkoxides.

1.6.5 Iminophenolates and related ligands

In 2004 Gibson and co-workers reported a series of Sn complexes bearing tridentate iminophenolate ligands in which an interesting shift of an amide lead to the formation of tetradentate diamidoaminophenolate ligands (Figure 1.21).$^{84-85}$
Complexes I-58-63 form from an amide attack on the imine group of the ligands in the reaction of Sn(NMe$_2$)$_2$ and the protio iminophenolate ligands or from the respective iminophenolate Sn chloride complexes and LiNMe$_2$, although reversion to the imine species is observed during the polymerization of lactide. Such species do not form when bulkier NR$_2$ amino groups are used (R = SiMe$_3$) and only the expected iminophenolate complexes are isolated (I-64-65). The respective alkoxide derivative (I-66) also only forms expected iminophenolate complex. The bulkier alkoxide (I-66) and amide (I-64-65) derivatives are relatively slow, polymerizing 100 eq. of rac-LA in toluene at 60 °C to 92% conversion in 4 hours for alkoxide I-66 and 64% and 93% conversion in 48 hours for amides I-64 and I-65, respectively. In comparison, complexes I-58-63 are much more active, reaching conversions of over 90% in only 2 hours, with the exception of the quinolyl complex I-58, which is slower, possibly due to the rigidity of the quinolyl backbone. The polymerizations are also more controlled with complexes
I-58-63 and the alkoxide complex I-66, with PDIs <1.4 vs. PDIs of 6.1 and 7.9 for complexes I-64 and I-65, respectively. There is also an increased activity in moving to the electron donating chloro and iodo groups on the phenoxy rings (complexes I-62-63). The selectivity of these systems is, however, apparently unchanged by the different ligand motifs and mildly heterotactic PLA is obtained in all cases (Pᵣ = 0.62 ± 0.03).

Lin et al. have extensively studied iminophenolate ligands with amine side arms in zinc and magnesium complexes for the polymerization of lactide.86-89 Two complexes bearing Salen-like ligands with methoxy functionalized aromatic arms were synthesized (I-67-68) and shown to bind in a tridentate manner in Mg and Zn complexes (Figure 1.22).86

Figure 1.22. Mg and Zn complexes with Salen-like iminophenolate ligands reported by Lin et al.86

The Mg complex I-67 was much more active than the Zn analogue I-68, converting L-LA (50 eq. in toluene at room temperature) to 98% conversion in 45 minutes for I-67 versus 90% conversion in 3.5 hours for I-68. These complexes are also active and selective for the polymerization of rac-LA with complex I-67 showing a strong solvent dependence on selectivity, such that it is mildly heteroselective (Pᵣ = 0.57) in THF at room temperature, but is
mildly isoselective ($P_m = 0.54 – 0.67$) in toluene or $\text{CH}_2\text{Cl}_2$ at room temperature or below. The zinc analogue I-68 is more selective, showing isoselectivity ($P_m = 0.75$) in $\text{CH}_2\text{Cl}_2$ at room temperature.

Lin and co-workers have also reported a large family of Zn and Mg complexes with differently functionalized iminophenolate ligands bearing an ethylenediamine backbone (Figure 1.23). As well, Daresbourg et al. have reported very closely related Ca and Zn complexes bearing similarly functionalized iminophenolate ligands (Figure 1.23).

Lin et al. showed that of the related Mg and Zn complexes (I-69-85) the Zn complexes were more active (high conversions in 30 min. for Zn vs. over 3 hours for Mg), although both polymerized L-LA with controlled molecular weights and low PDIs (<1.2). The substituent effects in these complexes are similar between the related Mg and Zn compounds. The change in the phenoxy backbone to naphthoxy as in zinc complexes I-69 vs. I-70 had little effect on the activity, however substitution of the phenoxy groups with electron withdrawing Cl or Br substituents (I-71/72, 75/76, 81/82, 79 and 85) lowered the activity compared to the unsubstituted analogues with no phenoxy substituents (I-69, 74, 78, 80, 84), in both Zn and Mg complexes. As well, substitution with an electron donating OMe on the phenoxy groups had little effect on the more active zinc complex (I-77 and I-74 have similar activity) but increased the rate in the less active Mg complexes (I-83 is more active than I-80).

The effect of the imine substituent was also investigated and it was shown that changing from H to Me/Ph in the zinc complexes (I-69-73 vs. I-74-79) increases the rates of polymerization, whereas in the related Mg complexes changing from Me to Ph substituents (I-80-83 vs. I-84-85) had a detrimental effect on the polymerization rate. Finally, zinc complexes I-69-73 were tested in the polymerization of rac-LA, showing controlled molecular weights and
low PDIs, and it was shown that increasing the steric bulk of the phenoxy substituents resulted in more heterotactic polymers (I-73 $P_t = 0.74$ vs. I-69 $P_t = 0.59$).

![Diagram of complexes]

**Figure 1.23.** Mg, Zn and Ca complexes bearing iminophenolate ligands reported by Lin et al.\(^87-\)\(^89\) and Darensbourg et al.\(^90-\)\(^93\)
The related Ca complexes (I-86-91) reported by Darensbourg et al. were shown to be more active than the Zn or Mg complexes reported by Lin et al, although the polymerization were carried out in the melt (110 °C). The amide complex with the dimethylethylenediamine backbone (I-86) was shown to convert 350 eq. of L-LA in just 15 minutes in the melt (110 °C) (the exact Zn analogue I-95 only reaches 16% conversion in the same time). The bulkier and more electron donating backbones (I-89-91) lead to slower polymerization rates such that I-91 only reached 39% conversion under similar melt conditions in 15 minutes. Complex I-86 was also shown to yield mildly heterotactic PLA in solution, with $P_r = 0.66$ in chloroform at room temperature, whereas the corresponding complex with less steric bulk I-88 produced only atactic PLA.

Darensbourg et al. also reported several chiral zinc complexes (I-92-94) based on amino acids. The rate was found to decrease with increasing steric bulk, such that the more hindered I-92/93 are less active than the unsubstituted compound I-95, although I-94 was found to be the least active, due to possible coordination of the sulfur to the zinc centre. The selectivity in the polymerization of rac-LA is similarly affected by the substitution of the backbone, such that I-94 has the highest heteroselectivity ($P_r = 0.83$) and I-95 the lowest ($P_r = 0.68$) with complexes I-92/93 having similar selectivities intermediate between the two ($P_r = 0.76$).

1.6.6 Diaminophenolate ligands

In 2003 Hillmyer and Tolman reported a highly active zinc catalyst (I-96) for the polymerization of lactide based on a tridentate diaminophenolate ligand (Figure 1.24). This complex is highly active for the controlled polymerization of rac-LA at room temperature in CH$_2$Cl$_2$ reaching high conversions in ~ 5 minutes. However, the complex is not stereoselective producing only atactic PLA.
The mechanism of polymerization with this catalyst was proposed to proceed through a mononuclear propagating species, where the dimer would break apart upon addition of lactide. This was made on the basis of solution state NMR spectroscopic experiments that confirm I-96 is mononuclear in solution, and therefore a mononuclear active species is most probable.

These promising results reported by Hillmyer and Tolman on the polymerization of lactide by zinc complexes bearing an achiral tridentate diaminophenolate proligand (L-1) prompted our group to develop a related chiral tridentate diaminophenolate ligand system (L-2 and L-3) first reported by Mitchell and Finney, for use on zinc and indium (Figure 1.25). We hoped to preserve the activity of the original system while increasing the chance for stereoselectivity in the polymerization of rac-LA by introducing a chiral trans-1,2-diaminocyclohexane ligand backbone.
Figure 1.25. Achiral proligand $\text{H(L}_\text{Me})$ (L-1) developed by Hillmyer and Tolman et al.\textsuperscript{94} and chiral proligands $\text{H(NMe}_2\text{NH}_2\text{OtBu)}$ (L-2) and $\text{H(NMe}_2\text{NMe}_2\text{OtBu)}$ (L-3) developed by Mitchell and Finney\textsuperscript{95} and Mehrkhodavandi et al.

In 2008 we published a report on the first indium catalyst active for the polymerization of lactide bearing proligand L-2 (Figure 1.26).\textsuperscript{96} The dinuclear indium catalyst $[\text{NMe}_2\text{NMe}_2\text{OtBu)}\text{InCl)]_2(\mu-\text{Cl})(\mu-\text{OEt})$ (1) is highly active in the polymerization of rac-LA, polymerizing 200 equivalents of monomer to over 90\% conversion in just 30 minutes at room temperature, with a modest isoselectivity ($P_m$ values up to 0.62). The polymerization is also living, with controlled molecular weights and low PDI. Our group subsequently published several analogues of this system, as well as investigated the mechanism of polymerization by both experimental and theoretical methods.\textsuperscript{97-99} In addition, we have utilized catalyst 1 for the controlled polymerization of other cyclic ester monomers as well as the synthesis of various types of block co-polymers.\textsuperscript{100-101} Subsequent to this report, other reports on the polymerization of lactide with indium catalysts have emerged,\textsuperscript{68,97,102-108} although they still remain rare in the literature.

Related zinc complexes were made with proligand L-3, but proved to be much less reactive towards lactide, with only the zinc phenolate ($\text{NMe}_2\text{NMe}_2\text{OtBu)}\text{Zn(OPh)}$ (Figure 1.26) showing polymerization activity.\textsuperscript{109} The rates with this catalyst were very slow compared to indium complex 1 and the related zinc complex reported by Hillmyer and Tolman 1-96\textsuperscript{94} bearing.
achiral ligand L-1. Complexes 1 and I-96 reach high conversions in just minutes versus almost 1 day for (N_{Me2}N_{Me}O_{tBu})Zn(OPh). The lower polymerization activity of this zinc complex, compared to I-96, was attributed to the rigidity of the cyclohexane backbone. Hemilability of the terminal amine was seen in complex I-96 with a flexible ethylene backbone, whereas no such lability was observed in (N_{Me2}N_{Me}O_{tBu})Zn(OPh). This flexibility was determined to be necessary for facile binding of lactide and therefore faster polymerization rates.

![Chemical Structures](image)

**Figure 1.26.** Zinc complex (N_{Me2}N_{Me}O_{tBu})Zn(OPh) and indium complex [(N_{Me2}N_{H}O_{tBu})InCl]_2(\mu-Cl)(\mu-OEt) (1) reported by Mehrkhodavandi et al. for the polymerization of lactide.\textsuperscript{96,109}

### 1.7 Project goals

Given the promising results on the polymerization of lactide by dinuclear indium catalysts bearing tridentate ligands we were interested in modifying this ligand set in a rational manner in order to probe structure-activity relationships in this system, with the goal of improving the selectivity and/or activity of indium catalysts bearing these ligands. This dissertation will outline the modifications that have been undertaken in four key areas (Figure 1.27).
Firstly, modifications to the terminal amine substituents (Chapter 2) of the chiral tridentate ligand will be discussed, and the structure-activity relationships in this ligand set will be outlined with a particular focus on the influence of substituents on the selectivity of the resulting indium catalysts. In Chapter 3 modifications to the central amine donor will be discussed for ligands with both chiral and achiral backbones, and an interesting relationship between the nature of this central amine donor and the activity of the resulting indium catalysts will be presented. In Chapter 4 modifications to the aromatic substituents of the phenolate rings will be outlined, and in Chapter 5 recent efforts in using pentadentate ligands capable of bridging two metal centres will be discussed. Finally, Chapter 6 will outline the future directions of these projects and discuss the broader implications of this project that have contributed to our understanding of the factors influencing the activity and selectivity of these indium catalysts in the polymerization of lactide.

Figure 1.27. Ligand designs discussed in each chapter of this work.
Chapter 2: Effects of varying terminal amine substituents

2.1 Introduction

As discussed in Chapter 1 dinuclear indium catalyst [(NM2NH2OtBu)InCl]2(µ-Cl)(µ-OEt) (1) is highly active but only modestly isoselective in the polymerization of rac-LA (Pm up to 0.62). Following these findings, our group became focused on establishing the mechanism of polymerization and gaining insight into the origin of the selectivity of this system to better inform the design of new, more selective catalysts. In our initial report we proposed that dimeric catalyst 1 would dissociate during polymerization forming a mononuclear propagating species and the inactive dichloride complex (NM2NH2OtBu)InCl2 (2) (Figure 2.1 A), similar to other dimeric lactide polymerization catalysts reported in the literature. For example, the closely related zinc catalyst I-96 reported by Hillmyer and Tolman was found to be dimeric in the solid-state yet mononuclear in solution, and therefore a mononuclear propagating species was proposed for this catalyst. However, the possibility that the catalyst remains dinuclear during the polymerization of lactide could not be excluded (Figure 2.1 B), and therefore we undertook detailed experimental and theoretical mechanistic studies of this system.
Figure 2.1. Possible mononuclear (A) and dinuclear (B) mechanisms for the polymerization of lactide with dinuclear catalyst 1.

Our experimental mechanistic studies led to the conclusion that catalysts such as 
\[ [(\text{Me}_2\text{N})_2\text{H}_2\text{O}_{\text{OtBu}}\text{InCl})_2(\mu-\text{Cl})(\mu-\text{OEt}) \] (1) and the related bis-ethoxide bridged dimer 
\[ [(\text{Me}_2\text{N})_2\text{H}_2\text{O}_{\text{OtBu}}\text{InCl}(\mu-\text{OEt}))_2 \] (3) remain dinuclear during the polymerization of lactide\(^9\) (Figure 2.1 B), and subsequent theoretical calculations further supported this mechanism.\(^9\) For a detailed discussion of how we reached this conclusion the reader is referred to our paper,\(^9\) but a few key pieces of evidence for a dinuclear mechanism will be discussed here.

Firstly, the dimeric structure of catalysts 1 and 3 is very thermodynamically favoured, although the dimers are fluctional to a certain degree. For example, the dimers are reactive in the presence of some donors (pyridine, alcohols and water) however mononuclear structures are never isolated as the products of these reactions. In addition, the dimeric structure of these catalysts in solution was confirmed by detailed NMR studies. Variable temperature NMR
experiments show no change over a large range of temperatures, something that is not observed with bulkier versions of these types of catalysts (vide infra). As well, $^1$H NOESY-2D NMR experiments show through space interactions consistent with dimeric structures for these complexes. Pulsed Field Gradient Spin-Echo (PGSE) NMR experiments, which allow for the calculation of the diffusion coefficient of a species in solution and therefore its hydrodynamic radius, support dinuclear structures based on agreement between the calculated hydrodynamic radii in solution and those calculated from the dimeric solid-state structures.98

More importantly, the selectivity of the enantiopure (RR/RR) versions of catalysts 1 and 3 in the polymerization of rac-LA are different, with $P_m$ values of 0.48 for 1 and 0.65 for 3. This would not be possible with a mononuclear mechanism, as these catalysts would dissociate to form the same mononuclear active species and would therefore have the same selectivities if a mononuclear mechanism was active. In fact, if a mononuclear mechanism is active for catalyst 1 there should be evidence of the dichloride complex 2 in the $^1$H NMR spectrum of the polymerization reaction, something which is not seen with this catalyst but is seen with the bulkier derivative that will be discussed in this chapter.98

As alluded to above, part of my research project was to synthesize and investigate the polymerization activity of bulkier derivatives of the parent catalyst system as part of our attempt to increase the selectivity of this system. We noticed that in the solid-state molecular structures of dinuclear indium catalysts such as $\left[(N_{Me2N_iO_iBu})InCl\right]_2(\mu-Cl)(\mu-OEt)$ (1) (Figure 2.2), where the ligand features a dimethyl substituted amine, that the steric bulk of these groups is far removed from the metal centres and therefore may not be exerting any significant steric influence on the environment around the metal centres. We hypothesized that this may therefore be partially responsible for the low selectivity of these systems (maximum $P_m = 0.62$).96-97
Figure 2.2. Chemdraw and solid-state molecular structure of [(NMe$_2$N$_{tBu}$O)$_2$InCl]$_2$(µ-Cl)(µ-OEt) (1) showing the small steric bulk of the NMe$_2$ groups (circled).

We sought to modify the steric bulk at this position of the ligand by introducing a variety of groups to probe the influence of these substituents on the selectivity of indium catalysts in the polymerization of rac-LA. The terminal amine part of the ligand is readily amenable to steric and/or electronic tuning because of the modularity of our ligand synthesis, and therefore it seemed a natural first step for modifications required to establish structure-activity relationships for this ligand system. However, we did not anticipate the profound effects these modifications would have on the resulting chemistry with indium and the stability and selectivity of a dinuclear
indium alkoxide complex made with one of these bulky ligand derivatives. These results will be discussed in this chapter with a focus on how they informed our understanding of both the mechanism of polymerization with the parent system, as discussed above, and the origin of selectivity in these systems. The majority of the work presented in this chapter has been previously published in *Dalton Transactions*¹ and is reproduced herein by permission of the Royal Society of Chemistry.

2.2 Results

2.2.1 Synthesis and characterization of proligands

A family of racemic chiral proligands bearing asymmetrically *N*-alkylated (±)-*trans*-1,2-diaminocyclohexane backbones was synthesized according to modified literature procedures.⁹⁵,¹¹⁰⁻¹¹³ The methodology relies on the selective protection and alkylation of (±)-*trans*-1,2-diaminocyclohexane ((±)-DACH) to yield various asymmetrically *N*-alkylated diamines (Scheme 2.1).

**Scheme 2.1.** Synthesis of racemic *N*-alkylated-*trans*-1,2-diaminocyclohexanes with various amine substituents.

Reaction of ethyl acetimidate hydrochloride and (±)-DACH forms a cyclic imidazole intermediate, which upon reflux in a mixture of EtOH and H₂O (1:1) forms the acyl protected (±)-*N*-acetyl-*trans*-1,2-diaminocyclohexane, (±)-DACHₐc.⁹⁵ Reductive amination of (±)-DACHₐc
with propanal, followed by deprotection in refluxing 4 M HCl, forms (±)-N,N-dipropyl-trans-1,2-diaminocyclohexane. The Buchwald-Hartwig coupling of (±)-DACHAc with mesityl bromide, followed by deprotection, yields the mesityl substituted (±)-N-mesityl-trans-1,2-diaminocyclohexane. Alternatively, this species can be synthesized via a direct Buchwald-Hartwig coupling of (±)-DACH and mesityl bromide.

The reductive amination of (±)-DACHAc with pivaldehyde does not yield the neopentyl (Np) substituted amine as expected, and instead forms an intractable mixture of products. It is necessary to use the bulkier Boc (-COOC(CH₃)₃) protected (±)-DACHBoc for this transformation, which can be synthesized according to published literature procedures. Reductive amination of (±)-DACHBoc with pivaldehyde and subsequent deprotection with 4 M HCl in MeOH affords the mono-neopentylated (±)-N-neopentyl-trans-1,2-diaminocyclohexane. Alternatively, reductive amination with pivaldehyde then formaldehyde followed by deprotection affords the di-alkylated (±)-N-methyl-N-neopentyl-trans-1,2-diaminocyclohexane.

Condensation of the substituted diamines with 3,5-di-tert-butyl-2-hydroxy benzaldehyde to form an intermediate imine and subsequent reduction with sodium borohydride affords the bis-n-propyl substituted proligand L-4 (H(Np₂N₇O₅Bu), mesityl substituted proligand L-5 (H(NMesH₇N₇O₅Bu), neopentyl substituted proligand L-6 (H(NpH₇N₇O₅Bu) and neopentyl-methyl substituted proligand L-7 (H(NpMe₇N₇O₅Bu) (Scheme 2.2).
Scheme 2.2. Synthesis of racemic proligands L-4-7 with various terminal amine substituents.

The $^1$H NMR spectra (CDCl$_3$, 25 °C) of the imine intermediates show characteristic
downfield singlets at 8-9 ppm for the imine N=CH protons. The $^1$H NMR spectra of proligands
L-4-7 (see Appendix A, Figures A.1-4) show the loss of the imine proton and the appearance of
the diagnostic methylene protons of the reduced backbone at 3-5 ppm. These protons are
diastereotopic because of the neighbouring chiral cyclohexyldiamine backbone. They are split
into two multiplets because of coupling to each other and the neighbouring amine NH proton,
when it is present in the spectra. The amine proton may or may not appear in the spectra of these
proligands due to its fast exchange with protic impurities present in the deuterated solvents used
for these experiments. A similar attenuation or loss of the amine proton signal due to exchange
was seen in the $^1$H NMR spectrum of the parent ligand L-2.$^{36}$ In addition, the diagnostic methyl
protons of the $n$-propyl groups in proligand L-4 are equivalent, appearing as one triplet at 0.84
ppm. In proligand L-5 the free rotation of the mesityl group about the N-C bond results in
diagnostic signals for the para- and ortho-methyl groups as singlets at 2.24 and 2.22 ppm. In
proligands L-6 and L-7 the neopentyl –CH₂C(CH₃)₃ protons appear as singlets at 0.88 and 0.85
ppm, respectively, while the N-CH₃ protons in L-7 appear as a singlet at 2.23 ppm. All these
signals are particularly useful spectroscopic handles and diagnostic shifts in these signals upon
coordination of the proligands to indium can be used to identify coordination to the metal centre,
as will be discussed in the next section.

2.2.2 Synthesis and characterization of indium dichloride complexes

Dichloro indium complexes can be synthesized using proligands L-4-7 in a salt
metathesis route similar to previously reported compounds (Scheme 2.3). Deprotonation
of the proligands with benzyl potassium or potassium tert-butoxide in toluene yields the
respective potassium salts. Benzyl potassium can be more useful here than potassium tert-
butoxide for the colour change that accompanies the deprotonation of the proligand (orange to
colourless). This is useful to avoid contamination of the potassium salts with unreacted base,
although careful control of stoichiometry is enough to avoid this problem.

Reaction of the potassium salts with InCl₃ yields the racemic indium dichloride
complexes (±)-(N₁R₁R₂N₂H₂O₂Bu)InCl₂ 4 (R₁ = R₂ = n-Pr), 5 (R₁ = Mes, R₂ = H) and 6 (R₁ = Np, R₂
= Me). The complex synthesized using the neopentyl substituted proligand L-6 was insoluble in
most common organic solvents and therefore purification and full characterization of this
complex was not possible and this analogue was not pursued further. In addition, complex 5 was
isolated as a mixture of products, and the ¹H NMR spectrum of this mixture does not show the
diagnostic signals indicative of these types of complexes (see below for discussion). Crystals
suitable for X-ray analysis could be grown from this mixture, however pure complex for full characterization could not be isolated.

Scheme 2.3. Synthesis of racemic indium dichloride complexes 4-6 with various terminal amine substituents.

The $^1$H NMR spectra of 4 and 6 (see Appendix A, Figures A.5-6) are similar to the parent dichloride complex 2 and show the characteristic methylene protons in the ligand backbone as two diastereotopic multiplets in the 3-5 ppm range, which are shifted further apart from each other than in the free proligands. In complex 4 the propyl groups are no longer equivalent and two triplets for the -(CH$_2$)$_2$CH$_3$ protons are observed at 0.74 and 0.98 ppm, instead of one triplet at 0.84 ppm for the free proligand. In complex 6 the neopenty1 –CH$_2$C(CH$_3$)$_3$ protons are shifted downfield from the free proligand at 0.85 ppm to 1.22 ppm, while the N-CH$_3$ protons are shifted slightly upfield from the free proligand at 2.23 ppm to 2.18 ppm.
The low solubility of the product formed from the synthesis of the neopentyl substituted dichloride complex using proligand L-6 suggests that aggregation of the product may be taking place. In fact, all of the dichloride complexes synthesized using these ligands are poorly soluble in most common organic solvents, including toluene, benzene, hexane, ether and even to some degree chloroform and CH$_2$Cl$_2$. However, they readily dissolve in coordinating solvents such as THF, which would facilitate the dissociation of any aggregates formed in solution. It is possible that the mixture of compounds isolated from the synthesis of the mesityl substituted dichloride complex 5 may also be caused by the formation of several aggregate species in solution. The isolation of crystals from this mixture, which were confirmed by X-ray crystallography to be complex 5 (see discussion below), does indicate that at least one of the species in solution is the desired complex. However, isolation of the pure complex could not be achieved and therefore further reactions were carried out using the crude mixture.

The mixture of compounds isolated from the synthesis of complex 5 may also be a mixture of different isomers. Various isomers of indium complexes in this ligand family are possible due to the several stereogenic centres present, as well as the different coordination geometries of the ligand that are possible to the indium centre. In addition to the two stereogenic carbon centres of the cyclohexyldiamine backbone, the central amine is also chiral and may adopt two different configurations. If inversion of the central amine is not taking place, or is taking place on a time scale slower than that of the NMR spectroscopy utilized to characterize these compounds, two diastereomers, and their corresponding enantiomers in the case of racemic compounds, are possible in which the central amine will be in a different relative configuration to the neighbouring methine stereogenic centre. We observed diastereomers of this type in related zinc complexes (N$_{Me2}$N$_{Me}$O$_{tBu}$)Zn(Et) bearing proligand L-3, where the central amine is
methylated. In these zinc complexes two separate sets of ligand peaks are seen in the $^1H$ NMR spectra, indicative of two diastereomers in solution. A similar situation may be occurring in complex 5, although the lack of two distinct sets of ligand peaks in the $^1H$ NMR spectrum of the crude mixture indicates that the situation is more nuanced and aggregation may also be occurring to form ill defined species in solution.

The molecular structures of 4-6 were determined by single-crystal X-ray diffraction (Figure 2.4 and Table 2.1; see Appendix A, Table A.1 for crystallographic parameters). The tau geometrical parameter ($\tau$) was calculated for each complex as a measure of the degree of either square pyramidal or trigonal bipyramidal geometry. This parameter takes the difference between the two largest angles in the complex and divides it by 60 degrees. Square pyramidal complexes will therefore have a $\tau = 0$, whereas trigonal bipyramidal complexes will have a $\tau = 1$ (Figure 2.3).

\[
\tau = (\beta - \alpha)/60^\circ
\]

\[\begin{align*}
\text{square pyramidal: } & \beta = \alpha = 180^\circ \text{ and } \tau = 0 \\
\text{trigonal bipyramidal: } & \beta = 180^\circ, \alpha = 120^\circ \text{ and } \tau = 1
\end{align*}\]

**Figure 2.3.** Calculation of the tau geometrical parameter ($\tau$).
Figure 2.4. Solid-state molecular structures of complexes 4 (top), 5 (middle) and 6 (bottom). Structures are depicted with thermal ellipsoids at 50% probability, and solvent and H atoms are omitted for clarity. Complexes 4 and 6 were isolated as two similar but unique molecules in the unit cell, only one is depicted in this figure.
Table 2.1. Selected bond distances, angles and τ values\textsuperscript{114} for related indium dichloride complexes.

<table>
<thead>
<tr>
<th>Bond lengths (Å)</th>
<th>Complex 4</th>
<th>Complex 5</th>
<th>Complex 6</th>
<th>Complex 2'</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-N1</td>
<td>2.269(2)</td>
<td>(2.2482)</td>
<td>2.239(7)</td>
<td>1.322(9)</td>
</tr>
<tr>
<td>In-N2</td>
<td>2.334(2)</td>
<td>(2.3795)</td>
<td>2.336(7)</td>
<td>1.146(5)</td>
</tr>
<tr>
<td>In-Cl1</td>
<td>2.4049(6)</td>
<td>(2.3655)</td>
<td>2.407(2)</td>
<td>1.976(5)</td>
</tr>
<tr>
<td>In-Cl2</td>
<td>2.4121(6)</td>
<td>(2.4019)</td>
<td>2.392(2)</td>
<td>1.742(4)</td>
</tr>
<tr>
<td>In-O1</td>
<td>2.054(2)</td>
<td>(2.0445)</td>
<td>2.039(5)</td>
<td>2.185(7)</td>
</tr>
<tr>
<td>O1-In-N1</td>
<td>89.42(6)</td>
<td>(87.9)</td>
<td>87.7(2)</td>
<td>84.84(5)</td>
</tr>
<tr>
<td>O1-In-N2</td>
<td>127.73(6)</td>
<td>(162.1)</td>
<td>111.2(2)</td>
<td>159.65(5)</td>
</tr>
<tr>
<td>O1-In-Cl1</td>
<td>98.72(4)</td>
<td>(95.7)</td>
<td>97.83(16)</td>
<td>96.04(4)</td>
</tr>
<tr>
<td>O1-In-Cl2</td>
<td>103.52(4)</td>
<td>(104.9)</td>
<td>109.30(17)</td>
<td>97.75(5)</td>
</tr>
<tr>
<td>Cl1-In-Cl2</td>
<td>99.76(2)</td>
<td>(116.4)</td>
<td>97.52(8)</td>
<td>113.839(18)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bond angles (°)</th>
<th>Complex 4</th>
<th>Complex 5</th>
<th>Complex 6</th>
<th>Complex 2'</th>
</tr>
</thead>
<tbody>
<tr>
<td>N1-In-Cl1</td>
<td>167.14(5)</td>
<td>(140.5)</td>
<td>166.75(19)</td>
<td>129.63(6)</td>
</tr>
<tr>
<td>N1-In-Cl2</td>
<td>87.89(5)</td>
<td>(100.4)</td>
<td>91.90(18)</td>
<td>115.91(6)</td>
</tr>
<tr>
<td>N2-In-Cl1</td>
<td>90.34(5)</td>
<td>(92.8)</td>
<td>89.62(17)</td>
<td>93.04(4)</td>
</tr>
<tr>
<td>N2-In-Cl2</td>
<td>125.56(5)</td>
<td>(85.3)</td>
<td>137.37(17)</td>
<td>95.16(4)</td>
</tr>
<tr>
<td>N1-In-N2</td>
<td>76.80(6)</td>
<td>(75.6)</td>
<td>77.2(2)</td>
<td>113.839(18)</td>
</tr>
</tbody>
</table>

| τ = (β - α)/60° | 0.66      | 0.36      | 0.49      | 0.50       |

*the structure of complex 2' has been previously reported; the original labeling of atoms N1/N2 and Cl1/Cl2 in complex 2' was opposite to those for complexes 4-6 and has been switched here for a more clear comparison.\textsuperscript{98}*

The τ values for complexes 4, 5 and 6 are 0.66, 0.36 and 0.49 respectively, and the value for the previously reported parent complex (N\textsubscript{Me2}N\textsubscript{H}O\textsubscript{iBuMe})InCl\textsubscript{2} (2'), where the para-tert-butyl group on the ligand has been replaced by a methyl group, is 0.50 (note that this complex is used for comparison as the crystal structure for complex 2 in not available).\textsuperscript{98} The complexes therefore show geometries ranging from distorted trigonal bipyramidal (4) to distorted square pyramidal (5), to geometries between the two (6, 2').
Inspection of the bond lengths and angles (Table 2.1) of these complexes reveals a more nuanced situation. The bond lengths between the bulkier analogues 4-6 are comparable, however the bond lengths for the less bulky parent complex 2’ are considerably shorter, with the In-N2 distance being the shortest due to the less bulky NMe₂ group. The differences in bond angles between complexes 4 (the most trigonal bipyramidal) and 5 (the most square pyramidal) are consistent with the switch in geometry between the two complexes, presumably due to their differing steric profiles. However, both complexes 6 and 2’ have geometries almost exactly between these two extremes (τ ~ 0.5) but show different manifestations of this geometry due to the differences in steric bulk between the complexes. The largest angle (β) switches from N1-In-Cl1 in complex 6 to O1-In-N2 in complex 2’. The large range of geometries seen in these dichloride complexes indicates that these tridentate ligands are quite flexible, a trait that is generally undesirable when designing ligands that can impart significant stereochemical control upon a catalytic process. In this case it proved to have important ramifications on the isolability and selectivity of indium alkoxide catalysts made with these ligands, which will be discussed in detail in the next two sections of this chapter.

2.2.3 Synthesis and characterization of dinuclear indium alkoxide complexes

Salt metathesis of the indium dichloride complexes with NaOEt or KOEt forms a mixture of products (Scheme 2.4). With strict control of reaction conditions the mono-alkoxide bridged complex (±)-(N₃Pr₂N₃H₂O₁Bu)₂InCl]₂(µ-Cl)(µ-OEt) (7) can be obtained with reasonable purity: reaction of complex 4 with 0.98 equivalents of potassium ethoxide in toluene at room temperature for 18 hours and subsequent purification reproducibly forms complex 7 with > 90% purity (based on ¹H NMR spectroscopy). However, reaction of complex 6 with NaOEt or KOEt under a variety of conditions only forms intractable mixtures of products, and therefore this
analogue was not pursued further. As previously mentioned, complex 5 was isolated as a mixture of products that could not be purified. However, test reactions of this mixture with sodium and potassium ethoxide under a variety of conditions were carried out, but produced only intractable mixtures of products, similar to complex 6, and therefore this analogue was also not pursued further.

Scheme 2.4. Synthesis of racemic indium ethoxide complexes with various terminal amine substituents.

The difficulties in synthesizing and isolating ethoxide complexes with these bulky indium dichlorides is in stark contrast to the parent system, where complexes of the type

\[(\text{NMe}_2\text{NtBu})\text{InX}_2\], such as the dichloride complex 2 \((X = \text{Cl})\) and the related bromide \((X = \text{Br})\) and iodide \((X = \text{I})\) complexes reproducibly form discrete mono-alkoxide \([(\text{NMe}_2\text{NtBu})\text{InX}]_2(\mu-\text{X})(\mu-\text{OEt})\) (such as 1) or bis-alkoxide \([(\text{NMe}_2\text{NtBu})\text{InX(\mu-OEt})]_2\) bridged complexes in varying amounts depending on the conditions used.\(^{96-98}\) The mixtures produced from complexes 4-6 are much more complex. The \(^1\text{H}\) NMR spectra of the mixtures formed from the reactions of
complexes 5 or 6 with 1 or more equivalents of NaOEt or KOEt do not contain peaks diagnostic of either mono or bis-alkoxide bridged complexes. Reactions with lower equivalents of NaOEt or KOEt led to mixtures of the starting dichloride complexes and the same complex mixture of products. Even reactions of complex 4 with NaOEt or KOEt only produced mixtures of the mono-alkoxide bridged complex 7 and complex by-products under very strict conditions, otherwise they produced similar intractable mixtures of products. The differences in reactivity of the dichloride complexes 4-6 towards alkoxides compared to the parent dimethyl substituted complex 2 may be caused by the structural flexibility seen in these analogues. The differences in steric bulk at the terminal amine of these ligand analogues may disrupt the formation of stable dimeric alkoxide species and allow for a greater range of different compounds to be formed. In addition, the flexibility of these ligands may allow for the formation of complex aggregates in solution, as was proposed for the dichloride complexes.

As was discussed for the dichloride complexes, these are racemic chiral compounds therefore there is the possibility of forming several different diastereomers. The situation is further complicated in the case of the indium alkoxide complexes due to the possible formation of dimeric structures. The parent dinuclear alkoxide bridged systems such as 
\[ [(\text{NMe}_2\text{N}_2\text{H}_2\text{O}_{\text{Me}})\text{InCl}]_2(\mu-\text{Cl})(\mu-\text{OEt}) \] (1) are remarkably stable. They remain dinuclear in solution over a wide range of temperatures, as well as show the formation of only one diastereomer, and its enantiomer for racemic compounds, for each type of complex.\textsuperscript{96-98} The bulkier ligand analogues most likely destabilize these dimeric structures and allow for the formation of multiple products and conformations, complicating their synthesis and isolation. This is partially confirmed by the structural analysis of complex 7, which in contrast to the parent system shows
fluctational behavior in solution as well as during the polymerization of lactide, as will be discussed below.

The $^1$H NMR spectrum of complex 7 (see Figure 2.5 and Appendix A, Figure A.7) shows broad doublets at 3.57 and 4.95 ppm for the N-CH$_2$-Ar methylene protons of the backbone. These signals flank the OCH$_2$CH$_3$ protons at 4.45 ppm, which appear as a broad multiplet. The three signals for the N-CH$_2$-Ar and OCH$_2$CH$_3$ protons appear in a 1:1:1 ratio. This is indicative of a mono-ethoxide bridged species and is consistent with previously reported complexes of this type.$^{96-98,109}$

**Figure 2.5.** Methylene region of the $^1$H NMR spectrum (600 MHz, CDCl$_3$, 25 °C) of complex 7.

The mixed-bridged nature of 7 is further supported by its COSY NMR spectrum (Figure 2.6). The backbone methylene NCH$_2$ signals at 3.57 and 4.95 ppm can be definitively assigned, as they correlate only to each other. Importantly, the peak attributed to the ethoxide methylene OCH$_2$CH$_3$ protons shows only one correlation with the methyl OCH$_2$CH$_3$ protons at 1.3 ppm (this signal is obscured by the $t$-butyl groups of the ligand).
The peaks in the $^1$H NMR spectrum of 7 are broad and suggest a possible equilibrium on the NMR time scale. Indeed, the variable temperature (VT) $^1$H NMR spectra of 7 (25 – 70 °C, C$_6$D$_6$) show significant changes in the mixture when heated to 70 °C (Figure 2.7, see Appendix A, Figure A.8 for full spectra). In particular, the OCH$_2$CH$_3$ protons, which appear as two multiplets centred at 4.85 ppm at 25 °C, coalesce into a single peak at 70 °C. As mentioned previously, the $^1$H NMR spectrum of the less bulky parent complex (±)-(N$_{Me2}$N$_{OtBu}$)InCl$_2$(µ-Cl)(µ-OEt) (1) does not change over a wide range of temperatures (–80 to 70 °C).$^{98}$
Figure 2.7. Methylene region of the VT $^1$H NMR spectra (400 MHz, C$_6$D$_6$) of complex 7. Moving from the bottom to the top spectrum represents heating from 25 – 70 °C and subsequent cooling from 70 – 25 °C.

Indirect evidence allowed us to identify a major by-product in the synthesis of 7 as the bis-ethoxide bridged complex $\left[(\text{NPr}_2\text{N}_2\text{H}_2\text{O}_{\text{Et}})\text{InCl}(\mu-\text{OEt})\right]_2$ (8). A reaction of complex 4 with 2 equivalents of sodium ethoxide at room temperature yielded a mixture in which all the starting material was consumed and a mixture of products remained, which did not include complex 7 as determined by $^1$H NMR spectroscopy. Crystals isolated from a saturated solution of the crude mixture in hexane were analysed by $^1$H NMR spectroscopy, and the spectrum shows peaks consistent with an ethoxide bridged structure, similar to those found in complex 7 (Figure 2.8, see Appendix A, Figure A.9 for full spectrum). Due to the small amount of crystals that could be isolated using this method full characterization of this complex was not possible.
Figure 2.8. $^1$H NMR spectra (400 MHz, CDCl$_3$, 25 °C) of (a) crystals isolated from a saturated hexane solution of the crude mixture resulting from the reaction of complex (±)-$(\text{NPr}_2\text{NHOtBu})\text{InCl}_2$ (4) with 2 eq. NaOEt and (b) complex (±)-[$(\text{NPr}_2\text{NHOtBu})\text{InCl}]_2(\mu-\text{Cl})(\mu-\text{OEt})$ (7).

Crystals isolated in a similar manner from an identical reaction and analysed by single-crystal X-ray diffraction show a homochiral hydroxide-ethoxide bridged complex $(RR/RR)$-$[(\text{NPr}_2\text{NHOtBu})\text{InCl}]_2(\mu-\text{OH})(\mu-\text{OEt})$ (9) (Figure 2.9 and Table 2.2; see Appendix A, Table A.1 for crystallographic parameters), presumably formed from the reaction of the major by-product with adventitious water present in the system. This structure is consistent with similar compounds made from the parent ligand system, where formation of homochiral dimeric structures is seen exclusively in complexes that are bridged by two different ligands.$^{96-98}$ The bond lengths and angles in complex 9 are also consistent with the related parent iodide hydroxide-ethoxide bridged complex $[(\text{NMe}_2\text{NHOtBu})\text{In}]_2(\mu-\text{OH})(\mu-\text{OEt})$ (10) (see Table 2.2).$^{97-98}$
Figure 2.9. Solid-state molecular structure of complex 9. Thermal ellipsoids are shown at 50% probability and H atoms and disorder of the ethoxide group are removed for clarity.

Table 2.2. Selected bond lengths and angles for complexes 9 and 10.

<table>
<thead>
<tr>
<th></th>
<th>Complex 9</th>
<th>Complex 10&lt;sup&gt;98&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bond lengths (Å)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In-N1</td>
<td>2.427(3)</td>
<td>2.3405* / 2.376(4)</td>
</tr>
<tr>
<td>In-N2</td>
<td>2.266(3)</td>
<td>2.264* / 2.273(4)</td>
</tr>
<tr>
<td>In-C11/I1</td>
<td>2.431(9)</td>
<td>2.7923(4) / 2.8030(4)</td>
</tr>
<tr>
<td>In-O1</td>
<td>2.070(2)</td>
<td>2.1065* / 2.090(3)</td>
</tr>
<tr>
<td>In-O2</td>
<td>2.147(2)</td>
<td>2.146(3) / 2.142(3)</td>
</tr>
<tr>
<td>In-O3</td>
<td>2.165(2)</td>
<td>2.211(3) / 2.182(3)</td>
</tr>
<tr>
<td><strong>Bond angles (°)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O2-In-O3</td>
<td>72.74(11)</td>
<td>74.58(12) / 75.24(12)</td>
</tr>
<tr>
<td>O2-In-O1</td>
<td>91.95(10)</td>
<td>98.6* / 92.49(12)</td>
</tr>
<tr>
<td>O1-In-N1</td>
<td>103.95(10)</td>
<td>99.3* / 103.29(14)</td>
</tr>
<tr>
<td>N1-In-C11/I1</td>
<td>93.34(7)</td>
<td>97.605* / 96.20(10)</td>
</tr>
</tbody>
</table>

* Because of structural disorder on one half of the ligand in this complex these numbers are an average of two values.

The formation of complexes 8 and 9 is consistent with previous work in our group (Scheme 2.5).<sup>96-98</sup> Reactions of the parent dihalide complexes (N<sub>Me2</sub>N<sub>H</sub>O<sub>Et</sub>)(InX)<sub>2</sub> with >1 eq. NaOEt will form a mixture of the mono- and bis-ethoxide bridged complexes [(N<sub>Me2</sub>N<sub>H</sub>O<sub>Et</sub>)InX]<sub>2</sub>(µ-X)(µ-OEt) and [(N<sub>Me2</sub>N<sub>H</sub>O<sub>Et</sub>)InX(µ-OEt)]<sub>2</sub>. It has been our experience that hydrolysis of these compounds will first proceed by replacement of one ethoxide bridge.
(with ~0.5 eq. H₂O) to form the hydroxide-halide and ethoxide-hydroxide bridged compounds [(NMe₂N₉O₉Bu)InX₂(µ-X)(µ-OH)] and [(NMe₂N₉O₉Bu)InX₂(µ-OH)(µ-OEt)], from the mono- and bis-ethoxide bridged compounds respectively. Further hydrolysis of both of these compounds (with >0.5 eq. H₂O) or hydrolysis of the mono- and bis-ethoxide bridged compounds with excess water (>1 eq. H₂O) forms the bis-hydroxide bridged dimers [(NMe₂N₉O₉Bu)InX(µ-OH)]₂.

Scheme 2.5. General scheme for water reactivity of parent ethoxide bridged complexes.

Assuming a similar reactivity pattern for the bulkier propyl substituted analogue it is reasonable to conclude that the bis-ethoxide bridged complex 8 may be the major product formed in the reaction of complex 4 with excess NaOEt or KOEt and that partial hydrolysis of this product would lead to complex 9 (Scheme 2.6).

Scheme 2.6. Possible route towards the formation of complex 9.
In contrast to the parent system, attempts to isolate complexes 8 and 9 by independent synthesis were unsuccessful. Direct reactions of dichloride complex 4 with excess water (1 - 2 equivalents) only leads to the isolation of starting material and free proligand L-4. As well, reaction of complex 7 with 0.5 - 1 equivalents of water leads to the isolation of mixtures of dichloride 4 and free proligand L-4, whereas reaction with 2 equivalents of water leads to the exclusive formation of free proligand L-4. This once again shows the stark contrast in stability between indium complexes made with the parent dimethyl substituted ligand system L-2, where stable indium bis-ethoxide and hydroxide compounds are easily isolable, and the bulkier propyl substituted ligand system L-4, where the bis-ethoxide and hydroxide compounds cannot be isolated. The hydroxide compounds with this bulkier ligand appear to be especially instable, directly decomposing to give free proligand.

2.2.4 Polymerization studies

Polymerization of 200 equivalents of rac-LA with complex 7 (>90% pure by \(^1\)H NMR spectroscopy) reaches 98% conversion in 23 minutes. The plot of ln([LA]) vs. time (Figure 2.10) is linear and shows an observed rate constant for the reaction of \(2.1 \times 10^{-3} \text{s}^{-1}\), which is comparable to the parent catalyst \((\pm)-[(\text{NMe}_2\text{N}o\text{tBu})\text{InCl}]_2(\mu-\text{Cl})(\mu-\text{OEt}) (1) (k_{obs} = 1.72 \times 10^{-3} \text{s}^{-1})\) under similar conditions.\(^{96,98}\)
Polymerization of rac-LA with complex 7 is reasonably controlled. Theoretical and experimental polymer molecular weights largely coincide and polydispersity indices (PDI) are low (Table 2.3). However, in contrast to the less bulky parent complex (±)-

\[
\text{[(NMe}_2\text{NH}_2\text{O}_\text{Bu})\text{InCl}_2(\mu-\text{Cl})(\mu-\text{OEt})]}
\]

(1), there is no stereochemical control and the resulting polymers are uniformly atactic.

