A study of the ring-opening of lactides and related cyclic esters by Ph_2SnX_2 and Ph_3SnX compounds (X = NMe_2, OR)†

Malcolm H. Chisholm* and Ewan E. Delbridge

Department of Chemistry, The Ohio State University, 100 W 18th Avenue, Columbus, OH, 43210-1185, USA. E-mail: chisholm@chemistry.ohio-state.edu; Fax: +1 614 292 0368; Tel: +1 614 292 7216

Received (in New Haven, CT, USA) 6th January 2003, Accepted 5th March 2003
First published as an Advance Article on the web 7th July 2003

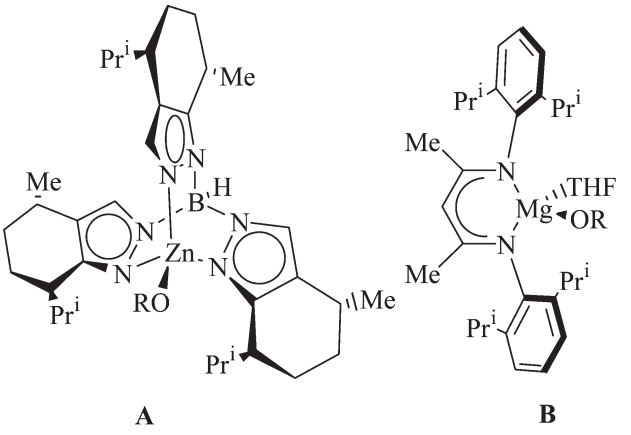
Ph_3SnX reacts with L-lactide in the order X = $NMe_2 \sim OMe \gg OPr^i > OBu^t$ in the initial ring-opening event. The rate of ring-opening of methyl substituted 1,4-dioxane-2,5-diones decreases with methyl substitution and ring-opening of 3,3,6,6-tetramethyl-1,4-dioxane-2,5-dione is not observed. From studies of the reaction between Ph_3SnOPr^i and L-lactide the activation parameters $\Delta H^{\neq} = 13(1)$ kcal mol^{-1} and $\Delta S^{\neq} = -37(3)$ eu have been determined. Ph_3SnNMe_2 reacts with cyclic esters and propylene carbonate at low temperatures to give isolable ring-opened products. The compound Ph_3Sn[OCHMeC(O)OCHMeC(O)X] (where X = NMe_2, OMe) are labile in solution at room temperature, yielding Ph_3Sn[OCHMeC(O)X] and Ph_3Sn[OCHMeC(O)]$_n$X, where $n \geq 3$, by transesterification, along with other minor products due to phenyl/OR group transfer (*i.e.*, Ph_4Sn). $Ph_2Sn(NMe_2)_2$ and L-lactide react to give Ph_2Sn[OCHMeC(O)NMe_2]$_2$ by ring-opening of L-lactide followed by rapid amidation. A related compound, Ph_2Sn[OCHMeC(O)OPr^i]$_2$, is also formed in the reaction between $Ph_2Sn(OPr^i)_2$ and L-lactide but is more labile toward further ring-opening of L-lactide.

Introduction

Interest in polylactides, PLAs, arises from their numerous potential applications, which range from environmentally friendly packaging materials[1] to drug-delivery agents,[2] biodegradable sutures[2,3] and polymer scaffolds for tissue engineering.[4] Ring-opening polymerization (ROP) of lactides (LA; L-, D-, *rac*- and *meso*- forms) to form polylactides by single-site metal alkoxide precursors has attracted considerable recent attention[5] since the properties of a given PLA are determined by its molecular weight, molecular weight distribution and molecular microstructure. Recent successes in the development of single-site catalysts include the preparation of syndiotactic[5a] and heterotactic[5c] polymers along with control of polydispersity. An excellent review documents recent endeavors in this field.[6] Much attention has been directed to understanding the stereosequences (the arrangement of the *R* and *S* chiral centers) of PLA with recent work by Hillmyer and coworkers addressing this issue by use of high resolution NMR spectroscopy.[7]

It is, however, fair to state that little is really understood in terms of what controls the intimate mechanistic steps of polymerization, how stereoselectivity is achieved and what factors influence the relative rates of ROP *versus* the often deleterious side reactions involving transesterification and chain transfer. For example, it is not clear why sterically demanding and chiral Tp*M(OR) compounds,[5e] **A**, of magnesium or zinc should yield only poor stereoselectivity when less sterically demanding achiral diiminato compounds **B** achieve significant stereoselectivity (>90%) under similar reaction conditions (Fig. 1).[5d,5g]

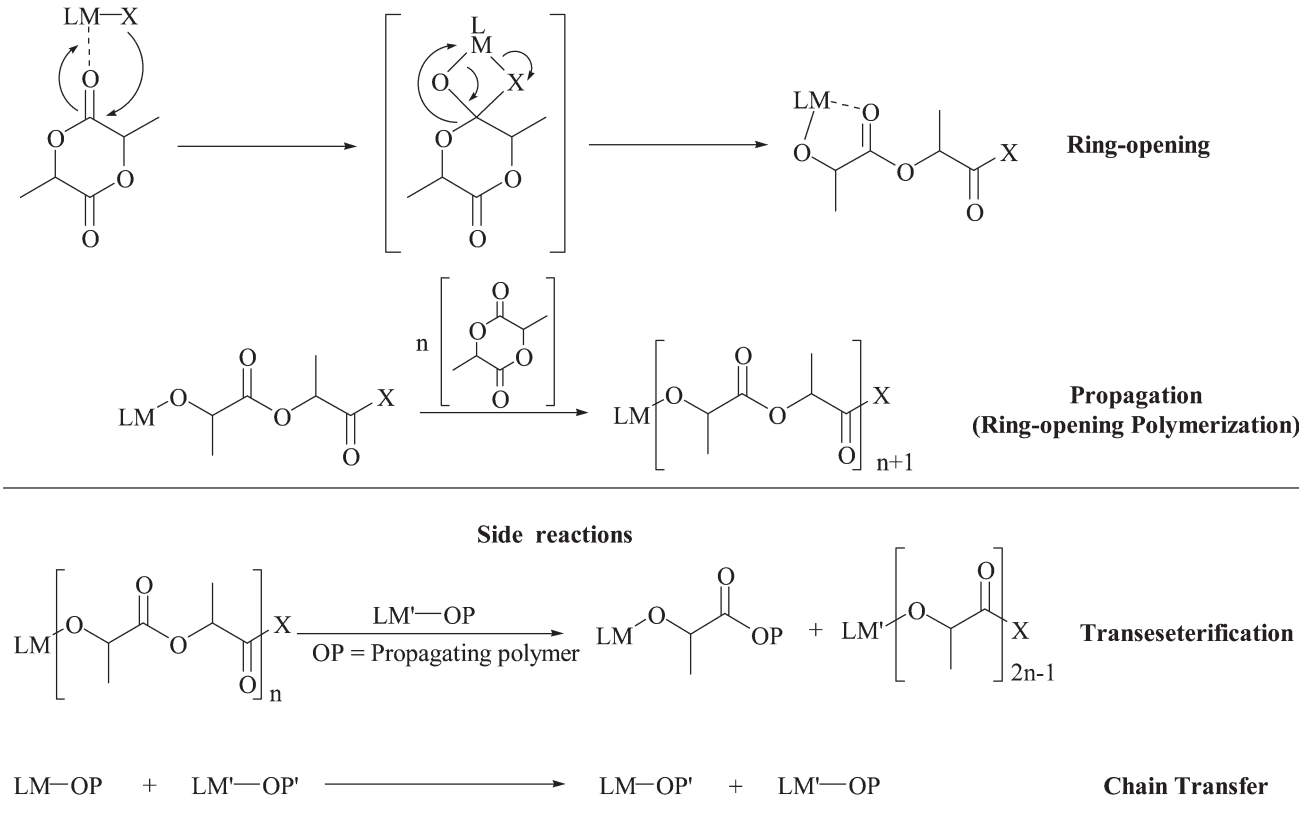
We reasoned that much might be learned from a study of the reactivity of Ar_3SnX and Ph_2SnX_2 precursors in their reactions with lactides and related cyclic esters since, unlike Tp or beta-diiminate (BDI) ligands, reversible metal-ligand dissociation in solvents such as benzene and methylene chloride could safely be ruled out. To date, there have been a number of interesting papers that have dealt with the polymerization of cyclic esters such as LA by tin(II) catalyst precursors[8] but there are few examples utilizing tin(IV) catalysts.[9] These Ar_3SnX and Ph_2SnX_2 precursors are kinetically slow relative to tin(II) and other zinc(II) and magnesium(II) catalysts. This allows for the possibility to study in isolation the three components of metal-mediated anionic lactide polymerization, namely the initial ring-opening event, the propagating reaction (also known as ring-opening polymerization, ROP) and the side



A **B**

Fig. 1 Zinc and magnesium catalyst precursors for the polymerization of lactide.

† Electronic supplementary information (ESI) available: preparation and characterization data for Ar_3SnX, Ph_2SnNMe_2 and $Ph_2Sn(OPr^i)_2$ compounds [X = NMe_2, OMe, OPr^i, OBu^t, OPh, $OCH(CF_3)_2$, PPh_2 and Ar = Ph, *o*-MeC_6H_4]; NOE data and NMR spectra available. See http://www.rsc.org/suppdata/nj/b3/b300101f/



Scheme 1 The three components of lactide polymerization: ring-opening, propagation and side reactions (transesterification and chain transfer).

reactions such as chain transfer and transesterification (Scheme 1).

