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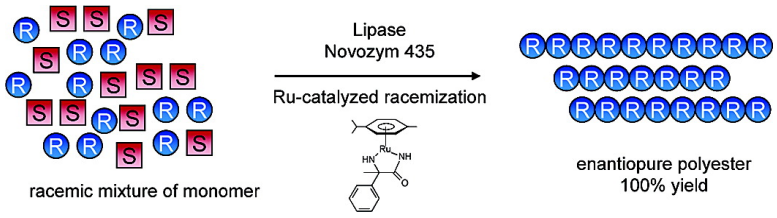


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# Chiral Oligomers by Iterative Tandem Catalysis

Bart A. C. van As,[†] Jeroen van Buijtenen,[†] Andreas Heise,[‡] Quirinus B. Broxterman,[§] Gerard K. M. Verzijl,[§] Anja R. A. Palmans,*[,†] and E. W. Meijer*[,†]

*Laboratory of Macromolecular and Organic Chemistry, Eindhoven University of Technology, PO Box 513, 5600 MB Eindhoven, The Netherlands, and DSM Research, PM-CT, LS-ASC&D, PO Box 18, 6160 MD Geleen, The Netherlands*

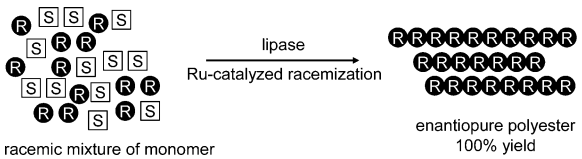
Received April 11, 2005; E-mail: E.W.Meijer@tue.nl

Tandem catalysis, that is, combined catalytic reactions without intermediate product recovery, attracts increasing interest from academia and industry as an alternative to multistep synthetic procedures.[1] Evidently, by carrying out multiple transformations in one pot, a substantial improvement in both the economics and the environmental acceptability of the process can be achieved. In concurrent tandem catalysis, multiple catalysts are operating simultaneously in a cooperative fashion. A prominent example is the dynamic kinetic resolution (DKR) of secondary alcohols.[2] In this process, a racemic mixture is completely converted into one enantiomer by coupling enzyme-catalyzed kinetic resolution to ruthenium-catalyzed racemization. To date, concurrent tandem catalysis has not been employed in an iterative way.

Here, we introduce *iterative tandem catalysis* as a flexible tool for obtaining chiral macromolecules from racemic or prochiral monomers. We define iterative tandem catalysis (ITC) as a polymerization in which the chain growth is effectuated by a combination of two (or more) intrinsically different catalytic processes that are both compatible and complementary.

Recently, we observed that Novozym 435-catalyzed polymerization of 6-methyl-$\epsilon$-caprolactone (6-MeCL) did not occur, in contrast to polymerization of other methyl-substituted caprolactones, such as 4-methyl-$\epsilon$-caprolactone.[3] Closer investigation revealed that ring-opening of racemic 6-MeCL did take place and is *S*-selective. Since 6-MeCL is an $\omega$-substituted lactone, ring-opening results in a terminal secondary alcohol, in this case, with the *S*-configuration. Following Kazlauskas' rule, these *S*-secondary alcohols are the slower reacting enantiomers in lipase-catalyzed reactions (typically $E > 100$). Consequently, the stereoconfiguration of the terminal secondary alcohol prevents propagation from taking place on a realistic time scale.[4] We anticipated that polymerization of 6-MeCL could be achieved in an approach analogous to DKR of secondary alcohols. In situ racemization of the terminal secondary alcohol of the propagating polymer chain should provide reactive chain ends, theoretically resulting in an enantiopure polymer in a 100% yield starting from the racemic monomer (Scheme 1). Here, we provide experimental evidence as a proof of principle.

***Scheme 1***




To confirm the observed absence of polymerization of 6-MeCL, benzyl alcohol (BA)-initiated enzymatic ring-opening of 6-MeCL was performed at a low 6-MeCL/BA ratio of 4/1. The reaction is complete after approximately 30 min when all of the BA initiator and 1 equiv of (*S*)-6-MeCL have been consumed (corresponding to 50% conversion of (*S*)-6-MeCL; Figure 1A). No further consumption of (*S*)-6-MeCL is observed, while the consumption of (*R*)-6-MeCL remains at an acceptable low rate.

