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Conversion of lactides into ethyl lactates and value-added products

Dominik Bykowski, Agnieszka Grala, Piotr Sobota *

Faculty of Chemistry, University of Wroclaw, F. Joliot-Curie 14, 50-383 Wroclaw, Poland

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ABSTRACT

This Letter describes an attractive and efficient method for $Mg(OR)_2$-mediated lactide alcoholysis. The catalysts were generated in situ from di-*n*-butylmagnesium and ROH to prevent aggregation of $Mg(OR)_2$. The reaction of ROH [R = Me, Et, $RCO_2(Me)CH$] with lactide initially yielded the ring-opened product $HO[CH(CH_3)CO]_nOR$ ($n = 2$ or 3). The complete consumption of lactide caused the reaction to proceed further, giving environmentally friendly lactic acid esters in excellent yields under ambient conditions.

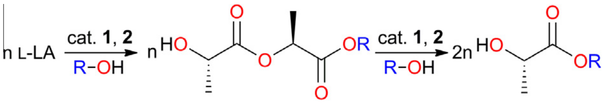
The production of chemical building blocks and polymer precursors from biorenewable and sustainable resources is an attractive method for bypassing traditional fossil-fuel-derived materials.[1] Lactide (LA), which is a cyclic dimer of lactic acid and is made by fermentation of carbohydrates such as corn, is not only a valuable chemical feedstock for the production of bioplastics,[2,3] but is also used to produce lactate esters, which are found in products such as cosmetics, perfumes, degreasers, food preservatives, and environmentally friendly solvents.[4,5] The concept of lactic acid ester synthesis from LA is very well established. As early as 1945, Claborn,[5] and later, in 1997, Wyffels,[6] showed that alkyl lactyllactates can be produced by heating a mixture of dry LA and the appropriate anhydrous alcohol in the presence of an acid catalyst at 70–90 °C for ca. 6–8 h. It is claimed that polylactide (PLA) undergoes depolymerization to methyl lactate at 150 °C in the presence of H_2SO_4.[4] Low molecular weight polylactates, $HO[CH(CH_3)CO]_nOR$ ($n = 3–7$), can also be formed by self-alcoholysis of alkyl lactates or by condensation of lactic acid.[7]

Currently, the simple and cheap alcoholysis of LA is attracting significant interest because it provides an environmentally friendly route to lactic acid esters. Phomphrai has shown that it is possible to convert LAs into alkyl lactates (*a*lacH), and lactyllactates (*a*$(lac)_2$-H), using a group 1 metal and a calcium alkoxide catalyst generated in situ.[8] Recently, Jones has shown that group 4 salalen complexes can be used to convert PLAs into lactate esters at room temperature.[9] Furthermore, Leibfarth reported the depolymerization of PLA into lactate esters through transesterification, using triazabicyclodecene as an organocatalyst.[10]

Our group has described the chemistry that enables the exclusive preparation of alkyl lactyllactates by chemoselective alcoholysis of L-LA mediated by a tetrahedral magnesium compound, $Mg(tbpca)_2$ (tbpca = *N*-[methyl(2-hydroxy-3,5-di-*tert*-butyphenyl)]-*N*-methyl-*N*-cyclohexylamine).[11] Based on this concept, we present an easy-to-use system, composed of a catalytic amount of an alkoxo-magnesium compound and excess ROH with respect to LA, for ring-opening alcoholysis, yielding valuable lactic acid esters under ambient conditions in excellent yields.

Initially, the alcoholysis of L-LA with ROH (R = Me, Et) in the presence of a catalytic amount of $[Mg(OR)_2]$ was studied as a model reaction (Scheme 1).

In the absence of a magnesium source, no ring-opening alcoholysis product was detected (Table 1, entry 1). Magnesium alkoxides $Mg(OR)_2$ are only slightly soluble in CH_2Cl_2 and toluene, and showed low catalytic activity. Turova[12] reported that solid $Mg(OMe)_2$ is built from four types of units: neutral $[Mg_4(\mu_3\text{-}OMe)_4(OMe)_4(MeOH)_8]$ cubane, $[Mg_4(\mu_3OMe)_4(OMe)_2(MeOH)_{10}]^{2+}$ cubane cations, $[(MeO)_2H]^-$ anions, and eight crystallographically independent noncoordinated solvating methanol molecules.[12] This structure derives from the bridging ability of alkoxo oxygen atoms,



Scheme 1. Ring-opening alcoholysis of L-LA with ROH[R = Me (**1**), Et (**2**)] in the presence of a catalytic amount of $Mg(OR)_2$.