If the relative rates of initial ring-opening, k_{ro}, and subsequent propagation, k_{prop}, markedly differ such that $k_{ro} > k_{prop}$ it should be possible to isolate products where just one LA monomer has been ring-opened. We first observed this for Ph_3SnNMe_2 and L-lactide[10] and have expanded our findings here. Specifically we have systematically investigated the effect of three parameters on the ring-opening event. (1) The effect of X, the initiating group, in Ph_3SnX on the ring-opening of LA. (2) The effect of methyl substitution on the cyclic monomer as in LA *vs.* GL (where GL = glycolide). (3) The effect of altering the Ar groups (the spectator ligands) on the Sn(IV) initiator. The results from this study are discussed below whilst a detailed description of the propagation kinetics[11] and side reactions of transesterification and chain transfer utilizing R_2SnX_2 and R_3SnX catalyst precursors will be discussed in subsequent publications.

Results and discussion

Ar_3SnX and Ph_2SnX_2 compounds

The dimethylamido compounds were all synthesized in a similar manner from the metathetic reaction between Ar_3SnCl and $LiNMe_2$ in benzene or THF to yield the corresponding Ar_3SnNMe_2 compounds, where Ar = Ph and *o*-MeC_6H_4, which were air-sensitive, white or colorless oils or waxy solids. $Ph_2Sn(NMe_2)_2$ was prepared in an analogous fashion from Ph_2SnCl_2 and 2 equiv. of $LiNMe_2$.

The corresponding alkoxides Ar_3SnOR and $Ph_2Sn(OR)_2$ were prepared by alcoholysis of the appropriate dimethylamides (R = Me, Pr^i, $CH(CF_3)_2$, Bu^t and Ph). Ph_3SnPPh_2 was likewise synthesized by treatment of Ph_3SnNMe_2 with excess $HPPh_2$. These compounds were similarly air-sensitive, white or colorless waxy solids or oils and were purified by vacuum distillation or crystallization.

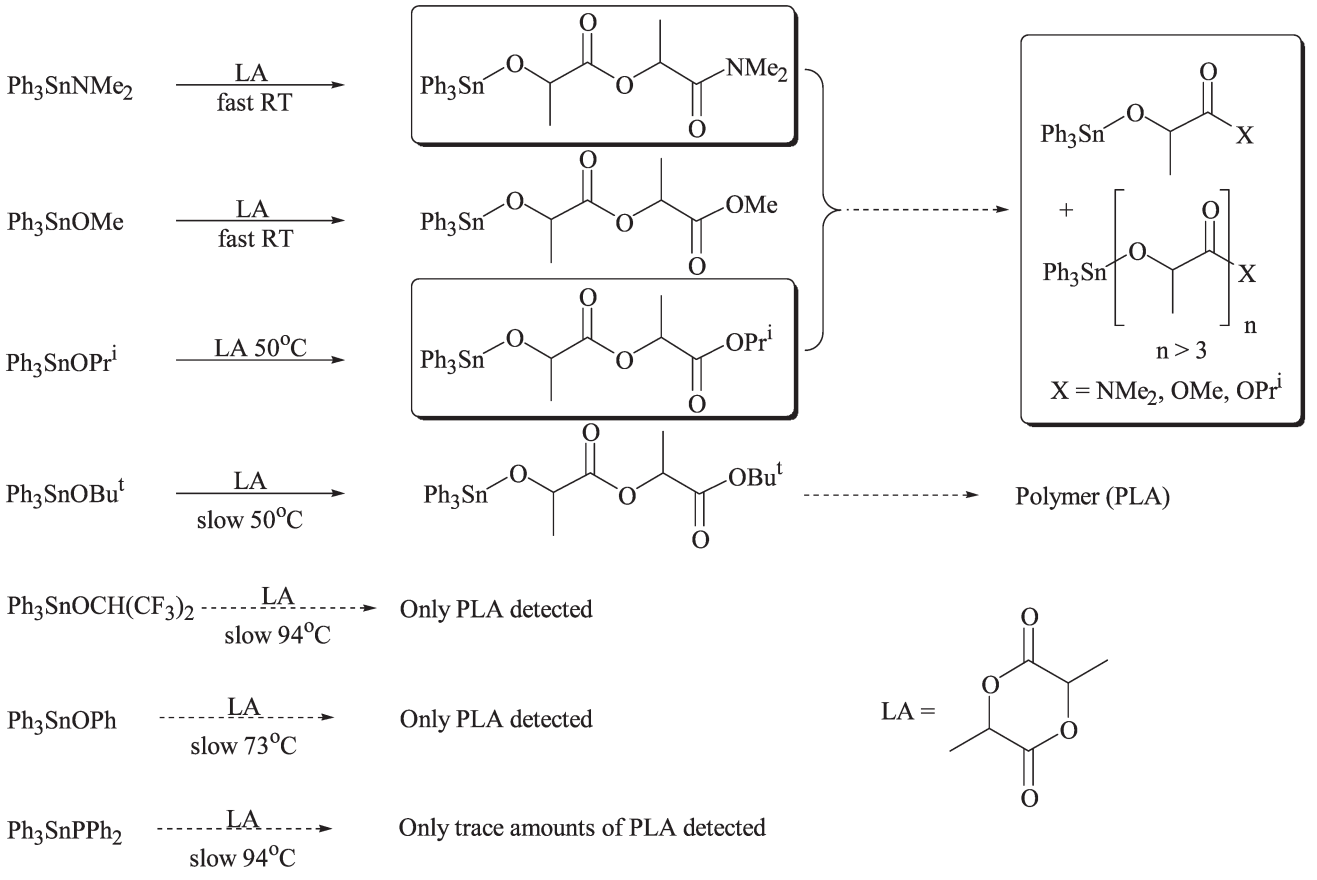
Characterization data for all compounds reported here are given in the Electronic supplementary information (ESI). The Ar_3SnOR compounds (R = Bu^t and Pr^i) were stable at 100 °C in anhydrous toluene for several days as evidenced by ^1H and ^{119}Sn NMR spectroscopy.

Discrete ring-opened lactide and related cyclic ester derivatives of Sn(IV)

These new compounds, described below, have been characterized by NMR [^1H, $^{13}C\{^1H\}$, ^{119}Sn] and IR spectroscopy, mass spectrometry and, in many cases, by elemental analyses. Data are reported in the Experimental in addition to our previous preliminary report on this chemistry.[10]

(a) Ring-opening of L-lactide by Ph_3SnX where X = NMe_2, OMe, OPr^i, $OCH(CF_3)_3$, OBu^t, OPh and PPh_2. In order to investigate the effect of the initiating group on the ring-opening of L-lactide a variety of Ph_3SnX compounds [X = NMe_2, OMe, OPr^i, $OCH(CF_3)_2$, OBu^t, OPh and PPh_2] were synthesized and treated with equiv. of L-lactide (Scheme 2). It is apparent from Scheme 2 that electronic and steric properties of the initiating group influence not only the ring-opening of L-lactide but also the stability of the ring-opened product. Scheme 2 reveals that Ph_3SnNMe_2 and Ph_3SnOMe rapidly ring-open L-lactide at room temperature in benzene to form the discrete and isolable products $Ph_3Sn[OCHMeC(O)OCHMeC(O)X]$ where X = NMe_2 or OMe. The ^1H NMR spectrum of $Ph_3Sn[OCHMeC(O)OCHMeC(O)NMe_2)$ is shown in Fig. 2, along with an assignment of the ligand resonances. The latter is possible from a COSY spectrum.

$Ph_3Sn[OCHMeC(O)OCHMeC(O)OMe]$ is less stable than the analogous NMe_2 compound and is more susceptible to intermolecular transesterification leading to $Ph_3Sn[OCHMeC(O)OMe]$ and $Ph_3Sn[OCHMeC(O)]_nOMe$, where $n > 3$ (see below for a discussion of stabilities and side reactions of these complexes).



Scheme 2 Reactions between Ph_3SnX compounds and L-lactide indicating the effect of initiating group. Compounds in boxes are isolable species.

The steric effect of X on ring-opening of L-lactide is best illustrated in the comparison between Ph_3SnOMe, Ph_3SnOPr^i and Ph_3SnOBu^t, where the order of reactivity decreases with increasing steric bulk of X. This is the inverse of the basicity of the alkoxide anions: $Bu^tO > Pr^iO > MeO$. Unlike Ph_3SnOMe, both Ph_3SnOPr^i and Ph_3SnOBu^t require heating in benzene (45–50 °C) to accomplish appreciable ring-opening. This decrease in reactivity for the more bulky X groups may reflect the increased steric crowding about the tin(IV) center, thereby suppressing the ability of L-lactide to coordinate to the tin(IV) metal center prior to ring-opening (Scheme 1). In addition, the X group may be too bulky to attack the ester carbonyl carbon atom. Furthermore, it appears that Ph_3Sn[OCHMeC(O)OCHMeC(O)X] with $X = OPr^i$ is more stable (Fig. 3) (forming a stable, isolable product) than for $X = OBu^t$, which probably is a result of two effects: (1) the relative rates of ring-opening, k_{ro}, and propagation or ROP,[11] k_{prop}, are such that $k_{ro} > k_{prop}$ for $X = OPr^i$ but $k_{prop} > k_{ro}$ for $X = OBu^t$, and (2) the poorer ability of the $-C(O)OBu^t$ group to chelate either inter- or intramolecularly to the tin(IV) center (see below for a discussion of the stability of these compounds).

