Chiral polymers by iterative tandem catalysis†

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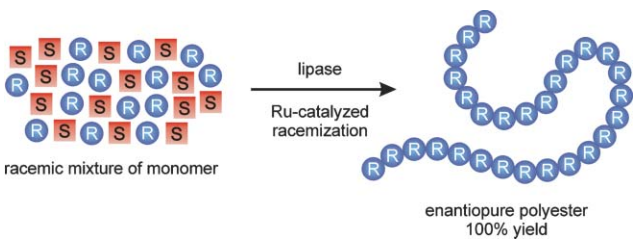
Racemic ω-substituted caprolactones can be completely converted into chiral polyesters of remarkable MW and high ee by combining lipase-catalyzed ring-opening polymerization with Ru-catalyzed racemization.

Owing to the inherent chirality of natural systems, there is an ever increasing demand for enantiopure compounds. One of the most frequently used methods to obtain these products involves resolution of the corresponding racemate with chemoenzymatic dynamic kinetic resolution (DKR) as a particularly elegant example.[1,2] In this application of tandem catalysis, *in situ* racemization enables complete conversion of the racemate into the desired enantiomer.

We and others have recently shown that, by employing tandem catalysis, a racemic monomer can be converted into chiral oligomers or low MW polymers.[3] The oligomerization of 6-methyl-ε-caprolactone (6-MeCL) leading to oligo-(*R*)-6-MeCL was demonstrated. Novozym 435 catalyzed ring-opening of this ω-substituted lactone is *S*-selective, yielding an *S*-secondary alcohol, which, following Kazlauskas' rule, is the slower reacting enantiomer in lipase-catalyzed reactions (typically $E > 100$).[4] *In situ* Ru-catalyzed racemization of the terminal secondary alcohol is, therefore, required for propagation, and iterative operation of these two reactions enables polymerization. This concept was presented as iterative tandem catalysis (ITC) (Scheme 1). Ru complex **1** (Fig. 1) was used as the racemization catalyst and oligo-(*R*)-6-MeCL with a degree of polymerization (DP) of 3.2 was obtained from (*S*)-6-MeCL. Ru-catalyzed hydrogenolysis of



Scheme 1 Example of iterative tandem catalysis.

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† Electronic supplementary information (ESI) available: Experimental details, reference experiments with catalyst **1**, ^{1}H NMR, MALDI-TOF MS and additional GPC data for polymers obtained by ITC. See DOI: 10.1039/b606241e

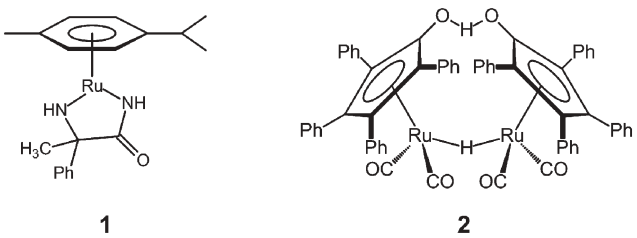
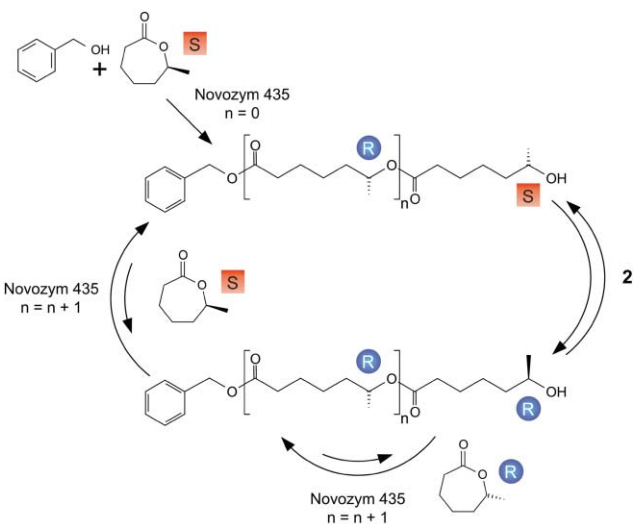


Fig. 1 Complexes **1** and **2**.

