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Iterative Tandem Catalysis of Secondary Diols and Diesters to Chiral Polyesters

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Abstract: The well-known dynamic kinetic resolution of secondary alcohols and esters was extended to secondary diols and diesters to afford chiral polyesters. This process is an example of iterative tandem catalysis (ITC), a polymerization method where the concurrent action of two fundamentally different catalysts is required to achieve chain growth. In order to procure chiral polyesters of high enantiomeric excess value (*ee*) and good molecular weight, the catalysts employed need to be complementary and compatible during the polymerization reaction. We here show that Shvo's catalyst and Novozym 435 fulfil these requirements. The optimal polymerization conditions of 1,1′-(1,3-phenylene) diethanol (1,3-diol) and diisopropyl adipate required 2 mol% Shvo's catalyst and 12 mg Novozym 435 per mmol alcohol group in the presence of 0.5 M 2,4-dimethyl-3-pentanol as the hydrogen donor. With these conditions, chiral polyesters were obtained with peak molecular weights up to 15 kDa, an *ee* value up to 99% and with 1–3% ketone end groups. Also with the structural isomer, 1,4-diol, a chiral polyester was obtained, albeit with lower molecular weight (8.3 kDa) and slightly lower *ee* (94%). Aliphatic secondary diols also resulted in enantio-enriched polymers but at most an *ee* of 46% was obtained with molecular weights in the range of 3.3–3.7 kDa. This low ee originates from the intrinsic low enantioselectivity of Novozym 435 for this type of secondary aliphatic diols. The results presented here show that ITC can be applied to procure chiral polyesters with good molecular weight and high *ee* from optically inactive AA–BB type monomers.

Keywords: enzyme catalysis · kinetic resolution · polymerization · racemization · ruthenium

Introduction

Tandem catalysis has attracted much interest in the past decade as an alternative to traditional step-by-step synthesis.[1–5] Reduction of waste, costs and energy are the primary driving forces for this development. A prominent example of tandem catalysis is the dynamic kinetic resolution (DKR) of racemic secondary alcohols or amines into enantiopure esters or amides in essentially 100% yield.[6,7] Extension of tandem catalysis to the field of polymer chemistry would allow for the synthesis of macromolecules of higher structural complexity.

Recently, we introduced the concept of iterative tandem catalysis (ITC). ITC is a novel polymerization strategy by which chain growth is effectuated by a combination of two (or more) intrinsically different catalytic processes that are both compatible and complementary.[8] Using ITC, a racemic mixture of monomers can be quantitatively turned into a homochiral polymer. Proof of principle was provided by the ITC of (*S*)-6-methyl-ε-caprolactone ((*S*)-6-MeCL). We showed that the lipase-catalyzed ring-opening of ω-substituted lactones, such as 6-MeCL, results in a ring-opening product bearing a secondary alcohol. Since lipases generally only accept the *R* enantiomer of a secondary alcohol as the nucleophile, propagation halts after the ring-opening of an (*S*)-6-MeCL molecule. Combining ruthenium-catalyzed racemization with lipase-catalyzed ring-opening enabled the two-pot oligomerization of (*S*)-6-MeCL.[8a] An efficient one-pot polymerization proved difficult using catalyst **1** (Figure 1). Recently, we achieved the synthesis of well-defined chiral poly((*R*)-6-methyl-ε-caprolactone) in one pot, with an *ee* up to 96% and M_n up to 25 kDa.[8b] This was realized by replacing racemization catalyst **1** by Shvo's catalyst, **2**.

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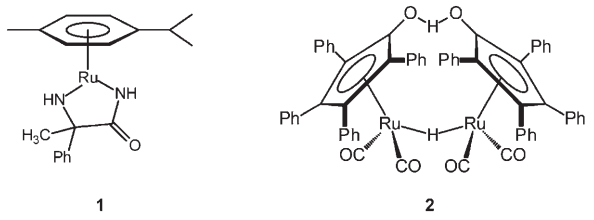
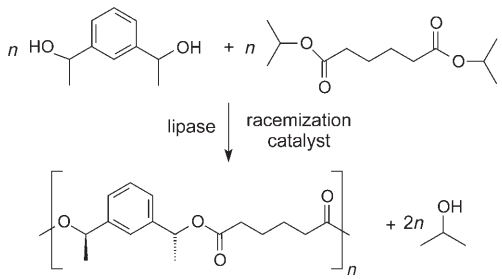


Figure 1. Racemization catalysts employed in ITC.

To broaden the applicability of ITC and to have easy access to a variety of chiral polyesters, we aimed at performing polycondensation type reactions with AA (secondary diols) and BB (diesters) type monomers, in analogy to the DKR of secondary alcohols. In contrast to the ITC of 6-MeCL, an AA–BB type system allows oligomerization to take place by the action of the lipase only since the R-secondary alcohols of the diols are readily esterified. However, polymers of reasonable molecular weight can only be attained when, at the same time, the remaining *S* alcohol groups undergo an inversion of the configuration by the racemization catalyst. Therefore, also in this polycondensation-type reaction, concurrent action of both the acylation and the racemization catalyst is required to procure polymers of good molecular weight, making an AA–BB polymerization under DKR conditions another example of ITC.

Recently, initial efforts on achieving such an extension of DKR were reported by Hilker et al. comprising 1,1′-(1,4-phenylene)diethanol and dimethyl adipate as the monomers and using Novozym 435 and complex **1** as the acylation and racemization catalysts, respectively.[9] Enantiomerically enriched oligomeric material (ratio *R*/*S* 33:1) was indeed obtained, although the molecular weight was moderate at best (3.0–4.0 kDa). It appeared that dehydrogenation of the alcohol end group to the ketone (creating chain stoppers) and lipase deactivation (requiring the addition of fresh lipase every 12 h) were primarily responsible for the lack of molecular weight built up.

