Supplementary Information

Chiral polymers by iterative tandem catalysis

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S-1. Synthetic procedures

Materials

(*S*)-6-MeCL (ee = 98%) was synthesized by a double enzymatic ring-opening ring-closure procedure.[1] Benzyl alcohol (BA) was purchased from Aldrich and distilled from CaH_2 before use. Novozym 435 was purchased from Novozymes A/S. All solvents were stored on dry molecular sieves (3 Å) to remove traces of water. All other chemicals were purchased from Aldrich and used as received unless otherwise noted.

Analytical methods

^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury Vx 400 spectrometer (400 Mhz for ^{1}H NMR, 101 MHz for ^{13}C NMR). Chiral gas chromatography (GC) was performed on a Shimadzu 6C-17A GC equipped with a Chrompack Chirasil-DEX CB (DF=0.25) column and an FID. Samples were injected using a Shimadzu AOC-20i autosampler. Injection and detection temperatures were set at 300 °C and separations were performed under isothermal conditions with the column temperature set at either 121 °C (6-MeCL) or 135 °C (6-EtCL), which afforded in all cases baseline separation of the enantiomers. Lactone conversions were determined by the internal standard method using either 1,3,5-tri-*tert*-butylbenzene (6-MeCL) or hexamethylbenzene (6-EtCL) as the internal standard. The ee was calculated as follows: ee = (R-S)/(R+S) where R and S represent the areas of the GC peaks of the *R*- and *S*-enantiomer, respectively. MALDI-TOF MS spectra were recorded on a PerSeptive Biosystems Voyager DE PRO spectrometer using a 50:50 mixture of α-cyano-4-hydroxycinnamic

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[1] Manuscript in preparation.

acid (CHCA) and trans-2-[3-(4-*tert*-butylphenyl)-2-methyl-2-propenylidene]malononitrile (DCTB) as a matrix. Gel permeation chromatography (GPC) was carried out on a Shimadzu HPLC system equipped with a Shimadzu LC-10AD VP pump, a Shimadzu RID-10A differential refractometer detector and two PL gel columns (mixed C and mixed D, 10 μm, 300 × 7.5 mm, Polymer Laboratories), using THF as the eluent. All molecular weights are given relative to polystyrene standards. Optical rotations were measured in chloroform on a Jasco DIP-370 polarimeter at a wavelength of 589 nm (NaD-line) using either a 5 cm or a 10 cm cuvette at a concentration of 0.025 g/mL at 25 °C.

Synthesis of -substituted caprolactones

6-MeCL and 6-EtCL were synthesized by Baeyer-Villiger oxidation of the corresponding ketone as described previously.[2] NMR and GC data are summarized below. Due to the limited selectivity of the oxidation, a small amount of the -methylated lactone is formed. In the synthesis of 6-MeCL and 6-EtCL this amounts to 5% of 2-MeCL and 3% of 2-EtCL, respectively. Lipase catalyzed ring-opening of these substrates is much slower than that of the -methylated lactones. In ITC of 6-MeCL, 2-MeCL eventually reacts as the conversion of 6-MeCL increases. However, this does not affect the reaction as is proven by ITC of (*S*)-6-MeCL (Table 1, entry 1), where no 2-MeCL is present. In ITC of 6-EtCL, no conversion of 2-EtCL is observed.

[2] L. Kondaveti, T. F. Al-Azemi, K. S. Bisht, *Tetrahedron: Asymmetry* 2002, **13**, 129.

6-Methyl- -caprolactone (6-MeCL)

bp = 58-60 °C/0.6 Torr. ^{1}H NMR (CDCl$_3$):   4.45 (m, 1H, C*H*OC=O); 2.60 (m, 2H, C*H*$_2$C=O); 1.90–1.40 (6H); 1.30 (d, 3H, C*H*$_3$). ^{13}C{^{1}H} NMR (CDCl$_3$):   175.4 (C=O); 76.60; 36.0; 34.8; 28.0; 22.7; 22.4. GC retention time: (*S*)-6-MeCL = 9.3 min; 2-MeCL = 10.1 min; (*R*)-6-MeCL = 10.5 min at 121 ºC.

