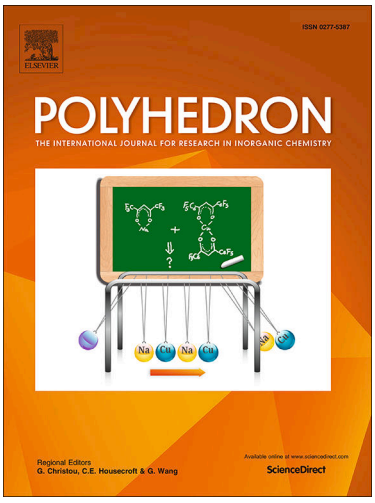

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Bis(phenyl-β-diketonato)titanium(IV) ethoxide complexes: ring-opening polymerization of L-lactide by solvent-free microwave irradiation

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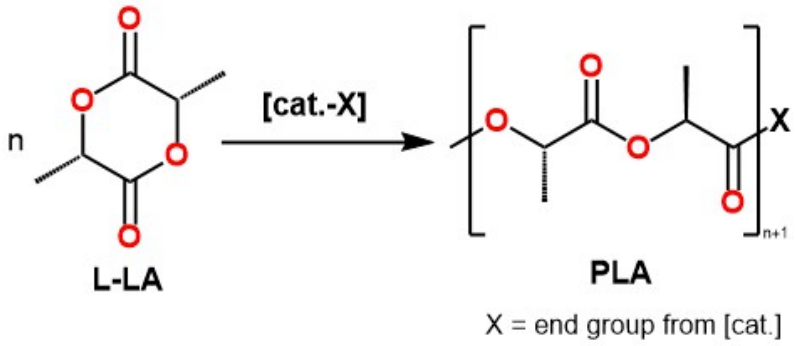
Key Word: β-Diketonate ligands; Polymerization; Titanium

Abstract

A range of functionalized bis(phenyl-β-diketonato)titanium(IV) ethoxide complexes of the type $[Ti(L)_2(OEt)_2]$, containing two asymmetric or symmetric phenyl-β-diketonate ligands (L), have been synthesized and fully characterized. Single crystal X-ray diffraction has been used to confirm that all structures crystallize with the ethoxide ancillary ligands in a *cis* arrangement and NMR spectra show characteristic ligand rearrangement in solution. The complexes have been screened as catalysts in the ring-opening polymerization (ROP) of L-lactide (L-LA) to yield polylactide (PLA), by using microwave (MW) and conventional heating. The resulting polymers have high molecular weights but high polydispersity index (PDI) which are suggestive of transesterification. However, unlike conventional heating methods, the polymerization by MW reaction leads to a retention in stereochemistry of the resulting polymer in significantly shorter time periods.

Introduction

Since the use of fossil fuels is still widely accepted for the manufacturing of plastics, there is an urgent need to provide more effective methods using renewable resources. An environmentally friendly pathway and possible alternative method is the ring-opening polymerization (ROP) of biodegradable starting materials such as L-lactide (L-LA), to yield polylactide (PLA) [1,2]. PLA is an aliphatic polyester which has many important uses, including packaging material, drug delivery systems and as tissue engineering scaffolds [3-6]. The most effective synthesis reported for high molecular weight PLA is the use of ROP from pure L-LA using an initiator or catalyst (**Scheme 1**) [7]. In 1996, Spassky et al. reported the first aluminium alkoxide complexes which were able to produce isotactic PLA [8], and since this ground-breaking work, metal coordination complexes been used to help increase polymer molecular weights and polymer tacticity. Polymerization reactions need to progress with increased conversion rates and stereocontrol, and a variety of initiators have been developed to address these factors [9-12]. Metal complexes have included, but are not limited to, calcium, zinc, magnesium, aluminium, yttrium, copper, indium and tin [13-21], whereby the choice of metal is important, and metals with low toxicity, high abundance and low costs are generally preferred.



Scheme 1 *The ring-opening polymerization (ROP) of L-lactide (L-LA) to polylactide (PLA) when using a catalyst [cat.]. with end group X.*

Titanium metal complexes have emerged as promising alternatives as ROP catalysts, as the metal is cheap, the coordinating ligands are easily modified, and high activity and selectivity have already been observed [22-24]. The most promising results were observed for a bis(8-quinolinolato)titanium(IV) isopropoxide complexes, $[Ti(L)_2(OiPr)_2]$, reported by Bakewell et al. [25], and although the initiators were still relatively slow (k_{obs} = 1.7–3.7×10^{-6} s^{-1}), they were comparable to their aluminium analogues. Research has shown that the ligand environment around the metal centre is essential for the catalytic behaviour, and that the steric effects of the ligand can block side reactions such as intramolecular and intermolecular transesterifications of PLA [26-28], leading to controllable polymerization with narrow molecular weight distributions [15,26]. Titanium(IV) complexes of the type $[Ti(L)_2(X)_2]$ (where L = a bidentate ligand) can exist in five possible structural arrangements (excluding enantiomers, **Figure 1**), although literature suggests the complexes exist predominantly in the *cis* arrangement [29-30]. Such results had already been reported for Budotitane, $[Ti(bzac)_2(OEt)_2]$ (bzac = phenyl-2,4-butanedione, compound **1**, **Scheme 2**) [31-32].

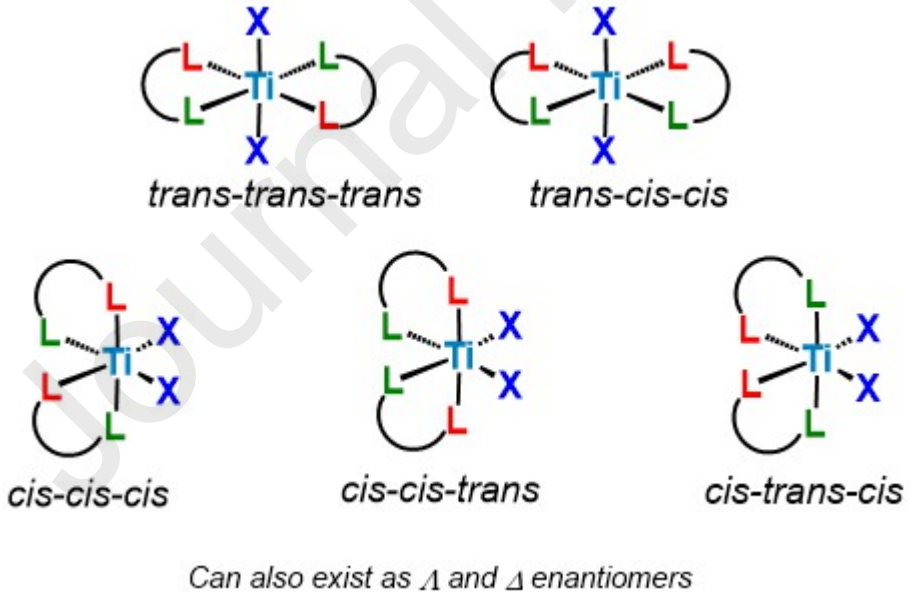


Figure 1 *Possible structural isomers of titanium(IV) complexes of the type $[Ti(L)_2(X)_2]$ where L = a bidentate ligand and X = monodentate ligand.*