A more pronounced effect of $k_{prop} > k_{ro}$ was seen in the reactions involving Ph_3SnX and L-lactide (1:1 equiv.) where $X = OCH(CF_3)_2$, OPh and PPh_2. Here heating in benzene-d_6 was required (73 and 94 °C, Scheme 2) before any reaction was observed and then only a small amount of Ph_3SnX was consumed and no discrete compounds of formula Ph_3Sn[OCHMeC(O)OCHMeC(O)X)] were detected by ^1H NMR spectroscopy. We can conclude that the observed rate order for the initial rate of ring-opening of L-lactide, which is $X = NMe_2 \sim OMe > OPr^i > OBu^t > OPh > OCH(CF_3)_2 > PPh_2$,

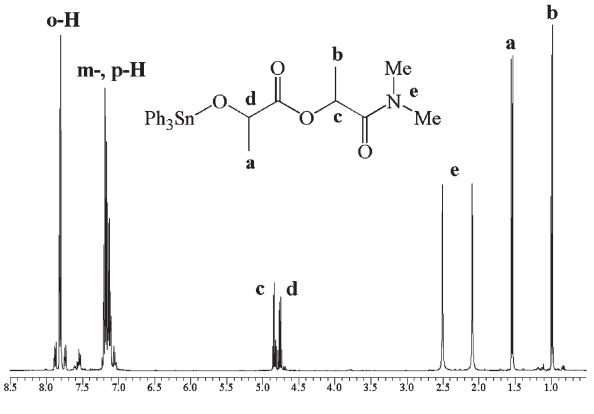


Fig. 2 ^1H NMR spectrum in benzene-d_6 of Ph_3Sn[OCHMeC(O)OCHMeC(O)ONMe$_2$]. Notice the inequivalent NMe_2 methyl signals.

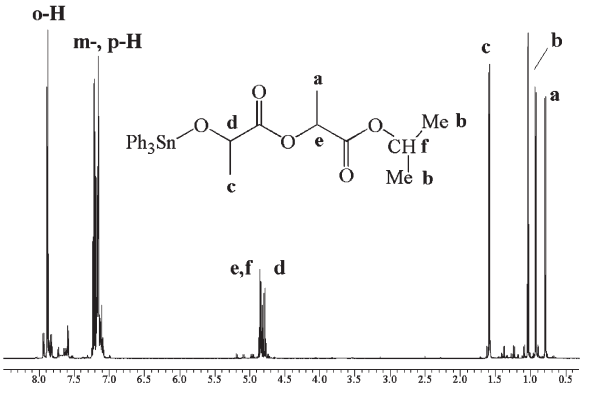


Fig. 3 ^1H NMR spectrum in benzene-d_6 of Ph_3Sn[OCHMeC(O)OCHMeC(O)OPr^i]. Notice the inequivalent OPr^i methyl signals.

represents a combination of electronic and steric factors. The rate is enhanced by the nucleophilicity/basicity of the anion X^- and is suppressed by steric factors. For $X = NMe_2$, OMe and OPr^i, $k_{ro} > k_{prop}$ but for $X = OCH(CF_3)_2$, OPh and PPh_2, $k_{prop} > k_{ro}$. The influence of steric factors is further underscored by the observation that $(o\text{-}MeC_6H_4)_3SnNMe_2$ and L-lactide do not react!.

(b) Kinetics of the ring-opening event. A reaction scheme for the initial ring-opening event can be represented by eqn. (1),

$$\text{(a)}\quad A + B \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} C \quad K_{eq}$$
$$\text{(b)}\quad C \xrightarrow{k_2} D \qquad (1)$$

where A represents the Ph_3SnX compound, B the L-lactide, C a kinetically labile adduct or reactive intermediate and D, the product of the ring-opening event. In the reaction scheme the rate of formation of the ring-opened product, $d[D]/dt$, is given by eqn. (2), according to the steady-state approximation.

$$\frac{d[D]}{dt} = \frac{k_2.k_1[A][B]}{k_{-1} + k_2} \qquad (2)$$

There are two limiting situations: (i) for $k_{-1} \gg k_2$, $k_{obs} = k_2{\cdot}k_1/k_{-1} \sim k_2{\cdot}K_{eq}$ and (ii) for $k_2 \gg k_{-1}$ when $k_{obs} = k_1$. In other cases the reaction scheme does not simplify and $k_{obs} = k_2{\cdot}k_1/(k_{-1} + k_2)$.

If the ring-opened product D closely resembles A then further reaction with substrate B can be expected and we will arrive at a kinetic situation where $k_{prop} \sim k_{ro}$. However, in order to study the initial ring-opening event and have this make a meaningful or at least a chemically interesting comparison with the ring-opening polymerization (propagation), k_{ro} must be greater but not very much greater than k_{prop}. In this study this situation is obtained for Ph_3SnOPr^i and we have examined the kinetics of the ring-opening event as a function of temperature (29 to 81 °C) in benzene-d_6. The reactions were followed by ^1H NMR spectroscopy by simultaneously following the decrease in L-lactide, the loss of $SnOPr^i$ signals and the growth of the product $Ph_3Sn[OCHMeC(O)OCHMeC(O)OPr^i]$ (see Experimental). The reaction proceeded as expected based on the reaction scheme shown in eqn. (1). Most significantly there was no evidence by NMR spectroscopy for the formation of a 1:1 adduct, supporting the notion that C is a reactive intermediate, with K_{eq} being small, not detected by NMR spectroscopy. This is further corroborated by the fact that ^{119}Sn NMR spectra of Ph_3SnOPr^i in toluene-d_8 at low temperatures are insensitive to the presence of excess lactide. Kinetic data are summarized in Table 1.

From a plot of $\ln(k/T)$ *vs.* $1/T$ (Fig. 4) we can obtain an estimate of the activation parameters: $\Delta H^{\neq} = 13(1)$ kcal mol^{-1} and $\Delta S^{\neq} = -37(3)$ eu. These are entirely reasonable values for the metal-mediated anionic ring-opening reaction proposed in Scheme 1. The enthalpy of activation is quite modest as expected for attack on a carbonyl group coordinated to the metal by an adjacent nucleophilic alkoxide ligand. The negative and modest magnitude of the entropy of activation is typical of many bimolecular processes and does not imply a uniquely high order in the transition state.

Table 1 Kinetics data for the 1:1 reaction between Ph_3SnOPr^i and L-lactide leading to formation of $Ph_3Sn[OCHMeC(O)OCHMeC(O)OPr^i]$ at various temperatures and in the presence of donors

Entry	k_{obs}/mol^{-1} dm^3 s^{-1})	T/°C
1	$2.0(2) \times 10^{-5}$	29
2	$4.1(2) \times 10^{-5}$	49
3	$1.3(2) \times 10^{-4}$	61
4	$6.1(2) \times 10^{-4}$	81
5[a]	$1.6(2) \times 10^{-5}$	29
6[b]	$3.0(2) \times 10^{-5}$	29

[a] With 5 equiv. of propylene carbonate. [b] With 5 equiv. of pyridine.