6-MeCL, yielding 1,6-heptanediol was identified as a side-reaction, leading to the initiation of additional chains.[5] The present challenge is to perform a large number of racemization–ring-opening sequences in order to obtain high molecular weight polymers, while the concentration of the substrate alcohol is dramatically lower than in a typical DKR. Here, we describe the complete conversion of (*rac*)-6-MeCL into poly-(*R*)-6-MeCL (Scheme 2). By optimizing both catalytic processes, we were able to obtain polymers of remarkable MW and high ee.

To enable a better understanding of the reaction, experiments with (*S*)-6-MeCL as the substrate were performed. The well-known SHVO catalyst (**2**, Fig. 1) was employed for the racemization and 2,4-dimethyl-3-pentanol was added as a hydrogen donor to counter the effect of dehydrogenation of the end-groups.[6,7] Polymerization of (*S*)-6-MeCL was complete within 318 h with benzyl alcohol (BA) as the initiator and a monomer-to-initiator molar ratio (*M*/*I*) of 50, yielding poly-(*R*)-6-MeCL with a



Scheme 2 Polymerization of 6-MeCL by iterative tandem catalysis.

Table 1 Iterative tandem catalysis of 6-MeCL and 6-EtCL[a]

Entry	Monomer	(*M*/*I*)	Ru/ mmol	Nov435/ mg mmol^{-1}	Time/ h	Conv. (%)[b]	$k_i \times 10^4$/ h^{-1} [c]	$ee_{polymer}$ (%)[d]	M_p/ kDa	Diol (mol%)[e]
1[f]	(*S*)-6-MeCL	50	0.06	13	318	98	32.2	86	8.2	0.58
2	(*rac*)-6-MeCL	40	0.06	7	220	99	53.8	92 (94)	9.4	0.33
3[g]	(*rac*)-6-MeCL	38	0.12	14	103	94	84.7	89	8.2	0.20
4	(*rac*)-6-MeCL	44	0.03	7	507	>99	27.9	85	11.0	0.28
5	(*rac*)-6-MeCL	40	0.06	13	147	97	62.2	87	9.4	0.22
6[h,i]	(*rac*)-6-MeCL	100	0.06	25	244	>99	43.5	83	14.5	0.30
7[h,i]	(*rac*)-6-MeCL	102	0.12	7	504	92	n.a.[j]	96	9.8	0.75
8[h,k]	(*rac*)-6-MeCL	206	0.07	27	170	98	56.6	76	20.8	0.69[l]
9[m]	(*rac*)-6-EtCL	39	0.07	14	241	99	51.5	93	6.4	0.44[n]

[a] Unless otherwise noted, Ru catalyst **2**, Novozym 435, 6-MeCL (5 mmol), BA (0.125 mmol), DMP (0.25 mmol) and 1,3,5-tri-*tert*-butylbenzene (0.20 mmol, internal standard) were stirred in toluene (2.5 mL) at 70 °C under an argon atmosphere. [b] Average conversion of both enantiomers, determined by GC. [c] Zero-order rate constant for the conversion of the *S*-lactone. [d] Determined by chiral GC after methanolysis of the polymer; the value obtained is impacted by the presence of the end-groups, which are racemic at best; the ee given between brackets is corrected for the amount of alcohol end-groups in ^{1}H NMR. [e] Amount of lactone (mol%) converted to the corresponding diol; determined by chiral GC after methanolysis of the polymer. [f] (*S*)-6-MeCL: 2.5 mmol. [g] DMP: 0.125 mmol. [h] DMP: 0.20 mmol. [i] BA: 0.05 mmol. [j] Zero-order kinetics are not obeyed. [k] 0.025 mmol of 1,6-heptanediol (initiator). [l] Includes 0.48 mol% that was added as the initiator. [m] 5 mmol of 6-EtCL. [n] Obtained from ^{1}H NMR.

promising $ee_{polymer}$ = 86% (Table 1, entry 1). The low rate of reaction compared to DKR (typically complete after 48 h with catalyst **2**) is attributed to the low concentration of the terminal alcohol as well as to the iterative nature of the system. Hydrogenolysis led to the formation of 0.58 mol% of 1,6-heptanediol, reducing the MW of the polymer by ~20%. SEC analysis of the crude polymer revealed M_p = 8.2 kDa. There is a trade-off between high MW and high $ee_{polymer}$ as a high rate of racemization, required for high ee, leads to a higher rate of hydrogenolysis, thereby reducing MW.