6-Ethyl- -caprolactone (6-EtCL)

^{1}H NMR (CDCl$_3$):   4.17 (m, 1H, C*H*OC=O); 2.64 (m, 2H, C*H*$_2$C=O); 2.00–1.50 (8H); 0.99 (t, 3H, C*H*$_3$). ^{13}C{^{1}H} NMR (CDCl$_3$):   175.9 (C=O); 81.90; 35.1; 34.2; 29.5; 28.4; 23.2; 10.0. GC retention time: (*S*)-6-EtCL = 6.8 min; 2-EtCL = 7.1 min; (*R*)-6-EtCL = 7.4 min at 135 ºC.

Iterative tandem catalysis of 6-MeCL

In a typical experiment a solution of 1,6-heptanediol (3 mg; 0.02 mmol), 6-MeCL (0.65 g; 5.1 mmol), 2,4-dimethyl-3-pentanol (23 mg, 0.20 mmol) and 1,3,5-tri-*tert*-butylbenzene (51 mg; 0.21 mmol) in toluene (2.5 mL) was stirred overnight at 50 °C over molecular sieves (3 Å) to remove traces of water. A Schlenk tube was charged with Novozym 435 (135 mg), catalyst **2** (37 mg, 0.04 mmol) and molecular sieves (3 Å) and put overnight in a vacuum oven (10 mm Hg) at 50 °C in presence of P$_2$O$_5$. The substrate solution was then added to the Schlenk tube and the reaction mixture was stirred at 70 ºC under an argon atmosphere for the indicated period of time. Small aliquots of reaction mixture were taken for GC analysis.

After reaction the mixture was diluted with toluene (10 mL) and the enzyme and molecular sieves were removed by centrifugation and subsequent filtration over a 1 µm PTFE syringe filter. The reaction mixture was concentrated in vacuo and the 2,4-

dimethyl-3-pentanol and 1,3,5-tri-*tert*-butylbenzene were removed by distillation using a Kugelrohr apparatus (T = 100 °C, 0.04 mm Hg). Crude yield: 449 mg (68%). After distillation, all end-groups are present as ketones, presumably due to Ru-catalyzed dehydrogenation during work-up. The crude product was dissolved in $CHCl_3$ (3 mL) and the catalyst was removed by precipitation in methanol (60 mL) and subsequent centrifugation. Yield: 134 mg (20%). $[\alpha]_D^{25} = -7.7°$ (*c* 2.44, $CHCl_3$). ^1H NMR ($CDCl_3$): 4.89 (m, C*H*CHOCO); 4.05 (t, C*H*$_2$OCO); 2.27 (t, C*H*$_2$COO); 2.14 (s, CH_2COCH_3); 1.70–1.25 (C*H*$_2$); 1.19 (d, C*H*$_3$). $^{13}C\{^1H\}$ NMR ($CDCl_3$): 173.3; 70.8; 35.8; 34.7; 25.2; 25.0; 20.1.

