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Facile alcoholysis of L-lactide catalysed by Group 1 and 2 metal complexes†

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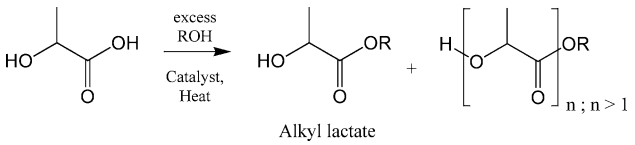
Alkyl (*S*)-lactate and alkyl (*S*,*S*)-lactyllactate were rapidly and conveniently synthesized from L-lactide using Group 1 and 2 metal complexes as catalyst in alcohol.

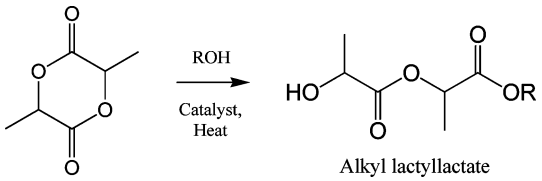
Lactic acid is one of the safe and environmentally friendly compounds used in the food, pharmaceutical, cosmetic, and textile industries.[1] The applications extend beyond its simple monomeric structure where esters, oligomers, and polymers of lactic acid have also found numerous uses. Lactate and lactyllactate esters of low molecular weight alcohols are colorless and odorless liquids. The low vapor pressure has made them suitable as green solvents and plasticizers.[2]

Alkyl lactates can simply be synthesized from the reaction of lactic acid with excess alcohol (Scheme 1).[3] However, the reaction usually required reflux at high temperature and long reaction times. Product distribution was also a major problem with this method where by-products such as short-chain oligomers of lactic acid were usually formed. Thus, product separation and purification were needed afterwards.



Scheme 1

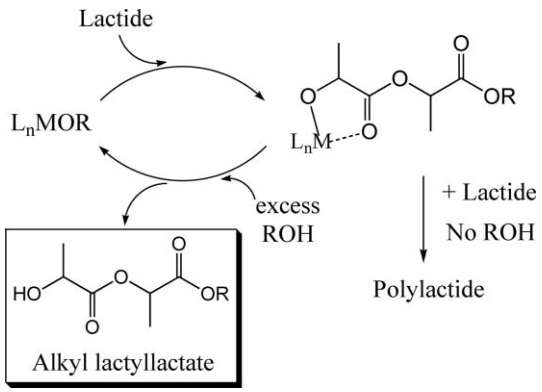
Because lactic acid has both hydroxyl and carboxylic groups in the same molecule, intermolecular esterification can easily occur giving oligolactates. One way to solve this problem was to use a protecting group strategy. Early synthesis of alkyl lactyllactates was from the reaction of potassium lactate and ethyl 2-chloropropionate. However, this method was complicated and inconvenient. A better synthesis was later developed by Claborn using alcoholysis of lactide in benzene with a trace of benzene sulfonic acid as catalyst (Scheme 2).[4] Nonetheless, this process required long reaction times at reflux temperature. Feijen *et al*. showed that calcium bisalkoxides generated *in situ* could ring-open lactides when [lactide] : [^{i}PrOH] : [Ca] = 2 : 8 : 1 was used in THF at room temperature giving isopropyl lactyllactate.[5] This method used a stoichiometric amount of calcium bisalkoxide to prevent further ring-opening polymerisation to polylactide. An interesting enzymatic system was recently developed by Lee *et al*.



Scheme 2

where Novozym 435 was used in the alcoholysis of *rac*-lactide selectively giving alkyl (*R*)-lactate and alkyl (*S*,*S*)-*O*-lactyllactate in 8 h at room temperature.[6] Most systems reported to date either required a protecting strategy, a stoichiometric amount of catalyst, or long reaction times at high temperatures. Thus, a more effective synthesis of alkyl lactate and alkyl lactyllactate is needed.