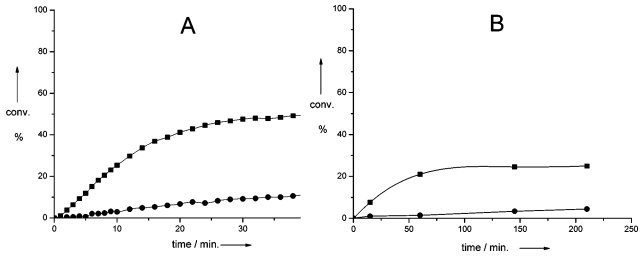
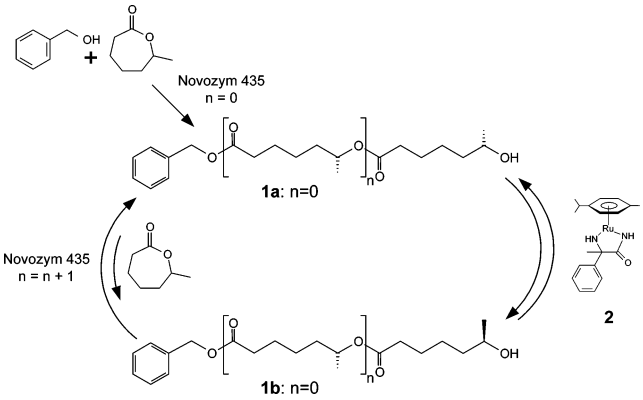



***Figure 1.*** (A) Enzymatic ring-opening of *rac*-6-MeCL by BA catalyzed by Novozym 435 [(*S*)-6-MeCL (■); (*R*)-6-MeCL (●); $T = 60$ °C; BA/6-MeCL = $^1/_4$]. (B) Enzymatic ring-opening of *rac*-6-MeCL [(*S*)-6-MeCL (■); (*R*)-6-MeCL (●)] by racemized **1**; **1**/6-MeCL = $^1/_4$.

***Scheme 2.*** Synthesis of Chiral 6-MeCL Oligomers by ITC




Product **1a** was subsequently racemized using catalyst **2** (Scheme 2), which is generated by complexation of $[RuCl_2(cymene)]_2$ with 2-phenyl-2-aminopropionamide in the presence of $K_2CO_3$.[5] 2-Propanol was added as a hydrogen donor to suppress dehydrogenation of the terminal alcohol. Furthermore, to avoid base-catalyzed transesterification, **2** was preformed and $K_2CO_3$ was removed by filtration prior to the start of reaction. Racemization of **1a** results in 50% of disfavored substrate **1a** and 50% of favored substrate **1b**.[6] When this product is reacted with 6-MeCL, a fast reaction is observed (with comparable kinetics to reaction of BA), with an ultimate conversion of racemized **1** of 50% and consumption of an additional 0.5 equiv of (*S*)-6-MeCL (Figure 1B). $^1$H NMR confirmed the formation of oligomer and indicated that indeed 50% of the molecules had propagated, hence, leading to an increase of the average degree of polymerization with 0.5.

[†] Eindhoven University of Technology.
[‡] DSM Research PM-CT.
[§] DSM Research LS-ASC&D.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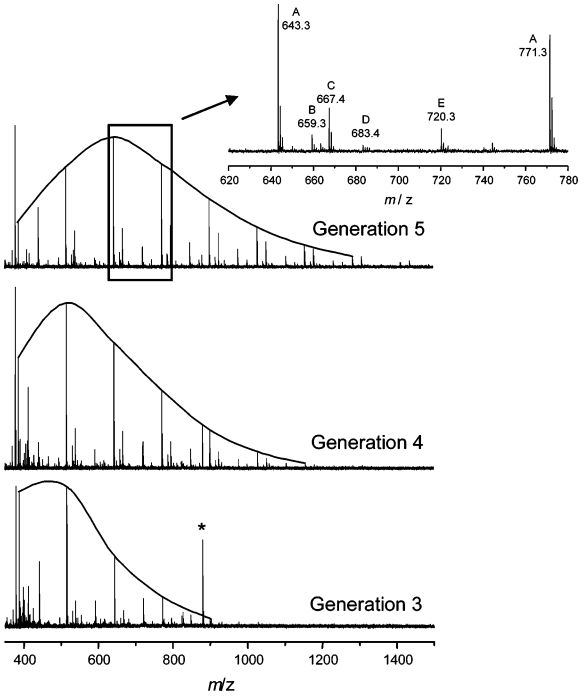