Here, we report on our efforts to improve the catalytic performance of ITC in an AA–BB polycondensation system by selecting two catalysts that are compatible and complementary during the polymerization process. Novozym 435, *Candida antarctica* lipase B immobilized on a resin, was selected as the acylation catalyst since it is well studied in DKR processes and has proven itself as a robust biocatalysts with a high enantioselectivity for benzylic *R* secondary alcohols.[9,10] Shvo's catalyst **2** was chosen as the racemization catalyst because we recently found it showed an excellent compatibility with Novozym 435 in the ITC of 6-MeCL.[8b] As model compounds, 1,1′-(1,3-phenylene)diethanol (1,3-diol) and diisopropyl adipate (DIA) were employed as the secondary diol and the diester, respectively (Scheme 1). In order to explore the generality of ITC in polycondensation type reactions, the 1,4-substituted structural isomer 1,1′-(1,4-phenylene)diethanol (1,4-diol) and aliphatic secondary diols were evaluated as well.



Scheme 1. ITC of 1,1′-(1,3-phenylene)diethanol (1,3-diol) and diisopropyl adipate (DIA).

Results and Discussion

ITC of 1,3-diol and DIA: For the ITC of 1,3-diol and DIA, we selected Shvo's catalyst **2** as the racemization catalyst and Novozym 435 as the acylation catalyst (Table 1, entry 1). The reaction was performed in toluene at 70 °C using 1 mol % of Ru catalyst **2** and 23 mg Novozym 435 mmol alcohol groups. In order to shift the equilibrium to polymers, a reduced pressure of 280 mbar was applied to remove isopropanol. 2,4-Dimethyl-3-pentanol (DMP) was added as a hydrogen donor to suppress dehydrogenation of

Table 1. Results of ITC of secondary diols and DIA.[a]

Entry[a]	Monomer	Ru [mol %][b]	Nov435 [mg mmol^{-1}][b]	DMP [M]	*t* [h]	Conv. [%][c]	$k_i \times 10^3$ [h^{-1}][d]	ee_p [%]	M_n [kDa]	Ketone [%]
1	1,3-diol	1	23	0.7	215	98	15.8	92	10.7	0.5
2	1,4-diol	2	23	0.5	171	97	9.1	94	8.3	2.4
3	**3a**	2	23	0.5	390	98	6.5	43	3.3	n.d.
4	**3b**	2	23	0.5	390	94	4.6	41	3.7	n.d.
5	**3c**	2	23	0.5	310	98	9.1	46	3.7	n.d.
6	1,3-diol	0.5	23	0.5	121	97	18.3	93	7.2	2.2
7	1,3-diol	1	12	0.5	121	98	25.8	98	5.2	2.2
8	1,3-diol	1	46	0.5	121	98	26.9	92	7.7	2.3
9	1,3-diol	2	23	0.5	121	99	48.5	95	12.3	1.9
10	1,3-diol	2	23	0.1	118	95	33.0	99	8.4	2.2
11	1,3-diol	4	23	0.1	118	99	26.9	99	15.4	3.1
12	1,3-diol	2	23	0.2	118	98	38.3	98	14.0	1.8
13	1,3-diol	1	23	0.7	223	96	12.0	95	4.5	0.8
14	1,3-diol	1	23	3.9	168	57	1.7	n.d.	n.d.	n.d.
15[e]	1,3-diol	2	23	0.5	98	78	12.5	n.d.	n.d.	n.d.
16[e]	1,3-diol	6	23	0.5	98	86	13.9	n.d.	n.d.	n.d.

n.d. = not determined. [a] Conditions, unless otherwise noted: 0.87 mmol diol, 0.87 mmol DIA, 3 Å MS, 2 mL dry toluene, $T = 70$ °C; $p = 280$ mbar (argon). [b] The catalyst loadings are calculated with respect to the total amount of alcohol groups. [c] Conversion is based on the total conversion of alcohol groups. [d] The initial rate constant k_i was determined by linear regression from the logarithmic plot of (1−conversion of alcohol groups) versus time. [e] 6 mL toluene was used instead of 2 mL.

end groups which results in inactive ketone chain ends. This strategy was successfully employed by us previously.[8]

Figure 2a shows the time-conversion plot for the acylation of the alcohol groups. Initially, the reaction proceeds quickly, with a conversion of 61% reached within 24 h. At this point, all *R* secondary alcohol functionalities have been acylated and the racemization reaction has now become rate-limiting. Although slower, conversion of the alcohol groups to ester groups proceeded steadily beyond this point: after 215 h, a conversion level of 98% was observed. Figure 2b shows the development of $-\ln(1-\text{conversion of alcohol groups})$ versus time once the 50% conversion threshold has been passed. An approximately linear relationship is observed which is indicative for first order kinetic behavior.[11] This linear relationship allows for the calculation of a pseudo first order rate constant, in this case $k_i = 15.8 \times 10^{-3}\ h^{-1}$.

Figure 3 shows the ^{1}H NMR spectrum obtained for this polymer. The end groups that appear at δ 4.9 and 5.0 ppm (designated with F and G in Figure 3) have almost fully disappeared and the intrachain β-hydrogens are observed at δ 5.8 ppm (designated with A). Analysis of the crude polymer by gel permeation chromatography (GPC) indicated that indeed polymeric material had been formed and a peak molecular weight M_p of 10.7 kDa was calculated (Figure 4). To confirm the formation of an enantiomerically enriched polyester, the polymer was degraded under basic conditions (overnight stirring at room temperature in 0.5 M NaOH in ethanol), restoring the 1,3-diol. Subsequent analysis by chiral GC indicated an *ee* of 92% for the alcohol groups in the polymer. A total amount of 0.5% of ketone functionalities was calculated from the chiral GC trace, which is surprisingly low considering the dehydrogenation potential of the Shvo catalyst.[12] Based on these results, we concluded that ITC of 1,3-diol and DIA using Novozym 435 and racemization catalyst **2** is feasible and an enantio-enriched polyester had been formed.