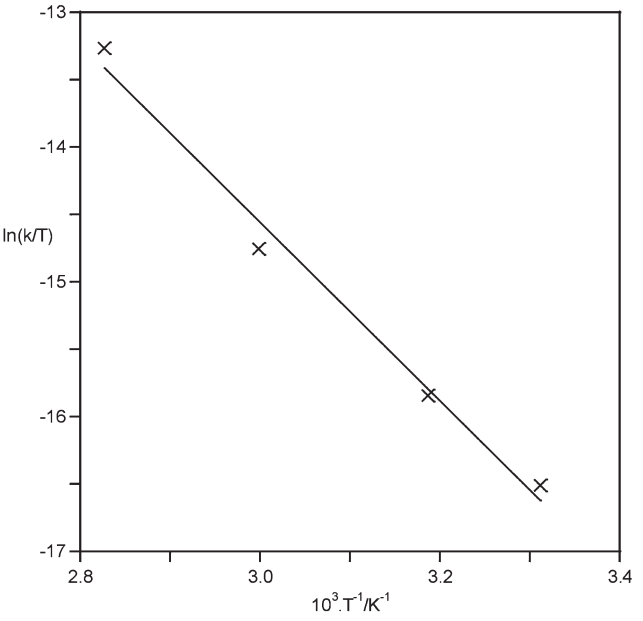


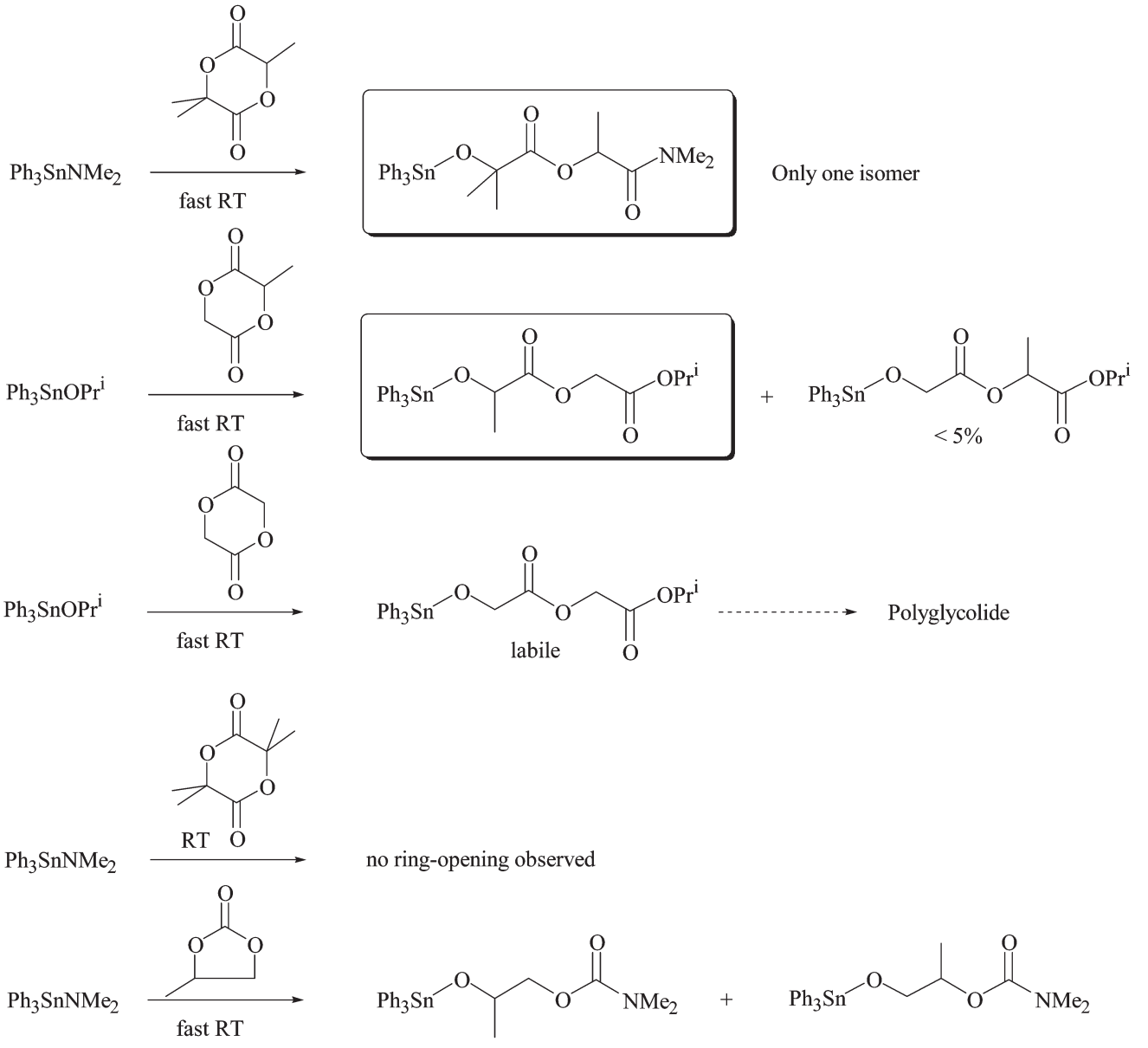
Fig. 4 Plot of $\ln(k_{obs}/T)$ *vs.* $1/T$ for the reaction between Ph_3SnOPr^i and L-lactide (1:1).

Since 4-coordinate tin(IV) compounds are well known to be able to increase their coordination numbers in associative reactions we examined the kinetics of the ring-opening of L-lactide by Ph_3SnOPr^i in the presence of added donors, specifically propylene carbonate (PC) and pyridine (py) (Table 1). Given that neither is susceptible to ring-opening but that both molecules could compete in a reversible association to tin(IV) with L-lactide, according to the scheme outlined in eqn. (1), the rate of ring-opening, k_{ro}, could be supressed. The added ligand, py or PC, was in five-fold excess of the lactide concentration. At 29 °C we observed no supression in the rate constant, k_{obs}, and for py a slight increase in k_{obs} was observed, which may be due to subtle changes in solvent polarity that, in turn, enhance the rate of ring-opening (Table 1).

(c) Ring-opening of related cyclic esters by Ph_3SnX where $X = NMe_2$ and OPr^i. It has been shown that the nature of the initiating group X and the ancillary ligands Ar can control the ring-opening event of L-lactide. However, it is not clear whether related cyclic esters have the same propensity to ring-open as L-lactide and, if so, whether there will be any regiospecificity in ring-opening of an unsymmetrical cyclic ester. To address these issues we have studied the reactions between Ph_3SnX compounds, where $X = NMe_2$ or OPr^i, and a variety of cyclic esters that are closely related to L-lactide (Scheme 3).

Ph_3SnNMe_2 was shown to react regioselectively with the asymmetrically substituted cyclic ester 3,3,6-trimethyl-1,4-dioxane-2,5-dione to give $Ph_3Sn[OCMe_2C(O)OCHMeC(O)NMe_2]$ whilst Ph_3SnOPr^i reacts with 3-methyl-1,4-dioxane-2,5-dione (methylglycolide) to give $Ph_3Sn[OCHMeC(O)OCH_2C(O)OPr^i]$ (95%). In both cases nucleophilic attack occurs at the less-hindered (and more electrophilic) carbonyl moiety (Scheme 3). The ^1H NMR spectrum of the compound $Ph_3Sn[OCMe_2C(O)OCHMeC(O)NMe_2]$ can be found in the ESI.

As is apparent, there is only one regioisomer for $Ph_3Sn[OCMe_2C(O)OCHMeC(O)NMe_2]$ and the specific isomer is established with confidence based on the presence or absence of coupling to $^{119}Sn/^{117}Sn$ in the ^1H and



Scheme 3 Reactions between Ph_3SnX ($X = NMe_2$, OPr^i) and methyl substituted lactide derivatives.

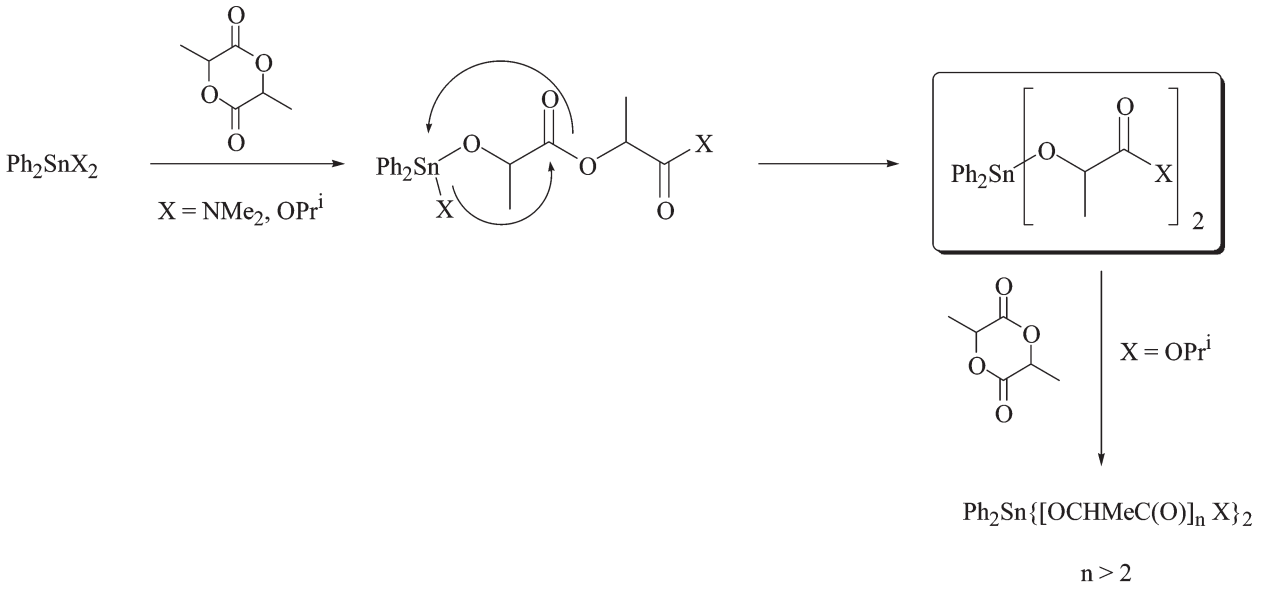
$^{13}C\{^1H\}$ spectra. This compound is notably less kinetically labile than its L-lactide counterpart and does not participate in self transesterification as observed for $Ph_3Sn[OCHMeC(O)OCHMeC(O)NMe_2]$. (See below for a discussion of the stabilities of these compounds.)

Treatment of Ph_3SnOPr^i with 1,4-dioxane-2,5-dione (glycolide) (1:1) does not lead to the isolable compound $Ph_3Sn[OCH_2C(O)OCH_2C(O)OPr^i]$ but rather to polyglycolide (Scheme 3), uggesting that the ratesof ring-opening and chain propagation are similar such that subsequent glycolide molecules are able to insert readily into the already formed ring-opened product. The relative stability of the $Ph_3Sn[CMe_2C(O)OCHMeC(O)NMe_2]$ and $Ph_3Sn[CHMeC(O)OCHMeC(O)X]$ ($X = NMe_2$, OPr^i) complexes (see above) is presumably related to the poorer substrate activation of the cyclic ester monomers by the ring-opened product relative to initial activation by Ph_3SnOPr^i or Ph_3SnNMe_2. This leads to the initial rate of ring-opening being greater than the subsequent rate of ROP ($k_{ro} > k_{prop}$). In contrast, the less hindered glycolide (and to a lesser extent methylglycolide) molecules can more readily coordinate to the tin center than L-lactide or 3,3,6-trimethyl-1,4-dioxane-2,5-dione, resulting in $k_{prop} \geq k_{ro}$.[12]

Ring-opening is not observed when Ph_3SnNMe_2 is treated with the tetramethylated cyclic ester derivative, 3,3,6,6-tetramethyl-1,4-dioxane-2,5-dione. This result complements the regiospecific ring-opening observed for the 3,3,6-trimethyl-1,4-dioxane-2,5-dione cyclic ester by Ph_3SnNMe_2, for which no activation was observed for the more hindered carbonyl ester.

Hence the degree of methyl substitution on the cyclic ester has a considerable effect on the relative rates and regiospecificity of ring-opening: the less hindered cyclic esters more rapidly ring-open in a less regiospecific fashion. In addition, the reactivity of the 1:1 ring-opened products is also related to the degree of methyl substitution in that the most kinetically persistent compounds are those with a high degree of methyl substitution of the cyclic ester. This "stability" may arise from the higher degree of steric crowding about the tin(IV) metal center in the more heavily substituted ring-opened systems, which supresses further bimolecular reactions.