Synthesis of 1,6-heptanediol

An oven-dried 250 mL Schlenk flask was charged with $LiAlH_4$ (1.5 g, 39.5 mmol) and freshly distilled Et_2O (75 mL) and placed under an argon atmosphere. A solution of 6-MeCL (8.0 g, 62.4 mmol) in freshly distilled THF (15 mL) was added dropwise via an addition funnel. After the addition was complete the mixture was heated at reflux for 1.5 h. The reaction mixture was then cooled to 0 °C in an ice-water bath and quenched by subsequent addition of water (3 mL), 3 M NaOH (3 mL) and water (9 mL). The reaction mixture was allowed to slowly warm to room temperature. The white solids were collected by vacuum filtration and washed with Et_2O. Concentration of the filtrate in vacuo yielded the crude product which was further purified by destillation. Yield: 2.9 g (35%). ^1H NMR and ^{13}C NMR data are in good agreement with those reported in literature.[3] ^1H NMR ($CDCl_3$): 3.78 (m, 1H, CH_3C*H*OH); 3.62 (t, *J* = 6.6Hz, 2H, C*H*$_2$OH); 1.81 (br, 2H, -O*H*) 1.56 (m, 2H); 1.48–1.32 (6H); 1.17 (d, *J* = 6.2Hz, 3H) $^{13}C\{^1H\}$ NMR ($CDCl_3$): 68.1; 62.8; 39.3; 32.7; 25.8; 25.6; 23.6.

[3] V. K. Yadav, K. Veejendra, K. G. Babu, M. Mittal, *Tetrahedron* 2001, **57**, 7047.

*Methanolysis of poly-(*R*)-6-MeCL*

The $ee_{polymer}$ and the amount of 1,6-heptanediol were determined by chiral GC analysis after acid catalyzed methanolysis of the polymer.[4] The $ee_{polymer}$ of poly-(*R*)-6-EtCL was determined analogously, while the amount of 1,6-octanediol was determined by ^{1}H NMR.

[4] B. A. C. van As, J. van Buijtenen, A. Heise, Q. B. Broxterman, G. K. M. Verzijl, A. R. A. Palmans, E. W. Meijer, *J. Am. Chem. Soc.* 2005, **127**, 9964.