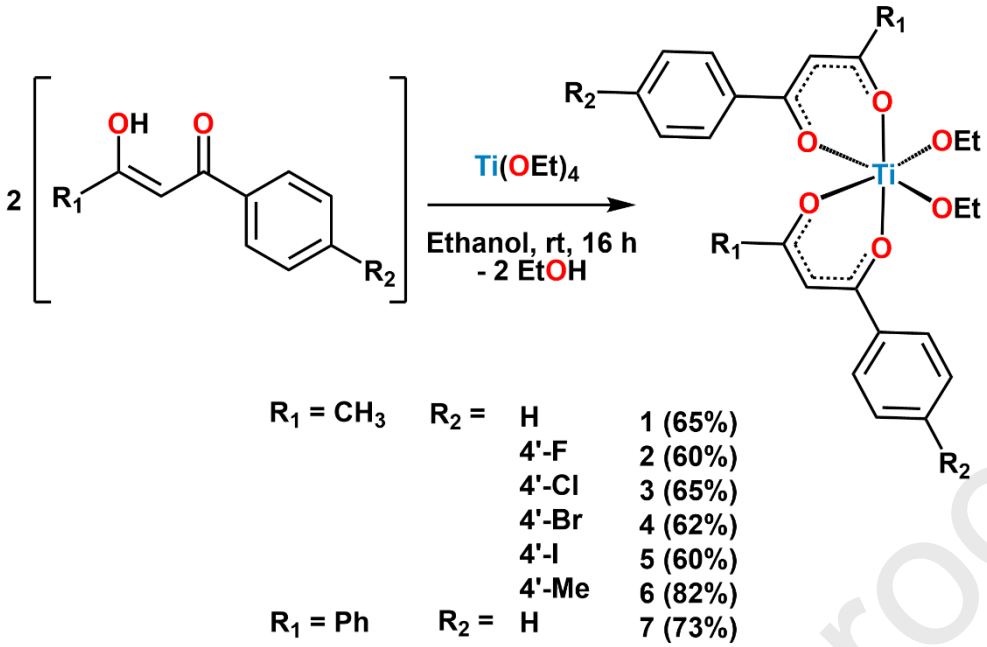
Zirconium(IV) acetylacetonate, $[Zr(acac)_4]$ (acac = acetylacetone), was shown to be an effective catalyst for the ROP of cyclic esters and yielded high conversions [33], due to a single-step polymerization of the monomers through the dissociation of an acetylacetone

ligand. Additionally, a functionalized dibenzoylmethane (dbm) iron complex, [Fe(dbm)$_3$] was used in the ROP of lactide and acted as both an initiator and a catalyst [34]. Metal acetylacetone complexes of Mg and metals of the 4th period have also been synthesized and tested for the ROP of benzoxazine, whereby manganese, iron and cobalt exhibited the highest activities [35]. It was also noted that ROP was greatly increased when the metal was functionalized with hexafluoroacetylacetonato (F_6-acac) ligands.

Microwave (MW) irradiation has been widely used for organic synthesize since the mid-1980s [36-37], and has several advantages over conventional heating, an important one being the reduction in reaction time due to heating efficiency and increased homogeneity. MW irradiation has been used in polymerization reactions, where Schubert and co-workers reported the rate acceleration by MW irradiation is due to a purely thermal effect.[38] Alongside the advantages of increased reaction time, it was reported that the homogeneous nature of MW heating eliminates any side products, and yields polymers of higher purity and higher yields. There have been many reports on the ROP of lactide, for example both Liu et al.[39] and Jing et al.[40] reported the ROP of D,L-Lactide (DLLA), with the latter group reporting reactions in the presence of a Sn(Oct)$_2$ (Oct = 2-ethylhexanoate) catalyst. Both groups noted the increases in reaction time when compared to conventional heating. There have also been reports on the MW irradiation ROP of L-LA (with Sn(Oct)$_2$), where the resulting poly-L-Lactide (PLLA) had high molecular weights (10^2-10^4 g/mol) and polydispersity index (PDI) of ~1.2. However, high molar ratios (12,000:1) and long reaction times of 24 h were employed.[41] Although there are many advantages of MW irradiation, which are beneficial for industrial scale-up, the reactions usually require the use a anhydrous solvent, e.g., toluene, and the removal of the solvent could further improve overall reaction costs. Many researchers have reported the solvent-free melt ROP of L-LA by conventional heating methods,[42–44] however, to the best of our knowledge, there are only few reports on solvent-free MW reactions of PLA.[45] In light of these, we report the synthesis and characterization of bis(phenyl-β-diketonato)titanium(IV) ethoxide catalysts, and their use in solvent-free MW irradiation methods to synthesize PLA, whilst comparing the results to solvent-free conventional heating methods.

Results and Discussion

Synthesis of bis(phenyl-β-diketonato)titanium(IV) ethoxide complexes: A series of functionalized phenyl-β-diketonate ligands (L) and bis(phenyl-β-diketonato)titanium(IV) ethoxide complexes, [Ti(L)$_2$(OEt)$_2$], have been synthesized using our previously published methods (**Scheme 2**).[29,30] The ligands were synthesized via a Claisen condensation between a functionalized acetophenone, NaOEt and EtOAc. Then under N_2, to a vigorously stirring solution of [Ti(OEt)$_4$] (1 eq.) in dry ethanol, was added a functionalized phenyl-β-diketonate ligand (2 eq.) in dry ethanol. The mixture was stirred overnight, and the resulting precipitates isolated and recrystallized. All complexes have been fully characterized by ^{1}H NMR and ^{13}C{^{1}H} NMR spectroscopy, mass spectrometry, elemental analysis and X-ray crystallography where possible.



Scheme 2 *Synthesis of bis(phenyl-β-diketonate)titanium(IV) ethoxide complexes* ***1-7****.*

NMR Spectroscopy: ^{1}H NMR spectra are characteristic by the phenyl-β-diketonate methine resonance at ~6.20 ppm, which in comparison with the ligand, is shifted by 0.1-0.3 ppm upon successful complexation. Due to the fluxionality of these complexes in solution,[29,30] broad signals are observed in all NMR spectra. Splitting patterns could not be assigned at room temperature and ^{1}H-^{1}H COSY (**Figure S5**) and NOESY (**Figure S10**) spectra were used to aid in their full assignment. Variable temperature (303-213 K) ^{1}H NMR spectra were recorded, and **Figure 2** shows an example for complex **4**. At room temperature, only one broad methine proton (Hc) is observed, and as the sample is cooled to 213 K, this resonance is resolved into four well-defined resonances. As shown in **Figure 1**, there are five possible structural isomers (plus two enantiomers), where the *cis-cis-trans* and *cis-trans-cis* arrangements have equivalent methine protons and have been assigned to two of the four resonances. The *cis-cis-cis* arrangement contains two non-equivalent ligands and has been assigned to the remaining two resonances in the methine region. Other notable changes are discussed in the *Supporting Information*, and all of the analysis gives strong evidence for the presence of the three structural isomers; *cis(OEt)-cis(ph)-trans(Me)*, *cis(OEt)-trans(ph)-cis(Me)* and *cis(OEt)-cis(ph)-cis(Me),* which has been previously reported for complex **1**.[31,32,46]