In order to maximize atom efficiency, we turned to the system shown in Scheme 2 where every atom in the starting materials was used in the reaction. Furthermore, the synthesis of alkyl lactate and alkyl lactyllactate needed to be catalytic rather than stoichiometric. Several research groups have shown that single-site metal alkoxide complexes containing suitable metals and ligand sets were fast and effective catalysts for the ring-opening polymerisation of lactides.[7] With this in mind, we focused on metal alkoxide complexes. In order to prevent polymerisation, excess dry alcohol was required to promote chain transfer (Scheme 3). However, excess alcohol such as methanol was normally added to quench the polymerisation in standard lactide polymerisation.



Scheme 3

Thus, if excess alcohol was used in our system, it would simply destroy the ligated metal alkoxide complexes. To allow the presence of excess alcohol in the reaction, we turn to a simple metal alkoxide MOR where M = Li, Na, or K. The excess alcohol would simply exchange rather than destroy the metal alkoxide.

In order to make the system simple to use and applicable to most alcohols, commercially-available and easy-to-handle metal amides $MN(SiMe_3)_2$ where M = Li, Na, K were used. Metal alkoxides will

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† Electronic supplementary information (ESI) available: Experimental procedures, characterization of all alkyl (*S*)-lactate, methyl (*S*,*S*)-lactyllactate, and methyl 6-hydroxyhexanoate. See DOI: 10.1039/b800308d

Table 1 Summary of methanolysis of L-lactide using metal amides as catalyst precursors

Catalyst	T/°C	t/min	%LA[a]	%MLL[b]
$LiN(SiMe_3)_2$	RT	10	55	45
		20	53	47
		30	53	47
		60	52	48
$NaN(SiMe_3)_2$	RT	10	42	58
		20	40	60
		30	39	61
		60	40	60
$KN(SiMe_3)_2$	RT	10	38	62
		20	25	75
		30	17	83
		60	16	84
$KN(SiMe_3)_2$	55	10	46	54
		20	28	72
		30	19	81
		60	3	97

Reaction conditions: Lactide (0.500 g, 3.47 mmol), methanol (8.0 mL), catalyst (1 mol%, 34.7 μmol). [a] LA = L-lactide. [b] MLL = methyl (*S*,*S*)-lactyllactate.

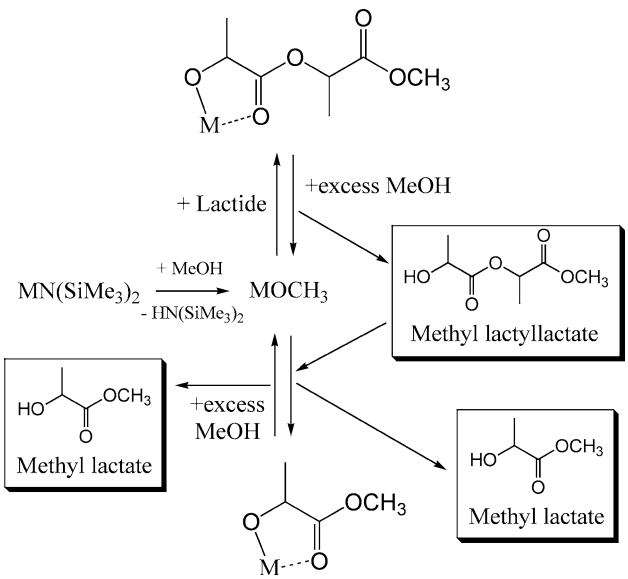
be generated *in situ* upon mixing with alcohol eliminating the need to synthesize MOR in advance. To test our hypothesis, excess dry methanol and L-lactide were added to a Schlenk flask at room temperature (RT). 1 mol% (compared to lactide) of $MN(SiMe_3)_2$ where M = Li, Na, or K was added. At different times, small aliquots were taken and quenched with 2 drops of acetic acid. After solvent removal, the samples were analysed by ^{1}H NMR. With time, ^{1}H NMR showed the disappearance of L-lactide resonances at δ_H 5.02 and 1.60 ppm and an appearance of new resonances at δ_H 1.46 (d, 3H), 1.49 (d, 3H), 3.72 (s, 3H), 4.33 (q, 1H), and 5.15 (q, 1H) ppm. The new compound was identified as methyl (*S*,*S*)-lactyllactate (see ESI†). The results are summarized in Table 1.