S-2. Reference experiments with catalyst 1.
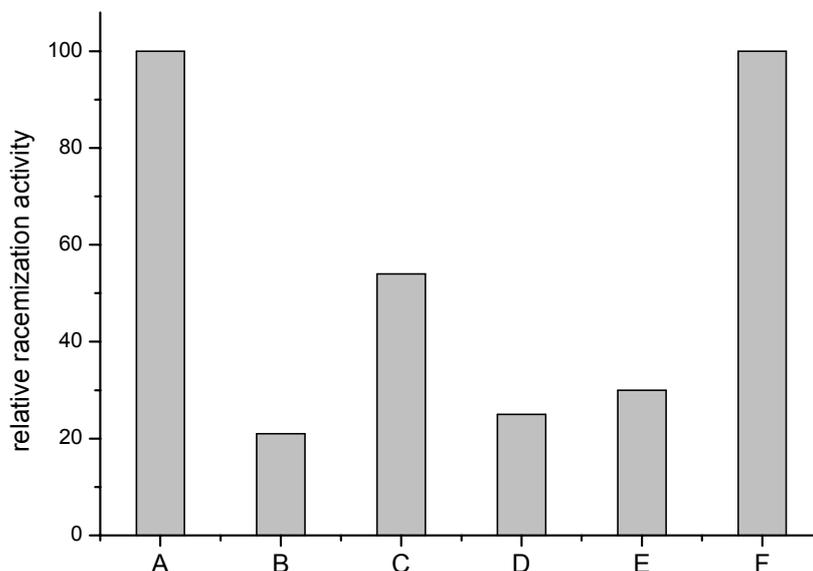
Figure S-1: Racemization activity of catalyst **1** at 70 ºC in the presence of (B) 1 eq of 6-MeCL, (C) 1 eq of ε-caprolactone (CL), (D) 1 eq of δ-hexalactone, (E) 1 eq of δ-valerolactone, and (F) 1 eq of pentadecalactone relative to a blanc experiment (A). Catalyst **1** was preformed at 70 ºC in 2-propanol/toluene (1:2) and 0.01 mmol of the catalyst was then added to a solution of (*S*)-1-phenylethanol (2 mmol) and the lactone (2 mmol) in toluene (2 mL).
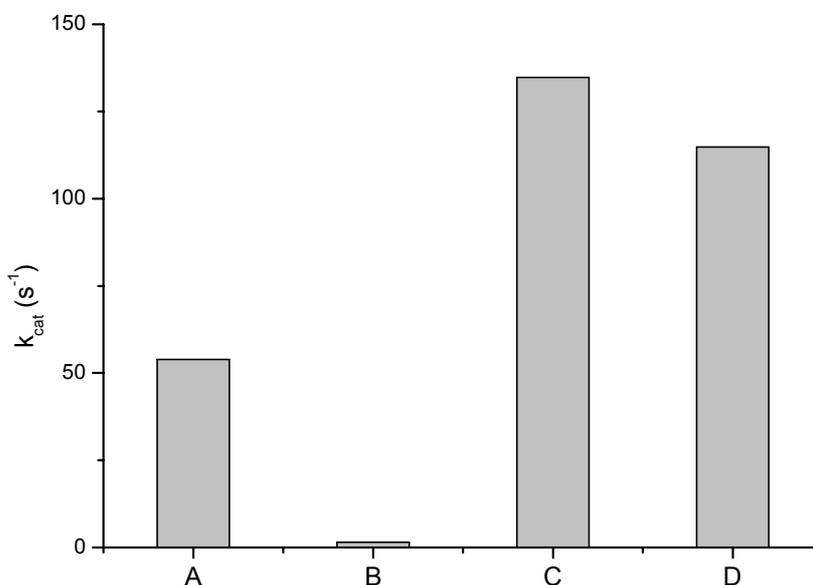
Figure S-2: Enzymatic activity (k_{cat}) in the ring-opening of (A) CL, (B) CL in the presence of 80 mg of K_2CO_3, (C) pentadecalactone (PDL), and (D) PDL in the presence of 80 mg of K_2CO_3. Conditions: BA (0.2 mmol), lactone (3 mmol), tri-*tert*-butylbenzene and Novozym 435 (25 mg) in toluene (2 mL) at 70 ºC. The enzyme and (if applicable) K_2CO_3 were first stirred overnight in toluene at 70 ºC; a stock solution of the lactone and BA was then added to start the reaction.