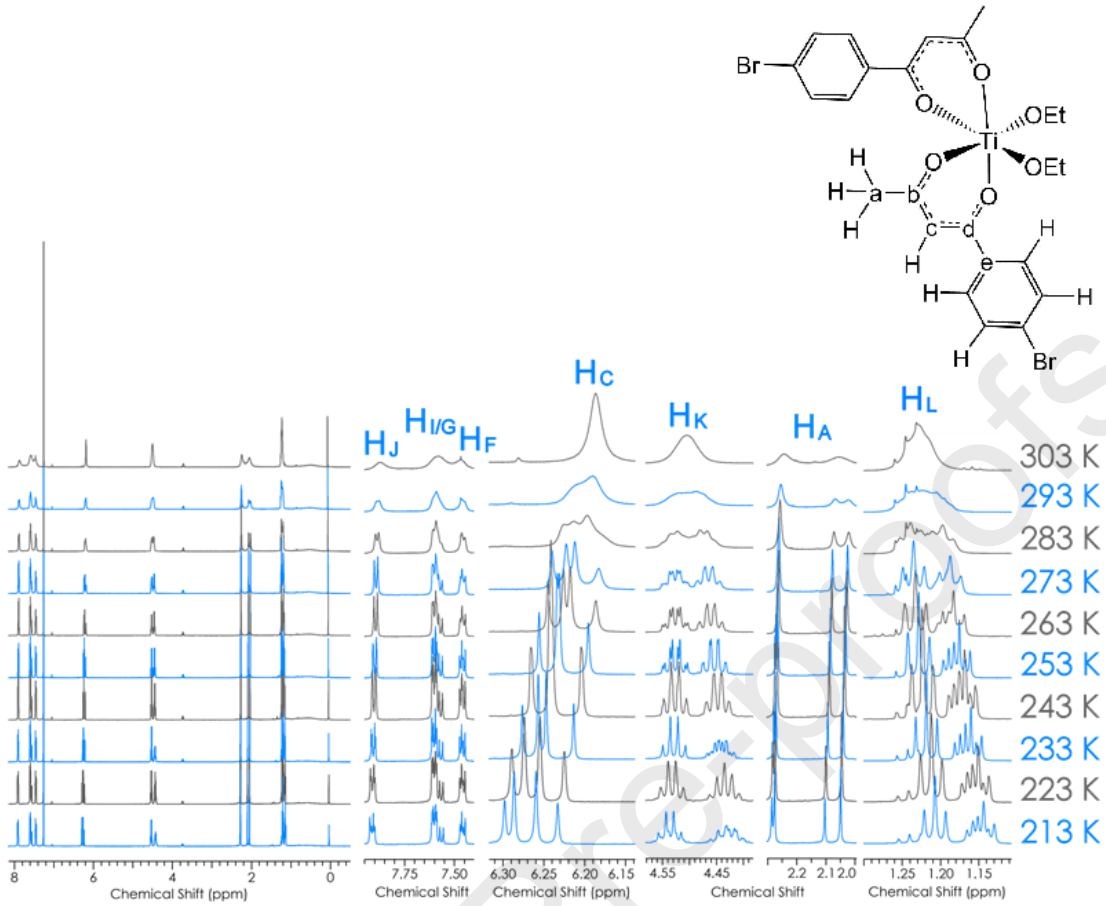


Figure 2 *^{1}H NMR spectra of complex **4**, showing the broad resonances at 303K, which resolve to multiple isomers when cooling to 213K ($CDCl_3$, 300 MHz)*

Single Crystal X-ray Crystallographic (SC-XRD) Analysis: Complex **1** has previously been reported, and is the well-known titanium anticancer compound Budotitane,[31,32,46] which was synthesized herein in order to gain structure-activity relationships (SARs) on catalytic behaviour. After recrystallization, complexes **2**, **4**, **6** and **7** all yielded yellow crystals suitable for SC-XRD analysis. Molecular structures are shown in **Figure 3**, and X-ray data are reported in **Table S1** (*Supporting Information*). Complexes **2**, **6** and **7** were all found to crystallize in a monoclinic unit cell in the space group $P2_1/n$ (**2**) and $P2_1/c$ (**6** and **7**), with the asymmetric unit containing one molecule, and a total of four molecules in the unit cell. Complex **4** crystallized in an orthorhombic unit cell in the space group *C*cc2, with only half a molecule in the asymmetric unit and eight molecules in the unit cell. In all cases, the ethoxide (X) ligands are in a *cis* arrangement, with complexes **2** and **4** crystallizing as the *cis(OEt)-cis(ph)-trans(Me)* isomer, and complex **6** crystallising as the *cis(OEt)-trans(ph)-cis(Me)* isomer. Selected bond lengths (Å) and angles (°) are stated in **Table 1** and **Table S2** (*Supporting Information*) respectively, and show the expected longer Ti-$O_{(1\text{-}4)}$ bond lengths of 2.02-2.10 Å for coordination to the phenyl-β-diketonate ligands, when compared to the shorter titanium-ethoxide Ti-$O_{(5\text{-}6)}$ bond lengths of 1.79-1.83 A (**Table 1**). The bond angles also show slight distortion from a true octahedral structure, with angles ranging from 80.2-100.5° (**Table S2**).

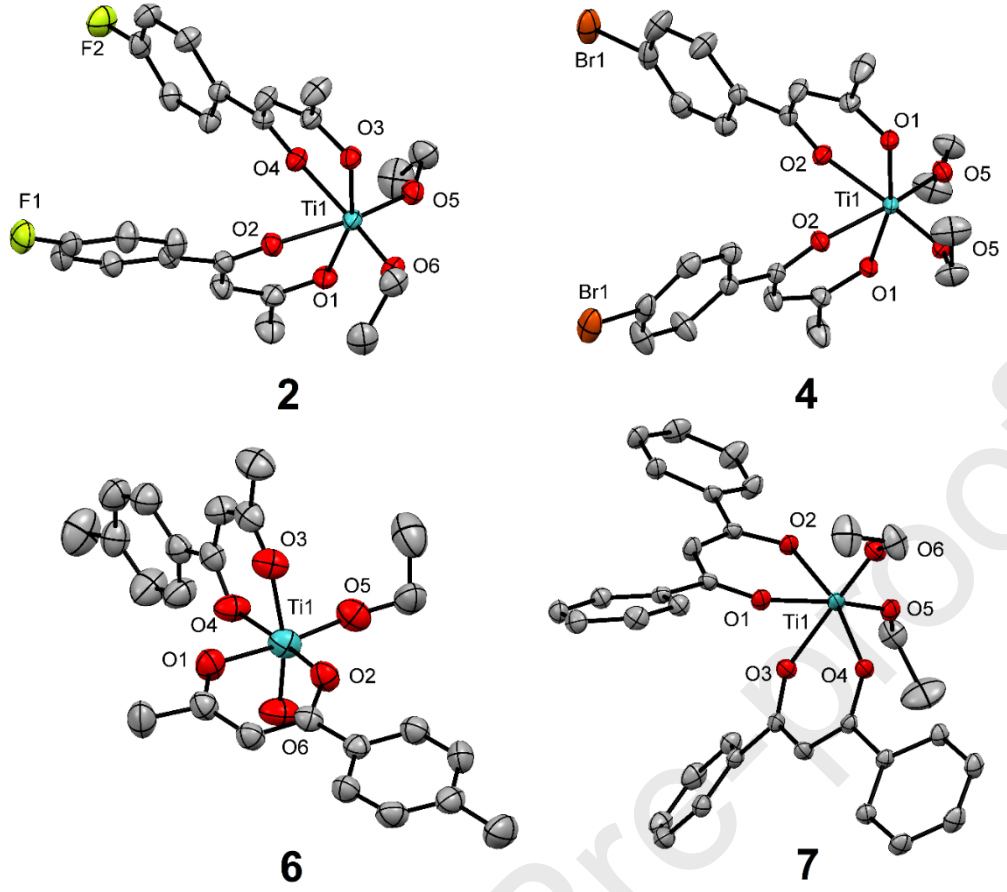


Figure 3 *Molecular structures for complexes* ***2****,* ***4****,* ***6*** *and* ***7****; hydrogen atoms are omitted for clarity and displacement ellipsoids are placed at the 50% probability level.*

Table 1 *Bond lengths (Å) of complexes* ***2****,* ***4****,* ***6*** *and* ***7,*** *with s.u.s in parenthesis.*