**Table 2.3. Results for the polymerization of rac-LA by catalyst 7.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>[LA]₀/[7]</th>
<th>Conv. (%)ᵃ</th>
<th>(M_n)theoᵇ (gmol⁻¹)</th>
<th>(M_n)GPCᶜ (gmol⁻¹)</th>
<th>PDIᶜ</th>
<th>(P_mᵈ)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>200</td>
<td>92</td>
<td>26445</td>
<td>30900</td>
<td>1.07</td>
<td>0.51</td>
</tr>
<tr>
<td>2</td>
<td>201</td>
<td>91</td>
<td>26456</td>
<td>30470</td>
<td>1.07</td>
<td>0.50</td>
</tr>
<tr>
<td>3</td>
<td>503</td>
<td>91</td>
<td>66325</td>
<td>65860</td>
<td>1.06</td>
<td>0.49</td>
</tr>
<tr>
<td>4</td>
<td>504</td>
<td>93</td>
<td>67434</td>
<td>73070</td>
<td>1.05</td>
<td>0.49</td>
</tr>
<tr>
<td>5</td>
<td>999</td>
<td>91</td>
<td>130707</td>
<td>116800</td>
<td>1.04</td>
<td>0.50</td>
</tr>
<tr>
<td>6</td>
<td>989</td>
<td>88</td>
<td>127205</td>
<td>114100</td>
<td>1.04</td>
<td>0.47</td>
</tr>
</tbody>
</table>

ᵃ Monomer conversion, determined by \(^1\text{H}\) NMR spectroscopy.ᵇ Calculated from \([\text{LA}]₀/[7] \times \text{LA}\) conversion \(\times M_w(144.13 \; \text{g/mol})\).ᶜ Determined by GPC measurements in THF.ᵈ Determined by \(^1\text{H}\) NMR spectroscopy and Bernoullian statistics. All reactions were carried out at 25 °C for 18 h in CH₂Cl₂.
The $^1$H NMR spectrum of a solution of 7 in the presence of 200 equivalents of rac-LA shows the signals for dichloride complex 4, implying that complex 7 dissociates in the presence of lactide (Figure 2.11). This is once again in stark contrast to the parent catalyst 1, which shows no indication of dissociation during polymerization of lactide.$^{98}$ This once again illustrates the significant effect that the bulky propyl substituents have on the stability of the dinuclear structure, which appears to easily dissociate in the presence of LA monomer. This leads to a decrease in the selectivity of the catalyst in the polymerization of rac-LA, although it does not appear to affect the activity.

![Figure 2.11. $^1$H NMR spectra (400 MHz, CD$_2$Cl$_2$, 25 °C) of (a) (±)-(N$_{Pr2}$N$_{H}$O$_{tBu}$)InCl$_2$ (4) and (b) reaction of (±)-[(N$_{Pr2}$N$_{H}$O$_{tBu}$)InCl]$_2$(µ-Cl)(µ-OEt) (7) with 200 eq. of rac-LA after 5 minutes ([LA] = 0.48 M, [7] = 2.4 mM).](image)

2.3 Discussion and conclusions

In this chapter we set out to investigate the role of steric bulk at the terminal amine position in our ligand system on the stereoselectivity of dinuclear indium alkoxide catalysts for ring opening polymerization of rac-LA. We compared our results to the parent catalyst (±)-[(N$_{Me2}$N$_{H}$O$_{tBu}$)InCl]$_2$(µ-Cl)(µ-OEt) (1), which is a highly active and modestly isoselective ($P_m$ up to 0.62) catalyst for the ROP of rac-LA and has been shown by detailed mechanistic studies to be dinuclear during polymerization.$^{96-98}$ To this end, we synthesized a family of terminal amine functionalized chiral diamino phenolate proligands H(N$_{R1R2}$N$_{H}$O$_{tBu}$) (L-4-7).
In a first step, these proligands were used to generate a family of indium dichloride complexes (4-7). From the outset it was clear that there is no simple correlation between the ligand steric and/or electronic properties and the geometry of the complexes. Complexes 4-6 have a range of geometries in the solid-state, from distorted trigonal bipyramidal geometry (n-propyl functionalized 4), to distorted square pyramidal geometry (mesityl functionalized 5), to a geometry between the two (neopentyl-methyl functionalized 6). These results illustrate the relatively large flexibility of this tridentate ligand, which can accommodate a variety of geometries depending on the steric bulk of the system.

The synthesis and isolation of discrete indium alkoxide complexes using these dichloride complexes proved difficult, most likely as a consequence of increased aggregation due to the flexibility of these ligands. Reaction of complexes 5 or 6 with sodium or potassium ethoxide gave only intractable mixtures of products, and reaction of complex 4 with sodium or potassium ethoxide, although successful, did not give the respective ethoxide species (±)-[(NPr2NHOtBu)InCl]2(µ-Cl)(µ-OEt) (7) cleanly. The identity of a major by-product of the reaction, the bis-alkoxide bridged [(NPr2NHOtBu)In(Cl)(µ-OEt)]2 (8), was indirectly determined via the isolation of its hydrolysis product [(NPr2NHOtBu)InCl]2(µ-OH)(µ-OEt) (9). Variable temperature 1H NMR spectra of 7 show fluctional behaviour at higher temperatures, suggestive of dissociation in solution. In contrast, similar spectra for [(NMe2NHOtBu)InCl]2(µ-Cl)(µ-OEt) (1) show no change over a large range of temperatures.98 It is reasonable to assume that the difficulties with the synthesis and purification of 7 are related to its fluctional behaviour, even at room temperature.

We observed this fluctional behaviour during the ROP of rac-LA with 7. In situ monitoring of the reaction mixture of the dinuclear complex in the presence of lactide clearly
shows the presence of dichloride complex 4, which results from dissociation of 7, suggesting that the active propagating species for this catalyst is mononuclear. Again, we do not observe this dissociation in the parent complex, and a dinuclear propagating species is proposed for this catalyst. The difference in mechanism is also evident in the selectivity for 7. The rates of polymerization for the bulkier complex 7 are similar to that of the parent complex 1, however in this case all selectivity is lost, presumably due to catalyst dissociation.

These studies illustrate the intricacies of steric manipulation and its effects on catalyst activity and selectivity in this family of ROP catalysts. We found that tuning the steric bulk of the terminal amine substituents in our ligand system had a profound effect on the stability of indium complexes made with these ligands. This was particularly evident in the case of the bulky n-propyl substituted alkoxide complex 7, where this dinuclear structure dissociates during the polymerization of rac-LA leading to a lowering of the selectivity of the system in comparison with the parent system. These results stress the importance of the dinuclear structure of these types of catalysts in their selectivity in the polymerization of rac-LA.

2.4 Experimental

General procedures

Unless otherwise specified all air and/or water sensitive reactions were carried out under N₂ using standard Schlenk techniques or in an MBraun glovebox. A Bruker Avance 400dir MHz spectrometer, a Bruker Avance 400inv MHz spectrometer, and a Bruker Avance 600 MHz spectrometer were used to record \(^1\)H NMR and \(^{13}\)C\{\(^1\)H\} NMR spectra. \(^1\)H\{\(^1\)H\} NMR spectra were recorded on the Bruker Avance 600 MHz spectrometer. \(^1\)H NMR chemical shifts are given in ppm versus residual protons in deuterated solvents as follows: \(\delta\) 5.32 for CD₂Cl₂, 7.27 for CDCl₃ and 7.16 for C₆D₆. \(^{13}\)C\{\(^1\)H\} NMR chemical shifts are given in ppm versus residual \(^{13}\)C in
solvents as follows: δ 54.00 ppm for CD₂Cl₂ and 77.23 ppm for CDCl₃. A Waters/Micromass LCT mass spectrometer equipped with an electrospray (ESI) ion source and a Kratos-50 mass spectrometer equipped with an electron impact ionization (EI) source were used to record low-resolution and high-resolution spectra. Diffraction measurements for X-ray crystallography were made on a Bruker X8 APEX II diffraction with graphite monochromated Mo-Kα radiation. The structures were solved by direct methods and refined by full-matrix least-squares using the SHELXTL crystallographic software of the Bruker-AXS. Unless specified, all non-hydrogens were refined with anisotropic displacement parameters, and all hydrogen atoms were constrained to geometrically calculated positions but were not refined. EA CHN analysis was performed using Carlo Erba EA1108 elemental analyser. The elemental composition of an unknown sample was determined by using a calibration factor. The calibration factor was determined by analysing a suitable certified organic standard (OAS) of a known elemental composition. Molecular weights were estimated by triple detection gel permeation chromatography (GPC - LLS) using a Waters liquid chromatograph equipped with a Waters 515 HPLC pump, Waters 717 plus autosampler, Waters Styragel columns (4.6 Å~ 300 mm) HR5E, HR4 and HR2, Waters 2410 differential refractometer, Wyatt tristar miniDAWN (laser light scattering detector) and a Wyatt ViscoStar viscometer. A flow rate of 0.5 mL/min was used and samples were dissolved in THF (ca. 2 mg/mL), and a dn/dc value of 0.042 mL/g was used. Narrow molecular weight polystyrene standards were used for calibration purposes.

Materials

Toluene, diethyl ether, hexane, and tetrahydrofuran were degassed and dried using alumina columns in a solvent purification system. Pentane was dried and degassed using 4 Å molecular sieves in an MBraun solvent purification system. In addition CH₃CN and CH₂Cl₂ were
refluxed over CaH$_2$ in a solvent still and transferred to a Straus flask where they were degassed prior to use. Deuterated solvents were dried over CaH$_2$ (CD$_2$Cl$_2$ and CDCl$_3$) or sodium ($C_6D_6$) and vacuum-transferred to a Straus flask and then degassed through a series of freeze-pump-thaw cycles. Deuterium-labelled NMR solvents were purchased from Cambridge Isotope Laboratory or Aldrich. InCl$_3$ was obtained from Strem Chemicals and used without further purification.

Benzyl potassium was synthesized using a modified literature preparation of $n$-butyl lithium, potassium tert-butoxide and toluene.$^{115}$ KOEt was generated by reacting KO'Bu with anhydrous ethanol. The solvent was removed under vacuum, and addition of hexane to the residual precipitated a white solid. The white solid, KOEt, was isolated by vacuum filtration and dried in vacuo for 4 h. Racemic acyl protected DACH ((±)-DACH$_{Ac}$) and racemic Boc protected DACH ((±)-DACH$_{Boc}$) were prepared from (±)-trans-1,2-diaminocyclohexane ((±)-DACH) according to literature procedures.$^{95,112}$ 3,5-di-tert-butyl-2-hydroxybenzaldehyde was prepared according to a literature procedure.$^{111}$ Lactide samples were obtained from Purac Biomaterials and recrystallized several times from hot toluene and dried under vacuum prior to use.

**Synthesis of (±)-N-acetyl-N’N’-dipropyl-trans-1,2-diaminocyclohexane**

The preparation and characterization of this compound has been previously reported in the literature, and the procedure reported here is modified from the literature.$^{113}$ A round bottom flask was charged with (±)-DACH$_{Ac}$ (3.56 g, 22.8 mmol), acetonitrile (100 mL), water (5 mL) and propionaldehyde (8.3 mL, 110 mmol) and the mixture was stirred for 15 minutes. Sodium cyanoborohydride (3.00 g, 47.9 mmol) was added and the mixture was stirred for an additional hour. Finally, glacial acetic acid (6.5 mL, 110 mmol) was added dropwise at 0 °C and the mixture was warmed to room temperature while stirring for ~18 h. The mixture was then diluted with 2% MeOH in CH$_2$Cl$_2$ (70 mL) and washed with 1M NaOH (3 × 40 mL). The organic
fraction was dried over MgSO₄, filtered and pumped to dryness in vacuo. The title compound was isolated as a thick, yellow oil which was used without further purification (4.71 g, 86%). ¹H NMR (300 MHz, CDCl₃, 25 °C): δ 6.23 (1H, s, NHOCO), 3.34 (1H, m, CHN), 2.57 (1H, m, CHN), 2.28 (4H, m, N(CH₂CH₂CH₃)₂), 1.92 (3H, s, CH₃CO), 1.72 (4H, m, N(CH₂CH₂CH₃)₂), 1.17 (8H, m, DACH), 0.85 (6H, t, N(CH₂CH₂CH₃)₂).

**Synthesis of (±)-N-acetyl-N’-mesityl-trans-1,2-diaminocyclohexane**

In a glovebox, Pd₂(dba)₃ (0.2636 g, 1.5 mol %) and BINAP (0.3820 g, 3.3 mol %) were dissolved in toluene (20 mL) and the solution was heated for 15 minutes. The mixture was filtered through Celite into a Schlenk flask. Toluene (200 mL), (±)-DACHAc (3 g, 20 mmol), NaO'Bu (2.76 g, 28.8 mmol) and 2-bromomesitylene (2.94 mL, 19.2 mmol) were added to this mixture. The Schlenk flask was fitted with a reflux condenser and sealed with vacuum adapters under N₂. The reaction mixture was stirred and refluxed at 110 °C in an oil bath and the consumption of 2-bromomesitylene was monitored by GC-MS. After 63 h the reaction mixture was cooled to room temperature, diluted with diethyl ether (200 mL), and washed with water (3 × 200 mL) and saturated NaCl solution (2 × 200 mL). The organic layer was dried over Na₂SO₄, filtered and pumped to dryness in vacuo, yielding the title compound as a dark brown solid which was used without further purification (3.87 g, 73 %). ¹H NMR (300 MHz, CDCl₃, 25 °C): δ 6.79 (2H, s, Mes-H), 5.66 (1H, m, NH), 3.73 (1H, m, CHN), 2.91 (1H, m, CHN), 2.21 (9H, m, Mes-CH₃), 1.89 (4H, m, OCH₃ + DACH), 1.68 (2H, m, DACH), 1.27 (2H, m, DACH), 1.14 (3H, m, DACH). ¹³C{¹H} NMR (75 MHz, CDCl₃, 25 °C): δ 170.57, 142.04, 130.56, 129.73, 128.79, 60.10, 55.66, 33.53, 33.21, 25.24, 24.99, 23.62, 20.61, 19.28. HRMS: calc. [M]+ 274.2045, found [M]+ 274.2044.
Synthesis of (±)-N-tert-butoxycarbonyl-N′-neopentyl-trans-1,2-diaminocyclohexane

Pivaldehyde (4.6 mL, 42 mmol) was added dropwise to a solution of (±)-DACH$_{\text{Boc}}$ (1.81 g, 8.45 mmol) in acetonitrile (35 mL) and water (3.2 mL) and the solution was stirred for 15 minutes.

Sodium cyanoborohydride (1.11 g, 17.8 mmol) was added, followed by acetic acid (3.6 mL, 42 mmol), and the solution was stirred for 18 h at room temperature. The reaction mixture was diluted with 2% MeOH in CH$_2$Cl$_2$ (50 mL) and washed with 1M NaOH (3 × 35 mL) and saturated NaCl solution (1 × 35 mL). The organic fraction was dried over MgSO$_4$, filtered and pumped to dryness in vacuo to afford an off-white solid. The crude material was recrystallized from acetonitrile to afford the title compound as a white crystalline solid (2.35 g, 97%).

$^1$H NMR (300 MHz, CDCl$_3$, 25 °C): δ 4.65 (1H, m, NHCO), 3.24 (1H, m, CHN), 2.46 (1H, d, $^2$J$_{HH}$ = 12.01 Hz, NH(CH$_2$C(CH$_3$)$_3$)$_3$, 2.19 (1H, m, CHN), 2.14 (2H, m, NH(CH$_2$C(CH$_3$)$_3$)$_3$, 1.69 (2H, m, DACH), 1.45 (9H, s, COC(CH$_3$)$_3$), 1.16 (2H, m, DACH), 1.12 (2H, m, DACH), 0.89 (9H, s, NH(CH$_2$C(CH$_3$)$_3$)$_3$). $^{13}$C({$^1$H}) NMR (100 MHz, CDCl$_3$, 25 °C): δ 156.33, 62.45, 58.88, 33.12, 32.04, 31.66, 28.59, 27.79, 25.00. Anal. Calc. for C$_{16}$H$_{32}$N$_2$O$_2$: C, 67.60; H, 11.27; N, 9.86. Found: C, 67.30; H, 11.17; N, 9.86. EI-HRMS: calc. [M]$^+$ 284.24638, found [M]$^+$ 284.24618.

Synthesis of (±)-N-tert-butoxycarbonyl-N′-methyl-N′-neopentyl-trans-1,2-diaminocyclohexane

Formaldehyde (1.83 mL of 37 wt.% in H$_2$O, 22.5 mmol) was added dropwise to a solution of (±)-N-tert-butoxycarbonyl-N′-neopentyl-trans-1,2-diaminocyclohexane (1.27 g, 44.7 mmol) in acetonitrile (40 mL) and the mixture was stirred for 15 min. Sodium cyanoborohydride (0.593 g, 9.46 mmol) was added, followed by acetic acid (1.3 mL, 23 mmol), and the solution was stirred for 18 h at room temperature. The reaction mixture was diluted with 2% MeOH in CH$_2$Cl$_2$ (50 mL) and washed with 1M NaOH (3 × 35 mL) and saturated NaCl solution (1 × 30 mL). The
organic fraction was collected and dried over MgSO₄, filtered and pumped to dryness in vacuo to give the crude compound as a light brown oil. Recrystallization of the crude compound from hot acetonitrile afforded the title compound as a yellow solid (0.75 g, 56 %). ¹H NMR (300 MHz, CDCl₃, 25 °C): δ 5.28 (1H, m, NHCOCO), 2.41 (1H, m, CHN), 2.37 (1H, m, CHN), 2.24 (3H, d, NCH₃), 1.78 (2H, m, DACH), 1.63 (2H, m, DACH), 1.45 (9H, s, COC(CH₃)₃), 1.23 (2H, m, DACH), 1.09 (2H, m, DACH), 0.89 (9H, s, N(CH₂C(CH₃)₃). ¹³C {¹H} NMR (100 MHz, CDCl₃, 25 °C): δ 156.56, 69.37, 67.35, 52.57, 38.70, 33.58, 28.61, 28.39, 25.80, 24.89, 23.53. EI-HRMS: calc. [M]+ 298.26203, found [M]+ 298.26179.

Synthesis of (±)-N,N-dipropyl-trans-1,2-diaminocyclohexane

The preparation and characterization of this compound has been previously reported in the literature, and the procedure reported here is modified from the literature.¹¹³ (±)-N-acetyl-N’,N’-dipropyl-trans-1,2-diaminocyclohexane (24.1 g, 101 mmol) was dissolved in 4M HCl (600 mL) and the solution was refluxed at 124 °C for ~18 hours. The reaction mixture was then diluted with 4M NaOH (700 mL) and washed with 5% MeOH in CH₂Cl₂ (3 x 500 mL). The combined organics were dried over MgSO₄, filtered and pumped to dryness in vacuo, yielding the title compound as a dark brown oil, which was used without further purification (16.7 g, 84%). ¹H NMR (300 MHz, CDCl₃, 25 °C): δ 2.53 (1H, m, CHN), 2.32 (4H, m, N(CH₂CH₂CH₃)₂), 2.01 (2H, m, CHN + DACH), 1.75 (2H, m, NH₂), 1.64 (2H, m, DACH), 1.41 (4H, m, N(CH₂CH₂CH₃)₂), 1.13 (4H, m, DACH), 0.92 (1H, m, DACH), 0.86 (6H, t, N(CH₂CH₂CH₃)₂).

Synthesis of (±)-N-mesityl-trans-1,2-diaminocyclohexane

Method 1: In a glovebox, Pd₂dba₃ (0.3450 g, 1.5 mol %) and BINAP (0.5160 g, 3.3 mol %) were dissolved in toluene (200 mL) and the solution was heated for 15 minutes. (±)-DACH (9 mL, 80 mmol), NaO’Bu (3.62 g, 37.7 mmol) and 2-bromomesitylene (3.84 mL, 25.1 mmol) were
added to this solution. The reaction mixture was stirred and refluxed under N₂ at 110 °C in an oil bath until the starting material, 2-bromomesitylene, was consumed as evident by GC-MS analysis (8 h). The reaction mixture was worked up in a similar manner as for (±)-N-acetyl-N′-mesityl-trans-1,2-diaminocyclohexane. The solvent was removed in vacuo to obtain a dark brown oil that was recrystallized in pentane to obtain a light brown solid (3.30 g, 57%).

**Method 2:** (±)-N-acetyl-N′-mesityl-trans-1,2-diaminocyclohexane (3.84 g, 14.1 mmol) was dissolved in 4M HCl (100 mL) and the solution was refluxed at 100 °C for 18 hours. The reaction mixture was then cooled to room temperature and diluted with 4M NaOH (250 mL) and washed with 2% MeOH in CH₂Cl₂ (3 x 400 mL). The combined organics were dried over Na₂SO₄, filtered and concentrated in vacuo to afford a brown, viscous oil. The oil was recrystallized in pentane yielding the title compound as a light brown solid (1.43 g, 50%).

**Synthesis of (±)-N-neopentyl-trans-1,2-diaminocyclohexane**

(±)-N-tert-butoxycarbonyl-N′-neopentyl-trans-1,2-diaminocyclohexane (0.51 g, 1.8 mmol) was dissolved in a mixture of 4M HCl (25 mL) and methanol (25 mL). The resulting solution was stirred for 18 h at room temperature. The solution was then diluted with 4 M NaOH (40 mL) and washed with 5% MeOH in CH₂Cl₂ (3 x 35 mL). The combined organics were dried over MgSO₄, filtered and pumped to dryness in vacuo to give a pale brown oil that was used without further purification (0.28 g, 84%). ¹H NMR (400 MHz, CDCl₃, 25 °C): δ 2.55 (1H, d, ²J_H-H = 8 Hz, 1.81 (1H, m, NH), 1.63 (2H, m, DACH), 1.22 (4H, m, DACH). ¹³C{¹H} NMR (75 MHz, CDCl₃, 25 °C): δ 142.25, 130.96, 129.79, 129.57, 63.63, 57.14, 35.22, 33.34, 25.68, 25.24, 20.67, 19.35. HRMS: calc. [M]⁺ 232.1939, found [M]⁺ 232.1937.
NH(CH₂C(CH₃)₃), 2.36 (1H, m, CHN), 2.11 (1H, d, ²J_H-H = 12 Hz, NH(CH₂C(CH₃)₃), 1.97 (2H, m, CHN + NH), 1.84 (4H, m, NH₂ + DACH), 1.67 (2H, m, DACH), 1.22 (4H, m, DACH), 0.88 (9H, s, NH(CH₂C(CH₃)₃).

Synthesis of (±)-N-methyl-N-neopentyl-trans-1,2-diaminocyclohexane

(±)-N-tert-butoxycarbonyl-N’-methyl-N’-neopentyl-trans-1,2-diaminocyclohexane (1.38 g, 4.63 mmol) was dissolved in a mixture of 4M HCl (20 mL) and methanol (20 mL) and the solution was refluxed at 90°C for ~18 hours. The mixture was cooled to room temperature and diluted with 4M NaOH (40 mL) and washed with 2% MeOH in CH₂Cl₂ (3 × 35 mL). The organic phase was dried over MgSO₄, filtered and pumped to dryness in vacuo affording the title compound as a brown oil that was used without further purification (0.63 g, 69%). ¹H NMR (400 MHz, CDCl₃, 25 °C): ²J_H-H = 12 Hz, N(CH₂C(CH₃)₃), 1.75 (1H, m, DACH), 1.67 (2H, s, DACH), 1.54 (3H, s, NCH₃), 2.08 (9H, s, N(CH₂C(CH₃)₃). ¹³C {¹H} NMR (100 MHz, CDCl₃, 25 °C): δ 72.11, 68.12, 52.10, 37.87, 35.06, 33.54, 28.12, 25.92, 25.20, 22.61. EI-HRMS: calc. [M]+ 198.20960, found [M]+ 198.20964.

General procedure for the synthesis of imines

To a solution of the appropriately functionalized diamine (1.2 g, 6.1 mmol) in dry methanol (15 mL) was added 3,5-di-tert-butyl-salicylaldehyde (1.18 g, 5.05 mmol). The mixture was stirred for 18 h at room temperature under N₂. The resulting reaction mixture was purified by a variety of methods depending on the diamine used (see below for details).
Synthesis of 2-((±)-trans-2-(dipropylamino)cyclohexylimino)methyl)-4,6-di-tert-butylphenol

A portion of the product was isolated as a yellow solid via vacuum filtration of the crude reaction mixture. The filtrate was pumped to dryness in vacuo yielding a dark brown oil, which was recrystallized from acetonitrile to yield a second portion of the product as a yellow solid. The two products were combined to yield the title compound as a yellow solid (1.80 g, 86%). $^1$H NMR (400 MHz, CDCl$_3$, 25 °C): $\delta$ 11.58 (1H, br s, O$H$), 8.24 (1H, s, CH=N), 7.36 (1H, d, $^4$J$_{H-H}$ = 4 Hz, Ar-$H$), 7.05 (1H, d, $^4$J$_{H-H}$ = 4 Hz, Ar-$H$), 3.15 (1H, m, CHN), 2.68 (1H, m, CHN), 2.38 (4H, m, N(CH$_2$CH$_2$CH$_3$)$_2$), 1.74 (4H, m, DACH), 1.45 (9H, s, C(CH$_3$)$_3$), 1.32 (9H, s, C(CH$_3$)$_3$), 1.28 (4H, m, DACH), 0.87 (4H, m, N(CH$_2$CH$_2$CH$_3$)$_2$), 0.77 (6H, t, $^3$J$_{H-H}$ = 6 Hz, N(CH$_2$CH$_2$CH$_3$)$_2$). $^{13}$C {$^1$H} NMR (100 MHz, CDCl$_3$, 25 °C): $\delta$ 197.44, 158.64, 139.52, 136.58, 126.35, 125.60, 118.18, 70.17, 64.05, 35.11, 31.71, 29.57, 26.03, 25.80, 24.97, 22.57, 11.98. EI-HRMS: calc. [M]$^+$ 414.36101, found [M]$^+$ 414.36075.

Synthesis of 2-((±)-trans-2-(mesitylaminocyclohexylimino)methyl)-4,6-di-tert-butylphenol

The crude reaction mixture was pumped to dryness in vacuo yielding the crude product as a yellow brown solid. Recrystallization of the solid from acetonitrile afforded the title compound as a yellow crystalline solid (3.42 g, 77%). $^1$H NMR (300 MHz, CDCl$_3$, 25 °C): $\delta$ 13.90 (1H, s, O$H$), 8.40 (1H, s, N=CH), 7.36 (1H, m, Ar-$H$), 7.07 (1H, m, Ar-$H$), 6.75 (2H, s, Mes-$H$), 3.13 (2H, m, CHN), 2.24 (6H, s, Mes-CH$_3$), 2.16 (3H, s, Mes-CH$_3$), 1.88 (6H, m, DACH), 1.47 (9H, s, C(CH$_3$)$_3$), 1.32 (9H, s, C(CH$_3$)$_3$), 1.26 (2H, m, DACH). $^{13}$C {$^1$H} NMR (75 MHz, CDCl$_3$, 25 °C): $\delta$ 165.30, 158.39, 142.02, 139.94, 136.69, 131.46, 130.86, 129.62, 126.80, 126.05, 117.99, 74.66, 60.61, 35.20, 34.30, 32.87, 31.73, 29.59, 25.13, 24.66, 20.71, 19.20. HRMS: calc. [M]$^+$ 448.3454, found [M]$^+$ 448.3466.
Synthesis of 2-(((±)-trans-2-(neopentylamino)cyclohexylimino)methyl)-4,6-di-tert-butylphenol

The crude reaction mixture was pumped to dryness in vacuo yielding the crude product as a yellow solid. This material was washed with cold acetonitrile and pentane and dried in vacuo to afford the title compound as a pale yellow powder (1.69 g, 85 %). $^1$H NMR (300 MHz, CDCl$_3$, 25 °C): δ 8.43 (1H, s, CH=N), 7.39 (1H, d, $^4$J$_{H-H}$ = 3 Hz, Ar-H), 7.09 (1H, d, $^4$J$_{H-H}$ = 3 Hz, Ar-H), 3.05 (1H, m, CHN), 2.60 (1H, m, CHN), 2.48 (1H, d, $^2$J$_{H-H}$ = 12 Hz, NH(CH$_2$C(CH$_3$)$_3$), 2.24 (1H, d, $^2$J$_{H-H}$ = 9 Hz, NH(CH$_2$C(CH$_3$)$_3$), 1.80 (2H, m, DACH), 1.45 (9H, s, C(CH$_3$)$_3$), 1.32 (9H, s, C(CH$_3$)$_3$), 1.29 (2H, m, DACH), 1.24 (2H, m, DACH), 0.82 (9H, s, NH(CH$_2$C(CH$_3$)$_3$). $^{13}$C{$^1$H} NMR (100 MHz, CDCl$_3$, 25 °C): δ 166.04, 158.28, 140.08, 136.78, 126.92, 125.95, 118.05, 73.20, 62.79, 59.98, 35.15, 34.10, 31.66, 31.06, 29.54, 27.85, 24.91.


Synthesis of 2-(((±)-trans-2-(methylneopentylamino)cyclohexylimino)methyl)-4,6-di-tert-butylphenol

The crude reaction mixture was filtered and the resulting precipitate was washed with cold methanol to afford a portion of the product as a yellow solid. The filtrate was pumped to dryness in vacuo yielding a yellow solid residue. This residue was recrystallized from hot acetonitrile to yield a second portion of the product as a yellow solid. The two solids were combined to yield the title compound as a yellow solid (1.02 g, 77%). $^1$H NMR (400 MHz, CDCl$_3$, 25 °C): δ 8.32 (1H, s, CH=N), 7.37 (1H, m, Ar-H), 7.08 (1H, m, Ar-H), 3.25 (1H, m, CHN), 2.59 (1H, m, CHN), 2.28 (3H, s, NCH$_3$), 2.27 (2H, s, N(CH$_2$C(CH$_3$)$_3$), 1.83 (2H, m, DACH), 1.77 (1H, m, DACH), 1.66 (1H, m, DACH), 1.46 (9H, s, C(CH$_3$)$_3$), 1.38 (1H, m, DACH), 1.32 (9H, s, C(CH$_3$)$_3$), 1.29 (3H, m, DACH), 0.75 (9H, s, N(CH$_2$C(CH$_3$)$_3$). $^{13}$C{$^1$H} NMR (100 MHz, CDCl$_3$, 25 °C): δ 166.04, 158.28, 140.08, 136.78, 126.92, 125.95, 118.05, 73.20, 62.79, 59.98, 35.15, 34.10, 31.66, 31.06, 29.54, 27.85, 24.91.

**General procedure for the synthesis of amine proligands (L-4-7)**

NaBH$_4$ (0.405 g, 10.1 mmol) was added to a solution of the appropriate imine (0.85 g, 2.1 mmol) in acetonitrile (35 mL) and the reaction mixture was stirred for 30 min. Acetic acid (1.4 mL) was added dropwise to the solution, and the solution was stirred at room temperature for 18 h. The mixture was diluted with 2% MeOH in CH$_2$Cl$_2$ (50 mL) and washed with 1M NaOH (3 × 35 mL). The organic layer was dried over MgSO$_4$, filtered, and pumped to dryness *in vacuo* to afford the crude compound. The crude compounds were purified by recrystallization from acetonitrile.

**Synthesis of 2-((±)-trans-2-(dipropylamino)cyclohexylamino)methyl)-4,6-di-tert-butylphenol (±)-H(N$_{Pr_2}$N$_OH$)$_{O}$ (L-4)**

The crude compound was isolated as a white solid that was recrystallized from acetonitrile to afford (±)-H(N$_{Pr_2}$N$_OH$)$_{O}$ (L-4) as a white crystalline solid (0.803 g, 94%). $^1$H NMR (300 MHz, CDCl$_3$, 25 °C): δ 11.80 (1H, br s, O$_H$), 7.20 (1H, d, $^4$J$_{H-H}$ = 3 Hz, Ar-H), 6.86 (1H, d, $^4$J$_{H-H}$ = 3 Hz, Ar-H), 4.00 (1H, m, NCH$_2$Ar), 3.76 (1H, m, NCH$_2$Ar), 3.56 (1H, m, NH), 2.37 (6H, m, DACH + N(CH$_2$CH$_2$CH$_3$)$_2$), 2.16 (1H, m, CHN), 1.81 (2H, m, DACH), 1.71 (1H, m, CHN), 1.43 (9H, s, C(CH$_3$)$_3$), 1.37 (4H, m, DACH), 1.30 (9H, s, C(CH$_3$)$_3$), 1.22 (4H, m, N(CH$_2$CH$_2$CH$_3$)$_2$), 0.84 (6H, t, $^3$J$_{H-H}$ = 8 Hz, N(CH$_2$CH$_2$CH$_3$)$_2$). $^{13}$C{$^1$H} NMR (100 MHz, CDCl$_3$, 25 °C): δ 155.01, 140.08, 135.85, 123.57, 122.73, 122.53, 63.76, 59.05, 51.52, 35.01, 34.27, 31.91, 31.87, 29.77, 25.92, 24.87, 23.22, 22.44, 12.04. Anal. Calc. for C$_{27}$H$_{48}$N$_2$O: C, 77.88; H, 11.54; N, 6.73. Found: C, 77.59; H, 11.34; N, 7.01. HRMS: calc. [M]$^+$ 416.37666, found [M]$^+$ 416.37621.
Synthesis of 2-((±)-trans-2-(mesitylamino)cyclohexylamino)methyl)-4,6-di-tert-butylphenol (±)-H(NMesHNtBu) (L-5)

The crude compound was recrystallized from acetonitrile to afford (±)-H(NMesHNtBu) (L-5) as an off-white solid (1.35 g, 77%). $^1$H NMR (300 MHz, CDCl$_3$, 25 °C): δ 7.22 (1H, d, $^4$J$_{H-H}$ = 2 Hz, Ar-H), 6.91 (1H, d, $^4$J$_{H-H}$ = 2 Hz, Ar-H), 6.81 (2H, s, Mes-H), 4.20 (1H, m, NC$_2$H$_2$Ar), 3.82 (1H, m, NC$_2$H$_2$Ar), 3.45 (1H, s, NH), 2.91 (1H, m, CHN), 2.56 (1H, m, NH), 2.46 (1H, m, CHN), 2.31 (1H, m, DACH), 2.24 (6H, s, Mes-C$_3$H$_3$), 2.22 (3H, s, Mes-CH$_3$), 1.89 (1H, m, DACH), 1.76 (1H, m, DACH), 1.66 (1H, m, DACH), 1.44 (9H, s, C(C$_3$H$_3$)$_3$), 1.30 (9H, s, C(C$_3$H$_3$)$_3$), 1.11 (4H, m, DACH).

Synthesis of 2-((±)-trans-2-(neopentylamino)cyclohexylamino)methyl)-4,6-di-tert-butylphenol (±)-H(NNpHNtBu) (L-6)

The crude compound was isolated as a cloudy white oil. Recrystallization of the oil from hot acetonitrile afforded (±)-H(NNpHNtBu) (L-6) as a white crystalline solid (0.18 g, 90%). $^1$H NMR (300 MHz, CDCl$_3$, 25 °C): δ 7.21 (1H, d, $^3$J$_{H-H}$ = 3.00 Hz, Ar-H), 6.87 (1H, s, Ar-H), 4.01 (1H, d, $^2$J$_{H-H}$ = 15 Hz, NCH$_2$Ar), 3.87 (1H, d, $^2$J$_{H-H}$ = 12 Hz, NCH$_2$Ar), 2.56 (1H, d, $^2$J$_{H-H}$ = 12 Hz, NH(CH$_2$C(CH$_3$)$_3$)), 2.26 (2H, m, CHN + DACH), 2.16 (1H, m, CHN), 2.14 (1H, d, $^2$J$_{H-H}$ = 12 Hz, NH(CH$_2$C(CH$_3$)$_3$)), 1.73 (2H, m, DACH), 1.43 (9H, s, C(CH$_3$)$_3$), 1.30 (9H, s, C(CH$_3$)$_3$), 1.22 (4H, m, DACH), 1.03 (1H, m, DACH), 0.89 (9H, s, NH(CH$_2$C(CH$_3$)$_3$)). $^{13}$C($^1$H) NMR (100 MHz, CDCl$_3$, 25 °C): δ 155.00, 140.22, 135.94, 123.36, 122.84, 62.29, 61.93, 59.17, 51.23, 35.02, 34.27, 32.17, 31.86, 31.79, 31.27, 29.80, 27.85, 25.42, 24.91. EI-LRMS: calc. [M]$^+$ 402.36, found [M]$^+$ 402.
Synthesis of 2-((±)-trans-2-(methylneopentylamino)cyclohexylamino)methyl)-4,6-di-tert-butylphenol (±)-H(N_{NpMe}N_{H}O_{tBu}) (L-7)

The crude compound was isolated as a clear, colourless oil. Recrystallization of the oil from hot acetonitrile afforded (±)-H(N_{NpMe}N_{H}O_{tBu}) (L-7) as a white solid (1.158 g, 83 %). $^1$H NMR (400 MHz, CDCl$_3$, 25 °C): δ 11.72 (1H, br s, OH), 7.20 (1H, m, Ar-H), 6.86 (1H, m, Ar-H), 4.05 (1H, m, NCH$_2$Ar), 3.81 (1H, m, NCH$_2$Ar), 3.41 (1H, br s, NH), 2.40 (1H, m, CHN), 2.23 (3H, s, NCH$_3$), 2.15 (4H, m, N(CH$_2$C(CH$_3$)$_3$) + CHN + DACH), 1.79 (2H, m, DACH), 1.70 (1H, m, DACH), 1.42 (9H, s, C(CH$_3$)$_3$), 1.30 (9H, s, C(CH$_3$)$_3$), 1.19 (4H, m, DACH), 0.85 (9H, s, N(CH$_2$C(CH$_3$)$_3$)). $^{13}$C $^1_1$H NMR (100 MHz, CDCl$_3$, 25 °C): δ 154.84, 139.90, 135.75, 123.26, 122.57, 122.41, 69.30, 59.23, 57.42, 51.21, 34.85, 34.12, 33.55, 33.35, 31.71, 31.65, 29.59, 28.23, 25.63, 24.78, 22.54. EI-HRMS: calc. [M]$^+$ 416.37666, found [M]$^+$ 416.37698.

**General procedure for the synthesis of indium dichloride complexes 4-6**

Benzyl potassium (0.1637 g, 1.257 mmol) was transferred using toluene (10 mL) to a solution of the appropriate proligand (±)-H(N$_{R1R2}N_{H}O_{tBu}$) (0.5237 g, 1.257 mmol) in toluene (5 mL). This solution was stirred at room temperature for 16 hours, and the solvent was removed *in vacuo* yielding the respective potassium salt in quantitative yield. The potassium salt (0.5716 g, 1.257 mmol) was dissolved in THF (10 mL). Indium trichloride (0.2777 g, 1.256 mmol) was transferred to this solution using THF (10 mL). The mixture was stirred at room temperature for 16 h, then filtered through glass fibre filter paper and pumped to dryness *in vacuo* to obtain the crude compound. The crude compounds were washed with diethyl ether three times, discarding the supernatant solution each time, and dried under vacuum yielding the purified complexes.
Synthesis of complex $\pm$-[N$_{Pr2}$N$_H$O$_{Bu}$]InCl$_2$ (4)

The crude complex was obtained as a yellow solid. The solid was washed 3 times with diethyl ether and dried under vacuum to afford complex 4 as a white solid (0.5003 g, 89%). $^1$H NMR (400 MHz, CDCl$_3$, 25 °C): δ 7.31 (1H, d, $^4$J$_{H-H}$ = 4 Hz, Ar-H), 6.80 (1H, d, $^4$J$_{H-H}$ = 4 Hz, Ar-H), 4.23 (1H, m, NCH$_2$Ar), 3.91 (1H, m, NCH$_2$Ar), 3.55 (1H, m, CHN), 2.95 (1H, m, CHN), 2.65 (4H, m, N(CH$_2$CH$_2$CH$_3$)$_2$), 2.43 (1H, m, N$H$), 1.99 (5H, m, DACH + N(CH$_2$CH$_2$CH$_3$)$_2$), 1.77 (2H, m, DACH), 1.60 (1H, m, DACH), 1.48 (9H, s, C(CH$_3$)$_3$), 1.30 (4H, m, DACH), 1.27 (9H, s, C(CH$_3$)$_3$), 0.98 (3H, t, $^3$J$_{H-H}$ = 8 Hz, N(CH$_2$CH$_2$CH$_3$)$_2$), 0.74 (3H, t, $^3$J$_{H-H}$ = 8 Hz, N(CH$_2$CH$_2$CH$_3$)$_2$). $^{13}$C{${^1}$H} NMR (100 MHz, CDCl$_3$, 25 °C): δ 161.34, 139.98, 138.50, 125.09, 124.27, 120.52, 62.65, 55.48, 55.39, 53.58, 51.84, 35.21, 33.99, 32.29, 31.70, 30.00, 24.92, 24.75, 23.22, 21.46, 19.58, 11.99, 11.52. Anal. Calc. for C$_{27}$H$_{47}$Cl$_2$InN$_2$O: C, 53.92; H, 7.88; N, 4.66. Found: C, 53.62; H, 7.85; N, 4.48.

Synthesis of complex $\pm$-[N$_{pMe}$N$_H$O$_{Bu}$]InCl$_2$ (6)

The crude complex was isolated as an off-white powder. The solid was washed 3 times with diethyl ether and dried under vacuum to afford complex 6 as a white solid (0.2106 g, 84%). $^1$H NMR (400 MHz, CDCl$_3$, 25 °C): δ 7.30 (1H, d, $^4$J$_{H-H}$ = 4 Hz, Ar-H), 6.82 (1H, d, $^4$J$_{H-H}$ = 4 Hz, Ar-H), 4.85 (1H, d, $^2$J$_{H-H}$ = 12 Hz, NCH$_2$Ar), 3.82 (1H, d, $^2$J$_{H-H}$ = 12 Hz, NCH$_2$Ar), 3.42 (1H, d, $^2$J$_{H-H}$ = 16 Hz, N(CH$_2$C(CH$_3$)$_3$)), 2.93 (1H, m, CHN), 2.72 (1H, m, NH), 2.51 (1H, m, CHN), 2.48 (1H, m, DACH), 2.43 (1H, d, $^2$J$_{H-H}$ = 16 Hz, N(CH$_2$C(CH$_3$)$_3$)), 2.18 (3H, s, NCH$_3$), 1.99 (1H, m, DACH), 1.86 (2H, m, DACH), 1.44 (9H, s, C(CH$_3$)$_3$), 1.31 (2H, m, DACH), 1.28 (9H, s, C(CH$_3$)$_3$), 1.22 (9H, s, N(CH$_2$C(CH$_3$)$_3$)), 1.15 (2H, m, DACH). $^{13}$C{${^1}$H} NMR (100 MHz, CDCl$_3$, 25 °C): δ 160.65, 139.39, 138.06, 125.62, 124.73, 118.62, 64.02, 60.91, 51.56, 48.30.
38.76, 35.29, 33.96, 31.72, 31.55, 30.06, 29.98, 29.82, 24.26, 24.20, 22.04. Anal. Calc. for C_{27}H_{47}Cl_2InN_2O: C, 53.92; H, 7.88; N, 4.66. Found: C, 53.78; H, 7.82; N, 4.54.

Synthesis of complex (±)-[(NPr_{2}NtBu)InCl]_2(μ-Cl)(μ-OEt) (7)

Toluene (15 mL) was used to transfer potassium ethoxide (0.0674 g, 0.8009 mmol) to a stirred suspension of complex 4 (0.4917 g, 0.8176 mmol) in toluene (15 mL), making a cloudy white mixture. The solution was stirred at room temperature for 19 hours, after which the mixture had turned clear with a fine precipitate. This mixture was filtered through glass fibre filter paper and pumped to dryness *in vacuo*, yielding the crude product as an off-white powder (0.4016 g, 81%). The product was purified by washing the crude solid several times with hexane, discarding the supernatant solution each time, and was dried under vacuum to yield complex 7 as a white powder (0.3036 g, 61%). This complex was found to be approximately 90% pure by ^1^H NMR spectroscopy. Attempts to purify the complex further were unsuccessful. As a result elemental analysis of this complex was not undertaken. ^1^H NMR (400 MHz, CDCl_3, 25 °C): δ 7.25 (1H, br m, Ar-H), 6.73 (1H, br m, Ar-H), 4.96 (1H, br d, NCH_2Ar), 4.45 (1H, br m, OCH_2CH_3), 3.58 (1H, br d, NCH_2Ar), 3.26 (1H, br m, CHN), 3.08 (2H, br m, CHN + DACH), 2.90 (1H, br m, DACH), 2.70 (1H, br m, NH), 2.52 (1H, br m, DACH), 2.37 (1H, br m, DACH), 1.87 (5H, br m, N(CH_2CH_2CH_3)_2 + DACH), 1.62 (2H, br m, N(CH_2CH_2CH_3)_2), 1.44 (9H, br s, C(CH_3)_3), 1.31 (5H, br m, DACH + N(CH_2CH_2CH_3)_2), 1.28 (9H, br s, C(CH_3)_3), 0.91 (3H, br m, N(CH_2CH_2CH_3)_2), 0.42 (3H, br m, N(CH_2CH_2CH_3)_2). ^13^C{^1^H} NMR (100 MHz, CDCl_3, 25 °C): δ 164.0, 138.2, 136.1, 125.6, 124.6, 118.6, 63.0, 62.3, 54.1, 53.9, 51.5, 50.4, 35.3, 33.9, 32.2, 31.8, 30.1, 27.2, 25.8, 25.3, 20.1, 19.0, 18.9, 18.8, 12.1.
Isolation of complex $(\pm)-[\text{NPr}_2\text{N}_2\text{H}O\text{Bu}]\text{InCl}]_2(\mu-\text{OH})(\mu-\text{OEt})$ (9)

Chlorobenzene (5 mL) was used to transfer sodium ethoxide (0.0454 g, 0.667 mmol) to a stirred suspension of complex 4 (0.1997 g, 0.3321 mmol) in toluene (5 mL), making a cloudy white mixture. The solution was stirred at room temperature for 18 hours, after which the mixture had turned cloudy pale yellow. This mixture was filtered through glass fibre filter paper and pumped to dryness *in vacuo*, yielding the crude product as a sticky yellow oil. The crude product was stirred in hexane (~5 mL) causing the precipitation of a pale yellow solid. The supernatant solution was removed and the solid was washed two more times with hexane (~5 mL), removing the supernatant solution each time. The hexane precipitate was dried under vacuum yielding a pale yellow solid (0.0687 g, 34%), and the supernatant solutions were dried under vacuum yielding a foamy yellow solid (0.1161 g, 58%). Both solids were found to be a complex mixture of unidentifiable species by $^1$H NMR spectroscopy. Crystals were grown from a saturated hexane solution of the product isolated from the supernatant hexane solutions. The crystals were identified by $^1$H NMR spectroscopy to have peaks consistent with complex 9, although further characterization was not possible due to the small amount of crystals that were isolated. An identical reaction yielded a similar product from which single crystals were grown under the same conditions. Analysis of these crystals by X-ray crystallography confirmed them to be complex 9. $^1$H NMR (400 MHz, CDCl$_3$, 25 °C): $\delta$ 7.26 (1H, d, $^4J_{HH} = 4$ Hz, Ar-H), 6.75 (1H, d, $^4J_{HH} = 4$ Hz, Ar-H), 4.83 (1H, d, $^2J_{HH} = 16$ Hz, NCH$_2$Ar), 4.34 (1H, m, OCH$_2$CH$_3$), 3.53 (1H, d, $^2J_{HH} = 16$ Hz, NCH$_2$Ar), 3.23 (1H, m, NH), 3.14 (1H, m, CHN), 2.80 (1H, m, CHN), 2.69 (1H, m, DACH), 2.55 (2H, m, DACH), 2.27 (1H, m, DACH), 2.02 (1H, m, DACH), 1.86 (5H, m, N(CH$_2$CH$_3$)$_2$ + DACH), 1.46 (9H, s, C(CH$_3$)$_3$), 1.33 (1.5H, t, OCH$_2$CH$_3$), 1.28 (9H, s,
C(CH$_3$)$_3$, 1.13 (6H, m, N(CH$_2$CH$_2$CH$_3$)$_2$ + DACH), 0.93 (3H, t, $^3$J$_{HH}$ = 8 Hz, N(CH$_2$CH$_2$CH$_3$)$_2$), 0.32 (3H, t, $^3$J$_{HH}$ = 8 Hz, N(CH$_2$CH$_2$CH$_3$)$_2$).

