Tandem Catalysis in Organic and Polymer Synthesis

Proefschrift

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Abstract

Tandem catalysis, i.e., combined catalytic reactions without intermediate product recovery, attracts increasing interest from academia and industry as an alternative to classical multistep synthetic procedures. In contrast to its increasingly successful applications in organic synthesis, applications in polymer chemistry are still limited.
1.1 Introduction

While organic chemists can currently synthesize almost any compound, the transformation is normally achieved by the classical step-by-step approach that has been around for over a century. In the separate reaction steps, either stoichiometric synthesis or catalysis is applied, but especially in case of catalyzed reactions only one reaction step is performed at a time. In the synthesis of product D from substrate A, intermediates B and C are isolated and purified before the next step in the conversion (Figure 1.1a). The synthesis of more complex molecules can easily require a great number of steps, resulting in low space-time yields and in the formation of huge amounts of waste.1

![Figure 1.1](image.png)

Figure 1.1 Synthetic efforts of mankind compared to those of Nature: (a) chemistry as it is performed in the laboratory or in a manufacturing plant traditionally involves iterative transformation and purification steps; (b) chemistry as it is performed in the cells of living organisms involves coupled transformations without intermediate recovery steps.2

This is in sharp contrast with Nature’s synthetic efforts.2 Biosynthesis in the cells of living organisms proceeds through a multistep cascade approach to convert a starting material A into the final product D without the requirement for isolation of intermediates B and C (Figure 1.1b).3 In these biological cascade systems, coupled reactions often enable the formation of products despite thermodynamically unfavorable intermediates.4 The well-known glycolysis pathway represents a good example of such an integrated system (Figure 1.2). In this coupled multienzymatic conversion complete transformation of fructose-1,6-diphosphate (A) to lactate (D) occurs, despite the highly unfavorable equilibrium between A, 1,3-dihydroxyacetone-1-phosphate (B), and glyceraldehyde-3-phosphate (C).
Figure 1.2 Transformation of fructose-1,6-diphosphate (A) into lactate (D) via 1,3-dihydroxyacetone-1-phosphate (B) and glyceraldehyde-3-phosphate (C) in the glycolysis pathway: (a) reaction scheme; (b) schematic representation of the thermodynamics of the conversion.

Evidently, by carrying out multiple transformations in one pot, a substantial improvement in both the economics and the environmental acceptability of a process can be achieved. Therefore, combined catalytic reactions without intermediate product recovery attract increasing interest from academia and industry as an alternative to classical step-by-step synthetic procedures. In literature, both the terms cascade catalysis and tandem catalysis have been used to describe such systems, the latter term being used more frequently. Bazan et al. recently proposed the term concurrent tandem catalysis (CTC) for applications that involve the cooperative action of two or more catalytic cycles in a single reaction. However, the distinction between CTC and tandem catalysis in general is usually not made.

The most important issue in tandem catalysis is catalyst compatibility (both mutual compatibility of the catalysts themselves and compatibility of the reaction conditions). In living cells this is achieved by site-isolation and substrate-selectivity. While it is almost impossible for chemocatalysts to even approach the substrate-selectivity of enzymes, compartmentalization of the catalysts enables site-isolation. Therefore, Kieboom et al. concluded that “Development of one-pot cascades in homogeneous systems is searching for exceptions, whereas a clever design of compartmentalization might lead to new concepts.”
1.2 Tandem catalysis in organic reactions

Many successful applications of tandem catalysis in organic synthesis have been described. These are covered extensively in the two abovementioned reviews on the subject from the groups of Kieboom and Bazan. Notably, Bäckvall et al. developed a highly efficient aerobic oxidation of alcohols via a biomimetic catalytic system (Scheme 1.1).7 A Ru catalyst dehydrogenates the alcohol and the hydrogen atoms are transferred to a quinone. The electron-rich hydroquinone formed is continuously reoxidized by air with the aid of an oxygen-activating Co-salen type catalyst. Goldman et al. combined alkane dehydrogenation and olefin metathesis in a one-pot tandem catalytic system, enabling alkane metathesis (Scheme 1.2).8 Catalyst productivity was low, however, and should be dramatically improved for the process to have any synthetic utility. Another exciting example is the one-pot synthesis of riboflavin from D-glucose.9 Six enzymes are involved in the various synthetic steps, while two other enzymes take care of in situ cofactor regeneration (Scheme 1.3).

Scheme 1.1 Efficient aerobic oxidation of alcohols via a biomimetic tandem catalytic system.

Scheme 1.2 Individual steps in the catalytic alkane metathesis by tandem alkane dehydrogenation – olefin metathesis: (a) alkane dehydrogenation produces a double bond; (b) the double bond is cleaved, and the fragments swap over in a metathesis reaction; (c) hydrogenation gives hydrocarbons with chain lengths differing from those of the starting material.8
Scheme 1.3 Enzymatic synthesis of riboflavin (G) from D-glucose (E) and 5-amino-6-ribitylamino-2,4(1H,3H)-pyrimidinedione (F) employing 8 enzymes with in situ cofactor regeneration.

Arguably the most prominent example of tandem catalysis in organic synthesis is dynamic kinetic resolution (DKR). Enantiopure compounds are often obtained via kinetic resolution (KR): an enantioselective catalyst – in many cases an enzyme – converts one enantiomer of the substrate, while the other enantiomer (ideally) only reacts very slowly or not at all. Usually, the desired product can be obtained with good enantiomeric excess (ee),\(^\text{11}\) although the maximum yield is inherently limited to 50%. In DKR this is overcome by employing a second catalyst to ensure a dynamic equilibrium between the two enantiomers of the substrate (Scheme 1.4a).\(^\text{12}\) Theoretically, the racemate can then be converted into the desired enantiomer of the product with 100% ee and 100% yield.

Scheme 1.4 (a) Principle of dynamic kinetic resolution (DKR): \(S_R, S_S\) = substrate enantiomers; \(P_R, P_S\) = product enantiomers. (b) Chemoenzymatic DKR of secondary alcohols employing a Ru catalyst for racemization and a lipase for enantioselective acylation.

For a successful DKR, the kinetic resolution should be efficient, sufficiently enantioselective and, preferably, irreversible. Obviously, the racemization should be efficient as well and the enantioselective catalyst that is employed for the kinetic resolution and the racemization catalyst should be mutually compatible. Moreover, the rates of reaction of the
kinetic resolution and the racemization should be adapted to each other. A very fast relative rate of racemization would furnish the product with the highest possible ee as the substrate for the kinetic resolution is racemic during reaction. This would, however, require a high loading of the racemization catalyst. A very low relative rate of racemization would generally result in a lower ee of the product, since more of the undesired substrate will react as the ratio between the two substrates becomes highly unfavorable. In most cases (but depending on the enantioselectivity of the kinetic resolution), an ee of the substrate during reaction below 80% is desirable. By adapting the amounts of the two catalysts, the desired rate of reaction and ee of the product can be realized at the most optimal loadings of both catalysts.

In the highly successful DKR of secondary alcohols, combination of a lipase with a Ru catalyst for racemization (via transfer-hydrogenation) furnishes the corresponding \( R \)-esters with both conversion and ee > 99% (Scheme 1.4b).\(^{13,14,15}\) Many substrates were converted into the enantiopure ester in good yields, including a broad range of substituted aromatic and aliphatic secondary alcohols and secondary diols.\(^{16}\) The corresponding \( S \)-esters could be obtained when using subtilisin instead of a lipase and with the appropriate ruthenium catalyst even secondary amines were selectively transformed into the corresponding \( R \)-amide via DKR.\(^{17,18}\) DKR of secondary alcohols has also been run on an industrial scale by DSM of the Netherlands.\(^{14}\)

**Scheme 1.5** (a) Synthesis of LLDPE via tandem catalysis. (b) Example of the synthesis of block copolymers via tandem catalysis.
1.3 Tandem catalysis in polymer chemistry

In contrast to its increasingly successful application in the transformation of single molecules, tandem catalysis is still rarely employed in the field of polymer chemistry. Applications are generally limited to polymerizations with in situ oligomerization of the monomer and to the one-pot synthesis of block or graft copolymers. For example, in the tandem catalytic synthesis of linear low-density polyethylene (LLDPE), one catalyst oligomerizes ethylene to α-olefins, while the second catalyst polymerizes these α-olefins as well as the remaining ethylene (Scheme 1.5a). The resulting polymer is less brittle and more easily processed than nonbranched high-density polyethylene (HDPE).

![Figure 1.3 Proposed mechanism for chain shuttling polymerization. Cat1 (solid circles) and Cat2 (solid triangles) represent catalysts with high and low monomer selectivity, respectively, whereas the chain shuttling agent (CSA, solid squares) facilitates the chain shuttling reaction. Cat1 produces a segment of hard polymer with low comonomer content. Shuttling occurs when this segment is exchanged with the CSA bearing a soft copolymer of higher comonomer content. Further chain growth at Cat1 then extends the soft copolymer chain with a hard segment, thus giving a block copolymer.](image)

Block copolymers were synthesized in one pot by combining ring-opening polymerization (ROP) with radical polymerization employing an unsymmetrical bifunctional initiator (Scheme 1.5b). Analogously, graft copolymers can be synthesized in one-pot by using a suitable monomer. In these polymerizations, however, the catalytic processes are not necessarily performed in one pot (i.e. if the two catalytic steps are carried out separately, a similar polymer would still result after two steps). Very few examples can be found where the catalytic processes involved in a polymerization are truly complementary and cannot be separated. Drent et al. described a copolymerization of ethylene and carbon monoxide, in which one palladium complex alternatively builds in both monomers via distinctively different catalytic mechanisms. In addition, a concept called chain shuttling polymerization was
recently introduced, where a growing chain is transferred repeatedly from one catalyst to another to achieve “multiblock” copolymer formation (Figure 1.3).\textsuperscript{10}

### 1.4 Iterative tandem catalysis

We introduce \textit{iterative tandem catalysis} as a novel polymerization method. Iterative tandem catalysis (ITC) is defined as a polymerization process in which chain growth is effectuated by a combination of two (or more) intrinsically different catalytic processes that are both compatible and complementary.\textsuperscript{24} This implies that both catalytic processes are truly required for chain growth to occur; therefore, the reaction is necessarily performed in a concurrent fashion. The simplest application of ITC would involve two catalytic cycles, with propagation by the first catalyst requiring a manipulation by the second catalyst (Scheme 1.6). The major advantage of such ITC systems is that a high degree of control over the chemical structure of the material can be achieved.

![Scheme 1.6](image)

**Scheme 1.6** Example of ITC in which a manipulation by a second catalyst (II) is required for propagation by the first catalyst (I) to occur.

![Scheme 1.7](image)

**Scheme 1.7** Principle of ITC leading to chiral polymers.

Conceptually, various applications of ITC can be imagined. Building on the concept of DKR, combination of a lipase and a racemization catalyst with a suitable monomer should furnish enantiopure polymers (Scheme 1.7). ITC of various monomers is envisaged, i.e., ω-substituted lactones, the combination of secondary diols with diesters as well as AB-molecules featuring ester and secondary alcohol functions (Scheme 1.8).\textsuperscript{25} For such
monomers it was previously reported that lipase-catalyzed polymerization could not be accomplished.\textsuperscript{21,26} The concept can also be extended to the synthesis of enantiopure polyamides by combining lipase-catalyzed enantioselective amidation with Ru-catalyzed racemization.\textsuperscript{27}

\begin{equation}
\text{(a)} \quad R-\text{OH} + \quad \text{lipase racemization catalyst} \quad \rightarrow \quad \text{R-OR} \quad \text{H}
\end{equation}

\begin{equation}
\text{(b)} \quad \text{HO-CH$_2$-OH} + \quad \text{R-O-CH$_2$-OR} \quad \text{lipase racemization catalyst} \quad \rightarrow \quad \text{R-OR} \quad + \quad \text{R-CH$_2$OH}
\end{equation}

\begin{equation}
\text{(c)} \quad \text{R-OR} \quad \text{lipase racemization catalyst} \quad \rightarrow \quad \text{R-OR} \quad + \quad \text{R-CH$_2$OH}
\end{equation}

Scheme 1.8 Different applications of ITC that can be envisaged based on the combination of enantioselective transesterification and racemization: synthesis of enantiopure polyesters by ITC of (a) $\omega$-substituted lactones; (b) secondary diols and diesters; (c) AB-molecules featuring ester and secondary alcohol functions.

1.5 Applications of enantiopure polymers

ITC would enable the conversion of simple, racemic (or achiral) monomers into high value, enantiopure polymers, potentially improving their accessibility. Reports on applications of such synthetic chiral polymers are scarce. However, it can be argued that if nature exploits chirality so extensively, there must be advantages of chiral polymers. Obviously, the crystallization behavior of the enantiopure polymer will be different from that of its racemic counterpart. In case of 6-methyl-$\varepsilon$-caprolactone (6-MeCL), atactic poly-$\varepsilon$-6-MeCL is a viscous oil at ambient temperature, while enantiopure poly-(R)-6-MeCL is semicrystalline. Possibly, ABA triblock copolymers with semicrystalline enantiopure hard blocks and the corresponding racemic polymer as the soft block would perform as thermoplastic elastomers. Furthermore, it has been reported that stereocomplexes of poly(l-lactide)/poly(d-lactide) exhibit a significantly higher melting temperature than the homopolymers (230 °C and 180 °C, respectively).\textsuperscript{28}

It can be argued, however, that the added value of chiral polymers should be derived from their interaction with other sources of chirality. They could, for example, be applied as a stationary phase for column chromatographic separations of racemates. Polysters are not very suitable due to their limited stability; chiral polyamides could be more interesting. Enantiopure polymers could also be applied as a chiral support for an otherwise achiral catalyst to enable asymmetric transformations.\textsuperscript{29} We are confident that many appealing applications will be
discovered in due time; however, current research is severely restricted by the limited availability of the polymers.

1.6 Aim of the thesis

The aim of this thesis is to introduce iterative tandem catalysis (ITC) as a novel polymerization method. ITC allows for increased control over the chemical structure of the material and in this thesis it is employed for the synthesis of enantiopure polyesters. The concept was jointly developed with B. A. C. van As. Intricate knowledge of Ru-catalyzed racemization and dynamic kinetic resolution (DKR) are important prerequisites for the development of these applications of ITC.

1.7 Outline of the thesis

The synthesis and characterization of a range of novel Ru complexes bearing tetrafluorosuccinate and phosphine ligands are described in Chapter 2. In addition, the dehydrogenation of 1-phenylethanol employing these catalysts is reported. Chapter 3 discusses application of the aforementioned catalysts in the dynamic kinetic resolution (DKR) of secondary alcohols. As a vital part of the tandem catalytic system, the racemization is investigated in detail. Chapter 4 deals with iterative tandem catalysis (ITC), focusing on 6-methyl-ε-caprolactone (6-MeCL) as the substrate. The complementarity and compatibility of the catalysts as well as side-reactions are discussed in detail. Proof of principle is provided by the synthesis of R-oligomers from (S)-6-MeCL in a 2-pot system. As a result of insufficient compatibility of the catalysts, a one-pot experiment failed to produce enantiopure polymers. In Chapter 5 we demonstrate that, with a different racemization catalyst, one-pot ITC of 6-MeCL is feasible. Enantiopure polyesters of remarkable molecular weight (MW) were obtained and 6-ethyl-ε-caprolactone (6-EtCL) was also successfully converted into a chiral polymer. The kinetics of the tandem catalytic system are described in detail. In Chapter 6 the Novozym 435-catalyzed ring-opening of other ω-methylated lactones is reported. Ring-opening of lactones of ring-sizes < 8 proved S-selective, while ring-opening of ring-sizes > 7 was R-selective. This (sharp) transition was explained by the (obligatory) cisoid conformation of the smaller lactones in contrast to the (predominantly) transoid conformation of the larger lactones. Of the smaller lactones only 6-MeCL proved a suitable substrate for ITC. Polymerization of the larger lactones by kinetic resolution polymerization (KRP) furnished the R-polyester with very high ee (>99%). The concluding remarks of this thesis focus on the scope and potential of ITC.
1.8 References and notes


3. It should be noted that the activation energies for the various reaction steps in such a biological cascade are typically lower compared to those of a typical chemical transformation as performed in the laboratory.


11. The enantiomeric excess (ee) is defined as $ee = \left(\frac{X_A - X_B}{X_A + X_B}\right) \cdot 100\%$ with $X_A > X_B$; in this equation $X_A$ and $X_B$ denote the fractions of the two enantiomers such that $X_A + X_B = 1$.


22. Arguably, the aforementioned copolymerization of ethylene and carbon monoxide as well as the chain shuttling polymerization can be classified as iterative tandem catalysis.


30. van As, B. A. C. Ph.D. Thesis in press, Eindhoven University of Technology. Chapter 2 extensively covers the Novozym 435-catalyzed ring-opening of ω-substituted caprolactones, while in Chapter 5 the application of ITC to the polycondensation of secondary diols and diesters is described.


34. Chapter 4 is a joint Chapter with B. A. C. van As.


36. van Buijtenen *et al.*, manuscript in preparation.
Dinuclear Ru(II) Complexes Bearing Dicarboxylate and Phosphine Ligands.

Acceptorless Catalytic Dehydrogenation of 1-Phenylethanol.

Abstract

A dinuclear bis(tetrafluorosuccinato)-bridged Ru(II) complex is readily formed upon reaction of Ru(H)₂(CO)(PPh₃)₃ with tetrafluorosuccinic acid at 100 °C. This highly stable complex is apparently stabilized by hydrogen bonding between the protons of two water ligands and the carbonyls of the tetrafluorosuccinates. A range of analogous complexes is accessible by exchange of PPh₃ with diphosphines. Reaction of the bis(tetrafluorosuccinato)-bridged complex with 1-phenylethanol at 130 °C or with 2-propanol/Et₃N at room temperature furnished a dinuclear dihydrido-bridged Ru(II) complex with concomitant loss of the water ligands as well as one of the tetrafluorosuccinate ligands. Both the bis(tetrafluorosuccinato)-bridged and dihydrido-bridged complexes catalyze the acceptorless dehydrogenation of 1-phenylethanol to acetophenone and dihydrogen with good yields and excellent selectivity under relatively mild conditions in the absence of acid or base. A tentative catalytic cycle for the dehydrogenation of secondary alcohols by the bis(tetrafluorosuccinato)-bridged Ru(II) complexes is presented.
2.1 Introduction

The development of catalytic oxidations of alcohols under mild reaction conditions is highly appealing because of its industrial significance. The need for environmentally acceptable processes has led to much effort in the development of sustainable technologies. Important criteria include high atom efficiency, formation of little (in)organic waste, use of benign solvents, and selective synthesis of the desired products.1

Various catalytic systems have been developed to meet these criteria, using environmentally acceptable oxidants such as hydrogen peroxide, molecular oxygen and to a lesser extent sodium hypochlorite.2 Nevertheless, the highest possible atom efficiency is achieved in acceptorless dehydrogenation of secondary alcohols to yield ketones along with dihydrogen as the sole byproduct. Homogeneous catalysts for this reaction are relatively rare, but the conversion was successfully achieved with Rh(III)-SnCl2/HCl,3 Rh(OAc)3/PR3,4 and Ru(OCOCF3)2(CO)(PPh3)2/CF3COOH (1).5-7 However, with these catalysts a catalytic amount of acid as a hydride ion acceptor is still required.

![Figure 2.1 Bis(trifluoroacetato) Ru(II) complex 1](image)

Moreover, most of these catalysts were investigated with the aim to produce hydrogen gas from simple alcohols and the concomitant conversion of secondary alcohols into ketones was not investigated in depth. More recently, Choi et al. reported on an immobilized hydroxycyclopentadienyl Ru(II) catalyst, based on the well-known Shvo catalyst.8 The Shvo catalyst is often used as a racemization catalyst in the dynamic kinetic resolution (DKR) of secondary alcohols (see Chapters 3 and 5). Employing the immobilized catalyst, the dehydrogenation of secondary alcohols proceeded in good yields without any additives, although a high metal loading was required. Zhang et al. reported on a Ru(II) complex bearing a t-Bu-PNP pincer ligand (Figure 2.2) that – after activation by a base – also catalyzed this reaction with good yield and selectivity, without the need for further additives.9 The same group reported on complexes bearing similar PNP and PNN pincer ligands which efficiently and selectively catalyze dehydrogenation of primary alcohols to esters and H2.10 Recently Kim et al. demonstrated that both primary and secondary alcohols can be dehydrogenated in the absence of a hydrogen acceptor using an air-stable heterogeneous Ru catalyst.11 The heterogeneous catalyst could be readily removed from the reaction mixture and excellent results were reported regarding yield and selectivity.
Previously, our group reported on the application of Ru complex \( \text{1} \) as a catalyst for the acceptorless catalytic dehydrogenation of secondary alcohols.\(^{12} \) Various aliphatic alcohols could be dehydrogenated with excellent results regarding yield and selectivity. However, the catalytic amount of trifluoroacetic acid (TFA) that is required for the activity and stability of the catalyst, combined with the high reaction temperature led to significant formation of byproducts, especially in the case of benzylic substrates. Indeed, considerable amounts of 1-phenylethyl trifluoroacetate and di(1-phenylethyl)ether could be detected in the catalytic dehydrogenation of 1-phenylethanol.

In this chapter, novel tetrafluorosuccinic acid (TFSA) analogs of \( \text{1} \) not requiring additional acid are reported. With these complexes, high activities and excellent selectivities were observed in the acceptorless dehydrogenation of 1-phenylethanol.

### 2.2 Synthesis and characterization of \([\text{Ru(μ-OCO-C}_2\text{F}_4\text{-OCO})(\text{CO})(\text{H}_2\text{O})(\text{PPh}_3)_2])_2, \text{2}\)

It was expected that substitution of the trifluoroacetate ligands in \( \text{1} \) by a bifunctional perfluorocarboxylate might lead to a catalytically active Ru complex of higher stability and reactivity than \( \text{1} \). Furthermore, an excess of TFA would no longer be required with such a catalyst. Therefore, in analogy to the synthesis of \( \text{1} \),\(^{13} \) Ru(H)\(_2\)(CO)(PPh\(_3\))\(_3\) was reacted with TFSA, followed by aqueous work-up, resulting in the formation of dinuclear complex \( \text{2} \) (Scheme 2.1).\(^{14} \)

\(^{31}\text{P}[^1\text{H}]\) NMR spectroscopy of \( \text{2} \) reveals two sharp doublets (\(^{2}J_{PP} = 29.2\) Hz) at 43.6 and 40.8 ppm, which can be assigned to two non-equivalent triphenylphosphine ligands. The observation of these sharp signals at room temperature is in contrast with the \(^{31}\text{P}[^1\text{H}]\) NMR spectrum of \( \text{1} \), which exhibits one broad signal at approximately 40 ppm corresponding to the triphenylphosphine ligands, presumably indicative of fast exchange between mono- and bidentate coordination of the two carboxylate ligands. At 220 K an AB pattern similar to that of \( \text{2} \) can be observed in the \(^{31}\text{P}[^1\text{H}]\) NMR spectrum of \( \text{1} \).\(^{15} \) Obviously, \( \text{2} \) lacks the dynamics of TFA complex \( \text{1} \) at room temperature, which can be attributed to hydrogen bonding between the protons of the water ligands and the carbonyl oxygens of the tetrafluorosuccinate (\textit{vide infra}).

In accordance with the apparent rigidity of complex \( \text{2} \), \(^{19}\text{F} \) NMR spectroscopy reveals four signals ranging from -123 to -118 ppm for the four different fluorine nuclei present in the two
equivalent tetrafluorosuccinate ligands.Geminal coupling constants of approximately 270 Hz are observed. In the \(^1\)H NMR spectrum a typical broad signal attributed to the two symmetrical water ligands is observed at 6.32 ppm. \(^{13}\)C\[^1\]H NMR spectroscopy reveals an unresolved triplet for the Ru–CO at 202.7 ppm as well as two unresolved triplets at 165.9 and 169.0 ppm which can be assigned to the carbonyls of the tetrafluorosuccinate ligand.

\[
\text{Ru(H)}_2(\text{CO})(\text{PPh}_3)_3 + \text{HOOC(CF}_2)_2\text{COOH} \rightarrow \text{PhCH}_3, 100^\circ \text{C} \quad -2\text{H}_2, -\text{PPh}_3
\]

<table>
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<tr>
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<th>Yield (%)</th>
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<td>PhCH(_3)</td>
<td>100</td>
</tr>
<tr>
<td>3b</td>
<td>dppb</td>
<td>CHCl(_3)</td>
<td>60(^b)</td>
</tr>
<tr>
<td>3c</td>
<td>dppf</td>
<td>PhCH(_3)</td>
<td>100</td>
</tr>
<tr>
<td>3d</td>
<td>rac-BINAP</td>
<td>PhCH(_3)</td>
<td>180(^c)</td>
</tr>
<tr>
<td>3e</td>
<td>(S)-BINAP</td>
<td>PhCH(_3)</td>
<td>180(^c)</td>
</tr>
</tbody>
</table>

\(^a\) Based on ruthenium. \(^b\) Reaction performed in CHCl\(_3\). \(^c\) Reaction performed under microwave assisted heating in a closed vessel.

Scheme 2.1 Synthesis of bis(tetrafluorosuccinate)-bridged Ru complexes 2 and 3.

Yellow prismatic crystals of 2 suitable for X-ray diffraction analysis were grown by slow diffusion of \(n\)-pentane into a solution of the complex in toluene/chloroform (1:1) at room temperature. The molecular structure of 2 is displayed in Figure 2.3. The existence of hydrogen bonds between the coordinated water and the acid moieties is confirmed by the donor--acceptor distances O2--O4 = 2.822(4) Å, O2--O11 = 2.591(3) Å, O7--O5 = 2.623(4) Å and O7--O10 = 2.733(3) Å. The structure contains an ordered chloroform solvent molecule, which is involved in a C–H--O interaction with O4; see Figure 2.3. The complex is apparently strongly stabilized by hydrogen bonding between the protons of the water ligands and the
carboxylate oxygens. $^1$H NMR spectroscopy reveals that the water ligands in 2 are readily displaced by alcohols (primary as well as secondary).

![Figure 2.3 ORTEP plot\textsuperscript{31} at 50\% probability level of the molecular structure of 2. For reasons of clarity, hydrogen atoms not involved in hydrogen bonding have been omitted and the P–Ph groups are represented as P–C.]

2.3 Synthesis and characterization of diphosphine complexes $[\text{Ru}(\mu-\text{OCO-C}_2\text{F}_4-\text{OCO})(\text{CO})(\text{H}_2\text{O})(\text{P–P})]_2$, 3a-e

Reaction of complex 2 with a slight excess of a diphosphine at elevated temperature gave rise to the formation of diphosphine complexes 3a-e (Scheme 2.1). Generally, the reactions proceeded in good yield and the resulting diphosphine complexes were isolated by crystallization.\textsuperscript{16} This straightforward ligand exchange in dinuclear complex 2 is in sharp contrast with the efforts required for achieving an analogous substitution in the mononuclear complex 1.\textsuperscript{7} Direct exchange of the triphenylphosphine ligands in 1 proved to be impossible and resulted in an ill-defined mixture of products. The same substitution could only be achieved, albeit in moderate yield, by exchange of PPh\textsubscript{3} with the diphosphine in its precursor, RuH\textsubscript{2}(CO)(PPh\textsubscript{3})\textsubscript{3}. It is reasonable to assume that the markedly higher rigidity and stability of complex 2 compared to that of complex 1, are responsible for the difference in behavior towards ligand substitution. This renders complex 2 an ideal platform for the synthesis of a series of phosphine bearing bis(tetrafluorosuccinato)-bridged Ru catalysts.
Whereas exchange of PPh$_3$ was easily accomplished with dppp, dppb and dppe, this did not hold for rac-BINAP. The reaction was not complete after 24 hours, even at 130 °C in $p$-xylene. Since such conditions were not desirable, the reaction was attempted under microwave-assisted heating. During a period of 80 min at 180 °C in toluene, under elevated pressure, complete conversion to and precipitation of Ru complex 3d from the reaction mixture occurred. The reaction of 2 with (S)-BINAP was performed under similar conditions, resulting in complete conversion and a clear yellow solution. After concentration and crystallization from CHCl$_3$, complex 3e was obtained in good yield.

$^{31}$P{$^1$H} NMR spectroscopy of 3a-e reveals two doublets for the two non-equivalent phosphorus atoms, similar to 2. In $^{19}$F NMR spectra geminal coupling is again observed for the fluorine nuclei of the two equivalent tetrafluorosuccinate ligands and in $^1$H NMR spectra the protons of the water ligands appear as a broad signal at approximately 6 ppm. The spectral similarity with compound 2 suggests for 3a-e a similar dinuclear structure with bridging tetrafluorosuccinate ligands. For the rac-BINAP complex 3d, signals for the two possible diastereomers are observed in $^1$H, $^{13}$C{$^1$H}, $^{19}$F, and $^{31}$P{$^1$H} NMR. The major compound (>80%) exhibits the same signals as the (S)-BINAP complex and can therefore be assigned to (R,R)- and (S,S)-3d. Overlapping signals and a low relative concentration prevented the determination of the exact chemical shifts and coupling constants in the NMR spectra of the (R,S)-3d diastereomer.

2.4 Reaction of complex 3e with 1-phenylethanol. Formation of the dihydrido-bridged complex [Ru(μ-H)(μ-OCO-C$_2$F$_4$-OCO)(CO)((S)-BINAP)]$_2$2H$_2$O, 4e

When complexes 3a-e are heated to 130 °C in the presence of 1-phenylethanol, dehydrogenation of the alcohol takes place and a new complex is quickly formed, accompanied by a color change. The new complexes that are formed during dehydrogenation of 1-phenylethanol with 3d and 3e, have been isolated as air-stable orange solids 4d and 4e, respectively (Scheme 2.2). In a separate experiment, the dihydrido-bridged complex 4e was also obtained in high yield by reaction of 3e with 500 eq of 2-propanol and 250 eq of triethylamine in toluene at 25 °C under an argon atmosphere. The structure of 4d and 4e was unequivocally assigned with the aid of NMR and X-ray diffraction analyses of the product.
Scheme 2.2 Synthesis of dihydrido-bridged Ru complexes 4 from bis(tetrafluorosuccinate)-bridged complexes 3

In the $^1$H NMR spectrum of 4e a triplet of triplets appears in the hydride region at -10.38 ppm ($^2$J$_{HP}$(trans) = 48.0 Hz, $^2$J$_{HP}$(cis) = 10.0 Hz). Integral values suggest two hydride ligands per dinuclear complex. These observations can be rationalized by adopting two equivalent bridging hydrides in a dinuclear complex that couple with two trans $^{31}$P nuclei atoms and two cis $^{31}$P nuclei. Apparently, the non-equivalence of the geminal phosphorus atoms on the same Ru center, due the chiral (S)-BINAP ligand does not have a significant effect on the coupling with the hydrides. The $^{31}$P-$^1$H NMR-spectrum reveals two double doublets at 38.8 and 46.3 ppm with $^3$J$_{PP}$ = 36.0 Hz and $^4$J$_{PP}$ = 26.1 Hz. This coupling originates from the non-equivalence of the geminal phosphorus atoms (vide supra) and a significant $^4$J$_{PP}$ is observed. This is in agreement with long-range phosphorus-phosphorus coupling reported for similar hydrido-bridged dinuclear complexes. In the $^{19}$F NMR spectrum four doublets are observed for the four non-equivalent fluorine nuclei with geminal couplings of 271 Hz. The $^{13}$C NMR spectrum reveals an unresolved triplet at 203.5 ppm due to the two equivalent Ru–CO groups and two unresolved triplets at 161.9 and 164.4 ppm assigned to the two carbonyls of the tetrafluorosuccinate ligand. The two Ru nuclei are bridged by one of the carboxylate functions of a tetrafluorosuccinate ligand with the other carboxylate function acting as the counter ion for the overall positive charge of the two Ru(II) centers. The NMR spectra of 4d are more complicated, due to the presence of signals for both diastereomers of the dinuclear rac-BINAP complex. However, the combination of NMR data and X-ray diffraction analysis of an isolated crystal (vide infra) confirms a similar dinuclear structure with two bridging hydrides for (R,S)-4d.
The structure assigned to dihydrido-bridged complexes 4 implies the loss of one of the tetrafluorosuccinate ligands during the reaction. The hydride ligands should originate from the dehydrogenation of two equivalents of alcohol, since Ru remains divalent. The second tetrafluorosuccinate ligand of the precursor is either lost as the reprotonated diacid in the reaction with 1-phenylethanol at 130 °C or as its triethylammonium salt in the reaction with triethylamine. In the dehydrogenation at elevated temperature this trace of carboxylic acid may be responsible for the formation of a trace amount of byproduct.