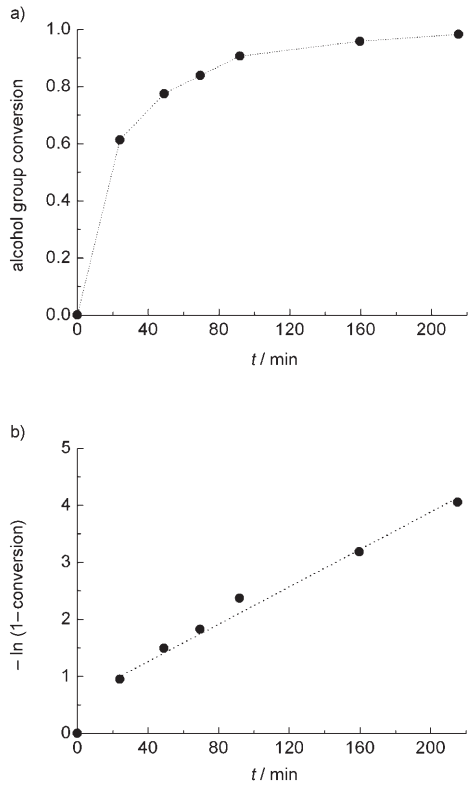


Figure 2. a) Time-conversion plot for the ITC of 1,3-diol and DIA using Novozym 435 and Shvo's catalyst **2**; 1 mol% Ru; 23 mg Novozym 435 per mmol alcohol functionality; 0.7 M DMP; $T = 70$ °C; solvent: toluene; $p = 280$ mbar. The conversion was determined by ^{1}H NMR. b) Logarithmic plot of $-(1-\text{conversion})$ versus time.

ITC of other diols and DIA: In order to investigate the scope of ITC employing AA–BB type monomers, we investigated the use of 1,4-diol and aliphatic diols (Figure 5). In all polymerizations, DIA was used as the diester. The reactions were performed in toluene at 70 °C with 2 mol% of catalyst **2** and 23 mg Novozym 435 mmol alcohol group. 0.5 M DMP was added as a hydrogen donor under reduced pressure (280 mbar) to remove isopropanol. The polymerization of 1,4-diol and DIA (Table 1, entry 2) proceeded smoothly to 97% conversion in 171 h. According to GPC, a polymer was obtained with a peak molecular weight of 8.3 kDa. The amount of ketone functionalities was 2.4%, while the *ee* of this polymer was 94%.

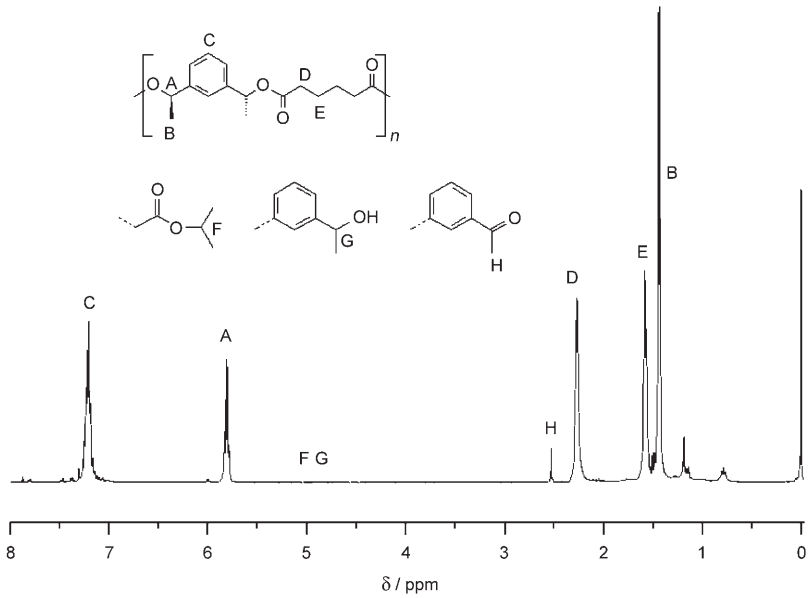


Figure 3. ^{1}H NMR spectrum of the polymer obtained from the ITC of 1,3-diol with DIA.

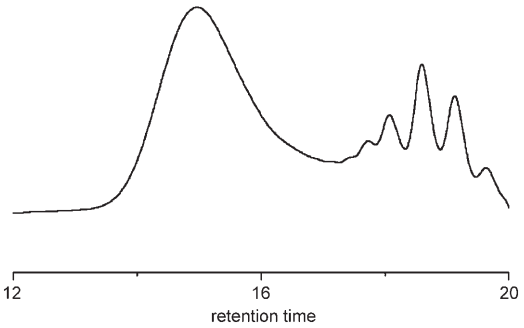


Figure 4. GPC trace of the crude polymer obtained from the ITC of 1,3-diol with DIA, $M_p = 10.7$ kDa. The peaks between 17 and 20 min arise from catalyst residues.

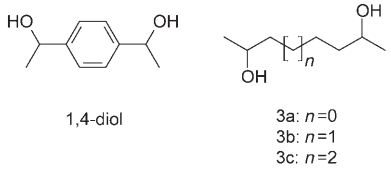


Figure 5. 1,4-Diol and aliphatic diols employed in ITC.

