Electronic Supplementary Information

Chemoselective Alcoholysis of Lactide Mediated by a Magnesium Catalyst: an Efficient Route to Alkyl Lactyllactate

Agnieszka Grala, Jolanta Ejfler, Lucjan B. Jerzykiewicz, Piotr Sobota*

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

1.1 Preparation of Compound.

General: All the reactions and operations were performed under an inert atmosphere of N_2 using standard Schlenk techniques. Reagents were purified by standard methods: thf, distilled from CuCl, predried over NaOH, and then distilled from Na/benzophenone; toluene, distilled from Na; CH_2Cl_2, distilled from P_2O_5, *n*-hexanes, distilled from Na; methanol distilled from Mg. *L*-LA (98%; Aldrich) were sublimed and recrystallized from toluene prior to use. $MgBu_2$ (1 M solution in hexanes) were purchased from Aldrich and were used as received. N-[methyl(2-hydroxy-3,5-di-*tert*-butyphenyl)]-N-methyl – N-cyclohexylamine ($L^{2\text{-}tBu}$-H) ligand was synthesized according to literature procedure[7]. ^1H and ^{13}C NMR spectra were detected at temperature range from 233K to 293K using a Bruker ESP 300E or 500 MHz spectrometer. Chemical shifts are reported in parts per million and referenced to the residual protons in deutered solvents. The weights and number-average molecular weights of PLAs were determined by gel permeation chromatography (GPC) using a HPLC-HP 1090 II with a DAD-UV/Vis and RI detector HP 1047A and polystyrene calibration. Mass spectrometric measurements were performed using a micrOTOF-Q (Bruker Germany) electrospray mass spectrometer on the basis of high-resolution mass measurements. Microanalyses were conducted with an ARL Model 3410 + ICP spectrometer (Fisons Instruments) and a VarioEL III CHNS. Specific rotation was measured using a Jasco DIP-100 Digital Polarimeter.

1.1.1 Complex Synthesis

To a solution of $L^{2\text{-}tBu}$-H (1.32 g, 4.00 mmol) in toluene (10 mL) $MgBu_2$ (2 mL, 2.00 mmol) was added dropwise. The reaction was stirred for 24 h and evaporated to yellow oil. Next *n*-hexane was added (20 mL) and after 1 day at room temperature colourless crystals precipitated. They were filtered off, washed with *n*-hexane (10 mL) and dried in vacuum to yield 1.19 g (87%, 1.74 mmol) of $Mg(L^{2\text{-}tBu})_2$. Anal. Calcd (found) for $C_{44}H_{72}N_2O_2Mg$ (%, 685.33): C 77.11 (76.95), H 10.61 (10.58), N 4.09 (4.00). ^{1}H NMR (C_6D_6, 298 K): δ = 7.66 (2H, s, Ar*H*), 7.08 (2H, s, Ar*H*), 4.12 (2H, s, br, NCH_2Ar), 3.44 (2H, s, NCH_2Ar), 2.27-2.39 (2H, m, C_6H_{11}), 2.02 (6H, s, NCH_3), 1.78 (18H, s, C(CH_3)$_3$), 1.60-1.70 (10H, m, C_6H_{11}), 1.56 (18H, m, C(CH_3)$_3$), 1.30-1.47 (10H, m, C_6H_{11}). ^{13}C NMR (76 MHz, C_6D_6, 298 K): δ = 25.2 (10C, C_6H_{11}), 25.5 (10C, C_6H_{11}), 29.4 (6C, C(CH$_3$)$_3$), 31.0 (2C, NCH$_3$), 31.5 (6C, C(CH$_3$)$_3$), 33.3 (2C, C(CH$_3$)$_3$), 34.7 (2C, C(CH$_3$)$_3$), 59.4 (2C, C_6H$_{11}$), 60.3 (2C, NCH$_2$Ar) 62.3, 136.8, 134.6, 125.0, 123.5, 121.0 (24 *C*, Ar).