![Figure 2.4 ORTEP plot at 50% probability level of the molecular structure of rac-4d. For reasons of clarity, hydrogen atoms have been omitted and the P–Ph groups are represented as P–C.](image)

Orange crystals of 4d suitable for X-ray diffraction analysis could be grown and depending on the selected conditions, either triclinic or monoclinic crystals were obtained. Slow diffusion of n-pentane into a solution of the complex in dichloromethane resulted in the formation of the triclinic crystals, while crystallization from methanol yielded the monoclinic crystals. The triclinic crystals contain two independent molecules of (R,R)-4d (Figure 2.4). Since they crystallize in the centrosymmetric space group P 1 the unit cell contains a racemic mixture of (R,R)-4d and (S,S)-4d. This form will be referred to as rac-4d throughout this chapter. The monoclinic crystals are of (R,S)-4d and also have a centrosymmetric space group (Figure 2.5). The bridging hydrides could not be resolved in the crystal structure, but their presence was substantiated by 1H NMR. The distance between the two Ru centers is 2.7270(19) Å in (R,S)-4d and 2.711(8) and 2.7205(9) Å in the two independent molecules of rac-4d. These distances are in the range observed for dihydrido-bridged Ru dimers (2.47-3.03 Å) included in the Cambridge Structural Database (CSD, version 5.26 of November 2004, updates 1 and 2 installed). This configuration would lead to an 18-electron configuration around both metal atoms, which is in agreement with the high stability. However, the distance between the Ru centers does not, by itself, exclude the possibility of a single hydrido-bridged dimer (observed
in the CSD: 2.59-3.23 Å) or a Ru–Ru bond (observed in the CSD: 2.17-3.38 Å). The C–O bond distances of the uncoordinated side of the tetrafluorosuccinate ligand suggest deprotonation, which is in agreement with the fact that the free side of the ligand acts as the counterion for the positively charged core of the complex.20

A similar Ru complex, [(Ph3P)4Ru2(μ-H)2(μ-CF3SO2)(CO)2]HC(SO2CF3)2, was reported by Siedle et al.21 The two bridging hydrides as well as the bridging trifluoromethanesulfinate ligand are similar to the structure proposed for 4, while HC(SO2CF3)2– acts as the counter-ion. Furthermore, the complex featured four equatorial triphenylphosphine ligands. NMR data (1H and 31P) for this complex, for which the structure was confirmed by X-ray diffraction analysis, are similar to the spectral data gathered for 4e.

2.5 Dehydrogenation of 1-phenylethanol at 130 °C

Heating 1-phenylethanol with 0.2 mol% of complexes 2 or 3a-e in p-xylene at 130 °C under an argon atmosphere resulted in dehydrogenation with the concomitant evolution of dihydrogen (Table 2.1). To allow for reproducible conditions, the catalyst and the reactants were first heated to 130 °C without solvent, which gives rise to very fast formation of the dihydrido-bridged dinuclear complex 4, after which p-xylene was added. The reactions are clearly not first-order in the substrate concentration, and product inhibition appears to limit the rate of reaction at higher conversions. As a reference the reaction was performed using Ru complex 1 with 12 equiv of TFA as the catalyst (entry 1). A significant amount of byproducts, predominantly 1-phenylethyl trifluoroacetate and di(1-phenylethyl)ether, were formed under these strongly acidic conditions. Byproduct formation was markedly reduced when using the
dininuclear Ru complex 2 as the catalyst (entry 2). However, this complex was clearly not very stable under the reaction conditions since the activity in dehydrogenation of 1-phenylethanol quickly decreased. Moreover, due to apparent decomposition of the catalyst a small amount of byproduct was still formed.

Table 2.1 Dehydrogenation of 1-phenylethanol at 130 °C using various catalysts.a

<table>
<thead>
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<th>yield (%)</th>
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<td>0.2</td>
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a Reaction conditions: 5 mmol of 1-phenylethanol, 0.25 mmol of 1,3,5-tri-tert-butylbenzene (internal standard); 2.5 mL of p-xylene; heated at 130 °C for 24 hours under an argon atmosphere in an open system. b Determined by GC; calculated values. c Turnover number. d 0.24 mmol TFA. e Catalyst is not completely dissolved during reaction. f Final conversion is given after 22 instead of 24 h. g 1.5 equiv of TFSA were added to the reaction.

The bidentate phosphine complexes 3a-e (entries 3-9) performed much better: no catalyst decomposition and no accompanying byproduct formation could be observed and the dehydrogenation activity was superior to that of complexes 1 and 2. The best results were obtained with complexes 3c and 3d. Remarkably, the solubility of the catalyst in the reaction medium is very limited in the case of the dppf complex 3c. With 0.2 mol% of 3c, part of the catalyst remained undissolved. This prompted us to repeat the reaction at lower concentrations of the catalyst (entries 6 and 7). The drop in conversion was clearly not proportional to the lower catalyst loading and a high TON of 651 for this reaction could be reached after 24 hours using 0.025 mol% of 3c, a catalyst loading guaranteeing a homogeneous reaction mixture. The reaction with bidentate complexes 3a-e eventually reaches complete conversion and with 0.2 mol% of rac-BINAP complex 3d a conversion of 92% was achieved after 48 hours,
corresponding to a TON of 230. Interestingly, no additives are required for this catalyst and it is active under relatively neutral conditions. This is in marked contrast to most other alcohol dehydrogenation catalysts, which require either excess base or acid (vide supra). Consequently, acid or base promoted byproduct formation is prevented when using the complexes 3a-e.

With the chiral (S)-BINAP catalyst 3e (entry 9), a slight enantiopreference for the dehydrogenation of (R)-1-phenylethanol could be observed. However, the enantiomeric excess (ee) of the remaining substrate never surmounted 4% and after 5 hours of reaction the unconverted substrate was again nearly racemic. This suggests that the enantioselectivity of the reaction is limited and that racemization is fast under these reaction conditions. The activity of 3e was slightly lower than that of the rac-BINAP catalyst 3d, presumably due to the absence of the more active meso-catalyst.

The isolated dihydrido-bridged Ru complex 4d was also applied as a catalyst in the dehydrogenation of 1-phenylethanol (entry 10). Although the catalyst was not completely dissolved, the observed rate of reaction is of the same order of magnitude as that for the reaction with 3d. Therefore, 4d appears to be a resting state in the catalytic cycle. In another experiment 4d was used as the catalyst along with 1.5 equivalents of free tetrafluorosuccinic acid (entry 11). However, this did not affect the rate of reaction. Since the activity of 4d is comparable to that of 3d and since addition of tetrafluorosuccinic acid in the dehydrogenation with 4d does not enhance the rate of reaction, free carboxylic acid does not seem to play a crucial role in the catalytic cycle.

2.6 Dehydrogenation of 1-phenylethanol at 100 °C

Interestingly, when the reaction was performed at 100 °C, it was first-order in substrate concentration (Table 2.2, Figure 2.6). Under these conditions no byproduct formation could be observed when employing catalysts 2 and 3, and depending on the catalyst a high yield of acetophenone was obtained after several days. Formation of the dinuclear Ru hydride complex 4 was very slow and almost inhibited: when using (S)-BINAP complex 3e as the catalyst, approximately 25% of the complex was converted to 4e and the rest could be recovered as 3e upon workup of the reaction mixture after 92 h as evidenced by 31P{1H} NMR. Decomposition of the catalyst was negligible. With the dpf complex 3c a similarly slow conversion of the complex into the dinuclear Ru hydride was observed, while solubility of the catalyst in the reaction medium was limited at catalyst loadings of 0.5 mol% and 0.25 mol% (entries 3 and 4). At a loading of 0.1 mol% the catalyst was almost completely dissolved (entry 5). At lower catalyst loadings an increasing deviation from first-order kinetics was observed (Figure 2.6). This can be rationalized by the formation of less active 4c, which is buffered by undissolved 3c at higher catalyst loadings. At a loading of 0.1 mol% of 3c a high initial TOF of 19.4 h⁻¹ and a
TON of 383 could be achieved. Again, no significant enantiopreference was observed using the chiral (S)-BINAP catalyst 3e (entry 6). Using complex 2 a TOF of 5.5 h\(^{-1}\) was achieved (entry 7). However, the stability of this catalyst was again limited and high conversions could not be reached, in contrast to dehydrogenation catalyzed by 3b, 3c and 3e.\(^{24}\)

<table>
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\(^{a}\) Reaction conditions: 0.5 mmol of 1-phenylethanol, 0.025 mmol of 1,3,5-tri-tert-butylbenzene (internal standard); 0.5 mL of toluene; reaction at 100 °C under an argon atmosphere in an open system. \(^{b}\) Turnover frequency; calculated according to: TOF = \(k \times (\text{initial substrate concentration}) / (\text{total Ru concentration})\) in which \(k\) is the rate constant as determined by fitting a straight line to the relationship between \(-\ln (1 - x)\) and time. \(^{c}\) Determined by GC; calculated values. \(^{d}\) Turnover number. \(^{e}\) Catalyst is not completely dissolved during reaction.

**Figure 2.6** Conversion data of the dehydrogenation of 1-phenylethanol catalyzed by complex 4c at 100 °C and with catalyst loadings of 0.5 (●), 0.25 (□) and 0.1 mol% (△) (Table 2.2, entries 3-5). The dashed line represents a fit of \(\ln(1-x) = -k\cdot t\) with the conversion data (0 – 24 h) of the experiment with a catalyst loading of 0.5 mol% (Table 2.2, entry 3, \(k = 3.5 \times 10^{-2} \text{ h}^{-1}\)).
2.7 Mechanism of the dehydrogenation of secondary alcohols

The behavior of $\text{PPh}_3$ complex 2 has been studied at elevated temperature by VT-NMR spectroscopy (Figure 2.7a). In $^{31}\text{P}[^1\text{H}]$ NMR, not only the two characteristic doublets coalesced at higher temperature, but judged from the appearance of a broad signal at 44.0 ppm, which is shifted downfield from the center of the two original doublets (at 40.2 and 45.4 ppm), another more flexible complex is apparently formed. It is reasonable to assume that at higher temperatures the water ligands are released and a mononuclear complex similar to complex 1 is formed. The original TFSA bridged dinuclear complex 2 was recovered upon cooling to room temperature. VT-NMR spectroscopy of complex 2 was then performed in the presence of 1-phenylethanol (Figure 2.7b). Coalescence is again observed at elevated temperatures but now a different complex is formed in the end, exhibiting a signal at 43.1 ppm. This complex is apparently a hydride complex as it also exhibits a (broad) signal at -16.7 ppm. Upon cooling to room temperature this complex is partly converted into the original dinuclear complex 2, while approximately half of the hydride complex remains. In the $^{19}\text{F}$ NMR spectrum two broad signals are observed at -123.8 and -119.2 ppm. The hydride complex rapidly decomposes upon exposure to air.

![Figure 2.7](image)

**Figure 2.7** (a) $^{31}\text{P}[^1\text{H}]$ NMR spectra of complex 2 in toluene-$d_8$ at (A) 25 °C; (B) 80 °C; (C) 90 °C; (D) 100 °C; and (E) after cooling to 25 °C. (b) $^{31}\text{P}[^1\text{H}]$ NMR spectra of complex 2 in the presence of 107 eq of 1-phenylethanol in toluene-$d_8$ at (A) 25 °C; (B) 60 °C; (C) 100 °C; and (D) after cooling to 25 °C.
Scheme 2.3 Tentative catalytic cycle for dehydrogenation of secondary alcohols by bis(tetrafluorosuccinato)-bridged complex 3

Considering the formation of these apparently mononuclear complexes under the reaction conditions and assuming catalytic behavior similar to that of the original TFA complex 1, a tentative catalytic cycle for the dehydrogenation of secondary alcohols by bis(tetrafluorosuccinato)-bridged complex 3 can be proposed (Scheme 2.3).\(^6\) At elevated temperature the dimer is assumed to be split into two mononuclear complexes I, both with one tridentate TFSA ligand. Coordination of an alcohol and subsequent transfer of its proton to the TFSA ligand will lead to the formation of complex II, in which one of the carboxylate functions of the TFSA ligand is converted to a carboxylic acid function. β-Hydride elimination produces a hydride ligand and a coordinated ketone while the carboxylate function of the TFSA ligand coordinates to the Ru with the carboxylic acid function uncoordinated (III). This is in contrast to the proposed catalytic cycle for the TFA complex 1 in which one of the two TFA ligands is released, necessitating an excess of acid and creating highly acidic reaction conditions. Loss of the weakly coordinated ketone results in the formation of complex IV. Attack of the carboxylic acid function in complex IV on the hydride would then liberate molecular hydrogen and restore the active catalyst I. The formation of dihydrido-bridged complex 4 is the result of a side reaction, which, depending on the reaction conditions can be suppressed. For the dehydrogenation results at 130 °C, presented in Table 2.1, fast formation of 4 was ensured. In that case the reaction involves a different, unknown, catalytic cycle.
2.8 Conclusion

A range of novel dinuclear Ru dicarboxylate complexes has been synthesized. Both bis(tetrafluorosuccinato)-bridged complexes 3 and dihydrido-bridged complexes 4 are highly stable and have been fully characterized. These complexes catalyze the acceptorless catalytic dehydrogenation of 1-phenylethanol with good yield and high selectivity under relatively mild conditions: no additives are required and the catalyst is active under neutral conditions. High turnover numbers up to 543 after five hours have been achieved with the ferrocene complex 3c. A tentative catalytic cycle for the acceptorless dehydrogenation of secondary alcohols by complexes 3a-e has been proposed. Complexes 3a-e are also highly active in the racemization of secondary alcohols and their application in the dynamic kinetic resolution (DKR) of secondary alcohols is reported in Chapter 3.26

2.9 Experimental section

General methods
All reactants and solvents were obtained from commercial suppliers and were used as received. Ru(OCOCF3)2(CO)(PPh3)2 (1) was synthesized according to a literature procedure.13 All experiments were carried out under a dry argon atmosphere using standard Schlenk techniques.

1H, 13C, and 31P NMR spectra were recorded on a Varian Mercury Vx 400 (400 Mhz for 1H NMR, 101 MHz for 13C NMR and 162 MHz for 31P NMR) or on a Varian Unity Inova 500 (500 MHz for 1H NMR, 126 MHz for 13C NMR and 202 MHz for 31P NMR) spectrometer. 19F NMR spectra were recorded on a Varian Mercury Vx 400 spectrometer at 376 MHz. 1H and 13C{1H} NMR chemical shifts are reported in ppm downfield of tetramethylsilane. 31P{1H} NMR chemical shifts are reported in ppm downfield from H3PO4 and are referenced to an external solution of 85% H3PO4 in D2O. 19F NMR chemical shifts are referenced to internal C6F6 at -162.9 ppm. Abbreviations used are: s, singlet; d, doublet; t, triplet; dd, double doublet; tt, triple triplet; m, multiplet; br, broad. IR-spectra were recorded on a Perkin Elmer ATR-IR Spectrum One. MALDI-TOF MS spectra were recorded on a PerSeptive Biosystems Voyager DE PRO spectrometer using trans-2-[3-(4-tert-butylphenyl)-2-methyl-2-propenylidene]malononitrile (DCTB) as a matrix. GC analyses was performed on a Shimadzu 6C-17A GC equipped with a Chrompack Chirasil-DEX CB (DF=0.25) column and an FID. Elemental analyses were performed on a Perkin Elmer 2400 series II CHN Analyzer.

Ru(μ-OCO-C2F4-OCO)(CO)(H2O)(PPh3)2, 2
A round-bottom flask was charged with RuH2(CO)(PPh3)3 (2.5 g, 2.7 mmol), tetrafluorosuccinic acid (0.8 g, 4.2 mmol) and toluene (60 mL). The reaction mixture was refluxed under a flow of argon for 1 h to yield a dark yellow solution. The solvent was evaporated in vacuo and the crude product was dissolved in CH2Cl2. The organic phase was washed with water (2x) and dried over MgSO4. The solvent was evaporated in vacuo and crystallization of the residue from CHCl3/n-pentane yielded the product as yellow needles. Yield: 1.5 g (64%).
IR (ATR): 1971 (νCO), 1652 (νCO,acid) cm−1. 31P{1H} NMR (CDCl3): 40.8 (d, 2JPP = 29.2 Hz, 2P), 43.6 (d, 2JPP = 29.2 Hz, 2P). 1H NMR (CDCl3): 6.32 (br, 4H, Ru−OH2), 7.00 (m, 12H, C6H5), 7.11 (m, 12H, C6H5), 7.31 (m, 36H, C6H5). 19F NMR (CDCl3): -123.0 (br d, 2JFF = 260 Hz, 2F), -120.3 (br d, 2JFF = 273 Hz, 2F). -
Chapter 2

Ru(μ-OCO-C₂F₄-OCO)(CO)(H₂O)(dppp)₂, 3a
A round-bottom flask was charged with 2 (175 mg, 0.10 mmol), 1,3-bis(diphenylphosphino)propane (88 mg, 0.21 mmol) and toluene (15 mL). The reaction mixture was allowed to react for 2 h at 100 °C. The solvent was evaporated in vacuo and the crude product was obtained upon precipitation from toluene by addition of n-pentane. Recrystallization from CHCl₃/methanol with slow diffusion of n-pentane gave yellow needles. Yield: 135 mg (89%).

IR (ATR): 1984 (ν CO), 1680 (ν CO,acid), 1625 (ν CO,acid) cm⁻¹. ³¹P{¹H} NMR (CDCl₃): 36.6 (d, 2JPP = 42.8 Hz, 2P), 40.1 (d, 2JPP = 42.8 Hz, 2P). ¹H NMR (CDCl₃): 1.76 (m, 2H), 2.17 (m, 4H), 2.41 (m, 2H), 2.78 (m, 4H), 5.52 (br, 4H, Ru−OH₂), 7.0 - 8.1 (C₆H₅, 40H). ¹⁹F NMR (CDCl₃): -123.6, (br d, 2JFF = 173 Hz, 2F), -122.9, (br d, 2JFF = 173 Hz, 2F), -118.2, (m, 2JFF = 218 Hz, 3JFF = 17 Hz, 3JFF = 9 Hz, 2F), -117.5, (m, 2JFF = 218 Hz, 2JFF = 17 Hz, 2JFF = 9 Hz, 2F). ¹³C{¹H} NMR (CDCl₃): 19.1 (m, 2C, P−CH₂−C₆H₂), 27.1 (m, 4C, P−C₆H₂−CH₂), 128.4-134.1 (aromatic, 48C), 164.0 (t, 2C, OCO), 170.0 (t, 2C, OCO), 202.9 (t, 2C, Ru−CO). MS (MALDI-TOF, matrix: DCTB): 1461 [M − 2 H₂O + H⁺], 731 [½M − H₂O + H⁺]. Anal. Calcd. for C₆₄H₅₆F₈O₁₂P₄Ru₂: C, 51.41; H, 4.06. Found: C, 51.39; H, 3.89.

Ru(μ-OCO-C₂F₄-OCO)(CO)(H₂O)(dppb)₂∙H₂O, 3b
A round-bottom flask was charged with 2 (176 mg, 0.10 mmol), 1,4-bis(diphenylphosphino)butane (90 mg, 0.21 mmol) and chloroform (15 mL). The reaction mixture was allowed to react for 1.5 h at 60 °C. The solvent was evaporated in vacuo and the crude product was obtained upon precipitation from chloroform by addition of n-pentane. Recrystallization from CHCl₃/methanol with slow diffusion of n-pentane gave yellow needles. Yield: 132 mg (85%).

IR (ATR): 1992 (ν CO), 1968 (ν CO), 1968 (ν CO,acid), 1645 (ν CO,acid) cm⁻¹. ³¹P{¹H} NMR (CDCl₃): 41.3 (d, 2JPP = 33.4 Hz, 2P), 41.7 (d, 2JPP = 33.4 Hz, 2P). ¹H NMR (CDCl₃): 1.76 (m, 8H), 1.7 (br, 2H, H₂O), 2.54 (m, 2H), 2.69 (m, 4H), 2.83 (m, 2H), 6.23 (br, 4H, Ru−OH₂), 7.3 - 7.8 (aromatic, 40H). ¹⁹F NMR (CDCl₃): -121.2, (4F), -120.5, (br d, 2JFF = 264 Hz, 2F), -118.2, (br d, 2JFF = 264 Hz, 2F). ¹³C{¹H} NMR (CDCl₃): 22.9 (m, 4C, P−CH₂−CH₂), 29.6 (m, 4C, P−CH₂−CH₂), 128.5 (m, 4C, m-C₆H₅-P), 128.8 (m, 4C, m-C₆H₅-P), 130.4 (br, 2C, p-C₆H₅-P), 130.8 (br, 2C, p-C₆H₅-P), 130.9 (br, 2C, i-C₆H₅-P), 130.9 (br, 4C, p-C₆H₅-P), 132.3 (d, 2JCP = 8.5 Hz, 2C, o-C₆H₅-P), 132.6 (d, 2JCP = 50.3 Hz, 2C, i-C₆H₅-P), 132.5 (d, 2JCP = 44.3 Hz, 2C, i-C₆H₅-P), 132.5 (d, 2JCP = 8.1 Hz, 2C, o-C₆H₅-P), 133.2 (d, 2JCP = 8.6 Hz, 2C, o-C₆H₅-P), 133.9 (d, 2JCP = 8.1 Hz, 2C, o-C₆H₅-P), 134.0 (d, 1JCP = 53.3 Hz, 2C, i-C₆H₅-P), 165.5 (t, 2JCP = 25.6 Hz, 2C, OCO), 168.9 (t, 2JCP = 26.8 Hz, 2C, OCO), 202.2 (t, 2JCP = 17.6 Hz, 2C, Ru−CO). MS (MALDI-TOF, matrix: DCTB): 1489 [M − 2 H₂O + H⁺], 745 [½M − H₂O + H⁺]. Anal. Calcd. for C₆₆H₆₄F₈O₁₃P₄Ru₂: C, 51.43; H, 4.06. Found: C, 51.39; H, 3.89.

Ru(μ-OCO-C₂F₄-OCO)(CO)(H₂O)(dppf)₂∙H₂O, 3c
A round-bottom flask was charged with 2 (199 mg, 0.12 mmol), 1,1’-bis(diphenylphosphino)ferrocene (147 mg, 0.27 mmol) and toluene (22 mL). The reaction mixture was allowed to react for 1 h at 100 °C, resulting in an orange suspension. The crude product precipitated from the reaction mixture upon
addition of n-pentane. Recrystallization from CHCl₃/methanol with slow diffusion of n-pentane gave orange crystals. Yield: 146 mg (71%).

IR (ATR): 1972 (νCO), 1651 (νCO,acid) cm⁻¹. ³¹P{¹H} NMR (CDCl₃): 45.1 (d, ²JPP = 30.5 Hz, 2P), 46.3 (d, ²JPP = 30.5 Hz, 2P). ¹H NMR (CDCl₃): 1.86 (br, 2H, H₂O), 4.29 (m, 2H, C₅H₄), 4.33 (m, 2H, C₅H₄), 4.36 (m, 2H, C₅H₄), 4.44 (m, 2H, C₅H₄), 4.47 (m, 2H, C₅H₄), 4.53 (m, 2H, C₅H₄), 4.80 (m, 2H, C₅H₄), 6.30 (br, 4H, Ru−O), 7.2 - 8.9 (56H, C₆H₅). ¹⁹F NMR (CDCl₃): -123.5, (br dd, 2JFF = 262 Hz, 3JFF = 16 Hz, 2F), -120.4, (br dd, 2JFF = 275 Hz, 3JFF = 16 Hz, 2F), -119.5, (br dd, 2JFF = 262 Hz, 3JFF = 16 Hz, 2F), -116.2, (br dd, ²JFF = 275 Hz, ³JFF = 16 Hz, 2F).

1H NMR (CDCl₃): 1.86 (br, 2H, H₂O), 4.29 (m, 2H, C₅H₄), 4.33 (m, 2H, C₅H₄), 4.36 (m, 2H, C₅H₄), 4.44 (m, 2H, C₅H₄), 4.47 (m, 2H, C₅H₄), 4.53 (m, 2H, C₅H₄), 4.80 (m, 2H, C₅H₄), 6.30 (br, 4H, Ru−O), 7.2 - 8.9 (56H, C₆H₅). ¹⁹F NMR (CDCl₃): -123.5, (br dd, 2JFF = 262 Hz, 3JFF = 16 Hz, 2F), -120.4, (br dd, 2JFF = 275 Hz, 3JFF = 16 Hz, 2F), -119.5, (br dd, 2JFF = 262 Hz, 3JFF = 16 Hz, 2F), -116.2, (br dd, ²JFF = 275 Hz, ³JFF = 16 Hz, 2F).

1H NMR (CDCl₃): 1.86 (br, 2H, H₂O), 4.29 (m, 2H, C₅H₄), 4.33 (m, 2H, C₅H₄), 4.36 (m, 2H, C₅H₄), 4.44 (m, 2H, C₅H₄), 4.47 (m, 2H, C₅H₄), 4.53 (m, 2H, C₅H₄), 4.80 (m, 2H, C₅H₄), 6.30 (br, 4H, Ru−O), 7.2 - 8.9 (56H, C₆H₅). ¹⁹F NMR (CDCl₃): -123.5, (br dd, 2JFF = 262 Hz, 3JFF = 16 Hz, 2F), -120.4, (br dd, 2JFF = 275 Hz, 3JFF = 16 Hz, 2F), -119.5, (br dd, 2JFF = 262 Hz, 3JFF = 16 Hz, 2F), -116.2, (br dd, ²JFF = 275 Hz, ³JFF = 16 Hz, 2F).

Ru(μ-OCO-C₂F₄-OCO)(CO)(H₂O)(rac-BINAP)₂, 3d

A 50 mL glass microwave reactor vessel (Milestone) was charged with 2 (246 mg, 0.14 mmol), rac-2,2’-bis(diphenylphosphino)-1,1’-binaphthylene (BINAP) (202 mg, 0.32 mmol) and toluene (30 mL). The reactor was flushed with argon. The reaction mixture was allowed to react at 180 °C for 80 min using a maximum power of 600 W. After cooling, n-pentane (15 mL) was added to the reaction mixture and 3d was subsequently obtained upon filtration and washing with n-pentane. Yield: 219 mg (80%).

Similarity of NMR (¹H, ¹³C, ¹⁹F and ³¹P) data to that of the (S)-BINAP complex 3e, indicated the major product to be the racemic complex. From ³¹P{¹H} NMR data the fraction of racemic product was estimated as > 80%. The signals for the meso-complex could not be resolved. IR (ATR): 1985 (νCO), 1979 (νCO), 1675 (νCO), 1667 (νCO) cm⁻¹. MS (MALDI-TOF, matrix: DCTB): 1745 [M − 2 H₂O + H⁺], 873 [½M - H₂O + H⁺]. Anal. Calcd. for C₇₈H₆₂F₈Fe₂O₁₃P₄Ru₂: C, 52.13; H, 3.48. Found: C, 52.09; H, 3.26.

Ru(μ-OCO-C₂F₄-OCO)(CO)(H₂O)((S)-BINAP)₂, 3e

A 50 mL glass microwave reactor vessel (Milestone) was charged with 2 (200 mg, 0.12 mmol), (R)-(−)-2,2’-bis(diphenylphosphino)-1,1’-binaphthylene (BINAP) (190 mg, 0.31 mmol) and toluene (25 mL). The reactor was flushed with argon. The reaction mixture was allowed to react at 180 °C for 40 min using a maximum power of 600 W. The solvent was evaporated in vacuo and the crude product was obtained by precipitation by addition of n-pentane to a CH₂Cl₂ solution. Recrystallization from CHCl₃ with slow diffusion of n-pentane gave yellow crystals. Yield: 164 mg (74%).

IR (ATR): 1977 (νCO), 1655 (νCO,acid) cm⁻¹. ³¹P{¹H} NMR (CDCl₃): 42.8 (d, ²JPP = 30.5 Hz, 2P), 44.4 (d, ²JPP = 30.5 Hz, 2P). ¹H NMR (CDCl₃): 6.07 (br, 4H, Ru−O), 6.4 - 7.8 (aromatic, 64H). ¹⁹F NMR (CDCl₃): -122.9 (br d, ²JFF = 256 Hz, 2F), -122.6 (br d, ²JFF = 260 Hz, 2F), -117.8 (br d, ³JFF = 260 Hz, 2F), -117.4 (br d, ³JFF = 256 Hz, 2F).

Ru(μ-OCO-C₂F₄-OCO)(CO)(H₂O)((S)-BINAP)₂, 3e

A 50 mL glass microwave reactor vessel (Milestone) was charged with 2 (200 mg, 0.12 mmol), (R)-(−)-2,2’-bis(diphenylphosphino)-1,1’-binaphthylene (BINAP) (190 mg, 0.31 mmol) and toluene (25 mL). The reactor was flushed with argon. The reaction mixture was allowed to react at 180 °C for 40 min using a maximum power of 600 W. The solvent was evaporated in vacuo and the crude product was obtained by precipitation by addition of n-pentane to a CH₂Cl₂ solution. Recrystallization from CHCl₃ with slow diffusion of n-pentane gave yellow crystals. Yield: 164 mg (74%).

IR (ATR): 1977 (νCO), 1655 (νCO,acid) cm⁻¹. ³¹P{¹H} NMR (CDCl₃): 42.8 (d, ²JPP = 30.5 Hz, 2P), 44.4 (d, ²JPP = 30.5 Hz, 2P). ¹H NMR (CDCl₃): 6.07 (br, 4H, Ru−O), 6.4 - 7.8 (aromatic, 64H). ¹⁹F NMR (CDCl₃): -122.9 (br d, ²JFF = 256 Hz, 2F), -122.6 (br d, ²JFF = 260 Hz, 2F), -117.8 (br d, ³JFF = 260 Hz, 2F), -117.4 (br d, ³JFF = 256 Hz, 2F).