Aliphatic diols **3a–c** were synthesized from the appropriate dienes by first converting the latter to the diepoxide by treatment with *m*-chloroperbenzoic acid. Reduction with $LiAlH_4$ furnished selectively the aliphatic secondary diols in overall yields of 38 to 59% (Scheme 2). The amount of primary alcohol groups could be limited to 2–3% during the reduction by carefully keeping the reaction mixture around 0°C. Since primary alcohols are readily acylated by the lipase, this impurity does not pose a problem in ITC. Subsequently, compounds **3a–c** were subjected to ITC using DIA as the diester (Table 1, entries 3 to 5). Gratefully, we concluded that for all monomers indeed polymerization took place and conversions of 94–98% were reached, although longer reaction times were necessary to reach this conversion level (310 to 390 h). The peak molecular weights of these polymers were in the range of 3.3–3.7 kDa; considerably lower than using aromatic diols. Presumably, these relatively low molecular weights can be attributed to a relatively high extent of dehydrogenation of end groups. Overlapping peaks in the ^{1}H NMR spectra unfortunately hampered the quantification of the amount of ketone end groups.

Surprisingly, the *ee* values of the polymer obtained from **3a–c** were low with values ranging from 41 to 46% (Table 1). Although the enantioselectivity of Novozym 435 towards linear secondary alcohols is very high (for 2-octanol an E value of 340 was reported)[13] this is not necessarily the case for aliphatic diols. Therefore, we first investigated the enantioselectivity of Novozym 435 towards aliphatic diols in a kinetic resolution experiment. 2,9-Decanediol (**3c**) was subjected to enzymatic acylation as depicted in Scheme 3.

Scheme 3. Lipase-catalyzed acylation of 2,9-decanediol with vinyl acetate as the acyl donor.

To ensure a fast reaction, vinyl acetate was selected as the acyl donor. If the enantioselectivity of Novozym 435 in the acylation of the first secondary alcohol group is sufficiently high, then a negligible amount of the *SS* diastereomer would react away. The time-conversion plot of this reaction is shown in Figure 6. The *RR* and *RS* diastereomers quickly react away, with—as expected—the highest reaction rate for the *RR* diastereomer. However, the *SS* diastereomer also shows considerable reactivity. This indicates that the enantioselectivity for Novozym 435 is considerably lower for **3c** than for regular secondary alcohols, such as 2-octanol.

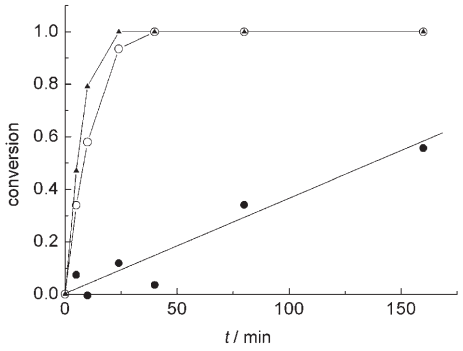
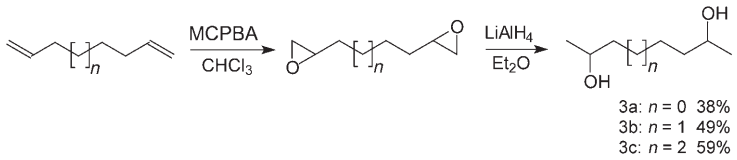


Figure 6. Time-conversion plot for the lipase-catalyzed acylation of 2,9-decanediol using vinyl acetate as the acyl donor; *SS*-diol (●), *RS*-diol (○), *RR*-diol (▲). Conditions: 25 mg Novozym 435, 1.15 mmol **3c**, 4.64 mmol vinyl acetate, 5 mL toluene, $T = 70$°C. Conversions are calculated from chiral GC spectra.

Optimization study: Encouraged by the promising result of the ITC of 1,3-diol and DIA, we selected this polymerization reaction for an optimization study. We focused on obtaining high molecular weight polymers with high optical purity, while minimizing the reaction time. Since the molecular weight in a polycondensation is highly dependent on stoichiometry, the percentage of ketone end groups is the



Scheme 2. Synthesis of aliphatic secondary diols from the corresponding dienes.

only reasonable parameter to consider, since ketone end groups act as chain stoppers. As DMP is used as a hydrogen donor in order to suppress dehydrogenation, the concentration of DMP is thought to be of importance. The reaction rates are expected to depend on the catalyst loadings. Since the racemization rate is the rate limiting step after acylation of all *R* alcohols (see above), increasing the amount of catalysts **2** will increase the reaction rate. Increasing the amount of Novozym 435 will also have a beneficial effect on the reaction rate in the initial state of the reaction but is also expected to lower the enantioselectivity. Therefore, we evaluated the effect of DMP concentration and the catalyst loadings employed on the kinetics, the optical purity and the percentage of end groups in the isolated polymers. In all experiments, first order kinetic behavior was observed after 50% of the alcohol groups were acylated. The calculated rate constants are related to this stage of the reaction. The results of this study are summarized in Table 1 (entries 6–16).