Bond	**2**	**4**[a]	**6**	**7**
Ti(1)-O(1)	2.0189(17)	2.0126(12)	2.060(2)	2.1038(16)
Ti(1)-O(2)	2.0987(17)	2.0893(17)	1.994(2)	2.0196(16)
Ti(1)-O(3)	2.0301(16)	--	2.058(2)	2.0961(16)
Ti(1)-O(4)	2.0925(17)	--	2.006(2)	2.0295(16)
Ti(1)-O(5)	1.8278(18)	1.8251(16)	1.795(2)	1.8349(16)
Ti(1)-O(6)	1.8335(17)	--	1.790(2)	1.8188(16)

[a] symmetry generated

Ring Opening Polymerization (ROP) of L-Lactide (L-LA)

1) Microwave (MW) Reactions: The isolated titanium(IV) complexes **1-7** were trialled for the ROP of L-LA using solvent-free MW conditions (180°C/400 W) at various time points (2, 5, 10, 20, 30 and 45 mins), with L-LA:complex ratios of [100:1] or [500:1] (*Supporting Information*). After the reaction times, the polymers were precipitated twice using chloroform (1-5 mL, 50%) and hot methanol (1-5 mL, 50%). Complexes **1** and **3** yielded a small amount of isolatable PLA for L-LA:complex ratios of [100:1] for reaction times 20 or 30 mins only (**Figure S14** and **Figure S23**). However, no PLA was isolated for the other complexes

presented herein at L-LA:complex ratios of [100:1]. All complexes yielded isolatable PLA for L-LA:complex ratios of [500:1], however, due to low PLA yields at the shorter reaction times, only reactions after 20, 30 and 45 mins have been fully analysed.

2) NMR Spectroscopy of resulting PLAs: ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra in $CDCl_3$ were obtained from the crude melt reaction mixtures, an example is shown for complex **3** in **Figure 4a**. As complex **4** only yielded enough isolatable pure PLA after 45 min, only the NMRs for polymers after 45 min polymers reaction times are shown in the *Supporting Information*. The conversions by NMR were calculated in all cases, and the results are shown in **Table 2**. Conversions could not be calculated for complexes **2** and **4**, as the PLA resonances are indistinguishable from L-LA (**Figure S17** and **Figure S27**, respectively). Although we could not confirm this by mass spectrometry, the NMR spectra all highlight quartets at 4.1-4.4 ppm and a broad triplet at ~1.5 ppm (e.g., complex **3**, **Figure 4b**), which are suggestive of an ethoxide end group. The nature of the two quartets present at 4.1-4.4 ppm is unknown, although in addition to the broad triplet, this resonance could be postulated to be lactic acid. Attempts were made to monitor the reaction kinetics by ^{1}H NMR spectroscopy, however, as can be observed for complex **1** (**Figure 5**), the conversions are not proportional to reaction time, and in fact the reaction after just 10 mins yielded the highest conversion of 62%. As the reaction times increase, the conversions fluctuate, showing MW-assisted synthesis leads to unpredictable rates of reaction and a lack of polymer control. The issues in reproducibility were also noted in our repeat reactions (e.g., **Figure S50**), which highlighted different conversions for complex **1** at each time point. Although all possible care was taken to perform these reactions in the absence of water and air, the crimped vials are likely not completely air-tight, so we cannot confirm complete elimination of moisture/air from these reactions. Further work is now required to (i) determine the optimal times and temperatures, (ii) repeat the reactions in completely moisture-/air-free conditions, and (iii) determine the role of the ethoxide initiator sites.

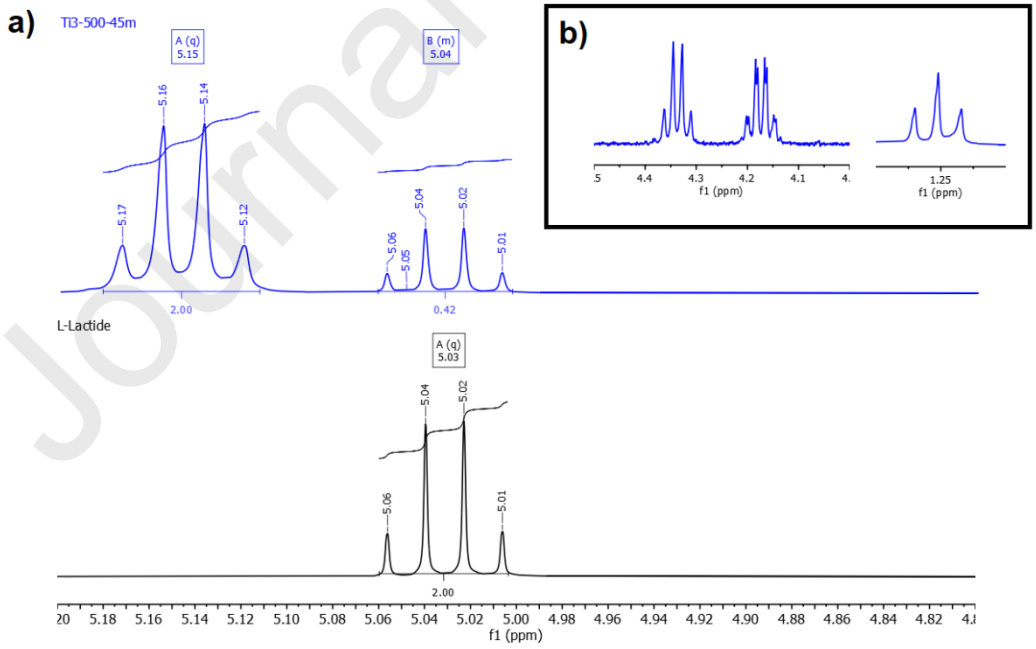


Figure 4 *Crude ^{1}H NMR spectra showing the* ***a)*** *83% conversion of L-LA to PLA after a 45 mins reaction with L-LA:complex* ***3*** *[500:1] and* ***b)*** *ethoxide end groups ($CDCl_3$, 300 K, 400 MHz).*

Table 2 *Percentage conversions (%) by NMR spectroscopy of L-LA:complexes* ***1-7*** *[500:1] (n.d. = not determined)*

Complex	Conversion (%) by NMR after 45 mins [500:1]
1	24%
2	n.d.
3	83%
4	n.d.
5	62%
6	71%
7	75%

