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COMMUNICATION

Chemoselective alcoholysis of lactide mediated by a magnesium catalyst: an efficient route to alkyl lactyllactate†

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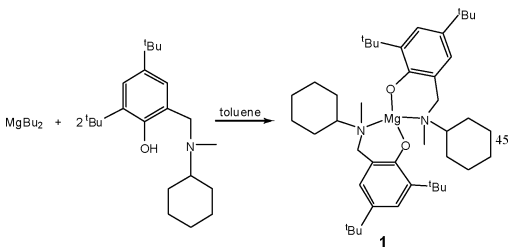
Alkyl-(*S*,*S*)-*O*-lactyllactate was prepared by chemoselective alcoholysis of lactide LA mediated by a magnesium catalyst. When ROH reacted with LA it yielded the ring-opened product R-(*S*,*S*)-*O*-lactyllactate exclusively, which remained intact as long as LA was present in the reaction mixture. Consumption of LA caused the reaction to proceed further giving R-(*S*)-lactate.

Lactide (*L*-LA, *D*-LA, *rac*-LA), a cyclic dimmer, is one of the simplest chiral compounds derived from lactic acid. It is made from the fermentation of carbohydrates such as corn - a renewable feedstock. A valuable reagent for organic syntheses,[1] and a useful monomer for polymerization,[2] very recently it has become a desirable starting material for the syntheses of lactate and lactyllactate esters.[3] The esters produced by alcoholysis of LA catalyzed by metal complexes have attracted great interest since they open up environmentally-friendly routes to alkyl lactates - compounds widely used in the cosmetic and food industries.[4] Earlier syntheses of alkyl lactates required a protective strategy, a stoichiometric amount of metal complexes, long reaction times and high temperatures.[5] Claborn[5b] later discovered that alkyl lactyllactate can be produced by heating a mixture of a dry lactate and the desired anhydrous alcohol in the range 70–90 °C for *ca.* 6 to 8 h in the presence of an acid catalyst under anhydrous conditions. The problem with these methods is the formation of polymer by-products and selectivity. Recently, Phomphrai used lithium, sodium, potassium and calcium alkoxide catalysts generated *in situ* to make a range of alkyl lactates from lactides and alcohols.[3b] However, the reaction course of LA transformation to alkyl (*S*,*S*)-lactyllactate decelerated after 20–30 min to achieve conversion from 48 to 84% for MOR where M = Li, Na and K, respectively, due to the aggregation of the active catalyst. For calcium alkoxide $Ca(OR)_2$ the reaction proceeded further and in 10 min methyl (*S*)-lactate was formed exclusively.

Recently our group has reported that the aminephenolate magnesium compounds, $[Mg(tbpoa)_2]$ (Htbpoa = *N*-[methyl(2-hydroxy-3,5-di-*tert*-butylphenyl)]-*N*-methyl-*N*-methyl-1,3-dioxolaneamine), are highly efficient initiators for lactide polymerization.[6] Here we report the use of tetrahedral magnesium complex $[Mg(tbpca)_2]$ where (Htbpca = *N*-[methyl(2-hydroxy-3,5-di-*tert*-butyphenyl)]-*N*-methyl-*N*-cyclohexylamine) as the catalyst for the alcoholysis of LA. This study demonstrated unique chemistry that allows for facile chemoselective catalytic incorporation of ROH into LA and pure alkyl lactyllactate formation. As shown in Scheme 1, $MgBu_2$ treated with 2 equivalents of Htbpca in toluene cleanly afforded the monomeric tetrahedral magnesium compound $[Mg(tbpca)_2]$ (**1**, 87%) by butane elimination. This was isolated as a colorless air and moisture sensitive solid or crystals in high yield, readily soluble in hydrocarbons, dichloromethane and thf. The aminephenolate ligand Htbpca was prepared following the Mannich reaction between *N*-cyclohexylamine, formaldehyde and substituted phenol as described in the literature.[7]



Scheme 1 Synthesis of $[Mg(tbpca)_2]$.

The structure of **1** was confirmed by elemental analysis and NMR spectroscopy, as well as X-ray crystallography. The ^1H NMR spectra of **1** were routine (see ESI†) and showed one set of resonances for aryl protons at 7.66 and 7.08 ppm, two singlets of *tert*-butyl groups at 1.78 and 1.56 ppm and a signal assigned to *N*-methyl protons at 2.02 ppm. The methylene protons from the phenyl-CH_2–N linker appeared as broad singlets at 4.12 and 3.44 ppm. The molecular structure of **1** is shown in Fig. 1 and selected bond lengths and angles are given in Table 1S.† X-ray analysis shows that the magnesium compound is a molecular monomer with the four-coordinated magnesium centre surrounded by two pairs of N,O atoms from two aminephenolate ligands forming a distorted tetrahedron. Although such coordination seems typical for magnesium, to our surprise only two monomeric four-coordinated magnesium complexes were found in the CCDC.[8]

In the standard procedure the magnesium compound **1**, lactide *L*-LA and dry ethanol in the molar ratio 1/50/200 was added