Ru(μ-OCO-C₂F₄-OCO)(CO)(H₂O)((S)-BINAP)₂, 3e
[Ru(μ-H)(μ-OCO-C$_2$F$_4$-OCO)(CO)(rac-BINAP)]$_2$$\cdot$3H$_2$O, 4d

A 100 mL flask was charged with 2 (500 mg, 0.29 mmol), rac-2,2'-bis(diphenylphosphino)-1,1'-binaphthalene (BINAP) (477 mg, 0.77 mmol) and p-xylene (25 mL). The reaction mixture was allowed to react for 20 h at 130 °C. $^1$H NMR data indicated that the reaction was not complete and additional rac-2,2'-bis(diphenylphosphino)-1,1'-binaphthalene (BINAP) (390 mg, 0.63 mmol) and p-xylene (20 mL) were added. The reaction mixture was allowed to react for 19 h at 138 °C under an argon atmosphere. The resulting suspension was centrifuged and the residue was used without further purification. A 50 mL flask was charged with the crude product and 20 mL of 1-phenylethanol. The reaction mixture was allowed to react for 1 h at 130 °C and then allowed to cool to room temperature. The solvent was evaporated in vacuo and the crude product was dissolved in CH$_2$Cl$_2$ (20 mL). Addition of ethanol (30 mL) resulted in the crystallization of excess rac-BINAP. Filtration and subsequent concentration of the filtrate in vacuo yielded the crude product which was further purified by precipitation by addition of n-pentane to a CH$_2$Cl$_2$ solution. Yield: 332 mg (65%). 4d was also synthesized on a small scale using the method reported for 4e.

NMR signals for rac-4d and (R,S)-4d overlap, rendering accurate assignment impossible. As expected, the signals for rac-4d correspond to the data reported for 4e. Selected NMR data for (R,S)-4d in CDCl$_3$: $^1$H NMR: -10.72 (tt, 1H, Ru-H-Ru), -10.60 (tt, 1H, Ru-H-Ru), 6.6 - 8.1 (64H, aromatic). $^{31}$P{1H} NMR: 41.4 (m, 2P), 44.5 (m, 2P). $^{19}$F NMR: -115.4 (br, 2F), -114.9 (br, 2F).

[Ru(μ-H)(μ-OCO-C$_2$F$_4$-OCO)(CO)((S)-BINAP)]$_2$$\cdot$3H$_2$O, 4e

A 100 mL flask was charged with 3e (209 mg, 0.11 mmol), 2-propanol (3.3 g, 55 mmol), and triethylamine (2.8 g, 28 mmol). The mixture was allowed to react for 2 h at 25 °C. The reaction mixture was then concentrated in vacuo and the crude product was purified by filtration over silica gel using ethyl acetate as the eluent. Yield: 136 mg (74%). IR (ATR): 1979 (νCO), 1679 (νCO,acid), 1614 (νCO,acid) cm$^{-1}$. $^{31}$P{1H} NMR (CDCl$_3$): 38.8 (dd, $^3$J$^\text{PP} = 36.0$ Hz, $^1$J$^\text{PP} = 26.1$ Hz, 2P), 46.4 (dd, $^3$J$^\text{PP} = 36.0$ Hz, $^1$J$^\text{PP} = 26.1$ Hz, 2P). $^1$H NMR (CDCl$_3$): -10.38 (tt, $^3$J$^\text{HP} = 48.0$ Hz, $^1$J$^\text{HP} = 10.0$ Hz, 2H, Ru-H-Ru), 1.78 (br, 6H, H$_2$O), 6.6 - 8.1 (64H, aromatic). $^{19}$F NMR (CDCl$_3$): -114.9 (br d, $^3$J$^\text{FF} = 271$ Hz, 1F), -114.4 (br d, $^3$J$^\text{FF} = 271$ Hz, 1F), -113.8 (br d, $^3$J$^\text{FF} = 271$ Hz, 1F), -113.4 (br d, $^3$J$^\text{FF} = 271$ Hz, 1F). $^{13}$C{1H} NMR (CDCl$_3$): 126 - 140 (aromatic, 88C), 161.9 (t, 1C, CO), 164.4 (t, 1C, OCO), 203.5 (t, 2C, Ru−CO). Anal. Calcd. for C$_{98}$H$_{68}$F$_8$O$_{12}$P$_4$Ru$_2$: C, 64.60; H, 4.15. Found: C, 64.40; H, 3.77.

Typical procedure for the dehydrogenation of 1-phenylethanol at 130 °C

An oven-dry 40 mL Radley carrousel reaction tube was charged with catalyst (0.01 mmol 2, 3 or 4, 0.02 mmol 1), 1-phenylethanol (5 mmol) and 1,3,5-tri-tert-butylbenzene (0.25 mmol). The reaction tube was placed in a 12 tube Radley reaction carrousel and heated to 130 °C under an argon atmosphere in an open system. At 130 °C p-xylene (2 mL) was added and the reaction was stirred for several hours (the pre-activation time was consequently of the order of 10 minutes). Small aliquots of reaction mixture were taken for GC analysis. [Due to reaction conditions (high temperature, open system) and the limited reflux ability of the caroussel reactor used, loss of a few percent of substrate/product could not be avoided. The internal standard could, therefore, not be used for the calculation of conversions. However, no byproducts were observed or expected based on GC and $^1$H NMR analysis except for a trace amount of byproducts originating from the second TFSA ligand.]
Table 2.3 Crystallographic data for crystal structure determinations 2, rac-4d, and (R,S)-4d.

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</tbody>
</table>

*a Excluding disordered solvent contribution, including hydride atom contribution. b \( R₁ = \Sigma||F_o| - |F_c|| / \Sigma|F_o| . c wR₂ = [\Sigma[w(Fo²-Fc²)^2] / \Sigma[w(Fo²)^2]]^{1/2} . d P = (Max(Fo²,0) + 2F_c²) / 3. \)
Chapter 2

Typical procedure for the dehydrogenation of 1-phenylethanol at 100 °C
A Schlenk tube was charged with catalyst (0.0025 mmol), 1-phenylethanol (0.5 mmol), 1,3,5-tri-tert-butylbenzene (0.025 mmol) and toluene (1 mL). The reaction mixture was heated at 100 °C for several hours under an argon atmosphere in an open system. Small aliquots of reaction mixture were taken for GC analysis.

X-ray crystal structure analyses. Pertinent data for the structure determinations are given in Table 2.3. Data was collected at 150 K on a Nonius KappaCCD diffractometer on rotating anode (graphite-monochromated Mo Kα radiation, λ = 0.71073 Å). The unit-cell parameters were checked for the presence of higher lattice symmetry.27 The structures were solved with direct methods using SHELXS8628 (compound 2) or automated Patterson and subsequent difference Fourier methods using DIRDIF9929 (compounds 4d). Refinement on $P^2$ was performed with SHELXL-97.30 All hydrogen atoms were included on calculated positions riding on their carrier atoms. The crystal of rac-4d turned out to be a twin. The twin operation was a rotation of 180 deg around the b-axis (twin matrix -1 0 0, 0.159 1 -0.713, 0 0 -1) with a minor twin component of 0.1713(19). The structure was refined on detwinned intensity data. All three structures showed a large area of disordered solvent for which no satisfactory atomic model could be obtained. The contribution of the disordered solvent to the scattered intensity was taken into account with the squeeze procedure, as incorporated in PLATON.31 The data set of (R,S)-4d showed a strong drop in intensity at higher diffraction angles. Data were therefore collected up till θ = 20 deg. To maintain a reasonable data:parameter ratio, the carbon atoms were refined with isotropic displacement parameters. The hydride atoms in the structures of (R,S)-4d and rac-4d could not be unambiguously located and were therefore left out of the refined model. Neutral atom scattering factors and anomalous dispersion corrections were taken from the International Tables for Crystallography.32 Validation, geometrical calculations, and illustrations were performed with PLATON.31

2.10 References and notes

14. Synthesis of analogous complexes with perfluoroglutaric acid or succinic acid yielded intractable solids which were not further investigated. A complex analogous to 2 with two 2,2-difluorosuccinic acid ligands was successfully synthesized, but catalytic performance was inferior to that of the perfluorosuccinic acid complex.
16. Complexes 3b and 3c were isolated as a complex containing an extra molecule of mobile water as judged from 1H NMR and elemental analysis.
17. Complex 4e was isolated as a trihydrate as judged from 1H NMR and elemental analysis.
18. The difference between both C-O bond lengths is 0.00(2) and 0.009(11) Å for both complexes in the unit cell of rac-4d and 0.12(4) Å for (R,S)-4d.
20. Sheldrick, G. M. SHELXS-97 Program for crystal structure refinement; University of Göttingen, Germany, 1997.
22. Sheldrick, G. M. SHELXS86 Program for crystal structure determination; University of Göttingen: Germany, 1986.
Racemization and Dynamic Kinetic Resolution of Secondary Alcohols by a bis(Tetrafluorosuccinato)-Bridged Ru(II) Complex

Abstract

The novel dinuclear bis(tetrafluorosuccinato)-bridged Ru(II) complexes that were introduced in Chapter 2 were investigated with regard to their potential in the racemization of secondary alcohols. A complex bearing rac-BINAP ligands proved an excellent catalyst for the racemization of 1-phenylethanol. Dynamic kinetic resolution (DKR) of 1-phenylethanol with isopropyl butyrate as the acyl donor and Novozym 435 as the enzyme was performed effectively at 70 °C requiring only 0.10 mol% of this racemization catalyst. Activation of the Ru catalyst with K$_2$CO$_3$ was necessary. Reaction in presence of ketone was complete within 10 h giving an ee exceeding 99%. Without ketone, complete reaction was achieved in 23 h, giving an equally high ee. Besides the aromatic alcohol 1-phenylethanol, four other substrates were shown to undergo the DKR successfully. These substrates represent an aliphatic secondary alcohol (2-octanol), an aromatic alcohol bearing an electron-withdrawing substituent on the phenyl ring (α-methyl-4-(trifluoromethyl)benzyl alcohol), an aromatic alcohol bearing an electron-releasing substituent on the ring (α-methyl-4-methoxybenzyl alcohol) and a heteroaromatic secondary alcohol (1-(2-furyl)ethanol). Reaction in presence of the ketone, corresponding to the alcohol, gave the best results.
3.1 Introduction

During the past decades, there has been an ever increasing demand for enantiopure compounds, mainly for pharmaceutical applications. Enantiomers in general exhibit different biological activities and easy access to both enantiomers is, therefore, of paramount importance. Optically active secondary alcohols are valuable building blocks for such pharmaceuticals. They can be produced by asymmetric synthesis from the corresponding ketone, which is usually readily available (using either bio- or chemocatalysis). However, on an industrial scale enantiopure alcohols are often isolated by resolution of the corresponding racemate. Many approaches are based on the R-selective lipase-catalyzed transesterification of secondary alcohols, which normally proceeds with high enantioselectivity. An inherent drawback of this strategy is that the maximum yield is limited to 50%.

A solution to this problem is presented by chemoenzymatic dynamic kinetic resolution (DKR). In this application of tandem catalysis, in situ racemization enables complete conversion of the racemate into the desired enantiomer (Scheme 3.1). In principle, 100% of the R-ester can hence be obtained with 100% ee from a racemic alcohol. Besides the requirement for efficient kinetic resolution and racemization, catalyst compatibility is obviously a key issue in the development of a successful DKR. Moreover, the rates of the two catalytic reactions have to be adapted to each other in order to achieve the desired results at minimal loadings of both catalysts (see section 1.2).

Scheme 3.1 DKR of secondary alcohols.

The performance of various Ru-based racemization catalysts has been reported previously. The catalysts that produced the most promising results are presented in Figure 3.1. The first successful DKR of secondary alcohols was reported by Bäckvall et al., employing catalyst A and Novozym 435 (Candida Antarctica Lipase B immobilized on an acrylic resin). Various secondary alcohols were thus converted into the corresponding R-acetate, with high ee and moderate isolated yields (60 – 80%). Typically the reaction was complete within 48 h,
although requiring at least 2 mol% of Ru catalyst A. In these experiments p-chlorophenylacetate was used as the acyl donor, since p-chlorophenol does not interfere with the racemization reaction. However, due to environmental and economic considerations, this acyl donor is highly undesirable. Therefore, Verzijl et al. developed a process to perform the DKR using simple esters such as isopropyl butyrate. The isopropanol formed by transesterification is continuously removed at reduced pressure. This process enables large scale application of DKR.

![Figure 3.1 Ru catalysts successfully applied in DKR of secondary alcohols.](image)

In contrast to the other catalysts in Figure 3.1, catalyst B can be synthesized in-situ from the commercially available precursor [RuCl₂(p-cymene)]₂ and 2-phenyl-2-amino-propionamide in the presence of K₂CO₃. Excellent results were obtained at 70 °C with only 0.2 mol% of this Ru catalyst, resulting in excellent yields and ee within 24 h. Racemization catalysts C and D enable DKR at ambient temperature. Catalyst C, which was introduced by Park et al., produced excellent yields and ee at 25 °C, although typically requiring several days of reaction and 4 mol% of catalyst. Catalyst D, developed by Bäckvall et al., represents the most active racemization catalyst for DKR known to date. Excellent results are normally obtained in 3 – 24 h, depending on the substrate, employing 5 mol% of Ru catalyst. Importantly, Park et al. recently reported that catalyst E, an air-stable racemization catalyst, enables DKR without the requirement of an inert atmosphere.

Many substrates were converted into the enantiopure ester in good yields, including a broad range of substituted aromatic and aliphatic secondary alcohols and secondary diols. The S-esters could be obtained when using subtilisin instead of a lipase and with the appropriate racemization catalyst, even secondary amines were selectively transformed into the corresponding R-amide via DKR. In an approach similar to DKR, we and others have recently
Chapter 3

reported on the conversion of a racemic monomer into the enantiopure polymer.\textsuperscript{15} R-polyesters were obtained in good yield and selectivity from ω-substituted ε-caprolactones.

In Chapter 2 we introduced a novel dinuclear Ru(II) complex bearing tetrafluorosuccinate and phosphine ligands (Figure 3.2).\textsuperscript{16} Promising results were obtained in the acceptorless dehydrogenation of 1-phenylethanol. We were then interested in its application as a racemization catalyst in DKR. In this chapter, DKR of various secondary alcohols using complex 3d as the racemization catalyst is described, giving excellent yields and ee.

![Figure 3.2 Dinuclear Ru complexes bearing tetrafluorosuccinate and phosphine ligands.](image)

**Scheme 3.2 Racemization of (S)-1-phenylethanol.**

### 3.2 Racemization of (S)-1-phenylethanol

The various complexes that were introduced in Chapter 2 of this thesis were screened in the racemization of (S)-1-phenylethanol ((S)-5a) at 70 °C (Scheme 3.2, Table 3.1). K\textsubscript{2}CO\textsubscript{3} was used to activate the catalyst. Additionally, the dihydrido-bridged Ru complex bearing S-BINAP ligands, 4e, and the mononuclear Ru complex bearing TFA and PPh\textsubscript{3} ligands, 1, were tested in the racemization reaction (Figure 3.3).
While PPh₃ complex 2 showed only limited racemization activity (entry 1), the complexes bearing bidentate phosphine ligands performed much better (entries 2-8). Most notably, nearly complete racemization was observed, when employing only 0.05 mol% of rac-BINAP complex 3d (entry 6). In the absence of K₂CO₃, no racemization was observed (entry 7). Complex 3e, bearing S-BINAP ligands, was only slightly less active in the racemization of (S)-5a. This is in agreement with the observation that dehydrogenation of 5a using this catalyst is hardly enantioselective (see Chapter 2). Complex 4e, which could be isolated after dehydrogenation of 5a, showed almost no racemization activity, indicating that this complex is not part of the catalytic cycle for the racemization (entry 9). Complex 1 also proved to be a poor racemization catalyst (entry 10). As a reference, the racemization of 5a was also performed with catalysts A and B (Figure 3.1, Table 3.1, entries 11 and 12). As expected, racemization activity of catalyst A was limited, while catalyst B performed much better. The racemization activity of complex 3d is clearly superior, however. Judging from these results, catalyst 3d is a very active catalyst for the racemization of 5a and, for this reason, this catalyst was employed for further racemization and DKR experiments described in this chapter.
3.3 Kinetics of the racemization of secondary alcohols

When it is assumed that intrinsic kinetics are obeyed and that the reaction follows first order kinetics, the racemization of an S-secondary alcohol can be represented as follows:

\[
S \xrightarrow{k_1} R
\]

\[
S \xleftarrow{k_{-1}} R
\]

(Eq. 3.1)

In this equation, \( S \) represents the \( S \)-enantiomer of the alcohol while \( R \) represents the \( R \)-enantiomer. By definition both rate constants should be equal in case of racemization by an achiral catalyst:

\[
k_1 = k_{-1} = k'
\]

(Eq. 3.2)

A mass balance for \( S \) in a batch process gives:

\[
-\frac{d[S]}{dt} = k_1 \cdot [S] - k_{-1} \cdot [R] = k'([S] - [R])
\]

(Eq. 3.3)

The ee of the alcohol is defined as:

\[
ee = \frac{[S] - [R]}{[S] + [R]}
\]

(Eq. 3.4)

During racemization the total alcohol concentration does not change:

\[
[S] + [R] = C
\]

(Eq. 3.5)

Combining Eq. 3.4 and 3.5 gives:
\[ ee = \frac{2 \cdot [S] - C}{C} \]  
(Eq. 3.6)

Changing from variable \([S]\) to variable \(ee\) in Eq. 3.3 leads to:

\[ \frac{d(ee)}{d[S]} = \frac{2}{C} \]  
(Eq. 3.7)

and:

\[ \frac{-C}{2} \frac{d(ee)}{dt} = k' C \cdot ee \]  
(Eq. 3.8)

This results in:

\[ \frac{d(ee)}{dt} = -2k' ee \]  
(Eq. 3.9)

The conversion can be defined as:

\[ X = \frac{ee_0 - ee}{ee_0} = 1 - \frac{ee}{ee_0} \]  
(Eq. 3.10)

In this equation \(ee_0\) represents the \(ee\) at the start of the reaction. Changing from variable \(ee\) to variable \(X\) in Eq. 3.9 leads to:

\[ \frac{d(ee)}{dX} = -ee_0 \]  
(Eq. 3.11)

and:

\[ -ee_0 \frac{dX}{dt} = -2k' ee_0 \cdot (1 - X) \quad \text{or:} \quad \frac{dX}{(1 - X)} = k'' dt \]  
(Eq. 3.12)

Therefore, when the conversion is defined as stated in Eq 3.10 the racemization obeys first order global kinetics so a linear relationship between \(-\ln(1-X)\) and time \((t)\) should exist.
Table 3.2 Racemization of 5a employing 3d as racemization catalyst.\textsuperscript{a}

<table>
<thead>
<tr>
<th>entry</th>
<th>T (°C)</th>
<th>ketone (mmol)</th>
<th>time (min.)</th>
<th>ee\textsuperscript{b} (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>70</td>
<td>No ketone</td>
<td>180</td>
<td>6.5</td>
</tr>
<tr>
<td>2</td>
<td>100</td>
<td>No ketone</td>
<td>180</td>
<td>27.1</td>
</tr>
<tr>
<td>3</td>
<td>70</td>
<td>6a (0.7 mmol)</td>
<td>180</td>
<td>0.5</td>
</tr>
<tr>
<td>4</td>
<td>100</td>
<td>6a (0.7 mmol)</td>
<td>40</td>
<td>0.1</td>
</tr>
<tr>
<td>5</td>
<td>100</td>
<td>6a (1.0 mmol)</td>
<td>80</td>
<td>0.4</td>
</tr>
<tr>
<td>6</td>
<td>100</td>
<td>7a (1.1 mmol)</td>
<td>80</td>
<td>1.0</td>
</tr>
<tr>
<td>7</td>
<td>100</td>
<td>7b (0.9 mmol)</td>
<td>40</td>
<td>0.2</td>
</tr>
<tr>
<td>8</td>
<td>100</td>
<td>7c (1.0 mmol)</td>
<td>180</td>
<td>3.3</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Reaction conditions: (S)-5a (4.5 mmol), toluene (4.5 mL), ketone 6a or 7a-c, catalyst 3d (0.0011 mmol) and K\textsubscript{2}CO\textsubscript{3} (1.5 mmol), Ar atmosphere. \textsuperscript{b} Determined by chiral GC.

3.4 Racemization of (S)-1-phenylethanol by catalyst 3d

The racemization of (S)-5a using catalyst 3d was then investigated in more detail. In order to determine optimal reaction conditions, the racemization of (S)-5a was performed at 70 and 100 °C without and in the presence of acetophenone (6a). These results are presented in Table 3.2 (entries 1 – 4). When the conversion is defined according to Eq. 3.10, the reaction should obey first order kinetics (vide supra) and a straight line should be observed in a plot of –ln(1-X) as a function of time (Figure 3.4). Figure 3.4 shows a short induction period during the initial period of the reaction, which is attributed to activation of the catalyst by K\textsubscript{2}CO\textsubscript{3}. In the absence of 6a first order kinetics are not obeyed (Figure 3.4, entries A + B) and a dramatic
decrease of the rate of racemization is observed upon longer reaction times, suggesting deactivation of the catalyst. Catalyst deactivation is faster at 100 °C. Racemization in presence of 6a resulted in first order behavior at 70 °C as well as at 100 °C. Especially at 100 °C the presence of acetophenone resulted in a drastic increase in rate of racemization (entries 4 + 5, Figure 3.4, case D).

Upon dehydrogenation of 1-phenylethanol (5a) by the active catalyst, acetophenone (6a) will be formed, as well as a hydride complex. This reaction is reversible and leads to the racemization of (S)-5a.\textsuperscript{17} The above results indicate that the stability of the hydride complex is limited, leading to deactivation of the catalyst. In the presence of additional ketone less of the unstable hydride complex will be present during reaction as the equilibrium is shifted to the more stable complex. Research into the mechanism of the racemization by catalyst 3d should reveal the nature of the intermediate complexes that are part of the catalytic cycle and should elucidate the actual role of acetophenone (6a) in preventing catalyst deactivation. However, this was beyond the scope of the present investigation.

An optimal rate of reaction was obtained when 0.7 mmol of 6a was added (16 mol% relative to the substrate) (entry 4, Figure 3.5). The racemization activity increased up to the addition of 16 mol% of 6a, while larger amounts reduced the rate of racemization again, probably because of occupation of the active site of the catalyst by 6a.

![Figure 3.4](image-url) 

**Figure 3.4** -ln(1-X) as a function of time for the racemization of (S)-5a catalyzed by complex 3d (0.025 mol%) without acetophenone at 70 °C (A; table 3.2, entry 1) and at 100 °C (B; table 3.2, entry 2) and in presence of acetophenone at 70 °C (C; table 3.2, entry 3) and at 100 °C (D; table 3.2, entry 4). The lines serve as a guide to the eye.

The influence of other ketones on the racemization of (S)-5a was also investigated (entries 6-8).\textsuperscript{18} Apparently, deactivation of the active catalyst was prevented with all ketones, as first order kinetics were obeyed in all cases. The results of racemization reactions in the presence of ketones benzophenone (7a) or 4-methyl-acetophenone (7b) demonstrated that the catalyst activity was similar to that with acetophenone 6a (entries 6 + 7). Transfer
hydrogenation is observed, resulting in the rapid formation of the corresponding alcohol as well as acetophenone (Scheme 3.3). At equilibrium 80% - 100% of the original ketone is converted to acetophenone. The equilibrium as depicted in Scheme 3.3 is reached before racemization is complete, indicating that the racemization occurs via transfer hydrogenation. This is in contrast with the racemization mechanism that was reported for catalyst D.\textsuperscript{11} For catalyst D, it was determined that the ketone obtained from the alcohol remains in the coordination sphere of the Ru atom during racemization and does not exchange with free ketone. With the aliphatic diisopropyl ketone (7c) transfer hydrogenation is considerably slower, resulting in a concomitantly lower rate of reaction (entry 8).

![Figure 3.5](image)

**Figure 3.5** Racemization of (S)-5\textsubscript{a} in the presence of various amounts of acetophenone at T=100 °C; values calculated in mol% relative to (S)-5\textsubscript{a}. 0.025 Mol% of complex 1 is used, K\textsubscript{2}CO\textsubscript{3} is used to activate this catalyst. Assuming first order kinetics, \(-\ln(1-X)\) is plotted versus time. \(^{a}\) No extra ketone is added, but 0.5% is present as an impurity in (S)-5\textsubscript{a}. The lines serve as a guide to the eye.

![Scheme 3.3](image)

**Scheme 3.3** Transfer hydrogenation of ketones and 1-phenylethanol.

### 3.5 DKR of secondary alcohols

DKR of 5\textsubscript{a} was carried out with immobilized *Candida antarctica* Lipase B (Novozym 435) as enantioselective acylating catalyst and Ru catalyst 3\textsubscript{d} as racemization catalyst (Table 3.3). Isopropyl butyrate was used as the acylating agent and isopropanol was removed at reduced pressure.\textsuperscript{7,8} DKR of 5\textsubscript{a} was performed without and in the presence of 6\textsubscript{a}, using only 0.1 mol% of complex 3\textsubscript{d} with respect to the substrate. DKR without a ketone is preferred, since isolation of the product is less complicated in that case.
High yields and excellent ee values were obtained for each experiment (Table 3.3). Figure 3.6a shows the conversion based on the enantiomeric balance (eb) versus time. The eb is a measure of the conversion of the S- into the R-enantiomer (see equation 3.13).\(^7\)

\[
X_{eb}(t) = \frac{N_{R\text{-alcohol}}(t) + N_{R\text{-ester}}(t) - N_{S\text{-alcohol}}(t) - N_{S\text{-ester}}(t)}{N_{R\text{-alcohol}}(t) + N_{R\text{-ester}}(t) + N_{S\text{-product}}(t) + N_{S\text{-ester}}(t)}
\]

(Eq. 3.13)

Table 3.3 DKR of 5a, using 3d as racemization catalyst and Novozym 435 as acylating catalyst under various conditions.\(^a\)

<table>
<thead>
<tr>
<th>entry</th>
<th>6a (mmol)</th>
<th>Novozym 435 (mg/mol)</th>
<th>time (h)</th>
<th>8a (%)</th>
<th>ee(^b) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.07(^c)</td>
<td>11</td>
<td>23</td>
<td>99</td>
<td>&gt;99</td>
</tr>
<tr>
<td>2</td>
<td>1.8</td>
<td>11</td>
<td>23</td>
<td>&gt;99</td>
<td>&gt;99</td>
</tr>
<tr>
<td>3</td>
<td>1.8</td>
<td>23</td>
<td>10</td>
<td>98</td>
<td>&gt;99</td>
</tr>
</tbody>
</table>

\(^a\) Reaction conditions: rac-5a (9 mmol), toluene (9 mL), isopropyl butyrate (18 mmol), catalyst 3d (0.009 mmol) and K\(_2\)CO\(_3\) (3.8 mmol), Ar atmosphere, T = 70 °C, reduced pressure to ensure gentle reflux (approximately 200 mbar). \(^b\) Determined by chiral GC. \(^c\) Reaction performed without addition of extra acetophenone; 0.07 mmol was present as an impurity in the starting alcohol, however.

In Figure 3.6b the ee of 5a during the reaction is depicted. Enzymatic transesterification results in a rapid increase of the ee of 5a during the first hours of the reaction (conversion of (R)-5a into (R)-8a). At higher conversions the amount of racemization catalyst 3d in the reaction mixture relative to the substrate increases, leading to a decrease of the ee. Reaction in the presence of 1.8 mmol of 6a led to a considerably lower ee of 5a, implying faster racemization (Figure 3.6b, case B) and a rate-limiting enzymatic reaction. Therefore, the reaction was performed with a double amount of enzyme, resulting in faster transesterification and therefore a higher ee of 5a during the reaction (Figure 3.6b, case C). Complete conversion with high ee of the product was achieved within 10 h (entry 3, Figure 3.6a, case C).
Figure 3.6 DKR of 5a at 70 °C, with 0.1 mol% 3d as a racemization catalyst in the absence of acetophenone (A; table 3.3, entry 1), in the presence of 1.8 mmol of 6a (B; table 3.3, entry 2) and in the presence of 1.8 mmol of 6a with double the amount of enzyme (C; table 3.3, entry 3). Toluene is used as the solvent. (a) Conversion based on enantiomeric balance (Xeb) versus reaction time. As first order kinetics are obeyed, -ln(1-Xeb) is plotted. (b) ee of 5a versus reaction time. The lines serve as a guide to the eye.

In order to investigate the scope of the catalyst, an aliphatic secondary alcohol as well as aromatic alcohols bearing either an electron-releasing or an electron-withdrawing substituent on the phenyl ring were subjected to DKR. Furthermore, a heteroaromatic alcohol, 2-furyl ethanol, was tested in DKR with catalyst 3d (Table 3.4). From a commercial point of view, it is more attractive to use one ketone for all substrates. DKR reactions with ketones, other than the corresponding one, showed disappointing results, however. In addition, there are no advantages with respect to the isolation of the product as a result of transfer-hydrogenation between ketone and substrate. For this reason, the ketone corresponding to the substrate was used for each DKR.
Table 3.4 Dynamic kinetic resolution of various racemic alcohols.