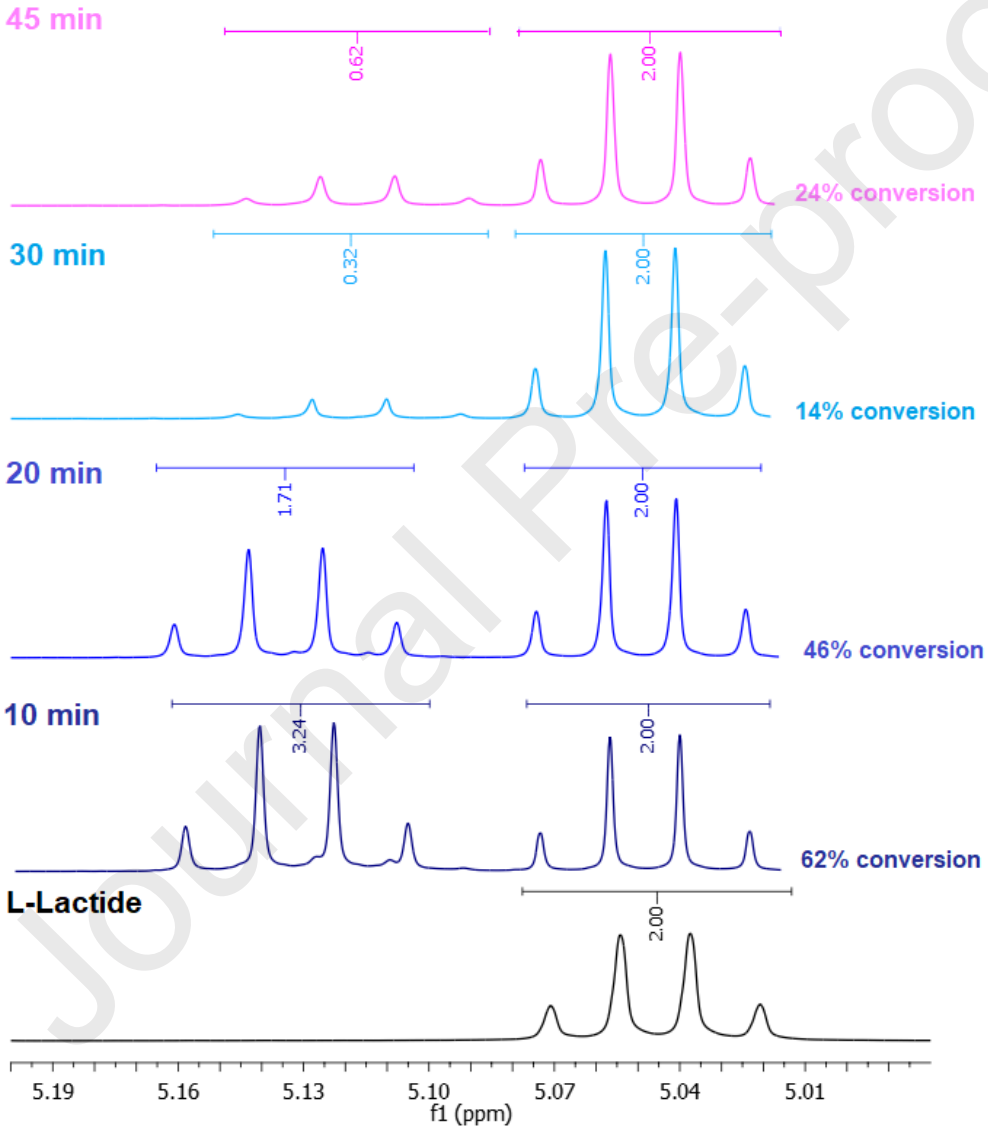


Figure 5 *Crude ^{1}H NMR spectra L-LA:complex* ***1*** *[500:1] at reaction times of 10, 20, 30 and 45 mins, with the percentage conversions highlighted at each time point ($CDCl_3$, 300 K, 400 MHz).*

3) Gel Permeation Chromatography (GPC): GPC has been used to determine the relative molecular weight and the distribution of molecular weights for all resulting polymers. The

results obtained from GPC are shown in **Table 3**, and in most cases, they do not show the general trends. As shown in **Figure 6** for complex **6**, the degree of polymerization control is lost as the reaction proceeds, with the shorter reaction times yielding better molecular weight distribution and possibly better polymer control. This also complements the results obtained for NMR conversions, whereby the short time points yield better percentage conversions, and the degree of control is lost as the reaction proceeds. The highest molecular weight was observed for complex **6**, however, the polymer has a very large distribution of weights and high PDI of 2.35. As with other titanium(IV) complexes, conventional thermal methods lead to a slightly better control of the molecular weight and molecular weight distribution, although the MW-assisted ROP induced an increase in polymerization rate.[47] The efficiency and control of molecular weight depends on the ratio $k_{propagation}/k_{initiation}$ and the extent of transesterification side reactions, and as shown in the previous NMR and this GPC data, the molecular weight distributions are large and the PDIs high, highlighting the possibility of transesterification. The non-functionalized complex **1** has the lowest PDI after 45 min, whilst the methyl functionalized complex **6** yields the highest molecular weight of 42,906 g/mol. With the exception of complex **4**, the following general trend in PDIs after 45 min were observed: H (**1**) < 4'-F (**2**) < 4'-Cl (**3**) < 4'-I (**5**) < 4'-Et (**6**) < diphenyl (**7**), highlighting the possibility that ligand size, sterics and electronics may play a role in the molecular weights and PDIs of the resulting polymers.

Table 3 *GPC data obtained for the polymerization of L-LA with complexes* ***1-7*** *at various reaction times*

Complex	Time (min)	C (mg/mL)	M_p (kg/mol)	M_n (kg/mol)	M_w (kg/mol)	PDI
1	20	2.35	12.81	5.28	29.43	2.76
	30	2.75	20.16	11.23	23.28	2.07
	45	2.85	15.59	9.41	16.29	1.73
2	30	2.40	13.40	11.84	16.13	1.36
	45	2.30	27.28	12.37	23.12	1.87
3	20	2.45	10.05	8.02	11.45	1.42
	30	2.55	10.84	8.68	13.29	1.53
	45	2.70	22.75	11.38	23.96	2.10
4	45	2.30	16.31	9.83	17.08	1.74
5	20	2.25	20.16	10.41	19.80	1.90
	30	2.35	22.75	13.59	22.62	1.66
	45	2.40	31.26	14.67	29.63	2.02
6	20	2.50	8.64	7.22	10.58	1.47
	30	2.35	10.84	8.28	13.73	1.66
	45	2.70	38.04	18.25	42.91	2.35
7	20	2.65	5.92	5.61	7.16	1.28
	30	2.45	6.20	5.86	7.80	1.33
	45	2.55	35.27	15.85	35.25	2.22

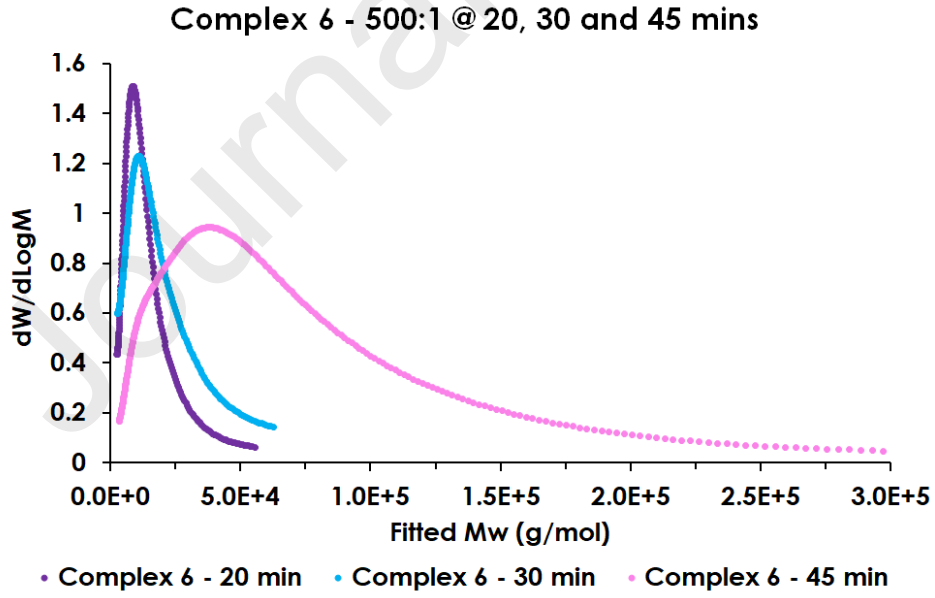


Figure 6 *GPC data for complex* ***6*** *after 20, 30, and 45 min reaction times.*

4) Differential Scanning Calorimetry (DSC): In this study we report the crystallization temperatures (T_c) and melting temperatures (T_m), which give exothermic and endothermic transitions, respectively. Approximately 1.3-1.4 mg of each pure polymer was weighed out and analysed by DSC. The following heat-cool-heat cycle was applied to each sample: 20 – 200 °C at 10 °C/ min heat and cooled from 200 – 20 °C at 10 °C/ min. The results are shown in the *Supporting Information*, and in all cases the first heat cycle shows additional crystallization peaks, which are no longer present after the second heat cycle. Generally, there is an increase in T_c as the molecular weight of the polymer increases, which is even more pronounced in the second heat cycle. For example, the peak temperatures for L-LA:complex **6** are: T_c = 156.6 °C (20 mins), T_c = 159.2 °C (30 mins) and T_c = 166.8 °C (45 mins) are shown in **Figure S44**.