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* Corresponding author. Tel.: +48 71 375 7306.
E-mail address: piotr.sobota@chem.uni.wroc.pl (P. Sobota).

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Table 1
Summary of the alcoholysis of L-LA using $Mg(OMe)_2$ (**1**) and $Mg(OEt)_2$ (**2**) as catalysts

Entry	Catalyst	Time (min)	% L-LA	% *a*(lac)$_2$H	% *a*lacH
1	1	1	0	91	9
2	1	5	0	72	28
3	1	15	0	50	50
4	1	30	0	0	100
5	2	1	0	92	8
6	2	5	0	69	31
7	2	15	0	45	55
8	2	30	0	0	100

L-LA = L-lactide, *a*(lac)$_2$H = alkyl lactyllactate, *a*lacH = alkyl lactate, reaction conditions: rt, CH_2Cl_2, **1** or **2**/[L-LA]/[ROH] = 1:50:200, ROH = MeOH (**1**), EtOH (**2**).

which causes aggregation. In this study, to prevent aggregation of $Mg(OR)_2$, the catalysts were generated in situ in CH_2Cl_2 from $MgBu_2$ and ROH [R = Me (**1**), Et (**2**)] before use. In a typical experiment, the monomer, that is, L-LA, in CH_2Cl_2 and previously dried ethanol or methanol were placed in a Schlenk flask and stirred under N_2. Next, commercially available $MgBu_2$ was added in a molar ratio of $[MgBu_2]$/[L-LA]/[ROH] = 1:50:200. The solvent and excess alcohol were removed to afford the desired lactate ester. Data for L-LA alcoholysis catalyzed by **1** and **2** are presented in Table 1.

Results showed that in the first step ROH reacts rapidly with L-LA, giving the ring-opened alkyl lactyllactate, (*a*(lac)$_2$H), nearly exclusively. When the L-LA has been completely consumed, the *a*(lac)$_2$H reacts further with the alcohol, giving alkyl lactate (*a*lacH) (Table 1, entries 1–8).

Once we had found a suitable system for the alcoholysis of LA into the corresponding lactate esters, we became interested in exploring the influence of L-LA on the final distribution of the reaction products. We used the standard conditions, that is, [**1**]/[L-LA]/[MeOH] = 1:50:200, and monitored the course of the reaction using ^1H NMR spectroscopy. Addition to the reaction mixture containing 72% methyl lactyllactate (*m*(lac)$_2$H) and 28% methyl lactate (*m*lacH) (Table 1, entry 2) of a new portion of LA, **1**/L-LA = 1:25 (Fig. 1, spectrum A, signal a), resulted in total consumption (within 2 min) of the added L-LA (spectrum B). Spectrum C, recorded after 3 min, shows the absence of signal b from the methine protons of *m*lacH as a result of self-alcoholysis; the signal reappeared after 5 min (spectrum D) (see Scheme 5).

When ethanol was used instead of methanol, the reaction course and reaction products were similar. However, the NMR spectrum was more complex because the L-LA and ethyl lactate (*e*lacH) methine signals overlapped. It follows that the highly active compounds **1** and **2** are able to catalyze not only the reaction between L-LA and ROH (Scheme 1), but also between L-LA and *a*lacH. It can be assumed that during alcoholysis with the participation of alkyl lactate hydroxyl groups, a trimer, HO[CH(CH)$_3$CO]$_3$OEt [*e*(lac)$_3$H] can be formed, in accordance with Scheme 2.