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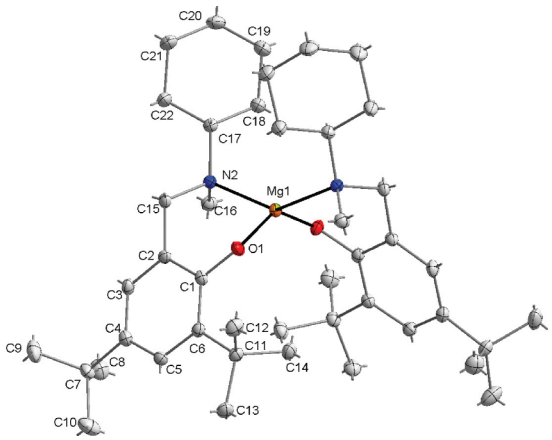


Fig. 1 View of [Mg(tbpca)$_2$]. Hydrogen atoms are omitted. Key bond lengths (Å) and angles (°): Mg(1)–O(1) 1.896(2), Mg(1)–O(2) 1.896(2), Mg(1)–N(1) 2.193(2), Mg(1)–N(2) 2.193(2), O(1)–Mg(1)–O(2) 133.19(7), O(1)–Mg(1)–N(1) 95.04(6), O(1)–Mg(1)–N(2) 99.80(6), O(2)–Mg(1)–N(1) 99.80(6), O(2)–Mg(1)–N(2) 95.04(6), N(1)–Mg(1)–N(2) 142.09(7).

at room temperature in dichloromethane. After 1 h the reaction was quenched with acetic acid and the product was isolated by distillation under vacuum. The ^{1}H NMR spectra shows two quartets (4.27, 5.04 ppm) and doublets (1.21, 1.46 ppm) due to methine and methylene protons of pure ethyl-(*S*,*S*)-*O*-lactyllactate as well as resonances for the ethyl group, triplet (0.88 ppm) and quartet (3.86 ppm), respectively (Fig. 2, Table 2, entry 1). Furthermore, when the reaction was carried out for 3 days at room temperature the solution consisted of 70% of ethyl-(*S*,*S*)-*O*-lactyllactate and 30% ethyl-(*S*)-lactate (Table 2, entry 2). Surprisingly, the analogous reaction with methanol is much faster and more complex. After 5 min besides methyl-(*S*,*S*)-*O*-lactyllactate (93.5%) methyl-(*S*)-lactate (6.5%) was also observed (Table 2, entry 3). To explain the reaction pathway and formation of intermediates in this multiple-step process the reaction course between **1**, LA and MeOH (1/50/200) in toluene was recorded at room temperature and various time intervals, generally up to 7 h and monitored by ^{1}H NMR (Fig. 3). The characteristic feature of the ^{1}H NMR spectrum is the disappearance of *L*-LA substrate and formation of two reaction products, first methyl-(*S*,*S*)-*O*-lactyllactate, which is formed as long as lactide is present in the reaction mixture; subsequently methyl-(*S*)-lactate appears. This indicates that the highly active compound **1** is able to catalyze not only the reaction between LA and alcohol but also the reaction among methyl-(*S*,*S*)-*O*-lactyllactate and ROH. In the first step the MeOH reacted with *L*-LA giving the ring-opened product methyl-(*S*,*S*)-*O*-lactyllactate exclusively (Scheme 2, cycle A). This remained intact as long as *L*-LA is present in the reaction mixture. As soon as *L*-LA is completely consumed the methyl-(*S*,*S*)-*O*-lactyllactate reacts with MeOH giving methyl-(*S*)-lactate (cycle B).

The study demonstrated that catalyst **1** had remarkable chemoselectivity and could specifically form methyl-(*S*)-lactate from methyl-(*S*,*S*)-lactyllactate only in the absence of *L*-LA. For the purpose of screening the catalyst activity, different alcohols (BnOH, EtOH, MeOH, ^{i}Pr-OH, ^{n}BuOH) were examined in the alcoholysis reaction of *L*-lactide as shown in Table 1 (entry 8–10). All reactions proceed catalytically to give the corresponding alkyl-

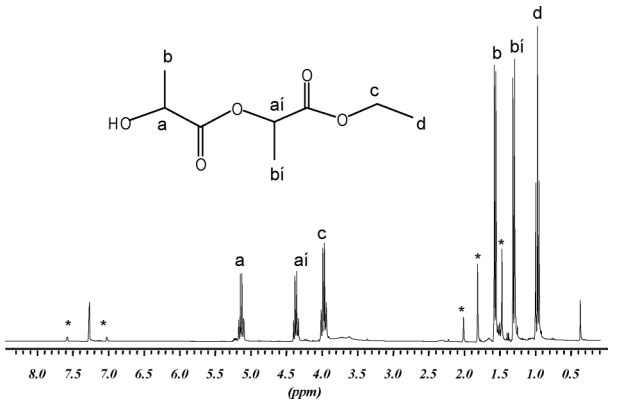


Fig. 2 ^{1}H NMR (C_6D_6, RT) spectrum of the alcoholysis of *L*-lactide catalysed by [Mg(tbpca)$_2$], (* signals of Htbpca). Reaction conditions [Mg(tbpca)$_2$]/*L*-LA/EtOH = 1/50/200, solvent CH_2Cl_2, [Mg(tbpca)$_2$] = 0.003 M, RT.