***Figure 2.*** MALDI-TOF MS spectra of generations 3, 4, and 5; A and B are $Na^+$ and $K^+$ ionized BA initiated oligomers of 6-MeCL, respectively; C and D are $Na^+$ and $K^+$ ionized 1,6-heptanediol initiated oligomers of 6-MeCL, respectively; E and * are MALDI-TOF MS related artifacts.

***Table 1.*** Chiral 6-MeCL Oligomers by Iterative Tandem Catalysis

| generation | DP[a] | $DP_{th}$[b] | % diol-initiated chains[a] |
|---|---|---|---|
| 1 | 1.03 | 1.0 | 0 |
| 2 | 1.47 | 1.5 | 0 |
| 3 | 2.02 | 2.0 | 9 |
| 4 | 2.54 | 2.5 | 15 |
| 5 | 3.15 | 3.0 | 25 |
| one-pot | 2.52 | n.a. | 20 |

[a] Determined by $^1$H NMR. [b] With every generation, 50% of the chains have propagated, leading to an increase in the DP of 0.5.

After this first successful racemization/ring-opening cycle, the procedure was repeated until the 5th generation of the oligomer was obtained.[7] Since any ring-opening of (*R*)-6-MeCL yields a reactive terminal secondary alcohol in the *R*-configuration, the enantioselectivity of the enzymatic ring-opening reaction partly determines the ultimate degree of polymerization obtained.[8] To exclude any enantioselectivity-related effects, all reactions were carried out with (*S*)-6-MeCL, synthesized with optical purity of 95% ee. The resulting products from generations 1−5 were analyzed by $^1$H NMR and MALDI-TOF MS (Figure 2; for $^1$H NMR spectra, see Supporting Information). $^1$H NMR confirmed the synthesis of oligomers and revealed that, as expected, with every generation, the average degree of polymerization increased by 0.5 (Table 1). From MALDI-TOF MS, it is clear that the molecular weight of the oligomers increases with every generation; in addition, the maximum of the distribution shifts to a higher mass. Next to distributions A and B ($Na^+$ and $K^+$ ionized oligomers of 6-MeCL), two different sets of distributions were observed. Distribution E is a MALDI-TOF MS artifact. Distributions C and D correspond to $Na^+$ and $K^+$ ionized oligomers of 6-MeCL, which are initiated by 1,6-heptanediol instead of benzyl alcohol. Several ruthenium complexes are known to catalyze ring-opening and subsequent hydrogenolysis of lactones, yielding the corresponding diol.[9] $^1$H NMR confirms the presence of 25% of 1,6-heptanediol-initiated 6-MeCL oligomers in the 5th generation oligomer.[10]

To prove that *R*-esters have indeed been formed in the process, generation 5 was degraded by methanolysis to afford methyl 6-hydroxyheptanoate. Analysis of the methyl ester by chiral GC revealed that 92% of the ester groups in the oligomer chains were in the *R*-configuration.[11] Evidently, the conversion of (*S*)-6-MeCL into *R*-esters was successful.

Encouraged by these promising results, we synthesized 6-MeCL oligomers in one pot from (*S*)-6-MeCL. The system had to be optimized to ensure compatibility of the catalysts in one pot. To accomplish this, we replaced 2-propanol with 2,4-dimethyl-3-pentanol, a sterically hindered hydrogen donor that will not initiate enzymatic ring-opening nor take part in chemical transesterification (as confirmed by a control experiment).[12] $NEt_3$ was added as a base to neutralize any hydroxyacid formed by ester hydrolysis. Oligomeric species corresponding to 6-MeCL oligomers were observed in MALDI-TOF MS analysis of the product (see Supporting Information). From $^1$H NMR, a DP of 2.52 could be calculated (Table 1). This clearly proves that ITC is operative in this one-pot system.