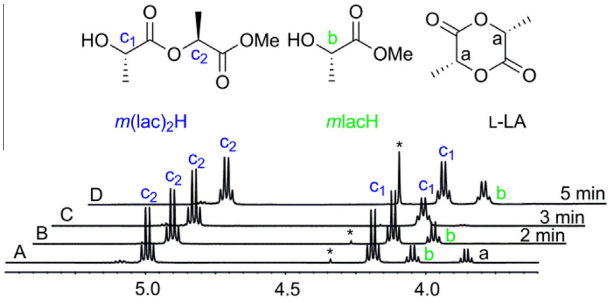
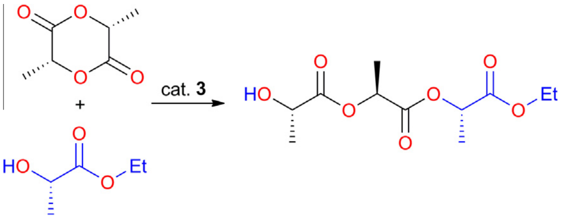
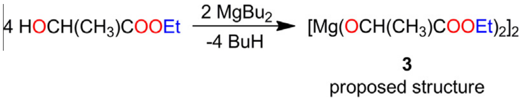


Figure 1. ^1H NMR (benzene-d_6, 293 K, 500 MHz) spectra, showing methine proton signals, recorded at various time intervals; *residual solvent. Initial conditions: room temperature, CH_2Cl_2, [**1**]/[L-LA]/[MeOH] = 1:50:200.



Scheme 2. Ring-opening alcoholysis of LA with alkyl lactate hydroxyl groups in the presence of a catalytic amount of [(Mg(*e*lac)$_2$]$_2$ (**3**).



$$4\ HOCH(CH_3)COOEt \xrightarrow[-4\ BuH]{2\ MgBu_2} [Mg(OCH(CH_3)COOEt)_2]_2$$

3
proposed structure

Scheme 3. Treatment of *e*lacH with $MgBu_2$ in CH_2Cl_2 at room temperature afforded **3** and stoichiometric butane elimination.

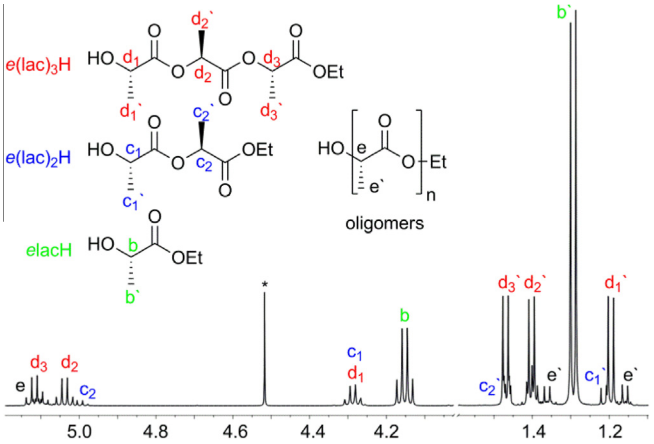


Figure 2. ^1H NMR (benzene-d_6, 293 K, 500 MHz) spectrum, showing proton signals, recorded after 1 min; *CH_2Cl_2. Initial conditions: room temperature, [**3**]/[L-LA]/[*e*lacH] = 1:50:200.

It is well known that alkyl lactate moieties, $-OCH(Me)CO_2R$ (R = Me, Et, ^{i}Pr), can be regarded as the propagating species in LA polymerization with aluminum,[13] zinc,[14] gallium,[15] and tin[16] initiators. For example, aluminum and gallium dimeric complexes of formula $[Me_2M(\mu\text{-}OCH(Me)CO_2Et)]_2$ (M = Al, Ga) mediated the insertions of L-LA monomers into the $M–OCH(Me)CO_2R$ bond to generate the PLA.[15] This led us to investigate the possibility of LA ring-opening by magnesium alkyl lactate [(Mg(*e*lac)$_2$]$_2$ (**3**), and we have used **3** generated in situ as a catalyst (Scheme 3).

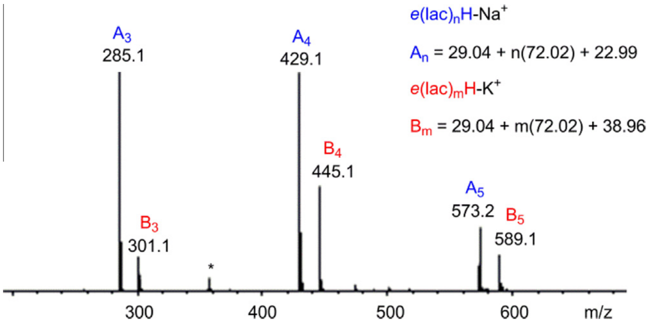


Figure 3. ESI-MS spectrum recorded after 1 min. Initial conditions: room temperature, [**3**]/[L-LA]/[*e*lacH] = 1:50:200.