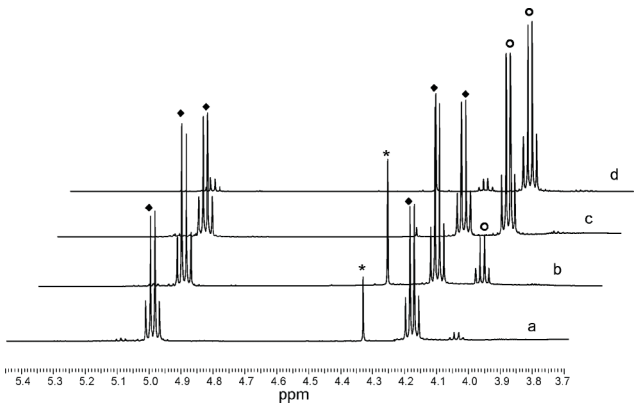
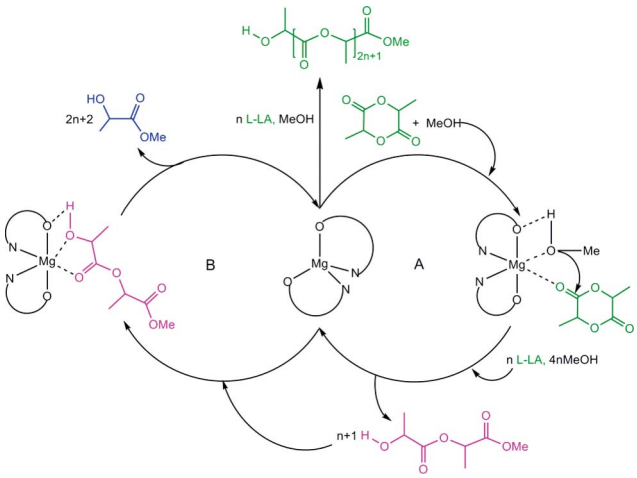


Fig. 3 ^{1}H NMR spectra presented for methine protons recorded at 273 K at various time intervals: a = 2 min, b = 4 min, c = 2 h, d = 7 h. Reaction condition: C_6D_6, RT [Mg(tbpca)$_2$]/LA/MeOH = 1/50/200. ♦ methyl-(*S*,*S*)-*O*-lactyllactate, **o** methyl-(*S*)-lactate, * CH_2Cl_2.



Scheme 2 Proposed mechanism for the alcoholysis and polymerisation of *L*-lactide.

(*S*,*S*)-*O*-lactyllactates with moderate yield. These observations suggested that the conversion of LA to alkyl lactyllactates, alkyl lactate or PLA depends on catalyst/LA/alcohol ratio as well as of the polarity of alcohol.

Table 1 Summary of alcoholysis[a] of *L*-lactide using [**I**], [Mg(tbpca)$_2$]/catalyst

Entry	*t* (h)	ROH	A-LL	A-L	*L*-LA
1	1	EtOH	98.0	0	2.0
2	72	EtOH	70.0	30.0	0
3	0.08	MeOH	93.5	6.5	0
4	0.5	MeOH	71.0	29.0	0
5	1	MeOH	62.0	38.0	0
6	3	MeOH	27.0	63.0	0
7	**6**	MeOH	0.5	99.5	0
8	2	^{n}BuOH	50.0	0	50.0
9	3	^{i}PrOH	48.0	0	52.0
10	18	BnOH	75.5	0	24.5
11[b]	0.25	BnOH[8]	0	0	0

[a] General reaction condition: [**1**] = 0.003, T = 25 °C, [**1**]/*L*-LA/ROH = 1/50/200, A-LL: alkyl-(*S*,*S*)-*O*-lactyllactate, A-L: alkyl-(*S*)-lactate. [b] Polymerization reaction conditions: [**1**]/*L*-LA/BnOH = 1/100/1, product PLA 100%.

A blank test was also performed in which no catalyst was added; no reaction was observed. Furthermore, it was found that compound **1** is also a very effective initiator for the ring-opening polymerization of *L*-LA. When **1** was allowed to react with 100 equiv. of *L*-LA and 1 equiv. of benzyl alcohol in toluene at room temperature, polymerization with 100% conversion was achieved in 15 min and produces PLA with the expected molecular weight M_w = 15 560 and low polydispersity PDI = 1.10 characteristic of well controlled living propagation.

In summary, we have developed a new, simple and efficient strategy for the preparation of a well-defined magnesium catalyst for selective conversion of lactides to alkyl-(*S*,*S*)-lactyllactates and to PLA in high yields. The study demonstrated that catalyst **1** is stable, and alkyl-(*S*,*S*)-*O*-lactyllactate is formed only in the presence of *L*-LA. In the absence of LA the reaction proceeds further giving methyl-(*S*)-lactate. The product selectivity and its easily extendable range might make this method convenient for wider application.

Acknowledgements

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