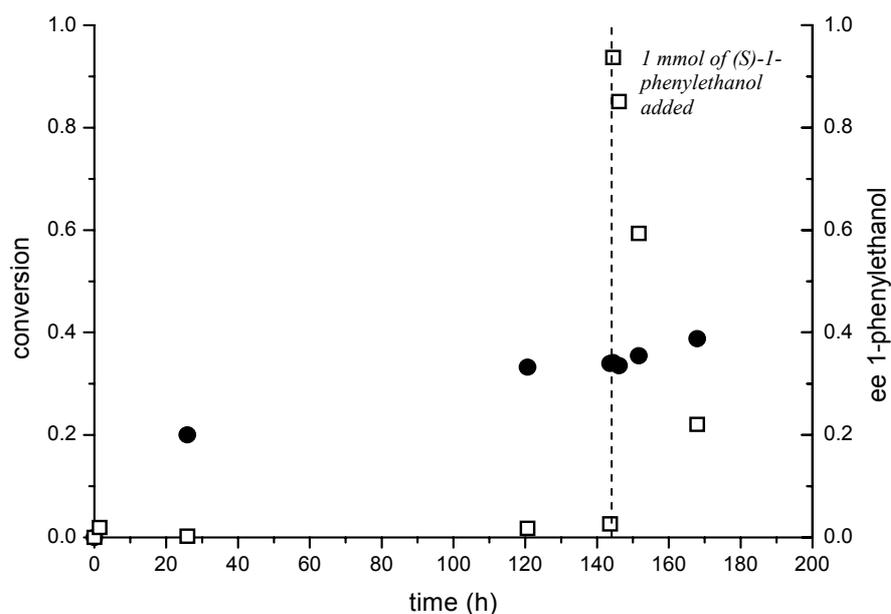
Figure S-3: Conversion of (*S*)-6-MeCL (•, left axis) and the ee of 1-phenylethanol (•, right axis) in an ITC experiment with catalyst **1**. Conditions: catalyst **1** (0.044 mmol), Novozym 435 (57 mg), (*S*)-6-MeCL (3.9 mmol), (*rac*)-1-phenylethanol (0.41 mmol), tri-*tert*-butylbenzene (0.33 mmol) and DMP (9 mmol) in toluene (4 mL) at 70 ºC. After 145 h, 1 mmol of (*S*)-1-phenylethanol (ee > 99%) is added to the reaction to determine the racemization activity. A TOF of 1.4 h^{-1} is calculated vs a TOF of 200-300 h^{-1} in a typical racemization of (*S*)-1-phenylethanol (no 6-MeCL).
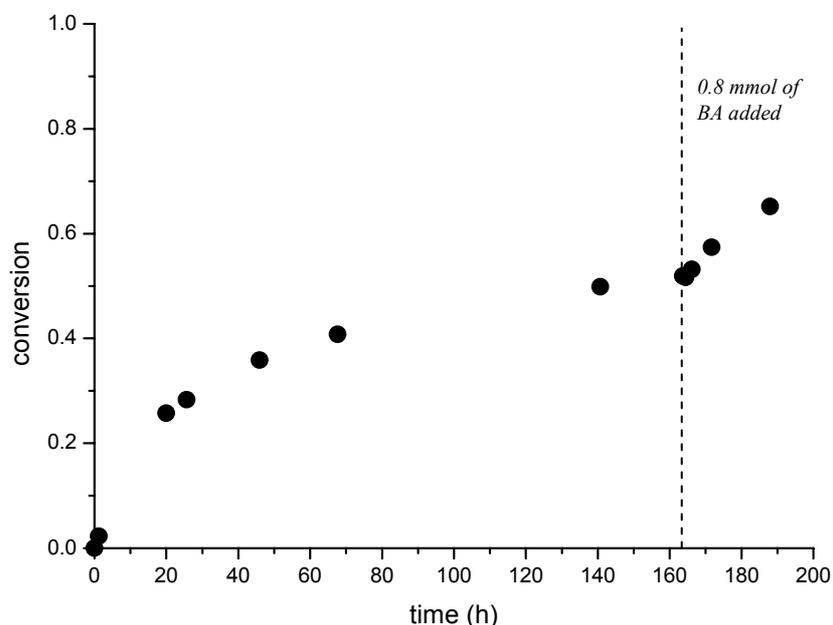
Figure S-4: ITC of (*S*)-6-MeCL. Conditions: catalyst **1** (0.046 mmol), Novozym 435 (57 mg), (*S*)-6-MeCL (3.9 mmol), BA (0.42 mmol), tri-*tert*-butylbenzene (0.33 mmol) and DMP (13 mmol) in toluene (4 mL) at 70 ºC. After 164 h, 0.8 mmol of BA is added to determine the enzymatic activity. A TOF of 155 h^{-1} is calculated vs 4.0·10^{4} h^{-1} in a typical experiment with 6-MeCL/BA = 4 at 70 ºC.