5) Complex 2 – comparison of MW and conventional heating: In order to compare our MW results with the use of solvent-free conventional heating, complex **2** was mixed with L-LA [500:1] in glass vials with aluminium/PTFE crimped caps, submerged in oil and agitated at 185°C. On each measurement, three vials were removed from the oil, cooled and quenched with $CDCl_3$. The conversion percentages were calculated and plotted against time/ mins. At 185°C a conversion of 96 ± 0.1 % was observed (**Table 4**), in contrast to the previous MW reactions, where complex **2** forms PLA which is indistinguishable from L-LA. As the temperatures in MW reactions can fluctuate, we assessed the possibility that temperature would affect the polymer conversions. Multiple vials were prepared of L-LA:complex **2** at ratios of [500:1], and heated at temperatures between 150-200°C. It is evident that as the temperature of polymerization increases, the time taken for complex **2** to convert 50% of the L-LA into PLA decreases (**Figure 7**), indicating an increased rate of reaction. With an increase in reaction temperature, an exponential decrease in the time taken to convert 50% of the L-LA is observed (**Figure S52**). Complex **2** was found to have a turnover number of 0.13 molecules/ sec, which represents low catalytic ability.

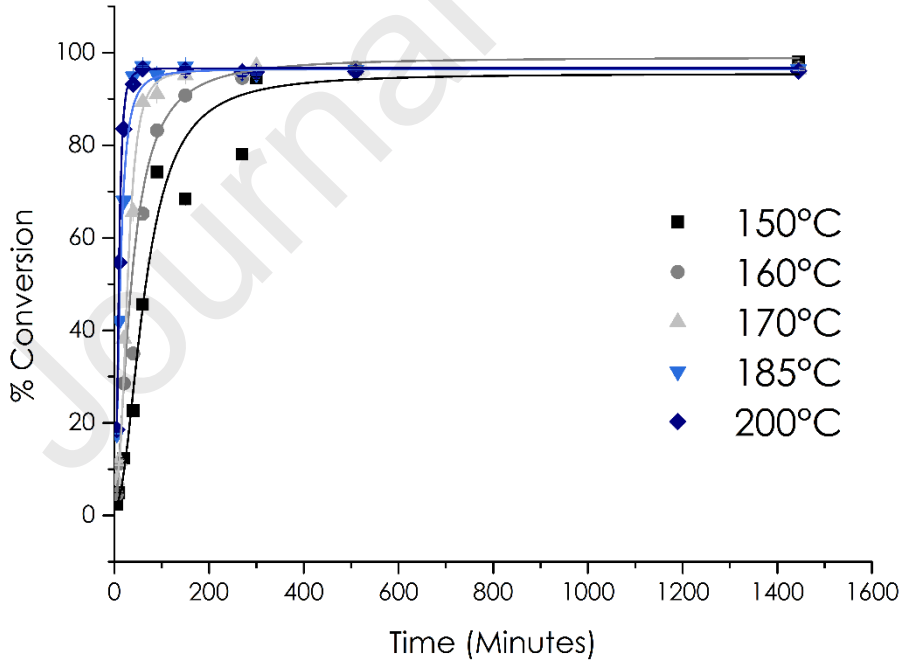


Figure 7 *Plot of % conversion verses time for the conventional heating reaction of complex* ***2*** *and L-LA at 150, 160, 170, 185 and 200°C ($CDCl_3$, 300K, 400 MHz)*

Table 4 *Degree of conversion after conventional heating of L-LA:complex* ***2*** *at 150, 160, 170, 185 and 200°C.*

Temperature (°C)	Degree of conversion (%)
150	98 ± 0.1
160	97 ± 0.2
170	96 ± 0.2
180	96 ± 0.1
200	96 ± 0.3

Notably, it was observed that even though conventional heating leads to NMR resonances which are distinctly different from L-LA, the PLA resonances are broad and appear to contain polymers with a loss of stereochemistry, where we noted that rac-PLA is likely formed (**Figure S53** and **Figure S54**). Therefore, although the MW synthesis gave uncontrollable yields which were not proportional to reaction time, in comparison to conventional heating, the polymers obtained from the MW reactions retain their stereochemistry. This is a significant advantage of this method and highlights the need to optimize this work. It is believed the removal of the solvent in the MW reactions is responsible for the lack heat dissipation, which was previous reported as an advantage, therefore our future work will focus on the solvent effects.

Conclusion

This work highlights six new functionalized bis(phenyl-β-diketonato)titanium(IV) ethoxide complexes $[Ti(L)_{2(}OEt)_2]$, which have been synthesized and fully characterized. SC-XRD for complexes **2**, **4**, **6** and **7**, highlighted all complexes have the ancillary ethoxide groups in a *cis* arrangement and NMR studies confirm the functionality of these complexes in solution. The complexes' ability to act as a catalyst in the ROP of L-LA has been determined by MW-assisted reactions. The percentage conversions were determined by ^{1}H NMR spectroscopy and confirms complex **3** (R = 4'-Cl) with the highest PLA conversion of 83%. The isolated PLA samples were analyzed by a variety of methods and show the general trend of increasing molecular weights and PDIs with an increase in reaction time. The non-functionalized complex **1** has the lowest PDI after 45 min, however, the methyl functionalized complex **6** yields the highest molecular weight of 42,906 g/mol. The following general trends are observed with PDIs: H (**1**) < F (**2**) < Cl (**3**) < I (**5**) < Et (**6**) < diphenyl (**7**), showing we could tune the functionality, whereby the larger the sterics of the ligand the higher the PDI. We used complex **2** to compare the results to conventional heating methods, and though this leads to distinct PLA resonances in the NMR (unlike the MW reactions which gave some indistinguishable PLA resonances), they are broad and appear to contain polymers with a loss of stereochemistry. Therefore, we can conclude that although the MW-assisted synthesis gave yields which were not proportional to reaction time, in comparison to conventional heating, the polymers obtained from the MW reactions retain their stereochemistry, which is a significant advantage of this method and highlights for future optimizations.

Appendix A. Supplementary data

CCDC 1939721-1939724 contains the supplementary crystallographic data for complexes **2**, **4**, **6** and **7**. These data can be obtained free of charge via https://eur01.safelinks.protection.outlook.com/?url=http%3A%2F%2Fwww.ccdc.cam.ac.uk%2Fconts%2Fretrieving.html&data=04%7C01%7CR.Lord%40uea.ac.uk%7Cd55b46cd5a0b45ec488208d962f0ef05%7Cc65f8795ba3d43518a070865e5d8f090%7C0%7C0%7C637649609206241674%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwiLCJXVCI6Mn0%3D%7C1000&sdata=b3hjAfjcQcqjdllt6ln9tTX2GuYQxiWSBAakoy8Hzjk%3D&reserved=0, or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or e-mail: deposit@ccdc.cam.ac.uk

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Experimental

Apparatus: All ligand syntheses were conducted using air-stable conditions, whilst all titanium complexation reactions were conducted using Schlenk line techniques with a N_2/high vacuum system, where the N_2 was passed over a dual column of P_2O_5 and activated 4 Å molecular sieves. All glassware, cannula and filter cannula were stored in an oven at 160°C prior to use. All liquid reagents were measured using N_2 purged needles and syringes.