<table>
<thead>
<tr>
<th>entry</th>
<th>alcohol</th>
<th>ketone (mmol)</th>
<th>time (h)</th>
<th>product</th>
<th>yield ab,c (%)</th>
<th>ee b (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5a</td>
<td>6a (1.8 mmol)</td>
<td>10</td>
<td>8a</td>
<td>98</td>
<td>&gt;99</td>
</tr>
<tr>
<td></td>
<td></td>
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<td>23</td>
<td></td>
<td>&gt;99</td>
<td>&gt;99</td>
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<tr>
<td>2</td>
<td>5a</td>
<td>no ketone d</td>
<td>10</td>
<td>8a</td>
<td>95</td>
<td>&gt;99</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>24</td>
<td></td>
<td>&gt;99</td>
<td>&gt;99 (87)</td>
</tr>
<tr>
<td>3e</td>
<td>5b</td>
<td>6b (1.6 mmol)</td>
<td>10</td>
<td>8b</td>
<td>99</td>
<td>98</td>
</tr>
<tr>
<td>4e</td>
<td>5b</td>
<td>no ketone</td>
<td>23</td>
<td>8b</td>
<td>86</td>
<td>87</td>
</tr>
<tr>
<td>5f</td>
<td>5c</td>
<td>6c (1.6 mmol)</td>
<td>30</td>
<td>8c</td>
<td>96</td>
<td>&gt;99 (79)g</td>
</tr>
<tr>
<td>6</td>
<td>5d</td>
<td>6d (1.5 mmol)</td>
<td>31</td>
<td>8d</td>
<td>98</td>
<td>98 (63)g</td>
</tr>
<tr>
<td>7</td>
<td>5e</td>
<td>6e (1.4 mmol)</td>
<td>23</td>
<td>8e</td>
<td>98</td>
<td>79</td>
</tr>
</tbody>
</table>

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* Reaction conditions: complex 3d (0.1 mol%), Novozym 435 (0.2 g), K$_2$CO$_3$ (0.5 g), alcohol (9 mmol), isopropyl butyrate (18 mmol) and corresponding ketone were stirred in toluene (9 mL) under an argon atmosphere at 70 ºC at reduced pressure (200 mbar). b Determined by chiral GC. c In parenthesis: isolated yield. d Reaction performed without addition of extra ketone, 0.07 mmol of ketone is present as an impurity in the starting alcohol, however. e Novozym 435: 0.05 g; Ru-catalyst: 0.4 mol%. f Novozym 435: 0.4 g. g Product not separated from ketone; calculated yield.
DKR of 2-octanol (5b) gave high yield and high ee within 10 h when 2-octanone (6b) was added. However, the amount of complex 3d was increased by a factor 4 and the amount of Novozym 435 was decreased by a factor 4, when compared to the DKR of 5a in presence of ketone. In the absence of 6b a considerably lower rate of reaction was obtained (entry 4). α-Methyl-4-(trifluoromethyl)benzyl alcohol (5c) (entry 5), a substrate bearing an electron-withdrawing substituent on the phenyl ring, gave a high yield with excellent ee. For this DKR, a slightly longer reaction time of 30 h and double the amount of enzyme were required, when compared to the DKR of 5a in presence of ketone. An aromatic alcohol bearing an electron-releasing substituent on the ring, α-methyl-4-methoxybenzyl alcohol (5d), was also successfully converted into the enantiomerically pure butyrate ester. A slightly longer reaction time was required (entry 6). Finally, the DKR of the heteroaromatic 1-(2-furyl)ethanol (5e) was investigated (entry 7). DKR of this substrate was complete after 23 h, resulting in a poor ee of 79%, however.19 Experiments with increased loading of racemization catalyst 3d did not lead to higher ee values. Verzijl et al. described that DKR of this substrate in combination with isopropyl butyrate as the acylating agent resulted in limited enantioselectivity. Improved results were reported employing methyl phenylacetate as the acyl donor.8

3.6 Conclusions

Dinuclear Ru complex 3d, bearing tetrafluoro-succinate and rac-BINAP ligands proved to be an excellent catalyst for the racemization of secondary alcohols. Furthermore, catalyst 3d was successfully applied in the DKR of various secondary alcohols. DKR of rac-1-phenylethanol (5a) with isopropyl butyrate as the acyl donor and Novozym 435 as the enzyme was performed effectively at 70 °C with only 0.10 mol% of complex 3d as the racemization catalyst. Activation of the Ru catalyst with K2CO3 was necessary. Reaction in presence of ketone was complete within 10 h with an excellent ee of the product (> 99%). Without ketone, complete reaction was achieved in 23 h, giving an ee > 99% as well.

Besides the aromatic alcohol 5a, four other substrates were shown to undergo the DKR successfully, using complex 3d as the racemization catalyst. Those substrates represent an aliphatic secondary alcohol (2-octanol), an aromatic alcohol bearing an electron-withdrawing substituent on the phenyl ring (α-methyl-4-(trifluoromethyl)benzyl alcohol), an aromatic alcohol bearing an electron-releasing substituent on the ring (α-methyl-4-methoxybenzyl alcohol) and a heteroaromatic secondary alcohol (1-(2-furyl)ethanol). Reaction in presence of the ketone, corresponding to the alcohol, gave the best results.
3.7 Experimental section

General methods
See General methods Chapter 2. All reactants were obtained from Aldrich, except for Novozym 435, which was obtained from Novozymes A/S. The synthesis of complexes 2, 3 and 4 is described in Chapter 2. Substrates, isopropyl butyrate and toluene were distilled before use. K$_2$CO$_3$ (-325 MESH, Aldrich, 347825) was used to activate complexes 2, 3 and 4. All experiments with metal complexes were carried out under a dry argon atmosphere using standard Schlenk techniques. 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.

General procedure for the screening of catalysts in the racemization of (S)-5a
A 6 mL vial equipped with a screw-cap and septum was charged with the appropriate Ru catalyst, (S)-5a (0.24 g, 2 mmol, ee = 99%), toluene (2 mL) and K$_2$CO$_3$ (0.11 g, 0.8 mmol). To remove oxygen, five consecutive vacuum-argon cycles were performed and the vial was sealed by putting silicon grease on the septum. It was then put in a reaction carousel at 70 °C, which indicated the start of the reaction. The reaction was terminated after 2 h and a sample was taken for chiral GC analysis.

General procedure for racemization of (S)-5a
A Schlenk tube was charged with (S)-1-phenylethanol (0.55 g, 4.5 mmol), complex 1 (2.15 mg, 0.0011 mmol) and toluene (4.5 mL) and then K$_2$CO$_3$ (0.2 g, 1.5 mmol) was added. At time $t = 0$, the Schlenk tube was inserted in an oil bath of the desired temperature. Small aliquots of reaction mixture were taken for GC analysis.

Racemization in the presence of ketone
Procedure similar to that of the general racemization procedure, but with initial addition of the ketone.

General DKR procedure
Novozym 435 (0.10 g), complex 3d (0.018 g, 0.0993 mmol) and K$_2$CO$_3$ (0.5 g, 3.8 mmol) were dried overnight in a Schlenk tube under vacuum at 50 °C in the presence of P$_2$O$_5$. The substrate (9 mmol), isopropyl butyrate (18 mmol) and toluene (9 mL) were then added and the Schlenk tube was inserted in an oil bath at 73 °C which indicated the started of the reaction. The reaction mixture was stirred at 70 °C for 23 h at a pressure of 200 mbar. Small aliquots of reaction mixture were taken for GC analysis. For preparative purposes the reaction mixture was concentrated, filtered, washed with toluene and concentrated in vacuum to yield the crude product.

DKR in the presence of ketone
Procedure similar to that of the general DKR procedure, but together with the substrate the corresponding ketone is added.
(R)-1-Phenylethyl butyrate 8a
Purification by Kugelrohr distillation provided (R)-1-phenylethyl butyrate 8a as a colourless liquid in a yield of 87%. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ (ppm) 0.95 (t, 3H, $C_3H_3$), 1.55 (d, 3H, $C_3H_3$), 1.63 (sextet, 2H, $CH_2$), 2.32 (t, 2H, $CH_2$), 5.92 (q, 1H, $CH$), 7.32 (5H, Ar-H). GC program: 10 min at 130 °C, 70 °C/min, 2 min at 200 °C. Retention times: (R)-1-phenylethanol: 5.9 min, (S)-1-phenylethanol: 6.2 min, tri-tert-butylbenzene: 9.7 min, (R)-1-phenylethyl butyrate: 8.9 min. $[\alpha]_D^{20} = +91.3^\circ \,(c \,0.98, \,CHCl_3)$

(R)-α-Methyl-4-(trifluoromethyl)benzyl butyrate 8c
Purification by Kugelrohr distillation provided (R)-α-methyl-4-(trifluoromethyl)benzyl butyrate 8c as a colourless liquid. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ (ppm) 0.95 (t, 3H, $C_3H_3$), 1.55 (d, 3H, $C_3H_3$), 1.69 (sextet, 2H, $C_2H_2$), 2.35 (t, 2H, $CH_2$), 5.94 (q, 1H, $CH$), 7.48 (d, 2H, Ar-H-2,6), 7.61 (d, 2H, Ar-H-3,5). GC program: 35 min at 110 °C, 90 °C/min, 2 min at 200 °C. Retention times: 4-trifluoromethylacetophenone: 6.3 min, (R)-α-methyl-4-(trifluoromethyl)benzyl alcohol: 23.0 min, (R)-α-methyl-4-(trifluoromethyl)benzyl butyrate: 26.7 min, (S)-α-methyl-4-(trifluoromethyl)benzyl alcohol: 28.6 min.

(R)-α-Methyl-4-methoxybenzyl butyrate 8d
Purification by Kugelrohr distillation provided (R)-α-methyl-4-methoxybenzyl butyrate 8d as a colourless liquid. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ (ppm) 0.95 (t, 3H, $C_3H_3$), 1.52 (d, 3H, $C_3H_3$), 1.69 (sextet, 2H, $CH_2$), 2.31 (t, 2H, $CH_2$), 3.80 (s, 3H, $C_3H_3$), 5.88 (q, 1H, $CH$), 6.89 (d, 2H, Ar-H-3,5), 7.32 (d, 2H, Ar-H-2,6). GC program: 20 min at 140 °C, 60 °C/min, 2 min at 200 °C. Retention times: 4-methoxyacetophenone: 8.2 min, (R)-α-methyl-4-methoxybenzyl alcohol: 10.8 min, (S)-α-methyl-4-methoxybenzyl alcohol: 11.5 min, (S)-α-methyl-4-methoxybenzyl butyrate: 20.0 min, (R)-α-methyl-4-methoxybenzyl butyrate: 20.7 min.

3.8 References and notes

6. Racemization catalyst A is described in more detail in Chapter 5 of this thesis.
9. Racemization catalyst B is described in more detail in Chapter 4 of this thesis.


17. The hydride complex that is part of the catalytic cycle is unrelated to dihydride-bridged complex 4e (Figure 3.3), since the latter complex was shown to be inactive in the racemization of secondary alcohols. Moreover, it was highly stable and could be isolated (see Chapter 2).

18. Reactions were performed at 100 °C as the strongest effect of addition of acetoephone was observed at this temperature.

19. A control experiment confirmed that the product ester is not racemized under these conditions.
Iterative Tandem Catalysis

Abstract

Iterative tandem catalysis (ITC) is introduced as a novel polymerization method for the synthesis of well-defined materials. In ITC, multiple catalysts are operating simultaneously in one pot and iterative action of each of the catalysts is required for chain growth. Proof of principle is provided by the synthesis of enantioenriched R-oligomers from (S)-methyl-ɛ-caprolactone (6-MeCL) in a two-pot system, employing Candida antarctica Lipase B as the transesterification catalyst and a Ru complex with p-cymene and rac-2-phenyl-2-amino-propionamide ligands as the racemization catalyst. Hydrogenation of 6-MeCL and dehydrogenation of the alcohol end-groups are identified as side reactions that may severely reduce molecular weight. Experiments in a one-pot system afford short oligomers only. This is caused by insufficient compatibility of the two catalysts. The presence of K₂CO₃ as a heterogeneous base in combination with highly polar small lactones dramatically reduces the enzymatic activity, while the racemization activity is severely impacted by the presence of these highly polar small lactones.
4.1 Introduction

Tandem catalysis, that is, combined catalytic reactions without intermediate product recovery, attracts increasing interest from academia and industry as an alternative to multi-step synthetic procedures.\(^1,2\) 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 (see Chapter 3).\(^3,4\) In this process, a racemic alcohol is completely converted into the corresponding \(R\)-ester by coupling enzyme-catalyzed kinetic resolution to Ru-catalyzed racemization. The \(S\)-esters could be obtained when using subtilisin instead of a lipase and with the appropriate Ru catalyst, even chiral primary amines were selectively transformed into the corresponding \(R\)-amide via DKR.\(^5,6,7\)

In contrast to its increasingly successful applications in the transformation of single molecules, tandem catalysis is still rarely employed in the field of polymer chemistry.\(^1\) Examples include the synthesis of linear low-density polyethylene (LLDPE) via concurrent tandem catalysis.\(^8\) Here, one catalyst oligomerizes ethylene to \(\alpha\)-olefins, while the second catalyst polymerizes these \(\alpha\)-olefins as well as the remaining ethylene. Furthermore, block copolymers were synthesized in one pot by combining ring-opening polymerization (ROP) with radical polymerization using an unsymmetrical bifunctional initiator.\(^9-12\) Analogously, graft copolymers can be synthesized in a one-pot procedure by using a suitable monomer.\(^13\)

In these polymerizations, however, the catalytic processes are not necessarily performed in one pot (i.e. if the two catalytic steps are carried out separately, a similar polymer would still result after two steps). In literature, few examples can be found where the catalytic processes involved in a polymerization are truly complementary and cannot be separated. Drent et al. described a copolymerization of ethylene and carbon monoxide where one palladium complex alternatively builds in both monomers via distinctively different catalytic mechanisms.\(^14\) In addition, a concept called *chain shuttling polymerization* was recently introduced, where a growing chain is transferred repeatedly from one catalyst to another to achieve “multiblock” copolymer formation.\(^15\)

Here, we introduce the concept of *iterative tandem catalysis* as a novel polymerization method.\(^16\) We define iterative tandem catalysis (ITC) as a polymerization process in which chain growth is effectuated by a combination of two (or more) intrinsically different catalytic processes that are both compatible and complementary. This implies that the catalytic processes must operate concurrently for propagation to occur. The major advantage of such ITC systems is that a high degree of control over the chemical structure of the material can be achieved, since the cooperative action of two catalytic processes is exploited.
This chapter focuses on the application of ITC for the synthesis of enantiopure polyesters from racemic ω-substituted lactones. As a model system, 6-methyl-ε-caprolactone (6-MeCL) is selected. Ring-opening of 6-MeCL by *Candida antarctica* Lipase B (CALB) is *S*-selective, giving an *S*-secondary alcohol (*vide infra*). This nucleophile is virtually unreactive in the lipase-catalyzed transesterification (typically E > 100) and, therefore, polymerization does not occur.¹⁷ *In situ* racemization of the terminal secondary alcohol of the propagating polymer chain provides reactive chain ends and enables polymerization. Theoretically, an enantiopure polyester can be obtained with full conversion of the racemic monomer (Scheme 4.1). This chapter deals with three major issues:

1. Selectivity and complementarity of the catalysts
2. Compatibility of the catalysts
3. Proof of principle of ITC by the synthesis of enantiopure oligomers in a two-pot system

4.2 Selectivity and complementarity of the catalysts

4.2.1 The transesterification catalyst

Lipases are excellent enantioselective transesterification catalysts and, as such, they are applied in a wide range of organic transformations.¹⁸ Many lipases have been reported to catalyze the ring-opening of lactones in organic solvents.¹⁹ For use in ITC, however, additional requirements exclude the use of most lipases. Next to the required compatibility with the racemization catalyst, sufficiently high activity under anhydrous conditions is highly important. Water is a competitive nucleophile in the transesterification reaction (the hydrolysis of ester bonds is the natural role of a lipase). When lactones are used as the monomer, this results in the initiation of extra chains, reducing the molecular weight of the product.

In DKR, the most frequently used lipase is *Candida antarctica* Lipase B (CALB).⁴ Generally, Novozym 435 is used, a commercially available formulation in which CALB is immobilized on an acrylic resin. This lipase formulation is an excellent enantioselective transesterification catalyst, since it combines high enantioselectivity towards *R*-secondary alcohols with a broad substrate tolerance.²⁰ Typically, toluene is used as the reaction medium,
but numerous publications exist describing the use and stability of this lipase in bulk, in ionic liquids, in supercritical CO₂ and in various conventional solvents including THF, chloroform and diethyl ether. The thermal stability of Novozym 435 can be described as exceptional, with prolonged activity even at temperatures of 150 °C.²¹,²² CALB is also widely used in ring-opening polymerization of lactones.²³ It is one of the few lipases showing activity even under nearly anhydrous conditions.¹¹,¹²,²⁴ In a typical polymerization of ε-caprolactone, we were able to synthesize benzyl alcohol (BA)-initiated poly(ε-caprolactone) with no detectable carboxylic acid headgroups originating from competing water initiation (Scheme 4.2).²⁵

**Scheme 4.2** Novozym 435-catalyzed ring-opening polymerization of ε-caprolactone.

![Scheme 4.2](image)

**Scheme 4.3** Reaction mechanism of CALB-catalyzed transesterification. TS-1 and TS-2 represent the transition state analogues in the acylation and deacylation steps, respectively.

Scheme 4.3 shows the generally accepted mechanism for CALB-catalyzed transesterification.²⁶ In the first step, the acyl donor is adsorbed in the active site of the lipase. Subsequently, the carbonyl is attacked by the serine hydroxyl residue, leading to transition state analogue TS-1. The alcohol leaves the active site, yielding the acyl enzyme in which the acyl group is covalently bonded to the serine residue. In the subsequent deacylation, an alcohol performs a nucleophilic attack on the carbonyl group of the acyl enzyme. Finally, the
transesterification product can leave the active site, reforming the original free enzyme. Enantioselectivity towards chiral esters is the result of the lower energy of the transition state of the acylation for the favored enantiomer, while the enantioselectivity towards secondary alcohols is the result of the lower energy of the transition state of the deacylation for the R-alcohol. X-ray crystallographic studies indicated that in the active site pocket an acyl side and an alcohol side can be distinguished. The acyl side of the active site pocket is more spacious than the alcohol side, and, as a result, a lower enantioselectivity can be expected for chiral esters than for chiral alcohols during transesterification.

_Pseudomonas cepacia_ is another frequently applied lipase, but due to its lower activity CALB is usually preferred. Although not a lipase but a peptidase (EC 3.4.21), _Subtilisin Carlsberg_ is sometimes employed in DKR, since it also displays transesterification activity. Its activity, selectivity and stability are inferior to that of lipases – at 70 °C within 35 minutes all its activity is lost – but its selectivity for S-secondary alcohols (in contrast to the R-selectivity that is commonly observed for lipases) renders it a very useful enzyme in DKR. For the ITC experiments on 6-MeCL described in this chapter, Novozym 435 was selected as the lipase.

### 4.2.2 Lipase-catalyzed ring-opening of 6-methyl-ε-caprolactone

Earlier work indicated that Novozym 435-catalyzed polymerization of 6-methyl-ε-caprolactone (6-MeCL) did not occur – in contrast to other methyl-substituted caprolactones such as 4-methyl-ε-caprolactone. Closer investigation revealed that ring-opening of racemic 6-MeCL did take place and is S-selective. Since 6-MeCL is an ω-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 stereo configuration of the terminal secondary alcohol prevents propagation from taking place on a realistic time scale. In a typical ring-opening experiment with a monomer/initiator ratio of 4:1 (Scheme 4.4), the initiator is quickly consumed in approximately 40 minutes (Figure 4.1a), and 1 eq of (S)-6-MeCL is consumed. Using the Chen equation for ee_monomer and conversion, an E-value of 12 was calculated (not shown). As a result, a considerable amount of (R)-6-MeCL is also ring-opened. The resulting R-secondary alcohol is a good nucleophile and will propagate, most probably with (S)-6-MeCL resulting in some dimer and trimer formation. Ultimately, all molecules are “end-capped” with S-secondary alcohols.

![Scheme 4.4](image)

_Scheme 4.4 Enzymatic ring-opening of rac-6-MeCL by BA catalyzed by Novozym 435._
Figure 4.1 Enzymatic ring-opening of rac-6-MeCL by BA catalyzed by Novozym 435 (BA ( ), (S)-6-MeCL ( ); (R)-6-MeCL ( ), T = 60 °C; BA / 6-MeCL = 1/4).

After 40 min. – when the initiator has been completely consumed – a continuing consumption of (R)-6-MeCL is observed (Figure 4.1b). After approximately 1.5 days the conversion of (R)-6-MeCL even surpasses the conversion of (S)-6-MeCL. This continuing consumption of (R)-6-MeCL after complete conversion of the initiator can be explained by the reversibility of the ring-opening reaction in combination with the moderate enantioselectivity of the lipase towards 6-MeCL (at 60 °C, E is about 10).

A reverse reaction of a ring-opening product would result in the S-lactone and the initiator being formed again (Scheme 4.5). This initiator molecule can subsequently react enzymatically with an S-lactone (non-productive, reforming the original dimer), or with an R-lactone. The latter reaction would lead to a molecule with a reactive R-alcohol end-group, which would immediately lead to another ring-opening reaction, most probably with an S-lactone. The net effect of this sequence of reactions is the insertion of an R-monomer into the S-alcohol ‘terminated’ dimer, leading to trimers and longer oligomers.

Scheme 4.5 Reversibility of the enzymatic ring-opening enables insertion of the R-lactone.

Further investigation revealed that the ee of the terminal alcohols indeed remained high in the experiment depicted in Figure 4.1. This is consistent with the fact that all chains are end-capped by a unit of (S)-6-MeCL, while (R)-6-MeCL is slowly inserted via the above-mentioned mechanism. Additionally, the formation of longer oligomers was demonstrated by $^{13}$C{¹H} NMR spectroscopy.³¹
4.2.3 The racemization catalyst

Racemization of the S-alcohols that are formed upon ring-opening of (S)-6-MeCl is required to enable polymerization. A wide range of Ru-based racemization catalysts has been successfully applied in the dynamic kinetic resolution (DKR) of secondary alcohols (see Chapter 3). For the ITC experiments described in this chapter, catalyst 1 was selected as the racemization catalyst. This is one of the best racemization catalysts known to date and it is readily accessible via in situ complexation of commercially available [RuCl₂(cymene)]₂ with rac-2-phenyl-2-amino-propionamide in the presence of K₂CO₃ (Scheme 4.6).

Scheme 4.6 Formation of the active racemization catalyst 1 from [RuCl₂(cymene)]₂ and rac-2-phenyl-2-amino-propionamide in the presence of K₂CO₃.

Scheme 4.7 Racemization of secondary alcohols by catalyst 1; for reasons of clarity, reversibility of the reactions is not shown.
Elimination of HCl provides a Ru complex with an anionic amido ligand. Loss of a second equivalent of HCl leads to the formation of the active 16 electron Ru(II) complex \( 1 \). For the racemization of secondary alcohols by catalyst \( 1 \), a metal-ligand bifunctional mechanism similar to that of analogous diamino and amino alcohol transfer hydrogenation catalysts is proposed (Scheme 4.7).\(^{34,35} \) Dehydrogenation of the S-secondary alcohol by complex \( 1 \) results in the formation of the corresponding ketone and the hydride complex \( 2 \). In this step, the hydride in the \( \alpha \)-position of the alcohol is transferred to the Ru, while its OH-proton ends up on the acidic nitrogen of the amino ligand. Conversely, hydrogenation of a ketone by complex \( 2 \) gives the corresponding alcohol with the overall transfer hydrogenation process resulting in racemization. Alternatively, hydride complex \( 2 \) can eliminate molecular hydrogen to reform complex \( 1 \). In DKR, this is only a minor side reaction, and no significant ketone formation is observed. However, in a polymerization, dehydrogenation of the terminal alcohol introduces a non-reactive terminal ketone, which acts as a chain-stopper, significantly reducing the molecular weight that can be achieved.

![Scheme 4.8](https://example.com/scheme48.png)

**Scheme 4.8** Carboxylic acids deactivate catalyst \( 1 \) by forming acetato complex \( 3 \); in the presence of \( \text{K}_2\text{CO}_3 \) the equilibrium is shifted to active complex \( 1 \).

Reaction of the active catalyst \( 1 \) with a carboxylic acid affords inactive complex \( 3 \) (Scheme 4.8). Small amounts of carboxylic acid are inevitably formed in the enzymatic transesterification as trace water in the lipase induces ester hydrolysis and, therefore, significant deactivation of the catalyst will occur. However, in the presence of \( \text{K}_2\text{CO}_3 \) the equilibrium of this reaction shifts to the side of the active catalyst \( 1 \). In a typical DKR experiment, a racemic secondary alcohol can be completely converted into the corresponding \( R \)-butyrate (ee > 99%) within 24 h, employing 0.1 mol% of catalyst \( 1 \) at 70 °C.\(^32 \)

### 4.3 Compatibility of the catalysts

#### 4.3.1 ITC of (S)-6-MeCL in a one-pot system

We then attempted to perform ITC in a one-pot system, employing complex \( 1 \) and Novozym 435 as the catalysts.\(^36 \) 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.\(^37 \) To
exclude any enantioselectivity-related effects, all reactions were carried out with (S)-6-MeCL (ee = 95%).\textsuperscript{22} Racemic 1-phenylethanol (1-PE) was used as the initiator – a secondary alcohol that is frequently used as a model substrate in DKR and that is known to be a good substrate for both the lipase and the racemization catalyst. CALB exhibits extremely high enantioselectivity towards (R)-1-PE (an E-value in excess of 1 million was recently reported)\textsuperscript{38} and, therefore, conversion of (S)-1-PE can only occur if the racemization catalyst is active. As a result, the conversion of (R)-1-PE gives immediate information on the enzymatic activity, while conversion of (S)-1-PE is a measure for the racemization activity. To compensate for dehydrogenation by the Ru catalyst (\textit{vide supra}), a hydrogen donor was added to the system. For this purpose, 2,4-dimethyl-3-pentanol (DMP) was selected, a secondary alcohol which is known to suppress net dehydrogenation of the substrate, while its steric hindrance renders it virtually unreactive in the enzymatic transesterification (as confirmed by a control experiment).\textsuperscript{39}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure4.2.png}
\caption{1-PE-initiated one-pot ITC of (S)-6-MeCL: (a) Conversion of (S)-6-MeCL (●) as function of time; (b) Conversion (●) and ee (○) of 1-PE as function of time. Reaction conditions: catalyst 1 (0.049 mmol), Novozym 435 (56 mg), (S)-6-MeCL (3.8 mmol), rac-1-PE (0.42 mmol, M/I = 9), K$_2$CO$_3$ (330 mg), 1,3,5-tri-tert-butylbenzene (0.25 mmol) and DMP (10 mmol) in toluene (5 mL) at 70 °C.}
\end{figure}

Unfortunately, oligomerization in a one-pot experiment proved to be very slow: a lactone conversion of 50% is only reached after 280 h in an experiment with M/I = 9 (Figure 4.2a). Although the Ru loading is 12 mol\% with respect to 1-PE (1.3 mol\% relative to (S)-6-MeCL), it takes 18 hours to reach a 1-PE conversion of 72% with a low ee (Figure 4.2b). The reaction mixture after 190 hours reaction time was analyzed by $^1$H NMR to confirm the formation of oligomers (Figure 4.3). The signal at 4.9 ppm (C) is attributed to the CH$_2$ next to intra-chain esters, indicating that propagation did indeed take place. Signal C* was found to belong to cyclic 6-MeCL dimers, which are always formed as a byproduct. Additionally, 1,6-heptanediol-initiated products, that are formed as a result of hydrogenation of the lactone, are clearly observed (Scheme 4.9). Several Ru complexes are known to catalyze this reaction and the
related hydrogenolysis of esters, although high temperature and high hydrogen pressure are normally applied.\(^4\) Apparently, this side reaction also takes place via transfer hydrogenation under ITC conditions (at 70 °C in the presence of a hydrogen donor).\(^4\) From the integral values of the various peaks, a degree of polymerization (DP) of only 2.5 was calculated, while 26% of the chains was initiated by 1,6-heptanediol instead of 1-PE.\(^4\)

**Figure 4.3** \(^1\)H NMR spectrum of the product mixture after 190 hours for the one-pot ITC experiment described in Figure 4.2. For reasons of clarity, only the relevant part of the spectrum is shown (3.5-6.5 ppm). Signal C* was attributed to cyclic 6-MeCL dimers, while signal E originates from 1,6-heptanediol-initiated oligomers.

**Scheme 4.9** Ru-catalyzed hydrogenation of 6-MeCL leading to the formation of 1,6-heptanediol.

Several attempts were then made to improve the catalyst activity in the one-pot system, including the use of alternative bases, but without success. In all experiments, catalyst activity was very low at best and short oligomers were only formed after prolonged reaction times (typically > 200 h).
4.3.2 Catalyst activity under ITC conditions

While oligomerization undeniably takes place in a one-pot system, the reaction is very slow and catalytic activity is dramatically lower than in DKR. In an attempt to rationalize the observed inhibition, the residual activity of both catalysts was determined in an actual ITC experiment. The residual racemization activity was determined in an experiment with 1-PE as the initiator (Figure 4.4). After 145 h, the rac-1-PE that was used as the initiator is largely consumed (82% conversion) and the ee is approximately 0%. Addition of (S)-1-PE results in an increase of the ee to 94% (Figure 4.4b). If the racemization catalyst is still active, this ee should decrease over time, which is indeed observed. However, a TOF of 1.4 h⁻¹ is calculated for the reaction, which is dramatically lower than the activity in a separate racemization experiment in the absence of 6-MeCL (TOF ~ 200 h⁻¹, see Table 4.2). The racemization of (S)-1-PE results in the formation of reactive R-alcohol and in a further increase of the conversion of (S)-6-MeCL.

Figure 4.4 One-pot ITC of (S)-6-MeCL employing racemization catalyst 1 and 1-PE as the initiator, with addition of (S)-1-PE after 146 h: (a) Conversion of (S)-6-MeCL (■) as a function of time; (b) conversion (●, left axis) and ee (□, right axis) of 1-PE as a function of time. Conditions: catalyst 1 (0.044 mmol), Novozym 435 (57 mg), (S)-6-MeCL (3.9 mmol), rac-1-PE (0.41 mmol), 1,3,5-tri-tert-butylbenzene (0.33 mmol) and DMP (9 mmol) in toluene (4 mL) at 70 °C. After 90 min. K₂CO₃ (330 mg) was added to the reaction mixture. After 145 h, (S)-1-PE (1 mmol, ee > 99%) was added to the reaction to determine the racemization activity.

The residual enzymatic activity was determined by addition of BA to an ITC experiment after 164 h (Figure 4.5). This should lead to an increased rate of conversion of (S)-6-MeCL as extra initiator is introduced. While this increased rate was observed indeed, a TOF of only 155 h⁻¹ was calculated compared to 4.0·10⁴ h⁻¹ in a reference experiment with 6-MeCL/BA = 4 at 70 °C.
Figure 4.5 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), 1,3,5-tri-tert-butylbenzene (0.33 mmol) and DMP (13 mmol) in toluene (4 mL) at 70 °C. After 90 min, K₂CO₃ (330 mg) was added to the reaction mixture. After 164 h additional BA (0.8 mmol) was added to determine the enzymatic activity.

In order to further investigate this very low catalytic activity in the one-pot ITC experiments, a number of reference experiments were carried out with both catalysts.

Activity of the lipase

The activity of Novozym 435 was investigated by performing a model reaction – the BA initiated polymerization of unsubstituted lactones – under various conditions. Enzymatic ring-opening polymerizations follow pseudo-first-order kinetics.⁴³ Therefore, a first-order rate constant and the turnover frequency (TOF) can be calculated. A quick screening (addition of the various components present in one-pot ITC) indicated that the presence of a (solid) base plays a crucial role for lipase activity. In order to investigate the effect of a solid base on the activity of Novozym 435 in more detail, the highly polar ε-caprolactone (CL) and pentadecalactone (PDL) were polymerized in the presence of several bases (see Table 4.1). All experiments were carried out at 70 °C, since this temperature is used in all ITC experiments.