S-3. ITC of (*S*)-6-MeCL, M/I = 50, M_p vs time (h)
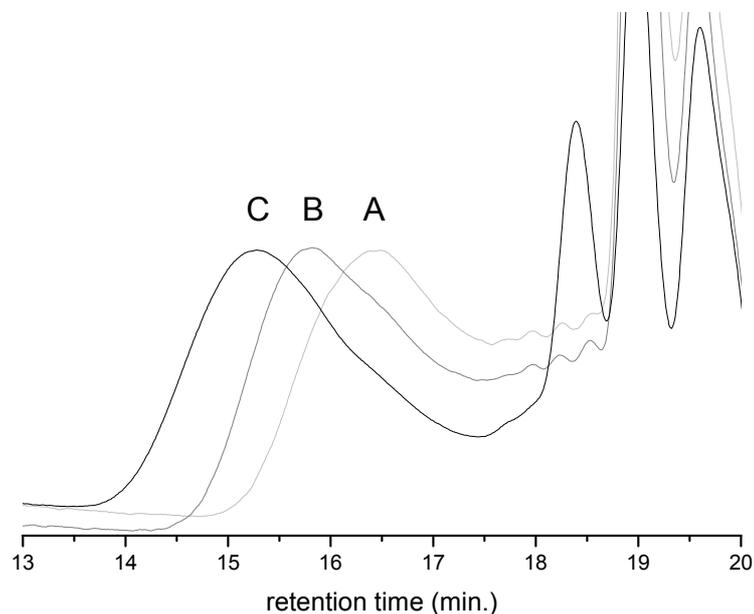
Figure S-5: SEC traces after (A) 126 h (2.7 kDa), (B) 192 h (4.7 kDa), and (C) 318 h (7.8 kDa) for ITC of (*S*)-6-MeCL, M/I = 50 (Table 1, entry 1).
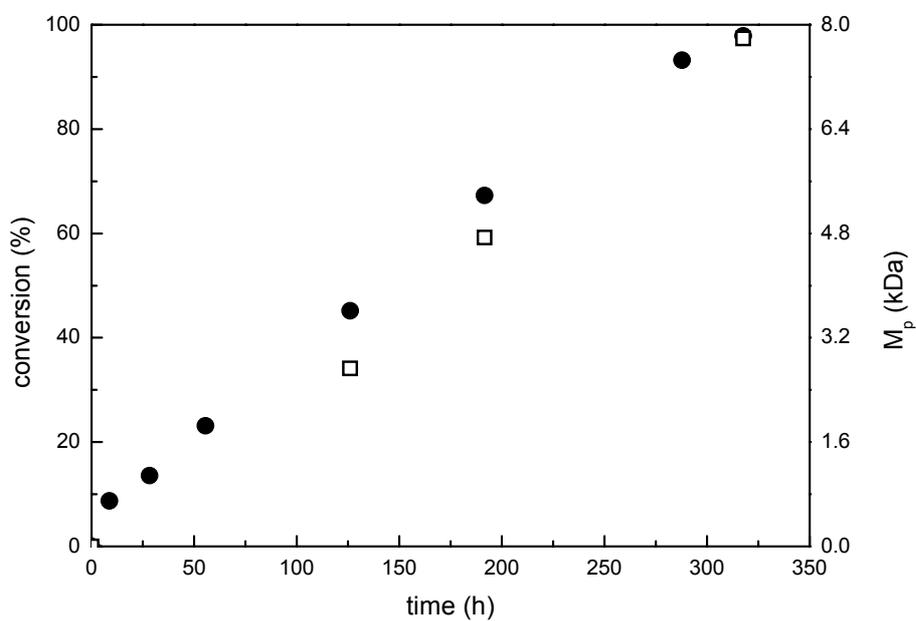
Figure S-6: Conversion (●, left axis) and M_p (□, right axis) vs time for ITC of (*S*)-6-MeCL, M/I = 50 (Table 1, entry 1).