Ph_3SnNMe_2 has also been shown to ring-open the cyclic carbonate, propylene carbonate, to give a mixture of the two regioisomers $Ph_3Sn[OCH_2CHMeOC(O)NMe_2]$ and $Ph_3Sn[OCHMeCH_2OC(O)NMe_2]$. The relative ratio of these regioisomers was little changed in reactions carried out at −78 °C.



Scheme 4 Reaction between Ph_2SnX_2 compounds (X = NMe_2, OPr^i) and L-lactide, indicating rapid intramolecular inter-chain esterification/amidation.

(d) Reaction between Ph_2SnX_2 and L-lactide where X = NMe_2 or OPr^i. $Ph_2Sn(NMe_2)_2$ and L-lactide (1:1) react in benzene to give $Ph_2Sn[OCHMeC(O)NMe_2]_2$ by an initial ring-opening event, following by a rapid intramolecular amidation (Scheme 4). This reaction is conceptually similar to that seen between Ph_3SnNMe_2 (2 equiv.) and L-lactide (1 equiv.), where the initially formed $Ph_3Sn[OCHMeC(O)OCHMeC(O)NMe_2]$ compound is also seen to react quickly with Ph_3SnNMe_2 to give $Ph_3Sn[OCHMeC(O)NMe_2]$ by an intermolecular amidation (see below).

The compound $Ph_2Sn[OCHMeC(O)NMe_2]_2$ has two IR bands, at 1596 and 1609 cm^{-1}, assignable to the organic amide moiety. These values are considerably lower than those found for $Ph_3Sn[OCRMeC(O)OCHMeC(O)NMe_2]$ (R = H or Me) compounds whose infrared spectra of the $C(O)NMe_2$ moieties show characteristic bands at *ca.* 1600–1650 cm^{-1}, notably lower than the ester carbonyl groups, which are at *ca.* 1700–1750 cm^{-1}. Furthermore, the ^{119}Sn NMR spectrum of $Ph_2Sn[OCHMeC(O)NMe_2]_2$ is also significantly different from that of the other compounds and shows complex variable temperature behavior similar to that recently observed for the analogous $Me_2Sn(OAr)_2$ compound.[13] It is believed that this, together with the lower values of ν(CO), is evidence for intra- or intermolecular amide group coordination to Sn (see below). Regrettably, crystals suitable for a single crystal X-ray determination were not obtained.

In an analogous fashion $Ph_2Sn(OPr^i)_2$ reacts with L-lactide (1:1) to form $Ph_2Sn[OCHMeC(O)OPr^i]_2$ (Scheme 4). This compound is much more susceptible to further L-lactide ring-opening than $Ph_2Sn[OCHMeC(O)NMe_2]_2$, making it impossible to isolate the OPr^i containing compound in its pure form. Presumably the $OCHMeC(O)NMe_2$ moiety forms a stronger, more stable chelate to Sn than does the $OCHMeC(O)OPr^i$ moiety. (See below for a discussion of stability and NOE data.)

The relative stability of these two compounds manifests itself in the polymerization studies where, depending upon which initiating group is used, NMe_2 *vs.* OPr^i, striking differences are observed in the molecular weight distribution and polymer type (chains or cycles).[11]

(e) Stability and reactivity of the ring-opened products, Ph_3Sn–(cyclic ester)–X and Ph_2Sn–[(cyclic ester)–X]$_2$. 1:1 reactions between Ph_3SnX or Ph_2SnX_2 and cyclic esters have lead to the formation of, in some cases, discrete compounds that have sufficient stability for isolation and characterization. None of these compounds are, however, indefinitely persistent in solution or at elevated temperatures {with the exception of $Ph_2Sn[OCHMeC(O)NMe_2]_2$}. It is clear from the above discussions that some of these compounds exhibit greater stability than others. It is believed that this stability arises from the formation of chelating C(O)X end groups to tin(IV) (Fig. 5).

NOE difference spectra were obtained for $Ph_3Sn[OCHMeC(O)OCHMeC(O)NMe_2]$, $Ph_3Sn[OCMe_2C(O)OCHMeC(O)NMe_2]$ and $Ph_2Sn[OCHMeC(O)NMe_2]_2$ compounds (see ESI). These indicate a significant $^1H\cdots{}^1H$ interaction involving the *ortho*-phenyl protons and the methine protons of the ligand. We propose that this arises from reversible chelation of the ligand through 5- and 8-membered rings of the type shown in **C**, **D** and **E** (Fig. 5). Although 5-membered rings are preferred over 8-membered rings, the latter may be favored by the terminal amide groups in the $Sn[OCHMeC(O)NMe_2]_2$ moiety.

The compounds $Ph_3Sn[OCHMeC(O)OCHMeC(O)X]$ (where X = NMe_2, OPr^i, OMe) display kinetic lability toward a ligand redistribution reaction that arises from intermolecular transesterification (Scheme 5, reaction i). This reaction proceeds over several hours at room temperature and is accelerated by heat in benzene-d_6 or toluene-d_8 solution and can readily be followed by ^1H NMR spectroscopy (see ESI for X = NMe_2). From these studies the stability of

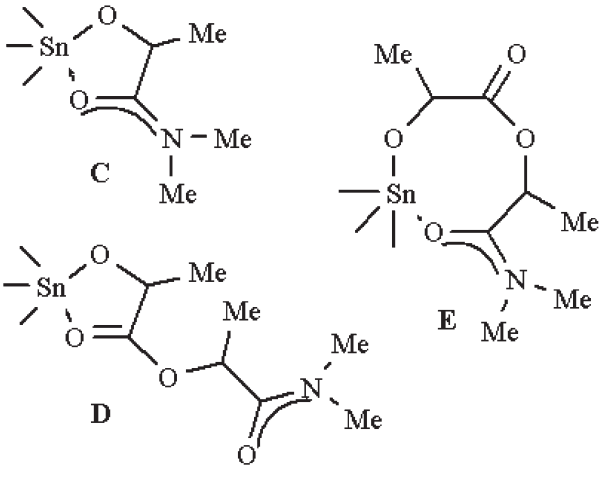
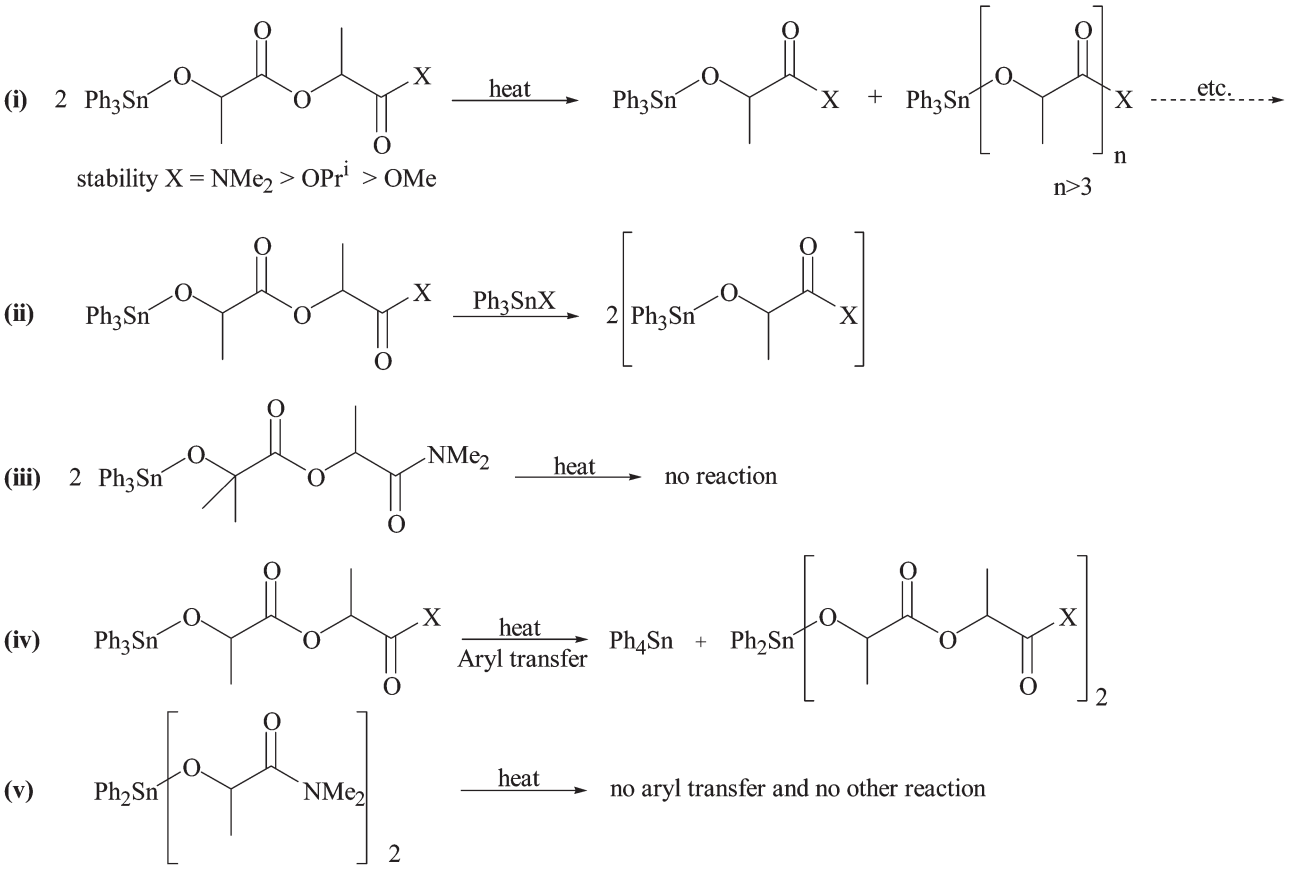


Fig. 5 Possible 5- and 8-membered rings of Ar_3SnOP compounds.