In a typical CL polymerization using BA as the initiator in the absence of a solid base, a TOF of 233 s⁻¹ was calculated (Table 4.1, entry 1). The addition of only a small amount of K₂CO₃ (entry 2, 5 mg K₂CO₃, source: Sigma-Aldrich, fine powder, -325 mesh) resulted in a 94% decrease in activity. Addition of 80 mg of K₂CO₃ lead to a further decrease in activity (entry 3). Experiments with an extra pure batch of K₂CO₃ that was obtained from Fluka (BioChemika Ultra grade) also resulted in a large decrease in activity (entries 4 and 5). Since this preparation consisted of a rather coarse granulate, it was used both as such and after grinding. Using the coarse granulate a relatively high TOF of 73 s⁻¹ was found (entry 4). However, after grinding the activity of the lipase was much lower and a TOF of only 12 s⁻¹ was calculated (entry 5). For
Cs₂CO₃ a detrimental effect on the activity of Novozym 435 similar to that of K₂CO₃ was observed, with a measured TOF of 23 s⁻¹ (entry 6). Surprisingly, the deactivation was not observed when BA and CL were reacted in equimolar amounts. Reaction rates were much lower (TOF = 18 s⁻¹, entry 7), but the presence of K₂CO₃ in this system, even in larger amounts, did not lead to deactivation (entries 8 and 9). Also in the polymerization of PDL no significant effect was observed (entries 10 and 11).

**Table 4.1** Activity of Novozym 435 in polymerization of CL and PDL using BA as the initiator in the presence of various solid bases.

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>[M]/[I]</th>
<th>additive</th>
<th>TOF (s⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CL</td>
<td>14</td>
<td>-</td>
<td>233</td>
</tr>
<tr>
<td>2</td>
<td>CL</td>
<td>14</td>
<td>5 mg K₂CO₃</td>
<td>15</td>
</tr>
<tr>
<td>3</td>
<td>CL</td>
<td>14</td>
<td>80 mg K₂CO₃</td>
<td>7.0</td>
</tr>
<tr>
<td>4</td>
<td>CL</td>
<td>14</td>
<td>80 mg K₂CO₃</td>
<td>73</td>
</tr>
<tr>
<td>5</td>
<td>CL</td>
<td>14</td>
<td>80 mg K₂CO₃</td>
<td>12</td>
</tr>
<tr>
<td>6</td>
<td>CL</td>
<td>14</td>
<td>160 mg Cs₂CO₃</td>
<td>23</td>
</tr>
<tr>
<td>7</td>
<td>CL</td>
<td>1</td>
<td>-</td>
<td>18</td>
</tr>
<tr>
<td>8</td>
<td>CL</td>
<td>1</td>
<td>80 mg K₂CO₃</td>
<td>12</td>
</tr>
<tr>
<td>9</td>
<td>CL</td>
<td>1</td>
<td>350 mg K₂CO₃</td>
<td>23</td>
</tr>
<tr>
<td>10</td>
<td>PDL</td>
<td>14</td>
<td>-</td>
<td>429</td>
</tr>
<tr>
<td>11</td>
<td>PDL</td>
<td>14</td>
<td>80 mg K₂CO₃</td>
<td>384</td>
</tr>
</tbody>
</table>

* Turnover frequency; defined as the number of turnovers per active site per second at the start of reaction; in order to calculate this number an active protein content of 2% (w/w) of the immobilized preparation is assumed. The TOF is calculated according to the formula TOF = kᵢ × (initial substrate concentration) / (total enzyme concentration), in which kᵢ is the rate constant as determined by fitting a straight line to the relationship between − ln (1 − x) and time, with x = conversion of the lactone. b K₂CO₃ used from Sigma-Aldrich (347825, -325 mesh). c K₂CO₃ used from Fluka (60108, Biochemika, extra pure with low non-potassium cation content). d K₂CO₃ used from Fluka, ground (60108, Biochemika, extra pure with low non-potassium cation content).

In conclusion, the presence of K₂CO₃ leads to a large decrease in lipase activity in the polymerization of CL. Since the use of extra pure K₂CO₃ results in a similar decrease in the rate of reaction, the deactivation should be attributed to the K₂CO₃ itself and not to the presence of impurities (anionic or cationic). The experiments with the coarse and ground granulate indicate that the particle size of the solid base is a determining factor in the degree of deactivation.

Lipase deactivation is not observed in the polymerization of PDL in presence of K₂CO₃. The polarity of the system might play an important role here. PDL is a large-ring lactone with little ring strain, and PDL is, therefore, much less polar than CL. The dipole moment of CL is 4.45 D while the dipole moment of PDL is only 1.86 D.₄₅,₄₆
When BA and CL are reacted in equimolar amounts, the activity is much lower compared to a CL polymerization. This might be attributed to the increased polarity of the system (the concentration of BA is much higher) or to the described inhibitory effect of the alcohol on CALB. In this system K₂CO₃ was found not to deactivate the lipase. This suggests that both K₂CO₃ and the presence of oligomers are important factors. The exact nature of the deactivation of the lipase remains concealed.

### Table 4.2 Racemization of (S)-1-PE in the presence of various lactones

<table>
<thead>
<tr>
<th>entry</th>
<th>[Ru] (mol%)</th>
<th>lactone</th>
<th>mmol</th>
<th>TOF (h⁻¹)</th>
<th>normalized activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.4</td>
<td>none</td>
<td>n.a.</td>
<td>179</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>0.4</td>
<td>6-MeCL</td>
<td>2</td>
<td>38</td>
<td>21</td>
</tr>
<tr>
<td>3</td>
<td>0.4</td>
<td>CL</td>
<td>2</td>
<td>97</td>
<td>54</td>
</tr>
<tr>
<td>4</td>
<td>0.4</td>
<td>PDL</td>
<td>2</td>
<td>178</td>
<td>99</td>
</tr>
<tr>
<td>5</td>
<td>0.4</td>
<td>none</td>
<td>n.a.</td>
<td>113</td>
<td>100</td>
</tr>
<tr>
<td>6</td>
<td>0.4</td>
<td>VL</td>
<td>2</td>
<td>34</td>
<td>30</td>
</tr>
<tr>
<td>7</td>
<td>0.4</td>
<td>5-MeVL</td>
<td>2</td>
<td>28</td>
<td>25</td>
</tr>
<tr>
<td>8</td>
<td>0.4</td>
<td>PDL</td>
<td>6</td>
<td>116</td>
<td>103</td>
</tr>
<tr>
<td>9e</td>
<td>0.2</td>
<td>none</td>
<td>n.a.</td>
<td>232</td>
<td>100</td>
</tr>
<tr>
<td>10e</td>
<td>0.2</td>
<td>6-MeCL</td>
<td>2</td>
<td>26</td>
<td>11</td>
</tr>
<tr>
<td>11e</td>
<td>0.2</td>
<td>6-MeCL</td>
<td>10</td>
<td>1.8</td>
<td>1</td>
</tr>
</tbody>
</table>

*Unless otherwise noted, Ru catalyst 1 was preformed for 2 h at 70 °C under an argon atmosphere in toluene/2-propanol (2:1) in the presence of K₂CO₃. This catalyst solution was then filtered and 0.20 mol% of the catalyst was added to a mixture of (S)-1-PE (ee = 99%, 2 mmol), the lactone and K₂CO₃ (50 mg). Amount of lactone added (mmol).  
Turnover frequency; the racemization obeys first-order kinetics (see Chapter 3) and the TOF can be calculated according to: TOF = kᵢ × (initial substrate concentration) / (total Ru concentration) in which kᵢ is the rate constant as determined by fitting a straight line to the relationship between – ln (1 – x) and time, with x = (1 – ee/ee₀) as defined in Chapter 3. Racemization activity relative to an experiment without lactone. No catalyst preformation; reaction performed in a 6 mL vial under an argon atmosphere.

### Racemization activity under ITC conditions

In order to investigate the activity of catalyst 1, the racemization of (S)-1-PE was studied in the presence of various lactones. These results are summarized in Table 4.2; the effect of addition of 6-MeCL and PDL on the racemization is also displayed graphically in Figure 4.6. When only 1 eq of 6-MeCL is added with respect to (S)-1-PE, the rate of racemization is reduced by ~ 80% (Table 4.2, entries 1 and 2). With 5 eq of 6-MeCL the effect is even more pronounced and almost no racemization activity was observed (entry 11). For other small-ring
lactones such as ε-caprolactone (CL), δ-valerolactone (VL) and 5-methylvalerolactone (5-MeVL) a similar reduction of the racemization activity was observed (entries 3, 6 and 7). In contrast, pentadecalactone (PDL), an apolar macrolactone, does not significantly reduce the rate of racemization (entries 4 and 8).

![Figure 4.6](image)

Figure 4.6 Racemization activity of catalyst 1 at 70 °C in the presence of 1 eq of 6-MeCL (B, Table 4.2, entry 2), 1 eq of 6-MeCL (C, Table 4.2, entry 10), 5 eq of 6-MeCL (D, Table 4.2, entry 11), 1 eq of PDL (E, Table 4.2, entry 4), 3 eq of PDL (F, Table 4.2, entry 8), relative to an experiment in the absence of lactone (A).

Judging from these results, racemization catalyst 1 is incompatible with small-ring lactones, which renders it an unsuitable catalyst for the one-pot ITC of 6-MeCL. The exact nature of this incompatibility remains unclear, however the high polarity of these small-ring lactones might play a role, since racemization activity is retained in presence of the (apolar) macrolactone PDL.49 Further investigation should reveal the cause of the incompatibility.

4.4 ITC of (S)-6-MeCL in a two-pot system

The difficulties encountered in the one-pot ITC experiments, prompted us to investigate the process in a two-pot system. Therefore, ring-opening product 4a (Scheme 4.10) was isolated and subsequently racemized by catalyst 1. Isopropanol was added as a hydrogen donor to compensate for dehydrogenation. To prevent base-catalyzed transesterification, the catalyst was preformed from [RuCl₂(cymene)]₂ and rac-2-phenyl-2-amino-propionamide in the presence of K₂CO₃. The solid base was removed by filtration before adding the catalyst solution to the reaction mixture. Racemization of 4a resulted in 50% of disfavored substrate 4a and 50% of favored substrate 4b, which was confirmed by ³¹P NMR spectroscopy of the diastereomers formed upon addition of PCl₃ to the alcohol.50 When the racemized product was reacted with
6-MeCL, a fast reaction was observed (with comparable kinetics to reaction of BA with 6-MeCL), with an ultimate conversion of racemized 4 of 50% and consumption of an additional 0.5 eq of (S)-6-MeCL (Figure 4.7). $^1$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.

![Scheme 4.10](image)

**Scheme 4.10** Synthesis of oligo-(R)-6-MeCL from (S)-6-MeCL by ITC.

![Figure 4.7](image)

**Figure 4.7** Enzymatic ring-opening of 6-MeCL by racemized 4 with (S)-6-MeCL : $4 = 2$. 

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After this first successful racemization/ring-opening cycle, the procedure was repeated until the 5th generation of the oligomer was obtained. The resulting products from generations 1 to 5 were analyzed by $^1$H-NMR and MALDI-TOF MS (Figures 4.8 and 4.9 respectively).

![Diagram of oligomeric species](image)

**Figure 4.8 $^1$H NMR spectrum of the oligomeric species obtained from generation 5. Both BA and 1,6-heptanediol-initiated oligomers are present. Signals with * are attributed to 6-MeCL monomer which was added in excess.**

$^1$H NMR confirmed the formation of oligomers and revealed that, as expected, with every generation, the average degree of polymerization increased by 0.5 (Table 4.3). 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 BA. This is attributed to Ru-catalyzed hydrogenation of 6-MeCL (Scheme 4.9). $^1$H NMR confirms the presence of 25% of 1,6-heptanediol-initiated 6-MeCL oligomers in the 5th generation oligomer.
To prove that $R$-esters have indeed been formed in the process, generation 5 was degraded by acid-catalyzed methanolysis to afford methyl 6-hydroxyheptanoate (Scheme 4.11). Analysis of the methyl ester by chiral GC revealed that 92% of the ester groups in the oligomer chains were in the $R$-configuration.\textsuperscript{54} Evidently, the conversion of (S)-6-MeCL into $R$-esters was successful.

**Figure 4.9** MALDI-TOF MS spectra of generations 3, 4 and 5; A and B correspond to Na\(^+\) and K\(^+\) ionized BA-initiated oligomers of 6-MeCL; C and D to Na\(^+\) and K\(^+\) ionized 1,6-heptanediol-initiated oligomers of 6-MeCL; E and * to MALDI-TOF MS related artifacts.

**Table 4.3** Chiral 6-MeCL oligomers by iterative tandem catalysis

<table>
<thead>
<tr>
<th>generation</th>
<th>DP\textsuperscript{a}</th>
<th>DP\textsubscript{th}\textsuperscript{b}</th>
<th>% diol-initiated chains\textsuperscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.0</td>
<td>1.0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>1.5</td>
<td>1.5</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>2.0</td>
<td>2.0</td>
<td>9</td>
</tr>
<tr>
<td>4</td>
<td>2.5</td>
<td>2.5</td>
<td>15</td>
</tr>
<tr>
<td>5</td>
<td>3.2</td>
<td>3.0</td>
<td>25</td>
</tr>
<tr>
<td>one-pot</td>
<td>2.5</td>
<td>n.a.</td>
<td>26</td>
</tr>
</tbody>
</table>

\textsuperscript{1} Determined by \(^1\)H NMR; \textsuperscript{2} Theoretical DP; with every generation, 50% of the chains have propagated leading to an increase in the DP of 0.5.
Iterative tandem catalysis was introduced as a novel polymerization method for the synthesis of well-defined materials. In ITC, multiple catalysts are operating simultaneously in one pot and iterative action of each of the catalysts is required for chain growth.

Proof of principle was provided by the synthesis of enantioenriched $R$-oligomers from $(S)$-6-MeCL in a two-pot system, employing *Candida antarctica* Lipase B as the transesterification catalyst and a Ru complex with $p$-cymene and rac-2-phenyl-2-amino-propionamide ligands as the racemization catalyst. Hydrogenation of 6-MeCL and dehydrogenation of the alcohol end-groups were identified as side reactions, which severely reduce molecular weight.

Experiments in a one-pot system only afforded short oligomers. It was shown that this was caused by insufficient compatibility of the two catalysts. The presence of $K_2CO_3$ as a heterogeneous base in combination with highly polar small lactones dramatically reduced the enzymatic activity, while the racemization activity was severely reduced by the presence of these highly polar small lactones.

Modification of the tandem catalytic system by using a different racemization catalyst ultimately enabled one-pot ITC of 6-MeCL. These results are described in Chapter 5 of this thesis. The successful tandem catalytic system was also extended to the polymerization of diols and diesters, a process which is called dynamic kinetic resolution polymerization (DKRP). This work is described in Chapter 5 of B. A. C. van As’ thesis.55

**4.6 Experimental section**

**General methods**

See General methods Chapter 2 and 3. Benzyl alcohol (BA) was obtained from Aldrich and distilled from CaH₂ before use. All solvents were stored on dry molecular sieves (3 Å) to remove traces of water. 6-Methyl-$\varepsilon$-caprolactone (6-MeCL) was synthesized by Baeyer-Villiger oxidation of 2-methylcyclohexanone following a reported procedure.56 $(S)$-6-MeCL was synthesized by a double enzymatic ring-opening/ring-closure procedure.52 All experiments with metal complexes were carried out under a dry argon atmosphere using standard Schlenk techniques. 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 temperature was set at 250 °C and detection temperature was set at 300 °C.
°C. Separations were performed under isothermal conditions with the column temperature set at 121 °C, which afforded in all cases baseline separation of the enantiomers of 6-MeCL. Lactone conversions were determined by the internal standard method using 1,3,5-tri-tert-butylbenzene as the internal standard. MALDI-TOF MS spectra were recorded on a PerSeptive Biosystems Voyager DE PRO spectrometer using a 50:50 mixture of α-cyano-4-hydroxycinnamic acid (CHCA) and trans-2-[3-(4-t-butylphenyl)-2-methyl-2-propenylidene]malononitrile (DCTB) as a matrix. The ee of the end-groups of the oligomers was determined according to a published method. The terminal alcohols were reacted with 0.5 eq of PCl3 and 31P NMR spectroscopy revealed different signals for the possible diastereomers, making discrimination between racemic and high ee end-groups possible.

**Novozym 435-catalyzed ring-opening of 6-MeCL by BA**

BA (0.92 g, 8.5 mmol), 6-MeCL (4.4 g, 34 mmol), 1,3,5-tri-tert-butylbenzene (0.50 g, 2.0 mmol) and toluene (8.8 mL) were added to a 25 mL round-bottom flask. The mixture was stirred at 60 °C. Novozym 435 (0.36 g) was added, which represented the start of reaction. After 10, 20, 40, 80, 120, 180, 300, 600, 1500, 1980, 3090, 4190 and 5670 minutes aliquots (~0.02 mL and ~0.1 mL) were withdrawn using a glass Pasteur pipette and diluted with dichloromethane. The enzyme was removed from the sample by filtration over cotton wool and the samples were analyzed by chiral GC.

**Synthesis of 4a using rac-6-MeCL**

Novozym 435 (0.30 g) and a magnetic stirring bar were added to a Schlenk tube. The tube was put overnight in a vacuum oven (10 mm Hg) at 50 °C in presence of P2O5. The oven was backfilled with nitrogen and the tube was removed from the oven. BA (1.3 g, 12 mmol), 6-MeCL (6.0 g, 47 mmol), 1,3,5-tri-tert-butylbenzene (0.50 g, 2.0 mmol) and toluene (7 mL) were added to the tube. The mixture was stirred at room temperature for 9 hours. During reaction, samples (~0.02 mL) were drawn from the reaction mixture using a glass Pasteur pipette. 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 conversion of BA and both enantiomers of 6-MeCL. At 90% BA conversion, the enzymatic reaction was stopped by filtration using a class 3 glass filter. The filtrate was concentrated and the remaining 6-MeCL and BA were removed by distillation using a Kugelrohr apparatus (T = 80 °C, 0.05 mm Hg). The product was used without further purification. Yield: 2.1 g (81%).

1H NMR δ (ppm) 7.3-7.4 (m, Ar-H), 5.1 (Ar-CH2-O), 3.8 (m, CH(CH3)OH), 2.4 (m, benzyl-CH2-OCOC6H4), 1.65-1.35 (m, OCOC6H4(CH2)3), 1.15 (d, CH3)

**Synthesis of 4a using (S)-6-MeCL**

Novozym 435 (0.10 g) and a magnetic stirring bar were added to a Schlenk tube. The tube was put overnight in a vacuum oven (10 mm Hg) at 50 °C in presence of P2O5. The oven was backfilled with nitrogen and the tube was removed from the oven. BA (0.78 g, 7.2 mmol), 6-MeCL (3.0 g, 23 mmol), 1,3,5-tri-tert-butylbenzene (0.05 g, 0.20 mmol) and toluene (8 mL) were added to the tube. The mixture was stirred at 80 °C for 16 hours. After completion of the reaction, which was confirmed by 1H NMR, the enzymatic reaction was stopped by filtration using a class 3 glass filter and the filter was flushed with dichloromethane. The filtrate was concentrated and the product was used without further purification. Yield: 3.49 g (93%).
Typical procedure for the racemization of 6-MeCL oligomers

[RuCl₂(cymene)]₂ (38 mg, 0.06 mmol), rac-2-phenyl-2-amino-propionamide (22 mg, 0.14 mmol), K₂CO₃ (0.50 g, 3.6 mmol), 2-propanol (5 mL, 65 mmol) and toluene (5 mL) were added to a 25 mL Schlenk tube. The system was stirred at 80 °C for 1 h. 6-MeCL oligomer (1.0 g, 1.3 mmol) was dissolved in a mixture of toluene (0.5 mL) and 2-propanol (0.5 mL). The mixture was transferred into a 15 mL Schlenk tube. 5 mL of the catalyst solution was filtered through a 1 μm PTFE syringe filter and added to the reaction mixture. The mixture stirred at 70 °C for 16 h. The reaction mixture was concentrated and the catalyst was removed by column chromatography over silica using dichloromethane and subsequently ethyl acetate as the eluent. Evaporation of the solvent yielded the racemized product. Yield: 0.97 g (97%).

Typical procedure for the addition of rac-6-MeCL to racemized 4

Novozym 435 (0.10 g) was added to a 10 mL sample vial. The vial was put overnight in a vacuum oven (10 mm Hg) at 50 °C in presence of P₂O₅. The oven was backfilled with nitrogen and the vial was removed from the oven. The racemized product 4 (1.3 g, 5.6 mmol), 6-MeCL (3.0 g, 24 mmol), 1,3,5-tri-tert-butylbenzene (0.47 g, 1.9 mmol), toluene (4 mL) and dry molecular sieves (3 Å) were added to a 50 mL round-bottom flask. The mixture was stirred at 45 °C for 16 hours to remove traces of water. The mixture was allowed to cool down to room temperature. The dried Novozym 435 was added, which represented the start of the reaction. During reaction, samples (~ 0.02 mL) were drawn from the reaction mixture using a glass Pasteur pipette. 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 conversion of both enantiomers of 6-MeCL. After completion of the reaction, the enzymatic reaction was stopped by filtration using a class 3 glass filter and the filter was flushed with toluene. The filtrate was concentrated and the remaining 6-MeCL was removed by distillation using a Kugelrohr apparatus (T = 80 °C, 0.05 mm Hg). The product was used without further purification (1.60 g).

¹H NMR δ (ppm) 7.3-7.4 (m, Ar-H), 5.1 (Ar-CH₂-O), 4.9 (m, CH(CH₃)OCOCH₂), 3.8 (m, CH(CH₃)OH), 2.3 (m, CH(CH₃)OCOCH₂), 1.65-1.35 (m, OCOCH₂(CH₃)₃), 1.15 (d, CH₃)

Typical procedure for the addition of (S)-6-MeCL to racemized 4

Novozym 435 (50 mg) was added to a 10 mL sample vial. The vial was put overnight in a vacuum oven (10 mm Hg) at 50 °C in presence of P₂O₅. The oven was backfilled with nitrogen and the vial was removed from the oven. The racemized product mixture (1.1 g; containing 2.1 mmol 4, 4.7 mmol (S)-6-MeCL and 1,3,5-tri-tert-butylbenzene), (S)-6-MeCL (1.0 g, 7.8 mmol), toluene (4 mL) and dry molecular sieves (3 Å) were added to a 50 mL round-bottom flask. The mixture was stirred at 45 °C for 16 h to remove traces of water. The dried Novozym 435 was added, which represented the start of the reaction. The mixture was stirred at 80 °C for 16 h. After completion of the reaction, which was confirmed by ¹H NMR, the enzymatic reaction was stopped by filtration using a class 3 glass filter and the filter was flushed with dichloromethane. The filtrate was concentrated. The product was quantitatively obtained and used without further purification.

Typical procedure for the one-pot synthesis of 6-MeCL oligomers

A 5 mL vial was charged with Novozym 435 (56 mg) and put overnight in a vacuum oven (10 mm Hg) at 50 °C in presence of P₂O₅. The oven was backfilled with nitrogen and the vial was removed from the oven. A Schlenk tube was charged with [RuCl₂(cymene)]₂ (15 mg, 0.024 mmol), rac-2-phenyl-2-amino-
propionamide (9.5 mg, 0.058 mmol), K$_2$CO$_3$ (0.33 g, 2.4 mmol), 1-PE (52 mg, 0.42 mmol), (S)-6-MeCL (0.48 g, 3.8 mmol), 1,3,5-tri-tert-butylbenzene (62 mg, 0.25 mmol), toluene (4.9 mL), 2,4-dimethyl-3-pentanol (1.4 mL, 10 mmol) and dry molecular sieves (3 Å). The mixture was stirred at 70 °C for 2.5 h to allow preformation of the catalyst. The dried enzyme was then added, indicating the start of the reaction. The reaction mixture was stirred at 70 °C for 282 h.

The reaction was stopped by filtration using a class 3 glass filter. The filtrate was concentrated in vacuo and the catalyst was removed by column chromatography over silica using dichloromethane and subsequently ethyl acetate as the eluent. Evaporation of the solvent yielded the product.

**Typical procedure for the enzymatic polymerization of ε-caprolactone in presence of a solid base**

Novozym 435 (25 mg), K$_2$CO$_3$ (80 mg) and toluene (2.25 mL) were added to a 5 mL vial. The mixture was stirred and heated to 70 °C in a carousel reactor. A mixture of BA (25 mg, 0.20 mmol) and ε-caprolactone (320 mg, 2.96 mmol) was added to the vial, which indicated the start of the reaction. After 0, 5, 10, 20, 40, 80 and 160 min., aliquots (~ 0.02 mL) were taken from the reaction mixture using a glass Pasteur pipette. The samples were diluted with dichloromethane and the enzyme was removed by filtration over cotton wool. The samples were analyzed by chiral GC.

**Typical procedure for the racemization of (S)-1-PE in the presence of lactones**

A Schlenk tube was charged with [RuCl$_2$(cymene)]$_2$ (17 mg, 0.03 mmol), rac-2-phenyl-2-amino-propionamide (10 mg, 0.06 mmol), K$_2$CO$_3$ (0.6 g, 4.3 mmol), 5 mL 2-propanol (65 mmol) and 10 mL toluene. The mixture was stirred at 70 °C for 2 h. (S)-1-PE (0.25 g, 2.0 mmol), rac-6-MeCL (0.25 g, 2.0 mmol) and K$_2$CO$_3$ (25 mg, 0.18 mmol) were added to a Schlenk tube. 2.3 mL of the catalyst solution were filtered through a 1 μm PTFE syringe filter and added to the reaction mixture. The mixture stirred at 70 °C for 4 h. Small aliquots of reaction mixture were taken for GC analysis.

**Hydrolysis of Generation 5 6-MeCL oligomers**

Oligomer of generation 5 (0.40 g) was dissolved in toluene (7 mL) in a 50 mL round-bottom flask. 1 mL MeOH and 2 drops of 37% v/v HCl$_{aq}$ were added to the mixture. The mixture was stirred at reflux for 21 h. After completion of the reaction, which was confirmed by $^1$H NMR, an aliquot of the reaction mixture was diluted with dichloromethane and 2 drops of trifluoroacetic anhydride were added. The mixture was analyzed on chiral GC (90 °C isothermal, r.t. = 26.34 and 26.99 min.).

By performing the same procedure with (S)-6-MeCL, the peak at r.t. = 26.99 min. was identified as the $S$-enantiomer of the secondary alcohol formed.

4.7 References and notes

17. The enantiomeric ratio, E, which indicates the selectivity of the enzyme for the fast reacting enantiomer relative to the slowly reacting enantiomer is defined as: 
\[ E = \left( \frac{V_{\text{max}}}{K_M} \right)^R / \left( \frac{V_{\text{max}}}{K_M} \right)^S. \]
In this equation \( V_{\text{max}} \) and \( K_M \) denote the maximum velocity and Michaelis constant, respectively. Under saturating conditions, E indicates the ratio between the initial reaction rates for both enantiomers. See also: Chen et al., *J. Am. Chem. Soc.* **1982**, *104*, 7294.
22. van As, B. A. C., manuscript in preparation.
25. The method used for end-group detection has an estimated detection limit of 5%. Therefore, we concluded that water initiation occurred to less than 5% of the polymer chains.
28. Pseudomonas cepacia immobilized on ceramic (PS-C) did not show any activity towards ring-opening of 6-MeCL; the formulation immobilized on celite (PS-D I) showed low ring-opening activity towards 6-MeCL with moderate enantioselectivity towards (R)-6-MeCL (E = 12 at 60 °C).
35. In metal-ligand bifunctional catalysis the metal and the surrounding ligand directly participate in the bond–forming and –breaking steps of the dehydrogenative and hydrogenative processes. This is in contrast to the mechanisms proposed for most other transition metal-catalyzed reactions.
36. An experiment in which ring-opening product 4a was racemized and an additional unit of 6-MeCL was subsequently added, confirmed our hypothesis regarding the requirement of racemization for the propagation of the ring-opening product.
37. The E-value of the ring-opening of 6-MeCL by Novozym 435 was determined to be 12 at 60 °C. The E-value was calculated according to Chen et al. *J. Am. Chem. Soc.* 1982, 104, 7294.
The diol-initiated oligomers have two secondary alcohol end-groups, hence the correction using the integral area of peak E. The DP calculated was not corrected for the presence of dimeric cycles.

van As, B. A. C. Ph.D. Thesis in press, Eindhoven University of Technology, Chapter 1.


Huisgen, R.; Ott, H., Tetrahedron 1959, 6, 253.

It is assumed that the dipole moment of 6-MeCL is similar to that of CL.


Catalyst 1 was preformed in the presence of 2-propanol and K$_2$CO$_3$. After preformation approximately 2 mL of the catalyst solution was filtered through a 1 μm PTFE syringe filter and added to the reaction mixture. Judging from the different values obtained for the TOF for the reference experiments without lactone, there is some variation between the different sets of experiments (Table 4.2, entries 1-4 and entries 5-8). In the experiments described in Table 4.2, entries 9-11, the catalyst was formed in situ.

The polarity of the lactones cannot explain the significantly higher racemization activity in presence of 2 eq of CL (Table 4.2, entry 3, TOF = 97 h$^{-1}$) than in presence of 2 eq of 6-MeCL (Table 4.2, entry 2, TOF = 38 h$^{-1}$) since 6-MeCL is slightly less polar than CL. Therefore, other factors should play a role.


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.

Upon the use of different matrices distribution E disappears or shifts to different masses; since the CHCA/DCTB matrix yields by far the clearest spectra, the spectra obtained using this matrix are displayed.

The amount of diol-initiated oligomer can be quantified by means of the characteristic CH$_2$OH-signal at δ = 4.0 ppm.

The percentage of intrachain esters in the R-configuration can be calculated using the following formula: fraction R-esters = $\frac{1}{2} \times \left( \frac{I}{E} + 1 \right)$ where I and E represent, respectively, the integrals in $^1$H NMR for the intrachain esters and the end-groups, and εε is the measured enantiomeric excess of the methyl ester.

van As, B. A. C.; van Buijtenen, J. et al., manuscript in preparation.

Abstract

Racemic ω-substituted caprolactones can be completely converted into the enantiopure R-polyesters of remarkable MW and high ee by combining lipase-catalyzed ring-opening polymerization with Ru-catalyzed racemization. Both 6-methyl-ε-caprolactone (6-MeCL) and 6-ethyl-ε-caprolactone (6-EtCL) were successfully converted into the corresponding chiral polyester. Furthermore, the kinetics of the tandem catalytic process were investigated, and zero-order behavior is typically observed for the overall reaction.
5.1 Introduction

In Chapter 4 it was shown that, by employing tandem catalysis, (S)-6-methyl-ε-caprolactone (6-MeCL) can be converted into R-oligomers.¹ This concept is referred to as iterative tandem catalysis (ITC). Furthermore, we proposed that insertion of (R)-6-MeCL into the growing chain via a related mechanism, should enable complete conversion of the racemic monomer into a chiral polymer. Hilker et al. have recently described the synthesis of enantiopure low MW polyesters from a racemic diol and a diester.² In these systems, catalyst 1 was employed for the racemization of the S-alcohols (Figure 5.1). Reference experiments as described in Chapter 4 revealed that this catalyst is incompatible with the lipase-catalyzed polymerization of small, highly polar lactones such as 6-MeCL, resulting in a dramatically lower activity for both the enzyme and the Ru catalyst under these reaction conditions.³ After screening several alternative racemization catalysts in this reaction, the well-known Shvo catalyst (2) appeared as a promising alternative for 1.⁴,⁵

![Figure 5.1 Racemization catalysts employed in ITC.](image)

This catalyst has been applied extensively in dynamic kinetic resolution (DKR) of secondary alcohols (see Chapter 3).⁶ The racemization occurs via transfer hydrogenation and a concerted mechanism for this reaction was proposed by Casey et al. (Scheme 5.1).⁷,⁸
**Scheme 5.1 Concerted mechanism for transfer hydrogenation by catalyst 2.**

Complex 2 dissociates into hydride complex 2a and the coordinatively unsaturated dienone dicarbonyl 2b. Ru(0) complex 2b can react with a secondary alcohol to form Ru(II) complex 2a and the corresponding ketone. In this concerted process the proton of the alcohol is transferred to the carbonyl group of the dienone ligand, while the hydride is transferred to the Ru. The ketone generated is reduced by 2a, reforming complex 2b and a racemic secondary alcohol. Continuous operation of this mechanism results in the racemization of the slower reacting S-secondary alcohol in DKR.