In ITC, Ru-catalyzed racemization leads to net conversion of the *S*-alcohol into the *R*-alcohol, while the lipase subsequently adds another monomeric unit. The mechanism of lipase catalyzed ring-opening polymerization (ROP) is generally accepted to proceed *via* an acyl-enzyme intermediate at a Ser-OH residue in the active site of the lipase.[8] Formation of this intermediate is normally rate-determining in the enzymatic reaction. However, when the nucleophile concentration is very low, nucleophilic attack on the activated substrate (deacylation) may become rate-limiting. We observe an approximately zero-order rate of consumption of (*S*)-6-MeCL (Fig. 2). If the overall effect of dehydrogenation and hydrogenolysis can be neglected, the concentration of alcohol

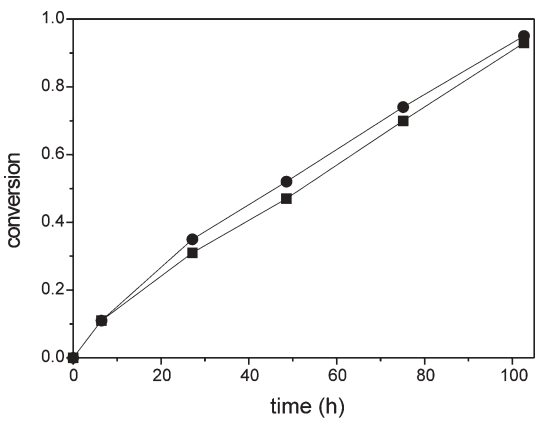


Fig. 2 Conversion of (*S*)-6-MeCL (■) and (*R*)-6-MeCL (●) *vs.* time in a typical ITC experiment with 40 eq. of 6-MeCL w.r.t. BA, 1.2 mol% of **2** and 14 mg Novozym 435 per mmol of 6-MeCL (Table 1, entry 3).

end-groups will be constant and rate-limiting nucleophilic attack (ee = 0%) or racemization (ee > 99%) will result in a constant ee of the end-groups and zero-order kinetics. At intermediate ee, increasing the amount of either one of the catalysts will accelerate the polymerization of (*S*)-6-MeCL as speeding up one reaction increases the substrate concentration for the other.[9] Therefore, zero-order kinetics will result, if the formation of the acyl-enzyme intermediate is significantly faster than the racemization and/or the nucleophilic attack. At high lactone conversion, formation of the acyl-enzyme intermediate is expected to become rate-limiting, resulting in a deviation from zero-order kinetics. This behavior is indeed observed.

We then switched to (*rac*)-6-MeCL as the substrate. The reversibility of the enzymatic reaction in combination with the low selectivity of the ring-opening of the lactone leads to net insertion of (*R*)-6-MeCL.[10] Coincidentally, comparable rates of reaction for both enantiomers are observed in a typical experiment (Fig. 2). With 0.6 mol% of **2** (0.06 mmol Ru), 7 mg Novozym 435 per mmol of 6-MeCL and *M*/*I* = 40, (*rac*)-6-MeCL was polymerized within 220 h with complete conversion of both enantiomers, yielding a high $ee_{polymer}$ = 92% (Table 1, entry 2). A k_i of 53.8 × 10^{-4} h^{-1} was calculated for the zero-order conversion of (*S*)-6-MeCL. Experiments with double and half the amount of **2** (Table 1, entries 3–4), resulted in correspondingly higher and lower rates, respectively. A reaction with double the amount of enzyme (Table 1, entry 5) was only slightly faster, indicating that the reaction is mainly limited by the racemization. No clear effect of the Ru loading on diol formation was observed. Hydrogenolysis resulted in only 0.2–0.3 mol% of 1,6-heptanediol, reducing the MW of the polymer by ~10%.