S-4. ^{1}H NMR spectrum of 1,6-heptanediol initiated poly-(R)-6-MeCL (Table 1, entry 8)
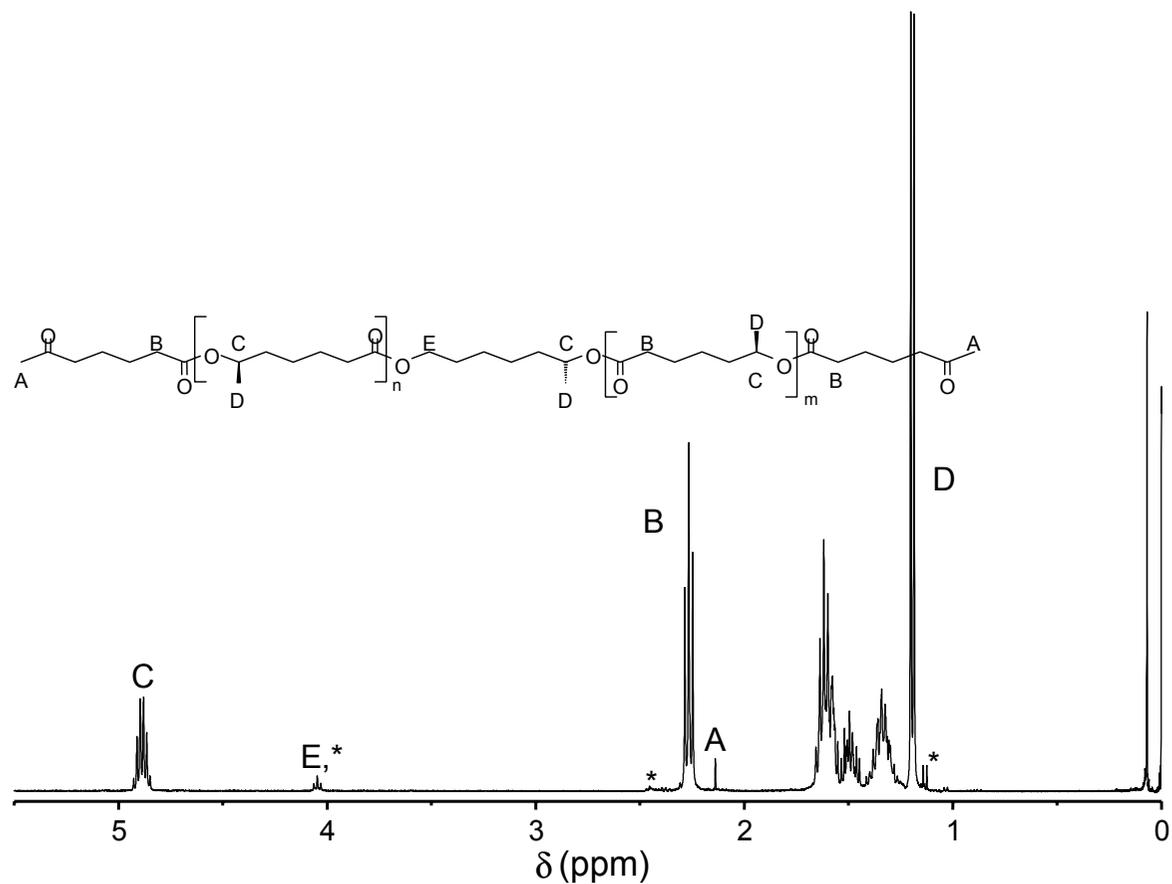
Figure S-7: ^{1}H NMR spectrum of 1,6-heptanediol initiated poly-(R)-6-MeCL (Table 1, entry 8). After work-up of the polymer using a Kugelrohr apparatus, all end-groups are present as ketones, presumably due to Ru-catalyzed dehydrogenation during work-up. Signals with * originated from ring-opening of 2-MeCL, which leads to a monomeric unit with a methyl in the α-position.