**Scheme 5.2 Principle of ITC leading to chiral polymers.**

Here, we describe ITC of 6-MeCL using the Shvo catalyst (2). The optimization of the tandem catalytic system is discussed, which affords polymers with $M_n$ up to 25.0 kDa and $ee_{\text{polymer}}$ up to 96%. Furthermore, 6-ethyl-$\varepsilon$-caprolactone (6-EtCL) is also used as a substrate.

**5.2 Synthesis of benzyl alcohol-initiated poly-(R)-6-MeCL**

In Chapter 4 it is described that upon addition of a unit of (S)-6-MeCL to the growing chain, propagation is only possible after the unreactive S-alcohol is converted into a reactive
$R$-alcohol by racemization. Reaction of $(R)$-6-MeCL, on the other hand, would lead to a reactive terminal $R$-alcohol, which can propagate without requiring racemization (Scheme 5.3).

**Scheme 5.3** Consumption of both enantiomers in ITC of 6-MeCL.

To enable a better understanding of the reaction, experiments with $(S)$-6-MeCL as the substrate were performed first. The well-known Shvo catalyst 2 was employed for the racemization and 2,4-dimethyl-3-pentanol (DMP) was added as a hydrogen donor to counter the effect of dehydrogenation of the end-groups.\(^9\) 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 promising $e_{\text{polymer}} = 86\%$ (Table 5.1, 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. Surprisingly, an approximately zero-order rate of consumption of $(S)$-6-MeCL is observed and a $k_c$ of $32.2 \times 10^{-4}\ \text{h}^{-1}$ was calculated (Figure 5.2).\(^10\) The kinetics of the reaction are explained in detail in section 5.3. Ru-catalyzed transfer hydrogenation of 6-MeCL led to the formation of 0.58 mol% of 1,6-heptanediol, reducing the MW of the polymer by $\sim 20\%$.\(^11\) GPC analysis of the crude polymer revealed $M_p = 8.2\ \text{kDa}$. There is a trade-off between high MW and high $e_{\text{polymer}}$ as a high rate of racemization, required for high ee, leads to a higher rate of hydrogenation of the lactone, thereby reducing MW.\(^12\) The $M_p$ as a function of time is displayed in Figures 5.2 and 5.3. As expected, an approximately linear increase of $M_p$ with time is observed for the zero-order reaction.
Figure 5.2 Conversion (●, left axis) and $M_p$ (□, right axis) as a function of time for ITC of (S)-6-MeCL, $N_{BA,0} = 0.05$ mmol, $N_{(S)-6-MeCL,0} = 2.63$ mmol, $M/I = 50$ (Table 5.1, entry 1).

Figure 5.3 GPC 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 5.1, entry 1).

While the synthesis of poly-(R)-6-MeCL from (S)-6-MeCL represents a very elegant application of ITC, it is arguably of no practical value: the chirality of the monomer is simply inverted and the same polymer can be obtained by chemical ring-opening polymerization of (R)-6-MeCL. Direct conversion of the racemate into the enantiopure polymer would be much more appealing.
As described in Chapter 4, the ring-opening of 6-MeCL is \( S \)-selective and the \( S \)-enantiomer reacts approximately 10 times faster than the \( R \)-enantiomer. In the absence of racemization, propagation does not occur due to the \( S \)-configuration of the alcohol that is formed. However, on long time scales the \( R \)-enantiomer is completely consumed; it was shown that the \( S \)-lactone and the reactive nucleophile can be reformed due to reversibility of the enzymatic reaction and that subsequently the \( R \)-lactone can be ring-opened. This results in net insertion of \((R)\)-6-MeCL (see Chapter 4, section 4.2.2).

In ITC of \((rac)\)-6-MeCL, the \( S \)-enantiomer is consumed via the iterative mechanism. The \( R \)-enantiomer will react slowly due to the low enantioselectivity of the enzymatic ring-opening, but also net insertion will take place due to the aforementioned reversibility of the enzymatic reaction (for this no racemization is required). Depending on the relative amounts of the lipase and the racemization catalyst, reaction of the \( R \)-enantiomer compared to that of the \( S \)-enantiomer can be significantly slower, approximately similar or much faster. In case of rate-limiting racemization, the lack of reactive nucleophiles will result in a similar situation to that of the experiment without racemization described above and the consumption of the \( R \)-enantiomer can be comparable to that of the \( S \)-enantiomer or even faster. Very fast racemization will lead to a rate-limiting enzymatic reaction and negligible consumption of the \( R \)-enantiomer via the net insertion mechanism; in this case consumption of the \( S \)-enantiomer will be much faster than that of the \( R \)-enantiomer.

In the ITC experiments described, conditions were chosen such that the enantiomers reacted at approximately the same rate (Figure 5.4). In summary, ring-opening of \((S)\)-6-MeCL furnishes an \( S \)-secondary alcohol, which has to be converted to the reactive \( R \)-secondary alcohol by the racemization catalyst for propagation to occur; ring-opening of \((R)\)-6-MeCL leads to an \( R \)-secondary alcohol which does not require racemization for propagation. In the overall ITC experiment, \((S)\)-6-MeCL is completely converted by the iterative mechanism, while \((R)\)-6-MeCL is build into the growing chain without requiring the action of the racemization catalyst.

With 0.6 mol\% of 2 (0.06 mmol Ru), 7 mg Novozym 435 / mmol 6-MeCL and \( M/I = 40 \), \((rac)\)-6-MeCL was polymerized within 220 h with complete conversion of both enantiomers, yielding a high \( ee_{\text{polymer}} = 92\% \) (entry 2). A \( k_0 \) of \( 53.8 \times 10^{-4} \text{h}^{-1} \) was calculated for the zero-order conversion of \((S)\)-6-MeCL. Experiments with double and half the amount of racemization catalyst 2 (entries 3-4), resulted in correspondingly higher and lower rates, respectively. A reaction with a double amount of enzyme (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. Hydrogenation of 6-MeCL resulted in the formation of only 0.2 – 0.3 mol\% of 1,6-heptanediol, reducing the MW of the polymer by \( \sim 10\% \).
Table 5.1 **Iterative tandem catalysis (ITC) of 6-MeCL, M/I = 40.**

<table>
<thead>
<tr>
<th>entry</th>
<th>Ru (mmol)</th>
<th>Nov435 (mg/mmol)</th>
<th>time (h)</th>
<th>conv. (%)</th>
<th>(k_i \times 10^4) (h(^{-1}))</th>
<th>ee(_{\text{polymer}}) (%)</th>
<th>(M_p) (kDa)</th>
<th>diol (mol%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1(^a)</td>
<td>0.06</td>
<td>13</td>
<td>318</td>
<td>98</td>
<td>32.2</td>
<td>86</td>
<td>8.2</td>
<td>0.58%</td>
</tr>
<tr>
<td>2</td>
<td>0.06</td>
<td>7</td>
<td>220</td>
<td>99</td>
<td>53.8</td>
<td>92 (94)</td>
<td>9.4</td>
<td>0.33%</td>
</tr>
<tr>
<td>3(^b)</td>
<td>0.12</td>
<td>14</td>
<td>103</td>
<td>94</td>
<td>84.7</td>
<td>89</td>
<td>8.2</td>
<td>0.20%</td>
</tr>
<tr>
<td>4</td>
<td>0.03</td>
<td>7</td>
<td>507</td>
<td>&gt;99</td>
<td>27.9</td>
<td>85</td>
<td>11.0</td>
<td>0.28%</td>
</tr>
<tr>
<td>5</td>
<td>0.06</td>
<td>13</td>
<td>147</td>
<td>97</td>
<td>62.2</td>
<td>87</td>
<td>9.4</td>
<td>0.22%</td>
</tr>
</tbody>
</table>

\(^a\) 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 (S)-6-MeCL, determined by fitting a straight line to regime B of the conversion-time history (see Figure 5.5). \(^d\) 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. \(^e\) Determined by GPC, relative to polystyrene standards. \(^f\) Amount of 6-MeCL (mol%) converted to 1,6-heptanediol; determined by chiral GC after methanolysis of the polymer. \(^g\) Monomer = (S)-6-MeCL: 2.5 mmol, BA: 0.05 mmol, M/I = 50. \(^h\) DMP: 0.125 mmol.

Figure 5.4 Conversion of (S)-6-MeCL ( ■ ) and (R)-6-MeCL ( ● ) as a function of time in a typical ITC experiment with 40 eq of 6-MeCL with respect to BA, 1.2 mol% of 2 and 14 mg Novozym 435 / mmol 6-MeCL (Table 5.1, entry 3).

5.3 Kinetic evaluation of iterative tandem catalysis of (S)-6-MeCL

The zero-order rate of consumption of (S)-6-MeCL in the ITC experiments can be explained by the kinetics of the tandem catalytic system. The following discussion of the kinetics focuses on the S-lactone, while the R-lactone is not taken into account. In ITC of (S)-6-MeCL two simultaneous catalytic reactions are taking place: enzymatic ring-opening
polymerization (eROP) and Ru-catalyzed racemization of secondary alcohols. The mechanism of eROP is proposed to proceed via an acyl enzyme (EM) at a Ser-OH residue in the active site of the lipase (see Scheme 4.3). Scheme 5.4 shows the Cleland plot for eROP of (S)-6-MeCL (A). This mechanism can be described as a “bi uni sequential ordered” mechanism. The formation of EM is normally the rate-determining step. In some cases nucleophilic attack by the hydroxyl chain ends (B) may become rate-limiting (e.g. sterically hindered nucleophiles, or in the case of a very low nucleophile concentration). The kinetics of such systems are often described using Michaelis Menten (MM) kinetics.

Scheme 5.4 Cleland plot for enzymatic ring-opening polymerization of (S)-6-MeCL.

As ring-opening of (S)-6-MeCL results in an S-secondary alcohol, while lipase-catalyzed transesterification of secondary alcohols is R-selective, Ru-catalyzed racemization is required for a polymerization on a realistic time scale. The rate of formation of reactive R-alcohol is first order in the S-secondary alcohol concentration (see Chapter 3). In theory, three reaction steps can be identified that can become rate-limiting depending on the reaction conditions:

1. Formation of the acyl enzyme EM
2. Nucleophilic attack on EM by the R-alcohol, forming EP
3. Ru-catalyzed racemization of the S-alcohols to provide the nucleophile for the enzymatic reaction

It is instructive to take a closer look at these three extreme cases (Table 5.2). Provided that the overall effect of dehydrogenation of the end-groups and hydrogenation of the lactone can be neglected, the concentration of alcohol end-groups will be constant. The substrate for the formation of EM is free (S)-6-MeCL (decreases during the reaction) and if this reaction step is rate-determining in the reaction, first-order kinetics will be observed. If the nucleophilic
attack on EM is rate-determining, the rate of reaction is dependent on the concentration of both free (S)-6-MeCL and reactive R-alcohol (constant during reaction, ee = 0%).\textsuperscript{15} Therefore, the reaction will still be dependent on the concentration of the lactone, resulting in pseudo first-order kinetics. In case of rate-limiting racemization, the ee of the end-groups will be high and the rate of reaction is proportional to the concentration of S-alcohol. This concentration remains virtually unchanged during most of the reaction and, therefore, the rate of production of reactive R-alcohol is approximately constant during reaction.\textsuperscript{16} This production of reactive R-alcohol enables the consumption of (S)-6-MeCL and overall zero-order behavior will be observed for the ITC experiment.

**Table 5.2 Kinetics of iterative tandem catalysis of 6-MeCL.**

<table>
<thead>
<tr>
<th>reaction kinetics</th>
<th>formation of the acyl enzyme</th>
<th>nucleophilic attack</th>
<th>racemization</th>
</tr>
</thead>
<tbody>
<tr>
<td>substrate</td>
<td>EA $\rightarrow$ EM</td>
<td>EMB $\rightarrow$ EP</td>
<td>$S \leftrightarrow R$</td>
</tr>
<tr>
<td></td>
<td>pseudo MM</td>
<td>pseudo MM</td>
<td>first-order</td>
</tr>
<tr>
<td></td>
<td>free (S)-6-MeCL</td>
<td>terminal alcohols + free (S)-6-MeCL</td>
<td>terminal alcohols</td>
</tr>
<tr>
<td>observed kinetics\textsuperscript{a}</td>
<td>first-order</td>
<td>first-order</td>
<td>zero-order</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Observed kinetics regarding lactone conversion if the indicated reaction is rate-determining.

In intermediate cases the kinetics of the ITC system will be in between the above-mentioned extreme situations (pseudo first-order or zero-order kinetics). Since zero-order kinetics are observed in a typical ITC experiment, the time-constant of the racemization will be high compared to that of the enzymatic reactions (i.e. the reaction will be mostly limited by the racemization) and the ee of the alcohol end-groups will be high. Increasing the amount of Ru catalyst and, thereby, the rate of racemization will obviously increase the rate of consumption of (S)-6-MeCL. Importantly, in most cases the ee will not be >99%, but for example 80%. In such cases, addition of extra enzyme will increase the consumption of reactive R-alcohol and hence the ee. The concomitant increase of the concentration of the S-alcohol will lead to faster racemization (proportional to the concentration of S-alcohol) and a faster overall consumption of (S)-6-MeCL. Increasing the amount of the racemization catalyst should, however, produce the greatest effect on the overall rate of reaction of the ITC experiment as was observed in the experiments listed in Table 5.1.

At high conversion (> 80%), the formation of the acyl enzyme EM is expected to become rate-limiting, resulting in a deviation from zero-order kinetics. This behavior is indeed observed depending on the reaction conditions (Figure 5.5). In the early stages of reaction, the initiation takes place (initiator + 1 eq of (S)-6-MeCL), leading to an initial jump in conversion (Figures 5.2, 5.4). After initiation has completed, zero-order kinetics are normally observed and a k-value [h\textsuperscript{-1}] can be determined for the various experiments.\textsuperscript{17}
5.4 Synthesis of 1,6-heptanediol-initiated poly-(R)-6-MeCL of remarkable MW

In order to evaluate whether polymers of higher MW are accessible, the reaction was performed at M/I = 100. With 0.6 mol% of 2 (0.06 mmol Ru) and 7 mg Novozym 435 / mmol 6-MeCL the polymerization was very slow and nearly complete conversion was only achieved after 576 h (Table 5.3, entry 1). Furthermore, the reaction did not obey zero-order kinetics and the MW of the polymer (M_p = 13.6 kDa) was significantly reduced by diol formation (0.48 mol%). We then repeated the experiment, both with extra enzyme and with a double amount of Ru (entries 2 and 3, respectively). Increasing the amount of enzyme to 25 mg/mmol resulted in zero-order kinetics again, indicating that the nucleophilic attack on EM is significantly slower at these low alcohol concentrations (see section 5.3). Complete conversion was achieved within 244 h with ee_{polymer} = 83% and diol formation was importantly reduced with 0.30 mol%, resulting in M_p = 14.5 kDa. As expected, a much higher ee_{polymer} (96%) is obtained for entry 3, since faster racemization leads to a lower ee of the alcohol end-groups during reaction. Concomitantly, hydrogenation of 6-MeCL is significantly increased (0.75 mol% of diol) leading to a low M_p = 9.8 kDa.

We then performed the reaction with 1,6-heptanediol as the initiator (entry 4). This reaction was significantly faster, which can be (partly) explained by the fact that the initiator is bifunctional. An experiment with M/I = 206 gave a polymer with a high M_p = 20.8 kDa (entry 5). The ee_{polymer} of the product of this unoptimized reaction was 76%. This polymer was precipitated from methanol to remove the catalyst (yield 34%) and the number-averaged MW
obtained from GPC analysis was 25.0 kDa with a PDI of 1.23 (Figure 5.6). In an attempt to improve the ee of the polymer, the reaction was then performed with increased Ru loading (entry 6). As expected this produced an improved ee = 88%, at the expense of a lower MW due to increased hydrogenation of the lactone. ITC of 6-MeCL was also performed in the absence of initiator (entry 7). In this case, 1,6-heptanediol should slowly be formed during reaction by hydrogenation, eventually resulting in the same polymer. This is indeed the case, resulting in a slower reaction with complete conversion only after 221 h. However, the MW of the polymer is lower than expected for the amount of 1,6-heptanediol formed, which can be explained by significant water initiation under these conditions (i.e. no other initiator was present at the start of the reaction). The conversion of (S)-6-MeCL as a function of time for the 1,6-heptanediol-initiated experiments is shown in Figure 5.7.

The 1,6-heptanediol-initiated polymers were also analyzed by MALDI-TOF MS and NMR spectroscopy (1H and 13C). The MALDI-TOF MS spectrum of the polymer obtained in entry 4 is shown in Figure 5.8. After work-up using a Kugelrohr apparatus, all end-groups were 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 in eROP. The 1H NMR spectrum of the polymer obtained in

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**Table 5.3 Iterative tandem catalysis (ITC) of 6-MeCL, aiming for higher MW.**

<table>
<thead>
<tr>
<th>entry</th>
<th>initiator, M/I</th>
<th>Ru (mmol)</th>
<th>Nov435 (mg/mmol)</th>
<th>time (h)</th>
<th>conv. (%)</th>
<th>k&lt;sub&gt;i&lt;/sub&gt;·10&lt;sup&gt;4&lt;/sup&gt; (h&lt;sup&gt;-1&lt;/sup&gt;)&lt;sup&gt;d&lt;/sup&gt;</th>
<th>ee&lt;sub&gt;polymer&lt;/sub&gt; (%)&lt;sup&gt;e&lt;/sup&gt;</th>
<th>M&lt;sub&gt;p&lt;/sub&gt; (kDa)&lt;sup&gt;f&lt;/sup&gt;</th>
<th>diol (mol%)&lt;sup&gt;g&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BA, 94</td>
<td>0.06</td>
<td>7</td>
<td>576</td>
<td>98</td>
<td>n.a.&lt;sup&gt;h&lt;/sup&gt;</td>
<td>89</td>
<td>13.6</td>
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</tr>
<tr>
<td>2</td>
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<td>25</td>
<td>244</td>
<td>&gt;99</td>
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<td>83</td>
<td>14.5</td>
<td>0.30%</td>
</tr>
<tr>
<td>3</td>
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<td>7</td>
<td>504</td>
<td>92</td>
<td>n.a.&lt;sup&gt;h&lt;/sup&gt;</td>
<td>96</td>
<td>9.8</td>
<td>0.75%</td>
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<td>4</td>
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<td>0.07</td>
<td>7</td>
<td>504</td>
<td>99</td>
<td>78.9</td>
<td>85</td>
<td>13.6</td>
<td>1.19%&lt;sup&gt;i&lt;/sup&gt;</td>
</tr>
<tr>
<td>5</td>
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<td>0.07</td>
<td>7</td>
<td>504</td>
<td>98</td>
<td>56.6</td>
<td>76</td>
<td>20.8</td>
<td>0.69%&lt;sup&gt;i&lt;/sup&gt;</td>
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<tr>
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<td>7</td>
<td>504</td>
<td>98</td>
<td>68.3</td>
<td>88</td>
<td>15.6</td>
<td>0.83%&lt;sup&gt;i&lt;/sup&gt;</td>
</tr>
<tr>
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<td>7</td>
<td>504</td>
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<tr>
<td>8</td>
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<td>7</td>
<td>575</td>
<td>95&lt;sup&gt;j&lt;/sup&gt;</td>
<td>87.5&lt;sup&gt;j&lt;/sup&gt;</td>
<td>94</td>
<td>19.2</td>
<td>0.24%</td>
</tr>
</tbody>
</table>

<sup>a</sup> Unless otherwise noted, Ru catalyst 2, Novozym 435, 6-MeCL (5 mmol), initiator, DMP (0.20 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. <sup>b</sup> Monomer-to-initiator molar ratio <sup>c</sup> Average conversion of both enantiomers, determined by GC. <sup>d</sup> Zero-order rate constant for the conversion of (S)-6-MeCL; determined by fitting a straight line to regime B of the conversion-time history (see Figure 5.5). <sup>e</sup> Determined by chiral GC after methanolysis of the polymer. <sup>f</sup> Determined by GPC, relative to polystyrene standards. <sup>g</sup> Amount of 6-MeCL (mol%) converted to 1,6-heptanediol; determined by chiral GC after methanolysis of the polymer. <sup>h</sup> Zero-order kinetics are not obeyed. <sup>i</sup> Includes approximately 0.50 mol% that was added as the initiator. <sup>j</sup> Three consecutive batches of approximately 40 eq of 6-MeCL were added consecutively (see text). <sup>k</sup> Overall conversion of cumulative amount of 6-MeCL added. <sup>l</sup> Calculated for the conversion of the first 40 eq of 6-MeCL.
entry 5 is shown in Figure 5.9. Again, only ketone end-groups are observed as a result of dehydrogenation during work-up.

![Figure 5.6](image6.png)

**Figure 5.6** GPC traces of polymer obtained by ITC of rac-6-MeCL (Table 5.3, entry 5) before (A) and after (B) precipitation in methanol ($M_n = 25.0 \text{ kDa}, \text{PDI} = 1.23$).

![Figure 5.7](image7.png)

**Figure 5.7** Conversion of (S)-6-MeCL as a function of time in 1,6-heptanediol-initiated experiments: $M/I = 102, 0.07 \text{ mmol Ru}$ (■, Table 5.3, entry 4), $M/I = 206, 0.07 \text{ mmol Ru}$ (●, Table 5.3, entry 5), $M/I = 202, 0.12 \text{ mmol Ru}$ (○, Table 5.3, entry 6), no initiator, $0.13 \text{ mmol Ru}$ (▲, Table 5.3, entry 7).
Figure 5.8 MALDI-TOF MS spectrum of 1,6-heptanediol-initiated poly-(R)-6-MeCL (Table 5.3, entry 4), 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.

Figure 5.9 ¹H NMR spectrum of 1,6-heptanediol-initiated poly-(R)-6-MeCL (Table 5.3, entry 5). 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 * originate from ring-opening of 2-methyl-ε-caprolactone, which is present as an impurity in 6-MeCL (see Experimental section).
5.5 Batchwise addition of 6-MeCL during ITC

A final experiment involved the batchwise addition (3 × ~40 eq with respect to BA) of rac-6-MeCL to a reaction mixture (Table 5.3, entry 8). The rate of consumption for the second and third batch of 6-MeCL was lower, but the tandem catalytic system clearly remained active throughout the experiment and 122 eq of 6-MeCL were eventually consumed (Figure 5.10). Besides possible deactivation of the catalysts, the increased concentration of ester groups after addition of the next batch of 6-MeCL will also lead to a lower rate of reaction. The amount of diol formation (0.24 mol%) and the ee\textsubscript{polymer} (94%) were similar to BA-initiated experiments with M/I = 40 and a high M\textsubscript{p} = 19.2 kDa was obtained.

This result easily represents the best ee\textsubscript{polymer} obtained for a product with high M\textsubscript{p}, which can be explained by the aforementioned trade-off between high MW and high ee\textsubscript{polymer} (Figure 5.11). The Ru catalyst not only catalyzes the racemization of the alcohol end-groups – which should be fast for obtaining a high ee\textsubscript{polymer} – but also the hydrogenation of 6-MeCL. While the concentration of alcohol end-groups is essentially constant during reaction, the concentration of 6-MeCL – the substrate for hydrogenation – decreases from e.g. 100 eq to 0 eq during reaction. The rate of hydrogenation of 6-MeCL depends on the concentration of 6-MeCL, in contrast to the rate of racemization. In order to avoid concomitantly faster diol formation with faster racemization, the concentration of 6-MeCL should be as low as possible during the experiment. This is achieved by batchwise addition of the lactone. As an extreme case of this approach the reaction can also be performed under starved-feed conditions – continuously adding the monomer by for example a syringe pump, while keeping the concentration below ~1 eq with respect to the alcohol and-groups. This was indeed attempted, but unsuccessful due to the air sensitivity of the reaction and concentration effects. It was not further pursued at this time.

(a) (b)

Figure 5.10 Batchwise addition of extra 6-MeCL to an ITC experiment (Table 5.3, entry 8). (a) Conversion as a function of time. (b) Cumulative conversion in eq of 6-MeCL as a function of time.
Investigation of the Novozym 435-catalyzed ring-opening of various $\omega$-substituted caprolactones revealed that 6-ethyl-$\varepsilon$-caprolactone (6-EtCL) is also a suitable substrate for ITC.\textsuperscript{19} Ring-opening of this lactone is $S$-selective as well, resulting in the formation of an $S$-secondary alcohol with an ethyl-substituent. Acylation of this alcohol occurs analogously to that of the methyl-substituted alcohol that is formed when using 6-MeCL, although the reaction is significantly slower.\textsuperscript{20,21} Gratifyingly, ITC of 6-EtCL also gave the chiral polymer with a high $ee_{\text{polymer}}$ up to 94\% (Table 5.4, Figure 5.12). In order to investigate the effect of the enzyme loading, the reaction was performed with varying amounts of Novozym 435 at constant Ru loading. In general, the reactions obey zero-order kinetics and by changing the amount of Novozym 435, the rate of the nucleophilic attack on EM relative to the rate of racemization is investigated. As expected, the effect of the increased enzyme loading on the overall rate of reaction decreases at higher amounts and the reactions with 51 and 111 mg/mmol produce similar results (entries 4 and 5). Presumably, the $ee$ of the end-groups is ~ 99\% at these loadings and the rate of reaction is completely limited by the racemization. In general, the $ee_{\text{polymer}}$ decreases as the $ee$ of the end-groups during reaction increases going from entry 1 to 5. A higher relative rate of racemization is expected to result in decreased acylation of the $S$-alcohols and, therefore, higher $ee_{\text{polymer}}$. The $ee$ obtained for the experiment with 51 mg Novozym 435 / mmol 6-EtCL is significantly lower than expected, however (entry 4). GPC analysis of these short polymers produces broad distributions and no trend can be distinguished.
Table 5.4 Iterative tandem catalysis (ITC) of 6-EtCL.\(^a\)

<table>
<thead>
<tr>
<th>entry</th>
<th>Ru (mmol)</th>
<th>Nov435 (mg/mmol)</th>
<th>time (h)</th>
<th>conv. (%)(^b)</th>
<th>(k_t\cdot10^4) (h(^{-1}))(^c)</th>
<th>ee(_{\text{polymer}}) (%)(^d)</th>
<th>(M_p) (kDa)(^e)</th>
<th>diol (mol%)(^f)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.06</td>
<td>6</td>
<td>313</td>
<td>93</td>
<td>30.4</td>
<td>94</td>
<td>2.8</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>0.07</td>
<td>14</td>
<td>241</td>
<td>99</td>
<td>51.5</td>
<td>93</td>
<td>6.4</td>
<td>0.44%</td>
</tr>
<tr>
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<td>25</td>
<td>146</td>
<td>98</td>
<td>72.1</td>
<td>91</td>
<td>4.4</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>0.06</td>
<td>51</td>
<td>96</td>
<td>97</td>
<td>n.a.(^g)</td>
<td>79</td>
<td>7.0</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>0.06</td>
<td>111</td>
<td>100</td>
<td>98</td>
<td>n.a.(^g)</td>
<td>87</td>
<td>8.9</td>
<td>-</td>
</tr>
</tbody>
</table>

\(^a\) Unless otherwise noted, Ru catalyst 2, Novozym 435, rac-6-EtCL (5 mmol), initiator, 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 (S)-6-EtCL; determined by fitting a straight line to regime B of the conversion-time history (see Figure 5.5). \(^d\) Determined by chiral GC after methanolysis of the polymer. \(^e\) Determined by GPC, relative to polystyrene standards. \(^f\) Amount of 6-EtCL (mol%) converted to 1,6-octanediol; determined by \(^1\)H NMR. \(^g\) Zero-order rate constant could not be calculated as a result of insufficient data points.

Figure 5.12 Conversion of (S)-6-EtCL as a function of time in experiments with varying enzyme loading: 6 mg/mmol (□, Table 5.4, entry 1), 14 mg/mmol (■, Table 5.4, entry 2), 25 mg/mmol (○, Table 5.4, entry 3), 51 mg/mmol (●, Table 5.4, entry 4), 111 mg/mmol (▲, Table 5.4, entry 5).

5.7 Conclusions

Racemic 6-MeCL was completely converted into poly-(R)-6-MeCL of high MW and high ee\(_{\text{polymer}}\) by employing tandem catalysis. Initial problems with compatibility were overcome and lipase-catalyzed ring-opening polymerization and Ru-catalyzed racemization were successfully combined in one pot. Furthermore, the kinetics of the reaction were described. It was shown that rate-limiting racemization of the alcohol end-groups normally resulted in zero-order
kinetics for the overall process. 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 realized. Furthermore, the concept of ITC was successfully extended to 6-EtCL and chiral polymers with high ee polymer were also obtained using this substrate. A fed-batch experiment in which three consecutive batches of 6-MeCL were added to the reaction mixture led to a polymer of high MW and high ee as the effect of hydrogenation of the lactone was reduced. This is in marked contrast to a normal batch experiment in which high MW leads to a concomitantly lower ee polymer. Clearly, working under starved-feed conditions – an extreme case of batchwise addition of 6-MeCL – is an appealing option to pursue.

5.8 Experimental section

General methods
See General methods Chapters 2, 3 and 4. All experiments with metal complexes were carried out under a dry argon atmosphere using standard Schlenk techniques. 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. 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, 5 μm, 300 × 7.5 mm, Polymer Laboratories), using THF as the eluent. All molecular weights are given relative to polystyrene standards. The ee polymer of poly-(R)-6-MeCL and the amount of 1,6-heptanediol were determined by chiral GC analysis after acid-catalyzed methanolysis of the polymer (see Chapter 4). The ee polymer of poly-(R)-6-EtCL was determined analogously, while the amount of 1,6-octanediol-initiated chains was determined by 1H NMR.