**In situ monitoring of the polymerization of rac-LA with complex 7**

A stock solution of complex 7 (0.0116 g, 0.00957 mmol) was made by weighing the complex into a 1 mL volumetric flask and making it up to the mark with CD$_2$Cl$_2$. Next, 0.25 mL of this solution was syringed into 2 J-Young NMR tubes and they were frozen using a liquid N$_2$ cold well. A buffer layer of 0.25 mL CD$_2$Cl$_2$ was syringed into each tube and frozen using the cold well. Next, a stock solution of rac-LA (0.2768 g, 1.920 mmol) and an internal standard 1,3,5-trimethoxybenzene (0.0214 g, 0.127 mmol) was made by weighing out the compounds into a 2 mL volumetric flask and making it up to the mark with CD$_2$Cl$_2$. 0.5 mL of this solution was syringed into each tube and frozen using the cold well. The tubes were quickly evacuated while frozen to remove N$_2$ gas from the headspace of the tubes. The solutions were thawed and quickly mixed before being loaded into the NMR spectrometer (400MHz Avance Bruker Spectrometer). The polymerization was monitored to over 90% conversion by $^1$H NMR spectroscopy (25 °C).

**Representative polymerization of rac-LA with complex 7**

A 20 mL glass vial was charged with a solution of complex 7 (e.g. for 200 eq. rac-LA: 0.0056 g, 0.0046 mmol) in 2 mL CH$_2$Cl$_2$. Rac-LA (0.133 g, 0.923 mmol) was transferred to this solution using CH$_2$Cl$_2$ (2 mL). The resulting mixture was stirred at room temperature for 16 h. The resulting clear solution was concentrated to dryness. A sample of the residue was dissolved in CDCl$_3$ to be analysed by $^1$H and $^1$H-$^1$H) NMR spectroscopy to determine conversion and tacticity, respectively. The remaining polymeric material was dissolved in a minimum of CH$_2$Cl$_2$ (<1 mL) and the pure polymer was precipitated out of this solution by the addition of MeOH. The supernatant solution was removed and this process was repeated 2 more times. The purified
polymer was dried under high vacuum overnight and checked by $^1$H NMR spectroscopy for remaining monomer, catalyst or solvent prior to GPC analysis in THF.
Chapter 3: Effects of secondary versus tertiary amine donors

3.1 Introduction

Given our reports of highly active dinuclear indium complexes, such as 
\[ [(\text{N}_\text{Me}_2\text{N}_\text{H}_\text{O}_\text{t}_\text{Bu})\text{InCl}]_2(\mu-\text{Cl})(\mu-\text{OEt}) \] (1), as catalysts for the polymerization of lactide, we were keen to explore the role of the amine donors in this ligand system in the activity of our complexes. As discussed in Chapter 2 our recent experimental and theoretical mechanistic investigation of this system showed that complexes such as 1 are dinuclear both in the solid-state and in solution and remain dinuclear during the polymerization reaction. Furthermore, the results discussed in Chapter 2 outline the importance of the dinuclear structure of these catalysts in their selectivity towards the polymerization of rac-LA, as perturbations to the terminal amine substituents of the tridentate ligand system have profound effects on the stability and selectivity of the resulting indium complexes. We were interested then in expanding this study to include modifications to the central amine donor of the ligand system.

Preliminary work in this area was completed by Insun Yu from our group through the synthesis of dinuclear indium catalyst [L-MeInCl]_2(\mu-\text{Cl})(\mu-\text{OEt}) (11), bearing achiral ligand L-Me with a central tertiary amine donor developed by Hillmyer and Tolman for use in zinc chemistry. Complex 11 was surprisingly only modestly active in the polymerization of rac-LA, taking several days to reach full conversion and producing only atactic PLA (Figure 3.1). This is in complete contrast to its chiral analogue [(\text{N}_\text{Me}_2\text{N}_\text{H}_\text{O}_\text{t}_\text{Bu})\text{InCl}]_2(\mu-\text{Cl})(\mu-\text{OEt}) (1) with a central secondary amine donor, which is highly active, taking only minutes to reach high conversions with modest isoselectivity \(P_m\) up to 0.62. Through these findings we became interested in investigating the effects that the nature of the central amine donor (secondary vs. tertiary) as well
as the ligand backbone (chiral vs. achiral) would have on the polymerization of lactide by
dinuclear indium catalysts bearing these ligands.

Figure 3.1. Activity and selectivity of dinuclear indium catalysts 1 and 11 bearing chiral and
achiral ligands with central secondary and tertiary amine donors.\textsuperscript{1,96,98}  

During these investigations it came to our attention that hydrogen bonding between the
secondary amine donor on the ligand backbone and the terminal chloride ligand on one half of
the asymmetric dinuclear structure may be playing a structural role in the stability of dinuclear
catalysts such as complex 1 (Figure 3.2). We hypothesized that this may in part explain the
activity differences seen between complexes with central secondary and tertiary amine donors.
The importance of the nature of amine donors in different ligand systems has been previously explored for other kinds of reactivity.\(^{116-128}\) For example, Stack and co-workers have recently reported the effects of primary versus secondary and tertiary diamine ligation on the stability and oxidation activity of dicopper(III) bis(\(\mu\)-oxo) complexes, which are structural models of the active site of the particulate methane monooxygenase enzyme.\(^{128}\) A series of dicopper(III) bis(\(\mu\)-oxo) complexes with propylenediamine, \(N,N\)-dimethylpropylenediamine and tetramethylpropylenediamine ligands show an increasing thermal stability of the bis(\(\mu\)-oxo) core and an increasing oxidative activity towards C-H bonds in moving from tertiary to primary diamine ligands. This effect was rationalized in this system based on the stronger donating ability of primary amines vs. their secondary or tertiary counterparts,\(^{116}\) as well as the reduced steric demands around the metal centres, which allow greater access of the substrate to the oxidizing core of the complex.\(^{128}\)

In this chapter we present our exploration into the role of secondary vs. tertiary amines in our ligand architecture and the impact, if any, of hydrogen bonding in these systems during the ring opening polymerization of lactide. The work presented in this chapter has been recently
Results

3.2.1 Synthesis and characterization of indium complexes

For this project we sought to synthesize indium complexes bearing both chiral and achiral ligands with both secondary and tertiary central amine donors. To accomplish this we synthesized analogues of the previously reported \( [(NMe_2NH_3O_{tBu})InCl]_2(\mu-\text{Cl})(\mu-\text{OEt}) \) (1) and \([LMeInCl]_2(\mu-\text{Cl})(\mu-\text{OEt}) \) (11) with central tertiary and secondary amine donors, respectively. The corresponding racemic chiral proligand \((\pm)-H(NMe_2NMeO_{tBu}) \) (L-3) and the achiral proligand \(H(L_H) \) (L-8) can be prepared according to previously published procedures from our group,\(^{96,109}\) although a more efficient synthesis of proligand L-8 was recently published in the literature.\(^{129}\)

The dichloro indium complexes \((\pm)-(NMe_2NMeO_{tBu})InCl_2 \) (12) and \(L_HInCl_2 \) (13) can be synthesized using these proligands in a similar manner to previously published compounds (Scheme 3.1).\(^{1,96-98}\) The proligands are first deprotonated with benzyl potassium or potassium \(\text{ tert-}^{t}\text{BuOxide to yield the respective potassium salts, which are then reacted in situ with InCl}_3 \) to yield complexes 12 and 13.

The $^1$H NMR spectrum of complex 12 (see Appendix B, Figure B.1) shows the diagnostic N-$^1$C$_2$-Ar methylene signals of the ligand backbone as two doublets at 4.17 and 3.86 ppm. Signals for three inequivalent N-$^1$C$_3$ protons are observed at 2.82, 2.62 and 2.29 ppm. The $^1$H NMR spectrum of complex 13 (see Appendix B, Figure B.2) is similar to the related methylated complex (L$_{Me}$)InCl$_2$ (14) with a central tertiary amine donor$^1$ and shows the central methylene protons as two doublets at 3.86 and 4.78 ppm. In addition, the two N(CH$_3$) signals appear as singlets at 2.40 and 2.69 ppm, with the corresponding NH proton at 2.54 ppm.

Reaction of complex 12 with 0.98 equivalents of NaOEt in THF forms the dinuclear indium ethoxide complex (±)-[(N$_{Me2}$N$_{Me}$O$_{tBu}$)InCl]$_2$(μ-Cl)(μ-OEt) (15) (Scheme 3.2). The choice of solvent for this reaction is important and can have an impact on the ease of purification: parent complex (±)-(N$_{Me2}$N$_{Me}$O$_{tBu}$)InCl$_2$ (12) is soluble in toluene, while 15 is insoluble in toluene and sparingly soluble in THF, making the removal of the NaCl byproduct of this reaction difficult.$^9$ Reasonable yields (70 %) of complex 15 can be achieved by dissolution and filtration of the crude precipitate in CH$_2$Cl$_2$ (see experimental for further details). In contrast, reaction of
complex 13 with 0.98 equivalents of NaOEt in toluene proceeds in a similar manner to previously reported compounds\textsuperscript{1,96-98} yielding the dinuclear indium ethoxide complex \([\text{L}_\mu\text{InCl}_2](\mu\text{-Cl})(\mu\text{-OEt})\text{ (16)}\) in modest yield (27\%) after purification (Scheme 3.2).

![Scheme 3.2. Synthesis of chiral and achiral dinuclear indium ethoxide complexes 15 and 16 with central tertiary and secondary amine donors.](image)

The \(^1\)H NMR spectrum of 15 (see Appendix B, Figure B.3) shows signals for the N-CH\textsubscript{2}\textsubscript{-}Ar protons as doublets at 4.75 and 3.38 ppm, which flank the OCH\textsubscript{2}CH\textsubscript{3} protons that appear as overlapping multiplets centered at 4.41 ppm. The \(^1\)H NMR spectrum of complex 16 (see Appendix B, Figure B.4) similarly shows the N-CH\textsubscript{2}\textsubscript{-}Ar protons of the backbone as two doublets at 5.04 and 3.63 ppm, which flank the OCH\textsubscript{2}CH\textsubscript{3} protons that appear as two overlapping multiplets centered at 4.44 ppm. In both complexes these three signals correspond to one proton each. This pattern is consistent with a single ethoxide ligand bridging the indium centres and is consistent with previously reported mono-ethoxide bridged dinuclear indium complexes.\textsuperscript{1,96-98}

The solid-state structures of complexes 15 and 16 were determined by single crystal X-ray diffraction and show distorted octahedral indium centres bridged by an ethoxide and chloride ligand (Figure 3.3 and Table 3.1; see Appendix B, Table B.1 for select crystallographic parameters). As for the related parent complex 1, complex 15 crystallizes as a homochiral dimer,
with the \((RR/RR)\) dimer in the asymmetric unit of the crystal structure. The \((SS/SS)\) dimer must also exist as the crystals were grown from a racemic mixture and crystallize in a centrosymmetric space group. However, in contrast to the parent complex 1\(^{96}\) the asymmetric unit is centrosymmetric and has a 2-fold rotational axis through the central bridging chloride. The ethoxide ligand is disordered about this axis with an occupancy of 0.5 for each site (the disorder has been removed from Figure 3.3 for clarity). In contrast, complex 16 is similar to the parent complex 1 and crystallizes as a non-centrosymmetric dimer in the asymmetric unit, with the two halves of the dimer having slightly different bond lengths and angles. Complexes 15 and 16 have similar bond lengths and angles despite the difference in backbone between the complexes (Table 3.1) with the exception of slight distortions due to the bulkier N1-Me group in complex 15. There is also a “cis” relationship between the phenoxy groups of the ligand in both structures, i.e. they are on the same side of the dimeric structures. This ligand configuration is observed for all related compounds generated from this family of tridentate ligands that are bridged by two different ligands.\(^{1,96-98}\)
Figure 3.3. Solid-state molecular structures of complexes 15 (top) and 16 (bottom). H atoms, solvent and disorder of the OEt group (for 15) are removed for clarity.
Table 3.1. Selected bond lengths and angles for complexes 15 and 16.

<table>
<thead>
<tr>
<th>Bond lengths (Å)</th>
<th>Complex 15</th>
<th>Complex 16*</th>
</tr>
</thead>
<tbody>
<tr>
<td>In1-N1</td>
<td>2.3633(15)</td>
<td>2.2902(14) / 2.2719(14)</td>
</tr>
<tr>
<td>In1-N2</td>
<td>2.3411(16)</td>
<td>2.3358(15) / 2.3970(14)</td>
</tr>
<tr>
<td>In1-Cl1</td>
<td>2.6439(5)</td>
<td>2.6253(5) / 2.6382(5)</td>
</tr>
<tr>
<td>In1-Cl2</td>
<td>2.4749(5)</td>
<td>2.4234(6) / 2.4268(5)</td>
</tr>
<tr>
<td>In1-O1</td>
<td>2.0838(12)</td>
<td>2.0670(12) / 2.0704(12)</td>
</tr>
<tr>
<td>In1-O2</td>
<td>2.1428(10)</td>
<td>2.1254(12) / 2.1143(12)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bond angles (°)</th>
<th>In1-Cl1-In1'/In2</th>
<th>89.45(2) / 117.34(5)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>In1-O2-In1'/In2</td>
<td>120.52(9) / 117.34(5)</td>
</tr>
<tr>
<td>O1-In1-N1</td>
<td>86.37(5)</td>
<td>86.83(5) / 87.63(5)</td>
</tr>
<tr>
<td>O2-In1-N1</td>
<td>104.71(4)</td>
<td>95.22(5) / 95.78(5)</td>
</tr>
<tr>
<td>O1-In1-N2</td>
<td>104.00(5)</td>
<td>104.03(5) / 99.30(5)</td>
</tr>
<tr>
<td>O2-In1-N2</td>
<td>162.64(6)</td>
<td>161.97(5) / 165.59(5)</td>
</tr>
<tr>
<td>N1-In1-N2</td>
<td>76.35(5)</td>
<td>76.77(5) / 76.08(5)</td>
</tr>
<tr>
<td>N1-In1-Cl2</td>
<td>161.81(4)</td>
<td>168.20(4) / 164.87(4)</td>
</tr>
<tr>
<td>N2-In1-Cl2</td>
<td>88.23(4)</td>
<td>92.04(4) / 89.73(4)</td>
</tr>
<tr>
<td>O1-In1-Cl1</td>
<td>167.54(4)</td>
<td>166.55(3) / 165.46(3)</td>
</tr>
<tr>
<td>O2-In1-Cl1</td>
<td>75.02(5)</td>
<td>77.04(3) / 76.93(3)</td>
</tr>
</tbody>
</table>

* the second set of numbers are for the In2 side of the complex.

3.2.2 Synthesis and characterization of deuterated indium complexes

We attempted many routes towards the synthesis of the deuterated analogue of 1, namely [(NMe2NDOtBu)InCl]2(µ-Cl)(µ-OEt) (1D) in order to directly probe the effects of changing the strength of any possible hydrogen bonding in this complex without changing the steric or electronic properties of the system. Two general strategies were used: use of D(NMe2NDOtBu) as the proligand and deuteration of the indium complexes. The difficulty of these proposed routes originates from the facile exchange of the secondary amine proton with any protic source, as evidenced by the loss of the NH signal in the 1H NMR spectrum of the ligand in the presence of protic impurities (water, alcohols).196-98
Scheme 3.3. Synthetic routes towards deuterated compound [(NMe2NDtBu)InCl]2(µ-Cl)(µ-OEt) (1D).

Our first strategy involved deuteration of the proligand L-2. We employed a simple exchange process involving adding excess D2O to a solution of the proligand in anhydrous THF (Scheme 3.3, Route 1). This route successfully yields the deuterated proligand D(NMe2NDtBu) (L-2D), with the 2H NMR spectrum of the resulting product showing two broad singlets of similar intensity at 11.5 ppm (OD) and 3.4 ppm (ND) (Figure 3.4 a). The inverse-gated and quantitative 1H{13C} NMR spectrum of the product shows a small protonated impurity (OH at 11.69 ppm and NH at 3.35 ppm) resulting in a percent deuteration of 98%, as determined from the intensities of the protonated signals to the Ar-H signals (Figure 3.4 b).
The deuterated proligand was then used to synthesize the indium alkoxide complex $^{1\text{D}}$ \text{I} using the usual route (Scheme 3.3). Unfortunately, despite showing a signal in the $^{2\text{H}}$ NMR spectrum of the intermediate indium dichloride complex (NMe$_2$ND$_2$O$_{tBu}$)InCl$_2$ ($^{2\text{D}}$\text{I}$^\text{Cl}$), $^{2\text{H}}$ NMR spectrum of the final indium ethoxide complex showed only a trace signal, indicative of the dominant product being the protonated [(NMe$_2$N$_{tBu}$)InCl]$_2$(µ-Cl)(µ-OEt) (I) (Figure 3.5). This was confirmed by the presence of the NH signal in the $^1\text{H}$ NMR spectrum of the product (Figure 3.6). This was in spite of all attempts at preventing exchange of the deuterium during the synthesis, including silylation of the glassware. This suggests that facile exchange is possible even when the ligand is complexed to indium, and that exchange of the deuterium is possible even in the presence of only trace amounts of protic impurities.

**Figure 3.4.** (a) $^2\text{H}$ NMR spectrum (400 MHz, CHCl$_3$, 25 °C) of D(NMe$_2$ND$_2$O$_{tBu}$) (L-$^{2\text{D}}$) and (b) $^1\text{H}$/$^1\text{C}$ inverse-gated NMR spectrum (400 MHz, CDCl$_3$, 25 °C) of D(NMe$_2$ND$_2$O$_{tBu}$) (L-$^{2\text{D}}$) showing 2% protonated impurity H(NMe$_2$NH$_{tBu}$) (L-2).
Figure 3.5. $^2$H NMR (400 MHz, CH$_2$Cl$_2$ with CD$_2$Cl$_2$ added for reference, 25 °C) of (a) D(NMe$_2$NDtBu) used to prepare indium complexes, (b) (NMe$_2$N$_{H/D}$OtBu)InCl$_2$ (2) formed from the deuterated proligand and (c) [(NMe$_2$N$_{H/D}$OtBu)InCl]$_2$(µ-Cl)(µ-OEt) (1) formed from the deuterated dichloride complex.

Figure 3.6. $^1$H NMR (400 MHz, CD$_2$Cl$_2$, 25 °C) of (a) D(NMe$_2$NdO$_{tBu}$) used to prepare indium complexes, (b) (NMe$_2$N$_{H/D}$OtBu)InCl$_2$ (2) formed from the deuterated proligand and (c) [(NMe$_2$N$_{H/D}$OtBu)InCl]$_2$(µ-Cl)(µ-OEt) (1) formed from the deuterated dichloride complex.
Taking advantage of the facile exchange of the amine proton we attempted instead to deuterate the final complex, \([\text{NMe}_2\text{N}_2\text{O}_{\text{tBu}}\text{InCl}]_2(\mu-\text{Cl})(\mu-\text{OEt})\) (1). We had previously observed that the ethoxide bridge in this complex can be readily exchanged with excess alcohol, reforming a new alkoxide bridged complex.\(^9\) We therefore proposed that deuterated ethanol, EtOD (CH\(_3\)CH\(_2\)OD), could provide a means to exchange the amine proton with deuterium, while still reforming the desired ethoxide-chloride bridged species (Scheme 3.3, Route 2). The protonated complex 1 was therefore stirred in EtOD overnight, after which the ethanol was removed \textit{in vacuo} and the resulting complex was characterized by \(^1\)H NMR spectroscopy. Unfortunately, the \(^1\)H and \(^2\)H NMR spectra (Figure 3.7a and b) of the resulting complex confirmed the presence of the related deuterated hydroxide-bridged dimer \([\text{NMe}_2\text{N}_2\text{O}_{\text{tBu}}\text{InCl}]_2(\mu-\text{Cl})(\mu-\text{OD})\), which would result from the reaction of the ethoxide-chloride bridged dimer with water (as described in Chapter 2), in this case D\(_2\)O impurities present in the EtOD (99% D with <6% D\(_2\)O purchased from Cambridge Isotope Laboratories). Attempts were made to dry the EtOD with anhydrous Na\(_2\)SO\(_4\) and activated molecular sieves that had been pretreated with D\(_2\)O. Although these methods yielded less decomposition of the ethoxide-chloride bridged species to the hydroxide-chloride bridged species (Figure 3.7c and d) these methods were insufficient to remove enough D\(_2\)O to prevent the formation of the hydroxide-bridged complex altogether. Because of the difficulties encountered in synthesizing a deuterated analogue of the parent complex we did not pursue this strategy further.
Figure 3.7. (a) $^2$H NMR spectrum (400 MHz, CHCl$_3$, 25 °C) of the crude product resulting from reaction of protonated complex [(N$_{Me2}$N$_{H}$O$_{tBu}$)InCl]$_2$(µ-Cl)(µ-OEt) (1) with EtOD overnight and $^1$H NMR spectra (400 MHz, CDCl$_3$, 25 °C) of the crude products resulting from the reactions of protonated complex [(N$_{Me2}$N$_{H}$O$_{tBu}$)InCl]$_2$(µ-Cl)(µ-OEt) (1) with (b) EtOD overnight, (c) EtOD for 1 hour that had been dried overnight over anhydrous Na$_2$SO$_4$ and (d) EtOD for 30 minutes that had been dried overnight over activated molecular sieves (4 Å) that had been pretreated with D$_2$O.

3.2.3 Examination of hydrogen bonding parameters in the solid-state

In order to determine if H--X hydrogen bonding plays a role in stabilizing the dimeric structure of these types of catalysts, we obtained an improved solid-state structure for compound $(\pm)$-[(N$_{Me2}$N$_{H}$O$_{tBu}$)InCl]$_2$(µ-Cl)(µ-OEt) (1) and also acquired the solid-state structure of the previously reported bromide complex $(\pm)$-[(N$_{Me2}$N$_{H}$O$_{tBu}$)InBr]$_2$(µ-Br)(µ-OEt) (17) by single crystal X-ray diffraction (Figure 3.8 and Table 3.2; see Appendix B, Table B.1 for select crystallographic parameters). Both compounds crystallize as homochiral dimers with the same “cis” relationship between the two ligands of the dimer as seen for previous compounds.$^{1,96-98}$ However, in contrast to previously reported compounds the crystals structures are racemic twins, meaning that both enantiomers crystallize in separate regions of the crystals resulting in chiral
crystals structures (non-centrosymmetric). Therefore, the asymmetric unit of the crystal structure contains both enantiomeric \((RR/RR)\) and \((SS/SS)\) dimers, which have only minor differences in bond lengths and angles (only the \((RR/RR)\) dimers are shown in Figure 3.8 for clarity). In general, the bond lengths and angles between the previously reported \((RR/RR)\) dimeric structure of complex 1\(^96\) and the new \((RR/RR)\) dimeric structure of this complex are slightly different, most likely due to the different ways the compound has crystallized. The bond lengths and angles are consistent between complexes 1 and 17, with slightly longer bond lengths and small distortions in the bond angles for complex 17 due to the bulkier bromide ligands.

![Solid-state molecular structures of \((RR/RR)\) dimers of complexes 1 (top) and 17 (bottom). Thermal ellipsoids are set at 50% probability. H atoms, solvent and the \((SS/SS)\) dimers are removed for clarity.](image)

**Figure 3.8.** Solid-state molecular structures of \((RR/RR)\) dimers of complexes 1 (top) and 17 (bottom). Thermal ellipsoids are set at 50% probability. H atoms, solvent and the \((SS/SS)\) dimers are removed for clarity.
Table 3.2. Selected bond lengths and angles for the (RR/RR) dimers in the previously reported solid-state structure of complex 1, new structure of complex 1 and structure of complex 17.

<table>
<thead>
<tr>
<th>Bond lengths (Å)</th>
<th>Complex 1 (previously reported)</th>
<th>Complex 1</th>
<th>Complex 17</th>
</tr>
</thead>
<tbody>
<tr>
<td>In1-N1</td>
<td>2.269(9)</td>
<td>2.269(18)</td>
<td>2.274(8)</td>
</tr>
<tr>
<td>In2-N3</td>
<td>2.257(8)</td>
<td>2.244(14)</td>
<td>2.264(7)</td>
</tr>
<tr>
<td>In1-N2</td>
<td>2.354(10)</td>
<td>2.36(2)</td>
<td>2.389(10)</td>
</tr>
<tr>
<td>In2-N4</td>
<td>2.334(10)</td>
<td>2.322(18)</td>
<td>2.370(9)</td>
</tr>
<tr>
<td>In1-C11/Br1</td>
<td>2.636(4)</td>
<td>2.562(6)</td>
<td>2.7181(12)</td>
</tr>
<tr>
<td>In2-C11/Br1</td>
<td>2.667(3)</td>
<td>2.700(6)</td>
<td>2.8679(12)</td>
</tr>
<tr>
<td>In1-C12/Br2</td>
<td>2.428(3)</td>
<td>2.432(6)</td>
<td>2.5943(11)</td>
</tr>
<tr>
<td>In2-C13/Br3</td>
<td>2.419(3)</td>
<td>2.398(6)</td>
<td>2.5504(12)</td>
</tr>
<tr>
<td>In1-O1</td>
<td>2.050(8)</td>
<td>2.041(16)</td>
<td>2.073(7)</td>
</tr>
<tr>
<td>In2-O3</td>
<td>2.084(7)</td>
<td>2.066(16)</td>
<td>2.093(6)</td>
</tr>
<tr>
<td>In1-O2</td>
<td>2.129(8)</td>
<td>2.157(14)</td>
<td>2.145(7)</td>
</tr>
<tr>
<td>In2-O2</td>
<td>2.112(8)</td>
<td>2.094(14)</td>
<td>2.164(6)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bond angles (°)</th>
<th>Complex 1 (previously reported)</th>
<th>Complex 1</th>
<th>Complex 17</th>
</tr>
</thead>
<tbody>
<tr>
<td>In1-C11/Br1-In2</td>
<td>86.62(9)</td>
<td>87.7(2)</td>
<td>83.70(4)</td>
</tr>
<tr>
<td>In1-O2-In2</td>
<td>118.1(3)</td>
<td>118.1(8)</td>
<td>119.8(3)</td>
</tr>
<tr>
<td>O1-In1-N1</td>
<td>89.0(3)</td>
<td>85.0(7)</td>
<td>85.6(3)</td>
</tr>
<tr>
<td>O3-In2-N3</td>
<td>91.8(3)</td>
<td>87.3(6)</td>
<td>87.7(3)</td>
</tr>
<tr>
<td>O2-In1-N1</td>
<td>93.8(4)</td>
<td>96.9(6)</td>
<td>97.1(3)</td>
</tr>
<tr>
<td>O2-In2-N3</td>
<td>91.8(3)</td>
<td>91.5(5)</td>
<td>91.0(3)</td>
</tr>
<tr>
<td>O1-In1-N2</td>
<td>102.8(4)</td>
<td>101.1(6)</td>
<td>101.0(3)</td>
</tr>
<tr>
<td>O3-In2-N4</td>
<td>102.1(3)</td>
<td>103.7(7)</td>
<td>101.4(3)</td>
</tr>
<tr>
<td>O2-In1-N2</td>
<td>161.8(4)</td>
<td>162.2(7)</td>
<td>163.5(3)</td>
</tr>
<tr>
<td>O2-In2-N4</td>
<td>161.4(3)</td>
<td>156.1(6)</td>
<td>156.8(3)</td>
</tr>
<tr>
<td>N1-In1-N2</td>
<td>77.9(4)</td>
<td>76.4(7)</td>
<td>76.3(3)</td>
</tr>
<tr>
<td>N3-In2-N4</td>
<td>78.0(4)</td>
<td>76.6(6)</td>
<td>75.8(3)</td>
</tr>
<tr>
<td>N1-In1-C12/Br2</td>
<td>170.4(3)</td>
<td>166.9(5)</td>
<td>167.2(2)</td>
</tr>
<tr>
<td>N3-In2-C13/Br3</td>
<td>171.4(3)</td>
<td>171.0(5)</td>
<td>170.8(2)</td>
</tr>
<tr>
<td>N2-In1-C12/Br2</td>
<td>92.7(3)</td>
<td>91.5(5)</td>
<td>92.0(2)</td>
</tr>
<tr>
<td>N4-In2-C13/Br3</td>
<td>94.0(3)</td>
<td>94.7(5)</td>
<td>95.7(2)</td>
</tr>
<tr>
<td>O1-In1-C11/Br1</td>
<td>168.1(2)</td>
<td>168.3(5)</td>
<td>169.41(19)</td>
</tr>
<tr>
<td>O3-In2-C11/Br1</td>
<td>166.8(2)</td>
<td>167.8(5)</td>
<td>168.54(18)</td>
</tr>
<tr>
<td>O2-In1-C11/Br1</td>
<td>77.6(2)</td>
<td>77.3(5)</td>
<td>79.35(19)</td>
</tr>
<tr>
<td>O2-In2-C11/Br1</td>
<td>77.1(2)</td>
<td>75.2(5)</td>
<td>75.7(2)</td>
</tr>
</tbody>
</table>

A comparison of the hydrogen bonding parameters was made between the related chiral complexes with chloride (1) and bromide (17) donors and the related hydroxide-ethoxide bridged complex with iodide acceptors, [(NMe2NH2OEt)InI2(µ-OH)(µ-OEt)] (10), as well as the hydroxide-ethoxide bridged complex with the bulkier propyl ligand described in Chapter 2.
[(NMe₂N₉H₉O₉tBu)InI]₂(µ-OH)(µ-OEt) (9) and the achiral complex [(L₄tInCl)]₂(µ-Cl)(µ-OEt) (16) (Table 3.3). The N₁-X distance for complex 15, with a central tertiary amine donor, is shown as a baseline, as hydrogen bonding is not possible in this complex. In addition to the H-X (d) and N₁-X (D) bond distances and the N-H-X bond angle (θ), Table 3.3 includes the ratio between the observed H-X distances and the sum of the Van der Waals radii of the H and X atoms (R₁HX).

This value normalizes the differences between the Van der Waals radii of the halogens and provides a useful way to compare the extent of hydrogen bonding in complexes with different halogen acceptors. A value of 1 for R₁HX would indicate the hydrogen bond distance is equal to the sum of the Van der Waals radii of the participating atoms and therefore the H-bond would be very weak or non-existent. Therefore, lower R₁HX numbers would indicate stronger hydrogen bonding is present in the system.

**Table 3.3.** Select solid-state structural data and hydrogen bonding parameters for related indium complexes.

<table>
<thead>
<tr>
<th>Complex</th>
<th>X</th>
<th>Y</th>
<th>N₁-X (Å)</th>
<th>H-X (Å)</th>
<th>N₁-H-X (°)</th>
<th>R₁HX</th>
</tr>
</thead>
<tbody>
<tr>
<td>1⁴</td>
<td>Cl</td>
<td>Cl</td>
<td>3.416 (4.517)</td>
<td>2.445 (3.788)</td>
<td>163.5 (131.8)</td>
<td>0.83 (1.28)</td>
</tr>
<tr>
<td>17⁴</td>
<td>Br</td>
<td>Br</td>
<td>3.535 (4.605)</td>
<td>2.662 (3.938)</td>
<td>160.9 (132.8)</td>
<td>0.87 (1.29)</td>
</tr>
<tr>
<td>1⁴</td>
<td>I</td>
<td>OH</td>
<td>3.803 (3.790)</td>
<td>2.926 (3.045)</td>
<td>149.5 (150.1)</td>
<td>0.93 (0.96)</td>
</tr>
<tr>
<td>9</td>
<td>Cl</td>
<td>OH</td>
<td>3.730</td>
<td>2.830</td>
<td>163.6</td>
<td>0.96</td>
</tr>
<tr>
<td>16</td>
<td>Cl</td>
<td>Cl</td>
<td>3.454 (4.518)</td>
<td>2.591 (3.641)</td>
<td>147.2 (150.4)</td>
<td>0.88 (1.23)</td>
</tr>
<tr>
<td>15</td>
<td>Cl</td>
<td>Cl</td>
<td>4.487</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values in parentheses are from the second half of the dimer in non-centrosymmetric complexes. ⁴Values are for the (RR/RR) dimer. ⁵Values not in parentheses are an average of two measurements due to structural disorder in the ligand on one half of the molecule.
Several comprehensive studies have been done of crystallographic databases, with researchers providing tabulated average hydrogen bonding parameters for various types of halogen based hydrogen bonds in a range of different structures.\textsuperscript{130-132} For NH-X type hydrogen bonds present in metal complexes, average N-X distances between several studies are 3.3 Å, 3.5 Å and 3.7 Å, H-X distances are 2.5 Å, 2.7 Å and 2.9 Å and R\textsubscript{HX} values are 0.85, 0.87 and 0.92 for chloride, bromide and iodide acceptors respectively.\textsuperscript{130-132} Our parameters for the chloride (1), bromide (17) and iodide (10) analogues with the parent ligand are in line with these literature values, and show a general trend of decreasing hydrogen bond strength in moving from chloride to iodide acceptors, as expected. However complex 9, where the N-Me\textsubscript{2} is replaced with a bulkier N(p^nPr)\textsubscript{2} group, has slightly longer bond distances and an R\textsubscript{HX} value close to 1, suggesting that this complex may only have very weak hydrogen bonds. The achiral complex 16 has larger H-X and R\textsubscript{HX} values than complex 1 but a similar N1-X value, suggesting that this complex may have similar or slightly weaker hydrogen bonding strength than its chiral analogue. Thus it is possible to compare complexes with a range of hydrogen bonding from fairly strong (1 and 16), to intermediate (17), to weak (10 and 9) and finally to non-existent (15).

In interpreting this data, however, it is important to note the structural differences between some of these complexes. The second bridging ligand between complexes 1 and 17, which have ethoxide and halide bridging ligands, is different from complexes 9 and 10, with ethoxide and hydroxide bridging ligands. Indeed complex 9 is further differentiated by the fact that it crystallizes as a symmetric molecule, with both sides of the dimer being equivalent. Unfortunately, structural data for the exact iodide and propyl analogues of complex 1 is unavailable. Therefore, it is unclear whether the weak H-bonding seen in complexes 9 and 10 is a
consequence of structural changes due to the hydroxide bridging ligand or is due to the direct influence of the iodide or propyl groups.

### 3.2.4 Polymerization studies

Polymerization studies with complexes 15, 16 and 17 were carried out and compared to previously studied systems\(^{1,96-98}\) in order to determine the effects of the central amine on the activity of these catalysts as well as determine the effects, if any, of hydrogen bonding in these systems (Table 3.4).

**Table 3.4.** Rates for the polymerization of rac-LA with select indium ethoxide complexes.

<table>
<thead>
<tr>
<th>Complex</th>
<th>(R_{\text{HX}}^a)</th>
<th>(k_{\text{obs}}) ((\times 10^{-3}) s(^{-1}))(^d)</th>
<th>(k_p) (M(^{-1}) s(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>1(^b)</td>
<td>0.83 (1.28)</td>
<td>1.7</td>
<td>0.57 (±0.05)</td>
</tr>
<tr>
<td>17(^b)</td>
<td>0.87 (1.29)</td>
<td>4.8</td>
<td>2.2 (±0.1)</td>
</tr>
<tr>
<td>10(^c)</td>
<td>0.93 (0.96)</td>
<td>3.5</td>
<td>1.5 (±0.1)(^f)</td>
</tr>
<tr>
<td>7</td>
<td>0.96(^e)</td>
<td>2.1</td>
<td>–</td>
</tr>
<tr>
<td>15</td>
<td>–</td>
<td>0.012</td>
<td>–</td>
</tr>
<tr>
<td>11</td>
<td>–</td>
<td>0.011</td>
<td>–</td>
</tr>
<tr>
<td>16</td>
<td>0.88 (1.23)</td>
<td>0.76</td>
<td>–</td>
</tr>
</tbody>
</table>

\(^a\)Values in parentheses are from the second half of the dimer in non-centrosymmetric complexes. \(^b\)Values are for the (RR/RR) dimer. \(^c\)Values not in parentheses are an average of two measurements because of structural disorder in the ligand on one half of the molecule. \(^d\)Calculated from the slopes of the linear portion of ln([LA]) vs. time plots for the polymerization of 200 eq. rac-LA (0.5 M) with [cat.] = 2 mM with 1,3,5-trimethoxybenzene (0.03 M) used as an internal standard. \(^e\)Value is for complex \([(\text{N}_{\text{nPr}_{2}}\text{NMe}_{2}\text{O}_{\text{tBu}})\text{InCl}]_2(\mu-\text{Cl})(\mu-\text{OEt})\) (9). \(^f\)Value is for complex \([(\text{N}_{\text{Me}_{2}}\text{NMe}_{2}\text{O}_{\text{tBuMe}})\text{InI}]_2(\mu-\text{OH})(\mu-\text{OEt})\) (18) with para-Me instead of para-tert-butyl substituents on the phenolate rings as for complex 10.

The effect of secondary vs. tertiary amine donors was studied through complexes 1 and 16 vs. complexes 15 and 11, respectively. The polymerization of 200 eq. of rac-LA by 15 can be monitored in CD\(_2\)Cl\(_2\) by \(^1\)H NMR spectroscopy. The plot of ln([LA]) versus time shows no significant induction period and the propagation proceeds with a \(k_{\text{obs}}\) value of 1.2 \(\times\) \(10^{-5}\) s\(^{-1}\) (Figure 3.9). The rate for 15 is two orders of magnitude lower than the rate for complex 1 (\(k_{\text{obs}}\) =

106
1.7 × 10^{-3} \text{ s}^{-1}) under similar conditions.\textsuperscript{98} The ring opening polymerization of 200 eq. of \textit{rac}-LA with 15 reaches >95\% conversion in 3 days. In stark contrast, a similar reaction catalyzed by complex 1 reaches >95\% conversion in 30 min.

\begin{figure}[h]
\centering
\includegraphics[width=0.8\textwidth]{figure3.9}
\caption{The plot of ln([LA]) vs. time for the ROP of 200 eq. of \textit{rac}-LA (0.47 M) with complex 15 (2.4 mM) monitored to 97\% conversion by $^1$H NMR spectroscopy (300 MHz, CD$_2$Cl$_2$, 25 °C). 1,3,5-trimethoxybenzene (0.031 M) was used as an internal standard.}
\end{figure}

A similar phenomenon is observed when comparing complex 16 to its methylated analogue 11. The polymerization of 200 eq. of \textit{rac}-LA by complex 16 proceeds to over 90\% conversion in 60 minutes. \textit{In situ} monitoring of this reaction by $^1$H NMR spectroscopy in CD$_2$Cl$_2$ shows a short induction period, and the propagation proceeds with a $k_{\text{obs}}$ value of 0.76 × 10^{-3} \text{ s}^{-1} (Figure 3.10). This rate is 2 orders of magnitude faster than the methylated analogue 11 ($k_{\text{obs}} = 1.1 \times 10^{-5} \text{ s}^{-1}$) under similar conditions. This is the same trend observed with the chiral complexes 1 and 15 as discussed above.
The plot of ln([LA]) vs. time for the ROP of 200 eq. of rac-LA (0.50 M) with complex 16 (2.5 mM) monitored to 93\% conversion by \textsuperscript{1}H NMR spectroscopy (400 MHz, CD\textsubscript{2}Cl\textsubscript{2}, 25 °C). 1,3,5-trimethoxybenzene (0.029 M) was used as an internal standard.

In order to more accurately compare the rates of polymerization between different catalysts we compared the concentration independent propagation rate constants \((k_p)\) for the parent chloride catalyst to its bromide and iodide analogues, for which the H-bonding is weaker (Table 3.3). The reported rates of propagation \((k_p)\) for 1 and an analogue of the iodide complex 10, where the para-tert-butyl groups on the phenolate rings have been replaced by methyl groups, \([\text{[(NMe}_2\text{NH}_2\text{O}_\text{tBuMe}]}\text{InI}_2(\mu-\text{OH})(\mu-\text{OEt})\text{]}\) (18), are 0.57 \((\pm0.05)\) and 1.5 \((\pm0.1)\) M\(^{-1}\)s\(^{-1}\) respectively.\textsuperscript{96,98} The rate of propagation of the bromide analogue 17 had not been previously determined, and therefore the relationship between the \(k_{\text{obs}}\) values and the concentration of catalyst 17 was determined through several kinetic experiments (Figure 3.11). The plot is linear, implying a first order dependence on the catalyst concentration as for previously reported complexes.\textsuperscript{96,98} The slope of this graph revealed a propagation rate constant \((k_p)\) for the bromide complex (17) of 2.2 \((\pm0.1)\) M\(^{-1}\)s\(^{-1}\) (Figure 3.11). This value is in the same range as those
reported for complexes 1 and 18 and indicates that there is little effect of the halide on the activity of these complexes. A similar determination of the \( k_p \) values of the methylated complexes 11 and 15 was not undertaken due to their slow rate of polymerization. However the comparisons of the observed rate constants at similar concentrations do indicate that the much lower rates for methylated complexes 15 and 11 are true outliers in the series.

**Figure 3.11.** The plot of observed rate constants \( (k_{obs}) \) at different catalyst concentrations for the polymerization of rac-LA by 17, monitored to >97% conversion by \(^1\)H NMR spectroscopy (400 MHz, 25 °C, CDCl\(_3\)). \([\text{LA}] = 0.45 \text{ M}, [17] = 0.7, 0.9, 1.1, 1.6 \text{ and } 2.2 \text{ mM with } 1,3,5\)-trimethoxybenzene (0.033 M) used as an internal standard.

We investigated two possibilities for the significant decrease in rate in moving from secondary to tertiary central amine donors: 1) the lack of hydrogen bonding in the system which may affect the stability of the dinuclear catalyst and lead to catalyst dissociation, and 2) a change in the electrophilicity of the metal centre in moving from secondary to tertiary amines.\(^{116}\) With the complexes at hand, however, it is challenging to separate the two effects: compounds that show no hydrogen bonding are also electronically different.
In situ observation of the polymerization of rac-LA with complex [(NMe₂NMeO₅Bu)InCl]₂(μ-Cl)(μ-OEt) (15) shows catalyst dissociation to the dichloride complex (NMe₂NMeO₅Bu)InCl₂ (12) and a polymeryl species immediately after preparation of the sample (Figure 3.12). We observed a similar dissociation process with the achiral complex [(L₅Me)InCl]₂(μ-Cl)(μ-OEt) (11) and the bulkier catalyst [(N₄Pr₂N₄H₃O)InCl]₂(μ-Cl)(μ-OEt) (7) (see Chapter 2), that we assume has little to no hydrogen bonding based on analogy with the structural parameters of its hydroxide-ethoxide bridged analogue [(N₄Pr₂N₄H₃O)InCl]₂(μ-OH)(μ-OEt) (9) (see Table 3.3).

Figure 3.12. ¹H NMR spectra (300 MHz, CD₂Cl₂, 25 °C) of (a) complex 15, (b) complex 12 and (c) polymerization of rac-LA (0.47 M) with complex 15 (2.4 mM) ~10 min after preparation of the sample.

In contrast, dissociation is not observed for catalyst [(L₄It)InCl]₂(μ-Cl)(μ-OEt) (16), which shows unreacted catalyst and a polymeryl species during the early stages of the polymerization and only the polymeryl species at the late stages of the polymerization (Figure 3.13). This is consistent with catalyst 1 (as was discussed in Chapter 2), where dissociation is also not
observed during polymerization and detailed mechanistic studies have revealed that a dimeric propagating species is most consistent with the observed experimental evidence.\textsuperscript{98}

\textbf{Figure 3.13.} \textsuperscript{1}H NMR spectra (400 MHz, CD\textsubscript{2}Cl\textsubscript{2}, 25 °C) of (a) complex 16, (b) polymerization of \textit{rac}-LA (0.50 M) with complex 16 (2.5 mM) ~7 min after preparation of the sample and (c) polymerization of \textit{rac}-LA (0.50 M) with complex 16 (2.5 mM) ~66 min after preparation of the sample.