Table 1 shows that methyl (*S*,*S*)-lactyllactate was formed catalytically for all metal complexes. The final conversions to methyl (*S*,*S*)-lactyllactate at 60 min were 48, 60, and 84% for $MN(SiMe_3)_2$ where M = Li, Na, and K, respectively. A blank test was also performed where no catalyst was added giving no reaction. From %conversion of methyl (*S*,*S*)-lactyllactate, the general reactivity of MOR (generated *in situ*) was in the order K > Na > Li attributed to the difference in polarity of the M–OR bond. For M = K, the metal is more electropositive. Thus, the alkoxide oxygen has more δ^- charge making it a better nucleophile to attack lactide.

For M = Li, 45% conversion to methyl (*S*,*S*)-lactyllactate was obtained in 10 min at room temperature. However, the reaction stopped shortly after that at about 48% conversion. Similar behaviors were observed for M = Na and K where the reactions decelerated after 20 and 30 min, respectively, possibly due to the formation of metal alkoxide aggregates of the type $[MOR]_n$. The aggregation decreased the amount of active MOR in the reaction. To increase the reactivity, the reaction was performed at 55 °C for $KN(SiMe_3)_2$. The methanolysis proceeded faster giving methyl (*S*,*S*)-lactyllactate in almost quantitative yield in 1 h.

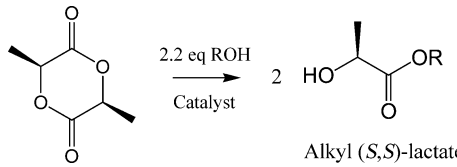
In addition to Group 1 metal complexes, Group 2 metal complexes were also surveyed. Chisholm and Feijen and co-workers reported that calcium alkoxide complexes were highly active for lactide polymerisation.[5,8–10] Thus, methanolysis of L-lactide was attempted using 1 mol% $Ca[N(SiMe_3)_2]_2{\cdot}2THF$ at room temperature. As anticipated, the reaction proceeded very quickly giving 87% methyl (*S*,*S*)-lactyllactate in only 5 min under the same conditions. However, a close inspection of the ^{1}H NMR spectra revealed new resonances at δ_H 1.34 (d, 3H), 3.70 (s, 3H), and 4.24 (q, 1H) ppm in addition to the chemical shifts of methyl (*S*,*S*)-lactyllactate. The new species was identified as methyl (*S*)-lactate (see ESI†) and found at about 4% compared to the original lactide concentration. That means the highly active calcium alkoxides are capable of attacking not only the cyclic lactide but also the less active linear methyl (*S*,*S*)-lactyllactate. At longer times, the concentration of methyl (*S*)-lactate continued to increase while the concentration of methyl (*S*,*S*)-lactyllactate decreased. Nonetheless, the formation of methyl (*S*)-lactate increased rather slowly from 4% in 5 min to 11% in 1 h. The considerably slow rate implied a catalyst deactivation possibly as metal alkoxide aggregation.

Subsequent experiments were then performed by increasing the amount of $Ca[N(SiMe_3)_2]_2{\cdot}2THF$ to 5 mol% in order to enhance the methyl (*S*)-lactate formation before the catalyst deactivation set in. At 5 min and room temperature, methyl (*S*)-lactate was obtained exclusively in quantitative yield. The mechanism for the formation of methyl (*S*,*S*)-lactyllactate and methyl (*S*)-lactate using metal amide as catalyst is proposed in Scheme 4. Metal amide did not directly attack lactide but was transformed into metal methoxide in the pressence of excess dry methanol before further methanolysis of L-lactide took place. This mechanism was confirmed by the absence of a $-C(O)N(SiMe_3)_2$ chemical shift in the ring-opening product. The metal methoxide reacted with lactide giving the ring-opened product. Chain transfer with excess methanol subsequently took place giving methyl (*S*,*S*)-lactyllactate and metal methoxide. This catalytic cycle continued giving methyl (*S*,*S*)-lactyllactate for Group 1 metal amides. For the more active Group 2 metal complex, methyl (*S*,*S*)-lactyllactate reacted further with metal methoxide giving methyl (*S*)-lactate. The other equivalent of methyl (*S*)-lactate was obtained subsequently after proton exchange with excess methanol. At the end of the