Synthesis of ω-substituted caprolactones
6-MeCL and 6-EtCL were synthesized by Baeyer-Villiger oxidation of the corresponding cyclic ketone as described previously. NMR and GC data are summarized below. Due to the regioselectivity of the BV oxidation, a small amount of the α-methylated lactone is formed. In the synthesis of 6-MeCL and 6-EtCL this amounts to 5% of 2-methyl-ε-caprolactone (2-MeCL) and 3% of 2-ethyl-ε-caprolactone (2-EtCL), respectively. Lipase-catalyzed ring-opening of these substrates is much slower than that of the corresponding ω-methylated lactones. In ITC of 6-MeCL, 2-MeCL eventually reacts as the reaction progresses. However, this does not affect the reaction as is proven by ITC of (S)-6-MeCL (Table 5.1, entry 1), where no 2-MeCL is present. In ITC of 6-EtCL, no conversion of 2-EtCL is observed at all.

6-Methyl-ε-caprolactone (6-MeCL)
Bp = 58-60 °C/0.6 Torr. 1H NMR (CDCl3); δ 4.45 (m, 1H, CHO-C=O); 2.60 (m, 2H, CH2-C=O); 1.90–1.40 (6H); 1.30 (d, 3H, CH3). 13C{1H} NMR (CDCl3); δ 175.4 (C=O); 76.6; 36.0; 34.8; 28.0; 22.7; 22.4. GC retention time: (S)-6-MeCL = 9.3 min; (R)-2-MeCL and (S)-2-MeCL = 10.1 min; (R)-6-MeCL = 10.5 min at 121 °C.
**6-Ethyl-ε-caprolactone (6-EtCL)**

\[ ^1H\text{ NMR (CDCl}_3\text{): } \delta 4.17 (m, 1H, CHOC=O); 2.64 (m, 2H, CH}_2\text{C}=O); 2.00–1.50 (8H); 0.99 (t, 3H, CH}_3\text{).} \]

\[ ^13C\{^1H\} \text{ NMR (CDCl}_3\text{): } \delta 175.9 (C=O); 81.9; 35.1; 34.2; 29.5; 28.4; 23.2; 10.0. \]

**GC retention time:** \((S)-6\text{-EtCL} = 6.8 \text{ min}; (R)-2-EtCL and (S)-2-EtCL = 7.1 \text{ min}; (R)-6-EtCL = 7.4 \text{ min at 135 °C}.\]

**rac-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\(_2\)O (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\(_2\)O. The combined filtrates were then neutralized with saturated NH\(_4\)Cl, the organic layer was separated and the aqueous layer was extracted with Et\(_2\)O. The combined organic layers were dried over MgSO\(_4\) and concentration of the filtrate in vacuo yielded the crude product which was further purified by vacuum distillation (oil bath temperature 110 °C, 0.04 mm Hg). Yield: 2.9 g (35%). \( ^1H\text{ NMR and } ^13C\{^1H\} \text{ NMR data are in agreement with those reported in literature.} \]

\[ ^1H\text{ NMR (CDCl}_3\text{): } \delta 3.78 (m, 1H, CH}_3\text{C}_2\text{H}_7\text{OH); 3.62 (t, } J = 6.6 \text{ Hz, 2H, C}_2\text{H}_2\text{OH); 1.81 (br, 2H, -OCH}_2\text{); 1.56 (m, 2H); 1.48–1.32 (6H); 1.17 (d, } J = 6.2 \text{ Hz, 3H) } ^13C\{^1H\} \text{ NMR (CDCl}_3\text{): } \delta 68.1; 62.8; 39.3; 32.7; 25.8; 25.6; 23.6. \]

**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), DMP (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 dry 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 dry 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 °C 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 DMP 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. 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^\circ (c 2.44, \text{CHCl}_3). \]

\[ ^1H\text{ NMR (CDCl}_3\text{): } \delta 4.89 (m, (CH}_3\text{)C}_2\text{H}_7\text{OCO); 4.05 (t, CH}_2\text{OCO); 2.27 (t, CH}_2\text{COO); 2.14 (s, CH}_2\text{COCH}_3); 1.70–1.25 (CH}_2); 1.19 (d, CH}_3). \]

\[ ^13C\{^1H\} \text{ NMR (CDCl}_3\text{): } \delta 173.3; 70.8; 35.8; 34.7; 25.2; 25.0; 20.1. \]

**Iterative tandem catalysis of 6-MeCL performed under fed-batch conditions**

A solution of BA (13 mg, 0.12 mmol), 6-MeCL (0.64 g, 5.0 mmol), DMP (29 mg, 0.25 mmol) and 1,3,5-tri-tert-butylbenzene (44 mg, 0.18 mmol) in toluene (2.5 mL) was stirred overnight at 50 °C over dry molecular sieves (3 Å) to remove traces of water. A Schlenk tube was charged with Novozym 435 (64 mg), catalyst 2 (62 mg, 0.06 mmol) and dry 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 °C for the indicated period of time. Small aliquots of reaction mixture were taken for GC analysis. After 150 h the conversion of 6-MeCL was >99% and a solution of 42 eq of 6-MeCL in toluene (0.5 mL) was added to the reaction. This procedure was repeated after 343 h (41 eq of 6-MeCL were added). The reaction was terminated after 575 h. The mixture was then 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 DMP and 1,3,5-tri-tert-butylbenzene were removed by distillation using a Kugelrohr apparatus (T = 100 °C, 0.03 mm Hg). Crude yield: 1.16 g (59%).

**Iterative tandem catalysis of 6-EtCL**

Experiments were performed analogously to the ITC of 6-MeCL. 1H NMR (CDCl₃): δ 5.11 (s, PhCH₂OR); 4.80 (m, (CH₂CH₃)CO); 4.04 (t, CH₂OCO); 3.53 (m, C(CH₂CH₃)OH end-group) 2.28 (t, CH₂COO); 1.70–1.20 (CH₂); 0.87 (t, CH₃).

5.9 References and notes

4. ITC of 6-MeCL with catalysts C and 3d, which are described in Chapter 3, did not yield polymers; both these catalysts are successful racemization catalysts in DKR of secondary alcohols.
9. Ru-catalyzed dehydrogenation of the secondary alcohol end-groups is a side reaction, which was described in Chapter 4.
10. The zero-order rate constant kᵢ was determined from the conversion time history of the experiment and, therefore, applies to the equation: dX₀/dt = kᵢ [h⁻¹] (with A = (S)-6-MeCL). With N₀ = 2.63 mmol this becomes kᵢ' = kᵢ ∙ N₀ = 8.47 × 10⁻³ mol∙h⁻¹ in the equation dN₀/dt = kᵢ'.
11. The hydrogenation of the 6-MeCL was quantified by acid-catalyzed methanolysis of the isolated polymer and subsequent chiral GC analysis. Ru-catalyzed hydrogenation of 6-MeCL...
is described in Chapter 4. Diol formation was significantly reduced compared to the initial experiments employing catalyst 1.

12. Despite the high enantioselectivity of the transesterification of the secondary alcohols (typically E > 100), some of the S-alcohol will inevitably react when the ratio between the slow reacting S-alcohol and the fast reacting R-alcohol becomes too large (at high ee).


14. Dehydrogenation of the terminal alcohols and hydrogenation of 6-MeCL, yielding 1,6-heptanediol are two side reactions that have been minimized. The former reaction reduces the number of end-groups, while the latter increases it. It is assumed that the combined effect of these two side reactions can be neglected. See Chapter 4.

15. Since the nucleophilic attack occurs after the formation of the acyl enzyme EM, the rate equation (which can be derived using MM-kinetics) contains both the concentration of free lactone and the concentration of nucleophile, i.e., R-alcohol.

16. It is assumed that the effect of polarity on the activity of catalyst 2 can be neglected; during reaction the polarity of the reaction medium decreases due to the conversion of lactone into in-chain ester.

17. Using Langmuir-Hinshelwood kinetics for the enzymatic reaction, the overall kinetics of ITC can be described and differential equations for the system can be derived. It was shown that in case of rate-limiting racemization zero-order kinetics are observed. See van As, B. A. C. *Ph.D. Thesis in press*, Eindhoven University of Technology, Chapter 6.

18. It is reasonable to assume that the hydrogenation of 6-MeCL obeys first-order kinetics in substrate concentration.

19. Ring-opening of both 6-MeCL and 6-EtCL is S-selective and at 45 °C TOF’s of 56 and 22 s⁻¹ and E-values of 12 and 4.8 were obtained, respectively. Ring-opening of 6-n-propyl-ε-caprolactone (6-PrCL) and 6-n-butyl-ε-caprolactone (6-BuCL) was much slower with TOF’s of 1.0 and 0.4 s⁻¹, respectively; both reactions were also S-selective with low E-values.


21. Acylation of n-propyl- and n-butyl-substituted secondary alcohols does not occur on a realistic time scale, rendering 6-PrCL and 6-BuCL unsuitable as substrates for ITC.


6

*Candida antarctica* Lipase B-Catalyzed Ring-Opening and Polymerization of ω-Substituted Lactones

Abstract

In this chapter, the Novozym 435-catalyzed ring-opening of a range of small and larger ω-methylated lactones is discussed. An intriguing switch from S- to R-selectivity was observed upon going from small (ring sizes < 8) to larger lactones (ring sizes > 7). This was attributed to the transition from a cisoid to a transoid conformational preference of the ester bond. The larger, transoid lactones could be polymerized, without exception, by straightforward kinetic resolution polymerization (KRP), yielding the enantiopure R-polyester with good MW and excellent ee.
6.1 Introduction

Access to synthetic chiral polymers is generally limited by the availability of chiral monomers. For example, Muñoz-Guerra et al. have synthesized chiral polyamides, poly(ester amide)s and polysters based on readily available D- and L-tartaric acid.\textsuperscript{1} Asymmetric catalysis enables the synthesis of chiral polymers from racemic monomers. Prominently, a range of chiral polysters has been synthesized by lipase-catalyzed ring-opening polymerization of substituted lactones.\textsuperscript{3-8} Promising results were obtained, although the e\textsubscript{e}polymer is generally moderate at best (< 90%).

The mechanism for \textit{Candida Antarctica} Lipase B (CALB) catalyzed transesterification is described in Chapter 4 of this thesis (see Scheme 4.3). In the enzymatic ring-opening polymerization (eROP) of a chiral lactone both the formation of the acyl enzyme and the nucleophilic attack by the alcohol end-group of the propagating chain will, in principle, be enantioselective. Since the alcohol side of the active site pocket is more confined than the acyl side, the enantioselectivity of the nucleophilic attack will often be higher than that of the formation of the acyl enzyme.\textsuperscript{8} This is most pronounced for the ring-opening of \(\omega\)-substituted lactones, which yields a secondary alcohol. Lipase-catalyzed transesterification of secondary alcohols is highly \(R\)-selective (typically \(E > 100\)), which is exploited in kinetic resolution of secondary alcohols.\textsuperscript{9} Ring-opening of the \(S\)-enantiomer of the \(\omega\)-substituted lactone is a problem in eROP because the \(S\)-secondary alcohol that is formed will act as a chain-stopper. This is indeed the case for the ring-opening of \(\omega\)-methylated \(\delta\)-valeralactone (5-MeVL) and \(\epsilon\)-caprolactone (6-MeCL) for which it was reported that eROP did not occur on a realistic time scale.\textsuperscript{3,5,6} Haufe et al. described eROP of macrolides (ring sizes 10 - 14) with a CH\textsubscript{2}F-substitution in the \(\omega\)-position, although the reaction was very slow and only low MW was obtained; unfortunately, the e\textsubscript{e}polymer was not determined.\textsuperscript{4}

Table 6.1 \(\omega\)-Methylated lactones of varying ring size.

<table>
<thead>
<tr>
<th>(n)</th>
<th>lactone(^a)</th>
<th>ring size</th>
<th>ester conformation(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>3-MePL</td>
<td>4</td>
<td>C</td>
</tr>
<tr>
<td>1</td>
<td>4-MeBL</td>
<td>5</td>
<td>C</td>
</tr>
<tr>
<td>2</td>
<td>5-MeVL</td>
<td>6</td>
<td>C</td>
</tr>
<tr>
<td>3</td>
<td>6-MeCL</td>
<td>7</td>
<td>C</td>
</tr>
<tr>
<td>4</td>
<td>7-MeHL</td>
<td>8</td>
<td>C + little T</td>
</tr>
<tr>
<td>5</td>
<td>8-MeOL</td>
<td>9</td>
<td>T + little C</td>
</tr>
<tr>
<td>9</td>
<td>12-MeDDL</td>
<td>13</td>
<td>T</td>
</tr>
</tbody>
</table>

\(^a\) PL = propiolactone, BL = butyrolactone, VL = valeralactone, CL = caprolactone, HL = heptalactone, OL = octalactone, DDL = dodecalactone. \(^b\) C represents the cisoid conformation, while T represents the transoid conformation; based on data for the non-methylated lactones obtained from ref 16; it is assumed that \(\omega\)-methylation of the lactone does not substantially influence the conformation of the ester bond.
In Chapter 5 we have shown that, by employing iterative tandem catalysis (ITC), 
rac-6-MeCL can be completely converted into the enantiopure polyester of high MW and high 
ee.6,10 This was achieved by combining the S-selective ring-opening of the lactone by Novozym 
435 – CALB immobilized on an acrylic resin – with Ru-catalyzed racemization of the alcohol end-groups.11 We were then interested in the Novozym 435-catalyzed ring-opening of other 
ω-methylated lactones in view of their potential for the synthesis of enantiopure polymers.

6.2 CALB-catalyzed ring-opening of ω-methylated lactones with various ring sizes

A range of ω-methylated lactones was subjected to Novozym 435-catalyzed ring-opening (Table 6.1). Ring-opening of 6-MeCL is S-selective; since ring-opening results in the formation 
of an S-secondary alcohol, which, according to Kazlauskas’ rule is the slower reacting 
enantiomer in the highly enantioselective lipase-catalyzed transesterification, no further 
propagation takes place. In an experiment with a monomer-to-initiator molar ratio (M/I) of 4, 
one eq of (S)-6-MeCL is quickly consumed by reaction with the initiator (Table 6.2, entry 3, 
Figure 6.1a); the S-secondary alcohol that is formed is not accepted as a nucleophile by the 
enzyme and, therefore, no further consumption of the monomer is observed. The results for 
the ring-opening of ω-methylated lactones are presented in Table 6.2.

<table>
<thead>
<tr>
<th>entry</th>
<th>lactone</th>
<th>ring size</th>
<th>kcat (s⁻¹)</th>
<th>enantioselectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>S-enantiomer</td>
<td>R-enantiomer</td>
</tr>
<tr>
<td>1</td>
<td>3-MePL</td>
<td>4</td>
<td>45.7</td>
<td>n.d.</td>
</tr>
<tr>
<td>2</td>
<td>5-MeVL</td>
<td>6</td>
<td>7.9</td>
<td>7.6</td>
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<td>3</td>
<td>6-MeCL</td>
<td>7</td>
<td>49.3</td>
<td>8.5</td>
</tr>
<tr>
<td>4</td>
<td>7-MeHL</td>
<td>8</td>
<td>0.01f</td>
<td>204.4</td>
</tr>
<tr>
<td>5</td>
<td>8-MeOL</td>
<td>9</td>
<td>n.d.</td>
<td>10.3</td>
</tr>
<tr>
<td>6g</td>
<td>12-MeDDL</td>
<td>13</td>
<td>n.d.</td>
<td>23.3</td>
</tr>
</tbody>
</table>

Table 6.2 CALB-catalyzed ring-opening of ω-methylated lactones at 70 °C.a

Ring-opening of 3-methylpropiolactone (3-MePL) is S-selective as well and a similar 
behavior is observed as for 6-MeCL (Table 6.2, entry 1, Figure 6.1b).3,12 As a result of a highly 
unfavorable ring-chain equilibrium for the 6-membered lactone, ring-opening of 5-MeVL with 
M/I = 4 and benzyl alcohol (BA) as the initiator did not produce meaningful results.13 The
reaction was, therefore, repeated with 1-octanol as the initiator and M/I = 0.5 and the reaction turned out to be virtually aselective (Table 6.2, entry 2, Figure 6.2).\(^{14}\) Both enantiomers of the lactone react at a similar rate and conversion reaches equilibrium at around 65%. Apparently, CALB is unable to discriminate between the enantiomers of this particular lactone. For the small lactones, the spatial orientation of the methyl substituent is highly dependent on the ring size, which can explain the differences in selectivity for the lactones with ring sizes < 8. Ring-opening of the 5-membered ring, 4-methylbutyrolactone (4-MeBL) does not occur at all due to its thermodynamic stability.

**Figure 6.1** Conversion as a function of time for CALB-catalyzed ring-opening with M/I = 4 of (a) 6-MeCL and (b) 3-MePL with (●) representing the S-lactone, ( ■ ) the R-lactone and (○) BA; reaction conditions: lactone (4 mmol), BA (1 mmol), Novozym 435 (27 mg), 1,3,5-tri-tert-butylbenzene (0.3 mmol, internal standard) in toluene (2 mL); reaction at 70 °C.

**Figure 6.2** CALB-catalyzed ring-opening of 5-MeVL with M/I = 0.5 (Table 6.2, entry 2); (a) conversion, \(x\), and (b) \(-\ln(1-x)\) of (S)-5-MeVL (△), (R)-5-MeVL (■) and 1-octanol (○) are plotted as a function of time; reaction conditions: 5-MeVL (4 mmol), 1-octanol (8 mmol), Novozym 435 (31 mg), 1,3,5-tri-tert-butylbenzene (0.3 mmol, internal standard) in toluene (2 mL); reaction at 70 °C.
In contrast to the ring-opening of the lactones with ring sizes < 8, ring-opening of the larger lactones with ring sizes between 8 and 13 was R-selective. This resulted in the formation of a reactive R-secondary alcohol and both equivalents of the R-lactone (with respect to BA, M/I = 4) were quickly consumed (entries 4-6). No consumption of the S-lactone could be observed in these cases. For (R)-7-methylheptalactone (7-MeHL) a $k_{\text{cat}}$ value of 204.4 s$^{-1}$ was calculated (Table 6.2, entry 4, Figure 6.3a). For ring-opening of isolated (S)-7-MeHL, a $k_{\text{cat}}$ value of only 0.01 s$^{-1}$ was calculated, indicative of a very high E-value for the reaction (Figure 6.3b). Similar behavior was observed for 8-methylloctalactone (8-MeOL) and 12-methyldodecalactone (12-MeDDL).

Figure 6.3 Conversion of (S)-7-MeHL (●), (R)-7-MeHL (■) and BA (○) as a function of time for CALB-catalyzed ring opening of 7-MeHL; (a) M/I = 4, reaction conditions: 7-MeHL (4 mmol), BA (1 mmol), Novozym 435 (25 mg), 1,3,5-tri-tert-butylbenzene (0.3 mmol, internal standard) in toluene (2 mL); reaction at 70 °C; (b) ring-opening of isolated (S)-7-MeHL with M/I = 2, reaction conditions: (S)-7-MeHL (2 mmol), BA (1 mmol), Novozym 435 (55 mg), 1,3,5-tri-tert-butylbenzene (0.3 mmol, internal standard) in toluene (2 mL); reaction at 70 °C.

6.3 Influence of the conformation of the ester function on the ring-opening of the lactone

In the 1950s Huisgen et al. described detailed studies on (non-methylated) lactones of different ring sizes to explain their deviating properties compared to linear esters.\textsuperscript{15,16} In lactones of small ring sizes (up to 7), the ester bond is forced into a cisoid conformation, resulting in high dipole moments and relatively high boiling points (Figure 6.4). The energy difference between the cisoid and the transoid conformation amounts to 15 kJ/mol.\textsuperscript{16} In larger lactones the ester bond can adopt the energetically favorable transoid conformation as is the case in linear esters. The transition from the cisoid conformation to the energetically favored transoid conformation takes place at the 8- and 9-membered lactones with the first predominantly in the cisoid conformation and the latter predominantly in the transoid.
conformation. Larger lactones are exclusively in the transoid conformation. Within our group the implications of this transition for the Novozym 435-catalyzed eROP of non-methylated lactones were already investigated and fascinating differences in the polymerization rates of the various lactones were revealed.\textsuperscript{17} Reactivity of the small ring lactones (ring sizes 5 – 7) was relatively low, which was attributed to low reactivity of cisoid esters in CALB-catalyzed ring-opening.\textsuperscript{18} The high reactivity of the 8-membered lactone and the low reactivity of the 10–12-membered lactones were attributed to the effect of conformational strain (the inability of C–C bonds to attain anti conformations in cyclic compounds) and transannular interactions (repulsion between non-neighbouring H-atoms), analogous to their effect on lactone hydrolysis. Novozym 435-catalyzed ring-opening of large ring lactones (ring sizes 13 and 16) was relatively fast. Reactivities that were obtained for the Novozym 435-catalyzed ring-opening of ω-methylated lactones are roughly in line with these results (Table 6.2). Notably, ring-opening of 7-MeHL is fastest and reactivity of the small lactones (ring size 4 - 7) was relatively low.

![Cisoid and transoid conformations of the ester bond](image)

**Figure 6.4** Cisoid and transoid conformations of the ester bond

It is reasonable to assume that ω-methylation does not substantially influence the conformation of the ester bond in the lactone; 6-MeCL will be exclusively in the cisoid conformation and starting with 7-MeHL a transition to the transoid conformation will take place. This transition coincides with the remarkably sharp transition that is observed in the enantioselectivity of the ring-opening of the lactones: ring sizes < 8 show limited selectivity for the S-enantiomer (3-MePL and 6-MeCL) or no selectivity at all (5-MeVL), while ring sizes > 7 exhibit very high selectivity for ring-opening of the R-enantiomer (see Table 6.2). As a substrate for the lipase, the large, transoid lactones are structurally similar to linear aliphatic (transoid) esters. Transesterification of the latter substrates represents the reverse reaction of the well-known R-selective esterification of secondary alcohols and, therefore, necessarily exhibits the same (R-) enantioselectivity.\textsuperscript{9,19} Surprisingly, the presence of the cisoid conformation in 7-MeHL and (to a lesser extent) 8-MeOL does not appear to influence the enantioselectivity of ring-opening, while it is reasonable to assume that – analogous to the smaller lactones – the selectivity of ring-opening of the cisoid conformation of the lactone will be limited and possibly even S-selective. Presumably, the transoid conformation reacts much faster than the cisoid conformation, which is also in agreement with the observation that ring-opening of the small, cisoid-only lactones is relatively slow, despite their high dipole moments.
The enantioselectivity of the 8-membered lactone is unexpectedly high with several orders of magnitude between $k_{cat}$ for the $S$- and the $R$-enantiomer of 7-MeHL.

6.4 Computer-aided molecular modelling of docking of $\omega$-methylated lactones in CALB

In order to verify our hypothesis regarding the reversed enantioselectivity for the ring-opening of the small cisoid lactones and the larger transoid lactones, computer-aided molecular modelling was performed. The molecular structure of the enantiomers of each lactone was docked flexibly into the active site cavity of CALB, specifically mimicking the interactions between the lactones with the catalytic triad (Ser105, His224, Asp187) before acylation. Furthermore, several expected stabilizing interactions between the protein and ligand were investigated by additional docking runs. While this is a very rough approximation, the difference between the calculated average free energy of binding of the complex for both enantiomers ($\Delta\Delta G$) can give an indication for the enantioselectivity of the protein.

Table 6.3 Average free energy of binding ($\Delta G$) of the protein-ligand complex for the different lactones.\(^a\)

<table>
<thead>
<tr>
<th>lactone</th>
<th>series 1 (kJ/mol)</th>
<th>series 2 (kJ/mol)</th>
<th>series 3 (kJ/mol)</th>
<th>series 4 (kJ/mol)</th>
<th>average (kJ/mol)</th>
<th>st. dev. (kJ/mol)</th>
<th>pref.(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(R)-3-MePL</td>
<td>-70.88</td>
<td>-69.96</td>
<td>-70.75</td>
<td>-69.96</td>
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<td>$S$</td>
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<tr>
<td>(S)-3-MePL</td>
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<td>-71.63</td>
<td>-71.84</td>
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<td>0.60</td>
<td>$S$</td>
</tr>
<tr>
<td>(R)-5-MeVL</td>
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<td>$S$</td>
</tr>
<tr>
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<td>-84.43</td>
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<td>$S$</td>
</tr>
<tr>
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<td>-82.39</td>
<td>-82.60</td>
<td>-79.13</td>
<td>-83.85</td>
<td>5.20</td>
<td>$S$</td>
</tr>
<tr>
<td>(S)-6-MeCL</td>
<td>-91.73</td>
<td>-88.92</td>
<td>-90.18</td>
<td>-90.47</td>
<td>-90.33</td>
<td>1.15</td>
<td>$S$</td>
</tr>
<tr>
<td>(R)-7-MeHL(^c)</td>
<td>-97.17</td>
<td>-93.24</td>
<td>-85.11</td>
<td>-87.58</td>
<td>-90.78</td>
<td>5.45</td>
<td>$R$</td>
</tr>
<tr>
<td>(S)-7-MeHL(^c)</td>
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<td>$R$</td>
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<td>(R)-7-MeHL(^d)</td>
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<td>-93.03</td>
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<tr>
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</tr>
<tr>
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<td>-96.50</td>
<td>-104.4</td>
<td>8.03</td>
<td>$R$</td>
</tr>
</tbody>
</table>

\(^a\) Four series of docking runs were performed with different distance constraints regarding the ligand and the protein backbone (see Experimental section). The average free energy of binding of the four docking runs is given with its standard deviation.\(^b\) Predicted enantioselectivity.\(^c\) Cisoid conformation of the lactone.\(^d\) Transoid conformation of the lactone.

The predicted $\Delta G$-values for the lactone enantiomers and the predicted enantiopreferences resulting from the docking study are listed in Table 6.3. Docking of the
S-enantiomer of the small cisoid-only lactones was energetically favored over that of the R-enantiomer, implying S-selectivity. However, differences in free energy between the enantiomers are small and in most cases within the margin of error of the calculation. For 7-MeHL the transoid conformation was lower in free energy than the cisoid conformation and for both conformations the calculated average free energy of binding suggests R-selectivity. R-enantioselectivity was also predicted for 8-MeOL and 12-MeDDL. For these larger lactones the differences in free energy are, in every case, significant.

![Figure 6.5a](image)

**Figure 6.5a** Lowest energy conformations of (cisoid) (S)-6-MeCL (yellow), transoid (R)-7-MeHL (green) and transoid (S)-7-MeHL (blue) docked in the active site pocket of CALB (oxygen atoms are colored red). The methyl-groups of (S)-6-MeCL and transoid (R)-7-MeHL point approximately in the same direction (see right side of the figure), while their rings nearly overlap; the carbonyl-groups point deeper into the active site. For transoid (S)-7-MeHL both the carbonyl- (center of the figure, pointing upwards) and the methyl group (right side of the figure, pointing upwards) are directed into a different part of the active site pocket than in case of (S)-6-MeCL.

![Figure 6.5b](image)

**Figure 6.5b** Lowest energy conformations of (cisoid) (S)-6-MeCL (yellow), cisoid (R)-7-MeHL (green) and cisoid (S)-7-MeHL (blue) docked in the active site pocket of CALB (oxygen atoms are colored red). The methyl-groups of (S)-6-MeCL and cisoid (S)-7-MeHL point approximately in the same direction (see right side of the figure), while their rings nearly overlap; the carbonyl-groups point deeper into the active site. For cisoid (R)-7-MeHL the methyl group points in a different direction (downward) and there is almost no overlap of the ring with that of (S)-6-MeCL.

The lowest energy conformations of (cisoid) (S)-6-MeCL and both enantiomers of cisoid and transoid 7-MeHL docked in the active site pocket of CALB are depicted in Figure 6.5. Clearly, there is a good agreement between the lowest energy conformations of (S)-6-MeCL – the fastest reacting enantiomer of the 7-membered lactone – and transoid (R)-7-MeHL (with respect to the ring itself, the carbonyl- and the methyl-group), while for transoid (S)-7-MeHL
both the carbonyl- and methyl-groups point in a completely different direction (Figure 6.5a). This is in agreement with the lower calculated free energy for the R-enantiomer compared to the S-enantiomer ($\Delta\Delta G = -7.5$ kJ/mol), implying R-selectivity; moreover, this matches the experimentally observed selectivity. For the cisoid conformation of 7-MeHL a different picture is obtained (Figure 6.5b): the lowest energy conformation of cisoid (S)-7-MeHL appears to be in good agreement with that of (S)-6-MeCL, while for that of cisoid (R)-7-MeHL a significantly different orientation is observed. However, a lower free energy is calculated for cisoid (R)-7-MeHL than for the S-enantiomer, indicating that more subtle interactions that are not obvious from this (2D) figure play an important role ($\Delta\Delta G = -14$ kJ/mol).

The combination of (1) the good agreement between the lowest energy conformations of transoid (R)-7-MeHL and the reactive (S)-6-MeCL in contrast to the (visually) significantly different orientation of cisoid (R)-7-MeHL with (2) the very high enantioselectivity that was observed experimentally for the ring-opening (while a limited enantioselectivity can be expected for ring-opening of the cisoid lactone, vide supra) suggests that the transoid conformation of 7-MeHL is the reactive conformation in CALB-catalyzed ring-opening. More detailed (quantum mechanical) molecular modelling studies should be performed to support this tentative conclusion.

6.5 Polymerization of ω-methylated lactones

6-MeCL was successfully polymerized by employing ITC (see Chapter 5). The well-known Shvo catalyst (2, see Chapter 5) was combined with Novozym 435 and the racemic monomer was completely converted into the enantiopure R-polyester with $M_n$ up to 25.0 kDa and $\text{ee}_{\text{polymer}}$ up to 96%. ITC of 3-MePL and 5-MeVL failed to produce useful results and these substrates were not investigated further. The R-selective ring-opening of the lactones with ring sizes > 7 combined with its very high enantioselectivity enables straightforward kinetic resolution polymerization (KRP) of these substrates. Results are presented in Table 6.4. 7-MeHL, 8-MeOL and 12-MeDDL were successfully polymerized with $M/I = 100$, yielding the R-polyester with excellent $\text{ee}_{\text{polymer}} > 99\%$ (Figure 6.6). The highest activity was observed for the polymerization of 7-MeHL, followed closely by that of 12-MeDDL (Figure 6.6). Polymerization of 8-MeOL was significantly slower. Additional experiments will be required in order to clarify the kinetics of the polymerization and to identify the rate-determining step (acylation or deacylation). GPC traces of poly-(R)-7-MeHL obtained by KRP of rac-7-MeHL (entry 1) before and after precipitation in methanol are presented in Figure 6.7. KRP of 7-MeHL and 8-MeOL was also performed at larger scale in order to enable isolation of the S-lactones by (vacuum) distillation. An optical rotation of $+58^\circ$ was obtained for (S)-7-MeHL (ee > 99%), while a value of $+50^\circ$ was obtained for (S)-8-MeOL (ee > 99%). An optical rotation of $-41^\circ$ was previously
reported for (R)-8-MeOL of 91% ee, confirming the enantioselectivity of the present polymerizations.\textsuperscript{23}

<table>
<thead>
<tr>
<th>entry</th>
<th>lactone</th>
<th>M/I</th>
<th>time (h)</th>
<th>conv (%)\textsuperscript{b}</th>
<th>ee\textsubscript{m} (%)\textsuperscript{c}</th>
<th>ee\textsubscript{p} (%)\textsuperscript{d}</th>
<th>% non-methylated (mol/mol)\textsuperscript{e}</th>
<th>Mn\textsubscript{NMR} (kDa)\textsuperscript{e}</th>
<th>Mn\textsubscript{GPC} (kDa)\textsuperscript{f}</th>
<th>PDI</th>
</tr>
</thead>
<tbody>
<tr>
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<td>7-MeHL</td>
<td>102</td>
<td>4</td>
<td>&gt;99</td>
<td>99</td>
<td>&gt;99</td>
<td>16</td>
<td>14.8</td>
<td>16.7</td>
<td>1.23</td>
</tr>
<tr>
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<td>8-MeOL</td>
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<td>24</td>
<td>&gt;99</td>
<td>99</td>
<td>&gt;99</td>
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<td>12-MeDDL</td>
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<td>&gt;99</td>
<td>&gt;99</td>
<td>&gt;99</td>
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</tbody>
</table>

\textsuperscript{a} Reaction conditions: lactone (5 mmol), BA (0.05 mmol), Novozym 435 (50 mg), 1,3,5-tri-tert-butylbenzene (0.25 mmol, internal standard) in toluene (2.5 mL); reaction at 70 °C under an argon atmosphere. \textsuperscript{b} Conversion of the R-lactone; the S-lactone is practically unreactive. \textsuperscript{c} Determined by chiral GC. \textsuperscript{d} Determined by chiral GC after acid-catalyzed methanolysis of the polymer. \textsuperscript{e} Determined by \textsuperscript{1}H NMR after precipitation of the polymer in methanol. \textsuperscript{f} Determined by GPC (relative to polystyrene standards) after precipitation of the polymer in methanol.