One interpretation of these results is that a lack of H-bonding, such as in complexes 7, 15 and 11, may lead to dissociation of the dimers during polymerization of lactide. However, comparison of polymerization rates suggests a more nuanced situation (Table 3.4). If this dissociation is responsible for the lowered activity of complexes 15 and 11 we would expect complex 7 to have a similarly slow rate of polymerization (if we assume the structure of complex 7 would be closely related to complex 9 and therefore also show a lack of H-bonding). This is not the case, however, as complex 7 shows a rate comparable to the parent system, with a $k_{\text{obs}}$ value of $2.1 \times 10^{-3}$ s\textsuperscript{-1}, two orders of magnitude higher than both complexes 15 and 11.\textsuperscript{1} Also, changing the halide group from chloride to iodide, which leads to decreased hydrogen bonding, has no major impact on the polymerization rate.

From these results we can infer that although H-bonding may be playing a role in the stability of the dimeric structure of these types of catalysts, it is likely not a universal
contributing factor in their activity towards lactide polymerization. We can then speculate that
the slower rates of polymerization may be due to the difference in the electronic nature of the
central metal. Complexes with tertiary amine donors, complexes 15 and 11, show considerably
slower rates compared to their secondary amine analogues, complexes 1 and 16. To investigate
the validity of this claim we turned to DFT calculations to give us insight into the electron
density at the indium center in the ground state, and how this might be affected by the nature of
the central amine donor.

DFT calculations were carried out using ORCA with a B3LYP functional. The available
Def2-SV(P) basis set was used for all atoms and geometric optimizations were carried out in the
gas-phase. Complexes 1 and 15 were optimized in these calculations. The validity of the
calculations was established by comparing the metrical parameters obtained after the
optimization, with those obtained from the X-ray structures of the complexes (see Appendix B,
Table B.2 for optimized parameters). In order to establish whether any electronic differences can
be observed at the indium centers of 1 and 15, the partial atomic charges were determined using
Mulliken population analysis and Löwdin analysis. The In Mulliken charge for both 1 and 15
was 1.05 and the corresponding Löwdin charges were 0.29 and 0.27. This indicates that no
significant difference exists in the electronics at the indium centers in the ground states of 1 and
15.

Finally, we have analyzed the polymers generated by the various catalysts to determine
whether there are differences in the systems with and without tertiary amine donors. Bulk
polymerizations of rac-LA with complexes 15, 16 and 17 with various equivalents of monomer
show molecular weights ($M_n$) fairly consistent with theoretical values and low polydispersity
(PDI) values indicative of controlled polymerization in all systems (Table 3.5). The bromide
catalyst 17 shows a slight isotactic bias in selectivity with $P_m = 0.58 - 0.61$ and is comparable to the parent system $[(\text{NMe}_2\text{N}_2\text{H}_2\text{O})\text{InCl}]_2(\mu-\text{Cl})(\mu-\text{OEt})$ (1) ($P_m \sim 0.62$). In contrast, catalysts 15 ($P_m = 0.43 - 0.44$) and 16 ($P_m = 0.50 - 0.55$) show no selectivity, with $P_m$ values consistent with loss of isotactic bias. A similar loss in isoselectivity was observed with complex 7 (see Chapter 2). Interestingly, these are the three compounds that definitively dissociate during polymerization, once again confirming our observations that isoselectivity is imparted by the dinuclear structure of these types of catalysts, as described in Chapter 2.

The experimental data shows that there is no real change in the catalyst performance with a change in halide, as both the activity, selectivity and molecular weight control of the bromide catalyst $[(\text{NMe}_2\text{N}_2\text{H}_2\text{O})\text{InBr}]_2(\mu-\text{Br})(\mu-\text{OEt})$ (17) is comparable to the parent chloride catalyst $[(\text{NMe}_2\text{N}_2\text{H}_2\text{O})\text{InCl}]_2(\mu-\text{Cl})(\mu-\text{OEt})$ (1). This is similar to our previous observations with the iodide analogue $[(\text{NMe}_2\text{N}_2\text{H}_2\text{O}_{\text{tBuMe}})\text{InI}]_2(\mu-\text{I})(\mu-\text{OEt})$, which was also shown to have similar performance to the parent system.
Table 3.5. Results for the polymerization of rac-LA by catalysts 15, 16 and 17.

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>[LA]₀/[cat.]</th>
<th>T (h)</th>
<th>Conv. (%)sup.a</th>
<th>Mₙ theo sup.b (Da)</th>
<th>Mₙ GPC sup.c (Da)</th>
<th>PDI</th>
<th>Pₘ sup.d</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>204</td>
<td>72</td>
<td>96</td>
<td>28330</td>
<td>23630</td>
<td>1.09</td>
<td>−</td>
</tr>
<tr>
<td>15</td>
<td>261</td>
<td>144</td>
<td>97</td>
<td>36480</td>
<td>39500</td>
<td>1.02</td>
<td>0.44</td>
</tr>
<tr>
<td>15</td>
<td>620</td>
<td>144</td>
<td>71</td>
<td>63480</td>
<td>57200</td>
<td>1.03</td>
<td>−</td>
</tr>
<tr>
<td>15</td>
<td>804</td>
<td>288</td>
<td>92</td>
<td>106610</td>
<td>85890</td>
<td>1.06</td>
<td>0.43</td>
</tr>
<tr>
<td>16</td>
<td>214</td>
<td>17</td>
<td>93</td>
<td>28710</td>
<td>30480</td>
<td>1.07</td>
<td>0.50</td>
</tr>
<tr>
<td>16</td>
<td>341</td>
<td>18</td>
<td>95</td>
<td>46710</td>
<td>49650</td>
<td>1.01</td>
<td>0.55</td>
</tr>
<tr>
<td>16</td>
<td>609</td>
<td>18</td>
<td>97</td>
<td>85170</td>
<td>93830</td>
<td>1.02</td>
<td>0.54</td>
</tr>
<tr>
<td>16</td>
<td>801</td>
<td>18</td>
<td>96</td>
<td>110890</td>
<td>114100</td>
<td>1.02</td>
<td>0.51</td>
</tr>
<tr>
<td>17</td>
<td>292</td>
<td>24</td>
<td>98</td>
<td>41290</td>
<td>45700</td>
<td>1.05</td>
<td>0.59</td>
</tr>
<tr>
<td>17</td>
<td>395</td>
<td>17</td>
<td>98</td>
<td>55850</td>
<td>57350</td>
<td>1.02</td>
<td>−</td>
</tr>
<tr>
<td>17</td>
<td>574</td>
<td>24</td>
<td>98</td>
<td>80770</td>
<td>82050</td>
<td>1.02</td>
<td>0.58</td>
</tr>
<tr>
<td>17</td>
<td>867</td>
<td>24</td>
<td>97</td>
<td>121690</td>
<td>111500</td>
<td>1.03</td>
<td>0.61</td>
</tr>
</tbody>
</table>

sup.a Monomer conversion, determined by sup.¹H NMR spectroscopy. sup.b Calculated from [LA]₀/[initiator] × LA conversion × Mₖ (144.13) + Mₖ₂ (46.07). sup.c Determined by GPC measurements in THF. sup.d Calculated from the sup.¹H sup.¹H{sup.¹H} NMR spectra and Bernoullian statistics.

3.3 Discussion and conclusions

In this study we found that there is a profound difference in polymerization activity between dinuclear indium complexes supported by tridentate diaminophenolate ligands where the central amine is secondary vs. tertiary. With secondary amine supports, such as in chiral indium complexes previously described by our group 1, 10⁹₆,⁹₈ and 7 (described in Chapter 2), and in the achiral indium complex 16 described in this chapter, the ring opening polymerization of 200 equivalents of rac-LA proceeds to high conversions at room temperature in under an hour. In contrast, when the central amine is methylated, as in the previously reported achiral complex 11 and the chiral complex 15 described in this chapter the rate of polymerization is two orders of magnitude slower under the same conditions.
Our preliminary computational study of the series showed no significance change in the electronics of the indium centre upon changing the central donor amine, thus we sought to gain more insight into this disparity by exploring the role of hydrogen bonding in the system. Our study shows that although there is evidence for hydrogen bonding in the chloride and bromide complexes 1 and 17, weakening of the hydrogen bonding (bulkier analogue 7) or removal of this ability (methylated analogues 15 and 11) comes with significant changes in the steric bulk of the system, leading to catalyst dissociation during polymerization. However, this dissociation does not translate into reduced activity, with catalyst 7 having similar activity to catalysts 1 and 17 and catalysts 15 and 11 being considerably slower. Thus, it is exceedingly difficult to isolate hydrogen bonding as the factor impacting activity in the system. We can only conclude that in catalyst systems with similar steric environments, a change of donors from tertiary to secondary amines can have a very significant impact on catalyst activity. This leads us to conclude that future ligand modifications may need to exclude the use of tertiary central amine donors to retain the high activity of these systems.

3.4 Experimental

General procedures

All air and/or water sensitive reactions were carried out under N₂ in an MBraun glovebox. The surface of all glassware used for deuteration studies was silylated by soaking the glassware in a solution of trimethylsilylchloride in CH₂Cl₂ (15% w/w) or in pure trimethylsilylchloride overnight under N₂ then rinsing with CH₂Cl₂ and drying in an oven prior to use. A Bruker Avance 300 MHz or 400inv MHz spectrometer was used to record the ¹H NMR kinetics experiments and a Bruker Avance 600 MHz spectrometer was used to record the ¹H NMR, ¹³C{¹H} NMR spectra and ¹H{¹H} NMR spectra. ¹H NMR chemical shifts are given in
ppm versus residual protons in deuterated solvents as follows: δ 5.32 for CD₂Cl₂ and 7.27 for CDCl₃. ¹³C{¹H} NMR chemical shifts are given in ppm versus residual ¹³C in solvents as follows: δ 54.00 for CD₂Cl₂ and 77.00 for CDCl₃. Diffraction measurements for X-ray crystallography were made on Bruker X8 APEX II and Bruker APEX DUO diffractometers with graphite monochromated Mo-Kα radiation. The structures were solved by direct methods and refined by full-matrix least-squares using the SHELXTL crystallographic software of the Bruker-AXS. Unless specified, all non-hydrogens were refined with anisotropic displacement parameters, and all hydrogen atoms were constrained to geometrically calculated positions but were not refined. EA CHN analysis was performed using a Carlo Erba EA1108 elemental analyzer. The elemental composition of an unknown sample was determined by using a calibration factor. The calibration factor was determined by analyzing a suitable certified organic standard (OAS) of a known elemental composition. Molecular weights were determined by GPC-LLS using an Agilent liquid chromatograph equipped with either an Agilent 1200 series pump and autosampler, three Phenogel 5 µm Narrow Bore columns (4.6 × 300 mm with 500 Å, 10³ Å and 10⁴ Å pore size), a Wyatt Optilab differential refractometer, Wyatt tristar miniDAWN (laser light scattering detector) and a Wyatt ViscoStar viscometer or an Agilent 1200 Series pump and autosampler, Phenomenex columns (Phenogel 5 µm 10E4A LC Column 300 × 4.6 mm, 5 K - 500 K MW; Phenogel 5 µm 10E3A LC Column 300 × 4.6 mm, 1 K - 75 K MW; Phenogel 5 µm 500 ÅLC Column 300 × 4.6 mm, 1 K - 15 K MW), Wyatt Optilab rEX (refractive index detector λ= 690 nm, 40 °C), Wyatt tristar miniDAWN (laser light scattering detector operating at λ = 690 nm), and a Wyatt ViscoStar viscometer. The column temperature was set at 40 °C. A flow rate of 0.5 mL/min was used and samples were dissolved in THF (ca. 5
mg/mL), and a dn/dc value of 0.042 mL/g was used. Narrow molecular weight polystyrene standards were used for calibration purposes.

Materials

Toluene, diethyl ether, hexane, and tetrahydrofuran were degassed and dried using alumina columns in a solvent purification system. The THF was further dried over sodium/benzophenone and vacuum transferred to a Straus flask where it was degassed prior to use. In addition CH\textsubscript{3}CN and CH\textsubscript{2}Cl\textsubscript{2} were dried over CaH\textsubscript{2} and vacuum transferred to a Straus flask where they were degassed prior to use. Deuterated chloroform (CDCl\textsubscript{3}) and dichloromethane (CD\textsubscript{2}Cl\textsubscript{2}) were dried over CaH\textsubscript{2} and vacuum transferred to a Straus flask and then degassed through a series of freeze-pump-thaw cycles. Deuterated ethanol (CH\textsubscript{3}CH\textsubscript{2}OD, 99% D with <6% D\textsubscript{2}O) was obtained from Cambridge Isotope Laboratories and was degassed prior to use and stored in silylated glassware. InCl\textsubscript{3} was obtained from Strem Chemicals and InBr\textsubscript{3} was obtained from Alfa Aesar. Both were used without further purification. Benzyl potassium was synthesized using a modified literature preparation of n-butyl lithium, potassium tert-butoxide and toluene. The proligands 2,4-di-tert-butyl-6-(((2-(dimethylamino)cyclohexyl)(methyl)amino)methyl)phenol H(NMe\textsubscript{2}NMeO\textsubscript{t}Bu\texttextsubscript{8}) and 2,4-di-tert-butyl-6-(((2-(dimethylamino)ethyl)(methyl)amino)methyl)phenol H(LMe\textsubscript{8}) and the bromide complex 17 were prepared according to previously published procedures.\textsuperscript{1,96-98,109} Lactide samples were obtained from Purac Biomaterials and recrystallized several times from hot, dry toluene and dried under vacuum prior to use.

Synthesis of proligand H(L-H) (L-8)

To a solution of 2,4-di-tert-butylsalicylaldehyde (2.135 g, 9.111 mmol) in methanol (25 mL) was added N,N-dimethylethlenediamine (0.804 g, 9.12 mmol). The solution was stirred at room
temperature for 20 h, then pumped to dryness in vacuo yielding the imine as a thick orange oil (2.73 g, 98%). The imine was dissolved in acetonitrile (30 mL). Sodium cyanoborohydride (2.824 g, 44.94 mmol) was added and the solution was stirred for 30 min. Acetic acid (2.5 mL, 44 mmol) was then added and the solution was stirred at room temperature for 16 h. The mixture was diluted with 5% MeOH in CH₂Cl₂ (50 mL) then washed with 1 M NaOH (3 × 50 mL). The organics were dried over MgSO₄ then filtered and pumped to dryness, yielding the crude product as a thick pale yellow oil (2.75 g, 100%). The oil was dissolved in hexanes, causing precipitation of a white solid. The solid was removed via filtration and the filtrate was collected and pumped to dryness in vacuo yielding a purer fraction of the product as a viscous pale yellow oil. This oil was taken into the glovebox and dissolved in hexanes, then dried over Na₂SO₄ to remove water impurities, filtered and pumped to dryness in vacuo yielding a thick pale yellow oil (1.55 g, 56%). The product was used without further purification. ¹H NMR (600 MHz, CDCl₃, 25 °C): δ 7.22 (1H, d, ⁴J₉H = 2 Hz, Ar-H), 6.87 (1H, d, ⁴J₉H = 2 Hz, Ar-H), 3.97 (2H, s, Ar-CH₂-N), 2.74 (2H, t, ²J₉H = 6 Hz, NCH₂CH₂N), 2.46 (2H, t, ²J₉H = 6 Hz, NCH₂CH₂N), 2.24 (6H, s, N(CH₃)₂), 1.43 (9H, s, C(CH₃)₃), 1.29 (9H, s, C(CH₃)₃). ¹³C{¹H} NMR (150 MHz, CDCl₃, 25 °C): δ 154.73, 140.25, 135.73, 123.09, 122.79, 122.05, 58.25, 53.39, 45.89, 45.42, 34.86, 34.11, 31.67, 29.61. Anal. Calc. for C₁₉H₃₄N₂O: C, 74.46; H, 11.18; N, 9.14. Found: C, 74.14; H, 11.20; N, 9.37.

Synthesis of complex 12

A suspension of benzyl potassium (0.1701 g, 1.306 mmol) in toluene (10 mL) was added to a solution of H(NMe₂NMeOtBu) (L-3) (0.4906 g, 1.310 mmol) in toluene (10 mL). The reaction mixture was stirred at room temperature for 15 h, and the solvent was removed in vacuo to obtain K(NMe₂NMeOtBu) as a pale yellow solid in quantitative yield. The potassium salt,
K(NMe2NMeO\textsubscript{tBu}) (0.5801 g, 1.406 mmol) was dissolved in THF (5 mL). To this solution was added a slurry of indium trichloride (0.3103 g, 1.403 mmol) in THF (10 mL). The mixture was stirred at room temperature for 17 h and then filtered through glass fibre filter paper. The clear pale orange filtrate was concentrated in vacuo until a solid precipitate formed, which was then filtered in vacuo to obtain a pale yellow solid. The solid was recrystallized by dissolving in a minimum of THF and cooling in the freezer (−35 °C) until white crystals had formed, which were filtered in vacuo. The crystals were then stirred in ether for ~30 min and filtered yielding complex 12 as a white powder, which was dried under vacuum several hours to remove residual solvents (0.34 g, 43 %). \textsuperscript{1}H NMR (600 MHz, CD\textsubscript{2}Cl\textsubscript{2}, 25 °C): δ 7.29 (1H, d, \textit{J}_{HH} = 6 Hz, Ar-H), 6.83 (1H, d, \textit{J}_{HH} = 6 Hz, Ar-H), 4.25 (1H, d, \textit{J}_{HH} = 12 Hz, Ar-CH\textsubscript{2}-N), 3.78 (1H, d, \textit{J}_{HH} = 12 Hz, Ar-CH\textsubscript{2}-N), 2.80 (1H, m, CHN), 2.78 (3H, s, NCH\textsubscript{3}), 2.73 (1H, m, CHN), 2.64 (3H, s, NCH\textsubscript{3}), 2.20 (4H, m, DACH + NCH\textsubscript{3}), 2.13 (1H, m, DACH), 1.92 (2H, m, DACH), 1.43 (2H, m, DACH), 1.42 (9H, s, C(CH\textsubscript{3})\textsubscript{3}), 1.27 (9H, s, C(CH\textsubscript{3})\textsubscript{3}), 1.24 (2H, m, DACH). \textsuperscript{13}C \{\textsuperscript{1}H\} NMR (151 MHz, CD\textsubscript{2}Cl\textsubscript{2}, 25 °C): δ 160.73, 139.57, 139.13, 125.83, 125.26, 120.90, 63.31, 62.72, 62.42, 45.24, 39.37, 38.53, 35.50, 34.45, 31.99, 30.09, 24.84, 24.78, 23.44, 23.11. Anal. Calc. for C\textsubscript{24}H\textsubscript{41}Cl\textsubscript{2}InN\textsubscript{2}O: C, 51.54; H, 7.39; N, 5.01. Found: C, 51.88; H, 7.69; N, 5.00.

**Synthesis of complex 13**

To a solution of H(L\textsubscript{8}) (L-\textbf{8}) (0.5057 g, 1.650 mmol) in toluene (5 mL) was added a slurry of potassium tert-butoxide (0.1850 g, 1.649 mmol) in toluene (10 mL). The solution was stirred at room temperature for 22 h then pumped to dryness in vacuo yielding the potassium salt as a yellow powder. This solid was stirred in hexane, filtered and dried under vacuum to yield the purified potassium salt as a pale off-white solid (0.4779 g). The salt (0.4779 g, 1.387 mmol) was dissolved in THF (5 mL) and a slurry of indium trichloride (0.3067 g, 1.387 mmol) in THF (10
mL) was added. The solution was stirred at room temperature for 20 h, then filtered through glass fiber filter paper. The crude mixture was concentrated \textit{in vacuo} until 1-2 mL of THF remained, then ether (5 mL) was added, causing the precipitation of a white solid. The solution was stirred for approximately 1 h then it was filtered on a glass frit yielding the purified product as a white solid (0.50 g, 73 %). \textsuperscript{1}H NMR (600 MHz, CDCl\textsubscript{3}, 25 °C): δ 7.26 (1H, d, \textit{J} \textsubscript{HH} = 2 Hz, Ar-\textit{H}), 6.79 (1H, d, \textit{J} \textsubscript{HH} = 2 Hz, Ar-\textit{H}), 4.78 (1H, m, Ar-\textit{CH}\textsubscript{2}-N), 3.86 (1H, m, Ar-\textit{CH}\textsubscript{2}-N), 3.51 (1H, m, \textit{N}H), 3.22 (1H, m, NCH\textsubscript{2}CH\textsubscript{2}N), 3.04 (1H, m, NCH\textsubscript{2}CH\textsubscript{2}N), 2.97 (1H, m, NCH\textsubscript{2}CH\textsubscript{2}N), 2.69 (3H, s, N(CH\textsubscript{3})\textsubscript{2}), 2.54 (1H, m, NCH\textsubscript{2}CH\textsubscript{2}N), 2.40 (3H, s, N(CH\textsubscript{3})\textsubscript{2}), 1.27 (9H, s, C(CH\textsubscript{3})\textsubscript{3}), 1.46 (9H, s, C(CH\textsubscript{3})\textsubscript{3}). \textsuperscript{13}C\{\textsuperscript{1}H\} NMR (151 MHz, CD\textsubscript{2}Cl\textsubscript{2}, 25 °C): δ 161.65, 138.95, 137.65, 125.43, 124.61, 119.65, 57.13, 53.82, 47.68, 45.97, 41.84, 35.32, 33.95, 31.73, 30.05. Anal. Calc. for C\textsubscript{19}H\textsubscript{33}Cl\textsubscript{2}InN\textsubscript{2}O: C, 46.46; H, 6.77; N, 5.70. Found: C, 43.08; H, 6.21; N, 5.19.

\textbf{Synthesis of complex 15}

To a solution of complex 12 (0.2179 g, 0.3896 mmol) in THF (5 mL) was added a suspension of sodium ethoxide (0.0260 g, 0.382 mmol) in THF (5 mL). The mixture was stirred for 19 h, after which the solution had turned cloudy off-white. The solution was filtered through glass fibre filter paper, removing a significant amount of white precipitate. The clear, off-white filtrate was concentrated \textit{in vacuo} until a white precipitate started to form, after which a few millilitres of ether were added. The solution was stirred for several minutes then filtered yielding a portion of the crude product as a white powder. The precipitate from the crude reaction mixture was dissolved in CH\textsubscript{2}Cl\textsubscript{2} and filtered, then this solution was combined with the solid obtained from THF-ether and pumped to dryness yielding a white powder. The combined solid was stirred in ether for ~30 minutes, then filtered \textit{in vacuo} to yield the pure product as a white powder, which was dried under vacuum for several hours to remove residual solvents (0.1531 g, 70 %).
Colourless needles suitable for x-ray analysis were grown from a saturated acetonitrile solution at room temperature. $^1$H NMR (600 MHz, CDCl$_3$, 25 °C): δ 7.24 (1H, d, Ar-H), 6.75 (1H, d, Ar-H), 4.75 (1H, d, $^2$J$_{HH}$ = 12 Hz, Ar-CH$_2$-N), 4.41 (1H, m, OCH$_2$CH$_3$), 3.38 (1H, d, $^2$J$_{HH}$ = 12 Hz, Ar-CH$_2$-N), 3.03 (3H, s, NCH$_3$), 2.76 (1H, m, CH$_2$N), 2.73 (3H, s, NCH$_3$), 2.69 (1H, m, CH$_2$N), 2.24 (3H, s, NCH$_3$), 1.96 (2H, m, DACH), 1.79 (2H, m, DACH), 1.45 (9H, s, C(CH$_3$)$_3$), 1.33 (1H, m, DACH), 1.27 (9H, s, C(CH$_3$)$_3$), 1.25 (1.5H, m, OCH$_2$CH$_3$), 1.18 (2H, m, DACH), 0.96 (1H, m, DACH). $^{13}$C$^1$H) NMR (151 MHz, CDCl$_3$, 25 °C): δ 161.55, 138.42, 136.16, 125.41, 124.27, 119.03, 62.99, 62.15, 61.55, 55.88, 44.65, 42.36, 38.43, 35.18, 33.86, 31.80, 29.97, 24.48, 24.00, 22.25, 21.69, 19.78. Anal. Calc. for C$_{50}$H$_{87}$Cl$_3$In$_2$N$_4$O$_3$: C, 53.23; H, 7.77; N, 4.97. Found: C, 53.54; H, 7.99; N, 5.00.

Synthesis of complex 16

To a solution of complex 13 (0.2052 g, 0.4178 mmol) in toluene (5 mL) was added a suspension of sodium ethoxide (0.0275 g, 0.4041 mmol) in toluene (10 mL). The solution was stirred at room temperature for 18 hours, then it was filtered through glass fiber filter paper. The crude solution was concentrated in vacuo until crystals of the product just began to form (1-2 mL). Hexane was added, causing the precipitation of a portion of the product as a white solid. The solution was again concentrated to 1-2 mL volume, then more hexane was added. This process was repeated one more time, then the whole solution was left in the freezer (−35 °C) for 30 minutes. The solution was filtered through a glass frit and the purified product was collected and dried under vacuum yielding a white solid. The solid was dissolved in ether, stirred for 30 minutes, then dried under vacuum to yield the final product as a white powder (0.0555 g, 27%). $^1$H NMR (600 MHz, CDCl$_3$, 25 °C): δ 7.25 (1H, d, $^4$J$_{HH}$ = 2 Hz, Ar-H), 6.77 (1H, d, $^4$J$_{HH}$ = 2 Hz, Ar-H), 5.04 (1H, d, $^2$J$_{HH}$ = 12 Hz, Ar-CH$_2$-N), 4.44 (1H, m, OCH$_2$CH$_3$), 3.63 (1H, d, $^2$J$_{HH}$ = 12
Hz, Ar-CH$_2$-N), 3.44 (1H, m, NH), 3.15 (1H, m, NCH$_2$CH$_2$N), 2.92 (2H, m, NCH$_2$CH$_2$N), 2.61 (3H, s, N(CH$_3$)$_2$), 2.33 (1H, m, NCH$_2$CH$_2$N), 2.25 (3H, s, N(CH$_3$)$_2$), 1.44 (9H, s, C(CH$_3$)$_3$), 1.31 (1.5 H, t, $^3$$J_{HH}$ = 9 Hz, OCH$_2$CH$_3$), 1.27 (9H, s, C(CH$_3$)$_3$). $^{13}$C {$^1$H} NMR (151 MHz, CDCl$_3$, 25 °C): δ 162.37, 138.80, 136.70, 125.79, 124.33, 119.10, 62.81, 57.13, 54.31, 47.49, 45.95, 41.60, 35.37, 33.90, 31.78, 29.94, 19.73. Anal. Calc. for C$_{40}$H$_{71}$Cl$_3$In$_2$N$_4$O$_3$: C, 48.43; H, 7.21; N, 5.65.

Found: C, 48.50; H, 7.11; N, 5.49.

**Representative polymerization of rac-LA**

To a solution of catalyst (e.g. for 200 eq. LA: 0.0046 mmol) in CH$_2$Cl$_2$ (1 mL) was added rac-LA (0.133 g, 0.923 mmol) in CH$_2$Cl$_2$ (1 mL). The mixture was allowed to stir at room temperature until over 90% conversion was reached as determined by $^1$H NMR spectroscopy. The solvent was then removed *in vacuo* and a small portion of the crude polymer was tested for tacticity via $^1$H {$^1$H} NMR spectroscopy (600 MHz, 25 °C, CDCl$_3$). The remaining crude polymer was redissolved in a minimum of dichloromethane (1-2 mL). Methanol (2-5 mL) was then added to this solution causing precipitation of the polymer. The solution was allowed to settle and the supernatant solution was removed. This process was repeated 2 more times, and the resulting polymer was dried under vacuum. The polymer was tested for the presence of remaining catalyst or monomer using $^1$H NMR spectroscopy before being tested for molecular weight and PDI using GPC in THF.

**In situ observation of the polymerization of rac-LA by catalyst 15**

A stock solution of catalyst 15 (0.0110 g, 0.00975 mmol) in CD$_2$Cl$_2$ was made in a 2 mL volumetric flask and 0.5 mL of this solution was syringed into two J-Young NMR tubes. A stock solution of rac-LA (0.2732 g, 1.896 mmol) and internal standard 1,3,5-trimethoxybenzene (0.0206 g, 0.122 mmol) was made in a 2 mL volumetric flask in CD$_2$Cl$_2$ and 0.5 mL of this
solution was syringed into the two J-Young tubes with the catalyst solution. The tubes were sealed and the solutions mixed. The reactions were then followed by $^1$H NMR spectroscopy (300 MHz, 25 °C) over the next 7 days until they reached over 97% conversion.

**In situ observations of the polymerization of rac-LA by catalysts 11 and 16**

A stock solution of *rac*-LA (970 mM) and an internal standard 1,3,5-trimethoxybenzene (60 mM) was made using CD$_2$Cl$_2$ and 0.5 mL of this solution was syringed into a J-Young NMR tube and frozen using a liquid N$_2$ cold well. A buffer layer of CD$_2$Cl$_2$ (0.25 mL) was syringed into the tube and frozen. A stock solution of the desired catalyst (10 mM) was made using CD$_2$Cl$_2$ and 0.25 mL of this solution was syringed into the tube and frozen. The tube was quickly evacuated and sealed while frozen to remove N$_2$ gas from the headspace of the tube. The tube was quickly warmed to room temperature before being inserted into the NMR spectrometer. The reaction was followed to over 90% conversion by $^1$H NMR spectroscopy (400 MHz, 25 °C).

**Determination of the $k_p$ value for the polymerization of rac-LA by catalyst 17**

A stock solution of *rac*-LA (0.6471 g, 4.490 mmol) and internal standard 1,3,5-trimethoxybenzene (0.0555 g, 0.330 mmol) in CDCl$_3$ was made in a 5 mL volumetric flask and 0.5 mL of this solution was syringed into 5 J-Young NMR tubes (samples 1-5) and frozen with a liquid N$_2$ cold well. Next a buffer layer of CDCl$_3$ was added to the tubes and frozen, with 0.25 mL, 0.18 mL, 0.12 mL, 0.10 mL and 0.08 mL used for samples 1-5, respectively. A stock solution of catalyst 17 (0.0220 g, 0.0178 mmol) in CDCl$_3$ was made in a 2 mL volumetric flask and 0.25 mL, 0.32 mL, 0.38 mL, 0.40 mL and 0.42 mL of this solution was syringed into samples 1-5, respectively, and frozen with the liquid N$_2$ cold well. The tubes were then quickly evacuated and sealed while frozen to remove N$_2$ from the headspace of the tube. The tubes were
quickly warmed to room temperature before being inserted into the NMR spectrometer. The reactions were followed to over 97% conversion by $^1$H NMR spectroscopy (400 MHz, 25 °C).

**DFT calculations**

Density Functional Theory (DFT) calculations were performed using the ORCA computational software package.$^{133}$ A B3LYP functional and the available Def2-SV(P) basis set were used for all atoms and geometric optimizations were carried out in the gas-phase.$^{134-136}$ Initial coordinates were obtained from the X-ray structures of the compounds. Increased integration grids (GRID4), slow convergence (SlowConv) and tight SCF convergence (TightSCF) criteria were also used in the optimization. Optimized coordinates are reported in our publication’s supporting information.$^2$
Chapter 4: Effects of varying phenolate substituents

4.1 Introduction

As discussed in Chapter 1, several groups have probed the influence of phenolate substituents on the polymerization of lactide by Sn, Mg, Zn and Ca complexes84-93 bearing related iminophenolate tridentate ligands. Similar effects have been studied in detail in catalysts bearing related tetradeutate Salen type ligands (Figure 4.1). For example, Gibson et al. have shown the non-intuitive effects of the phenolate substituents on the lactide polymerization activity and selectivity of a large family of aluminum Salen catalysts.137 An increase in activity was seen in moving from less flexible (ethylene) to more flexible (propylene) backbones, as well as by using less bulky substituents on the ortho positions of the phenolate rings (H vs. tert-butyl). Electron-withdrawing groups (Cl) on the phenolate rings also increased the rates of polymerization in complexes with flexible backbones, however the same trend was not found in related complexes made with rigid aryl based backbones (naphthyl, biphenyl and others), as chlorine substituents led to a decrease in activity.

The trends seen in the selectivity of these catalysts was similarly complex. Complexes with flexible ethylene or propylene backbones showed higher isoselectivity (Pm ~ 0.83) for bulkier ortho phenolate substituents (tert-butyl) compared to the unsubstituted derivatives (Pm ~ 0.69), however the chlorine substituents led to a decrease in selectivity (Pm ~ 0.60). Again, these effects were not translated to derivatives with rigid aryl backbones. For example, in complexes with biphenyl backbones the unsubstituted derivatives showed the highest isoselectivities (Pm = 0.84 for H vs. 0.63 for t-butyl substituents) and surprisingly the electron-withdrawing chlorine substituents led to heterotactically biased polymers (Pm = 0.37).
Figure 4.1. Examples of Al Salen catalysts with various backbones and phenolate substituents reported by Gibson et al.\textsuperscript{137}

These systems highlight the different effects of the steric and/or electronic properties of the ligands on the polymerization rate and selectivity of the resulting catalysts. However, as shown above and in Chapter 1 these effects are generally metal or ligand-dependent and cannot be generalized for different catalyst systems.

The challenges we encountered in producing selective and active indium catalysts for the polymerization of lactide with modifications to the terminal amine (Chapter 2) or central amine donors (Chapter 3) of our tridentate ligand system prompted us to explore the role of the phenolate substituents on the activity and selectivity of indium complexes in the polymerization of lactide. The synthesis of a family of indium ethoxide catalysts bearing tridentate ligands with phenolate substituents with varying steric and/or electronic properties was therefore undertaken. We were particularly interested in discerning not only the influence of the phenolate substituents but also the influence of the ligand chirality on the polymerization behavior of these indium complexes. This chapter will detail the results of these studies and outline some interesting and unique structural features we discovered in indium dichloride complexes made with this ligand family, in addition to the activity and selectivity of related indium alkoxide complexes in the polymerization of rac-LA.
4.2 Results and discussion

4.2.1 Synthesis and characterization of proligands

A family of racemic and enantiopure diaminophenolate proligands with triphenylsilyl (SiPh\(_3\)), adamantyl (Ad) and cumyl (Cm = C(CH\(_3\))\(_3\)Ph) \textit{ortho}-phenolate substituents was prepared according to previously published procedures (Scheme 4.1).\(^{96-98}\) Condensation of (±) or (R,R)- \(N,N\)-dimethyl-\textit{trans}-1,2-diaminocyclohexane with the appropriate salicylaldehyde followed by gentle reduction with NaCNBH\(_3\) yields proligands (±)- and (R,R)- L-9 (R\(_1\) = Me, R\(_2\) = SiPh\(_3\)), L-10 (R\(_1\) = ’Bu, R\(_2\) = Ad) and L-11 (R\(_1\) = R\(_2\) = Cm). The corresponding salicylaldehyde starting materials were prepared according to published literature procedures.\(^{111,138-139}\)

![Chemical structure](image)

**Scheme 4.1.** Synthesis of racemic and enatiopure diaminophenolate proligands (±)- and (R,R)-H(N\(_{Me2}N_HO\_R\_2\)) (L-9-11) with various phenolate substituents.

These proligands are both polar and highly soluble in most organic solvents, complicating the purification process and occasionally resulting in low yields. Purification can
be achieved in most cases by precipitation and recrystallization of the compounds from acetonitrile or methanol, with the exception of \((R,R)-H(N_{Me2}N_HO_{Cm})\) (L-11), which can only be obtained as an oil.

The \(^1\)H NMR spectra of (±)- and \((R,R)-H(N_{Me2}N_HO_{R2})\) (L-9-11) analogues are identical (see Appendix C, Figures C.1-3 for the racemic compounds) and show the diagnostic methylene protons of the ligand backbone as two diastereotopic doublets in the 3.8 – 4.1 ppm range for L-9 and L-10. Interestingly, in L-11 these protons appear a singlet at 3.81 ppm, although broadness of this peak suggests that coupling may be present but is not resolved under the conditions used.

### 4.2.2 Synthesis and characterization of indium dichloride complexes

Deprotonation of proligands (±)- or \((R,R)-L-9-11\) with KOtBu, followed by salt metathesis with InCl\(_3\), affords the dichloride intermediates (±)- or \((R,R)-(N_{Me2}N_HO_{R2})InCl_2\) \((R_2 = SiPh_3, 19; Ad, 20; Cm, 21) in isolated yields of 30 – 88 % (Scheme 4.2).

![Scheme 4.2. Synthesis of indium dichloride complexes (±)- and \((R,R)-19-21\) with various phenolate substituents.](image-url)
As for the proligands, the purification of these dichloride analogues proved to be challenging. Racemic complex 19 was isolated as a mixture of the desired complex and unidentified by-products, and (R,R)-19 was isolated as a similar mixture of products. Precipitation from acetonitrile allowed for both complexes to be isolated reproducibly with approximately 90% purity as estimated by \(^1\)H NMR spectroscopy. Complexes (±)-20 and (±)-21 could be reproducibly synthesized with only minor impurities, compared to those present in the synthesis of complexes (±)- and (R,R)-19. Purification by precipitation allowed for these complexes to be isolated in over 90% purity by \(^1\)H NMR spectroscopy. The synthesis and purification of (R,R)-20 proved to be irreproducible, with purification procedures needing to be optimized for each new batch of complex. Small batches of pure material (> 95% pure by \(^1\)H NMR spectroscopy) could be isolated for further reactions in some cases (see experimental section for an example of the best purification procedure found for this complex). Complex (R,R)-21 was isolated as a complex mixture of products and could not be purified on a large scale due to the high solubility of the mixture. However, a small amount of pure complex was isolated via precipitation from a saturated hexane solution and used for characterization of this complex by NMR spectroscopy (see below). Due to the variable purity of these complexes elemental analysis of some of these analogues was not pursued or was outside acceptable error limits (see experimental section).

The formation of multiple species in the synthesis of these dichloride complexes is similar to the related complexes discussed in Chapter 2, and may be a consequence of aggregation to form ill-defined species and/or the formation of multiple, discrete species in solution, such as different diastereomers or monomers/dimers. This was supported by the solid-
state molecular structures of single crystals isolated from saturated solutions of complexes (±)-19 and (±)-20 (see experimental for details), which confirmed aggregation of these complexes in the solid-state to form discrete dimeric species (Figure 4.2). Single crystals of (±)-21 and the (R,R) indium dichloride analogues could not obtained due to their high solubility.

Complexes (±)-19 and (±)-20 crystallize as heterochiral (RR/SS) dimers with distorted octahedral indium centers bridged by chloride ligands. The two complexes are nearly isostructural, with similar bond lengths and angles (Figure 4.2 and Table 4.1; see Appendix C, Table C.1 for select crystallographic parameters). The orientation of the NNO framework is rotated 180° between the two sides of the dimer in these complexes. The formation of heterochiral dimers with a “trans” ligand orientation between the two sides of the dimer is consistent with previously reported dimeric indium complexes within this ligand family that have identical bridging ligands.97-98 However, the formation of dimeric indium dichloride complexes in the solid-state is in contrast to previously reported indium dichloride analogues with ortho-tert-butyl and para-tert-butyl or methyl substituents such as the parent analogue (NMe2NHoBuMe)InCl2 (2')98 and complexes (NR1R2NHoBu)InCl2 (4-6) described in Chapter 2, which are mononuclear in the solid-state.
Figure 4.2. Solid-state molecular structures of complexes (RR/SS)-19 (top) and (RR/SS)-20 (bottom). Ellipsoids are depicted at 50% probability and H atoms and solvent are removed for clarity.
Table 4.1. Select bond lengths and angles for complexes (RR/SS)-19 and (RR/SS)-20.

<table>
<thead>
<tr>
<th>Bond lengths (Å)</th>
<th>Complex (RR/SS)-19</th>
<th>Complex (RR/SS)-20</th>
</tr>
</thead>
<tbody>
<tr>
<td>In1-N1</td>
<td>2.2747(12)</td>
<td>2.2623(13)</td>
</tr>
<tr>
<td>In1-N2</td>
<td>2.3152(12)</td>
<td>2.3281(11)</td>
</tr>
<tr>
<td>In1-Cl1</td>
<td>2.5788(4)</td>
<td>2.5622(4)</td>
</tr>
<tr>
<td>In1-Cl1(\dagger)</td>
<td>2.6160(4)</td>
<td>2.6686(4)</td>
</tr>
<tr>
<td>In1-Cl2</td>
<td>2.3938(4)</td>
<td>2.4058(4)</td>
</tr>
<tr>
<td>In1-O1</td>
<td>2.0586(10)</td>
<td>2.0833(10)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bond angles (°)</th>
<th>Complex (RR/SS)-19</th>
<th>Complex (RR/SS)-20</th>
</tr>
</thead>
<tbody>
<tr>
<td>In1-Cl1-In1(\dagger)</td>
<td>94.901(12)</td>
<td>99.365(13)</td>
</tr>
<tr>
<td>O1-In1-N1</td>
<td>88.02(4)</td>
<td>88.31(4)</td>
</tr>
<tr>
<td>O1-In1-N2</td>
<td>98.88(4)</td>
<td>104.24(4)</td>
</tr>
<tr>
<td>O1-In1-Cl1</td>
<td>168.19(3)</td>
<td>168.54(3)</td>
</tr>
<tr>
<td>O1-In1-Cl1(\dagger)</td>
<td>86.09(3)</td>
<td>89.54(3)</td>
</tr>
<tr>
<td>O1-In1-Cl2</td>
<td>98.16(3)</td>
<td>97.05(3)</td>
</tr>
<tr>
<td>N1-In1-N2</td>
<td>78.12(4)</td>
<td>77.38(4)</td>
</tr>
<tr>
<td>N1-In1-Cl1</td>
<td>83.92(3)</td>
<td>85.29(3)</td>
</tr>
<tr>
<td>N1-In1-Cl1(\dagger)</td>
<td>88.65(3)</td>
<td>85.29(3)</td>
</tr>
<tr>
<td>N1-In1-Cl2</td>
<td>173.76(3)</td>
<td>174.36(3)</td>
</tr>
<tr>
<td>N2-In1-Cl1</td>
<td>87.92(3)</td>
<td>83.63(3)</td>
</tr>
<tr>
<td>N2-In1-Cl1(\dagger)</td>
<td>165.63(3)</td>
<td>158.55(3)</td>
</tr>
<tr>
<td>N2-In1-Cl2</td>
<td>99.99(3)</td>
<td>99.50(3)</td>
</tr>
<tr>
<td>Cl1-In1-Cl1(\dagger)</td>
<td>85.099(12)</td>
<td>80.636(13)</td>
</tr>
</tbody>
</table>

Interestingly, the \(^1\)H NMR spectra of complexes (±)- and (R,R)- 19-21 are not identical, and this suggests that aggregation may also be occurring in solution to form different structures from the racemic and enantiopure complexes. The methylene protons of the ligand backbone appear as two multiplets at significantly different shifts in the racemic analogues as compared to their enantiopure counterparts (Figure 4.3). In addition, there are small differences in the shifts of the aromatic protons around 7 ppm and the N-CH\(_3\) protons around 2.3 ppm (see Appendix C, Figures C.4-9 for full spectra). Surprisingly, this disparity is not unique to these analogues, as closer inspection of the \(^1\)H NMR spectra of the parent complexes, (±)- and (R,R)-(N\(_{Me2}N_{H}O_{Bu}\))InCl\(_2\) (2), also reveals similar small differences that were not commented on in prior reports (Figure 4.5).
There is a range in the shift differences between the two methylene protons in each set of analogues, with the \((R,R)\) complexes showing a smaller difference in shift between the two methylene protons than their racemic counterparts. This suggests a difference in the environment around these protons in each complex as might be expected for different dimeric structures for the racemic and enantiopure complexes (see below for details). There is also a stark contrast between the tert-butyl (2), adamantyl (20) and cumyl (21) substituted complexes, which have similar peak multiplicities and differences in shift of the methylene protons, and the silyl substituted complexes (19), which have different peak multiplicities and a much larger difference in shift between the two methylene protons. In fact, the peak multiplicities and shift differences in the silyl complexes are very similar to related dinuclear ethoxide complexes synthesized using this ligand type, such as \(\left[[\text{NMe}_2\text{NHOBu}]\text{InCl}\right]_2(\mu-\text{Cl})(\mu-\text{OEt})\) (1), which are dinuclear in solution.\(^98\)
This suggests that the silyl substituted complexes may have a dinuclear structure in solution and that the other analogues may therefore remain mononuclear in solution, however this would not explain the disparity between the enantiopure and racemic complexes of the same ligand analogues.

We hypothesized that the differences in the solution state $^1$H NMR spectra of racemic and enantiopure dichloride analogues, as well as the contrast between the parent tert-butyl, adamantyl and cumyl complexes and the silyl complexes may be due to differences in their nuclearity in solution. We have previously observed that heterochiral (RR/SS) dimers for dinuclear complexes with the same bridging ligand, such as the bis-ethoxide bridged $[(NMe_2N_HO_tBu)InCl(\mu-OEt)]_2$, are more thermodynamically stable.$^{98}$ For example, when such symmetrically bridged species are synthesized from racemic ligand, heterochiral (RR/SS) dimers are seen exclusively in the solid-state. In fact, 1:1 mixtures of the enantiopure (RR/RR) and (SS/SS) $[(NMe_2N_HO_tBu)InCl(\mu-OEt)]_2$ dimers, formed from enantiopure ligands, will reorganize in solution to form the heterochiral species. In contrast, for the asymmetrically bridged $[(NMe_2N_HO_tBu)InCl]_2(\mu-Cl)(\mu-OEt)$ (1) only homochiral dimers are observed in solution and the solid-state. Assuming a similar stability of heterochiral dimers in these dichloride complexes, we can hypothesize that the racemic complexes will form heterochiral dimers if they are dinuclear in solution, similar to their solid-state structures. The enantiopure analogues may either form homochiral dimers, or due to thermodynamic instability, remain mononuclear in solution. Either situation could lead to the disparity seen in the NMR spectra of the racemic and enantiopure dichloride complexes.