The ligands were all synthesized by our previously published method,[29,30] which is a modification of the synthesis originally reported by Hollick et al.[48] These were then recrystallized and desiccated before use. Titanium(IV) ethoxide was stored under a N_2 atmosphere in a sealed ampoule and was purchased from Sigma-Aldrich Chemical Company. All other reagents were purchased from Sigma-Aldrich Chemical Company, Acros Organics, Fisher Scientific, VWR International or the in-house stores in the School of Chemistry, University of Leeds. The complexation reactions used ethanol which was dried by passing over a copper catalyst and activated alumina columns using a Pure Solvent MD Solvent Purification System. Washing and/or recrystallization was conducted using petroleum ether (40-60°), which was distilled over wired sodium and stored under a N_2 atmosphere after degassing using three freeze-pump-thaw cycles. NMR spectra were recorded in deuterated chloroform which was dried by refluxing over calcium hydride and stored under N_2 atmosphere after degassing using three freeze-pump-thaw cycles. After drying all solvents were stored in Young's tap glass ampoules.

Nuclear Magnetic Resonance (NMR): Deuterated NMR solvents were purchased from Sigma-Aldrich Chemical Company, Acros Organics or GOSS Scientific. All samples were prepared in a Braun Labmaster 100 glove box and were stored in ampoules under N_2 atmosphere. NMR spectra were collected using a Bruker DRX 500 MHz, Bruker DRX 500 MHz or Bruker DPX 300 MHz spectrometers.

Microanalysis and Mass Spectrometry: Microanalyses were collected by Mr. Ian Blakeley and Ms. Tanya Marinko-Covell at the University of Leeds microanalysis service. Electrospray mass spectrometry was collected by Ms. Tanya Marinko-Covell at the University of Leeds mass spectrometry service.

X-ray Crystallographic Analysis (XRD): X-ray diffraction data was collected on a Bruker X8 diffractometer using monochromated Mo-Kα (graphite) X-ray radiation of wavelength 0.71073 Å. Diffraction data was detected using a Kappa Apex II CCD detector. Suitable crystals were mounted on a MiTeGen micromesh and cooled to 150K using an Oxford cryostream low temperature device.[49] The data was scaled and prepared using APEX2 software and error calculations were performed using SADABS. The data was solved by direct methods using the Olex2[50,51] and ShelXL[52] packages. Structure refinement was achieved using ShelXS/ShelXL or Olex2.

Microwave Reactions: All MW reactions were conducted in a Biotage Initiator using 2-5 mL Biotage microwave vials with crimped caps. Prior to the reactions, the L-lactide (L-LA) was recrystallized and dried under an N_2 atmosphere, and all samples were prepared in a Glovebox. The MW vials were loaded with dry L-LA (100 or 500 eq.), dry titanium complex (1 eq.) and a magnetic stirrer bar. The lids were crimped and with stirring, the MW reactions were conducted for 2-45 minutes at 180 °C (400 W). NMR analyses were conducted by dissolving the crude products in $CDCl_3$, whilst the pure PLA was obtained from chloroform:hot methanol in a 1:1 or 1:2 v/v.

Conventional Heating: Under a N_2 atmosphere, L-lactide was mixed with one equivalent of compound **2** in a pestle and mortar and sealed into MW crimp-cap vials. The vials were submerged into rigorously stirred oil at temperatures between 150-185 °C. Three sample vials were removed at 5, 10, 20, 40, 60, 90, 150 min, then 4, 5, 8.5 and 12 h. Each sample vial was exposed to air and the polymer inside analysed by ^{1}H NMR in $CDCl_3$. The degree of polymerization was calculated by single-blind integration of the area under the peaks of polymerized lactide against total area of unreacted and polymerized lactide and the percentage conversion calculated for each of the vials. The average was calculated and plotted using Origin pro 8. Origin was further used to model appropriate lines of best fit for all of the data points, and a logarithmic fit was selected. The general formula was rearranged to calculate the 50% conversion.

Differential scanning calorimetry (DSC): DSC measurements were conducted on a TA Q5000 DSC and the TA Universal Analysis 2000 was used to process and analyse the results. Sample sizes between 1.3 – 1.4 mg were heated in aluminium pans/lids and the following cycles applied: heat 1: 20 – 200 °C at 10 °C/ min, cool: 200 – 20 °C at 10 °C/ min and heat 2: 20 – 200 °C at 10 °C/ min.

Gel Permeation Chromatography (GPC): The data was collected using an Agilent GPC System equipped with Auto-sampler and PolarGel column. Detectors: UV-vis, RI, & viscometer. Calibration: PMMA standards (see **Figure S1**); concentration range Mp (g/mol) = 2,000 – 2,000,000 (12 points) with average PD value = 1.3 Mobile phase: Chloroform (GPC grade).

Synthesis and Characterization:

General synthetic procedures and protocols are stated in the *Supporting Information*. Complex **1** was previously synthesized by Keppler et al.[32,46] and ^{1}H NMR spectroscopy used to confirm successful synthesis. All β-diketonate ligands were prepared using our previously

reported method.[29,30] Generally, a functionalized β-diketonate ligand (2 eq.) in dry ethanol was added dropwise to titanium(IV) ethoxide (1 eq.) in dry ethanol. The mixture was stirred at room temperate for 16 h, then isolated by either filtration or removal of the solvent and recrystallized from a suitable solvent.

$[Ti(O_2C_{10}H_8F)_2(OC_2H_5)_2]$ (2): This complex was recrystallized from hot ethanol to yield light yellow crystals. **Yield:** 2.61 g, 5.26 mmol, 60%; **^{1}H NMR (500 MHz, 300 K, $CDCl_3$, δ):** 8.04-7.77 (br. d, 4H, ArH *meta* to C-F), 7.12-7.00 (m, 4H, ArH *ortho* to C-F), 6.20 (s, 2H, methine COCHCO), 4.52 (m, 2H, ethoxide OCH_2CH_3), 2.17 (s, 6H, methyl $COCH_3$), 1.24 (m, 3H, ethoxide OCH_2CH_3); **^{13}C{^{1}H} NMR (125 MHz, 300 K, $CDCl_3$, δ):** 166.0 (Q, C=O), 164.0 (Q, C=O), 140.0 (Q, ArC], 133.4 (Q, ArC-F), 130.2 (ArCH *ortho t*o C-F), 111.4 (ArCH *meta* to C-F), 72.4 (ethoxide OCH_2CH_3), 33.6 (methyl $COCH_3$), 18.5 (ethoxide OCH_2CH_3); **ES-MS ($CHCl_3$, *m/z*):** 519.1 [M+Na]; **Anal. calcd for $C_{24}H_{26}F_2O_6Ti$:** C 57.8, H 5.7; **Found:** C 57.7; H 5.3%.