Effect of the lipase loading: The amount of lipase that is used in ITC may affect both the kinetics as well as the optical purity of the polymer obtained. In DKR experiments using racemization catalyst **2**, usually racemization is the rate-limiting process, since the racemization activity of catalyst **2** is much lower than the acylation activity of the lipase. If this is also the case in ITC, the observed kinetics would not change when increasing or decreasing the lipase catalyst loading. The optical purity might decrease if the amount of lipase is increased. The rate of acylation of *S* secondary alcohols is very low, and insignificant with respect to overall rate of acylation. However, the effect of more lipase can have a significantly negative effect on the *ee* of the polymer. By performing the ITC at lipase catalyst loadings of 12 and 46 mg per mmol alcohol functionality, the effect on these parameters was investigated. Entries 7 and 8 show that indeed the lipase loading does not have an influence on the net rate of reaction; the calculated reaction rate constants for the experiments with 12 and 46 mg Novozym 435 per mmol alcohol functionality were 25.8 and $26.9\times10^{-3}\,h^{-1}$, respectively. Apparently, the racemization is rate-limiting even when using only 12 mg Novozym 435 per mmol alcohol functionality. The optical purity of the polymer, however, does depend on the amount of lipase used. Entries 7 and 8 clearly show that an increase in the amount of enzyme from 12 to 46 mg per mmol alcohol functionality leads to a decrease in the *ee* of the polymer from 98 to 92%.

Effect of the ruthenium loading: Since the racemization is rate-limiting after 50% conversion, we expected that the kinetics are dependent on the ruthenium loading. To investigate this, ITC was carried out with ruthenium loadings of 0.5 mol% to 4 mol% (entries 6 and 8 to 11). Also, the effect of the concentration of ruthenium was investigated by diluting the system (entries 15 and 16). The results are visualized in Figure 7. Entries 6, 8 and 9 show that an increase from 0.5 to 2 mol% results in a faster rate of reaction (left part of Figure 7): the calculated rate constants were 18.3, 26.9 and $48.5\times10^{-3}\,h^{-1}$, respectively. As shown by entries 10 and 11, surprisingly, a further increase to 4 mol% leads to slightly slower kinetics (right part of Figure 7): the calculated rate constants were 33.0 and $26.9\times10^{-3}\,h^{-1}$, respectively.[14]

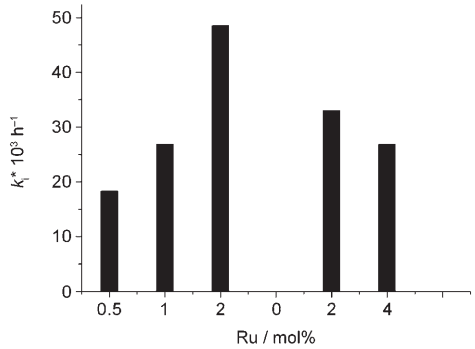


Figure 7. Effect of the ruthenium loading on the kinetics of the polymerization (Table 1, entries 6, 8, 9, 10 and 11). The two experiments with 2 mol% Ru are at different DMP concentration and, therefore, display different reaction rates.

A threefold dilution of the system by using more solvent resulted in a sharp decrease in reaction rate (entry 15); a rate constant of only $12.5\times10^{-3}\,h^{-1}$ was calculated. This is attributed to slower racemization kinetics due to the lower alcohol concentration.[15] An alternative explanation would be that the equilibrium between the inactive dimeric ruthenium precursor and the active 16-electron Ru^0- and 18-electron Ru^{II} complexes is affected by the dilution.[16] However, the experiment with a threefold dilution while keeping the ruthenium concentration constant with respect to the undiluted experiments with 2 mol% (thus effectively increasing the ruthenium loading to 6 mol%) shows that this is not the case, as the kinetics of this experiment are equally slow with a k_i of $13.9\times10^{-3}\,h^{-1}$ (entry 16).

Effect of the DMP concentration: DMP is added to the polymerization system to suppress dehydrogenation of alcohols group. Therefore, it is of interest to investigate the effect of different concentrations of DMP on the amount of ketone end groups in the isolated polymers. Although DMP is a sterically hindered hydrogen donor, it acts a competitive substrate for the racemization catalyst. Thus, it is expected that DMP has an influence on the racemization kinetics. By changing the DMP concentration from 0.1 to 3.9 M, these effects were investigated (entries 8 to 10 and 12 to 14). Increasing the DMP concentration from 0.1 to 0.5 M lead to significantly faster kinetics with k_i values of 33.0, 38.3 and $48.5\times10^{-3}\,h^{-1}$, respectively (entries 10, 12 and 9; left part of Figure 8). A further increase from 0.5 to 3.9 M resulted in a sharp decrease in reaction rate (entries 8, 13 and 14; right part of Figure 8); the calculated k_i values were 26.9, 12.0 and $1.7\times10^{-3}\,h^{-1}$, respectively.[17] Apparently, the addition of a limited amount of DMP results in faster kinetics; possibly the change in polarity affects the equilibrium between inactive dimeric ruthenium precursor and the active monomeric

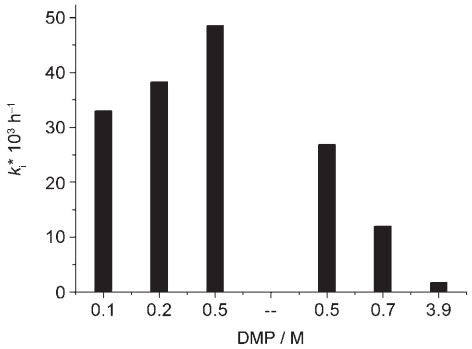


Figure 8. Effect of the amount of hydrogen donor DMP on the kinetics of the polymerization (Table 1, entries 11, 13, 10, 9, 14 and 15). The two experiments with 0.5 M DMP are at different catalyst loadings and, therefore, display different reaction rates.

complexes, or in higher activity of these active complexes. At higher concentrations, substrate competition by DMP prevails, and net kinetics slow down severely. Finally, the amount of ketone functionalities appeared to be independent of the DMP concentration; percentages of ketone always were in the 0.5–3.1 % range and no clear trend could be observed.