In order to confirm the nuclearity of these complexes in solution we carried out Pulsed Field Gradient Spin Echo (PGSE) NMR experiments in order to determine the diffusion
coefficients ($D_t$) of these species in solution (see Figure 4.4 and Table 4.2). Experiments were conducted with the racemic and enantiopure silyl substituted dichloride complexes, (±)- and ($R,R$)- 19, as well as the corresponding proligand (±)-L-9 and the dinuclear ethoxide complex (±)-[(NMe2NHOSiPh3)InCl]2(µ-Cl)(µ-OEt) (22) for comparison (see the next section for a discussion of the synthesis of complex 22). The diffusion coefficients of the adamantyl substituted proligand (±)-L-10 and dichloride complex (±)-20 were also determined for comparison.

**Figure 4.4.** Plot of ln(I/I₀) vs. $\gamma^2 \delta^2 G^2 [\Delta-(\delta/3)] \times 10^{10}$ (m$^{-2}$ s) from PGSE NMR experiments (400 MHz, CD₂Cl₂, 25 °C). I = intensity of the observed spin-echo, I₀ = intensity of the spin-echo in the absence of gradients, G = varied gradient strength, $\gamma$ = gyromagnetic ratio (2.675 x 10⁸ rad s$^{-1}$ T$^{-1}$), $\delta$ = length of the gradient pulse, $\Delta$ = delay between the midpoints of the gradients. The hydrodynamic radius ($r_H$) of each compound was calculated by using the slopes ($D_t$) of the linear fits to this data.
Table 4.2. Diffusion coefficients and radii for select compounds determined by PGSE NMR\textsuperscript{a} experiments.

<table>
<thead>
<tr>
<th>Compound</th>
<th>$D_t \times 10^{10}$ (m$^2$ s$^{-1}$)\textsuperscript{b}</th>
<th>$r_H$ (Å)\textsuperscript{c}</th>
<th>$r_{x-ray}$ (Å)\textsuperscript{d}</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\pm$-H(NMe$_2$N$<em>2$O$</em>{tBu}$) (L-2)\textsuperscript{98}</td>
<td>12.0</td>
<td>5.2</td>
<td>–</td>
</tr>
<tr>
<td>$\pm$-(NMe$_2$N$<em>2$O$</em>{tBu}$)InCl$_2$ (2)\textsuperscript{98}</td>
<td>10.4</td>
<td>5.9</td>
<td>–</td>
</tr>
<tr>
<td>$\pm$-[NMe$_2$N$<em>2$O$</em>{tBu}$]InCl]$_2$(μ-Cl)(μ-OEt) (1)\textsuperscript{98}</td>
<td>7.8</td>
<td>7.5</td>
<td>7.3</td>
</tr>
<tr>
<td>$\pm$-H(NMe$_2$N$<em>2$O$</em>{SiPh_3}$) (L-9)</td>
<td>9.1</td>
<td>6.4</td>
<td>–</td>
</tr>
<tr>
<td>$\pm$-(NMe$_2$N$<em>2$O$</em>{SiPh_3}$)InCl$_2$ (19)</td>
<td>7.1</td>
<td>7.9</td>
<td>5.8</td>
</tr>
<tr>
<td>($R,R$)-(NMe$_2$N$<em>2$O$</em>{SiPh_3}$)InCl$_2$ (19)</td>
<td>7.0</td>
<td>8.1</td>
<td>–</td>
</tr>
<tr>
<td>$\pm$-[NMe$_2$N$<em>2$O$</em>{SiPh_3}$]InCl]$_2$(μ-Cl)(μ-OEt) (22)</td>
<td>6.5</td>
<td>8.7</td>
<td>–</td>
</tr>
<tr>
<td>$\pm$-H(NMe$_2$N$<em>2$O$</em>{Ad}$) (L-10)</td>
<td>10.2</td>
<td>6.0</td>
<td>–</td>
</tr>
<tr>
<td>$\pm$-(NMe$_2$N$<em>2$O$</em>{Ad}$)InCl$_2$ (20)</td>
<td>9.1</td>
<td>6.5</td>
<td>5.0</td>
</tr>
</tbody>
</table>

\textsuperscript{a}[Compound] = 4.5 mM in 1 mL of a 0.94 mM CD$_2$Cl$_2$ solution of tetrakis(trimethylsilyl)silane (TMSS) as an internal standard. \textsuperscript{b} Calculated from the slopes of the linear portions of the plots shown in Figure 4.4. \textsuperscript{c} Calculated from the observed $D_t$ values and the modified Stokes-Einstein equation according to the literature.\textsuperscript{141} \textsuperscript{d} Calculated from the volume (V) and the number of molecules (Z) in the unit cell of the X-ray structure assuming a spherical molecular shape, $r_{x-ray} = \sqrt[3]{3V/4\pi Z}$. 

We have previously published the diffusion coefficients of the parent tert-butyl substituted proligand L-2, dichloride complex $\pm$-(NMe$_2$N$_2$O$_{tBu}$)InCl$_2$ (2) and ethoxide complex $\pm$-[NMe$_2$N$_2$O$_{tBu}$]InCl]$_2$(μ-Cl)(μ-OEt) (1) (Table 4.2).\textsuperscript{98} In this case the diffusion coefficient of the dichloride complex is 13% smaller than the corresponding proligand, however there is a larger decrease (25%) between the diffusion coefficients of the dichloride and ethoxide complexes. A decrease of ~20% has been reported in the literature, for a related bis-phenolate amine zinc complex, as indicative of a switch from monomer to dimer in solution.\textsuperscript{140} This suggested to us that our dichloride complex is mononuclear in solution (as is seen in the solid-state), and that the ethoxide complex remains dinuclear in solution.
The diffusion coefficients for the silyl substituted proligand (±)-L-9 and complexes (±)- and (R,R)- 19 and (±)-22 are 9.1, 7.1, 7.0 and 6.5 ($\times 10^{-10}$ m$^2$ s$^{-1}$) respectively (Table 4.2). Here there is a 22% decrease in the diffusion coefficient in moving from the proligand to the dichloride complexes, almost twice the difference seen for the parent proligand and dichloride complex. Notably the diffusion coefficient of the ethoxide complex is similar to the dichlorides, with an average decrease of only 8%. This suggests that in contrast to the parent system, both the dichlorides (±)- and (R,R)- 19 remain dinuclear in solution, consistent with their structure in the solid-state. As well, these results suggest that the silyl substituted ethoxide complex (±)-22 also remains dinuclear in solution, as was observed for the parent ethoxide complex (±)-1. This observation explains, in part, the differences seen in the solution $^1$H NMR spectra of the racemic and enantiopure dichlorides in this family, which should form different dinuclear complexes with (RR/SS) and (RR/RR) ligand stereochemistry, respectively.

The diffusion coefficients of the adamantyl substituted proligand (±)-L-10 and dichloride complex (±)-20 are 10.2 and 9.2 ($\times 10^{-10}$ m$^2$ s$^{-1}$) respectively, a decrease of only 10%. This observation, as well as the similarities in the shifts and peak multiplicities in the $^1$H NMR spectra of the parent tert-butyl substituted complex 2, which was shown to be mononuclear in solution, and the adamantyl (20) and cumyl (21) substituted complexes, suggests these analogues may also remain mononuclear in solution. However, further PGSE NMR experiments would need to be undertaken in order to confirm whether this is the case.

The hydrodynamic radii of the complexes were also calculated from the diffusion coefficients using published procedures and were compared to the radii of the complexes calculated from the X-ray crystal structures, where available (Table 4.2). The $r_H$ and $r_{\text{x-ray}}$ for the parent complex 1 are in good agreement, adding further support to the conclusion that this
complex remains dinuclear in solution. In contrast, complexes (±)-19 and (±)-20 have a difference between $r_{\text{H}}$ and $r_{\text{x-ray}}$ of over 20%. Reports in the literature suggest that discrepancies between these numbers are often seen in non-predictable ways. In particular, the situation is complicated because of the possibility of a monomer/dimer equilibrium in solution and hydrodynamic radii calculated for a such a fluctional system may have little physical meaning. It is difficult, however, to gain a full understanding of this system, and the solution state behavior of these complexes, without conducting further experiments to probe whether such an equilibrium exists. However, because these dichloride complexes are only intermediates towards the synthesis of active indium ethoxide complexes for the polymerization of lactide, a detailed study of this kind was not undertaken.

4.2.3 Synthesis and characterization of dinuclear indium ethoxide complexes

Salt metathesis of (±)- or ($R,R$)- $(N_{\text{Me2}}NHOR_2)\text{InCl}_2$ complexes with NaOEt yields the dinuclear indium ethoxide complexes (±)- or ($R,R$)- $[(N_{\text{Me2}}NHOR_2)\text{InCl}]_2(\mu-\text{Cl})(\mu-\text{OEt})$ ($R_2 = \text{SiPh}_3$, 22; Ad, 23; Cm, 24) in isolated yields of 42-58% (Scheme 4.3). Due to the insufficient purity of complex ($R,R$)-21 it was not utilized for this reaction.

![Scheme 4.3. Synthesis of dinuclear indium ethoxide complexes (±)- or ($R,R$)- $[(N_{\text{Me2}}NHOR_2)\text{InCl}]_2(\mu-\text{Cl})(\mu-\text{OEt})$ (22-24) with various phenolate substituents.](image-url)
As with the dichloride precursors, purification of these complexes proved to be difficult. Complexes (±)- and (R,R)-22 could be synthesized and purified reproducibly on a reasonable scale (see experimental for details), however the \(^1\)H NMR spectra of these complexes showed minor unknown impurity peaks, giving approximately 90 % purity by \(^1\)H NMR spectroscopy. As well, the elemental analysis did not match within acceptable error limits (>±0.4 %) for complex (±)-22. However, all attempts at further purification were unsuccessful. Complexes (±)-23 and 24 could be synthesized with only minor impurities and purified relatively easily by precipitation from ether and hexane (see experimental for details). Elemental analysis was within acceptable error limits (±0.4 %) and \(^1\)H NMR spectroscopy showed only trace impurity peaks (>95 % purity by \(^1\)H NMR spectroscopy). Because of the high solubility of complex (R,R)-23 purification was difficult and the complex was used without further purification, however the \(^1\)H NMR spectrum did show the presence of minor unknown impurity peaks and elemental analysis was not within acceptable error limits.

In contrast to the dichloride complexes, but in line with previously reported indium ethoxide complexes,\(^{98}\) the \(^1\)H NMR spectra of the resulting (±)- or (R,R)- [(NMe\(_2\)N\(_2\)O\(_2\)R\(_2\))InCl]\(_2\)(µ-Cl)(µ-OEt) complexes are identical, suggesting that any structural differences in the racemic and enantiopure dichloride complexes in solution are not translated to the resulting dinuclear ethoxide complexes. The \(^1\)H NMR spectra show the µ-OCH\(_2\)CH\(_3\) protons as two sets of multiplets at ~4 ppm (Figure 4.5). These are flanked by the diastereotopic –NCH\(_2\) protons of the ligand backbone which appear as doublets at ~5 and 3.5 ppm. A similar pattern of resonances is observed for other dimeric mono-alkoxide bridged complexes [(NMe\(_2\)N\(_2\)O\(_2\)Bu)InX]\(_2\)(µ-X)(µ-OEt) (X = Cl, Br, I).\(^{1-2,96-98}\) The multiplicity of the µ-OCH\(_2\)CH\(_3\) protons in complexes 22-24 is due to complex coupling between these protons and their
neighbours due to limited rotation of the ethoxide group, which is suggestive of the dimeric structure in solution as was observed with the previously reported complexes. As was discussed in the previous section, the silyl substituted complex (±)-22 was confirmed by PGSE NMR experiments to be dinuclear in solution.

![Figure 4.5. Methylene region of the $^1$H NMR spectra (600 MHz, CDCl$_3$, 25°C) of (a) (±)-22, (b) (±)-23 and (c) (±)-24.](image)

Single crystals of complex (±)-23 were obtained from a saturated solution of the complex in acetonitrile at room temperature and single crystals of (±)-24 were obtained from a saturated solution of the complex in toluene at room temperature. Their molecular structures were determined using single crystal X-ray crystallography (Figure 4.6 and Table 4.3; see Appendix C, Table C.1 for select crystallographic parameters). The solid-state structures are in agreement with previous compounds in the series with both complexes crystallizing as homochiral dimers, with the (SS/SS) dimer in the asymmetric unit of the crystal structure (Figure 4.6). The (RR/RR) dimer must also exist as the crystals were grown from a racemic mixture and crystallize in a centrosymmetric space group. There is also a cis relationship between the two ligands where both NNO frameworks are oriented towards the same side of the dimers. Both indium centers have distorted octahedral geometry and display similar bond lengths and angles (Table 4.3) around the central core of the molecules as compared to the parent system.
Figure 4.6. Solid-state molecular structures of complexes (±)-23 (top) and (±)-24 (bottom). Ellipsoids are depicted at 50% probability, and H atoms and solvent are removed for clarity.
Table 4.3. Select bond lengths and angles for complexes (±)-23 and (±)-24.

<table>
<thead>
<tr>
<th>Bond lengths (Å)</th>
<th>Complex (±)-23</th>
<th>Complex (±)-24</th>
</tr>
</thead>
<tbody>
<tr>
<td>In1-N1</td>
<td>2.2708(16)</td>
<td>2.2769(17)</td>
</tr>
<tr>
<td>In2-N3</td>
<td>2.2594(16)</td>
<td>2.2721(17)</td>
</tr>
<tr>
<td>In1-N2</td>
<td>2.3806(17)</td>
<td>2.3468(18)</td>
</tr>
<tr>
<td>In2-N4</td>
<td>2.3680(16)</td>
<td>2.3554(17)</td>
</tr>
<tr>
<td>In1-Cl1</td>
<td>2.6525(5)</td>
<td>2.7023(9)</td>
</tr>
<tr>
<td>In2-Cl1</td>
<td>2.6523(5)</td>
<td>2.6388(8)</td>
</tr>
<tr>
<td>In1-Cl2</td>
<td>2.4221(5)</td>
<td>2.4218(9)</td>
</tr>
<tr>
<td>In2-Cl3</td>
<td>2.4200(5)</td>
<td>2.4301(8)</td>
</tr>
<tr>
<td>In1-O1</td>
<td>2.0792(13)</td>
<td>2.0902(14)</td>
</tr>
<tr>
<td>In2-O3</td>
<td>2.0590(13)</td>
<td>2.0748(15)</td>
</tr>
<tr>
<td>In1-O2</td>
<td>2.1411(13)</td>
<td>2.1308(15)</td>
</tr>
<tr>
<td>In2-O2</td>
<td>2.1486(13)</td>
<td>2.1288(15)</td>
</tr>
<tr>
<td>In1-C11-In2</td>
<td>86.835(15)</td>
<td>86.076(19)</td>
</tr>
<tr>
<td>In1-O2-In2</td>
<td>116.42(6)</td>
<td>117.71(6)</td>
</tr>
<tr>
<td>O1-In1-N1</td>
<td>87.86(5)</td>
<td>87.26(6)</td>
</tr>
<tr>
<td>O3-In2-N3</td>
<td>87.88(6)</td>
<td>87.36(6)</td>
</tr>
<tr>
<td>O2-In1-N1</td>
<td>94.42(5)</td>
<td>92.41(6)</td>
</tr>
<tr>
<td>O2-In2-N3</td>
<td>91.83(5)</td>
<td>95.13(6)</td>
</tr>
<tr>
<td>O1-In1-N2</td>
<td>104.55(5)</td>
<td>102.35(6)</td>
</tr>
<tr>
<td>O3-In2-N4</td>
<td>99.38(6)</td>
<td>100.99(6)</td>
</tr>
<tr>
<td>O2-In1-N2</td>
<td>160.08(4)</td>
<td>159.88(6)</td>
</tr>
<tr>
<td>O2-In2-N4</td>
<td>160.64(5)</td>
<td>163.22(6)</td>
</tr>
<tr>
<td>N1-In1-N2</td>
<td>76.07(6)</td>
<td>76.57(6)</td>
</tr>
<tr>
<td>N3-In2-N4</td>
<td>76.60(6)</td>
<td>76.48(6)</td>
</tr>
<tr>
<td>N1-In1-Cl2</td>
<td>168.08(4)</td>
<td>169.87(4)</td>
</tr>
<tr>
<td>N3-In2-Cl3</td>
<td>169.65(4)</td>
<td>169.13(4)</td>
</tr>
<tr>
<td>N2-In1-Cl2</td>
<td>92.03(4)</td>
<td>94.42(4)</td>
</tr>
<tr>
<td>N4-In2-Cl3</td>
<td>93.42(4)</td>
<td>92.66(4)</td>
</tr>
<tr>
<td>O1-In1-Cl1</td>
<td>165.13(4)</td>
<td>165.17(4)</td>
</tr>
<tr>
<td>O3-In2-Cl1</td>
<td>168.94(4)</td>
<td>166.05(4)</td>
</tr>
<tr>
<td>O2-In1-Cl1</td>
<td>77.31(4)</td>
<td>76.73(4)</td>
</tr>
<tr>
<td>O2-In2-Cl1</td>
<td>77.19(4)</td>
<td>78.21(4)</td>
</tr>
</tbody>
</table>

4.2.4 Polymerization studies

The kinetics of the polymerization of rac-, L- and D- LA with the catalysts (±)- and (R,R)-22 and 23 and (±)-24 was studied via in situ $^1$H NMR spectroscopy (Table 4.4). The plots of ln([LA]) versus time show initiation periods followed by a linear portion from which $k_{obs}$ data was extracted (see Appendix C, Figures C.10-14).
### Table 4.4. Kinetic data for the polymerization of rac, L and D-LA by catalysts (±)- and (R,R)-22 and 23 and (±)-24.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Monomer</th>
<th>$k_{\text{obs}}$ (x $10^{-3}$ s$^{-1}$)$^b$</th>
<th>$k_{\text{rel}}$ ($k_L/k_D$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1$^{98}$</td>
<td>(±)-I</td>
<td>rac-LA</td>
<td>1.72</td>
<td>1</td>
</tr>
<tr>
<td>2$^{98}$</td>
<td>(±)-I</td>
<td>L-LA</td>
<td>2.98</td>
<td></td>
</tr>
<tr>
<td>3$^{98}$</td>
<td>(±)-I</td>
<td>D-LA</td>
<td>2.95</td>
<td></td>
</tr>
<tr>
<td>4$^{98}$</td>
<td>(R,R)-I</td>
<td>rac-LA</td>
<td>0.62 (0.21)$^c$</td>
<td></td>
</tr>
<tr>
<td>5$^{98}$</td>
<td>(R,R)-I</td>
<td>L-LA</td>
<td>3.4</td>
<td>14</td>
</tr>
<tr>
<td>6$^{98}$</td>
<td>(R,R)-I</td>
<td>D-LA</td>
<td>0.25</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>(±)-22</td>
<td>rac-LA</td>
<td>1.01</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>(±)-22</td>
<td>L-LA</td>
<td>1.06</td>
<td>1</td>
</tr>
<tr>
<td>9</td>
<td>(±)-22</td>
<td>D-LA</td>
<td>1.21</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>(R,R)-22</td>
<td>rac-LA</td>
<td>0.40</td>
<td>6</td>
</tr>
<tr>
<td>11</td>
<td>(R,R)-22</td>
<td>L-LA</td>
<td>1.48</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>(R,R)-22</td>
<td>D-LA</td>
<td>0.24</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>(±)-23</td>
<td>rac-LA</td>
<td>2.44</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>(±)-23</td>
<td>L-LA</td>
<td>3.42</td>
<td>1</td>
</tr>
<tr>
<td>15</td>
<td>(±)-23</td>
<td>D-LA</td>
<td>3.39</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>(R,R)-23</td>
<td>rac-LA</td>
<td>0.74</td>
<td>12</td>
</tr>
<tr>
<td>17</td>
<td>(R,R)-23</td>
<td>L-LA</td>
<td>3.37</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>(R,R)-23</td>
<td>D-LA</td>
<td>0.28</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>(±)-24</td>
<td>rac-LA</td>
<td>1.40</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>(±)-24</td>
<td>L-LA</td>
<td>1.66</td>
<td>1</td>
</tr>
<tr>
<td>21</td>
<td>(±)-24</td>
<td>D-LA</td>
<td>1.76</td>
<td></td>
</tr>
</tbody>
</table>

$^a$All polymerizations were carried out with 200 eq. LA and followed by in situ $^1$H NMR spectroscopy (400 MHz, CDCl$_3$, 25 °C) to over 90% conversion with [LA] = 0.48 M and [catalyst] = 2.4 mM and 1,3,5-trimethoxybenzene (0.03 M) used as an internal standard; $^b$Determined from the negative of the slope of the linear portion of the plots of ln([LA]) vs. time. $^c$This catalyst displays two linear regions in the plot of ln([LA]) vs. time, the first from 0% to 64% conversion and the second from 73% to 90% conversion ($k_{\text{obs}}$ in brackets).

The kinetic data for the racemic catalysts (±)-22-24 shows that there is no significant preference for one enantiomer of lactide over the other, as $k_{\text{obs}}$ values for rac, L- and D-LA are comparable, and the $k_L/k_D$ ($k_{\text{rel}}$) is approximately 1 for all three catalysts. This is not the case with (R,R)-22 and 23. These catalysts show a clear preference for L-LA, with the adamantyl catalyst (R,R)-23 showing the highest preference, with a $k_{\text{rel}}$ of 12. The kinetic behavior of this catalyst is...
similar to the parent system, \([(\text{NMe}_2\text{N}_\text{H}_\text{O}_\text{Bu})\text{InCl}]_2(\mu-\text{Cl})(\mu-\text{Et})\) (1), which has similar observed rate constants under the same conditions and a $k_{\text{rel}}$ for the (R,R) catalyst of 14. The silyl catalyst (R,R)-22 has a comparatively low $k_{\text{rel}}$ of only 6.

In following the polymerization by $^1\text{H}$ NMR spectroscopy it was possible to identify the presence of varying amounts of unreacted catalyst during the polymerization of rac-, L- and D-LA by catalysts 22-24 (see Figure 4.8 for examples with rac-LA). This is consistent with the parent system (Figure 4.8 d), where unreacted catalyst is also observed during the polymerization of rac-LA under similar conditions. The adamantyl catalyst (±)-23 shows a similar amount of unreacted catalyst to the parent system under these conditions, and both catalysts appear to have fully reacted as the conversion reaches 97 % (Figure 4.7). In contrast, catalysts (±)-22 and (±)-24 show a larger amount of unreacted catalyst during the polymerization, with a significant amount still left unreacted at 97 % conversion (Figure 4.8). This observation may explain the slightly lower $k_{\text{obs}}$ values of the racemic silyl and cumyl catalysts (Table 4.4 entries 7-9 and 19-21) compared with the adamantyl analogue (Table 4.4 entries 13-15). If the catalyst is not fully initiating for these two analogues under these conditions, then the amount of catalyst actually polymerizing LA is less than anticipated, and therefore one would expect the rates to be lower (i.e. less concentrated catalyst means slower rates for the same amount of LA). It is unclear from this data, however, whether this lack of full initiation is a consequence of the particular catalyst structure or whether it is related to the conditions under which the kinetic experiments are carried out. These experiments are set up in NMR tubes and monitored without stirring, which may have an effect on initiation due to the limited mixing of the reagents. Further studies would be needed to elucidate the source of this phenomenon.
Figure 4.7. $^1$H NMR spectra (400 MHz, CDCl$_3$, 25 °C) of the polymerization of rac-LA (0.48 M) at 29% (bottom) and 97% (top) conversion with racemic catalysts (2.4 mM): (a) 23 and (b) the parent catalyst 1. The blue dots mark unreacted catalyst peaks and the red dots mark the indium-polymeryl species.

Figure 4.8. $^1$H NMR spectra (400 MHz, CDCl$_3$, 25 °C) of the polymerization of rac-LA (0.48 M) at 29% (bottom) and 97% (top) conversion with racemic catalysts (2.4 mM): (a) 22 and (b) 24. The blue dots mark unreacted catalyst peaks and the red dots mark the indium-polymeryl species.
Bulk polymerizations of rac-LA with complexes (±)-22, 23 and 24 with various equivalents of monomer show molecular weights ($M_n$) fairly consistent with theoretical values and low polydispersities (PDI) (Table 4.5).

### Table 4.5. Results for the polymerization of rac-LA by catalysts 22-24.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>[LA]/[cat.]</th>
<th>Conv. (%)$^a$</th>
<th>$M_n$theo$^b$ (g mol$^{-1}$)</th>
<th>$M_n$GPC$^c$ (g mol$^{-1}$)</th>
<th>PDI$^c$</th>
<th>$P_m$$^d$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(±)-22</td>
<td>550</td>
<td>96</td>
<td>76000</td>
<td>84270</td>
<td>1.04</td>
<td>0.53</td>
</tr>
<tr>
<td>2</td>
<td>(±)-22</td>
<td>930</td>
<td>94</td>
<td>130000</td>
<td>153100</td>
<td>1.02</td>
<td>0.53</td>
</tr>
<tr>
<td>3</td>
<td>(±)-23</td>
<td>530</td>
<td>96</td>
<td>73000</td>
<td>53100</td>
<td>1.04</td>
<td>0.58</td>
</tr>
<tr>
<td>4</td>
<td>(±)-23</td>
<td>820</td>
<td>96</td>
<td>110000</td>
<td>96680</td>
<td>1.08</td>
<td>0.58</td>
</tr>
<tr>
<td>5</td>
<td>(±)-24</td>
<td>540</td>
<td>99</td>
<td>77000</td>
<td>68930</td>
<td>1.03</td>
<td>0.58</td>
</tr>
<tr>
<td>6</td>
<td>(±)-24</td>
<td>880</td>
<td>95</td>
<td>120000</td>
<td>86220</td>
<td>1.16</td>
<td>0.57</td>
</tr>
</tbody>
</table>

$^a$ Monomer conversion determined by $^1$H NMR spectroscopy. $^b$ Calculated from [LA]/[initiator] x LA conversion x $M_{LA}$ (144.13) + $M_{EtOH}$ (46.07). $^c$ Determined by GPC measurements in THF. $^d$ Determined by $^1$H($^1$H) NMR spectroscopy and Bernoullian statistics.

The adamantyl and cumyl catalysts (±)-23 and 24 show slight isotactic biases, with $P_m$ values of ~ 0.6 (Table 4.5, entries 7-12), which are comparable to the parent system under similar conditions. In contrast, catalyst (±)-22 has little selectivity, with $P_m$ values indicative of atactic polymers (~ 0.5).

### 4.3 Discussion and conclusions

In this chapter we set out to investigate the role of the aromatic substituents and the chirality of our tridentate ligand system on the stereoselectivity of dinuclear indium alkoxide catalysts for the ring opening polymerization of rac-LA. To this end, we synthesized a family of racemic and enantiopure $H(NMe_2NH_2OR_2)$ diaminophenolate proligands (L-9-11) with various aromatic substituents and used them to generate a family of indium dichloride complexes as intermediates towards the synthesis of active indium alkoxide complexes.
In contrast to previously reported dihalide complexes made with the parent ortho/para di-tert-butyl substituted ligand system, such as \((\text{NMe}_2\text{NH}_2\text{O}_\text{Bu})\text{InCl}_2\) (2), as well as the dichloride complexes discussed in the previous chapters of this thesis, such as the bulky \(n\)-propyl functionalized \((\text{NPr}_2\text{NH}_2\text{O}_\text{Bu})\text{InCl}_2\) (4), the dichloride complexes discussed in this chapter, namely complexes \((\pm)-(\text{NMe}_2\text{NH}_2\text{OSiPh}_3)\text{InCl}_2\) (19) and \((\pm)-(\text{NMe}_2\text{NH}_2\text{OA}_\text{d})\text{InCl}_2\) (20), are dinuclear in the solid-state, forming heterochiral \((RR/SS)\) dimers bridged by chloride ligands.

Solution state \(^1\text{H} \) NMR spectroscopy of dichloride complexes 19-21 also revealed differences between the spectra of racemic and enantiopure analogues of the same ligand, something that is surprisingly also the case with the parent tert-butyl substituted dichloride complexes but had not been previously commented upon.\(^98\) In light of the ability of these complexes to aggregate in the solid-state, we attempted to probe whether the discrepancies in the solution NMR spectral data were due to formation of different species in solution for the racemic versus enantiopure complexes.

For example, the racemic complexes form heterochiral dimers in the solid-state, something that has been observed for all related dimeric complexes with identical bridging groups made with this ligand family.\(^1-2,96-98\) It was also previously observed that enantiopure homochiral dimers, such as the parent bis-ethoxide \([\text{NMe}_2\text{NH}_2\text{O}_\text{Bu}]\text{InCl(\mu-}O\text{Et})_2\], are less thermodynamically stable than the related heterochiral dimers, and mixtures of the \((RR/RR)\) and \((SS/SS)\) dimers will reorganize in solution to form the heterochiral \((RR/SS)\) dimers.\(^98\) We therefore hypothesized that the discrepancies in the solution state data for the racemic and enantiopure dichloride complexes may be due to the formation of two different dimeric structures in solution. Alternatively, if the enantiopure homochiral dimers are sufficiently unstable, a monomeric form may predominate in solution.
To probe whether this was the case we performed PGSE NMR experiments to calculate the diffusion coefficients ($D_t$) of these species in solution, and therefore also calculate their hydrodynamic radii ($r_{H}$) and compare with the radii calculated from the solid-state molecular structures ($r_{X-ray}$). The results with the parent tert-butyl system, where there is a 25% decrease in $D_t$ between the dichloride complex ($\pm$)-2 and the ethoxide complex ($\pm$)-1 and good agreement between the calculated hydrodynamic radius of complex ($\pm$)-1 and the radius estimated from its dinuclear solid-state structure, indicated that the dichloride remains mononuclear in solution whereas the ethoxide is dinuclear in solution.\(^{98}\) The $D_t$ values for the silyl substituted dichloride complexes ($\pm$)- and ($R,R$)-19 as well as the ethoxide complex ($\pm$)-22 were similar and >20\% lower than the free proligand, indicating that all three complexes may remain dinuclear in solution. In contrast, the adamantyl substituted dichloride complex ($\pm$)-20 has a $D_t$ values similar to the free proligand, indicating that, as for the parent system, this complex may remain mononuclear in solution, in contrast to its structure in the solid-state. However, the comparison of the hydrodynamic radii and those obtained from the solid-state structures of complexes ($\pm$)-19 and 20 are not in agreement, as they were for the parent system.

The discrepancy here is not unusual for these types of experiments\(^ {141}\) and may simply be an artefact of the experimental error associated with these measurements. However, it is important to note here that if there is an equilibrium between monomeric and dimeric forms of these complexes in solution, both the diffusion coefficients and hydrodynamic radii may lack any real physical meaning.\(^ {141}\) Further exploration of the solution state behaviour of these indium dichloride complexes would be needed to establish whether such an equilibrium exists in solution, however due to their nature as intermediates in the synthesis of more desirable ethoxide complexes for the polymerization of rac-LA, such detailed studies were not undertaken.
Despite the lack of conclusive data to support either a mononuclear or dinuclear structure for the indium dichloride complexes (±)- and (R,R)-19-21 in solution, or the existence of a monomer/dimer equilibrium in solution, indium ethoxide complexes (±)- and (R,R)-[(NMe2N1HOr2)InCl]2(µ-Cl)(µ-OEt) (22-24) were synthesized using these complexes. The solution state and solid-state structural data for these complexes are the same between the racemic and enantiopure analogues, which is consistent with the parent system as well as other indium ethoxide complexes reported in the earlier chapters of this thesis.1-2,96-98

The polymerization of lactide with these complexes indicated that the adamantyl substituted analogues (23) are most similar to the parent system (1), with similar kinetics of polymerization for rac-, L- and D-LA and similar stereoselectivity of the racemic analogue in the polymerization of rac-LA (Pm ~ 0.6). The racemic cumyl substituted analogue (24) showed a similar stereoselectivity to the adamantyl analogue (Pm ~ 0.6), however the rates of polymerization were slightly slower for this catalyst and in situ monitoring (1H NMR spectroscopy) of the polymerization of lactide by this catalyst showed the presence of unreacted catalyst, even at high conversions of monomer. This is contrast to the parent tert-butyl or adamantyl substituted systems which show unreacted catalyst only at the beginning stages of the polymerization. A similar situation was observed with the silyl substituted analogues (22), which also have lower rates of polymerization and show unreacted catalyst at high conversions of monomer. The racemic silyl catalyst is also less stereoselective, producing atactic PLA (Pm ~ 0.5).

The rates of polymerization for cumyl and silyl substituted complexes are only marginally slower than the adamantyl or tert-butyl substituted catalysts, and therefore the incomplete initiation observed in the in situ monitored polymerization of lactide by these
catalysts does not seem to have a large impact on the activity of these catalysts, and may in fact be a consequence of the polymerization set-up for these particular experiments. All catalyst analogues appear to have similar molecular weight control with relatively low PDIs (Table 4.5), suggesting that the bulkier aromatic substituents utilized in these analogues have little effect on the lactide polymerization activity or control of these catalysts in comparison to the parent tert-butyl substituted systems. Furthermore, the adamantyl and cumyl substituents appear to have little effect on the stereoselectivity of these catalysts in the polymerization of rac-LA, and only the silyl substituents were shown to have a detrimental effect on the stereoselectivity.

We can conclude that changing the steric bulk and/or electronic properties of the aromatic substituents in this tridentate ligand system does not lead to more active and/or selective indium catalysts for lactide polymerization. Our experience with the different indium complexes made within this tridentate ligand family (as described in Chapters 2-4) show that the different aggregation modes possible for these indium complexes will complicate any effort to enhance selectivity by ligand system. Therefore other avenues towards producing more selective catalysts must be pursued. These will be discussed in the next chapter.

4.4 Experimental

General procedures

Unless otherwise specified all air and/or water sensitive reactions were carried out using standard Schlenk techniques under N₂ or in a N₂ filled MBraun glovebox. A Bruker Avance 600 MHz spectrometer was used to record the \(^1\)H NMR, \(^{13}\)C\{\(^1\)H\} NMR, and \(^1\)H\{\(^1\)H\} NMR spectra. \(^1\)H NMR chemical shifts are given in ppm versus residual protons in deuterated solvents as follows: \(\delta\) 5.32 for CD\(_2\)Cl\(_2\) and \(\delta\) 7.27 for CDCl\(_3\). \(^{13}\)C\{\(^1\)H\} NMR chemical shifts are given in ppm versus residual \(^{13}\)C in solvents as follows: \(\delta\) 54.00 for CD\(_2\)Cl\(_2\) and \(\delta\) 77.23 for CDCl\(_3\).
Diffraction measurements for X-ray crystallography were made on a Bruker X8 APEX II diffraction with graphite monochromated Mo-K\(\alpha\) radiation. The structures were solved by direct methods and refined by full-matrix least-squares using the SHELXTL crystallographic software of the Bruker-AXS. Unless specified, all non-hydrogens were refined with anisotropic displacement parameters, and all hydrogen atoms were constrained to geometrically calculated positions but were not refined. EA CHN analysis was performed using Carlo Erba EA1108 elemental analyzer. The elemental composition of an unknown sample was determined by using a calibration factor. The calibration factor was determined by analyzing a suitable certified organic standard (OAS) of a known elemental composition. Molecular weights were determined using an Agilent 1200 Series pump and autosampler, Phenomenex columns (Phenogel 5 µm 10E4A LC Column 300 × 4.6 mm, 5 K - 500 K MW; Phenogel 5 µm 10E3A LC Column 300 × 4.6 mm, 1 K - 75 K MW; Phenogel 5 µm 500 ÅLC Column 300 × 4.6 mm, 1 K - 15 K MW), Wyatt Optilab rEX (refractive index detector \(\lambda= 690\) nm, 40 °C), Wyatt tristar miniDAWN (laser light scattering detector operating at \(\lambda = 690\) nm), and a Wyatt ViscoStar viscometer. The column temperature was set at 40 °C. A flow rate of 0.5 mL/min was used and samples were dissolved in CHCl\(\textsubscript{3}\) (ca. 20 mg/mL) and a \(dn/dc\) value of 0.0234 mL/g was used. Narrow molecular weight polystyrene standards were used for calibration purposes.

**Materials**

Toluene, diethyl ether, hexane, and tetrahydrofuran were degassed and dried using alumina columns in a solvent purification system. The tetrahydrofuran was further dried over sodium/benzophenone and vacuum transferred to a Straus flask and degassed prior to use. In addition CH\(3\)CN and CH\(2\)Cl\(2\) were refluxed over CaH\(2\) in a solvent still and transferred to a Straus flask where they were degassed prior to use. Deuterated solvents were dried over CaH\(2\)
and vacuum-transferred to a Straus flask and then degassed through a series of freeze-pump-thaw cycles. Deuterium-labeled NMR solvents were purchased from Cambridge Isotope Laboratory or Aldrich. InCl₃ was obtained from Strem Chemicals and used without further purification. Potassium tert-butoxide was sublimed prior to use. (±) and (R,R)-N,N-dimethyl-trans-1,2-diaminocyclohexane, 2-hydroxy-5-methyl-3-(triphenylsilyl)benzaldehyde, 2-hydroxy-3,5-bis(2-phenylpropan-2-yl)benzaldehyde and 3-((3r,5r,7r)-adamantan-1-yl)-5-(tert-butyl)-2-hydroxybenzaldehyde were prepared according to modified literature procedures. Lactide samples were obtained from Purac Biomaterials and recrystallized several times from hot toluene and dried under vacuum prior to use.

**General procedure for the synthesis of imines**

The desired amine (±)- or (R,R)-N,N-dimethyl-trans-1,2-diaminocyclohexane (9.60 mmol) was transferred using methanol (25 mL) to a solution of the appropriate salicylaldehyde (8.00 mmol) in methanol (25 mL). The mixture was stirred for 18 h at room temperature. The resulting suspension was either filtered yielding the crude product as a yellow solid or pumped to dryness yielding the crude product as a yellow foamy residue depending on the solubility of the imine. Further purification was achieved through recrystallization in a variety of solvents (see below for details).

**Synthesis of 2-(((±)-trans-2-(dimethylamino)cyclohexylimino)methyl)-4-methyl-6-(triphenylsilyl)phenol**

The title compound was isolated as a bright yellow solid after filtration of the crude reaction mixture. The crude solid was dissolved in a minimum of hot methanol and the solution was cooled to 0 °C causing precipitation of the pure product, which was isolated via vacuum filtration as a yellow solid and dried under vacuum prior to use (1.42 g, 86 %). ¹H NMR (600
MHz, 25 °C, CDCl$_3$): δ 8.30 (1H, s, CH=N), 7.64 (6H, m, SiPh$_3$), 7.36 (9H, m, SiPh$_3$), 7.15 (1H, m, Ar-H), 7.01 (1H, m, Ar-H), 3.22 (1H, m, CHN), 2.54 (1H, m, CHN), 2.25 (6H, s, N(CH$_3$)$_2$), 2.19 (3H, s, Ar-CH$_3$), 1.79 (3H, m, DACH), 1.71 (1H, m, DACH), 1.54 (1H, m, DACH), 1.26 (3H, m, DACH). $^{13}$C{$^{1}$H} NMR (150 MHz, 25 °C, CDCl$_3$): δ 164.47, 163.13, 141.55, 136.36, 134.87, 133.86, 129.16, 127.60, 126.94, 121.24, 117.97, 69.98, 66.57, 40.77, 34.74, 25.29, 25.19, 24.54, 20.45. Anal. Calc. for C$_{34}$H$_{38}$N$_2$OSi: C, 78.72; H, 7.38; N, 5.40. Found: C, 78.80; H, 7.32; N, 5.17.

Synthesis of 2-((R,R)-trans-2-(dimethylamino)cyclohexylimino)methyl)-4-methyl-6-(triphenylsilyl)phenol

The title compound was isolated as a bright yellow solid after filtration of the crude reaction mixture. The solid was dried under vacuum with no further purification necessary (1.016 g, 78 %). $^1$H NMR (600 MHz, 25 °C, CDCl$_3$): δ 8.29 (1H, s, CH=N), 7.64 (6H, m, SiPh$_3$), 7.35 (9H, m, SiPh$_3$), 7.16 (1H, m, Ar-H), 7.01 (1H, m, Ar-H), 3.22 (1H, m, CHN), 2.53 (1H, m, CHN), 2.25 (6H, s, N(CH$_3$)$_2$), 2.19 (3H, s, Ar-CH$_3$), 1.78 (3H, m, DACH), 1.71 (1H, m, DACH), 1.54 (1H, m, DACH), 1.27 (3H, m, DACH). $^{13}$C{$^{1}$H} NMR (150 MHz, 25 °C, CDCl$_3$): δ 164.47, 163.13, 141.55, 136.35, 134.87, 133.86, 129.15, 127.60, 126.94, 121.24, 117.97, 69.98, 66.57, 40.77, 34.73, 25.29, 25.18, 24.54, 20.44. Anal. Calc. for C$_{34}$H$_{38}$N$_2$OSi: C, 78.72; H, 7.38; N, 5.40. Found: C, 78.85; H, 7.27; N, 5.08.

Synthesis of 2-((±)-trans-2-(dimethylamino)cyclohexylimino)methyl)-4-tert-butyl-6-(adamantan-1-yl)phenol

The reaction mixture was filtered yielding the title compound as a yellow solid. This solid was dried under vacuum with no further purification necessary (2.06 g, 74 %). $^1$H NMR (600 MHz, 25 °C, CDCl$_3$): δ 8.31 (1H, s, CH=N), 7.30 (1H, m, Ar-H), 7.07 (1H, m, Ar-H), 3.20 (1H, m, CHN), 2.64 (1H, m, CHN), 2.29 (6H, s, N(CH$_3$)$_2$), 2.20 (6H, m, Ad), 2.10 (3H, m, Ad), 1.88
(1H, m, DACH), 1.81 (9H, m, Ad + DACH), 1.66 (1H, m, DACH), 1.32 (9H, s, C(CH₃)₃), 1.30 (3H, m, DACH). ¹³C{¹H} NMR (150 MHz, 25 °C, CDCl₃): δ 164.30, 158.56, 139.72, 136.81, 126.46, 125.58, 118.05, 69.76, 66.74, 40.77, 40.30, 37.17, 35.00, 34.14, 31.51, 29.11, 25.22, 24.65, 23.94. Anal. Calc. for C₂₉H₄₄N₂O: C, 79.76; H, 10.16; N, 6.42. Found: C, 79.92; H, 10.37; N, 6.28.

**Synthesis of 2-((R,R)-trans-2-(dimethylamino)cyclohexylimino)methyl)-4-tert-butyl-6-(adamantan-1-yl)phenol**

The reaction mixture was filtered yielding the title compound as a yellow solid. This solid was dried under vacuum with no further purification necessary (0.552 g, 77 %). ¹H NMR (600 MHz, 25 °C, CDCl₃): δ 8.31 (1H, s, C=H), 7.31 (1H, m, Ar-H), 7.07 (1H, m, Ar-H), 3.20 (1H, m, C(HN)), 2.64 (1H, m, C(HN)), 2.28 (6H, s, N(CH₃)₂), 2.20 (6H, m, Ad), 2.10 (3H, m, Ad), 1.88 (1H, m, DACH), 1.81 (9H, m, Ad + DACH), 1.65 (1H, m, DACH), 1.32 (9H, s, C(CH₃)₃), 1.30 (3H, m, DACH). ¹³C{¹H} NMR (150 MHz, 25 °C, CDCl₃): δ 164.29, 158.55, 139.72, 136.81, 126.45, 125.58, 118.04, 69.77, 66.73, 40.77, 40.31, 37.18, 35.01, 34.15, 31.52, 29.12, 25.23, 24.66, 23.91. Anal. Calc. for C₂₉H₄₄N₂O: C, 79.76; H, 10.16; N, 6.42. Found: C, 79.60; H, 10.35; N, 6.01.

**Synthesis of 2-((±)-trans-2-(dimethylamino)cyclohexylimino)methyl)-4,6-bis(2-phenylpropan-2-yl)phenol**

The title compound was isolated as a yellow solid after filtration of the crude reaction mixture. The solid was dried under vacuum with no further purification necessary (2.199g, 80 %) ¹H NMR (600 MHz, 25 °C, CDCl₃): δ 8.20 (1H, s, CH=N), 7.29 (5H, m, Ar-H + C(CH₃)₂Ph), 7.21 (5H, m, C(CH₃)₂Ph), 7.13 (1H, m, C(CH₃)₂Ph), 7.01 (1H, m, Ar-H), 3.11 (1H, m, C(HN)), 2.52 (1H, m, C(HN)), 2.20 (6H, s, N(CH₃)₂), 1.78 (5H, m, NH + DACH), 1.71 (6H, s, C(CH₃)₂Ph), 1.69 (3H, s, C(CH₃)₂Ph), 1.66 (3H, s, C(CH₃)₂Ph), 1.50 (1H, m, DACH), 1.21 (3H, m, DACH).
\(^{13}\)C\^{1}H} NMR (150 MHz, 25 °C, CDCl\(_3\)): δ 163.70, 157.99, 150.85, 150.65, 139.10, 135.85, 128.74, 127.96, 127.76, 127.63, 126.76, 125.60, 125.55, 124.96, 118.16, 69.80, 66.51, 42.40, 42.17, 40.62, 34.91, 30.98, 30.91, 29.71, 29.15, 25.18, 24.61, 23.83. Anal. Calc. for C\(_{33}\)H\(_{42}\)N\(_2\)O: C, 82.11; H, 8.77; N, 5.80. Found: C, 82.11; H, 8.41; N, 5.69.