$[Ti(O_2C_{10}H_8Cl)_2(OC_2H_5)_2]$ (3): This complex was recrystallized twice from dry petrol ether (40-60°C) to yield a pale-yellow powder. **Yield:** 0.43 g, 0.81 mmol, 65%; **^{1}H NMR (500 MHz, 300 K, $CDCl_3$, δ):** 7.96 (br. s, 2H, ArH *meta* to C-Cl), 7.70 (br. s, 2H, ArH *meta* to C-Cl), 7.41 (br. s, 2H, ArH *ortho* to C-Cl), 7.32 (br. s, 2H, ArH *ortho* to C-Cl), 6.21 (br. s, 2H, methine COCHCO), 4.53 (m, 4H, ethoxide OCH_2CH_3), 2.26 (br. s, 3H, methyl $COCH_3$), 2.08 (br. s, 3H, methyl $COCH_3$), 1.25 (m, 6H, ethoxide OCH_2CH_3]; **^{13}C{^{1}H} NMR (500 MHz, 300 K, $CDCl_3$, δ):** 193.4 (Q, C=O), 190.6 (Q, C=O), 181.7 (Q, ArC), 178.6 (Q, C=O), 137.9 (Q, ArC), 135.6 (Q, ArC-Cl), 129.0 (ArCH *meta* to C-Cl), 128.6 (ArCH *ortho* to C-Cl], 99.3 (methine COCHCO), 99.0 (methine COCHCO), 72.4 (ethoxide OCH_2CH_3), 27.6 (methyl $COCH_3$), 27.1 (methyl $COCH_3$), 18.5 (ethoxide OCH_2CH_3); **ES-MS ($CHCl_3$, *m/z*):** 469.0 [M-$C_{10}H_8O_2Cl$+2$NaCO_2H$]; **Anal. calcd for $C_{24}H_{26}Cl_2O_6Ti$:** C 54.5, H 5.0, Cl 13.4; **Found:** C 54.6, H 4.9, Cl 13.5%,

$[Ti(O_2C_{10}H_8Br)_2(OC_2H_5)_2]$ (4): This complex was recrystallized from hot ethanol to yield light yellow crystals. **Yield:** 0.62 g, 1.01 mmol, 62%; **^{1}H NMR (500 MHz, 300 K, $CDCl_3$, δ):**7.89 (d. 2H, ArH *meta* to C-Br), 7.60 (s, 4H, ArH *ortho* to C-Br), 7.48 (s, 2H, ArH *meta* to C-Br), 6.20 (s, 2H, methine COCHCO), 4.52 (br. m, 4H, ethoxide OCH_2CH_3), 2.26 (s, 3H, methyl $COCH_3$), 2.07 (s, 3H, methyl $COCH_3$), 1.24 (br. m, 6H, ethoxide OCH_2CH_3); **^{13}C{^{1}H} NMR (500 MHz, 300 K, $CDCl_3$, δ):**192 ppm (Q, C=O), 181.8-178.7 (Q, C=O), 140.0 (Q, ArC), 126.5 (Q, ArC-Br), 29.1 (ArCH *meta* to C-Br), 131.6 (ArCH *ortho* to C-Br), 99.3-98.9 (methine, COCHCO), 72.5 (ethoxide OCH_2CH_3), 27.7 (methyl $COCH_3$), 27.0 (methyl $COCH_3$), 18.5 (ethoxide OCH_2CH_3); **Anal. calcd for $C_{24}H_{26}Br_2O_6Ti$**: C 46.6, H 4.2, Br 25.9; **Found:** C 46.6, H 4.2, Br 25.6%

$[Ti(O_2C_{10}H_8I)_2(OC_2H_5)_2]$ (5): This complex was recrystallized from hot ethanol to yield a dark brown solid. **Yield:** 0.37 g, 0.53 mmol, 60%; **^{1}H NMR (500 MHz, 300 K, $CDCl_3$, δ):**7.74 (m, 3H, ArH *ortho* and ArH *meta* to C-I), 7.46 (br. s, 1H, ArH *ortho t*o C-I), 6.19 (s, 1H, methine COCHCO), 4.51 (br. m, 2H, ethoxide OCH_2CH_3), 2.26-2.07 (s, 3H, methyl $COCH_3$), 1.23 (m, 3H, ethoxide OCH_2CH_3); **^{13}C{^{1}H} NMR (500 MHz, 300 K, $CDCl_3$, δ):**193.7 (Q, C=O), 190.8 (Q, C=O), 182.1 (Q, ArC), 178.9 (Q, ArC-I), 137.6-136.7 (ArCH *meta* to C-I), 129.1 (ArCH *ortho* to C-I), 98.9 (methine COCHCO), 72.4 (ethoxide OCH_2CH_3), 27.7-27.0 (methyl $COCH_3$), 18.6 (ethoxide OCH_2CH_3); **ES-MS ($CHCl_3$, *m/z*):** 734.9 [M+Na]; **Anal. Calc. for $C_{24}H_{26}I_2O_6Ti$:** C 40.5; H 3.7%; **Found:** C 40.8%, H 3.6%.

$[Ti(O_2C_{11}H_{11})_2(OC_2H_5)_2]$ (6): This complex was recrystallized from hot ethanol to yield a white powder. **Yield:** 0.33 mg, 0.68 mmol, 82%; **^{1}H NMR (500 MHz, 300 K, $CDCl_3$, δ):** 7.97

(s, 4H, ArH *meta* to ArCH3), 7.38 (s, 4H, ArH *ortho* to $ArCH_3$) 7.03 (s, 2H, methine COCHCO), 4.57 (q, 4H, $^3J(^1H\text{-}^1H)$ = 7.1 Hz, ethoxide OCH_2CH_3), 2.41 (s, 6H, methyl $ArCH_3$), 2.27 (s, 6H, methyl $COCH_3$), 1.25 (t, 6H, $^3J(^1H\text{-}^1H)$ = 6.9 Hz, ethoxide OCH_2CH_3); **$^{13}C\{^1H\}$ NMR (500 MHz, 300 K, $CDCl_3$, δ):** 165.3 (Q, C=O), 132.5 (Q, $ArCCH_3$) 129.7 (ArCH *ortho* to $ArCH_3$), 114.5 (ArCH *meta* to $ArCH_3$), 113.7 (ArCH *meta* to $ArCH_3$), 96.8 (methine COCHCO), 71.6 (ethoxide OCH_2CH_3), 29.5 (methyl $COCH_3$), 21.3 (methyl $ArCH_3$), 18.5 (ethoxide OCH_2CH_3); **ES-MS ($CHCl_3$, *m/z*):** 489.2 [M+H]; **Anal. calcd for $C_{26}H_{32}O_6Ti$:** C 63.9, H 6.6; **Found:** C 63.7, H 6.9%.

$[Ti(O_2C_{15}H_{11})_2(OC_2H_5)_2]$ (7): This complex was recrystallized from hot ethanol to yellow crystals. **Yield:** 0.45 mg, 0.77 mmol, 73%; **^1H NMR (500 MHz, 300 K, $CDCl_3$, δ):** 8.10 (d, 8H, $^3J(^1H\text{-}^1H)$ = 7.5 Hz, ortho ArH), 7.54 (t, 4H, $^3J(^1H\text{-}^1H)$ = 7.5 Hz, *para* ArH), 7.45 (br. d, 8H, $^3J(^1H\text{-}^1H)$ = 7.5 Hz, *meta* ArH), 7.25 (s, 2H, methine COCHCO), 4.52 (q, 4H, $^3J(^1H\text{-}^1H)$ = 7.1 Hz, ethoxide OCH_2CH_3), 1.24 (t, 6H, $^3J(^1H\text{-}^1H)$ = 6.9 Hz, ethoxide OCH_2CH_3); **$^{13}C\{^1H\}$ NMR (500 MHz, 300 K, $CDCl_3$, δ):** 182.3(Q, C=O), 137.9 (Q, ArC), 133.5 (*para* ArCH), 128.9 (*ortho* ArCH), 128.2 (*meta* ArCH), 99.2 (methine COCHCO), 71.9 (ethoxide OCH_2CH_3), 18.7 (ethoxide OCH_2CH_3); **ES-MS ($CHCl_3$, *m/z*):** 585.2 [M+H]; **Anal. calcd for $C_{34}H_{32}O_6Ti$**: C 69.9, H 5.5; **Found:** C 69.8, H 5.6%.

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