Scheme 5 Reactivity of Ph_3Sn–(cyclic ester)–X and Ph_2Sn–[(cyclic ester)–X]$_2$ compounds towards transesterification and chain transfer reactions.

Ph_3Sn[OCHMeC(O)OCHMeC(O)X] compounds follows the order X = NMe_2 > OPr^i > OMe, where the OMe compound is impossible to isolate free from any transesterification reactions. This observed order of stability probably reflects both the superior chelating ability of the –C(O)NMe_2 moiety (if an 8-membered chelate forms) and steric factors where the –C(O)OMe group provides less steric protection through chelation to tin(IV) *versus* the corresponding –C(O)OPr^i moiety. If chelation to the metal center is strong then Sn–OR migration (which is necessary for transesterification) will be less facile.

The transesterification products, Ph_3Sn[OCHMeC(O)X] (where X = NMe_2, OMe) can be independently prepared from the direct reaction between Ph_3SnX (2 equiv.) and L-lactide (1 equiv.) (Scheme 5, reaction ii). This reaction is similar to that seen between $Ph_2Sn(NMe_2)_2$ and L-lactide (1:1 ratio), where the initially formed Ph_2Sn[OCHMeC(O)OCHMeC(O)NMe_2](NMe_2) rapidly undergoes an intramolecular transamidation reaction to give Ph_2Sn[OCHMeC(O)NMe_2]$_2$ (see above).

Remarkable stability is seen for the Ph_3Sn[$OCMe_2$-C(O)OCHMeC(O)NMe_2] compound where no transesterification is seen, even upon heating (Scheme 5, reaction iii). This increased stability must arise from the presence of the tin(IV) tertiary alkoxide, $SnOCMe_2R$, and the increased shielding of the ketonic C=O group. Both factors suppress intermolecular reactions.

The lability of ligand exchange in these reactions is also manifest by the fact that some Ph_4Sn and Ph_2Sn[OCHMeC(O)NMe_2]$_2$ are also formed (as identified by mass spectrometry and ^1H, ^{13}C and ^{119}Sn NMR spectroscopy) in the decomposition of Ph_3Sn[OCHMeC(O)OCHMeC(O)NMe_2] (Scheme 5, reaction iv). These side-reactions become more prevalent upon heating to 60–80 °C.

A very important observation was the stability of Ph_2Sn[OCHMeC(O)NMe_2]$_2$, which does not experience aryl group migration whilst all Ph_3Sn[OCHMeC(O)OCHMeC(O)X] compounds do (Scheme 5, reactions iv and v). This has significant ramifications in ROP studies since the kinetic analysis is not complicated by the formation of kinetically inactive species such as Ph_4Sn.

Concluding remarks

The reactions between Ph_3SnX and Ph_2SnX_2, where X = NMe_2 or an alkoxide, and L-lactide have allowed us to examine the influence of the initiator group on the rate of ring-opening. The order of reactivity X = NMe_2 ~ OMe > OPr^i > OBu^t > OPh > $OCH(CF_3)_2$ > PPh_2 clearly implicates the combined influence of electronic and steric factors. The importance of steric factors is also seen in the complete lack of reactivity between (o-$MeC_6H_4)_3SnNMe_2$ and L-lactide and between Ph_3SnNMe_2 and the tetramethylated cyclic ester, 3,3,6,6-tetramethyl-1,4-dioxane-2,5-dione. The ring-opened products Ph_3Sn[OCHMeC(O)OCHMeC(O)X] were shown to be kinetically labile to an intermolecular transesterification reaction and the stability of the –OCHMeC(O)NMe_2 ligand can be understood in terms of chelation *via* the nucleophilic carbonyl group, which is stabilized by the NMe_2 group to form a 5-membered ring involving Sn. From the studies of the kinetics of the ring-opening event in the 1:1 reaction between Ph_3SnOPr^i and L-lactide the activation parameters $\Delta H^{\neq}$ = 13(1) kcal mol^{-1} and $\Delta S^{\neq}$ = −37(3) eu have been determined. These are entirely consistent with a bimolecular reaction wherein the tin-alkoxide moiety adds across the ketonic C–O bond of the lactide. The metal center serves to assist in the activation of the C=O moiety by acting as a weak electrophile while the neighboring alkoxide ligand participates in the nucleophilic attack on the carbon of the coordinated carbonyl moiety. It is reasonable to suppose that this is slow for Sn(IV)

relative to say Sn(II), Zn(II) and Mg(II) because the Sn–OR bond is notably less polar.

Experimental

General considerations

Caution: organotin(IV) compounds are highly toxic and require appropriate handling!

The manipulation of air-sensitive compounds involved standard Schlenk line and dry box techniques. All solvents were distilled under nitrogen from alkali metals (sodium or sodium/potassium alloy) and stored over 4 Å molecular sieves. L-Lactide was purchased from Aldrich and sublimed prior to use. Propylene carbonate was purchased from Aldrich and was degassed and stored over activated sieves. *o*-Bromotoluene, chlorotriphenyltin(IV), tetrachlorotin(IV), magnesium turnings, benzene-d_6, toluene-d_8, anhydrous *tert*-butanol and *iso*-propanol were purchased from Acros Scientific whilst diphenyltin(IV) dichloride was purchased from Alfa Aesar. Benzene-d_6 and toluene-d_8 were dried over sodium and vacuum transferred to a Schlenk flask containing activated molecular sieves. All aryl bromides were stored over calcium hydride and tetrachlorotin(IV) was stored over phosphorus pentoxide whilst all other reagents were used as received. The $(o\text{-}MeC_6H_4)_3SnCl$ complex was synthesized by literature procedures[14] where the Grignard reagent was generated in either THF or diethyl ether from magnesium and the appropriate arylbromide. This Grignard reagent was then treated *in situ* with tetrachlorotin(IV) (4:1), dissolved in either benzene or hexanes, to afford Ar_4Sn. The Ar_3SnCl complex is formed from reaction between Ar_4Sn and tetrachlorotin(IV) (3:1) *via* the Kocheshkov redistribution reaction.[15] Lithium dimethylamide was synthesized by treating *n*-butyllithium in hexanes with excess dimethylamine at −78 °C. After allowing the reaction mixture to warm to room temperature, the solvent and excess amine were removed to quantitatively yield white lithium dimethylamide. Synthesis of lactide-like compounds such as 3-methyl-1,4-dioxane-2,5-dione (methylglycolide) and 3,3,6-trimethyl-1,4-dioxane-2,5-dione were based on reported methods.[16]

The synthesis of Ar_3SnNMe_2 (Ar = Ph, $o\text{-}MeC_6H_4$,) and $Ph_2Sn(NMe_2)_2$ complexes was based on the reported synthesis[17] of Ph_3SnNMe_2 and $Ph_2Sn(NMe_2)_2$ where Ar_3SnCl or Ph_2SnCl_2 was treated with 1 or 2 equiv. of $LiNMe_2$, respectively. The major difference in the synthesis was that $LiNMe_2$ was not generated *in situ*. The full preparation and characterization of Ph_3SnX and $Ph_2Sn(NMe_2)_2$ compounds where X = NMe_2, OMe, OPr^i, OPh, OBu^t, $OCH(CF_3)_2$, PPh_2 is given in the ESI.

Measurements and analyses

^1H, $^{13}C\{^1H\}$ and ^{119}Sn spectra were obtained from either Bruker DPX-400 or DRX-500 NMR spectrometers using either benzene-d_6 or toluene-d_8 solvents. Spectra were referenced internally to the residual protio impurities for ^1H and ^{13}C (C_6D_6 δ 7.15 ^1H, 128.0 ^{13}C; $C_6D_5CD_3$ δ 2.09) or externally to Me_4Sn ($\delta = 0$) for ^{119}Sn. Infrared data were obtained from a Perkin Elmer Spectrum GX spectrophotometer with samples sandwiched between potassium bromide or sodium chloride plates as Nujol® mulls (solids) or as neat liquids/semi-solids. Mass spectra were obtained with a Mircomass QTOF. Elemental analyses were performed by Atlantic Microlab, Inc., with samples sealed under nitrogen in glass ampoules.