**Synthesis of 2-((R,R)-trans-2-(dimethylamino)cyclohexylimino)methyl)-4,6-bis(2-phenylpropan-2-yl)phenol**

The reaction mixture was pumped to dryness *in vacuo* yielding the crude product as a yellow foamy residue. This residue was dissolved in a minimum of hot petroleum ether and the solution was cooled to 0 °C causing the precipitation of the pure product, which was isolated via vacuum filtration as a yellow solid and dried under vacuum prior to use (0.555 g, 41 %). \(^{1}\)H NMR (600 MHz, 25 °C, CDCl\(_3\)): δ 8.18 (1H, s, CH=\text{N}), 7.28 (5H, m, Ar-H + C(CH\(_3\))\(_2\)Ph), 7.19 (5H, m, C(CH\(_3\))\(_2\)Ph), 7.11 (1H, m, C(CH\(_3\))\(_2\)Ph), 6.99 (1H, m, Ar-H), 3.09 (1H, m, CHN), 2.50 (1H, m, CHN), 2.17 (6H, s, N(CH\(_3\))\(_2\)), 1.77 (5H, m, NH + DACH), 1.69 (6H, s, C(CH\(_3\))\(_2\)Ph), 1.67 (3H, s, C(CH\(_3\))\(_2\)Ph), 1.64 (3H, s, C(CH\(_3\))\(_2\)Ph), 1.48 (1H, m, DACH), 1.19 (3H, m, DACH). \(^{13}\)C\^{1}H} NMR (150 MHz, 25 °C, CDCl\(_3\)): δ 163.67, 157.96, 150.81, 150.61, 139.07, 135.83, 128.70, 127.93, 127.74, 127.59, 126.72, 125.56, 125.52, 124.94, 118.14, 69.77, 66.46, 42.36, 42.14, 40.57, 34.89, 30.96, 30.89, 29.65, 29.16, 25.15, 24.60, 23.71. Anal. Calc. for C\(_{33}\)H\(_{42}\)N\(_2\)O: C, 82.11; H, 8.77; N, 5.80. Found: C, 82.02; H, 8.87; N, 5.56.

**General procedure for the synthesis of proligands (±)- and (R,R)- H(N\(_{\text{Me2N}}\)H\(_{\text{O}}\)R\(_2\))**

NaCNBH\(_3\) (23 mmol) was added to a solution of the appropriate imine (4.5 mmol) in acetonitrile (100 mL) and the reaction mixture was stirred for 30 min. Acetic acid (23 mmol) was added dropwise to the solution and it was stirred at room temperature for 18 h. The mixture was diluted with 2% MeOH in CH\(_2\)Cl\(_2\) (100 mL) and washed with 1M NaOH (3 × 100 mL). The organic
layer was dried over MgSO₄, filtered, and pumped to dryness in vacuo to afford the crude compound. The crude compounds were purified using a variety of methods (see below for details). The purified ligands were then stirred in the glovebox under N₂ atmosphere with dry hexane and either filtered (if insoluble) or pumped to dryness (if soluble) to remove trace water and/or methanol impurities before use in metal chemistry.

Synthesis of 2-((±)-trans-2-(dimethylamino)cyclohexylamino)methyl)-4-methyl-6-(triphenylsilyl)phenol (±)-H(NMe₂NHOSiPh₃) (L-9)

The crude product was isolated as an off-white coloured foamy residue. The residue was dissolved in a minimum of hot methanol and the solution was cooled to 0 °C causing precipitation of the pure product, which was isolated via vacuum filtration as an off-white solid and dried under vacuum prior to use (0.227 g, 48 %). ¹H NMR (600 MHz, 25 °C, CDCl₃): δ 7.64 (6H, m, SiPh₃), 7.34 (9H, m, SiPh₃), 6.93 (1H, m, Ar-H), 6.82 (1H, m, Ar-H), 4.07 (1H, d, ²JHH = 12 Hz, N-CH₂-Ar), 3.89 (1H, d, ²JHH = 12 Hz, N-CH₂-Ar), 3.35 (1H, m, NH), 2.37 (1H, m, NCH), 2.17 (6H, s, N(CH₃)₂), 2.14 (3H, s, Ar-CH₃), 2.13 (1H, m, NCH), 2.00 (1H, m, DACH), 1.77 (2H, m, DACH), 1.63 (1H, m, DACH), 1.11 (4H, m, DACH). ¹³C{¹H} NMR (150 MHz, 25 °C, CDCl₃): δ 161.64, 137.13, 136.40, 135.49, 130.91, 128.94, 127.46, 127.14, 123.63, 120.02, 66.46, 59.67, 51.31, 40.04, 31.59, 25.27, 24.68, 20.86, 20.58. Anal. Calc. for C₃₄H₄₀N₂OSi: C, 78.41; H, 7.74; N, 5.38. Found: C, 78.17; H, 7.50; N, 5.21.

Synthesis of 2-((R,R)-trans-2-(dimethylamino)cyclohexylamino)methyl)-4-methyl-6-(triphenylsilyl)phenol (R,R)-H(NMe₂NHOSiPh₃) (L-9)

The crude product was isolated as an off-white coloured foamy residue. The residue was dissolved in a minimum of hot methanol and the solution was cooled to 0 °C causing precipitation of the pure product, which was isolated via vacuum filtration as a pale off-white solid and dried under vacuum prior to use (0.293 g, 58 %). ¹H NMR (600 MHz, 25 °C, CDCl₃): δ
7.65 (6H, m, SiPh3), 7.34 (9H, m, SiPh3), 6.93 (1H, m, Ar-H), 6.83 (1H, m, Ar-H), 4.07 (1H, d, 2\textsuperscript{JHH} = 12 Hz, N-CH\textsubscript{2}-Ar), 3.90 (1H, d, 2\textsuperscript{JHH} = 18 Hz, N-CH\textsubscript{2}-Ar), 3.36 (1H, m, NH), 2.37 (1H, m, NCH), 2.17 (6H, s, N(CH\textsubscript{3})\textsubscript{2}), 2.15 (3H, s, Ar-CH\textsubscript{3}), 2.14 (1H, m, NCH), 2.01 (1H, m, DACH), 1.77 (2H, m, DACH), 1.64 (1H, m, DACH), 1.12 (4H, m, DACH). 13C{\textsuperscript{1}H} NMR (150 MHz, 25 °C, CDCl\textsubscript{3}): δ 161.60, 137.16, 136.39, 135.46, 130.96, 128.96, 127.47, 127.18, 123.58, 120.02, 66.43, 59.61, 51.23, 40.03, 31.54, 25.25, 24.67, 20.87, 20.58. Anal. Calc. for C\textsubscript{34}H\textsubscript{40}N\textsubscript{2}OSi: C, 78.41; H, 7.74; N, 5.38. Found: C, 78.09; H, 7.94; N, 5.22.

Synthesis of 2-((±)-trans-2-(dimethylamino)cyclohexylamino)methyl)-4-tert-buyl-6-(adamantan-1-yl)phenol (±)-H(NMe\textsubscript{2}N\textsubscript{H}O\textsubscript{Ad}) (L-10)

The crude compound was isolated as an off-white oily residue. The residue was dissolved in a minimum of hot acetonitrile and the solution was cooled to 0 °C causing precipitation of the pure product, which was isolated by vacuum filtration as an off-white solid and dried under vacuum prior to use (0.365 g, 41 %). 1H NMR (600 MHz, 25 °C, CDCl\textsubscript{3}): δ 7.16 (1H, m, Ar-H), 6.89 (1H, m, Ar-H), 4.06 (1H, d, 2\textsuperscript{JHH} = 12 Hz, N-CH\textsubscript{2}-Ar), 3.72 (1H, d, 2\textsuperscript{JHH} = 12 Hz, N-CH\textsubscript{2}-Ar), 2.36 (1H, m, NCH), 2.30 (1H, m, NCH), 2.20 (6H, s, N(CH\textsubscript{3})\textsubscript{2}), 2.18 (6H, m, Ad), 2.08 (3H, m, Ad), 1.78 (9H, m, Ad + DACH), 1.63 (1H, m, DACH), 1.30 (9H, s, C(CH\textsubscript{3})\textsubscript{3}), 1.21 (4H, m, DACH). 13C{\textsuperscript{1}H} NMR (150 MHz, 25 °C, CDCl\textsubscript{3}): δ 154.94, 140.17, 136.19, 123.54, 122.66, 122.49, 66.55, 58.72, 51.40, 40.45, 40.03, 37.22, 37.01, 34.18, 31.70, 29.69, 29.19, 25.36, 24.67, 20.90. Anal. Calc. for C\textsubscript{29}H\textsubscript{46}N\textsubscript{2}O: C, 79.40; H, 10.57; N, 6.39. Found: C, 79.51; H, 10.96; N, 6.10.

Synthesis of 2-((R,R)-trans-2-(dimethylamino)cyclohexylamino)methyl)-4-tert-buyl-6-(adamantan-1-yl)phenol (R,R)-H(NMe\textsubscript{2}N\textsubscript{H}O\textsubscript{Ad}) (L-10)

The crude compound was isolated as a pale yellow oily residue. The residue was dissolved in a minimum of hot acetonitrile with a small amount CH\textsubscript{2}Cl\textsubscript{2} added to fully dissolve the oil. The
solution was cooled to 0 °C causing precipitation of the pure product, which was isolated by vacuum filtration as an off-white solid and dried under vacuum prior to use (0.924 g, 40 %). $^1$H NMR (600 MHz, 25 °C, CDCl₃): $\delta$ 7.17 (1H, m, Ar-H), 6.90 (1H, m, Ar-H), 4.07 (1H, d, $^2J_{HH} = 12$ Hz, N-CH₂-Ar), 3.73 (1H, d, $^2J_{HH} = 12$ Hz, N-CH₂-Ar), 3.38 (1H, m, NH), 2.37 (1H, m, NCH), 2.29 (1H, m, NCH), 2.21 (6H, s, N(CH₃)₂), 2.19 (6H, m, Ad), 2.09 (3H, m, Ad), 1.82 (9H, m, Ad + DACH), 1.72 (1H, m, DACH), 1.31 (9H, s, C(CH₃)₃), 1.22 (4H, m, DACH).


**Synthesis of 2-((±)-trans-2-(dimethylamino)cyclohexylamino)methyl)-4,6-bis(2-phenylpropan-2-yl)phenol (±)-H(NMe₂NHOc₅) (L-11)**

The crude product was isolated as an off-white foamy residue. The residue was dissolved in a minimum of hot methanol and the solution was cooled to 0 °C causing crystallization of the pure product, which was isolated via vacuum filtration as off-white crystals and dried under vacuum prior to use (0.752 g, 65 %). $^1$H NMR (600 MHz, 25 °C, CDCl₃): $\delta$ 7.28 (4H, m, C(CH₃)₂Ph), 7.19 (6H, m, Ar-H + C(CH₃)₂Ph), 7.12 (1H, m, C(CH₃)₂Ph), 6.76 (1H, m, Ar-H), 3.81 (2H, m, N-CH₂-Ar), 3.18 (1H, m, NH), 2.26 (1H, m, NCH), 2.14 (6H, s, N(CH₃)₂) 2.13 (1H, m, NCH), 1.89 (1H, m, DACH), 1.74 (2H, m, DACH), 1.70 (9H, s, C(CH₃)₂Ph), 1.66 (3H, s, C(CH₃)₂Ph), 1.60 (1H, m, DACH), 1.09 (3H, m, DACH), 0.98 (1H, m, DACH). $^{13}$C{¹H} NMR (150 MHz, 25 °C, CDCl₃): $\delta$ 154.49, 151.50, 151.42, 139.27, 134.98, 127.81, 127.59, 126.76, 125.71, 125.30, 124.72, 124.55, 123.80, 66.32, 59.11, 51.45, 42.40, 42.10, 39.99, 31.50, 31.04, 29.95, 29.21, 25.23, 24.61, 20.80. Anal. Calc. for C₃₃H₄₄N₂O: C, 81.77; H, 9.15; N, 5.78. Found: C, 81.48; H, 9.41; N, 5.67.
Synthesis of 2-((R,R)-trans-2-(dimethylamino)cyclohexylamino)methyl)-4,6-bis(2-phenylpropan-2-yl)phenol (R,R)-H(NMe2NHO)(L-11)

The crude product was isolated as a thick, yellow coloured oil. The oil was washed with petroleum ether several times, decanting the supernatant solution each time, until no more oil appeared to dissolve. The supernatant petroleum ether solutions were combined together and pumped to dryness in vacuo yielding the desired product as a thick, off-white coloured oil (2.71 g, 54%).

$^1$H NMR (600 MHz, 25 °C, CDCl$_3$): $\delta$ 7.28 (4H, m, C(CH$_3$)$_2$Ph), 7.17 (6H, m, Ar-H + C(CH$_3$)$_2$Ph), 7.11 (1H, m, C(CH$_3$)$_2$Ph), 6.74 (1H, m, Ar-H), 3.80 (2H, m, N-CH$_2$-Ar), 2.25 (1H, m, NCH), 2.12 (6H, s, N(CH$_3$)$_2$) 2.09 (1H, m, NCH), 1.87 (1H, m, DACH), 1.72 (2H, m, DACH), 1.68 (9H, s, C(CH$_3$)$_2$Ph), 1.65 (3H, s, C(CH$_3$)$_2$Ph), 1.58 (1H, m, DACH), 1.08 (3H, m, DACH), 0.96 (1H, m, DACH).

$^{13}$C{$^1$H} NMR (150 MHz, 25 °C, CDCl$_3$): $\delta$ 154.45, 151.48, 151.38, 139.28, 134.97, 127.80, 127.58, 126.74, 125.70, 125.29, 124.71, 124.53, 123.76, 66.30, 59.06, 51.38, 42.38, 42.08, 39.97, 31.45, 31.03, 29.93, 29.20, 25.22, 24.59, 20.78. Anal. Calc. for C$_{33}$H$_{44}$N$_2$O: C, 81.77; H, 9.15; N, 5.78. Found: C, 81.61; H, 9.15; N, 5.43.

General procedure for the synthesis of indium dichloride complexes (±)- and (R,R)-(NMe$_2$NHO)$_2$InCl$_2$

Potassium tert-butoxide (0.040 mmol) was transferred using toluene (5 mL) to a solution of the appropriate proligand (±)- or (R,R)- H(NMe$_2$NHO)$_2$ (0.040 mmol) in toluene (5 mL). This solution was stirred at room temperature for 16 hours, and the solvent was removed in vacuo yielding (±)- or (R,R)- K(NMe$_2$NHO)$_2$ in quantitative yield. The potassium salt (±)- or (R,R)- K(NMe$_2$NHO)$_2$ (0.040 mmol) was dissolved in THF (5 mL). Indium trichloride (0.040 mmol) was transferred to this solution using THF (5 mL). The mixture was stirred at room temperature for 18 h, then filtered through glass fibre filter paper and pumped to dryness in vacuo to obtain
the crude compound. The crude compounds were purified by a variety of methods depending on the proligand used (see below for details).

**Synthesis of complex (±)-(NMe₂N₃HOSiPh₃)InCl₂ (19)**

The crude complex was isolated as a white foamy residue. Acetonitrile was added to the residue and the solution was stirred for several minutes causing precipitation of a white solid. The solution was filtered on a glass frit and a white powder was collected and stirred with ether for approximately 30 minutes. The solution was pumped to dryness in vacuo yielding the desired compound as a white solid in approximately 90% purity as determined by ¹H NMR spectroscopy (0.2008 g, 79%). Attempts at further purification were unsuccessful. Single crystals of complex (±)-19 were grown by slow diffusion of hexane into a saturated solution of the complex in THF at room temperature and were analysed by single crystal X-ray diffraction.

¹H NMR (600 MHz, 25 °C, CD₂Cl₂): δ 7.63 (6H, m, SiPh₃), 7.31 (9H, m, SiPh₃), 7.04 (1H, m, ArH), 6.83 (1H, m, ArH), 5.02 (1H, d, ²J_HH = 12 Hz, CH₂N), 3.78 (1H, d, ²J_HH = 12 Hz, CH₂N), 2.94 (1H, m, NH), 2.74 (1H, m, CHN), 2.54 (1H, m, CHN), 2.44 (1H, m, DACH), 2.38 (3H, s, NCH₃), 2.12 (3H, s, NCH₃), 1.83 (3H, m, DACH), 1.27 (1H, m, DACH), 1.20 (2H, m, DACH), 1.12 (3H, s, Ar-CH₃), 0.98 (1H, m, DACH). ¹³C {¹H} NMR (151 MHz, 25 °C, CD₂Cl₂): δ 169.25, 139.65, 137.52, 137.30, 136.78, 134.99, 129.07, 127.83, 127.77, 124.84, 124.65, 118.80, 65.77, 50.46, 44.20, 37.12, 31.09, 25.14, 24.95, 22.20, 20.58. Anal. Calc. for C₃₄H₃₉Cl₂InN₂OSi: C, 57.88; H, 5.57; N, 3.97. Found: C, 58.30; H, 5.68; N, 4.79.

**Synthesis of complex (R,R)-(NMe₂N₃HOSiPh₃)InCl₂ (19)**

The crude complex was obtained as an off-white foamy residue. Acetonitrile was added to this residue and the solution was stirred for several minutes causing precipitation of an off-white solid. The solution was filtered on a glass frit and an off-white solid was collected and stirred
with ether for approximately 30 minutes. The solution was pumped to dryness in vacuo yielding the desired compound as an off-white solid in approximately 90 % purity as determined by $^1$H NMR spectroscopy (0.1246 g, 57 %). Attempts at further purification were unsuccessful. $^1$H NMR (600 MHz, 25 °C, CD$_2$Cl$_2$): δ 7.64 (6H, m, SiPh$_3$), 7.31 (9H, m, SiPh$_3$), 7.07 (1H, m, ArH), 6.87 (1H, m, ArH), 5.16 (1H, d, $^2$J$_{HH}$ = 18 Hz, CH$_2$N), 3.80 (1H, d, $^2$J$_{HH}$ = 12 Hz, CH$_2$N), 2.96 (1H, m, NH), 2.67 (1H, m, CHN), 2.54 (1H, m, CHN), 2.45 (1H, m, DACH), 2.33 (3H, s, NCH$_3$), 2.15 (3H, s, NCH$_3$), 1.78 (3H, m, DACH), 1.17 (3H, m, DACH), 1.05 (3H, s, Ar-CH$_3$), 0.95 (1H, m, DACH). $^{13}$C($^1$H) NMR (151 MHz, 25 °C, CD$_2$Cl$_2$): δ 169.35, 139.60, 137.57, 137.30, 136.78, 135.16, 129.10, 127.84, 127.77, 124.90, 124.65, 118.86, 65.59, 53.76, 50.48, 44.10, 37.04, 31.16, 25.07, 24.95, 22.09, 20.62. Anal. Calc. for C$_{34}$H$_{39}$Cl$_2$InN$_2$OSi: C, 57.88; H, 5.57; N, 3.97. Found: C, 57.70; H, 5.50; N, 4.04.

**Synthesis of complex (±)-(NMe$_2$NH$_2$OAd)InCl$_2$ (20)**

The crude complex was isolated as a yellow, foamy residue. Toluene was added until the residue just dissolved (1-3 mL), then hexane was added until a precipitate just began to form (2-5 mL). The solution was left in the freezer (-35 °C) overnight, causing the precipitation of a pale yellow solid. The solution was filtered on a glass frit yielding the purified complex as a pale yellow powder, which was dried under vacuum prior to use (0.2518 g, 80 %). Single crystals of complex (±)-20 were grown from a saturated solution of the complex in toluene at room temperature and were analysed by single crystal X-ray diffraction. $^1$H NMR (600 MHz, 25 °C, CD$_2$Cl$_2$): δ 7.17 (1H, m, Ar-H), 6.84 (1H, m, Ar-H), 4.43 (1H, m, N-CH$_2$-Ar), 4.00 (1H, m, N-CH$_2$-Ar), 2.76 (1H, m, NCH), 2.72 (3H, s, N(CH$_3$)$_2$), 2.56 (2H, m, NCH + NH), 2.42 (1H, m, DACH), 2.29 (3H, s, N(CH$_3$)$_2$), 2.22 (3H, m, Ad), 2.17 (3H, m, Ad), 2.03 (3H, m, Ad), 2.00 (1H, m, DACH), 1.89 (2H, m, DACH), 1.83 (3H, m, Ad), 1.75 (3H, m, Ad), 1.34 (1H, m, DACH), 1.28 (9H, s,
\(C(CH_3)_3\), 1.22 (3H, m, DACH). \(^{13}\)C\(^{1}\)H NMR (151 MHz, 25 °C, CD\(_2\)Cl\(_2\)): \(\delta\) 161.83, 140.05, 138.74, 125.50, 124.92, 121.22, 66.29, 55.23, 51.88, 44.66, 41.03, 38.27, 37.89, 37.73, 34.50, 32.02, 31.61, 30.02, 25.04, 25.00, 22.46. Anal. Calc. for C\(_{29}\)H\(_{45}\)Cl\(_2\)InN\(_2\)O: C, 55.87; H, 7.28; N, 4.49. Found: C, 56.16; H, 7.27; N, 4.51.

**Synthesis of complex \((R,R)\)-(N\(_2\)Me\(_2\)N\(_2\)H\(_2\)O\(_\text{Ad}\))InCl\(_2\) (20)**

The crude complex was isolated as a yellow residue. The residue was dissolved in a minimum of ether, then hexane was added causing precipitation of a yellow solid. The supernatant solution was removed and the resulting solid was washed 2x with more hexane. The solid was dried under vacuum yielding the purified complex as a pale yellow powder (0.0213 g, 30 %). \(^1\)H NMR (600 MHz, 25 °C, CD\(_2\)Cl\(_2\)): \(\delta\) 7.19 (1H, m, Ar-H), 6.88 (1H, m, Ar-H), 4.16 (1H, m, N-CH\(_2\)-Ar), 4.10 (1H, m, N-CH\(_2\)-Ar), 2.74 (3H, s, N(CH\(_3\))\(_2\)), 2.66 (1H, m, NCH), 2.59 (2H, m, NCH + NH), 2.43 (3H, s, N(CH\(_3\))\(_2\)), 2.21 (4H, m, DACH + Ad), 2.17 (3H, m, Ad), 2.09 (1H, m, DACH), 2.04 (3H, m, Ad), 1.90 (1H, m, DACH), 1.88 (1H, m, DACH), 1.83 (3H, m, Ad), 1.75 (3H, m, Ad), 1.34 (1H, m, DACH), 1.28 (9H, s, C(CH\(_3\))\(_3\)), 1.20 (3H, m, DACH). \(^{13}\)C\(^{1}\)H NMR (151 MHz, 25 °C, CD\(_2\)Cl\(_2\)): \(\delta\) 161.37, 140.47, 139.25, 125.10, 121.89, 66.78, 55.89, 52.34, 44.65, 41.03, 38.07, 37.88, 37.71, 34.56, 32.01, 31.85, 30.01, 25.02, 25.00, 22.51.

**Synthesis of complex \((\pm)-(\text{N}_2\text{Me}_2\text{N}_2\text{H}_{\text{Cm}})\text{InCl}_2\) (21)**

The crude complex was isolated as a pale off-white residue. This residue was stirred with ether for approximately 30 minutes, causing the precipitation of a white solid. This solution was filtered on a glass frit yielding the pure complex as a white powder, which was dried under vacuum prior to use (0.2459 g, 88 %). \(^1\)H NMR (600 MHz, 25 °C, CD\(_2\)Cl\(_2\)): \(\delta\) 7.31 (1H, m, Ar-H), 7.27 (4H, m, C(CH\(_3\))\(_2\)Ph), 7.24 (2H, m, C(CH\(_3\))\(_2\)Ph), 7.16 (3H, m, C(CH\(_3\))\(_2\)Ph), 7.03 (1H, m, C(CH\(_3\))\(_2\)Ph), 6.69 (1H, m, Ar-H), 4.35 (1H, d, \(J_{HH} = 12\) Hz, N-CH\(_2\)-Ar), 3.84 (1H, m, N-CH\(_2\)-
Ar), 2.63 (1H, m, NCH), 2.54 (3H, s, N(CH$_3$)$_2$), 2.40 (2H, m, NCH + DACH), 2.34 (1H, m, NH), 1.91 (1H, m, DACH), 1.84 (1H, m, DACH), 1.78 (4H, m, C(CH$_3$)$_2$Ph + DACH), 1.73 (3H, s, N(CH$_3$)$_2$), 1.68 (3H, s, C(CH$_3$)$_2$Ph), 1.67 (3H, s, C(CH$_3$)$_2$Ph), 1.57 (3H, s, C(CH$_3$)$_2$Ph), 1.27 (1H, m, DACH), 1.11 (3H, m, DACH). $^{13}$C{$^1$H} NMR (151 MHz, 25 °C, CD$_2$Cl$_2$): δ 161.37, 152.27, 151.62, 139.11, 137.60, 128.34, 128.03, 127.96, 127.23, 127.19, 126.89, 125.81, 125.05, 120.91, 65.98, 54.98, 51.49, 44.39, 42.72, 42.54, 37.45, 31.73, 31.40, 31.31, 31.27, 27.81, 24.94, 22.36.

Anal. Calc. for C$_{33}$H$_{43}$ClInN$_2$O: C, 59.21; H, 6.47; N, 4.18. Found: C, 59.36; H, 6.51; N, 4.96.

**Synthesis of complex (R,R)-(NMe$_2$NHOC$_6$H$_5$)InCl$_2$ (21)**

The crude complex was isolated as a pale yellow, foamy solid. The solid was dissolved in a minimum of ether then hexane was added causing precipitation of a small amount of off-white solid, which was filtered on a glass frit. The filtrate was pumped to dryness and this process was repeated, yielding a second portion of the product. The solids were combined and dried under vacuum yielding an off-white solid (0.3198 g, 74%). The $^1$H NMR spectrum of the solid showed a mixture of the desired complex and a significant amount of unknown impurities. A small amount of pure complex was obtained by precipitation from a saturated solution of this crude complex in hexane, however large scale purification using this method was not successful and purification of this complex was not pursued further. $^1$H NMR (600 MHz, 25 °C, CD$_2$Cl$_2$): δ 7.32 (1H, m, Ar-H), 7.28 (4H, m, C(CH$_3$)$_2$Ph), 7.21 (2H, m, C(CH$_3$)$_2$Ph), 7.16 (3H, m, C(CH$_3$)$_2$Ph), 7.04 (1H, m, C(CH$_3$)$_2$Ph), 6.74 (1H, m, Ar-H), 4.02 (1H, m, N-CH$_2$-Ar), 3.96 (1H, m, N-CH$_2$-Ar), 2.63 (3H, s, N(CH$_3$)$_2$), 2.55 (1H, m, NCH), 2.42 (2H, m, NCH + DACH), 2.16 (3H, s, N(CH$_3$)$_2$), 2.00 (2H, m, NH + DACH), 1.88 (1H, m, DACH), 1.81 (1H, m, DACH), 1.75 (3H, m, C(CH$_3$)$_2$Ph), 1.68 (3H, s, C(CH$_3$)$_2$Ph), 1.67 (3H, s, C(CH$_3$)$_2$Ph), 1.60 (3H, s, C(CH$_3$)$_2$Ph), 1.27 (1H, m, DACH), 1.11 (3H, m, DACH). $^{13}$C{$^1$H} NMR (151 MHz, 25 °C, CD$_2$Cl$_2$): δ 160.88,
General procedure for the synthesis of indium ethoxide complexes (±)- and (R,R)-
\([\text{NMe}_2\text{NH}_2\text{O}_\text{R}_2]\text{InCl}_2(\mu-\text{Cl})(\mu-\text{OEt})\)

Toluene (5 mL) was used to transfer sodium ethoxide (0.1394 mmol) to a solution of the
appropriate indium dichloride complex (0.1422 mmol) in toluene (5 mL). The solution was
stirred at room temperature for ~ 18 hours, then the mixture was filtered through glass fibre filter
paper and purified by a variety of methods depending on the dichloride used (see below for
details).

Synthesis of complex (±)-\([\text{NMe}_2\text{NH}_2\text{O}_\text{SiPh}_3]\text{InCl}_2(\mu-\text{Cl})(\mu-\text{OEt})\) (22)

The filtered crude reaction mixture was concentrated \textit{in vacuo} until a white precipitate just began
to form (1-2 mL). Ether (~ 5 mL) was then added and the solution was stirred for several
minutes. The solution was filtered on a glass frit yielding a white solid. The solid was collected
and stirred with ether for approximately 30 minutes, then pumped to dryness for several hours to
remove residual solvents. This yielded the purified complex as a white solid (0.0306 g, 58 %). \(^1\)H
NMR spectroscopy confirmed the presence of small unknown impurities in the purified complex,
however attempts at further purification were unsuccessful. \(^1\)H NMR (600 MHz, 25 °C, CDCl\(_3\)):
\(\delta\) 7.71 (6H, m, SiPh\(_3\)), 7.32 (9H, m, SiPh\(_3\)), 7.24 (1H, m, ArH), 6.80 (1H, m, ArH), 4.92 (1H, d,
\(^2\)J\(_{\text{HH}}\) = 12 Hz, CH\(_2\)N), 3.93 (1H, m, OCH\(_2\)CH\(_3\)), 3.64 (1H, d, \(^2\)J\(_{\text{HH}}\) = 12 Hz, CH\(_2\)N), 2.84 (1H, m,
N\(_2\)), 2.76 (1H, m, CHN), 2.37 (2H, m, CHN + DACH), 2.30 (3H, s, NCH\(_3\)), 2.17 (3H, s, NCH\(_3\)),
1.75 (3H, m, DACH), 1.13 (4H, m, DACH), 0.92 (3H, s, Ar-CH\(_3\)), 0.84 (1.5H, t, \(^3\)J\(_{\text{HH}}\) = 12 Hz,
OCH\(_2\)CH\(_3\)). \(^1\)C\{\(^1\)H\} NMR (151 MHz, 25 °C, CDCl\(_3\)):
\(\delta\) 165.52, 139.88, 137.00, 136.84, 136.06,
Anal. Calc. for C\textsubscript{70}H\textsubscript{83}Cl\textsubscript{3}In\textsubscript{2}N\textsubscript{4}O\textsubscript{3}Si\textsubscript{2}:  C, 59.18; H, 5.89; N, 3.94.  Found: C, 58.84; H, 5.99; N, 4.07.

**Synthesis of complex (R,R)-[(N\textsubscript{Me2}N\textsubscript{H}O\textsubscript{SiPh\textsubscript{3}})InCl\textsubscript{2}](\mu-Cl)(\mu-OEt) (22)**

The crude complex was isolated as a clear, colourless oily residue. The residue was dissolved in a minimum of toluene, then hexane was added until a white solid precipitated out of solution. The supernatant solution was removed, then the solid was washed 2x with more hexane. The solid was dried under vacuum yielding the purified complex as a white solid (0.0532 g, 42 %). \(^{1}\text{H}\) NMR spectroscopy confirmed the presence of small unknown impurities in the purified complex, however attempts at further purification were unsuccessful. \(^{1}\text{H}\) NMR (600 MHz, 25 °C, CDCl\textsubscript{3}): \(\delta\) 7.70 (6H, m, SiPh\textsubscript{3}), 7.32 (9H, m, SiPh\textsubscript{3}), 7.24 (1H, m, Ar\textsubscript{H}), 6.79 (1H, m, Ar\textsubscript{H}), 4.92 (1H, d, \(\text{J}_{\text{HH}} = 12\) Hz, CH\textsubscript{2}N), 3.93 (1H, m, OCH\textsubscript{2}CH\textsubscript{3}), 3.64 (1H, d, \(\text{J}_{\text{HH}} = 12\) Hz, CH\textsubscript{2}N), 2.83 (1H, m, NH), 2.76 (1H, m, CHN), 2.36 (2H, m, CH\textsubscript{N} + DACH), 2.30 (3H, s, NCH\textsubscript{3}), 2.16 (3H, s, NCH\textsubscript{3}), 1.75 (3H, m, DACH), 1.13 (4H, m, DACH), 0.91 (3H, s, Ar-CH\textsubscript{3}), 0.84 (1.5H, t, \(\text{J}_{\text{HH}} = 12\) Hz, OCH\textsubscript{2}CH\textsubscript{3}). \(^{13}\text{C}\{^{1}\text{H}\} NMR (151 MHz, 25 °C, CDCl\textsubscript{3}): \delta\) 165.52, 139.88, 137.00, 136.07, 135.29, 128.42, 127.39, 124.21, 123.53, 118.92, 64.18, 62.64, 52.61, 50.17, 43.56, 36.54, 30.59, 24.75, 24.55, 21.51, 20.37, 19.65. Anal. Calc. for C\textsubscript{70}H\textsubscript{83}Cl\textsubscript{3}In\textsubscript{2}N\textsubscript{4}O\textsubscript{3}Si\textsubscript{2}:  C, 59.18; H, 5.89; N, 3.99.

**Synthesis of complex (±)-[(N\textsubscript{Me2}N\textsubscript{H}O\textsubscript{Ad})InCl\textsubscript{2}](\mu-Cl)(\mu-OEt) (23)**

The crude complex was isolated as a pale yellow residue. The residue was dissolved in ether (1-2 mL) and hexane was added until a pale yellow precipitate began to form (~ 5 mL). The solution was concentrated in vacuo to < 2 mL volume, then more hexane (1-2 mL) was added causing precipitation of more solid. This process was repeated 1 more time, yielding a cloudy pale
yellow solution, which was filtered on a glass frit. The resulting pale yellow solid was collected and dried under vacuum. The filtrate was dissolved in ether (1-2 mL) and hexane was added (~ 5 mL). This solution was filtered a second time yielding more pale yellow solid, which was combined with the first batch and dried under vacuum several hours to yield the purified complex as a pale yellow solid (0.0603 g, 42 %). Single crystals of complex (±)-23 were grown from a saturated solution of the complex in acetonitrile at room temperature and were analysed by single crystal X-ray diffraction. $^1$H NMR (600 MHz, 25 °C, CDCl$_3$): $\delta$ 7.14 (1H, m, Ar-H), 6.73 (1H, m, Ar-H), 4.99 (1H, d, $^2$J$_{HH} = 12$ Hz, N-CH$_2$-Ar), 4.48 (0.5H, m, -OCH$_2$CH$_3$), 4.40 (0.5H, m, -OCH$_2$CH$_3$), 3.74 (1H, d, $^2$J$_{HH} = 12$ Hz, N-CH$_2$-Ar), 2.84 (1H, m, NCH), 2.77 (1H, m, NCH), 2.69 (3H, s, N(CH$_3$)$_2$), 2.56 (1H, m, DACH), 2.48 (1H, m, NH), 2.27 (3H, m, Ad), 2.18 (3H, m, Ad), 2.03 (3H, s, Ad), 2.02 (3H, s, N(CH$_3$)$_2$), 1.91 (1H, m, DACH), 1.86 (2H, m, DACH), 1.82 (3H, m, Ad), 1.73 (3H, m, Ad), 1.32 (1.5H, t, $^3$J$_{HH} = 6$ Hz, -OCH$_2$CH$_3$), 1.28 (9H, s, C(CH$_3$)$_3$), 1.25 (2H, m, DACH), 1.13 (1H, m, DACH), 1.03 (1H, m, DACH). $^{13}$C{$^1$H} NMR (151 MHz, 25 °C, CDCl$_3$): $\delta$ 162.47, 139.04, 136.35, 125.74, 123.79, 118.68, 64.63, 62.79, 52.57, 50.84, 44.18, 40.45, 38.10, 37.43, 37.40, 33.92, 31.83, 30.77, 29.41, 24.82, 24.71, 21.86, 19.52. Anal. Calc. for C$_{60}$H$_{95}$Cl$_3$In$_2$N$_4$O$_3$: C, 57.36; H, 7.62; N, 4.46. Found: C, 57.37; H, 7.52; N, 4.47.

**Synthesis of complex (R,R)-[(N$_{Me2}$N$_{H}$O$_{Ad}$)InCl]$_2$(μ-Cl)(μ-OEt) (23)**

The crude reaction mixture was filtered and pumped to dryness in vacuo yielding a pale yellow foamy solid. This solid was stirred in ether for approximately 30 minutes, then pumped to dryness in vacuo yielding the product as a pale yellow foamy solid (0.0483 g, 44 %). Due to the high solubility of this compound in all common organic solvents it was used without further purification. $^1$H NMR (600 MHz, 25 °C, CDCl$_3$): $\delta$ 7.13 (1H, m, Ar-H), 6.72 (1H, m, Ar-H), 6.59 (1H, m, Ar-H), 4.98 (1H, d, $^2$J$_{HH} = 11$ Hz, N-CH$_2$-Ar), 4.52 (0.5H, m, -OCH$_2$CH$_3$), 3.84 (1H, d, $^2$J$_{HH} = 11$ Hz, N-CH$_2$-Ar), 2.77 (1H, m, NCH), 2.66 (3H, s, N(CH$_3$)$_2$), 2.52 (1H, m, DACH), 2.48 (1H, m, NH), 2.26 (3H, m, Ad), 2.16 (3H, m, Ad), 2.02 (3H, s, Ad), 2.00 (3H, s, N(CH$_3$)$_2$), 1.91 (1H, m, DACH), 1.86 (2H, m, DACH), 1.81 (3H, m, Ad), 1.72 (3H, m, Ad), 1.31 (1.5H, t, $^3$J$_{HH} = 6$ Hz, -OCH$_2$CH$_3$), 1.28 (9H, s, C(CH$_3$)$_3$), 1.24 (2H, m, DACH), 1.12 (1H, m, DACH), 1.03 (1H, m, DACH). $^{13}$C{$^1$H} NMR (151 MHz, 25 °C, CDCl$_3$): $\delta$ 162.47, 139.04, 136.35, 125.74, 123.79, 118.68, 64.63, 62.79, 52.57, 50.84, 44.18, 40.45, 38.10, 37.43, 37.40, 33.92, 31.83, 30.77, 29.41, 24.82, 24.71, 21.86, 19.52. Anal. Calc. for C$_{60}$H$_{95}$Cl$_3$In$_2$N$_4$O$_3$: C, 57.36; H, 7.62; N, 4.46. Found: C, 57.37; H, 7.52; N, 4.47.
4.99 (1H, d, $^2J_{HH} = 12$ Hz, N-CH$_2$-Ar), 4.48 (0.5H, m, -OCH$_2$CH$_3$), 4.40 (0.5H, m, -OCH$_2$CH$_3$), 3.74 (1H, d, $^2J_{HH} = 12$ Hz, N-CH$_2$-Ar), 2.84 (1H, m, NCH), 2.77 (1H, m, NCH), 2.69 (3H, s, N(CH$_3$)$_2$), 2.57 (1H, m, DACH), 2.48 (1H, m, NH), 2.27 (3H, m, Ad), 2.18 (3H, m, Ad), 2.03 (3H, s, Ad), 2.02 (3H, s, N(CH$_3$)$_2$), 1.91 (1H, m, DACH), 1.86 (2H, m, DACH), 1.82 (3H, m, Ad), 1.73 (3H, m, Ad), 1.32 (1.5H, t, $^3J_{HH} = 6$ Hz, -OCH$_2$CH$_3$), 1.28 (9H, s, C(CH$_3$)$_3$), 1.25 (2H, m, DACH), 1.13 (1H, m, DACH), 1.03 (1H, m, DACH). $^{13}$C{$_1$H} NMR (151 MHz, 25 °C, CDCl$_3$): δ 162.47, 139.03, 136.34, 125.74, 123.79, 118.68, 64.62, 62.79, 52.57, 50.83, 44.18, 40.45, 38.10, 37.42, 37.39, 33.92, 31.83, 30.76, 29.41, 24.82, 24.71, 21.86, 19.52. Anal. Calc. for C$_{60}$H$_{95}$Cl$_3$In$_2$N$_4$O$_3$: C, 57.36; H, 7.62; N, 4.46. Found: C, 54.82; H, 7.29; N, 4.93.

**Synthesis of complex (±)-[(N$_2$Me$_2$N$_3$O$_{cm}$)InCl]$_2$(µ-Cl)(µ-OEt) (24)**

The crude complex was isolated as a clear, colourless residue. This residue was stirred with hexane for approximately 30 minutes, causing the precipitation of a white solid. The solution was filtered yielding the purified complex as a white powder, which was dried under vacuum prior to use (0.0402 g, 78 %). Single crystals of complex (±)-24 were grown from a saturated solution of the complex in toluene at room temperature and were analysed by single crystal X-ray diffraction. $^1$H NMR (600 MHz, 25 °C, CDCl$_3$): δ 7.37 (1H, m, Ar-H), 7.26 (6H, m, C(CH$_3$)$_2$Ph), 7.15 (3H, m, C(CH$_3$)$_2$Ph), 6.99 (1H, m, C(CH$_3$)$_2$Ph), 6.55 (1H, m, Ar-H), 4.82 (1H, d, $^2J_{HH} = 12$ Hz, N-CH$_2$-Ar), 3.99 (0.5H, m, -OCH$_2$CH$_3$), 3.81 (0.5H, m, -OCH$_2$CH$_3$), 3.55 (1H, d, $^2J_{HH} = 12$ Hz, N-CH$_2$-Ar), 2.66 (1H, m, NCH), 2.59 (1H, m, NCH), 2.42 (3H, s, N(CH$_3$)$_2$), 2.27 (2H, m, NH + DACH), 1.78 (3H, s, C(CH$_3$)$_2$Ph), 1.74 (3H, m, DACH), 1.72 (3H, s, C(CH$_3$)$_2$Ph), 1.70 (3H, s, C(CH$_3$)$_2$Ph), 1.64 (3H, s, C(CH$_3$)$_2$Ph), 1.16 (1H, m, DACH), 1.15 (3H, s, N(CH$_3$)$_2$), 1.05 (1H, m, DACH), 0.96 (1H, m, DACH), 0.90 (1.5H, m, -OCH$_2$CH$_3$), 0.85 (1H, m, DACH). $^{13}$C{$_1$H} NMR (151 MHz, 25 °C, CDCl$_3$): δ 161.91, 152.30, 151.22, 138.08, 135.21,
128.80, 127.66, 127.29, 126.86, 126.72, 125.68, 125.14, 124.14, 118.70, 64.28, 62.64, 52.36, 50.38, 43.76, 42.17, 41.97, 36.47, 31.07, 31.04, 30.99, 30.49, 27.64, 24.72, 24.54, 21.73, 19.22

Anal. Calc. for \( \text{C}_6\text{H}_{91}\text{Cl}_3\text{In}_2\text{N}_4\text{O}_3 \): C, 60.57; H, 6.80; N, 4.15. Found: C, 60.66; H, 6.99; N, 4.03.

**Determination of the kinetics of rac-, L- and D-LA polymerization**

Three stock solutions of rac-, L- and D-LA (960 mM) and an internal standard 1,3,5-trimethoxybenzene (60 mM) were made in 1 mL volumetric flasks in CDCl_3 and 0.5 mL of each solution was syringed into three separate Teflon-sealed NMR tubes and frozen using a liquid N\(_2\) cold well. Next, a buffer layer of CDCl_3 (0.25 mL) was added to each tube and frozen using the liquid N\(_2\) cold well. Then, a catalyst stock solution (9.6 mM) was made in a 2 mL volumetric flask in CDCl_3 and 0.25 mL of this solution was syringed into each of the three tubes and frozen using the liquid N\(_2\) cold well. The tubes were quickly evacuated while frozen and sealed under vacuum to remove N\(_2\) from the headspace of the tube. The tubes were kept frozen in liquid N\(_2\) until use. Each sample was quickly warmed to room temperature before inserting into the NMR spectrometer (400 MHz Inverse Avance Bruker Spectrometer). The polymerization was monitored to over 90% conversion by \(^1\)H NMR spectroscopy.

**Representative polymerization of rac-LA**

The appropriate amount of catalyst (e.g. for 200 eq. LA, 0.0069 mmol) was transferred using CH\(_2\)Cl\(_2\) (~ 3 mL) to a stirring solution of rac-LA (0.200 g, 1.39 mmol) in CH\(_2\)Cl\(_2\) (~ 2 mL). The resulting mixture was stirred overnight at room temperature and a test sample was removed and pumped to dryness, then dissolved in CDCl\(_3\) and analysed by \(^1\)H and \(^1\)H{\(^1\)H} NMR spectroscopy to determine conversion and tacticity, respectively. The rest of the reaction mixture was concentrated in air under vacuum to < 1 mL volume, then methanol was added while stirring to
precipitate the pure polymer as a white solid. The supernatant solution was removed and the resulting polymer was dissolved in a minimum of CH₂Cl₂ (< 1 mL). Again, methanol was added while stirring to precipitate the pure polymer and the supernatant solution was removed. This process was repeated 1 more time and the resulting polymer was washed once with pure methanol, then dried under vacuum overnight at room temperature. The polymer was then dried under vacuum overnight at ~ 50 °C in a vacuum oven and the ¹H NMR spectrum was taken of the dried polymer to confirm that no catalyst or solvent remained before analysis by GPC in chloroform.
Chapter 5: Indium complexes with pentadentate dinucleating ligands

5.1 Introduction

Our efforts to modify the tridentate ligand system developed by our group (Chapters 2-4) did not result in the isolation of either more active or more selective indium catalysts for the polymerization of lactide. We found that modifications to the ligand system had complex and often non-intuitive effects on the resulting chemistry of this ligand family with indium. In particular, modifications that led to destabilization of the dinuclear structure of the resulting indium ethoxide complexes made their isolation difficult and often led to multiple species in solution, possibly due to complex aggregation phenomena. The catalysts that could be isolated either had similar performance in the polymerization of rac-LA to the parent system or resulted in a decrease in either activity or selectivity. We found decreases in activity to be related to the substitution of the central secondary amine donor with a tertiary amine donor, for reasons as yet to be determined, and decreases in selectivity to be related to disruption of the dinuclear structure of the catalyst during the polymerization of lactide, for example due to the introduction of more sterically bulky substituents.