1.1.2 Alkyl lactyllactate

Representative procedure. The magnesium complex, monomer *L*-LA in CH_2Cl_2 was placed in a Schlenk flask and stirred for 10 minutes, next appropriate alcohol was added in desired molar ratio. The reaction mixture was stirred at room temperature and at certain time intervals about 1 cm^3 aliquots were taken, quenched with 2 drops of acetic acid, dried under vacuum and analyzed by ^{1}H NMR. After reaction was completed it was quenched with acetic acid, the solution was dried in vacuum and the product was isolated by distillation under reduced pressure as colorless oil.

Methyl (*S,S*)-*O*-lactyllactate. δ_H (300 MHz; C_6D_6): 1.14 (3H, d, *J* = 6.89, CH_3), 1.41 (3H, d, *J* = 7.26, CH_3), 3.22 (3H, s, OCH_3), 4.18 (1H, q, *J* = 6.88, C*H*), 5.00 (1H, q, *J* = 6.88, C*H*), 5. δ_C (75 MHz, C_6D_6): 13.9 (CH$_3$), 20.8 (CH$_3$), 56.5 (OCH$_3$), 65.6 (CH), 69.1 (CH), 170.4 (C=O), 174.1(C=O).

Methyl (*S*)-lactate. δ_H (300 MHz; C_6D_6): 1.20 (3H, d, *J* = 6.88, CH_3), 3.20 (3H, s, OCH_3), 4.01 (1H, q, *J* = 6.88, C*H*). δ_C (75 MHz, C_6D_6): 20.2 (CH$_3$), 51.5 (OCH$_3$), 66.5 (CH), 175.8 (C=O).

Ethyl (*S,S*)-*O*-lactyllactate. δ_H (300 MHz; C_6D_6): 0.88 (3H, t, *J* = 7.18, OCH_2CH_3), 1.21 (3H, d, *J* = 7.17, CH_3), 1.46 (3H, d, *J* = 7.17, CH_3), 3.86 (2H, q, *J* = 7.12, OCH_2CH_3), 4.27 (1H, q, *J* = 6.88, C*H*), 5.04 (1H, q, J = 7.12, C*H*). δ_C (75 MHz, C_6D_6): 14.1 (OCH_2CH_3), 16.8 (CH_3), 20.8 (CH_3), 61.4 (OCH_2CH_3), 67.1 (*C*H), 69.6 (*C*H), 170.46 (*C*=O), 175.9 (*C*=O); MS (ESI): *m/z* = 213.05, $[M\text{-}Na]^+$. $[\alpha]^{20}_D$ = -39.4 (c 0.009 in methanol).

Isopropyl (*S,*S)-*O*-Lactyllactate. δ_H (300 MHz; C_6D_6): 0.94 (6H, d, *J* = 6,50 $CH_2(CH_3)_2$, 1.2 (3H, d, *J* = 6.88, CH_3), 1.46 (3H, d, *J* = 6.88, CH_3), 4.25 (1H, q, *J* = 6.89, C*H*), 4.91 (1H, m, $CH(CH_3)_2$), 5.01 (1H, q, J = 7.01, C*H*). δ_C (75 MHz, C_6D_6): 16.6 (CH_3), 20.7 (CH_3), 21.5 ($CH(CH_3)_2$), 66.9 ($CH(CH_3)_2$), 69.0 (*C*H), 69.6 (*C*H), 169.9 (*C*=O), 175.5 (*C*=O).

Butyl (*S,S*)-*O*-lactyllactate. δ_H (300 MHz; C_6D_6): 0.84 (3H, t, *J* = 7.41, $CH_2CH_2CH_3$), 1.11 (3H, m, CH_2CH_3), 1.21 (3H, t, *J* = 6.92, CH_3), 1.32 (3H, d, *J* = 6.91, CH_3),1.44 (2H, m, $CH_2CH_2CH_3$), 3.49 (2H, t, *J* = 6.65, $COOCH_2$), 4.18 (1H, q, *J* = 6.92, C*H*), 5.02 (1H, q, J = 7.00, C*H*). δ_C (75 MHz, C_6D_6): 13.9 (CH_2CH_3), 16.4 (CH_3), 20.5 (CH_3), 21.3 (CH_2CH_3), 30.9 (OCH_2CH_2), 66.8 (OCH_2), 69.4 (*C*H), 70.1 (*C*H), 169.7 (*C*=O), 175.3 (*C*=O).