Scheme 4

Table 2 Summary of alcoholysis of L-lactide using $Ca[N(SiMe_3)_2]_2 \cdot 2THF$ as a catalyst precursor



Alkyl (*S*,*S*)-lactate

Entry	R	*T*/°C	*t*/min	%AL[a]
1	Me	30	10	94
2	Et	30	10	92
3	^{n}Bu	30	10	92
4	CH_2Ph	30	5	95
5	^{i}Pr	30	60	48

Reaction condition: Lactide (0.500 g, 3.47 mmol), HOR (2.2 equiv., 6.94 mmol), $Ca[N(SiMe_3)_2]_2 \cdot 2THF$ (5 mol%, 174 μmol), toluene (4 mL), room temperature. [a] AL = alkyl (*S*,*S*)-lactate.

reaction, excess methanol can be removed under reduced pressure for recycling. The result from chiral HPLC of methyl (*S*)-lactate revealed no sign of methyl (*R*)-lactate indicating that epimerisation was negligible in this system.

In addition to methyl (*S*)-lactate, we have attempted to synthesize other alkyl (*S*)-lactates using ethanol, isopropanol, n-butanol, and benzyl alcohol with a similar approach. We also attempted to minimize the amount of alcohol for future applications where alcohol could be expensive or difficult to remove from the product. The results are summarized in Table 2. By using only a slight excess of alcohol (2.2 equiv.) in toluene as a solvent, we were able to synthesize alkyl (*S*)-lactate rapidly in high yield for primary alcohols (entries 1–4). For a secondary alcohol (entry 5, ^{i}PrOH), the reaction proceeded much more slowly giving 48% isopropyl (*S*)-lactate in 1 h. Data at shorter sampling times revealed interesting information. NMR data of entry 5 at 5 min revealed a complete consumption of lactide giving 59% isopropyl (*S*,*S*)-lactyllactate, 13% isopropyl (*S*)-lactate and 27% oligomers. At longer times, isopropyl (*S*,*S*)-lactyllactate and oligomers were slowly consumed giving isopropyl (*S*)-lactate. This observation suggested that the transesterification of alkyl (*S*,*S*)-lactyllactate was slower for secondary alkoxides compared to the primary alkoxides.

To further demonstrate the effectiveness of alcoholysis of cyclic esters using metal amides as catalyst, methanolysis of ε-caprolactone was performed using 1 mol% $Ca[N(SiMe_3)_2]_2 \cdot 2THF$ in excess dry methanol at room temperature. The reaction proceeded very rapidly and the ring-opened product methyl 6-hydroxyhexanoate (see ESI†) was obtained in quantitative yield in only 5 min.

In conclusion, we have demonstrated the application of simple metal amides as effective catalysts for the alcoholysis of cyclic esters. Group 1 metal complexes catalyzed the methanolysis of L-lactide giving methyl (*S*,*S*)-lactyllactate rapidly in high yield. For the more active calcium amides, the reaction proceeded further giving methyl (*S*)-lactate very rapidly and exclusively. Alcoholysis of L-lactide using a slight excess of ethanol, n-butanol, and benzyl alcohol gave alkyl (*S*)-lactate very rapidly in high yield. The application also extended to other cyclic esters such as ε-caprolactone where the ring-opened product was obtained rapidly in quantitative yield. This method was proven to be much more effective and more selective than the conventional acid-catalyzed esterification method where short-chain oligomers of lactic acid were usually formed. Well-defined single-site catalysts for alcoholysis and transesterification are being developed in our laboratory to solve the problems of metal alkoxide aggregation.

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