These observations led us to the conclusion that this tridentate ligand system is not an ideal framework for future efforts to produce more active and/or selective indium catalysts for the polymerization of cyclic esters. We were particularly concerned with the observation that the dinuclear structure of these catalysts appears to be crucial in retaining their isoselectivity in the polymerization of rac-LA. Therefore, we envisioned moving towards a new ligand framework that could bridge two metal centres and encourage the isolation of dinuclear catalysts without relying on dimerization through co-ligands bound to the indium centres (ethoxide, chloride etc.), as was necessary for the tridentate ligand system.
The concept of dinucleating ligands that can bridge two metal centres has been utilized in many areas of chemistry and the design of such ligands has been thoroughly reviewed. These types of ligands are widely used in the modeling and mimicking of biological systems, such as enzyme active sites, which often include two or more metal centres that work in tandem to catalyze a particular transformation.

The incorporation of such ligand designs in cyclic ester polymerization catalysts has been less well studied. Interesting bimetallic group 13 alkyl complexes were recently investigated by Carpentier et al. for lactide polymerization and showed a significant rate enhancement by the bimetallic aluminum complexes versus their monometallic analogues, possibly due to cooperation of the two metal centres, although no such effect was seen for the indium analogues.

The most notable system among these examples is that of Hillmyer, Tolman and Williams et al. first introduced in Chapter 1 (Figure 5.1).

![Figure 5.1](image)

**Figure 5.1.** Catalysts with a pentadentate dinucleating ligand investigated by Hillmyer, Tolman and Williams et al. for the polymerization of cyclic esters.

Preliminary investigations of the zinc analogue proved it to be a highly controlled, living and active catalyst for the polymerization of lactide, converting 300 equivalents rac-LA to over
90% conversion in only 30 minutes at room temperature, although it was not stereoselective producing only atactic PLA.\textsuperscript{38} Subsequent investigations focused on Co and Mg analogues, however these were found to be much less active and controlled, needing long reaction times, up to 5 hours for Co and 23 hours for Mg, at much higher catalyst loadings in order to reach high conversions of monomer with controlled molecular weights. The lower control exhibited by the Co and Mg analogues was attributed to deactivation processes causing catalyst death, which were most prevalent at longer reaction times or at low catalyst loadings.\textsuperscript{155}

Williams \textit{et al.} subsequently investigated a series of zinc analogues with two additional ligands having imine and secondary amine donors (Figure 5.2).\textsuperscript{39} In addition to discovering a more general synthesis of these complexes, via a salt metathesis route through trihalide intermediates, the effect of the halide ligand was investigated by synthesizing the corresponding bromide and iodide analogues of the original zinc catalyst (Figure 5.2).

![Figure 5.2](image)

\textbf{Figure 5.2.} Dinuclear zinc catalysts with pentadentate dinucleating ligands investigated by Williams \textit{et al.} for the polymerization of lactide.\textsuperscript{39}

In these systems, the polymerization of \textit{rac}-LA (200 eq. in CH\textsubscript{2}Cl\textsubscript{2} at room temperature to ~90% conversion) proceeds with decreasing rate in the order Br (22 min) > Cl (183 min) > I (1453 min) and therefore only the bromide analogues of the other two ligands were used for
polymerization studies. Under the same conditions, the imine analogue proved to be much slower, needing 4299 minutes (~72 hours) to reach ~90% conversion. The secondary amine analogue is the fastest of the three catalysts, reaching ~90% conversion in only 1 minute. All three catalysts show controlled molecular weights with low PDIs (< 1.2), however the molecular weight control is the greatest with the fastest catalyst, with the secondary amine donors. No selectivity data for these catalysts was reported.

These promising results inspired our group to use similar ligands to synthesize dinuclear indium catalysts and investigate their lactide polymerization behavior. We therefore synthesized a family of pentadentate proligands, both achiral and chiral. This chapter will focus on the synthesis of these proligands and the subsequent complexation of indium, and will outline the lactide polymerization behavior of an indium ethoxide complex supported by one such ligand.

5.2 Results and discussion

5.2.1 Synthesis and characterization of achiral pentadentate proligands

Achiral pentadentate phenolate proligands with central tertiary amine (L-12), imine (L-13) and secondary amine (L-14) donors on each side arm were synthesized via modified literature procedures (Scheme 5.1).

A simple Mannich condensation of 4-tert-butylphenol and N,N,N’-trimethylethylenediamine with paraformaldehyde affords proligand HO_{tBu}(L_{Me})_2 (L-12). Alternatively, condensation of 4-tert-butyl-2,6-diformylphenol with N,N-dimethylethylenediamine affords the imine proligand HO_{tBu}(L) (L-13), which can be reduced with NaBH₄ to yield proligand HO_{tBu}(L_H) (L-14) with central secondary amine donors.
Scheme 5.1. Synthesis of achiral pentadentate proligands HO$_{tBu}(L_{Me})_2$ (L-12) and HO$_{tBu}(L_H)_2$ (L-14) with central tertiary and secondary amine donors and HO$_{tBu}(L)_2$ (L-13) with central imine donors.

The purification of these proligands proved challenging. Contrary to what had been reported in the literature for the para-methyl substituted analogues, the synthesis of the analogues we had targeted, with para-tert-butyl groups, did not provide pure material, as evidenced by the presence of unknown impurity peaks in the $^1$H NMR spectra of the crude products. Purification by column chromatography on silica was not successful, as the highly polar nature of these compounds made removal from silica difficult. Crystallization was also unsuccessful as the compounds were found to be soluble, thick oils under all conditions tested. Flash column chromatography using alumina provided a means to remove some of the impurities present in proligands L-12 and L-14, as evidenced by $^1$H NMR spectroscopy, and they were used without further purification. Proligand L-13 was used as the crude compound without purification.
The $^1$H NMR spectra of proligands L-12-14 indicate that they are symmetric in solution (see Appendix D, Figures D.1-3). Only one singlet for both aromatic protons appears in the $^1$H NMR spectra of proligands L-12 and L-14 at ~7 ppm. Interestingly, in proligand L-13 the aromatic protons appear as a very broad singlet at 7.69 ppm, as does the imine proton (N=CH) at 8.61 ppm, and the integrations of these peaks are significantly reduced from the expected values. This observation is consistent with the para-methyl substituted analogues reported in the literature$^{39}$ and suggests some functionality on the NMR time scale that is specific to the imine proligand L-13, as no broadness is observed in the aromatic peaks of the reduced amine proligands L-12/14. Further studies would be needed in order to elucidate the cause of this functionality. The spectra of all three proligands show the diagnostic methylene NCH$_2$CH$_2$N peaks of the ligand backbone as two triplets in the 2.4 – 4 ppm range. In addition, the diagnostic methylene Ar-CH$_2$-N protons of the reduced backbone in proligands L-12 and L-14 appear as a singlet in the 3.6 – 3.8 ppm range.

5.2.2 Synthesis and characterization of chiral pentadentate proligands

We were interested in synthesizing a chiral pentadentate proligand with a diaminocyclohexane backbone similar to our tridentate ligand system L-2 (Scheme 5.2). We envisioned synthesizing this analogue in a similar manner to the achiral analogue L-14, via condensation of 4-tert-butyl-2,6-diformylphenol with racemic or enantiopure $N,N$-dimethyl-trans-1,2-diaminocyclohexane to form the imine precursor HO$_{Bu}$(NNMe$_2$)$_2$ (L-15) and subsequent reduction to form the desired proligand HO$_{Bu}$(NHMe$_2$)$_2$ (L-16) (Scheme 5.2).
Scheme 5.2. Synthesis of chiral pentadentate ligands L-15-16 with cyclohexyldiamine backbones.

We encountered unexpected difficulties in the synthesis of the imine precursor L-15.

Condensation of 4-tert-butyl-2,6-diformylphenol with 2 or more equivalents of racemic or enantiopure \(N,N\)-dimethyl-trans-1,2-diaminocyclohexane \((NN_{Me2})\) invariably led to a mixture of the mono- and bis-substituted products (Scheme 5.3). For example, the \(^1\)H NMR spectrum of the crude mixture from the reaction of 4-tert-butyl-2,6-diformylphenol and 2 equivalents of \((\pm)\)-\(NN_{Me2}\) in anhydrous methanol at room temperature under \(N_2\) shows the formation of two products, presumably the mono- and bis-imines, in a ratio of approximately 1:1 (mono:bis) after \(\sim\) 3.5 days. This ratio increases to 1:9 (mono:bis) after the addition of another equivalent of \((\pm)\)-\(NN_{Me2}\) and stirring for an additional 18 hours (Scheme 5.3 and Figure 5.3). These reaction times were not optimized and similar reactions produced the same ratio of products after only a few hours (1-2) of stirring at room temperature. Therefore, the prolonged reactions times used for this example are not necessary for the formation of the products nor do they alter the ratio of the two products formed.
Scheme 5.3. Product distributions in the synthesis of chiral imine proligand L-15.

Figure 5.3. $^1$H NMR spectra (300 MHz, CDCl$_3$, 25 °C) of the crude product mixtures resulting from the reaction of 4-tert-butyl-2,6-diformylphenol with (a) 1 eq. (±)-NN$_{Me2}$ for 1 hour, (b) 2 eq. (±)-NN$_{Me2}$ for 3.5 days and (b) an additional 1 eq. (±)-NN$_{Me2}$ added to reaction (b) for 18 hours. The reactions were carried out in methanol at room temperature.
The peaks in the $^1$H NMR spectra (Figure 5.3, see Appendix D, Figure D.4 for full spectrum) in the product mixture assigned to the desired bis-L-15 are similar to the related achiral bis-imine L-13, with broad singlets appearing at 7.65 and 8.53 ppm for the Ar-H and imine N=CH protons, respectively. The mono-substituted product (mono-L-15) shows sharp singlets at 8.24 and 10.54 ppm for the imine (N=CH) and aldehyde (CHO) protons, respectively. In addition, the asymmetry of the mono-L-15 product results in two doublets for the Ar-H peaks, which appear at 7.92 and 7.44 ppm. The assignment of the mono-L-15 product was further supported by its independent synthesis from the reaction of 4-tert-butyl-2,6-diformylphenol with only 1 equivalent of ($\pm$)-NNMe$_2$ (Figure 5.3a).

The condensation of 4-tert-butyl-2,6-diformylphenol and (R,R)-N,N-dimethyl-trans-1,2-diaminocyclohexane leads to the same products as the reactions from racemic diamine, as described above (as determined by $^1$H NMR spectroscopy). Therefore, we assume that the products formed from using the racemic diamine are a mixture of homochiral (RR/RR) and (SS/SS) enantiomers, and the “meso” (RR/SS) compound is not formed.

The purification of these compounds proved difficult. In addition to containing both the mono- and bis-imine products, the crude mixtures contain excess diamine, which is necessary to push the reaction towards the bis-imine product. Column chromatography was attempted on the crude reaction mixtures (silica and alumina) but conditions that could separate the two products from either each other or the unreacted diamine could not be found.

Several strategies were attempted to remove the water byproduct of the condensation reaction, in order to push the reaction to completion and therefore towards the desired bis-imine product without the use of excess diamine. First, simple strategies involving the use of desiccating agents (molecular sieves, MgSO$_4$, tetraethyl orthosilicate) were used, however these
did not result in any changes to the product distributions. Next, Dean-Stark conditions were employed to remove the water using toluene as a solvent for the reaction and heating at 160 °C, but again this process did not result in a change to the product distribution. Attempts were also made to push the reaction to completion by the addition of an acid catalyst. Under acid catalyzed conditions with either MeOH/formic acid or toluene/p-toluene sulfonic acid there was little improvement in the product distribution. As well, with MeOH/formic acid a third unidentified byproduct was seen in the reaction mixture.

Despite the difficulties in obtaining the pure bis-imine L-15 from these condensation reactions, we attempted the reduction of the mixture of products by reaction with NaBH₄ in MeOH (Scheme 5.4).

\[
\begin{align*}
&\text{Scheme 5.4.} & \text{Synthesis of chiral amine proligand L-16 from reduction of crude mixture of imine products L-15 and unreacted diamine.} \\
&\text{The reduction of the mixture containing the bis-imine L-15 led to the formation of one major product, which is consistent with the desired amine proligand L-16, as well as unknown by-products resulting from the reaction of the mono-L-15 and diamine impurities present in the starting mixture with NaBH₄. In the } ^1\text{H NMR spectrum of the crude product (Figure 5.4, see Appendix D, Figure D.5 for full spectrum) the major product shows two singlets in the aromatic region at 7.00 and 7.02 ppm (~4H total) as well as what appears to be four overlapping doublets.}
\end{align*}
\]
in the methylene region at ~4 ppm and ~3.8 ppm (8H total). The relative integration of these peaks is consistent with the desired reduced ligand with two amine arms, confirming the major product is the result of reduction of bis-L-15. As well, the coupling patterns are consistent with this formulation, as no coupling between the aromatic protons would be expected for the symmetric L-16 structure (only singlets are observed) and the chiral nature of the backbone would cause the methylene N-CH2-Ar protons of the reduced backbone to become diastereotopic and couple to each other, forming doublets. The existence of two sets of signals in the aromatic and methylene regions, as well as two N(CH$_3$)$_2$ signals at 2.14 and 2.15 ppm (see Appendix D, Figure D.5), suggests that two diastereomers may be present in solution.

![Figure 5.4](image)

**Figure 5.4.** $^1$H NMR spectrum (600 MHz, CDCl$_3$, 25 °C) of crude proligand L-16 showing the aromatic and methylene regions.

As for the imine L-15, purification of the crude product mixture containing L-16 was difficult. A small improvement in purity, as determined by $^1$H NMR spectroscopy, could be achieved by filtration of the crude reaction mixture through alumina (see experimental), however complete separation of the desired product from the unknown by-products could not be achieved. The purity of the product is difficult to estimate by $^1$H NMR spectroscopy as the identity of the by-products is unclear. Therefore, elemental analysis of this product was not undertaken, however low resolution electron-ionization (EI) mass spectrometry did show the presence of the desired parent mass at 458 (theo = 458.40). The purification of proligand L-16 was not pursued
further, and along with achiral proligands L-12-14 it was utilized for the formation of indium complexes, as will be discussed in the next section.

5.2.3 Synthesis and characterization of indium complexes

Despite the difficulties in purifying the achiral proligands L-12-14 and chiral proligand L-16, they were utilized for the synthesis of indium complexes. Deprotonation of the proligands with potassium tert-butoxide was carried out to form the potassium salts. Subsequent salt metathesis of the potassium salts with 2 equivalents of indium trichloride was attempted in order to form dinuclear indium chloride complexes, bridged by the pentadentate ligand (Scheme 5.5).

Using proligand L-12, complex \([\text{L}_{\text{Me}}\text{InCl}_2]_2(\mu-\text{O}_{\text{Bu}})(\mu-\text{Cl})\) (25) could be synthesized under these conditions, however all reactions of the achiral imine L-13 and amine L-14 proligands as well as the chiral amine proligand L-16 gave intractable mixtures of products under a variety of conditions. It is possible to form a variety of isomers with these pentadentate ligands, for example coordination may occur to only one indium centre or alternatively the ligands can bridge multiple indium centres forming complex aggregates. In addition, several diastereomers can form for both the achiral proligands, based on the orientation of the chelate rings formed from the ethylenediamine backbone, an observation that was previously described for the related zinc complexes reported by Williams et al.\textsuperscript{39} In addition, the chirality of the cyclohexyldiamine backbone of proligand L-16 can also lead to the formation of several diastereomers. The impurities present in these ligands may also contribute to the formation of undesired by-products. It is not surprising, therefore, that a complex mixture of products is formed with some of these ligand analogues. However, because of the complexity of the product mixtures seen in the \(^1\text{H}\) NMR spectra of these complexes as well as the fact that impure proligands were utilized in their
synthesis, it is difficult to identity the products formed in these reactions. Therefore, proligands L-13-14 and L-16 were not utilized further for the formation of metal complexes.

**Scheme 5.5.** Synthesis of dinuclear indium chloride complex 25 with bridging pentadentate ligands L-12-14 and L-16.

The $^1$H NMR spectrum of the crude reaction mixture from the formation of complex 25 shows peaks consistent with the desired complex as the major product, however a complex mixture of peaks is seen in addition to this major product, most likely as a result of several possible diastereomers of the complex as described above (Figure 5.5). However, the major product can be easily crystallized from this mixture in acetonitrile, chloroform or THF although the crystallization is low yielding (15-30 %).

The $^1$H NMR spectrum of crystals of complex 25 suggests that the complex is symmetric about the central phenol in solution, with only a singlet appearing at 7.05 ppm for the two aromatic protons (Figure 5.5b, see Appendix D, Figure D.6 for full spectrum). The central Ar-$CH_2$-N methylene protons appear as two diastereotopic doublets at 5.36 and 3.27 ppm, with the
other methylene N-CH$_2$CH$_2$-N protons appearing as two pairs of diastereotopic multiplets in the 2-3 ppm range. The central N-CH$_3$ protons appear as a sharp singlet at 3.02 ppm, whereas the N(CH$_3$)$_2$ protons appear as very broad singlets at 2.87 and 2.60 ppm. This suggests possible fluctionality in this complex, possibly between different conformations of the ethylenediamine backbone as was proposed for the related zinc complexes reported by Williams et al.,$^{39}$ although further studies would be needed to confirm this hypothesis.

![Figure 5.5. $^1$H NMR spectra (300 MHz, CDCl$_3$, 25 °C) of (a) crude complex 25 and (b) crystals of complex 25 isolated from a saturated solution of the crude complex in THF.](image)

Reaction of complex 25 with an excess of sodium ethoxide yields the ethoxide-bridged complex [(L$_{Me}$)InCl$_2$](µ-O$_{tBu}$)(µ-OEt) (26) (Scheme 5.6). The excess of sodium ethoxide appears to be necessary for the reaction to go to completion, as reactions with less than 2 equivalents of NaOEt result in mixtures of the desired complex and unreacted complex 25. This may be due to the low solubility of the starting materials and product, as complex 25 and NaOEt are only sparingly soluble in toluene, as is complex 26. Reactions in toluene invariably lead to very opaque reaction mixtures with large amounts of crude precipitate formation, much more than would be expected for just the NaCl byproduct. Filtration of the crude reaction mixture can
be facilitated by adding THF, and the pure complex can be crystallized directly from the crude mixture in yields of 30 – 50 %. Alternatively, the reaction can be carried out in THF, yielding similar yields of the crystallized complex.

**Scheme 5.6.** Synthesis of dinuclear indium ethoxide complex 26 bridged by an achiral pentadentate ligand.

Surprisingly, reaction of crude complex 25 (Figure 5.5a) with 2 equivalents of NaOEt also leads to complex 26 with little to no increase in the amount of impurity peaks in the $^1$H NMR spectrum of the crude compound, as compared to reactions of crystallized complex 25 with NaOEt as described above. It is possible that complex 25 may have several different conformations in solution, leading to a complex mixture of peaks in the $^1$H NMR spectrum of the crude compound, with one major conformation, which can be crystallized, being dominant. This is supported by the broadness of the $N(CH_3)_2$ methyl peaks in the $^1$H NMR spectrum of this complex, which suggests that some fluctuationality is at least a possibility in this system. It is possible that the same degree of fluctuationality is not present in the ethoxide complex and that a single dominant conformation would result from reaction of the mixture of conformations of the chloride complex with NaOEt. Further studies would be needed, however, to elucidate whether this is the case.
As for complex 25, the $^1$H NMR spectrum (see Appendix D, Figure D.7) of complex 26 suggests that the complex is symmetric about the central phenol in solution, showing only a singlet for both aromatic protons at 7.03 ppm. The Ar-$CH_2$-N methylene protons appear as two diastereotopic doublets at 5.36 and 3.25 ppm, which flank the $OCH_2CH_3$ protons that appear as two multiplets at 4.41 and 4.32 ppm, similar to dinuclear indium ethoxide complexes with related tridentate ligands discussed in the other chapters of this thesis. These signals appear in a 2:1:1:2 ratio indicative of a single ethoxide ligand, consistent with the proposed structure. As for complex 25, the central N-$CH_3$ protons appear as a sharp singlet at 3.02 ppm, whereas the N($CH_3$)$_2$ protons appear as broad singlets at 2.86 and 2.57 ppm. This suggests possible flexibility of the amine arms in solution similar to complex 25.

Single crystals of complex 26 were grown from a saturated solution of the complex in toluene, and its solid-state molecular structure was determined using single crystal X-ray crystallography (Figure 5.6 and Table 5.1; see Appendix D, Table D.1 for crystallographic parameters). The complex crystallizes as two separate molecules in the unit cell (only one is depicted in Figure 5.6) that differ in the orientation of their ethoxide groups. The complexes show distorted octahedral metal centres bridged by the phenolic oxygen of the ligand as well as the oxygen of the ethoxide ligand.

Attempts to grow single crystals of the indium chloride complex 25 from a saturated solution of the complex in THF resulted in the isolation of crystals of the related hydroxide bridged complex [(L$_{Me}$)InCl$_2$]$_2$(µ-O$_{Bu}$)(µ-OH) (27), as determined by single crystal X-ray crystallography. The solid-state molecular structure of the same complex had been previously solved by Insun Yu in our group, from single crystals isolated from a saturated solution of complex 25 in acetonitrile (Figure 5.6 and Table 5.1; see Appendix D, Table D.1 for...
crystallographic parameters). Complex 27 most likely forms as a result of hydrolysis of one of the chloride ligands in complex 25 with adventitious water present in the system. As discussed in Chapter 2, hydroxide bridged complexes can also be isolated by hydrolysis of related indium complexes within our tridentate ligand family, however reaction of the indium dichloride complexes in that family only results in hydrolysis of the chloride ligands in the presence of large excesses of water.\textsuperscript{96-98} This suggests that the indium chloride complexes isolated within this pentadentate ligand family may be less stable to hydrolysis. Complex 27 is nearly isostructural with complex 26, differing only slightly in bond lengths and angles (Table 5.1).

![Solid-state molecular structures of complexes 26 (left) and 27 (right). Thermal ellipsoids are set at 50% probability and H atoms and solvent removed for clarity. The unit cell for complex 26 contains two distinct molecules differing in the position of their ethoxide groups, only one of which is depicted here.](image)

**Figure 5.6.** Solid-state molecular structures of complexes 26 (left) and 27 (right). Thermal ellipsoids are set at 50% probability and H atoms and solvent removed for clarity. The unit cell for complex 26 contains two distinct molecules differing in the position of their ethoxide groups, only one of which is depicted here.
Table 5.1. Selected bond lengths and angles for complexes 26 and 27.

<table>
<thead>
<tr>
<th>Bond lengths (Å)</th>
<th>Complex 26</th>
<th>Complex 27</th>
</tr>
</thead>
<tbody>
<tr>
<td>In1-N1</td>
<td>2.353(5)</td>
<td>2.3689(17)</td>
</tr>
<tr>
<td>In2-N3</td>
<td>2.382(4)</td>
<td>2.3904(18)</td>
</tr>
<tr>
<td>In1-N2</td>
<td>2.284(6)</td>
<td>2.2847(17)</td>
</tr>
<tr>
<td>In2-N4</td>
<td>2.264(5)</td>
<td>2.2933(19)</td>
</tr>
<tr>
<td>In1-Cl1</td>
<td>2.4601(15)</td>
<td>2.4761(6)</td>
</tr>
<tr>
<td>In2-Cl3</td>
<td>2.4683(15)</td>
<td>2.5055(6)</td>
</tr>
<tr>
<td>In1-Cl2</td>
<td>2.4547(18)</td>
<td>2.4599(6)</td>
</tr>
<tr>
<td>In2-Cl4</td>
<td>2.4431(17)</td>
<td>2.4524(6)</td>
</tr>
<tr>
<td>In1-O1</td>
<td>2.219(4)</td>
<td>2.2569(15)</td>
</tr>
<tr>
<td>In2-O1</td>
<td>2.231(3)</td>
<td>2.2441(14)</td>
</tr>
<tr>
<td>In1-O2</td>
<td>2.110(4)</td>
<td>2.0947(16)</td>
</tr>
<tr>
<td>In2-O2</td>
<td>2.097(4)</td>
<td>2.0938(17)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bond angles (°)</th>
<th>Complex 26</th>
<th>Complex 27</th>
</tr>
</thead>
<tbody>
<tr>
<td>In1-O1-In2</td>
<td>102.01(13)</td>
<td>101.08(5)</td>
</tr>
<tr>
<td>In1-O2-In2</td>
<td>110.60(16)</td>
<td>112.13(7)</td>
</tr>
<tr>
<td>O1-In1-O2</td>
<td>73.69(13)</td>
<td>73.17(6)</td>
</tr>
<tr>
<td>O1-In2-O2</td>
<td>73.69(14)</td>
<td>73.46(6)</td>
</tr>
<tr>
<td>O1-In1-N1</td>
<td>87.14(16)</td>
<td>86.25(6)</td>
</tr>
<tr>
<td>O1-In2-N3</td>
<td>85.27(13)</td>
<td>85.97(6)</td>
</tr>
<tr>
<td>O2-In1-N1</td>
<td>103.5(2)</td>
<td>101.06(6)</td>
</tr>
<tr>
<td>O2-In2-N3</td>
<td>104.71(15)</td>
<td>105.74(7)</td>
</tr>
<tr>
<td>O1-In1-N2</td>
<td>86.44(16)</td>
<td>86.53(6)</td>
</tr>
<tr>
<td>O1-In2-N4</td>
<td>86.80(14)</td>
<td>86.32(6)</td>
</tr>
<tr>
<td>O2-In1-N2</td>
<td>159.86(18)</td>
<td>159.70(6)</td>
</tr>
<tr>
<td>O2-In2-N4</td>
<td>160.00(15)</td>
<td>159.19(6)</td>
</tr>
<tr>
<td>N1-In1-N2</td>
<td>78.3(2)</td>
<td>77.44(6)</td>
</tr>
<tr>
<td>N3-In2-N4</td>
<td>77.40(16)</td>
<td>77.04(7)</td>
</tr>
<tr>
<td>N1-In1-Cl1</td>
<td>166.54(19)</td>
<td>166.75(4)</td>
</tr>
<tr>
<td>N3-In2-Cl3</td>
<td>166.38(12)</td>
<td>165.29(5)</td>
</tr>
<tr>
<td>N2-In1-Cl2</td>
<td>100.38(16)</td>
<td>99.47(5)</td>
</tr>
<tr>
<td>N4-In2-Cl4</td>
<td>100.28(11)</td>
<td>98.77(5)</td>
</tr>
<tr>
<td>O1-In1-Cl2</td>
<td>170.12(10)</td>
<td>170.91(4)</td>
</tr>
<tr>
<td>O1-In2-Cl4</td>
<td>169.48(9)</td>
<td>170.42(4)</td>
</tr>
<tr>
<td>O2-In1-Cl1</td>
<td>89.94(11)</td>
<td>92.19(5)</td>
</tr>
<tr>
<td>O2-In2-Cl3</td>
<td>88.86(11)</td>
<td>88.93(5)</td>
</tr>
</tbody>
</table>

5.2.4 Polymerization studies

The polymerization of 200 equivalents rac-LA was undertaken with catalyst 26. The catalyst is active, but the polymerization is very slow, reaching only 71% in CH$_2$Cl$_2$ at room temperature in 1 week. The rate is slower in THF under similar conditions, reaching only 49%
conversion in 1 week and only 88% conversion after several weeks (Table 5.2). This may be due to competition of the THF for coordination to the metal centre, thereby reducing the polymerization rate. The temperature of the reaction was increased to 40 °C in both solvents, however the conversions did not increase over a 1 week period, suggesting that the catalyst may be unstable at higher temperatures.

Polymer molecular weights and PDIs were determined for the polymerization of 200 equivalents of rac-LA by catalyst 26 in CH₂Cl₂ at room temperature and 40 °C (Table 5.2). The molecular weights are higher than the expected values under both conditions, however the PDIs are low (<1.1) suggesting the polymerization is still reasonably controlled. A slow initiation rate, relative to propagation, but an otherwise controlled polymerization may be the case with this catalyst under these conditions.

When the polymerizations were carried out in THF the crude polymers isolated were very soluble and could not be precipitated from MeOH, indicating low molecular weight PLA was formed. This is consistent with the low conversions reached. Consequently, the molecular weights and PDI values could not be determined for the polymers resulting from reactions in THF.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solv.</th>
<th>Temp.</th>
<th>T (d)</th>
<th>Conv. (%)</th>
<th>Mₙthetab (Da)</th>
<th>MₙGPCc (Da)</th>
<th>PDIc</th>
<th>Prc²</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH₂Cl₂</td>
<td>R.T.</td>
<td>7</td>
<td>71</td>
<td>13452</td>
<td>48260</td>
<td>1.03</td>
<td>0.93</td>
</tr>
<tr>
<td>2</td>
<td>CH₂Cl₂</td>
<td>40 °C</td>
<td>7</td>
<td>72</td>
<td>13448</td>
<td>53930</td>
<td>1.08</td>
<td>0.92</td>
</tr>
<tr>
<td>3</td>
<td>THF</td>
<td>R.T.</td>
<td>7</td>
<td>49</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>0.88</td>
</tr>
<tr>
<td>4</td>
<td>THF</td>
<td>40 °C</td>
<td>7</td>
<td>39</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>0.85</td>
</tr>
<tr>
<td>5</td>
<td>THF</td>
<td>R.T.</td>
<td>52</td>
<td>88</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>0.92</td>
</tr>
</tbody>
</table>

*aMonomer conversion, determined by ¹H NMR spectroscopy. bCalculated from [LA]₀/[initiator] × LA conversion × Mₖ (144.13) + Mₖ (46.07). cDetermined by GPC measurements in THF. dCalculated from the ¹H{¹H} NMR spectra and Bernoullian statistics.
In contrast to the low rac-LA polymerization activity and varying molecular weight control exhibited by catalyst 26 the selectivity is remarkably high (Table 5.2). There is also no significant solvent or temperature dependence of the selectivity of the system, as the polymers produced in CH$_2$Cl$_2$ ($P_r = 0.92 – 0.93$) and THF ($P_r = 0.85 – 0.92$) are highly heterotactic under all conditions tested, indicating a high degree of chain end control is present in this system.

5.3 Discussion and conclusions

In this chapter we synthesized a family of pentadentate proligands capable of bridging two metal centres. The synthesis of achiral proligands L-$12$-$14$ with ethylenediamine backbones was based on previously published procedures,$^{38-39,159}$ however their purification proved difficult. A chiral proligand L-$16$ with cyclohexyldiamine backbones was synthesized via a similar route, however the synthesis was complicated by difficulties in the condensation of the starting materials, 4-tert-butyl-2,6-diformylphenol and $N,N$-dimethyl-trans-1,2-diaminocyclohexane, to produce the desired bis-substituted imine, a precursor to the desired amine proligand L-$16$. Consequently, this proligand could only be isolated as a mixture of the desired product and unidentified by-products, and it was therefore used without further purification, along with proligands L-$12$-$14$ in the synthesis of indium complexes.

The synthesis of discrete indium chloride complexes with these proligands proved difficult. Complex 25 could be easily synthesized from achiral proligand L-$12$, with central tertiary amine donors, however the synthesis of indium chloride complexes from the other proligands only gave intractable mixtures of products. The possibility of forming several different diastereomers of these complexes, even those with achiral proligands, is most likely responsible for the complex mixture of products formed in these reactions. This is consistent with the related zinc complexes with the same series of proligands, bearing para-methyl instead
of para-tert-butyl substituents on the central phenol, reported by Williams et al.\textsuperscript{39} In their zinc trihalide complexes, mixtures of several different diastereomers were seen in solution and in some cases even in the solid-state. It is reasonable to assume then that similar mixtures of diastereomers may form for these related indium chloride complexes. However, it is important to note that the impurities present in the proligand starting materials, particularly those in the chiral proligand L-16, may also lead to the formation of undesired products, and therefore the mixtures most likely contain the different possible indium chloride diastereomers as well as unknown by-products. For this reason metal complexes with proligands L-13-14 and L-16 were not pursued further, although further detailed characterization studies could be pursued in the future in order to confirm the identity of the product mixtures.

Salt metathesis of the indium chloride complex 25 led to the formation of the ethoxide bridged complex 26. The proposed structure was confirmed from the solid state molecular structure, although broad resonances in the \textsuperscript{1}H NMR spectrum of this complex suggest some fluctionality is present in solution. The solid-state molecular structure of the related hydroxide bridged complex 27 was isolated from the crystallization of the chloride complex 25, and presumably results from reaction of the complex with adventitious water present in the system. It is nearly isostructural with the ethoxide bridged complex, with similar bond lengths and angles.

The polymerization of rac-LA (200 eq.) with complex 26 is very slow, with only \textasciitilde70\% conversion being reached after 1 week at room temperature in CH\textsubscript{2}Cl\textsubscript{2}. This is in complete contrast to the related zinc analogue, which reaches high conversions in only \textasciitilde30 minutes at room temperature under similar conditions.\textsuperscript{38-39,155} The polymerization rate is even slower in THF, with conversions of only \textasciitilde50\% being reached in 1 week at room temperature under the same conditions, presumably due to competition of the solvent with lactide for coordination to
the metal centre. Increasing the temperature did not have an impact on the conversions of lactide to PLA, which may indicate the catalyst is not stable at higher temperatures.

The molecular weights of the resulting polymers were not controlled using complex 26, with higher than theoretical molecular weights being seen for polymerizations carried out in CH₂Cl₂. The PDIs of the resulting polymers were low, however, indicating that poor initiation but fast and controlled propagation may be the case with this catalyst in CH₂Cl₂.

Polymers isolated from reactions in THF were very soluble and could not be purified and analyzed by GPC measurements. This is consistent with the low conversions of monomer seen in this solvent and indicates that only low molecular weight polymers were made. This may be a result of competition of the THF for coordination to the metal centre, which would slow the rate of initiation even further than reactions in CH₂Cl₂.

Despite the lack of molecular weight control for complex 26, it is highly selective in the polymerization of rac-LA, producing heterotactic PLA (Pₜ ~ 0.9). The high selectivity of this system is in direct contrast to the related zinc complex reported in the literature, which produces only atactic PLA.³⁸⁻³⁹,¹⁵⁵ This contrast may in part be due to the larger steric bulk of the indium complex, which is six coordinate at each metal centre instead of five coordinate in the zinc system, although it is unclear how metal size would affect the overall steric bulk around the metal centres. However, greater steric bulk at the indium centres compared to the zinc analogue may also explain the reduced rates of polymerization, which are presumably due to the poor initiation of the system due to the inaccessibility of the indium centres to the incoming lactide monomer. This is also consistent with the high chain end control exhibited by the system, which produces highly heterotactic PLA.
It is interesting that a similarly low activity is seen with complex 26, which has central tertiary amine donors, as compared to complexes 15 and 11 described in Chapter 3, with related tridentate ligands also having central tertiary amine donors. It is still unclear from these results the exact cause of the decrease in polymerization activity in these “N-methylated” analogues, although a clear trend has emerged towards decreased activity upon methylation of the central amine in the family of aminophenolate ligands utilized by our group. However, as the analogue of complex 26 with central secondary amine donors (from proligand L-14) could not be isolated, it is unclear if the same trend in activity would be present in this series of dinuclear indium ethoxide complexes with pentadentate ligands. Therefore, the direct contribution of N-methylation on the low polymerization activity of complex 26 is unclear and may be due to a combination of complex steric and/or electronic factors that have yet to be determined.

In moving forward with these bridging ligand systems future work should focus on reducing the steric bulk around the indium centres to allow better initiation of the polymerization, while still retaining sufficient bulk to promote stereoselective polymerization. It would also be interesting to synthesize new chiral ligand backbones that may allow for the polymerization to be site controlled and produce isotactic PLA microstructures. As well, future directions may need to include removing some of the flexibility of the ligand backbone in order to prevent the formation of complex mixtures of indium complexes due to conformational flexibility, while still retaining enough flexibility to allow for the formation of stable dimeric indium complexes.
5.4 Experimental

General procedures

All air and/or water sensitive reactions were carried out under N\textsubscript{2} in an MBraun glovebox. A Bruker Avance 600 MHz spectrometer was used to record the \textsuperscript{1}H NMR, \textsuperscript{13}C\{\textsuperscript{1}H\} NMR spectra and \textsuperscript{1}H\{\textsuperscript{1}H\} NMR spectra. \textsuperscript{1}H NMR chemical shifts are given in ppm versus residual protons in deuterated solvents as follows: δ 57.27 for CDCl\textsubscript{3}. \textsuperscript{13}C\{\textsuperscript{1}H\} NMR chemical shifts are given in ppm versus residual \textsuperscript{13}C in solvents as follows: δ 77.00 for CDCl\textsubscript{3}. Diffraction measurements for X-ray crystallography were made on Bruker X8 APEX II and Bruker APEX DUO diffractometers with graphite monochromated Mo-K\textsubscript{α} radiation. The structures were solved by direct methods and refined by full-matrix least-squares using the SHELXTL crystallographic software of the Bruker-AXS. Unless specified, all non-hydrogens were refined with anisotropic displacement parameters, and all hydrogen atoms were constrained to geometrically calculated positions but were not refined. EA CHN analysis was performed using a Carlo Erba EA1108 elemental analyzer. The elemental composition of an unknown sample was determined by using a calibration factor. The calibration factor was determined by analyzing a suitable certified organic standard (OAS) of a known elemental composition. Molecular weights were determined by GPC-LLS using an Agilent liquid chromatograph equipped with an Agilent 1200 series pump and autosampler, three Phenogel 5 μm Narrow Bore columns (4.6 × 300 mm with 500 Å, 10\textsuperscript{3} Å and 10\textsuperscript{4} Å pore size), a Wyatt Optilab differential refractometer, Wyatt tristar miniDAWN (laser light scattering detector) and a Wyatt ViscoStar viscometer. The column temperature was set at 40 °C. A flow rate of 0.5 mL/min was used and samples were dissolved in THF (ca. 2 mg/mL), and a dn/dc value of 0.042 mL/g was used. Narrow molecular weight polystyrene standards were used for calibration purposes.
**Materials**

Toluene, diethyl ether, hexane, and tetrahydrofuran were degassed and dried using alumina columns in a solvent purification system. The THF was further dried over sodium/benzophenone and vacuum transferred to a Straus flask where it was degassed prior to use. In addition CH$_3$CN, CHCl$_3$ and CH$_2$Cl$_2$ were dried over CaH$_2$ and vacuum transferred to a Straus flask where they were degassed prior to use. Deuterated chloroform (CDCl$_3$) was dried over CaH$_2$ and vacuum transferred to a Straus flask and then degassed through a series of freeze-pump-thaw cycles. Trifluoroacetic acid was purchased from Alfa Aesar and dried over activated 4 Å molecular sieves and stored under N$_2$ prior to use. InCl$_3$ was obtained from Strem Chemicals and used without further purification. Lactide samples were obtained from Purac Biomaterials and recrystallized several times from hot, dry toluene and dried under vacuum prior to use.

**Synthesis of 4-tert-butyl-2,6-diformylphenol**

This synthesis was adapted from the literature.$^{39,159}$ A Schlenk flask was charged with 4-tert-butylphenol (15.089 g, 100.4 mmol) and hexamethylenetetramine (28.190 g, 201.1 mmol). Anhydrous trifluoroacetic acid (200 mL) was transferred to the flask under N$_2$ using a plastic cannula. The solution was refluxed under N$_2$ at 120 °C for 20 hours. The mixture was cooled, then poured into 4M HCl (400 mL) and stirred for approximately 10 minutes. The solution was extracted with CH$_2$Cl$_2$ (2 x 400 mL) and the organics were collected and washed with 4M HCl (2 x 400 mL), water (400 mL) and brine (400 mL). The organics were collected and dried over MgSO$_4$, filtered and pumped to dryness in vacuo yielding the crude compound as a bright yellow coloured solid. The solid was redissolved in CH$_2$Cl$_2$ and vacuum filtered through a small silica plug, washing with CH$_2$Cl$_2$ until no more colour was removed from the silica. The CH$_2$Cl$_2$ filtrates were pumped to dryness in vacuo yielding a bright yellow solid (16.15 g, 78 %). The
solid was dissolved in a minimum of hot cyclohexane and filtered. Crystals formed as the solution cooled to room temperature. The solution was vacuum filtered yielding the first portion of the product as bright yellow crystals. The filtrate was concentrated in vacuo causing precipitation of a second portion of the product, which was collected via vacuum filtration. This process was repeated again yielding a third portion of the product. The products were combined and dried under vacuum yielding the purified compound as bright yellow crystals (10.91 g, 53%). ^1H NMR (300 MHz, CDCl$_3$, 25 °C): δ 11.49 (1H, s, OH), 10.26 (2H, s, CHO), 7.99 (2H, s, Ar-H), 1.36 (9H, s, C(CH$_3$)$_3$).

Synthesis of 4-(tert-butyl)-2,6-bis(((2-(dimethylamino)ethyl)(methyl)amino)methyl)phenol $\text{HO}_{\text{Bu}}(\text{L}_\text{Me})_2$ (L-12)

This synthesis was adapted from the literature. To a solution of 4-tert-butylphenol (5.251 g, 34.96 mmol) and $N,N,N'$-trimethylethylenediamine (10.0 mL, 76.9 mmol) in ethanol (100 mL) was added paraformaldehyde (2.205 g, 73.43 mmol). The solution was refluxed at 80 °C for 3 days, then it was cooled and the solvent was removed in vacuo to yield the crude product as a thick, pale orange coloured oil (13.87 g). The crude oil was redissolved in CH$_2$Cl$_2$ (~10 mL) and vacuum filtered through a small alumina plug. The alumina plug was washed with CH$_2$Cl$_2$ (200 mL), then the filtrate was collected and pumped to dryness in vacuo yielding a yellow oil. The oil was dissolved in hexane, and the supernatant solution was decanted from the insoluble portion of the oil, which was discarded. The hexane supernatant solution was pumped to dryness in vacuo yielding a pale yellow oil (9.52 g, 72 %). The compound was used without further purification. ^1H NMR (600 MHz, CDCl$_3$, 25 °C): δ 7.02 (2H, s, Ar-H), 3.59 (4H, s, Ar-CH$_2$-N), 2.55 (4H, t, $^3J_{HH} = 6$ Hz, NCH$_2$CH$_2$N), 2.48 (4H, t, $^3J_{HH} = 6$ Hz, NCH$_2$CH$_2$N), 2.27 (6H, s, N(CH$_3$)$_2$), 2.21 (12H, s, N(CH$_3$)$_3$), 1.26 (9H, s, C(CH$_3$)$_3$). ^13C{^1H} NMR (150 MHz, CDCl$_3$, 25
δ 153.75, 140.68, 122.57, 58.66, 57.11, 54.83, 45.66, 42.31, 31.55, 33.80, 31.55.


Synthesis of 4-(tert-butyl)-2,6-bis(((2-(dimethylamino)ethyl)imino)methyl)phenol HO₆Bu(L)₂ (L-13)

To a solution of 4-tert-butyl-2,6-diformylphenol (3.925 g, 19.03 mmol) in methanol (50 mL) was added N,N-dimethylethylenediamine (4.5 mL, 41 mmol). The solution was stirred at room temperature for 19 hours, then pumped to dryness yielding the crude compound as a thick, orange coloured oil (6.593 g, 100%). The compound was used without further purification.

¹H NMR (600 MHz, CDCl₃, 25 °C): δ 8.61 (1H, br s, N=C), 7.69 (1H, br s, Ar-H), 3.76 (4H, t, ³JHH = 6 Hz, NCH₂CH₂N), 2.66 (4H, t, ³JHH = 6 Hz, NCH₂CH₂N), 2.33 (12H, s, N(CH₃)₂), 1.32 (9H, s, C(CH₃)₃).


Synthesis of 4-(tert-butyl)-2,6-bis(((2-(dimethylamino)ethyl)amino)methyl)phenol HO₆Bu(LH)₂ (L-14)

This synthesis was adapted from the literature.³⁹ A solution of L-13 (0.588 g, 1.28 mmol) in methanol (20 mL) was cooled in an ice bath to 0 °C then NaBH₄ (0.194 g, 5.13 mmol) was added to the solution in small portions. Note that alternatively, the imine L-13 does not need to be isolated (as described above) and the NaBH₄ may be added in situ after the formation of the imine is complete. The solution was stirred at room temperature for 16 hours, then the solvent was removed in vacuo. The resulting residue was redissolved in CH₂Cl₂ (~5 mL) and the solution was vacuum filtered through a small plug of alumina. The alumina plug was washed with CH₂Cl₂ (5x10 mL) then methanol (~100 mL) until no more colored was removed into the filtrate. The solution was pumped to dryness and the residue was redissolved in CH₂Cl₂ and
filtered through celite. The filtrate was pumped to dryness yielding a pale brown oil (0.39 g, 87%)
. The compound was used without further purification. $^1$H NMR (600 MHz, CDCl$_3$, 25 °C): δ
7.01 (2H, s, Ar-H), 3.89 (4H, s, Ar-CH$_2$-N), 2.73 (4H, t, $^3$J$_{HH}$ = 6 Hz, NCH$_2$CH$_2$N), 2.44 (4H, t,
$^3$J$_{HH}$ = 6 Hz, NCH$_2$CH$_2$N), 2.21 (12H, s, N(CH$_3$)$_2$), 1.27 (9H, s, C(CH$_3$)$_3$). $^{13}$C{$^1$H} NMR (150
MHz, CDCl$_3$, 25 °C): δ 154.15, 140.95, 124.86, 123.68, 58.66, 51.29, 46.36, 45.47, 33.86, 31.57.
Anal. Calc. for C$_{20}$H$_{38}$N$_4$O: C, 68.53; H, 10.93; N, 15.98. Found: C, 67.78; H, 10.68; N, 16.27.