In order to evaluate whether polymers of higher MW are accessible, the reaction was performed at *M*/*I* = 100, both with extra enzyme and with a double amount of Ru (Table 1, entries 6 and 7, respectively). The impact of diol formation is more profound at higher *M*/*I*, limiting the M_p of entry 6 to 14.5 kDa. The k_i is only slightly lower than for entry 2, indicating that the effect of the lower concentration of end-groups is limited. As expected, a much higher $ee_{polymer}$ (96%) is obtained for entry 7 as the enzymatic reaction becomes rate-limiting. Concomitantly, hydrogenolysis is significantly increased (0.75 mol% of diol)

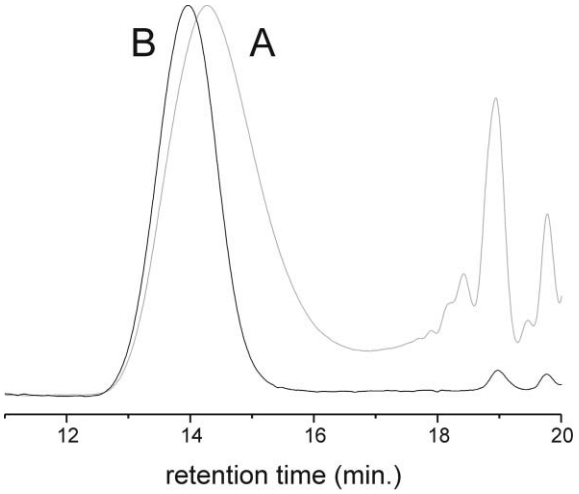


Fig. 3 SEC traces of polymer obtained by ITC of (*rac*)-6-MeCL (Table 1, entry 8) before (A) and after (B) precipitation from methanol (M_n = 25.0 kDa, PDI = 1.23).

leading to a lower M_p = 9.8 kDa. An experiment with 1,6-heptanediol as the initiator and M/I = 206 gave a polymer with a high M_p = 20.8 kDa. The $ee_{polymer}$ of the product of this unoptimized reaction was 76% (Table 1, entry 8). This polymer was precipitated from methanol to remove the catalyst (yield 34%) and the number-averaged MW obtained from SEC analysis was 25.0 kDa with a PDI of 1.23 (Fig. 3).

Gratifyingly, ITC of 6-ethyl-ε-caprolactone (6-EtCL) also gave the chiral polymer with a high $ee_{polymer}$ = 93% (Table 1, entry 9). The amount of enzyme was increased to 14 mg $mmol^{-1}$ as ethyl substituted secondary alcohols exhibit significantly lower transesterification rates than their methyl substituted analogs using Novozym 435 as the catalyst.[11] With this increased loading, the rate of reaction is comparable to that of 6-MeCL, resulting in a polymer with M_p = 6.4 kDa.

In conclusion, we have, for the first time, obtained chiral polymers of high MW and high $ee_{polymer}$ from racemic monomer by tandem catalysis. Both 6-MeCL and 6-EtCL were successfully converted into the chiral polymer by iterative tandem catalysis. Furthermore, the kinetics of the reaction were described and with this knowledge, the reaction conditions could be optimized. Successful polymerizations with more than 100 consecutive and iterative enzymatic additions and Ru-catalyzed racemizations on one polymer chain were realised.

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7 High conversions and polymers of significant length could not be obtained using Novozym 435 in combination with racemization catalyst **1**. Closer investigation revealed that both catalysts were almost completely inhibited in one-pot ITC of 6-MeCL by the combination of K_2CO_3 (used to activate the Ru complex) with the highly polar lactone (see Electronic Supplementary Information†).

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9 Faster racemization (the rate of reaction is proportional to the concentration of *S*-alcohol) will result in a decrease of the ee of the end-groups and, therefore, a higher concentration of the *R*-alcohol. Faster nucleophilic attack (substrate = *R*-alcohol) will result in a higher ee and a higher concentration of the *S*-alcohol.

10 At 60 °C an *E*-value of 12 was obtained (6-MeCL/BA = 5, toluene).

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