In conclusion, we have, for the first time, provided proof of principle of iterative tandem catalysis. We combined enzymatic ring-opening with ruthenium-catalyzed racemization, yielding enantioenriched oligomers of 6-MeCL. Future work is aimed at obtaining high molecular weight, enantiopure macromolecules through the one-pot process. This challenge requires the optimization of two catalytic processes simultaneously.

**Supporting Information Available:** Experimental procedures; $^1$H NMR spectra; MALDI-TOF MS spectrum. This material is available free of charge via the Internet at http://pubs.acs.org.

## References

(1) (a) Wasilke, J. C.; Obrey, S. J.; Baker, R. T.; Bazan, G. C. *Chem. Rev.* **2005**, 105, 1001. (b) Bruggink, A.; Schoevaart, R.; Kieboom, T. *Org. Proc. Res. Dev.* **2003**, *7*, 622.
(2) (a) Larsson, A. L. E.; Persson, B. A.; Bäckvall, J.-E. *Angew. Chem., Int. Ed. Engl.* **1997**, 36, 1211. (b) Pamiès, O.; Bäckvall, J.-E. *Chem. Rev.* **2003**, *103*, 3247. (c) Pamiès, O.; Bäckvall, J.-E. *TIBTECH* **2004**, *22*, 130. (d) Choi, J. H.; Choi, Y. K.; Kim, Y. H.; Park, E. S.; Kim, E. J.; Kim, M. J.; Park, J. W. *J. Org. Chem.* **2004**, *69*, 1972. (e) Martín-Matute, B.; Edin, M.; Bogár, K.; Bäckvall, J.-E. *Angew. Chem., Int. Ed.* **2004**, *43*, 6535. (f) Verzijl, G. K. M.; De Vries, J. G.; Broxterman, Q. B. *Tetrahedron: Asymmetry* **2005**, *16*, 1603.
(3) (a) Peeters, J.; Palmans, A. R. A.; Veld, M.; Scheijen, F.; Heise, A.; Meijer, E. W. *Biomacromolecules* **2004**, *5*, 1862. (b) van As, B. A. C.; Thomassen, P.; Kalra, B.; Gross, R. A.; Meijer, E. W.; Palmans, A. R. A.; Heise, A. *Macromolecules* **2004**, *37*, 8973.
(4) (a) Janes, L. E.; Kazlauskas, R. J. *Tetrahedron: Asymmetry* **1997**, *8*, 3719. (b) Rotticci, D.; Haeffner, F.; Orrenius, C.; Norin, T.; Hult, K. *J. Mol. Catal., B* **1998**, *5*, 267.
(5) Verzijl, G. K. M.; De Vries, J. G.; Broxterman, Q. B. *PCT Int. Appl.* **2001**, WO2001090396.
(6) The reaction was monitored using $^{31}$P NMR following a literature procedure: Feringa, B. L.; Smaardijk, A.; Wynberg, H. *J. Am. Chem. Soc.* **1985**, *107*, 4798.
(7) The generation of the oligomer equals the number of enzymatic ring-opening reactions performed in its synthesis. The term generation was inspired by dendrimer nomenclature.
(8) The *E* ratio of the ring-opening of 6-MeCL by Novozym 435 was determined to be 12 at 45 °C. The *E* ratio was calculated according to Chen et al. *J. Am. Chem. Soc.* **1982**, *104*, 7294.
(9) Hara, Y.; Inagaki, H.; Nishimura, S.; Wada, K. *Chem. Lett.* **1992**, 1983.
(10) The amount of diol-initiated oligomer can be quantified by means of the characteristic $CH_2OH$ signal at $\delta = 4.0$ ppm.
(11) The percentage of intrachain esters in the *R*-configuration can be calculated using the following formula: fraction *R*-esters $= {}^1/_2 I^{-1} (I + E)$ (ee + 1), where *I* and *E* represent, respectively, the integrals in $^1$H NMR for the intrachain esters and the end-groups, and ee is the measured enantiomeric excess of the methyl ester.
(12) Pamiès, O.; Bäckvall, J.-E. *J. Org. Chem.* **2002**, *67*, 1261.

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