In summary, the amount of lipase has no significant influence on the overall kinetics of ITC. The optical purity of the polymer, however, was optimal at 12 mg lipase per mmol alcohol functionality. The overall kinetics were fastest when using 2 mol % ruthenium catalyst reducing the reaction time to ≈120 h. The DMP concentration had no influence on the amount of ketone functionalities in the isolated polymers; the overall kinetics of the polymerization, however, were fastest at 0.5 M. From these results, we concluded that the optimal conditions for the ITC of 1,3-diol and DIA are 2 mol % ruthenium catalyst **2**, 12 mg Novozym 435 per mmol alcohol functionality and 0.5 M DMP.

Conclusion

ITC of 1,1′-(1,3-phenylene)diethanol (1,3-diol) and DIA resulted in a chiral polyester using Shvo's catalyst **2** and Novozym 435. An optimization study was performed, which lead to the optimal conditions of 2 mol % **2**, 12 mg Novozym 435 per mmol alcohol group in the presence of 0.5 M DMP as the hydrogen donor. With these conditions, chiral polymers were obtained with peak molecular weights up to 15 kDa, *ee* values up to 99 % and with 1–3 % ketone functionalities in ≈120 h. Also with the structural isomer 1,4-diol, a chiral polyester was obtained, albeit with lower molecular weight (8.3 kDa) and slightly lower *ee* (94 %), which can probably be attributed to the lack of optimization for this particular monomer. ITC using aliphatic diols also succeeded, but did not lead to enantiopure polymers. At most, an *ee* of 46 % was obtained with low molecular weights in the range of 3.3–3.7 kDa. The latter was attributed to the low of selectivity of Novozym 435 for these secondary diols. The results presented here illustrate that chiral polyesters are readily accessible from optically inactive monomers by the concurrent use of different catalysts, a process referred to as iterative tandem catalysis. The reaction times are still relatively long which results from the slow racemization activity of the Shvo's catalyst under the conditions employed. Nevertheless, ITC is an effective way to prepare chiral polymers from a variety of optically inactive monomers.

Experimental Section

Materials: 1,1′-(1,3-Phenylene)diethanol (1,3-diol) and 1,1′-(1,4-phenylene)diethanol (1,4-diol) were synthesized by reduction of the corresponding ketone with $NaBH_4$ according to a literature procedure.[18] Diisopropyl adipate (DIA) was purchased from TCI Europe. Novozym 435 was purchased from Novozymes A/S. All solvents were purchased from Biosolve and stored on dry molecular sieves 4 Å) prior to use to remove traces of water. Shvo's catalyst **2** was purchased from Strem Chemicals. All other chemicals were purchased from Aldrich and used as received unless otherwise noted.

Analytical methods: ^{1}H and ^{13}C NMR spectra were measured in $CDCl_3$ at 400, 300 or 200 MHz (1H NMR) and 100, 75 or 50 MHz (^{13}C NMR) using a Varian Mercury Vx 400, 300 or 200 spectrometer. Chiral gas chromatography (GC) was performed on a Shimadzu 6C-17 A GC equipped with a Chrompack Chirasil-DEX CB (i.d. = 0.25 mm, D_f = 0.25 μm) column and an FID. Samples were injected using a Shimadzu AOC-20i autosampler. Injection and detection temperatures were set at 250 and 300 °C, respectively. Conversions were determined by the internal standard method using 1,3,5-tri-*tert*-butylbenzene as the internal standard. The *ee* value was calculated as follows: $ee = (R-S)/(R+S)$ where *R* and *S* represent the area of the GC peaks of the *R* and *S* enantiomer, respectively. Samples containing 1,3-diol were analyzed directly while samples containing 1,4-diol were derivatized with butyric anhydride for 16 h at 80 °C in toluene prior to analysis. GC-MS spectra were taken with a Shimadzu GC-17 A employing a Zebron-ZB-5 column (i.d. = 0.25 mm, D_f = 0.25 μm). Injector and detector temperatures were set at 300 °C. Gel permeation chromatography (GPC) was carried out on a Shimadzu HPLC system equipped with a Shimadzu LC-10 AD VP pump, a Shimadzu RID-10 A 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.

Typical procedure for ITC: Novozym 435 (40 mg), **2** (18 mg, 0.017 mmol), 3 Å molar sieves and a magnetic stirring bar were put in a 15 mL Schlenk tube. The tube was put overnight in a vacuum oven (10 mm Hg) at 50 °C in presence of P_2O_5. The oven was backfilled with nitrogen and the tube was removed from the oven. 1,3-Diol (144 mg, 0.87 mmol), DIA (199 mg, 0.87 mmol), dry toluene (2 mL) and 2,4-dimethyl-3-pentanol (120 mg) were added to a 5 mL round bottom flask and were stirred at 45 °C for 16 h in presence of 3 Å molar sieves to remove traces of water. The mixture was allowed to cool to room temperature and subsequently transferred to the Schlenk tube. Five vacuum-argon cycles were performed to remove oxygen. The mixture was stirred at 70 °C for 120 h at reduced pressure (280 mbar). During reaction, aliquots (≈0.05 mL) were drawn from the reaction mixture using a syringe, which was flushed with argon prior to use. The sample was diluted with $CDCl_3$ analyzed by ^{1}H NMR. After reaction, the enzyme was removed by filtration over a class 3 glass filter. The filter was flushed with dichloromethane. The crude product was obtained after removal of the organics by rotary evaporation as a brownish oil (120 mg). ^{1}H NMR ($CDCl_3$, 25 °C, TMS): δ = 7.21 (m, Ar-H), 5.80 (m, $CH(CH_3)(OCO)$), 2.53 (br s, Ar-CO-CH_2), 2.30 (br s, $OCOCH_2$), 1.55 (br s, $OCOCH_2CH_2$), 1.45 ppm (d, CH_3).