Syntheses

$Ph_3Sn[OCHMeC(O)OCHMeC(O)NMe_2]$. To a cooled toluene solution (0 °C 10 mL) of dimethylamidotriphenyltin(IV) (0.39 g, 1.00 mmol), a toluene (10 mL) solution of L-lactide (0.14 g, 1.00 mmol) was slowly added. The colorless reaction solution was stirred for 30 min after which time the toluene was removed under vacuum to give an opaque semi-solid (yield 0.42 g, 78%). Anal. calcd for $C_{26}H_{29}NO_4Sn$: C, 58.02; H, 5.43; N, 2.60; found: C, 58.08; H, 5.88; N, 2.85. IR (liquid)/cm^{-1}: 3081 w, 2987 w, 2934 w, 1755 m, 1713 m, 1667 s, 1617 m, 1480 m, 1429 s, 1403 w, 1376 w, 1331 w, 1303 w, 1259 m, 1235 m, 1192 m, 1148 s, 1075 s, 1024 m, 997 m, 938 w, 870 w, 812 w, 730 vs, 699 vs, 501 m, 450 m. ^1H NMR (400 MHz, benzene-d_6): δ 0.99 [d, CH*Me*-C(O)NMe_2, 3H], 1.53 (d, SnOCH*Me*, 3H), 2.11 (s, NMe_2, 3H), 2.47 (s, NMe_2, 3H), 4.75 (q, SnOC*H*Me, 1H), 4.83 [q, C*H*MeC(O)NMe_2, 1H], 7.16 (m, *m*-H and *p*-H, 9H), 7.80 (dd, *o*-H, 6H, J_{HH} 7.9 and 1.5 Hz, $^{119/117}Sn$ satellites J_{SnH} ^{117}Sn 64, ^{119}Sn 49 Hz). $^{13}C\{^1H\}$ NMR (126 MHz, benzene-d_6): δ 16.30 [s, CH*Me*C(O)NMe_2], 23.25 (s, SnOCH*Me*), 35.31 (s, NMe_2), 35.74 (s, NMe_2), 68.55 [s, *C*HMeC(O)NMe_2], 69.24 (s, SnO*C*HMe, $^{119/117}Sn$ satellites J_{SnC} ^{117}Sn 46, ^{119}Sn 44 Hz), 128.83 (s, *m*-C), 129.45 (s, *p*-C), 137.27 (s, *o*-C, $^{119/117}Sn$ satellites J_{SnC} 47 Hz), 142.21 (s, *ipso*-C), 168.74 [s, CHMe-*C*(O)NMe_2], 180.74 [s, SnOCHMe*C*(O)O]. ^{119}Sn NMR (149 MHz, benzene-d_6): δ −124 (s). ESI-HRMS (m/z) calcd for $C_{26}H_{29}NO_4Sn$ [MNa^+]: 562.1016; found: 562.1056 (7.1 ppm).

$Ph_2Sn[OCHMeC(O)NMe_2]_2$. To a cooled toluene solution (0 °C 10 mL) of bis(dimethylamido)diphenyltin(IV) (72 mg, 0.20 mmol), a toluene (15 mL) solution of L-lactide (29 mg, 0.20 mmol) was slowly added. The colorless reaction solution was stirred for 30 min after which time a white precipitate formed, which was filtered off to give the title complex (yield 78 mg, 77%). Anal. calcd for $C_{22}H_{30}N_2O_4Sn$: C, 52.31; H, 5.99; found: C, 51.54; H, 5.92. IR (Nujol)/cm^{-1}: 1609 vs, 1596 vs, 1404 w, 1330 w, 1256 w, 1180 w, 1129 s, 1074 m, 1047 w, 906 w, 781 w, 730 m, 704 m, 656 w, 637 w, 551 w, 456 m, 443 m.^1H NMR (400 MHz, benzene-d_6): δ 1.43 (d, SnOCH*Me*, 6H), 1.87 (s, NMe_2, 6H), 2.26 (s, NMe_2, 6H), 4.87 (q, SnOC*H*Me, 2H), 7.21 (t, *p*-H, 2H), 7.35 (t, *m*-H, 4H), 8.37 (dd, *o*-H, 4H, J_{HH} 7.6 and 1.2 Hz, $^{119/117}Sn$ satellites: J_{SnH} ^{117}Sn 75, ^{119}Sn 59 Hz). $^{13}C\{^1H\}$ NMR (126 MHz, benzene-d_6): δ 22.85 (s, SnOCH*Me*), 35.42 (s, NMe_2), 35.93 (s, NMe_2), 66.13 [s, SnO*C*HMeC(O)NMe_2, $^{119/117}Sn$ satellites: J_{SnC} 36 Hz], 127.83 (s, *m*-C), 128.36 (s, *p*-C), 136.88 (s, *o*-C, $^{119/117}Sn$ satellites: J_{SnC} 47 Hz), 152.83 (s, *ipso*-C), 181.39 (s, CO). ^{119}Sn NMR (149 MHz, benzene-d_6, 300 K): δ −346 (br s). ^{119}Sn NMR (187 MHz, THF-d_8, 300 K): δ −350 (br s); (233 K): δ −360 (s), −362 (br); (213 K): δ −360 (s, 3Sn), −362 (s, 1Sn). ESI-HRMS (m/z) calcd for $C_{22}H_{30}N_2O_4Sn$ [MNa^+]: 529.1125; found: 529.1130 (0.9 ppm).

$Ph_3Sn[OCMe_2C(O)OCHMeC(O)NMe_2]$. To a cooled toluene solution (0 °C 10 mL) of dimethylamidotriphenyltin(IV) (0.39 g, 1.00 mmol), a toluene (10 mL) solution of 3,3,6-trimethyl-1,4-dioxane-2,5-dione (0.13 g, 1.00 mmol) was added slowly. The colorless solution was stirred for 30 min after which time the toluene was reduced and hexanes were added to the reaction, which was then cooled to −20 °C for 12 h, causing precipitation of the complex. Subsequent filtration afforded the title complex (yield 0.39 g, 71%). Anal. calcd for $C_{27}H_{31}NO_4Sn$: C, 58.72; H, 5.63; N, 2.54; found: C, 58.40; H, 5.60; N, 2.42. IR (Nujol)/cm^{-1}: 3062 m, 3042 m, 1695 m, 1507 w, 1481 m, 1429 s, 1354 m, 1311 m, 1260 w, 1168 s, 1116 w, 1077 s, 1025 m, 1007 w, 997 w, 916 vw, 888 vw, 845 w, 789 w, 762 vw, 731 vs, 702 s, 661 m, 619 vw, 570 w, 531 w, 448 m. ^1H NMR (500 MHz, benzene-d_6): δ 1.06 (d, CH*Me*-CONMe_2, 3H), 1.56 (s, SnOC*Me*$_2$, 3H), 1.65 (s, SnOC*Me*$_2$, 3H), 2.12 (s, NMe_2, 3H), 2.47 (s, NMe_2, 3H), 4.87 [q, C*H*Me-C(O)NMe_2, 1H], 7.17 (m, *p*-H, 3H), 7.23 (m, *m*-H, 6H), 7.87 (dd, *o*-H, 6H, J_{HH} 8.2 and 1.3 Hz, $^{119/117}Sn$ satellites: J_{SnH} ^{117}Sn 64, ^{119}Sn 48 Hz). $^{13}C\{^1H\}$ NMR (125 MHz, benzene-d_6):

δ 16.38 [s, CH*Me*C(O)NMe$_2$], 29.50 (s, SnOC*Me*$_2$), 29.94 (s, SnOC*Me*$_2$), 35.38 (s, NMe$_2$), 36.77 (s, NMe$_2$), 67.02 [s, *C*HMeC(O)NMe$_2$], 73.31 (s, SnO*C*Me$_2$, $^{119/117}$Sn satellites: J_{SnC}29 Hz), 128.72 (s, *m*-C), 129.36 (s, *p*-C), 137.32 (s, *o*-C, $^{119/117}$Sn satellites: J_{SnC}44 Hz), 143.19 (s, *ipso*-C), 168.66 [s, CHMe*C*(O)NMe$_2$], 183.01 [s, SnOCMe$_2$*C*(O)]. ^{119}Sn NMR (187 MHz, benzene-d_6): δ −141 (s). ESI-LRMS (*m*/*z*): 554 [MH$^+$].

Ph$_3$Sn[OCHMeC(O)OCHMeC(O)OPr^i]. *iso*-Proproxytriphenyltin(IV) (0.13 g, 0.32 mmol) was added to L-lactide (45 mg, 0.31 mmol) in benzene. The colorless solution was stirred for 1 day at 60 °C after which time the benzene was removed to afford a white semi-solid compound (yield 0.10 g, 58%). Anal. calcd for $C_{27}H_{30}O_5Sn$: C, 58.62; H, 5.47; found: C, 57.90; H, 5.22. IR (Nujol)/cm^{-1}: 1740 vs, 1457 s, 1261 m, 1071 vs, 800 s, 730 s 698 s. ^{1}H NMR (500 MHz, benzene-d_6): δ 0.78 [d, CH*Me*C(O)OCHMe$_2$, 3H], 0.92 (d, OCH*Me*$_2$, 3H), 1.03 (d, OCH*Me*$_2$, 3H), 1.58 (d, SnOCH*Me*, 3H), 4.79 (q, SnOC*H*Me, 1H), 4.84 [overlapping signals: q, C*H*MeC(O)OCHMe$_2$; sept., OC*H*(CH$_3$)$_2$1H], 7.15 (m, *p*- and *m*-H, 6H), 7.87 (dd, *o*-H, 6H J_{HH} 8.4 and 1.4 Hz, $^{119/117}$Sn satellites: J_{SnH} ^{117}Sn 62, ^{119}Sn 46 Hz). ^{13}C{^{1}H} NMR (125 MHz, benzene-d_6): δ 16.47 [s, CH*Me*C(O)OCHMe$_2$], 21.32 (s, SnOCH*Me*$_2$), 21.43 (s, SnOCH*Me*$_2$), 28.11 (s, SnOCH*Me*), 68.94 [s, *C*HMeC(O)OCHMe$_2$)], 69.15 (s, SnO*C*HMe), 70.13 (s, SnOCH*Me*$_2$) 128.76 (s, *m*-C), 129.23 (s, *p*-C), 137.31 (s, *o*-C), 142.01 (s, *ipso*-C), 169.39 [s, CHMe*C*(O)OCHMe$_2$], 180.58 [s, SnOCHMe*C*(O)]. ^{119}Sn NMR (187 MHz, benzene-d_6): δ −123 (s).