Benzyl *(S,S)-O*-lactyllactate. δ_H (300 MHz, C_6D_6): 1.09 (3H, d, *J* = 7.29, CH_3), 1.31 (3H, d, *J* = 6.94, CH_3), 4.11 (1H, q, *J* = 6.94, C*H*), 4.34 (2H, s, CH_2OBn), 4.92 (1H, q, *J*= 6.99, C*H*), 7.09 (5H, m, Ar-*H*). δ_C 15.97 (CH_3), 19.95 (CH_3), 64.27 (CH_2OBn) 66.62 (*C*H), 68.84 (*C*H), 169.88 (*C*=O), 174.67 (*C*=O).

1.2 Polymer Synthesis

Representative procedure. The monomer *L*-LA was placed in a Schlenk flask and metal complex in CH_2Cl_2 was added. The reaction was stirred at the desired temperature for the prescribed time. Next, at certain time intervals about 1 cm^3 aliquots were removed for determination of the conversion using ^1H NMR. After reaction was completed it was quenched with methanol, the solution was concentrated in vacuum and the polymer was precipitated with an excess of cold methanol. Filtration and drying in vacuum yielded a white polymer.

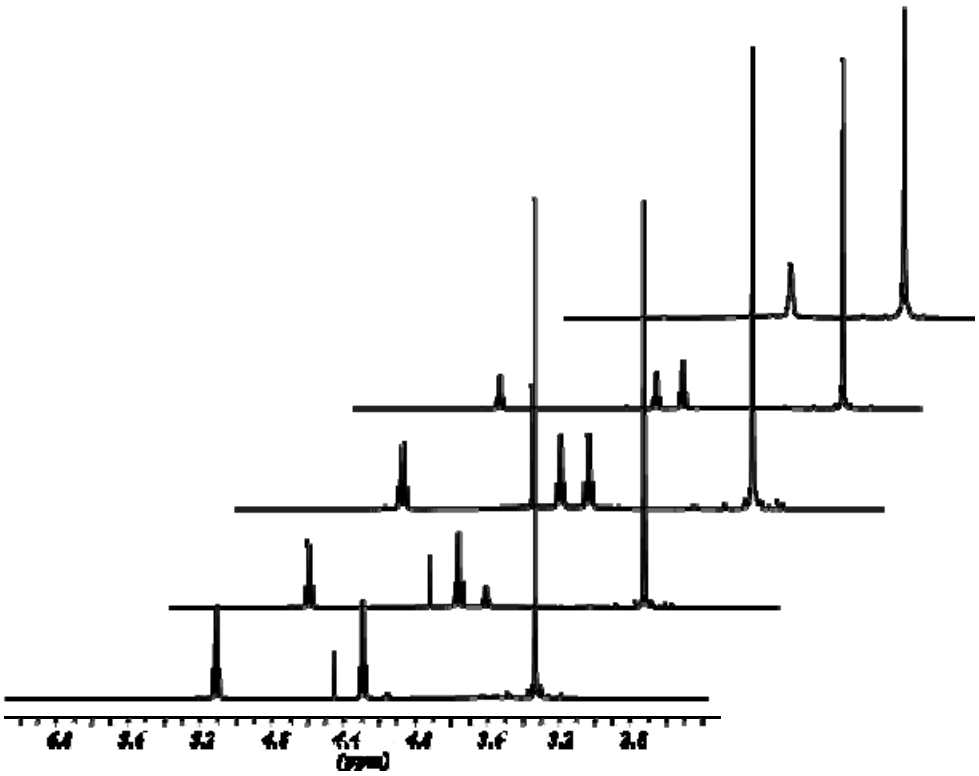

Figure 1S. ^{1}H NMR spectra presented for methine and methyl protons recorded at 273 K at various time intervals. Reaction condition: C_6D_6, RT [$Mg(tbpca)_2$]/LA/MeOH = 1/50/200. (see also Figure 3 in MS)