1,2,9,10-Diepoxydecane: 1,9-Decadiene (10.6 g, 77 mmol) was dissolved in chloroform (100 mL) and added dropwise in 1 h using a dropping

funnel to a suspension of 77% *m*-chloroperbenzoic acid (34 g, 197 mmol) in chloroform (150 mL). The mixture was stirred overnight at room temperature. Then, the solution was filtered over Celite and the filtrate was washed with $Na_2S_2O_3$ solution (150 mL, 10%), Na_2CO_3 solution (3× 150 mL, saturated) and brine (150 mL). The organic layer was dried with $MgSO_4$, filtered and concentrated in vacuo. The resulting clear liquid (12.4 g, 98%) was characterized by ^{1}H NMR and used in the second step without further purification. ^{1}H NMR ($CDCl_3$, 25°C, TMS): $\delta = 2.90$ (m, CH_2-O-C*H*), 2.75 (dd, C*H*$_2$-O-CH), 2.45 (dd, C*H*$_2$-O-CH), 1.2–1.8 ppm (CH_2-R).

1,2,7,8-Diepoxyoctane: ^{1}H NMR ($CDCl_3$, 25°C, TMS): $\delta = 2.90$ (m, CH_2-O-C*H*), 2.75 (dd, C*H*$_2$-O-CH), 2.45 (dd C*H*$_2$-O-CH), 1.2–1.8 ppm (CH_2-R).

1,2,8,9-Diepoxynonane: ^{1}H NMR ($CDCl_3$, 25°C, TMS): $\delta = 2.90$ (m, CH_2-O-C*H*), 2.75 (dd, C*H*$_2$-O-CH), 2.45 (dd C*H*$_2$-O-CH), 1.2–1.8 ppm (CH_2-R).

2,9-Decanediol (3c): 1,2,9,10-Diepoxydecane (12.4 g, 76 mmol) was dissolved in diethyl ether (300 mL) and added dropwise in 1 h using a dropping funnel to an ice cooled suspension of $LiAlH_4$ (2.22 g, 59.25 mmol) in diethyl ether (300 mL). The reaction was performed under a nitrogen atmosphere. The resulting suspension was stirred overnight. After completion of the reaction (as confirmed by ^{1}H NMR), the mixture was quenched with water and aqueous HCl was added (200 mL, 1 M). The organic layer was separated and the aqueous layer was washed with dichloromethane (2×200 mL). The organic layers were combined and concentrated in vacuo. The resulting liquid was distilled (b.p. 100°C at $p =$ 0.03 mbar). The product was characterized by ^{1}H NMR, ^{13}C NMR and GC/MS. According to ^{1}H NMR, the product contained 97% secondary alcohol groups and 3% primary alcohol groups impurity (7.5 g, 60%). Prior to GC analysis, the sample was derivatized using trifluoroacetic anhydride. ^{1}H NMR ($CDCl_3$, 25°C, TMS): $\delta = 3.78$ (m, CH_3CH(OH)), 3.63 (t, CH_2CH_2OH, impurity), 1.2–1.6 (m, CH(C*H*$_2$)$_6$), 1.18 ppm (d, C*H*$_3$CH(OH)); ^{13}C NMR ($CDCl_3$, 25°C, TMS): $\delta = 67$ (CH_3*C*H(OH)), 39 (CH_2), 30 (*C*H$_2$), 26 (CH_2), 24 ppm (CH_3)); GC-MS ($F_W = 174.28$): *m*/*z* (%): 155 (1); GC-FID retention times (temperature program: 105°C isothermal for 30 min, temperature gradient 50°C per min to 200°C, isothermal at 200°C for 10 min, temperature gradient 25 to 225°C): *SS*-diol 23.74 min, *RS*-diol 24.15 min, *RR*-diol 24.96 min. ^{1}H NMR of the polymer obtained from the ITC of 2,9-decanediol and DIA ($CDCl_3$, 25°C, TMS): $\delta = 4.98$ (m, COOC*H*(CH_3)$_2$), 4.89 (m, C*H*(CH_3)(OCO)), 4.05 (t, C*H*$_2$-(OCO)), 3.79 C*H*(CH_3)OH), 2.30 (br s, OCOC*H*$_2$), 2.10 (s, $COCH_3$), 1.78–1.22 (m, OCOCH$_2$C*H*$_2$ and COOCH(CH_3)(C*H*$_2$)$_3$), 1.19 ppm (d, CH_3).

2,7-Octanediol (3a): Yield: 2.55 g (38%). B.p. 82°C at $p = 0.03$ mbar. According to ^{1}H NMR, the product contained 98% secondary alcohol groups and 2% primary alcohol groups. Prior to GC analysis, the sample was derivatized using trifluoroacetic anhydride. ^{1}H NMR ($CDCl_3$, 25°C, TMS): $\delta = 3.78$ (m, CH_3CH(OH)), 3.63 (t, CH_2CH_2OH, impurity), 1.2–1.6 (m, CH(C*H*$_2$)$_4$), 1.18 ppm (d, C*H*$_3$CH(OH)); ^{13}C NMR ($CDCl_3$, 25°C, TMS): $\delta = 68$ (CH_3*C*H(OH)), 39 (CH_2), 26 (*C*H$_2$), 24 ppm (CH_3); GC/MS ($F_W = 146.23$): *m*/*z* (%): 126 (1); GC-FID retention times (temperature program: 95°C isothermal for 20 min, temperature gradient 50°C per min to 200°C, isothermal at 200°C for 10 min, temperature gradient 25 to 225°C): *SS*-diol 12.1 min, *RS*-diol 12.4 min, *RR*-diol 13.0 min. ^{1}H NMR of the polymer obtained from the ITC of 2,7-octanediol and DIA ($CDCl_3$, 25°C, TMS): $\delta = 4.98$ (m, COOC*H*(CH_3)$_2$), 4.89 (m, C*H*(CH_3)-(OCO)), 4.05 (t, C*H*$_2$(OCO)), 3.79 (m, C*H*(CH_3)OH), 2.30 (br s, OCOC*H*$_2$), 2.10 (s, $COCH_3$), 1.78–1.22 (m, OCOCH$_2$C*H*$_2$ and COOCH-(CH_3)(C*H*$_2$)$_2$), 1.19 ppm (d, CH_3).