S-5. MALDI-TOF MS spectrum of 1,6-heptanediol initiated poly-(*R*)-6-MeCL
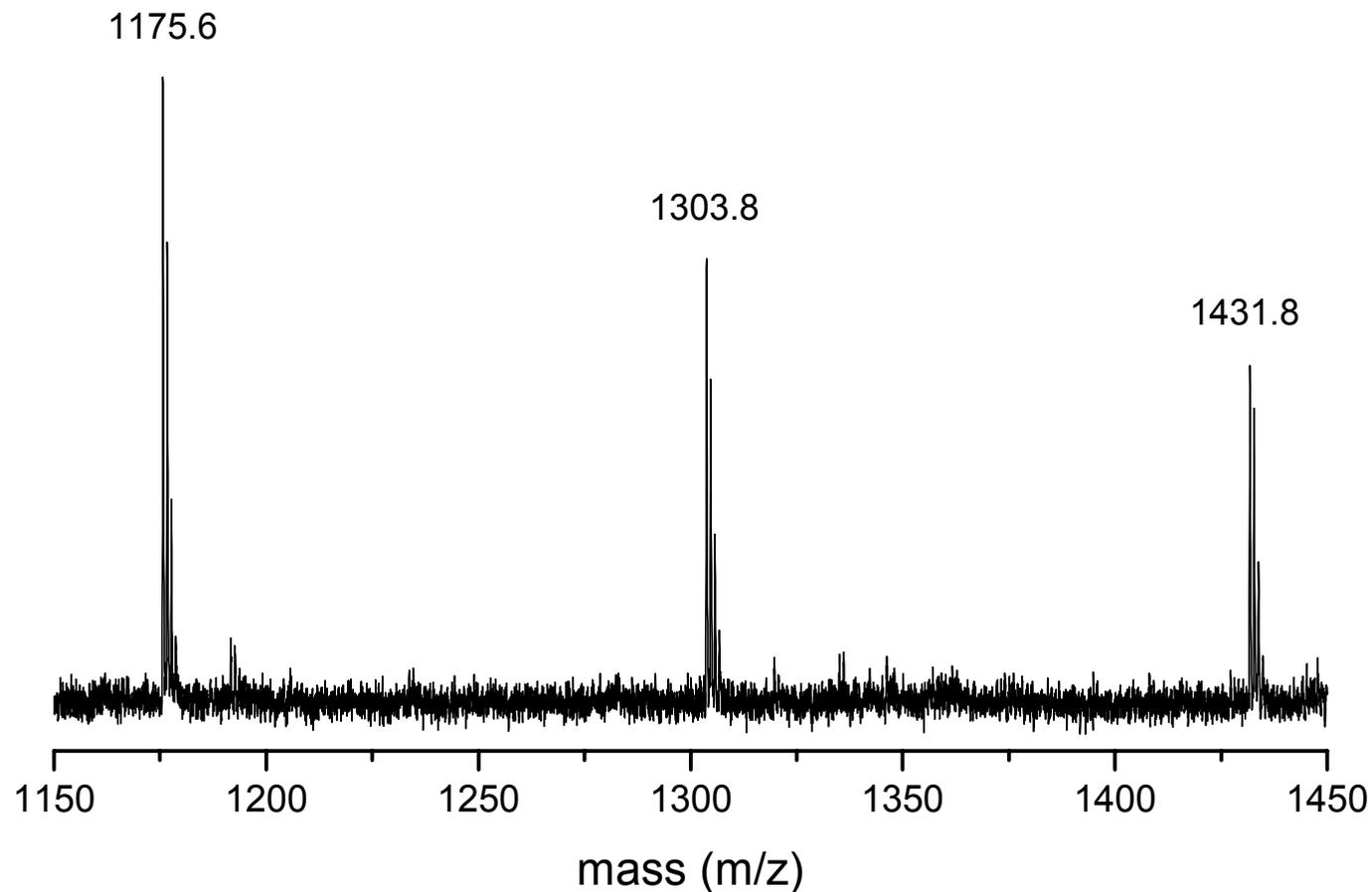
Figure S-8: MALDI-TOF MS spectrum of 1,6-heptanediol initiated poly-(*R*)-6-MeCL (M/I = 102, 0.07 mmol Ru, 26 mg Novozym 435 / mmol 6-MeCL, M_p = 13.6 kDa, $ee_{polymer}$ = 85%), measured in reflective mode. After work-up of the polymer using a Kugelrohr apparatus, all end-groups are present as ketones, presumably due to Ru-catalyzed dehydrogenation during work-up. As a result, diol initiated oligomers have the same molecular masses as ring structures, which are always formed to some extent. The peaks observed correspond to the Na^+ ionized oligomers.