Ph$_3$Sn[OCHMeC(O)OCHMeC(O)OMe]. Methoxyoxytriphenyltin(IV) (93 mg, 0.24 mmol) dissolved in benzene (40 mL) was slowly added to L-lactide (35 mg, 0.24 mmol) in benzene (40 mL). The colorless solution was stirred for <5 min at room temperature after which time the benzene was removed to afford a clear liquid, which was extracted with hexane to remove any unreacted L-lactide. Removal of the hexane gave 82 mg (64%) of the title compound. This compound readily undergoes self-transesterification, hence the product has only been characterized by NMR spectroscopy. ^{1}H NMR (400 MHz, benzene-d_6): δ 1.00 [d, CH*Me*C(O)OMe, 3H], 1.55 (d, OCH*Me*, 3H), 3.15 (s, O*Me*, 3H), 4.77 and 4.81 [overlapping q, SnOC*H*MeC(O)OC*H*MeC(O)OMe, 2H], 7.16 (m, *p*- and *m*-H, 6H), 7.85 (d, *o*-H, 6H, $^{119/117}$Sn satellites: J_{SnH} ^{117}Sn 63, ^{119}Sn 49 Hz). ^{13}C{^{1}H} NMR (100 MHz, benzene-d_6): δ 16.46 [s, CH*Me*C(O)OMe], 23.20 (s, SnOCH*Me*$_2$), 51.68 (s, O*Me*), 69.37 [s, *C*HMeC(O)OMe], 71.86 (s, SnO*C*HMe), 128.90 (s, *m*-C), 129.37 (s, *p*-C), 137.26 (s, *o*-C, $^{119/117}$Sn satellites: J_{SnH} $^{117/119}$Sn 45 Hz), 141.89 (s, *ipso*-C), 170.19 [s, CHMe*C*(O)OMe], 180.43 [s, SnOCHMe*C*(O)]. ^{119}Sn NMR (149 MHz, benzene-d_6): δ −121 (s).

Reaction between Ph$_3$SnNMe$_2$ and propylene carbonate. To a cooled toluene solution (0 °C, 10 mL) of dimethylamidotriphenyltin(IV) (0.39 g, 1.00 mmol) a toluene–hexane (50:10 mL) solution of propylene carbonate (0.10 g, 1.00 mmol) was added slowly. The colorless solution was stirred for 30 min at 0 °C after which time the toluene was removed. An opaque semi-solid, 0.23 g, of a mixture of Ph$_3$SnOCH$_2$CHMeOC(O)NMe$_2$ and Ph$_3$SnOCHMeCH$_2$OC(O)NMe$_2$ (40:60) was identified by ^{1}H NMR spectroscopy (see below). Modification of the reaction conditions (RT and −50 °C) did not cause a change in product ratio. IR (liquid)/cm^{-1}: 3066 m, 3049 m, 3019 w, 2966 m, 2931 m, 2870 m, 1810 br m, 1702 br vs, 1580 w, 1569 wv, 1495 m, 1482 m, 1455 m, 1430 s, 1397 s, 1375 m, 1304 w, 1275 m, 1262 m, 1193 vs, 1153 m, 1120 m, 1077 m, 1023 w, 997 m, 939 w, 860 w, 799 w, 770 m, 730 vs, 699 vs, 661 w, 618 w, 539 w, 451 s, 370 vw, 386 w, 374 s. ^{1}H NMR (500 MHz, benzene-d_6): δ 1.21 (d, SnOCH*Me*CH$_2$) and 1.28 (d, SnOCH$_2$CH*Me*), 2.37 and 2.56 [overlapping br s, OC(O)N*Me*$_2$), 4.05 (dd, overlapping H$_a$ and H$_b$, SnOC*H*$_2$-CHMe), 4.25 (dd, overlapping H$_a$ and H$_b$, SnOCHMeC*H*$_2$), 4.40 (sextet, SnOC*H*MeCH$_2$), 5.28 (sextet, SnOCH$_2$C*H*Me) 7.15 (m, *m*- and *p*-H), 7.67 (m, *o*-H).

Kinetics analysis

Standard solutions of Ph$_3$SnOPr^i and L-lactide were made in benzene-d_6 and stored in the dry box. Appropriate aliquots of both reagents were transferred to a J. Young® NMR tube. The total volume was made up to 800 μL with benzene-d_6 to ensure a constant initial L-lactide concentration (0.039 M). The reaction temperatures were regulated *via* a thermostatically controlled oil bath.

An overall second-order process, first-order in both Ph$_3$SnOPr^i [A] and L-lactide [B], was assumed. The rate of disappearance of both [A] and [B] {based on the formation of Ph$_3$SnOCHMeC(O)OCHMeC(O)OPr^i [C]} was determined by plotting ln([B]/[A]) *vs.* time (s). The rate constants for these reactions were determined from the gradient of the graph *via* $m = k([B_o] - [A_o])$.

Acknowledgements

The authors wish to acknowledge the financial support from the Department of Energy, Office of Basic Sciences, Chemistry Division, and the reviewers for their careful reading of the manuscript and their helpful comments.

References

1 Ecochem is a polylactide based packaging material developed by DuPont ConAgra.
2 Leupron Depot is a product of Takeda Chemical Industries, Ltd., Japan for drug delivery purposes.
3 (*a*) E. E. Schmitt and R. A. Polistina, *U.S. Pat.*, 1969, 3463158; (*b*) E. J. Frazza and E. E. Schmitt, *J. Biomed. Mater. Res. Symp.*, 1971, **1**, 43; (*c*) Dexon and Vicry are products of Davis & Geek Corporation (Wayne, NJ) and Ethicon, Inc. (Somerville, NJ), respectively; (*d*) J. P. Pennings, H. Dijkstra and A. J. Pennings, *Polymer*, 1993, **34**, 942.
4 (*a*) J. A. Hubbell and R. Langer, *Chem. Eng. News*, March 13, 1995, p. 42; (*b*) R. Langer and J. P. Vacanti, *Science*, 1993, **260**, 920.
5 (*a*) T. M. Ovitt and G. W. Coates, *J. Am. Chem. Soc.*, 1999, **121**, 4072; (*b*) C. P. Radano, G. L. Baker and M. R. Smith, *J. Am. Chem. Soc.*, 2000, **122**, 1552; (*c*) M. Cheng, A. B. Attygalle, E. B. Lobkovsky and G. W. Coates, *J. Am. Chem. Soc.*, 1999, **121**, 11 584; (*d*) M. H. Chisholm, J. Gallucci and K. Phomphrai, *Inorg. Chem.*, 2002, **41**, 2785; (*e*) M. H. Chisholm, N. W. Eilerts, J. C. Huffman, S. S. Iyer, M. Pacold and K. Phomphrai, *J. Am. Chem. Soc.*, 2000, **122**, 11 845; A. P. Dove, V. C. Gibson, E. L. Marshall, A. J. P. White and D. J. Williams, *Chem. Commun.*, 2001, 283; (*g*) B. M. Chamberlain, M. Cheng, D. R. Moore, T. M. Ovitt, E. B. Lobkovsky and G. W. Coates, *J. Am. Chem. Soc.*, 2001, **123**, 3229.
6 B. J. O'Keefe, M. A. Hillmyer and W. B. Tolman, *J. Chem. Soc., Dalton Trans.*, 2001, 2215.
7 M. T. Zell, B. E. Padden, A. J. Paterick, K. A. M. Thakur, R. T. Kean, M. A. Hillmyer and E. J. Munson, *Macromolecules*, 2002, **35**, 7700.
8 (*a*) Recent examples include: K. B. Aubreecht, M. A. Hillmyer and W. B. Tolman, *Macromolecules*, 2002, **35**, 650; (*b*) M. Moller, F. Nederberg, L. S. Lim, R. Kange, C. J. Hawker, J. L. Hedrick, Y. Gu, R. Shah and N. L Abbott, *J. Polym. Sci., Part A: Polym. Chem.*, 2001, **39**, 3529; (*c*) M. Ryner, A.-C. Albertsson and H. R. Kricheldorf, *Macromolecules*, 2001, **34**, 7281; (*d*) J. Libiszowski, A. Kowalski, A. Duda and S. Penczek, *Macromol. Chem. Phys.*, 2002, **203**, 1694.
9 (*a*) A. Kowalski, J. Libiszowski, A. Duda and S. Penczek, *Macromolecules*, 2000, **33**, 1964; (*b*) J. E. Kemnitzer, S. P. McCarthy and R. A. Gross, *Macromolecules*, 1993, **26**, 6144.
10 M. H. Chisholm and E. E. Delbridge, *Chem. Commun.*, 2001, 1308.

11 M. H. Chisholm and E. E. Delbridge, *New J. Chem.*, 2003, **27**, 10.1039/b300351e (following paper).
12 ROP studies of L-lactide, methylglycolide and glycolide suggest that ROP is more rapid for glycolide and methylglycolide *vs.* L-lactide such that $k_{prop} \geq k_{ro}$[11].
13 H. Yasuda, J.-C. Choi, S.-C. Lee and T. Sakakura, *J. Organomet. Chem.*, 2002, **659**, 133.
14 (*a*) I. Wharf, *Inorg. Chim. Acta*, 1989, **159**, 41; (*b*) B. King, H. Eckert, D. Z. Denney and R. H. Herber, *Inorg. Chim. Acta*, 1986, **122**, 45; (*c*) A. Stern and E. I. Becker, *J. Org. Chem.*, 1964, **29**, 3221; (*d*) I. Wharf and M. G. Simard, *J. Organomet. Chem.*, 1997, **532**, 1.
15 G. Eng and C. R. Dillard, *Inorg. Chim. Acta*, 1978, **28**, 99.
16 (*a*) Z.-R. Shen, J.-H. Zhu and Z. Ma, *Makromol. Chem. Rapid Commun.*, 1993, **14**, 457; (*b*) T. A. Augurt, M. N. Rosensaft and V. A. Perciaccante, *U.S. Pat.*, 1977, 4033938.
17 K. Jones and M. F. Lappert, *J. Chem. Soc. A*, 1965, 1944.