2,8-Nonanediol (3b): Yield: 3.14 g (49%). B.p. 95°C at $p = 0.03$ mbar. According to ^{1}H NMR, the product contained 98% secondary alcohol groups and 2% primary alcohol groups. Prior to GC analysis, the sample was derivatized using trifluoroacetic anhydride. ^{1}H NMR ($CDCl_3$, 25°C, TMS): $\delta = 3.78$ (m, CH_3CH(OH)), 3.63 (t, CH_2CH_2OH, impurity), 1.2–1.6 (m, CH(C*H*$_2$)$_5$), 1.18 ppm (d, C*H*$_3$CH(OH)); ^{13}C NMR ($CDCl_3$, 25°C, TMS): $\delta = 68$ (CH_3*C*H(OH)), 39 (CH_2), 30 (CH_2), 26 (CH_2), 23 ppm (CH_3); GC/MS ($F_W = 160.25$): *m*/*z* (%): 141 (1); GC-FID retention times (temperature program: 95°C isothermal for 20 min, temperature gradient 50°C per min to 200°C, isothermal at 200°C for 10 min, temperature gradient 25 to 225°C): *SS*-diol 21.5 min, *RS*-diol 22.5 min, *RR*-diol 23.1 min. ^{1}H NMR of the polymer obtained from the ITC of 2,8-nonanediol and DIA ($CDCl_3$, 25°C, TMS): $\delta = 4.98$ (m, COOC*H*(CH_3)$_2$), 4.89 (m, C*H*-(CH_3)(OCO)), 4.05 (t, C*H*$_2$(OCO)), 3.79 (m, C*H*(CH_3)OH), 2.30 (br s, OCOC*H*$_2$), 2.10 (s, $COCH_3$), 1.78–1.22 (m, OCOCH$_2$C*H*$_2$ and COOCH-(CH_3)(C*H*$_2$)$_2$), 1.19 ppm (d, CH_3).

Kinetic resolution of 2,9-decanediol using vinyl acetate as the acyl donor: Novozym 435 (25 mg), 2,9-decanediol (200 mg, 1.15 mmol), vinyl acetate (400 mg, 4.64 mmol), tri-*tert*-butylbenzene (40 mg, 0.16 mmol), dry toluene (5 mL), dry 2,4-dimethyl-3-pentanol (1 mL) and a magnetic stirring bar were put in a 10 mL vial. The mixture was stirred at 70°C. At 5, 10, 24, 40, 80, 160, 360 and 1500 min samples (≈0.02 mL) were withdrawn from the reaction mixture using a syringe, which was flushed with argon prior to use. The sample was diluted with dichloromethane and the enzyme was removed from the sample by filtration over cotton wool. The samples were analyzed by chiral GC. For determination of the conversions of the separate enantiomers, the samples were derivatized using trifluoroacetic anhydride prior to analysis. Temperature program underivatized samples: 125°C isothermal for 20 min, temperature gradient 20°C per min to 200°C, isothermal at 200°C for 25 min, temperature gradient 25 to 225°C). GC retention times: diol 23.50 min, *S*-ester-*S*-alcohol 23.80 min, *SS*-diester 23.97 min, *R*-ester-*R*-alcohol + *R*-ester-*S*-alcohol 24.01 min, *RS*-diester 24.24 min, *RR*-diester 24.49 min. The peaks were tentatively assigned based on deduction and mass balance consistency. Temperature program derivatized samples: 105°C isothermal for 30 min, temperature gradient 50°C per min to 200°C, isothermal at 200°C for 10 min, temperature gradient 25 to 225°C). GC retention times: *SS*-diol 23.74 min, *RS*-diol 24.15 min, *RR*-diol 24.96 min.

Typical procedure for the hydrolysis of chiral polymers: Chiral polymer (40 mg) was dissolved in EtOH (2 mL). NaOH (42 mg, 1.0 mmol) was added, and the mixture was stirred for 16 h at room temperature. The mixture was poured into a solution of 300 mg NH_4Cl in 10 mL H_2O. A few drops of concentrated HCl were added, until pH ≈7 as evidenced by the use of pH paper. The EtOH was removed by concentration in vacuo and the mixture was extracted with ethyl acetate (3×20 mL). The organics were combined, washed with brine and dried over $MgSO_4$. After concentration, the resulting mixture (40 mg) was analyzed by ^{1}H NMR to confirm full degradation of the polymeric material and subsequently analyzed by chiral GC for determination of the *ee* of the diol (the 1,4-diol was measured after derivatization with butyric anhydride). GC retention times: 1,3-Diol: diketone 7.76 min, *R*-alcohol-ketone 19.44 min, *S*-alcohol-ketone 20.06 min, *SS*-diol 32.1 min, *RS*-diol 32.8 min, *RR*-diol 34.9 min (temperature program 150°C isothermal for 45 min, temperature gradient 50°C per min to 200°C, isothermal at 200°C for 40 min, temperature gradient 25 to 225°C). 1,4-Diester: *SS*-diester 38.1 min, *RS*-diester 38.4 min, *RR*-diester 38.6 min (temperature program 160°C isothermal for 35 min, temperature gradient 40°C per min to 200°C, isothermal at 200°C for 10 min).

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