Synthesis of (±)-4-(tert-butyl)-2,6-bis((2-(dimethylamino)cyclohexyl)imino)methylphenol
(±)-HO$_{t}$Bu(NNMe$_2$)$_2$(bis-L-15)

To a solution of 4-tert-butyl-2,6-diformylphenol (0.512 g, 2.48 mmol) in methanol (20 mL) was
added (±)-N,N-dimethyl-trans-1,2-diaminocyclohexane (1.109 g, 7.796 mmol). The solution was
stirred at room temperature for 19 hours, then pumped to dryness yielding a thick, dark brown
coloured oil (1.469 g, 129%). The compound was used without further purification. The product
was confirmed by $^1$H NMR spectroscopy to be a mixture of the bis-imine compound (bis-L-15)
and excess diamine starting material (approximately a 1:1 ratio), with a small amount of the
mono-imine compound (mono-L-15) (approximately 15:1, bis:mono). Resolution of every peak
for the different compounds in the $^1$H NMR spectrum of the mixture was not possible, but a
selection of diagnostic peaks follows. $^1$H NMR (300 MHz, CDCl$_3$, 25 °C): δ for bis-L-15: 8.53
(2H, br s, N=CH), 7.65 (2H, br s, Ar-H), 3.29 (2H, m, CHN), 2.67 (2H, m, CHN), 2.56 (2H, m,
DACH), 2.29 (12H, s, N(CH$_3$)$_2$), 1.32 (9H, s, C(CH$_3$)$_3$); for mono-L-15: 10.54 (1H, s, CHO),
8.24 (1H, s, N=CH), 7.92 (1H, d, $^4$J$_{HH}$ = 3 Hz, Ar-H), 7.44 (1H, d, $^4$J$_{HH}$ = 3 Hz, Ar-H), 2.28 (6H,
s, N(CH$_3$)$_2$), 1.31 (9H, s, C(CH$_3$)$_3$); for (±)-NN$_2$N 2.23 (6H, s, N(CH$_3$)$_2$).
Synthesis of 4-(tert-butyl)-2,6-bis(((2-(dimethylamino)cyclohexyl)amino)methyl)phenol
HO\textsubscript{tBu}(N\textsubscript{H}N\textsubscript{Me}2)\textsubscript{2} (L-16)

A solution of bis-L-15 (1.141 g, 2.509 mmol) in methanol (50 mL) was cooled in an ice bath to 0 °C then NaBH\textsubscript{4} (0.387 g, 10.2 mmol) was added to the solution in small portions. The solution was stirred at room temperature for 16 hours, then the solvent was removed \textit{in vacuo}. The resulting brown residue was redissolved in CH\textsubscript{2}Cl\textsubscript{2} (~10 mL) and vacuum filtered through a small plug of alumina. The alumina plug was washed with CH\textsubscript{2}Cl\textsubscript{2} (~100 mL) until no more colored was removed into the filtrate. The filtrate was pumped to dryness yielding a dark brown oil (0.958 g, 83 %). The compound was used without further purification. The product was confirmed by \textsuperscript{1}H NMR spectroscopy to be a mixture of compounds, with the major compound having peaks consistent with the desired proligand L-16 in two diastereomeric forms. Low-resolution electron-ionization (EI) mass spectrometry of the mixture also confirmed the presence of the desired compound. Resolution of all peaks for the desired compound from the unidentified by-products in the \textsuperscript{1}H NMR spectrum of the mixture was not possible, but a selection of diagnostic peaks follows. \textsuperscript{1}H NMR (600 MHz, CDCl\textsubscript{3}, 25 °C): δ 7.02 (s, 2H, Ar-H), 7.00 (s, 2H, Ar-H), 3.99 (4H, overlapping doublets, NCH\textsubscript{2}Ar), 3.76 (4H, overlapping doublets, NCH\textsubscript{2}Ar), 2.15 (12H, s, N(CH\textsubscript{3})\textsubscript{2}), 2.14 (12H, s, N(CH\textsubscript{3})\textsubscript{2}), 1.27 (18H, s, C(CH\textsubscript{3})\textsubscript{3}). EI-LRMS: calc. [M]\textsuperscript{+} 458.40, found [M]\textsuperscript{+} 458.

Synthesis of complex 25

To a solution of the proligand L-12 (0.5301 g, 1.400 mmol) in toluene (5 mL) was transferred potassium tert-butoxide (0.1567 g, 1.396 mmol) using toluene (10 mL). The solution was stirred at room temperature for 16 hours, after which it was pumped to dryness yielding a wet, yellow solid residue. Hexane was added to this residue, causing precipitation of a pale yellow solid. The
solution was stirred for several minutes, then it was left to settle and the supernatant solution was removed. This process was repeated 2x with more hexane, and the resulting solid was dried under vacuum yielding the purified potassium salt as a pale yellow powder (0.4252 g, 73 %).

The potassium salt (0.4252 g, 1.020 mmol) was dissolved in THF (5 mL) and indium trichloride (0.4516 g, 2.042 mmol) was transferred to this solution using THF (10 mL). The solution was stirred at room temperature for 21 hours, after which it was filtered through glass fibre filter paper and concentrated in vacuo until crystals began to form (~1-2 mL volume). The solution was left in the freezer (-35 °C) for several minutes, causing more crystals to form. The solution was then filtered on a glass frit, washing with cold THF, allowing the isolation of a white crystalline solid (0.2606 g, 33 %). The filtrate was concentrated in vacuo yielding a yellow, foamy residue (0.5821 g, 73 %). The crystals and filtrate residue were stirred in ether for ~ 30 minutes and dried under vacuum several hours with periodic heating to remove residual THF and ether solvents before use. \(^1\)H NMR of each product revealed the crystals to be pure complex 25 whereas the filtrate residue yielded a mixture of complex 25 and unidentified by-products.

Crystals suitable for X-ray analysis were grown from a saturated solution of the crystalline product in THF at room temperature, however single crystal X-ray crystallography of these crystals revealed them to be the related hydroxide-bridged complex 27. The fully solved structure of these crystals was not obtained due to an analogous structure obtained by Insun Yu in our group from single crystals obtained from a saturated solution of the complex in acetonitrile. \(^1\)H NMR (600 MHz, CDCl$_3$, 25 °C): δ 7.05 (2H, s, Ar-H), 5.36 (2H, d, \(^2\)J$_{HH}$ = 12 Hz, Ar-CH$_2$-N), 3.47 (2H, t, \(^3\)J$_{HH}$ = 12 Hz, NCH$_2$CH$_2$N), 3.27 (2H, d, \(^2\)J$_{HH}$ = 12 Hz, Ar-CH$_2$-N), 3.10 (2H, t, \(^3\)J$_{HH}$ = 12 Hz, NCH$_2$CH$_2$N), 3.02 (6H, s, N(CH$_3$)$_2$), 2.87 (6H, br s, N(CH$_3$)$_2$), 2.60 (6H, br s, N(CH$_3$)$_2$), 2.46 (2H, d, \(^2\)J$_{HH}$ = 18 Hz, NCH$_2$CH$_2$N), 2.08 (2H, d, \(^2\)J$_{HH}$ = 18 Hz, NCH$_2$CH$_2$N),
1.29 (9H, s, C(CH₃)₃). ¹³C {¹H} NMR (150 MHz, CDCl₃, 25 °C): δ 158.99, 142.02, 131.66, 122.01, 63.48, 55.53, 50.82, 48.14, 47.79, 45.64, 33.86, 31.40. Anal. Calc. for C₂₂H₄₁Cl₃In₂N₄O: C, 33.68; H, 5.27; N, 7.14. Found: C, 33.31; H, 5.33; N, 7.04.

**Synthesis of complex 26**

To a solution of complex 25 (0.1116 g, 0.1423 mmol) in toluene (5 mL) was transferred NaOEt (0.0193 g, 0.284 mmol) using toluene (10 mL). The solution was stirred at room temperature for 23 hours, then the toluene was removed *in vacuo* and the crude residue was redissolved in THF and filtered through glass fibre filter paper. The solution was concentrated *in vacuo* to 1-2 mL volume, then ether was added causing precipitation of an off-white solid. The solution was filtered on a glass frit and washing with ether. This yielded the purified complex as a pale off-white solid (0.0330 g, 29 %). Single crystals of complex 26 were obtained from a saturated solution of the purified complex in toluene and were analysed by single crystal X-ray crystalloidy. ¹H NMR (600 MHz, CDCl₃, 25 °C): δ 7.03 (2H, s, Ar-H), 5.36 (2H, d, ²J_HH = 18 Hz, Ar-CH₂-N), 4.41 (1H, m, OCH₂CH₃), 4.32 (1H, m, OCH₂CH₃), 3.51 (2H, t, ³J_HH = 12 Hz, NCH₂CH₂N), 3.25 (2H, d, ²J_HH = 18 Hz, Ar-CH₂-N), 3.04 (2H, t, ³J_HH = 12 Hz, NCH₂CH₂N), 3.02 (6H, s, N(CH₃)), 2.86 (6H, br s, N(CH₃)₂), 2.57 (6H, br s, N(CH₃)₂), 2.43 (2H, d, ²J_HH = 12 Hz, NCH₂CH₂N), 2.04 (2H, d, ²J_HH = 12 Hz, NCH₂CH₂N), 1.28 (9H, s, C(CH₃)₃). ¹³C {¹H} NMR (150 MHz, CDCl₃, 25 °C): δ 158.93, 141.96, 131.61, 122.03, 63.46, 61.53, 55.41, 50.82, 47.96, 45.60, 33.82, 31.38, 19.14. Anal. Calc. for C₂₄H₄₆Cl₄In₂N₄O₂: C, 36.30; H, 5.84; N, 7.06. Found: C, 36.61; H, 5.86; N, 7.01.

**Representative polymerization of rac-lactide**

To a solution of complex 26 (0.007 mmol) in CH₂Cl₂ or THF (2 mL) was added rac-LA (1.4 mmol) in CH₂Cl₂ or THF (2 mL). The mixture was allowed to stir at room temperature in a vial
or at 40 °C in a vacuum-sealed bomb for 1 week. The solvent was then removed in vacuo and a small portion of the crude polymer was tested for conversion and tacticity via $^1$H and $^1$H($^1$H) NMR spectroscopy (25 °C, CDCl$_3$). The remaining crude polymer was redissolved in a minimum of dichloromethane (1-2 mL). Methanol (2-5 mL) was then added to this solution causing precipitation of the polymer only for the polymer samples obtained in CH$_2$Cl$_2$. For those obtained in THF, the crude polymers were soluble in this CH$_2$Cl$_2$-MeOH mixture and could not be purified. The solution was allowed to settle and the supernatant solution was removed. This process was repeated 2 more times, and the resulting polymer was dried under vacuum. The polymer was tested for the presence of remaining catalyst or monomer using $^1$H NMR spectroscopy before being tested for molecular weight and PDI using GPC in THF.
Chapter 6: Conclusions and future work

The main goal of this work has been to develop a family of tridentate diaminophenolate ligands and study their coordination chemistry with indium in order to establish detailed structure-activity relationships within a family of dinuclear indium catalysts for the polymerization of lactide. In order to achieve this goal three main areas of ligand modifications were investigated and the results were discussed in Chapters 2-4 of this thesis.

In Chapter 2, modifications to the terminal amine substituents of the chiral tridentate ligand system developed by our group were discussed. It was found that this family of tridentate ligands is relatively flexible and can adopt a range of geometries upon coordination to indium depending on the steric bulk of the terminal amine substituents. Difficulties in isolating discrete indium chloride and/or ethoxide complexes with the bulkier ligand analogues described in this chapter is most likely due to this large flexibility. It may allow for increased aggregation and/or the formation of multiple isomers of indium complexes made with these ligands as compared to the parent ligand system with dimethyl substituents at the terminal amine donors. In addition, although the activity of a sterically bulky dinuclear indium ethoxide complex (complex 7 with bulky $n$-propyl substituents) was unchanged compared to the parent dimethyl substituted system, the steric bulk at the terminal amine position was found to be key in controlling the selectivity of this catalyst in the polymerization of $rac$-LA. The bulkier substituents lead to dissociation of the dinuclear structure during polymerization and therefore lower selectivity. These results illustrate the profound effects that modifications in the steric properties of these tridentate ligands can have on their coordination chemistry with indium and stress the importance of the dinuclear structure of indium ethoxide complexes in this ligand family in the stereoselective polymerization of $rac$-LA.
In Chapter 3 the role of the central amine donor and the effect, if any, of intramolecular hydrogen bonding in the stability of dinuclear indium complexes in this ligand family and their selectivity and activity in the polymerization of rac-LA was investigated. Structural hydrogen bonding parameters in the solid-state for a range of indium ethoxide complexes in this family were compared and the results indicate that moderate to weak hydrogen bonding may be present in the solid-state for some of these complexes. However, the contribution of hydrogen bonding in the stabilization of these dinuclear complexes in solution could not be accurately determined. In addition, no correlation between possible hydrogen bonding of these complexes in the solid-state and their activity and selectivity in the polymerization of rac-LA could be made.

The larger contribution to changes in polymerization activity appears to be the nature of the central amine donor. Complexes with tertiary amine donors (11 and 15) are orders of magnitude less active than their direct analogues with secondary amine donors (16 and 1) or in fact any of the catalysts reported in this family of ligands with secondary amine donors. The origin of this “N-methylation” effect is unclear in this case, as DFT calculations suggest there is little electronic difference at the metal centres between complexes with central secondary and tertiary amine donors, at least in the ground state. Similar effects reported in the literature for other types of chemistry\textsuperscript{116-128} suggest that there is no universal underlying reason for the profound effects often seen upon N-methylation in a particular ligand system. Therefore, a complex interplay of different effects that have yet to be determined, including steric and electronic factors, may be at play in this system.\textsuperscript{116}

Chapter 4 outlined modifications to the phenolate substituents of our tridentate ligand system. As for the analogues described in Chapter 2, modifications to the phenolate rings complicated the resulting coordination chemistry with indium, leading in some cases to
difficulties in the isolation and purification of the desired indium complexes. In general, no
improvements to the activity or selectivity of these dinuclear indium ethoxide complexes in the
polymerization of rac-LA was seen with substitutions of the phenolate rings with adamantyl or
cumyl substituents. Substitutions with triphenylsilyl substituents led to a decrease in selectivity,
although the activity was largely unchanged. PGSE NMR spectroscopic data and in situ
observations of the polymerization of lactide by these catalysts suggests that, like the parent
system with tert-butyl substituents on the phenolate rings, they remain dinuclear during the
polymerization of lactide. Therefore, substitutions of the phenolate substituents, at least in this
limited set of analogues, appears to have a smaller effect on the polymerization behavior of these
indium catalysts than the substitution of the amine substituents as described in Chapters 2 and 3.
It would be interesting in the future to expand the range of substituents used in order to gain a
more complete picture of the how the phenolate substituents affect the selectivity and/or activity
of this family of indium complexes in the polymerization of lactide.

In our investigations of the structure-activity relationships in our tridentate ligand system
we concluded that this system may not be ideal for producing highly selective catalysts in the
polymerization of rac-LA, and therefore further modifications to this system may not be the best
future direction for this project. We therefore began to investigate a related pentadentate ligand
system, first used for lactide polymerization in zinc catalysts reported by Hillmyer, Tolman and
Williams. These pentadentate ligands are capable of bridging two metal centres, thereby
enforcing a dinuclear catalyst structure. Chapter 5 outlines our efforts at synthesizing dinuclear
indium ethoxide complexes with a family of achiral proligands, related to those reported by
Williams et al., as well as our efforts in developing a chiral analogue of this ligand design.
The synthesis of discrete indium complexes using these ligands was complicated, most likely due
the formation of either complex aggregated structures or several isomers in solution, as had been reported for the related zinc chemistry.\textsuperscript{38-39,155} Only indium complexes with achiral proligand L-12, with central tertiary amine donors, could be synthesized cleanly. The dinuclear indium ethoxide complex synthesized using this ligand (complex 26) is active in the polymerization of rac-LA, however it is orders of magnitude less active than the related indium ethoxide complexes within our tridentate ligand family that have secondary central amine donors. The activity of complex 26 is similar to the related indium ethoxide complexes within our tridentate ligand family that also have central tertiary amine donors. However, the higher than theoretical polymer molecular weights and low PDIs seen with this catalyst suggests that slow initiation is a major contributor to its low activity. Therefore, the contribution of the “$N$-methylation” effect in this system may be simply due to the larger steric bulk of these groups, which may prevent fast initiation. However, this cannot be confirmed at present, due to the lack of a direct comparison to a similar system with secondary amine donors (L-14), which could unfortunately not be isolated. Catalyst 26 is highly chain end controlled, producing heterotactic PLA with $P_t$ values of up to 0.93. This system therefore holds great promise, despite its low activity, that the highly stereoselective polymerization of lactide may be achievable with ligands of this type. Future efforts in this area will focus on controlling the formation of discrete, isolable dinuclear indium complexes using pentadentate ligands of this type. This may be achieved by controlling the flexibility, topology and/or chirality of both the side arms as well the bridging group, in order to gain access to highly selective and active lactide polymerization catalysts.
References


Appendices

Appendix A

A.1 Characterization of compounds in solution

Figure A.1. $^1$H NMR spectrum (600 MHz, CDCl$_3$, 25 °C) of proligand H(N$_{Pr_2}N_HO_{Bu}$).
Figure A.2. $^1$H NMR spectrum (400 MHz, CDCl$_3$, 25 °C) of proligand H(N$_{Mesh}$N$_{H}$O$_{tBu}$).
Figure A.3. $^1$H NMR spectrum (400 MHz, CDCl$_3$, 25 °C) of proligand H(N$_{NpH}$N$_2$O$_{tBu}$).
Figure A.4. $^1$H NMR spectrum (400 MHz, CDCl$_3$, 25 °C) of proligand H(N$_{\text{pMe}_3}$N$_{\text{tBu}}$O)$_2$. 
Figure A.5. $^1$H NMR spectrum (600 MHz, CDCl$_3$, 25 °C) of complex (N$_2$H$_2$O$_2$Bu)InCl$_2$ (4).
Figure A.6. $^1$H NMR spectrum (600 MHz, CDCl$_3$, 25 °C) of complex (N$_{NpMe}$N$_{tBu}$)InCl$_2$ (6).
Figure A.7. $^1$H NMR spectrum (600 MHz, CDCl$_3$, 25 °C) of complex [(N$_{Pr}$$_2$N$_{O}$Bu)$_2$InCl]$_2$(µ-Cl)(µ-OEt) (7).
### A.2 Characterization of compounds in the solid-state

**Table A.1.** Selected crystallographic parameters for complexes 4, 5, 6 and 9.

<table>
<thead>
<tr>
<th></th>
<th>Complex 4</th>
<th>Complex 5</th>
<th>Complex 6</th>
<th>Complex 9</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>empirical formula</strong></td>
<td>(\text{C}<em>{27}\text{H}</em>{47}\text{Cl}<em>{2}\text{InN}</em>{2}\text{O}_{2})</td>
<td>(\text{C}<em>{30}\text{H}</em>{53}\text{Cl}<em>{2}\text{InN}</em>{2}\text{O}_{2})</td>
<td>(\text{C}<em>{31}\text{H}</em>{55}\text{Cl}<em>{2}\text{InN}</em>{2}\text{O}_{2})</td>
<td>(\text{C}<em>{56}\text{H}</em>{99}\text{Cl}<em>{2}\text{In}</em>{2}\text{N}<em>{4}\text{O}</em>{4})</td>
</tr>
<tr>
<td><strong>Fw</strong></td>
<td>601.39</td>
<td>707.5</td>
<td>673.49</td>
<td>1192.98</td>
</tr>
<tr>
<td><strong>T (K)</strong></td>
<td>173</td>
<td>173</td>
<td>173</td>
<td>173</td>
</tr>
<tr>
<td><strong>(a) (\text{Å})</strong></td>
<td>8.6106(10)</td>
<td>11.1457(3)</td>
<td>13.1666(7)</td>
<td>36.9023(16)</td>
</tr>
<tr>
<td><strong>(b) (\text{Å})</strong></td>
<td>18.028(2)</td>
<td>17.5129(4)</td>
<td>26.4092(16)</td>
<td>10.2529(5)</td>
</tr>
<tr>
<td><strong>(c) (\text{Å})</strong></td>
<td>20.770(2)</td>
<td>17.1967(4)</td>
<td>10.3219(6)</td>
<td>17.8775(9)</td>
</tr>
<tr>
<td><strong>(\alpha) (deg)</strong></td>
<td>112.588(5)</td>
<td>90</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td><strong>(\beta) (deg)</strong></td>
<td>99.361(6)</td>
<td>104.3240(10)</td>
<td>111.782(4)</td>
<td>116.647(2)</td>
</tr>
<tr>
<td><strong>(\gamma) (deg)</strong></td>
<td>90.583(6)</td>
<td>90</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td><strong>volume (Å(^3))</strong></td>
<td>2927.9(6)</td>
<td>3331.12(14)</td>
<td>3332.9(3)</td>
<td>6045.6(5)</td>
</tr>
<tr>
<td><strong>Z</strong></td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td><strong>crystal system</strong></td>
<td>triclinic</td>
<td>monoclinic</td>
<td>monoclinic</td>
<td>monoclinic</td>
</tr>
<tr>
<td><strong>space group</strong></td>
<td>P-1</td>
<td>P2(_1)/c</td>
<td>Pc</td>
<td>C2/c</td>
</tr>
<tr>
<td><strong>(d_{\text{calc}}) (g/cm(^3))</strong></td>
<td>1.364</td>
<td>1.411</td>
<td>1.342</td>
<td>1.311</td>
</tr>
<tr>
<td><strong>(\mu) (MoK(\alpha)) (\text{cm}^{-1})</strong></td>
<td>10.01</td>
<td>9.02</td>
<td>8.98</td>
<td>8.95</td>
</tr>
<tr>
<td><strong>2(\theta)max (deg)</strong></td>
<td>55.1</td>
<td>58.4</td>
<td>55.8</td>
<td>55.1</td>
</tr>
<tr>
<td><strong>absorption correction (T(<em>{\text{min}}, T</em>{\text{max}}))</strong></td>
<td>0.7448, 0.8593</td>
<td>0.7806, 0.8734</td>
<td>0.5261, 0.9561</td>
<td>0.8792, 0.9562</td>
</tr>
<tr>
<td><strong>total no. of reflections</strong></td>
<td>59 526</td>
<td>52 518</td>
<td>28266</td>
<td>40 441</td>
</tr>
<tr>
<td><strong>no. of indep reflections (R(_{\text{int}}))</strong></td>
<td>13 413 (0.027)</td>
<td>9024 (0.030)</td>
<td>28266 (0.0000)</td>
<td>6964 (0.082)</td>
</tr>
<tr>
<td><strong>residuals (refined on F(^2), all data): R(_1); wR(_2)</strong></td>
<td>0.032, 0.074</td>
<td>0.036, 0.080</td>
<td>0.0992, 0.1991</td>
<td>0.058, 0.112</td>
</tr>
<tr>
<td><strong>GOF</strong></td>
<td>1.028</td>
<td>1.054</td>
<td>1.009</td>
<td>1.025</td>
</tr>
<tr>
<td><strong>no. observations [I &gt; 2s(I)]</strong></td>
<td>12 039</td>
<td>7927</td>
<td>28266</td>
<td>5023</td>
</tr>
<tr>
<td><strong>residuals (refined on F(^2)): R(^1); wR(_2)</strong></td>
<td>0.027, 0.067</td>
<td>0.030, 0.076</td>
<td>0.0701, 0.1770</td>
<td>0.031, 0.074</td>
</tr>
</tbody>
</table>

\(^a\) R\(_1\) = \frac{\sum |F\(_o\)| - |F\(_c\)| / \sum |F\(_o\)|; \(^b\) wR\(_2\) = [\sum w(F\(_o\)^2 - F\(^2\)) / \sum w(F\(_o\)^2)]^{1/2}. 

---

222
Appendix B

B.1 Characterization of compounds in solution

Figure B.1. $^1$H NMR spectrum (600 MHz, CD$_2$Cl$_2$, 25 °C) of complex (±)-(N$_2$Me$_2$N$_2$O$_{tBu}$)InCl$_2$ (12).
Figure B.2. $^1$H NMR spectrum (600 MHz, CDCl$_3$, 25 °C) of complex (L$_4$)InCl$_2$ (13).
Figure B.3. $^1$H NMR spectrum (600 MHz, CDCl$_3$, 25 °C) of complex [(N$_2$Me$_2$N$_2$O$_2$Bu)$_2$InCl]$_2$(µ-Cl)(µ-OEt) (15).
Figure B.4. $^1$H NMR spectrum (600 MHz, CDCl$_3$, 25 °C) of complex [(L$_H$)InCl$_2$(μ-Cl)(μ-OEt)] (16).
### Characterization of compounds in the solid-state

#### Table B.1. Selected crystallographic parameters for complexes 1, 15, 16 and 17.

<table>
<thead>
<tr>
<th></th>
<th>Complex 1</th>
<th>Complex 15</th>
<th>Complex 16</th>
<th>Complex 17</th>
</tr>
</thead>
<tbody>
<tr>
<td>empirical formula</td>
<td>C(<em>{62})H(</em>{99})Cl(_{3})In(_2)N(_4)O(_3)</td>
<td>C(<em>{58})H(</em>{103})N(_8)O(_3)Cl(_3)</td>
<td>C(<em>{42})H(</em>{74})Cl(_3)In(_2)N(_5)O(_3)</td>
<td>C(<em>{62})H(</em>{99})Br(_3)In(_2)N(_4)O(_3)</td>
</tr>
<tr>
<td>Fw</td>
<td>1284.44</td>
<td>1296.47</td>
<td>1033.05</td>
<td>1413.79</td>
</tr>
<tr>
<td>T (K)</td>
<td>90(2)</td>
<td>100.0(2)</td>
<td>90(1)</td>
<td>90.0(1)</td>
</tr>
<tr>
<td>a (Å)</td>
<td>16.916(4)</td>
<td>16.9326(7)</td>
<td>15.283(2)</td>
<td>16.954(2)</td>
</tr>
<tr>
<td>b (Å)</td>
<td>20.267(5)</td>
<td>10.5828(4)</td>
<td>29.747(4)</td>
<td>20.345(3)</td>
</tr>
<tr>
<td>c (Å)</td>
<td>18.221(4)</td>
<td>18.5416(7)</td>
<td>10.5653(15)</td>
<td>18.616(2)</td>
</tr>
<tr>
<td>α (deg)</td>
<td>90</td>
<td>90</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>β (deg)</td>
<td>91.699(3)</td>
<td>97.046(2)</td>
<td>93.482(4)</td>
<td>91.959(3)</td>
</tr>
<tr>
<td>γ (deg)</td>
<td>90</td>
<td>90</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>volume (Å(^3))</td>
<td>6244(2)</td>
<td>3297.5(2)</td>
<td>4794.5(12)</td>
<td>6417.6(14)</td>
</tr>
<tr>
<td>Z</td>
<td>4</td>
<td>2</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>crystal system</td>
<td>monoclinic</td>
<td>monoclinic</td>
<td>monoclinic</td>
<td>monoclinic</td>
</tr>
<tr>
<td>space group</td>
<td>P(_{2})_1</td>
<td>P(_{2}/c)</td>
<td>P(_{2}/c)_1</td>
<td>P(_{2})_1</td>
</tr>
<tr>
<td>d(_{calc}) (g/cm(^3))</td>
<td>1.366</td>
<td>1.306</td>
<td>1.431</td>
<td>1.463</td>
</tr>
<tr>
<td>μ (MoK(_{α})) (cm(^{-1}))</td>
<td>9.13</td>
<td>8.66</td>
<td>11.70</td>
<td>26.31</td>
</tr>
<tr>
<td>2(θ)max (deg)</td>
<td>50.986</td>
<td>57.4</td>
<td>60.344</td>
<td>65.84</td>
</tr>
<tr>
<td>absorption correction ((T_{\min}), (T_{\max}))</td>
<td>0.4399, 0.7452</td>
<td>0.838; 0.966</td>
<td>0.5845, 0.7459</td>
<td>0.455, 0.748</td>
</tr>
<tr>
<td>total no. of reflections</td>
<td>36138</td>
<td>32278</td>
<td>14174</td>
<td>82942</td>
</tr>
<tr>
<td>no. of indep reflections ((R_{int}))</td>
<td>12008 (0.1118)</td>
<td>8379 (0.045)</td>
<td>14174 (0.575)</td>
<td>39410 (0.0630)</td>
</tr>
<tr>
<td>residuals (refined on (F^2), all data): (R_1^a); (wR_2^a)</td>
<td>0.1172; 0.2342</td>
<td>0.042; 0.059</td>
<td>0.0307; 0.0549</td>
<td>0.1209; 0.2210</td>
</tr>
<tr>
<td>GOF</td>
<td>1.021</td>
<td>0.98</td>
<td>1.095</td>
<td>1.041</td>
</tr>
<tr>
<td>no. observations [(1 &gt; 2\sigma(I))]</td>
<td>27515</td>
<td>6534</td>
<td>12789</td>
<td>27754</td>
</tr>
<tr>
<td>residuals (refined on (F^2)): (R_1^b); (wR_2^b)</td>
<td>0.0846; 0.2044</td>
<td>0.029; 0.056</td>
<td>0.0258; 0.0533</td>
<td>0.0803; 0.1978</td>
</tr>
</tbody>
</table>

\(^a R_1 = \sum ||F_o| - |F_c|| / \sum |F_o|; \(^b wR_2 = [\sum w(F_o^2 - F_c^2)^2]/\sum w(F_o^2)]^{1/2} \)
### B.3 DFT studies

**Table B.2.** Comparison of metrical parameters for calculated (ORCA, gas phase) and X-ray structures for complexes 1 and 15.

<table>
<thead>
<tr>
<th>Complex</th>
<th>Parameter</th>
<th>Theoretical (ORCA)</th>
<th>Experimental (X-ray)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Structure 1" /></td>
<td>In1-O1</td>
<td>2.11 Å</td>
<td>2.07 Å</td>
</tr>
<tr>
<td></td>
<td>In1-N1</td>
<td>2.34 Å</td>
<td>2.24 Å</td>
</tr>
<tr>
<td></td>
<td>In1-N2</td>
<td>2.47 Å</td>
<td>2.32 Å</td>
</tr>
<tr>
<td></td>
<td>In1-Cl1</td>
<td>2.73 Å</td>
<td>2.70 Å</td>
</tr>
<tr>
<td></td>
<td>In1-O2</td>
<td>2.19 Å</td>
<td>2.09 Å</td>
</tr>
<tr>
<td></td>
<td>N1-In1-N2</td>
<td>74.6 °</td>
<td>76.7 °</td>
</tr>
<tr>
<td></td>
<td>O1-In1-O2</td>
<td>96.0 °</td>
<td>96.2 °</td>
</tr>
<tr>
<td></td>
<td>Cl1-In1-O2</td>
<td>77.2 °</td>
<td>75.2 °</td>
</tr>
<tr>
<td><img src="image2.png" alt="Structure 15" /></td>
<td>In1-O1</td>
<td>2.11 Å</td>
<td>2.08 Å</td>
</tr>
<tr>
<td></td>
<td>In1-N1</td>
<td>2.44 Å</td>
<td>2.36 Å</td>
</tr>
<tr>
<td></td>
<td>In1-N2</td>
<td>2.46 Å</td>
<td>2.34 Å</td>
</tr>
<tr>
<td></td>
<td>In1-Cl1</td>
<td>2.70 Å</td>
<td>2.64 Å</td>
</tr>
<tr>
<td></td>
<td>In1-O2</td>
<td>2.18 Å</td>
<td>2.14 Å</td>
</tr>
<tr>
<td></td>
<td>N1-In1-N2</td>
<td>74.6 °</td>
<td>76.3 °</td>
</tr>
<tr>
<td></td>
<td>O1-In1-O2</td>
<td>95.4 °</td>
<td>93.4 °</td>
</tr>
<tr>
<td></td>
<td>Cl1-In1-O2</td>
<td>75.5 °</td>
<td>75.0 °</td>
</tr>
</tbody>
</table>
Appendix C

C.1 Characterization of compounds in solution

Figure C.1. $^1$H NMR spectrum (600 MHz, CDCl$_3$, 25 °C) of proligand ($\pm$)-H(N$_{Me2N}O$SiPh$_3$).
**Figure C.2.** $^1$H NMR spectrum (600 MHz, CDCl$_3$, 25 °C) of proligand (±)-H(N$_{Me2}$N$_H$O$_{Ad}$).
Figure C.3. $^1$H NMR spectrum (600 MHz, CDCl$_3$, 25 °C) of proligand (±)-H(N$_{Me2}$N$_H$O$_{Cm}$).
Figure C.4. $^1$H NMR spectrum (600 MHz, CDCl$_3$, 25 °C) of (a) (±)- and (b) (R,R)-($N_{Me_2N}O_{SiPh_3}$)InCl$_2$ (19).

Figure C.5. $^1$H NMR spectrum (600 MHz, CDCl$_3$, 25 °C) of (a) (±)- and (b) (R,R)-($N_{Me_2N}O_{Ad}$)InCl$_2$ (20).
Figure C.6. $^1$H NMR spectrum (600 MHz, CDCl$_3$, 25 °C) of (a) (∓)- and (b) (R,R)-($N_{Me2}N_{H_{O_{Cm}}}$InCl$_2$ (21).
Figure C.7. $^1$H NMR spectrum (600 MHz, CDCl₃, 25 °C) of (±)-[($\text{NMe}_2$)$_2$N$_2$O$_{\text{SiPh}_3}$]InCl$_2$(μ-Cl(μ-OEt) (22).
**Figure C.8.** $^1$H NMR spectrum (600 MHz, CDCl$_3$, 25 °C) of (±)-[$(\text{NMe}_2\text{N}_2\text{H}_2\text{Ad})\text{InCl}_2](\mu\text{-Cl}(\mu\text{-OEt}))$ (23).
Figure C.9. $^1$H NMR spectrum (600 MHz, CDCl$_3$, 25 °C) of (±)-[(N$_{Me_2}N$)$_2$InCl]$_2$($\mu$-Cl($\mu$-OEt) (24).
## Characterization of compounds in the solid-state

**Table C.1.** Select crystallographic parameters for complexes (±) - 19, 20, 23 and 24.

<table>
<thead>
<tr>
<th>Complex</th>
<th>19</th>
<th>20</th>
<th>23</th>
<th>24</th>
</tr>
</thead>
<tbody>
<tr>
<td>empirical formula</td>
<td>C\textsubscript{34}H\textsubscript{39}Cl\textsubscript{2}In\textsubscript{2}O\textsubscript{2}Si</td>
<td>C\textsubscript{24}H\textsubscript{33}ClIn\textsubscript{0.5}N\textsubscript{0.5}O\textsubscript{0.5}</td>
<td>C\textsubscript{61}H\textsubscript{97}Cl\textsubscript{3}In\textsubscript{2}N\textsubscript{5}O\textsubscript{3}</td>
<td>C\textsubscript{79}H\textsubscript{105}Cl\textsubscript{3}In\textsubscript{2}N\textsubscript{4}O\textsubscript{3}</td>
</tr>
<tr>
<td>F\textsubscript{w}</td>
<td>705.48</td>
<td>426.86</td>
<td>1276.92</td>
<td>1486.63</td>
</tr>
<tr>
<td>T (K)</td>
<td>90</td>
<td>90</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>a (Å)</td>
<td>9.4897(10)</td>
<td>10.0632(12)</td>
<td>12.8751(10)</td>
<td>18.854(5)</td>
</tr>
<tr>
<td>b (Å)</td>
<td>15.9328(16)</td>
<td>15.5923(19)</td>
<td>16.5097(12)</td>
<td>32.910(10)</td>
</tr>
<tr>
<td>c (Å)</td>
<td>12.2095(12)</td>
<td>14.7651(17)</td>
<td>15.9412(12)</td>
<td>11.886(4)</td>
</tr>
<tr>
<td>α (deg)</td>
<td>105.831(2)</td>
<td>89.620(3)</td>
<td>64.991(2)</td>
<td>90</td>
</tr>
<tr>
<td>β (deg)</td>
<td>91.856(2)</td>
<td>73.121(3)</td>
<td>87.640(2)</td>
<td>100.603(7)</td>
</tr>
<tr>
<td>γ (deg)</td>
<td>111.387(2)</td>
<td>73.901(3)</td>
<td>87.658(2)</td>
<td>90</td>
</tr>
<tr>
<td>volume (Å\textsuperscript{3})</td>
<td>1635.7(3)</td>
<td>2123.1(4)</td>
<td>3067.2(4)</td>
<td>7249(4)</td>
</tr>
<tr>
<td>Z</td>
<td>2</td>
<td>4</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>crystal system</td>
<td>triclinic</td>
<td>triclinic</td>
<td>triclinic</td>
<td>monoclinic</td>
</tr>
<tr>
<td>space group</td>
<td>P-1</td>
<td>P-1</td>
<td>P-1</td>
<td>P\textsubscript{2}\textsubscript{1}/n</td>
</tr>
<tr>
<td>d\textsubscript{calc} (g/cm\textsuperscript{3})</td>
<td>1.432</td>
<td>1.335</td>
<td>1.383</td>
<td>1.362</td>
</tr>
<tr>
<td>μ (MoKα) (cm\textsuperscript{-1})</td>
<td>9.52</td>
<td>7.19</td>
<td>9.29</td>
<td>7.97</td>
</tr>
<tr>
<td>2θ\text{max} (deg)</td>
<td>60.16</td>
<td>61.324</td>
<td>60.52</td>
<td>61.192</td>
</tr>
<tr>
<td>absorption correction (T\text{min}, T\text{max})</td>
<td>0.8177, 0.8752</td>
<td>0.677, 0.806</td>
<td>0.7956, 0.8539</td>
<td>0.6469, 0.7461</td>
</tr>
<tr>
<td>total no. of reflections</td>
<td>108779</td>
<td>76944</td>
<td>173951</td>
<td>110250</td>
</tr>
<tr>
<td>no. of indep reflections (R\text{int})</td>
<td>9600 (0.0378)</td>
<td>13104 (0.0662)</td>
<td>18161 (0.0559)</td>
<td>22143 (0.0708)</td>
</tr>
<tr>
<td>residuals (refined on F\textsuperscript{2}, all data):</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R\textsubscript{1}; wR\textsubscript{2}</td>
<td>0.0292, 0.0572</td>
<td>0.0381, 0.0505</td>
<td>0.0417, 0.0766</td>
<td>0.0554, 0.0750</td>
</tr>
<tr>
<td>GOF</td>
<td>1.066</td>
<td>0.926</td>
<td>1.021</td>
<td>1.026</td>
</tr>
<tr>
<td>no. observations ([I &gt; 2s(I)])</td>
<td>9600</td>
<td>13104</td>
<td>18161</td>
<td>22143</td>
</tr>
<tr>
<td>residuals (refined on F\textsuperscript{2}):</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R\textsubscript{1}\textsuperscript{a}; wR\textsubscript{2}\textsuperscript{b}</td>
<td>0.0228, 0.0537</td>
<td>0.0282, 0.0486</td>
<td>0.0294, 0.0719</td>
<td>0.0353, 0.0679</td>
</tr>
</tbody>
</table>

\(\text{a } R_1 = \Sigma ||F_o| - |F_c|| / \Sigma |F_o|; \text{ b } wR_2 = \left[ \Sigma (w(F_o^2 - F_c^2)^2) / \Sigma w(F_o^2)^2 \right]^{1/2}.\)
C.3 Kinetic data for the polymerization of lactide

Figure C.10. Plots of the ln([LA]) vs. time for the polymerization of rac-, L- and D-LA (0.5 M) by complex (+)-22 (2.4 mM) monitored to >97% conversion by $^1$H NMR spectroscopy in CDCl$_3$ with 1,3,5-trimethoxybenzene used as an internal standard (0.03 M).

Figure C.11. Plots of the ln([LA]) vs. time for the polymerization of rac-, L- and D-LA (0.5 M) by complex (R,R)-22 (2.4 mM) monitored to >86% conversion by $^1$H NMR spectroscopy in CDCl$_3$ with 1,3,5-trimethoxybenzene used as an internal standard (0.03 M).
Figure C.12. Plots of the ln([LA]) vs. time for the polymerization of rac-, L- and D-LA (0.5 M) by complex (±)-23 (2.4 mM) monitored to >98% conversion by $^1$H NMR spectroscopy in CDCl$_3$ with 1,3,5-trimethoxybenzene used as an internal standard (0.03 M).

Figure C.13. Plots of the ln([LA]) vs. time for the polymerization of rac-, L- and D-LA (0.5 M) by complex (R,R)-23 (2.4 mM) monitored to >80% conversion by $^1$H NMR spectroscopy in CDCl$_3$ with 1,3,5-trimethoxybenzene used as an internal standard (0.03 M).
Figure C.14. Plots of the ln([LA]) vs. time for the polymerization of rac-, L- and D-LA (0.5 M) by complex (±)-24 (2.4 mM) monitored to >98% conversion by $^1$H NMR spectroscopy in CDCl$_3$ with 1,3,5-trimethoxybenzene used as an internal standard (0.03 M).
Appendix D

D.1 Characterization of compounds in solution

Figure D.1. $^1$H NMR spectrum (600 MHz, CDCl$_3$, 25 °C) of HO$_{iBu}(L_{Me})_2$ (L-12).
Figure D.2. $^1$H NMR spectrum (600 MHz, CDCl$_3$, 25 °C) of HO$_{iBu}(L)_2$ (L-13).
Figure D.3. $^1$H NMR spectrum (600 MHz, CDCl$_3$, 25 °C) of HO$_2$Bu(L1H)$_2$ (L-14).
Figure D.4. $^1$H NMR spectrum (300 MHz, CDCl$_3$, 25 °C) of (±)-HO$_{Bu}$(NNMe$_2$)$_2$ (L-15).

Figure D.5. $^1$H NMR spectrum (600 MHz, CDCl$_3$, 25 °C) of (±)-HO$_{Bu}$(NNH$_{Me2}$)$_2$ (L-16).
Figure D.6. $^1$H NMR spectrum (600 MHz, CDCl$_3$, 25 °C) of $[(L_{Me})InCl_2]_2(\mu-O_{\text{Bu}})(\mu-Cl)$ (25).
Figure D.7. $^1$H NMR spectrum (600 MHz, CDCl$_3$, 25 °C) of [(L$_{Me}$)InCl$_2$]$_2$(µ-O$_{Bu}$)(µ-OEt) (26).
D.2 Characterization of compounds in the solid-state

Table D.1. Select crystallographic parameters for complexes 26 and 27.

<table>
<thead>
<tr>
<th></th>
<th>Complex 26</th>
<th>Complex 27</th>
</tr>
</thead>
<tbody>
<tr>
<td>empirical formula</td>
<td>C_{69}H_{113}Cl_{8}In_{4}N_{8}O_{4}</td>
<td>C_{24}H_{45}Cl_{4}In_{2}N_{5}O_{2}</td>
</tr>
<tr>
<td>Fw (g/mol)</td>
<td>1856.18</td>
<td>807.09</td>
</tr>
<tr>
<td>T (K)</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>a (Å)</td>
<td>11.307(5)</td>
<td>15.310(2)</td>
</tr>
<tr>
<td>b (Å)</td>
<td>18.369(5)</td>
<td>11.2460(17)</td>
</tr>
<tr>
<td>c (Å)</td>
<td>22.010(5)</td>
<td>19.389(3)</td>
</tr>
<tr>
<td>α (deg)</td>
<td>84.491(5)</td>
<td>90</td>
</tr>
<tr>
<td>β (deg)</td>
<td>83.099(5)</td>
<td>104.472(4)</td>
</tr>
<tr>
<td>γ (deg)</td>
<td>83.917(5)</td>
<td>90</td>
</tr>
<tr>
<td>volume (Å³)</td>
<td>4497(3)</td>
<td>3232.4(8)</td>
</tr>
<tr>
<td>Z</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>crystal system</td>
<td>triclinic</td>
<td>monoclinic</td>
</tr>
<tr>
<td>space group</td>
<td>P-1</td>
<td>P 2_{1}/c</td>
</tr>
<tr>
<td>d_{calc} (g/cm³)</td>
<td>1.371</td>
<td>1.658</td>
</tr>
<tr>
<td>μ (MoKα) (cm⁻¹)</td>
<td>12.94</td>
<td>17.87</td>
</tr>
<tr>
<td>2θ max (deg)</td>
<td>58.106</td>
<td>72.24</td>
</tr>
<tr>
<td>absorption correction (T_{min}, T_{max})</td>
<td>0.6316, 0.7458</td>
<td>0.8832, 0.9478</td>
</tr>
<tr>
<td>total no. of reflections</td>
<td>93165</td>
<td>73072</td>
</tr>
<tr>
<td>no. of indep reflections (R_{int})</td>
<td>23586 (0.0520)</td>
<td>15357 (0.0714)</td>
</tr>
<tr>
<td>residuals (refined on F^2, all data): R$_1$; wR$_2$</td>
<td>0.1027, 0.1441</td>
<td>0.0694, 0.0685</td>
</tr>
<tr>
<td>GOF</td>
<td>1.022</td>
<td>1.000</td>
</tr>
<tr>
<td>no. observations [I &gt; 2s(I)]</td>
<td>23586</td>
<td>15357</td>
</tr>
<tr>
<td>residuals (refined on F^2): R$_1$; wR$_2$</td>
<td>0.0571, 0.1194</td>
<td>0.0355, 0.0605</td>
</tr>
</tbody>
</table>

$^a R_1 = \frac{\sum |F_o| - |F_c||}{\Sigma |F_o|}; \quad wR_2 = [\Sigma (w(F_o^2 - F_c^2)^2)/\Sigma w(F_o^2)^2]^{1/2}.$