1.3 X-ray crystallography

Crystal data and refinement details for all compounds are given in Table **S1**. The crystals were mounted on glass fibers and then flash-frozen to 100(2) K (Oxford Cryosystem-Cryostream Cooler). Preliminary examination and intensities data collections were carried out on a Kuma KM4CCD κ-axis diffractometer with graphite-monochromated MoK_α radiation. All data were corrected for Lorentz, polarization and absorption effects. Data reduction and analysis were carried out with the Kuma Diffraction programs[i]. The structure was solved by direct methods and refined by the full-matrix least-squares method on all F^2 data using the SHELXTL software[ii]. Carbon bonded hydrogen atoms were included in calculated positions and refined in the riding mode using SHELXTL default parameters.

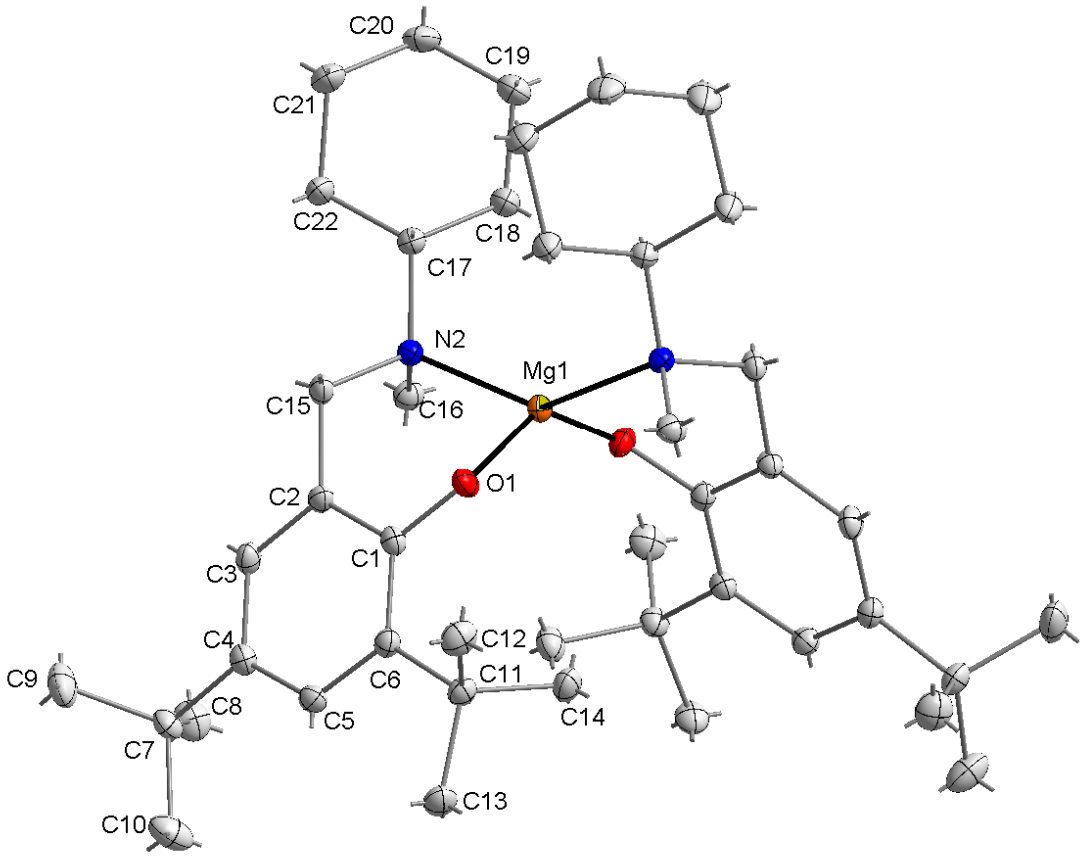

Figure S2. Molecular structure of the title compound with hydrogen atoms omitted.

Table S1. Experimental details

No. CCDC.	799087
Crystal data	
Chemical formula	$C_{44}H_{72}MgN_2O_2$
M_r	685.35
Crystal system, space group	Monoclinic, *C*2/*c*
Temperature (K)	100
a, *b*, *c* (Å)	16.324 (5), 11.954 (4), 21.154 (6)
β (°)	90.93 (5)
V (Å^3)	4127 (2)
Z	4
Radiation type	Mo *K*α
μ (mm^{-1})	0.08
Crystal size (mm)	0.18 × 0.18 × 0.05
Data collection	
Diffractometer	Kuma KM-4 CCD kappa-axis diffractometer
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	27609, 4976, 3384
R_{int}	0.063
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.041, 0.101, 1.02
No. of reflections	4976
No. of parameters	229
No. of restraints	0
H-atom treatment	H-atom parameters constrained
$\Delta\rangle_{max}$, $\Delta\rangle_{min}$ (e Å^{-3})	0.32, -0.21

Computer programs: *CrysAlis CCD*. Version 1.171.31 (Oxford Diffraction, 2006), *CrysAlis RED*. Version 1.171.31 Oxford Diffraction, 2006), *CrysAlis RED*. Version 1.171.31 (Oxford Diffraction, 2006), *SHELXTL*. Version 6.14 (Bruker, 2003), *DIAMOND*. Version 3.1f. (Brandenburg, K. 2007).

Table S2. Selected geometric parameters (Å, º).

Mg1—O1	1.896 (2)	Mg1—C1^{i}	2.786 (2)
Mg1—N2	2.193 (2)	O1—C1	1.338 (2)
Mg1—C1	2.786 (2)	N2—C15	1.507 (2)
Mg1—O1^{i}	1.896 (2)	N2—C16	1.486 (2)
Mg1—N2^{i}	2.193 (2)	N2—C17	1.505 (2)
O1—Mg1—N2	95.04 (6)	Mg1—O1—C1	117.88 (9)
O1—Mg1—C1	25.13 (6)	Mg1—N2—C15	106.01 (9)
O1—Mg1—O1^{i}	133.19 (7)	Mg1—N2—C16	109.84 (9)
O1—Mg1—N2^{i}	99.80 (6)	Mg1—N2—C17	109.96 (9)
O1—Mg1—C1^{i}	118.14 (7)	C15—N2—C16	108.74 (11)
N2—Mg1—C1	77.95 (6)	C15—N2—C17	110.10 (11)
O1^{i}—Mg1—N2	99.80 (6)	C16—N2—C17	112.01 (11)
N2—Mg1—N2^{i}	142.09 (7)	Mg1—C1—O1	36.99 (8)
N2—Mg1—C1^{i}	124.29 (6)	Mg1—C1—C2	93.82 (9)
O1^{i}—Mg1—C1	118.14 (7)	Mg1—C1—C6	136.86 (10)
N2^{i}—Mg1—C1	124.29 (6)	O1—C1—C2	119.08 (13)
C1—Mg1—C1^{i}	113.81 (7)	O1—C1—C6	122.22 (12)
O1^{i}—Mg1—N2^{i}	95.04 (6)	N2—C15—C2	114.19 (12)
O1^{i}—Mg1—C1^{i}	25.13 (6)	N2—C17—C18	110.99 (11)
N2^{i}—Mg1—C1^{i}	77.95 (6)	N2—C17—C22	116.10 (12)

Symmetry code(s): (i) -*x*, *y*, -*z*+1/2.

Table S3. Selected hydrogen-bond parameters

D—H···*A*	*D*—H (Å)	H···*A* (Å)	*D*···*A* (Å)	*D*—H···*A* (°)
C12—H12B···O1	0.98	2.32	3.01 (2)	126
C14—H14B···O1	0.98	2.40	3.06 (2)	125

[i] Oxford Diffraction (2006). *CrysAlis CCD* and *CrysAlis RED*. Versions 1.171.31. Oxford Diffraction Poland, Wroclaw, Poland.

[ii] Bruker (2003). *SHELXTL*. Version 6.14. Bruker AXS Inc., Madison, Wisconsin, USA.