**Figure 6.6** Conversion of the R-lactone as a function of time in KRP of 7-MeHL (■), 8-MeOL (▲) and 12-MeDDL (○); reaction conditions: lactone (5 mmol), BA (0.05 mmol), Novozym 435 (50 mg), 1,3,5-tri-tert-butylbenzene (0.25 mmol, internal standard) in toluene (2.5 mL); reaction at 70 °C under an argon atmosphere.
6.6 Conclusions

Novozym 435-catalyzed ring-opening of ω-methylated lactones exhibits fascinating variations in reactivity and enantioselectivity. Ring-opening of the small, cisoid lactones is S-selective (3-MePL and 6-MeCL) or aselective (5-MeVL). Ring-opening of the larger lactones for which the ester bond can adopt a transoid conformation is R-selective with a very high enantioselectivity. For the intermediate ring sizes – 7-MeHL (8) and 8-MeOL (9) – the presence of the cisoid conformation does not appear to affect the enantioselectivity of the ring-opening. Molecular modelling studies supported the reversal of selectivity observed upon going from the small, cisoid-only lactones to the larger lactones which can adopt a transoid conformation. The R-selectivity for the transoid lactones was related to the R-selectivity of the transesterification of (transoid) linear, aliphatic esters. Importantly, this selectivity enabled the Novozym 435-catalyzed kinetic resolution polymerization (KRP) of these lactones. Poly-(R)-7-MeHL, poly-(R)-8-MeOL, poly-(R)-12-MeDDL were all obtained with good MW and excellent ee (> 99%). To the best of our knowledge, this ee represents by far the best value obtained for CALB-catalyzed eROP of chiral lactones.

6.7 Experimental section

General methods
See General methods Chapters 2, 3 and 4. 3-MePL and 5-MeVL were obtained from Aldrich. The ω-methylated lactones that were not commercially available were synthesized by methylation of the corresponding ketone followed by Baeyer-Villiger oxidation. 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 (injection temperature was set at 250 °C and detection temperature was set at 300 °C) or on a Perkin Elmer Autosystem GC equipped with a Chiraldex G-TA (DF=0.125) column and an FID (injection and detection temperatures were set at 200 °C). Lactone conversions were determined by the internal standard method using 1,3,5-tri-tert-butylbenzene as the internal standard. 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 a ResiPore column, using CHCl₃ as the eluent. All molecular weights are given relative to polystyrene standards. For the ring-opening experiments with M/I = 4, the turnover frequency (TOF) was calculated according to the formula $TOF = \frac{k_i \times (\text{initial substrate concentration})}{(\text{total enzyme concentration})}$, in which $k_i$ is the initial rate constant as determined by fitting a straight line to the relationship between $-\ln(1-x)$ and time, with $x = \text{conversion}$. In order to calculate the TOF an active protein content of Novozym 435 of 2% (w/w) was assumed. Under certain conditions $[\text{lactone}] > \sim 10 \times K_M$ the TOF equals $k_{\text{cat}}$. Since this is generally true for the experiments presented in Table 6.2, $k_{\text{cat}}$ is given.

2-Methylcycloheptanone
A 500 mL flask was charged with diisopropylamine (12.9 g, 127 mmol) and freshly distilled THF (225 mL) and placed under a nitrogen atmosphere. The solution was then stirred and cooled to 0 °C in an ice-water bath. A solution of 2.5 M n-butyllithium in hexane (50.8 mL, 127 mmol) was added dropwise via an addition funnel. After the addition was complete the mixture was stirred for 30 min. A solution of cycloheptanone (15.0 mL, 127 mmol) in freshly distilled THF (75 mL) was added dropwise via an addition funnel at 0 °C. After the addition was complete the mixture was stirred for 30 min. at 0 °C. The reaction mixture was then cooled to -78 °C in an acetone-dry ice bath. Methyl iodide (10.3 mL, 165 mmol, 1.3 eq.) was also cooled to -78 °C in an acetone-dry ice bath for 5 min. and subsequently added to the reaction mixture. After 15 min. the acetone-dry ice bath was removed and the reaction mixture was stirred overnight. The mixture was then poured in a saturated NH₄Cl solution (150 mL) and diethyl ether (150 mL) was added. The water layer was removed and the organic layer was washed with respectively saturated Na₂CO₃ solution (150 mL), a 1 M HCl solution (100 mL) and a saturated MgCl₂ solution (150 mL), and dried with MgSO₄. Concentration of the filtrate in vacuo yielded the crude product which was further purified by vacuum distillation. Yield: 12.2 g (75%). According to GC-MS a purity of 92% was obtained, with the non-methylated ketone present as the main impurity. ¹H NMR (CDCl₃): $\delta$ 2.60 (m, COC₃H₇), 2.49 (m, CH₂CO), 1.9 – 1.2 (C₄H₉), 1.07 (m, COCH₂CH₃).

2-Methylcyclooctanone
A 500 mL flask was charged with diisopropylamine (12.9 g, 127 mmol) and freshly distilled THF (225 mL) and placed under a nitrogen atmosphere. The solution was then stirred and cooled to 0 °C in an ice-water bath. A solution of 2.5 M n-butyllithium in hexane (55 mL, 138 mmol) was added dropwise via an addition funnel. After the addition was complete the mixture was stirred for 30 min. at 0 °C. A solution of cyclooctanone (15.9 g, 126 mmol) in freshly distilled THF (75 mL) was added dropwise via an addition funnel at 0 °C. After the addition was complete the mixture was stirred for 30 min. at 0 °C. The reaction mixture was then cooled to -78 °C in an acetone-dry ice bath. Methyl iodide (11.0 mL, 176 mmol, 1.4 eq.) was also cooled to -78 °C in an acetone-dry ice bath for 5 min. and subsequently added to the reaction mixture. After 15 min. the acetone-dry ice bath was removed and the reaction mixture was stirred overnight. The mixture was then poured in a saturated NH₄Cl solution (150 mL) and diethyl ether (150 mL) was added. The water layer was removed and the organic layer was washed with respectively saturated Na₂CO₃ solution (150 mL), a 1 M HCl solution (100 mL) and a saturated MgCl₂.
solution (150 mL), and dried with MgSO₄. Concentration of the filtrate in vacuo yielded the crude product which was further purified by vacuum distillation. Yield: 14.1 g (81%). According to GC-MS a purity of 87% was obtained, with the non-methylated ketone present as the main impurity. ¹H NMR (CDCl₃): δ 2.58 (m, COCH₃), 2.37 (m, CH₂CO), 2.0 – 1.1 (C₆H₁₀), 1.03 (m, COCH₂).

2-Methylcyclododecanone

A 250 mL flask was charged with diisopropylamine (8.59 g, 84.9 mmol) and freshly distilled THF (150 mL) and placed under a nitrogen atmosphere. The solution was then stirred and cooled to 0 °C in an ice-water bath. A solution of 2.5 M n-butyllithium in hexane (33.0 mL, 82.5 mmol) was added dropwise via an addition funnel. After the addition was complete the mixture was stirred for 30 min. at 0 °C. A solution of cyclooctododecanone (15.0 g, 82.2 mmol) in freshly distilled THF (50 mL) was added dropwise via an addition funnel at 0 °C. After the addition was complete the mixture was stirred for 30 min. at 0 °C. The reaction mixture was then cooled to -78 °C in an acetone-dry ice bath. 6.60 mL of methyl iodide (105 mmol, 1.3 eq.) was also cooled to -78 °C in an acetone-dry ice bath for 5 min. and subsequently added to the reaction mixture. After 15 min. the acetone-dry ice bath was removed and the reaction mixture was stirred overnight. The mixture was then poured in a saturated NH₄Cl solution (100 mL) and diethyl ether (100 mL) was added. The water layer was removed and the organic layer was washed with respectively saturated Na₂CO₃ solution (100 mL), a 1 M HCl solution (75 mL) and a saturated MgCl₂ solution (100 mL), and dried with MgSO₄. Concentration of the filtrate in vacuo yielded the crude product which was further purified by vacuum distillation. Yield: 13.3 g (82%). According to GC-MS a purity of 80% was obtained, with the non-methylated ketone present as the main impurity. ¹H NMR (CDCl₃): δ 2.65 (m, COCH₃), 2.39 (m, CH₂CO), 1.9 – 1.1 (C₉H₁₈), 1.04 (m, COCH₃).

7-Methylheptalactone (7-MeHL)

2-Methylcycloheptanone (11.1 g, 86.8 mmol) was added to chloroform (200 mL) in a 500 mL flask. m-Chloroperbenzoic acid (MCPBA, 30.0 g, 173 mmol, 1.99 eq.) was added to the solution. The mixture was stirred for one week. The mixture was filtered over celite and washed with chloroform. The mixture was then concentrated in vacuo and the residue was dissolved in diethyl ether (220 mL). The organic layer was washed with respectively a saturated Na₂CO₃ solution (2 × 200 mL), a saturated Na₂CO₃ solution (2 × 200 mL), and a saturated MgCl₂ solution (200 mL), and dried with MgSO₄. Concentration of the filtrate in vacuo yielded the crude product which was further purified by vacuum distillation over CaH₂. Yield: 12.2 g (66%). According to GC-FID a purity of 93% was obtained, with the non-methylated lactone present as the main impurity. ¹H NMR (CDCl₃): δ 4.75 (m, 1H, CHOC=O); 2.54 (m, 2H, CH₂C=C-O); 2.0–1.3 (8H); 1.35 (d, 3H, CH₃). ¹³C{¹H} NMR (CDCl₃): δ 176.8 (C=O); 75.0 (C-7); 39.1; 32.4; 28.9; 26.4; 24.1; 21.8. GC retention times (Chiralsil-DEX CB column): (R)-7-MeHL = 22.1 min; (S)-7-MeHL = 22.9 min; HL at 26.4 min at 90 °C.

8-Methyloctalactone (8-MeOL)

2-Methylcyclooctanone (13.3 g, 95.2 mmol) was added to chloroform (110 mL) in a 250 mL flask. MCPBA (30.0 g, 173 mmol, 1.82 eq.) was added to the solution. The mixture was stirred for 11 days. The reaction was very slow, so additional MCPBA was added and the reaction mixture was heated to 70 °C. The reaction mixture was then refluxed at 70 °C for four days. The mixture was filtered over celite and washed with chloroform. The mixture was then concentrated in vacuo and the residue was dissolved in diethyl ether (100 mL). The organic layer was washed with respectively a saturated Na₂S₂O₃ solution (2 × 100 mL), a saturated Na₂CO₃ solution (2 × 100 mL), and a saturated MgCl₂ solution (100 mL), and dried with MgSO₄. Concentration of the filtrate in vacuo yielded the crude product which was further purified by vacuum distillation over CaH₂. Yield: 13.3 g (82%). According to GC-FID a purity of 93% was obtained, with the non-methylated lactone present as the main impurity. ¹H NMR (CDCl₃): δ 4.75 (m, 1H, CHOC=O); 2.54 (m, 2H, CH₂C=O); 2.0–1.3 (8H); 1.35 (d, 3H, CH₃). ¹³C{¹H} NMR (CDCl₃): δ 176.8 (C=O); 75.0 (C-7); 39.1; 32.4; 28.9; 26.4; 24.1; 21.8. GC retention times (Chiralsil-DEX CB column): (R)-8-MeOL = 22.1 min; (S)-8-MeOL = 22.9 min; HL at 26.4 min at 90 °C.
mL), and dried with MgSO₄. Concentration of the filtrate in vacuo yielded the crude product which was further purified by vacuum distillation over CaH₂. Yield: 8.32 g (56%). According to GC-FID a purity of 84% was obtained, with the non-methylated lactone present as the main impurity. ¹H NMR (CDCl₃): δ 5.08 (m, 1H, CHO=C=O); 2.27 (m, 2H, CH₂C=O); 2.0–1.2 (10H); 1.26 (d, 3H, CH₃). ¹³C[¹H] NMR (CDCl₃): δ 175.4 (C=O); 71.7 (C-8); 35.9; 35.3; 29.6; 25.2; 24.1; 22.0; 20.9. GC retention times (Chiralsil-DEX CB column): (R)-8-MeOL = 7.4 min; (S)-8-MeOL = 7.6 min at 117 ºC.

12-Methyldecanolactone (12-MeDDL)
2-Methylcyclododecanone (11.5 g, 58.2 mmol) was added to chloroform (200 mL) in a 500 mL flask. MCPBA (30.0 g, 173 mmol, 1.99 eq.) was added to the solution. The mixture was refluxed at 70 ºC for one week. The mixture was filtered over celite and washed with chloroform. The mixture was then concentrated in vacuo and the residue was dissolved in diethyl ether (220 mL). The organic layer was washed with respectively a saturated Na₂S₂O₃ solution (2 × 200 mL), a saturated Na₂CO₃ solution (2 × 200 mL), and a saturated MgCl₂ solution (200 mL), and dried with MgSO₄. Concentration of the filtrate in vacuo yielded the crude product which was further purified by vacuum distillation over CaH₂. Yield: 8.00 g (65%). According to GC-FID a purity of 82% was obtained, with the non-methylated lactone present as the main impurity. ¹H NMR (CDCl₃): δ 4.98 (m, 1H, CHO=C=O); 2.34 (m, 2H, CH₂C=O); 1.8–1.2 (8H); 1.21 (d, 3H, CH₃). ¹³C[¹H] NMR (CDCl₃): δ 173.9 (C=O); 71.2 (C-12); 35.3; 35.2; 26.9; 26.6; 26.3; 25.6; 25.2; 24.7; 24.7; 23.2; 20.9. GC retention times (Chiralsil-DEX CB column): (S)-12-MeDDL = 16.7 min; (R)-12-MeDDL = 17.4 min; DDL = 18.0 min at 140 ºC.

Typical procedure for the enzymatic ring-opening of ω-methylated lactones with M/I = 4
A Schlenk tube was charged with benzyl alcohol (1.0 mmol), the appropriate lactone (4.0 mmol), 1,3,5-tri-tert-butylbenzene (0.3 mmol), toluene (2 mL) and a magnetic stirring bar. The mixture was stirred at 70 ºC for 5 min. and then Novozym 435 (27 mg) was added, indicating the start of the reaction. Small aliquots of reaction mixture were taken for GC analysis. The samples were analyzed by chiral GC to determine the conversion of benzyl alcohol and of both enantiomers of the lactone. GC retention times for 3-MePL (Chiralsil-DEX CB column): (R)-3-MePL = 6.2 min; (S)-3-MePL = 6.5 min at 75 ºC. GC retention times for 5-MeVL (ChiralDEX G-TA column): (R)-5-MeVL = 16.3 min; (S)-5-MeVL = 17.2 min at 130 ºC. GC retention times for 6-MeCL (Chiralsil-DEX CB column): (S)-6-MeCL = 9.3 min; (R)-2-MeCL and (S)-2-MeCL = 10.1 min; (R)-6-MeCL = 10.5 min at 121 ºC.

Typical procedure for the KRP of ω-methylated lactones
A Schlenk tube was charged with Novozym 435 (50 mg), dry molecular sieves (3 Å) and a magnetic stirring bar. The tube was put overnight in a vacuum oven (10 mm Hg) at 50 ºC in presence of P₂O₅. Benzyl alcohol (0.05 mmol), the appropriate lactone (5.0 mmol), 1,3,5-tri-tert-butylbenzene (0.25 mmol), toluene (2.5 mL) and dry molecular sieves (3 Å) were added to a 6 mL vial. The mixture was stirred overnight at 35 ºC to remove traces of water. The mixture was transferred to the Schlenk tube containing the enzyme and stirred at 70 ºC under an argon atmosphere. Small aliquots of the reaction mixture were taken for GC analysis and the reaction was terminated when the conversion of the R-lactone was >99%. The reaction mixture was then filtered over a glass filter and the residue was washed with toluene. Concentration in vacuo yielded the crude reaction product, which was then precipitated by slowly adding a solution in CHCl₃ to methanol at 0 ºC. Centrifugation yielded the crude polymer, which was further purified by evaporation of impurities in a Kugelrohr apparatus (T = 100 ºC, 0.05 mm Hg). Poly-(R)-7-MeHL. Yield: 125 mg (27%). ¹H NMR (CDCl₃): δ 5.11 (s, PhCH₂OR), 4.89 (m,
C(CH₃)HOCO), 3.78 (m, C(CH₃)HOH end-group), 2.26 (t, CH₂COO), 1.70 – 1.25 (CH₂), 1.19 (d, C(CH₃)HOCO. 1H NMR indicated that 16% of monomeric units was non-methylated as a result of ring-opening of HL: 4.05 (t, CH₂OCO). *Poly-(R)-8-MeOL*. Yield: 159 mg (20%). 1H NMR (CDCl₃): δ 5.11 (s, PhCH₂OR), 4.88 (m, C(CH₃)HOCO), 3.78 (m, C(CH₃)HOH end-group), 2.26 (t, CH₂COO), 1.70 – 1.25 (CH₂), 1.19 (d, C(CH₃)HOCO. 1H NMR indicated that 11% of monomeric units was non-methylated as a result of ring-opening of OL: 4.05 (t, CH₂OCO). *Poly-(R)-12-MeDDL*. Yield: 364 mg (35%). 1H NMR (CDCl₃): δ 5.11 (s, PhCH₂OR), 4.88 (m, C(CH₃)HOCO), 3.78 (m, C(CH₃)HOH end-group), 2.25 (t, CH₂COO), 1.65 – 1.22 (CH₂), 1.19 (d, C(CH₃)HOCO. 1H NMR indicated that 22% of monomeric units was non-methylated as a result of ring-opening of DDL: 4.04 (t, CH₂OCO).

**Molecular modelling studies**

All molecular modelling work was performed using MOE v2005.06 (Chemical Computing Group Inc.). The crystal structures of *Candida Antarctica* Lipase B (Novozym 435) were retrieved from the Protein Data Bank (PDB codes: 1TCA, 1TCB and 1TCC). The root mean square deviation of all crystal structures is less than 0.4 Å; only structure 1TCA was used. After careful investigation of the active site, it was observed that Asp134 did not possess any stabilizing interactions in the crystal structure. To compensate, the side chain of Gln157 was rotated to allow a hydrogen bond between its amide moiety and Asp134, as well as with Thr40. Explicit hydrogens were added to the structure and minimized using MOE energy minimization with the CHARMM27 force field. All heavy atoms were kept fixed during minimization. Finally, the protein structure was prepared for docking by omitting all water molecules and introducing a negative charge on the catalytic Ser105, transferring its hydrogen atom onto His224. This last action was performed to mimic the formation of the protein-ligand transition state.

The three dimensional structures of the lactones were built using MOE, and multiple conformations were generated for each structure. For 7-MeHL, both cisoid and transoid conformations were found. For the smaller lactones only the cisoid conformation was created and for the larger lactones only the transoid conformation. The docking of the ligands was performed using GOLD version 3.0.1. Genetic Algorithm parameters for docking were taken from the default 1 GOLD GA settings. These settings were used for all docking runs presented in this study. For each ligand the top 5 poses were kept and the average free energy of binding (ΔG) was calculated with the Chemscore scoring function (Table 6.3, series 1). All ligands were docked with a distance constraint of 2.0 Å between the ester carbon atom and the oxygen atom of Ser105 and a spring constant of 21 kJ/mol Å, mimicking the formation of the protein-ligand transition state. All docking runs were performed in the absence of water molecules. For each ligand, three additional docking runs were performed with added distance constraints between the carbonyl oxygen of the ligand and the backbone of Thr40 and Gln106, which make up the protein oxyanion hole (either one of these constraints or both; series 2: Thr40; series 3: Gln106; series 4: Thr40 and Gln106; see Table 6.3).
6.8 References and notes


11. Since ring-opening results in the formation of an S-secondary alcohol, which, according to Kazlauskas’ rule is the slower reacting enantiomer in lipase-catalyzed transesterification (typically E > 100), no further propagation takes place after initiation. Ru-catalyzed racemization is, therefore, required to yield reactive R-terminal alcohols and to enable polymerization.


14. 1-Octanol is a better nucleophile and a worse leaving group than benzyl alcohol. As a result, the ring-chain equilibrium is more favorable with 1-octanol than with benzyl alcohol. Analogously, it can be expected that ring-opening will not occur with an aliphatic secondary alcohol as the nucleophile (such as the alcohol that is formed upon ring-opening of 5-MeVL).


18. The high dipole moment of the small cisoid lactones results in high rates in alkaline hydrolysis; in contrast, activities in CALB-catalyzed ring-opening are in line with that of the larger transoid lactones and, therefore, relatively low.


20. The reaction mechanism of CALB-catalyzed transesterification is described in Chapter 4, section 4.2.1.

21. Kobayashi *et al.* reported that Novozym 435-catalyzed polymerization of 3-MePL did not occur; copolymerization with ε-caprolactone (CL) or dodecalactone (DDL) was successful and S-selective; see Kobayashi *et al.*, *Macromolecules* **2000**, *33*, 8971. ITC under similar conditions produced results comparable to a reference experiment without racemization catalyst and no significant polymerization was observed within a reasonable amount of time; ITC of 3-MePL was not pursued further.

22. For 5-MeVL this was attributed to the highly unfavorable ring-chain equilibrium when using a secondary alcohol (which will be the end-group in a polymerization of 5-MeVL) as the initiator. Kobayashi *et al.* reported that copolymerization of 5-MeVL with ε-caprolactone (CL) or macrolides was successful (see Kobayashi *et al.*, *Macromolecules* **2000**, *33*, 8971); in this case 5-MeVL is ring-opened by the primary alcohol formed upon reaction of the unsubstituted lactone. Copolymerization of 5-MeVL with CL with 1-octanol as the initiator (M/I = 2 × 40) employing ITC conditions was successful: CL reacted almost instantly, while 65% of the 5-MeVL had reacted after 965 h. GC analysis revealed an ee of the unreacted monomer of only 3% and an eepolymer of 77%, indicating that ITC is operative.


Concluding Remarks

In this thesis iterative tandem catalysis (ITC) has been introduced as a novel polymerization method. By exploiting the cooperative action of two catalytic processes, excellent control over the chemical structure of the material can be achieved, making high-value polymers (more easily) accessible. Proof of principle was provided by the polymerization of ω-substituted ε-caprolactones, see Chapters 4 and 5. By combining lipase-catalyzed transesterification with Ru-catalyzed racemization the racemic monomer could be completely converted into the corresponding enantiopure polyester. In related work by Bart van As, this was extended to the enantioselective polymerization of secondary diols (in combination with diesters). Analogously, enantiopure polyamides can presumably be obtained from suitable diamines. Research into possible applications of these materials is, at present, clearly limited by the availability of the polymers, see Chapter 1. We are confident, however, that with improved accessibility many applications will be discovered in due time. In this respect, the results presented in Chapter 6 are also highly appealing. Novozym 435-catalyzed ring-opening of the larger ω-methylated lactones, which can adopt a transoid conformation of the ester bond, turned out to be R-selective with almost complete enantioselectivity, enabling straightforward kinetic resolution polymerization (KRP) to yield the enantiopure R-polyesters (ee > 99%). This represents by far the best lipase-catalyzed asymmetric synthesis of chiral polymers from racemic monomers to date.

The combination of lipase-catalyzed transesterification and Ru-catalyzed racemization that is employed in the aforementioned ITC experiments, is well-known from the dynamic kinetic resolution (DKR) of secondary alcohols, see Chapter 3. This tandem catalytic system is probably the most thoroughly investigated application of tandem catalysis in organic chemistry. Current racemization catalysts enable the conversion with excellent yields and ee’s. Catalyst compatibility – both mutual compatibility and compatibility with the reaction conditions – is a key factor in achieving these results. While important for the synthesis of small molecules, it is even more relevant when tandem catalysis is applied to polymer synthesis. In the former case, suboptimal yields and selectivities are acceptable as impurities can simply
be separated from the desired product after reaction. In case of iterative operation of the catalysts to yield a polymer, however, these catalyst imperfections will accumulate and will effectively prevent polymer formation. In the ITC polymerization of 6-methyl-ε-caprolactone (6-MeCL) we eventually realized more than 100 consecutive and iterative enzymatic additions and Ru-catalyzed racemizations on one polymer chain to yield truly enantiopure polyesters. Unexpectedly, this result could only be achieved using the Shvo catalyst, which was used in the first successful DKR in 1997, while racemization catalysts that were supposedly superior, failed to produce polymer – including the novel racemization catalysts described in Chapters 2 and 3. Similar results were obtained in related ITC experiments with diols/diesters. This underlines the fact that success of tandem catalysis in organic synthesis far from automatically translates into an application of ITC. After all, the ideal case represented by the DKR of secondary alcohols ‘only’ resulted in a successful polymerization after much effort.

The elegant synthesis of enantiopure polyesters (and possibly polyamides) by ITC should also be put into perspective by noting that these polymers can be synthesized via an alternative route. In every one of the above-mentioned cases the chiral monomer is accessible – by (D)KR or a related approach – and the enantiopure polymer can be subsequently synthesized by straightforward chemical polymerization. (D)KR and chemical polymerization are commercialized processes and their application in a 2-pot system would likely be successful as well. On the other hand, an actual ITC process based on the results presented in Chapter 5 would feature very low space-time yields and/or extremely high catalyst cost, despite the obvious advantage of a one-pot process. Enough potential for the optimization of the tandem catalytic process remains, including application of starved-feed conditions and development of novel, heterogeneous racemization catalysts tailored to the challenge of iterative operation (pursuing compartmentalization of the catalysts as was already mentioned in Chapter 1). It is, however, unlikely that the resulting iterative process will be able to compete with the combination of (D)KR and chemical polymerization – two very mature processes by comparison. For this reason, the major contribution of the ITC polymerization of 6-MeCL and related monomers to the field of tandem catalysis will likely be the mechanistic insight that it provides rather than the actual synthetic routes that it enables.
All the same, ITC is a very elegant application of tandem catalysis in polymer chemistry, like DKR is in organic synthesis. It is tempting to assume that many novel applications will eventually be developed, devising combinations of the many known bio- and chemocatalytic processes. Conceptually, opportunities are almost unlimited, especially if three or more catalytic processes are combined in one tandem catalytic system in a productive manner. The present example, which is based on DKR, however, clearly demonstrates that the actual development of such a system is highly challenging. Demands on the tandem catalytic system in a polymerization are very strict and it is far from guaranteed that a successful polymerization can be developed from a combination of catalysts that is successful in the synthesis of small molecules. Moreover, in many cases a more straightforward, albeit less elegant approach, will yield the same polymer in a more efficient way. There will, however, always be exceptions in which ITC will be the most efficient route to an attractive macromolecule as is evident from the examples of the copolymerization of ethylene and carbon monoxide and the chain shuttling polymerization (see Chapter 1). In both these examples, which can be classified as ITC, two catalytic processes are combined in a cooperative fashion and the product cannot be obtained by an alternative, 2-pot approach.
Summary of the thesis

Tandem Catalysis in Organic and Polymer Synthesis

Tandem catalysis, that is, combined catalytic reactions without intermediate product recovery, attracts increasing interest from academia and industry as an alternative to multi-step synthetic procedures. Many successful applications of tandem catalysis in organic synthesis have been reported, of which dynamic kinetic resolution (DKR) is arguably the most prominent. In the highly successful DKR of secondary alcohols, combination of lipase-catalyzed transesterification with Ru-catalyzed racemization (via transfer-hydrogenation) furnishes the corresponding R-esters with both conversion and ee > 99%. In contrast, tandem catalysis is still rarely employed in the field of polymer chemistry. Very few examples can be found where the catalytic processes involved in a polymerization are truly complementary and cannot be separated. In this thesis, a novel polymerization method based on tandem catalysis is introduced. Furthermore, the development of a range of novel Ru-based racemization catalysts is described, including their successful application in the DKR of secondary alcohols.

The synthesis and characterization of a range of Ru complexes bearing tetrafluorosuccinate and phosphine ligands (see figure) are described in Chapter 2. These complexes catalyze the acceptorless dehydrogenation of 1-phenylethanol to acetophenone and dihydrogen with good yields and excellent selectivity under relatively mild conditions in the absence of acid or base. In addition, these Ru catalysts were investigated with regard to their potential in the racemization of secondary alcohols, see Chapter 3. Excellent results were obtained in the DKR
with only 0.10 mol% of the racemization catalyst. Novozym 435 (*Candida Antarctica* Lipase B adsorbed on a macroporous resin) was employed as the transesterification catalyst.

In Chapter 4, iterative tandem catalysis (ITC) is introduced as a novel polymerization method. ITC is defined as a polymerization process in which chain growth is effectuated by a combination of two (or more) intrinsically different catalytic processes that are both compatible and complementary. The major advantage of such ITC systems is the high degree of control over the chemical structure of the material that can be achieved, since the cooperative action of two catalytic processes is exploited. Proof of principle was provided by the oligomerization of (S)-6-methyl-є-caprolactone (6-MeCL), yielding oligo-(R)-6-MeCL. Novozym 435 and a Ru-based racemization catalyst were employed for the reaction and catalyst compatibility proved to be a determining factor. Optimization of the catalytic system enabled the complete conversion of rac-6-MeCL into poly-(R)-6-MeCL with $M_n$ up to 25.0 kDa and ee up to 96% (Chapter 5, see scheme). Additionally, 6-ethyl-є-caprolactone (6-EtCL) was converted into poly-(R)-6-EtCL. Zero-order behavior in substrate concentration is typically observed for the overall reaction and this is explained by a kinetic analysis of the tandem-catalytic system.

In Chapter 6, the Novozym 435-catalyzed ring-opening of a range of small and larger ω-methylated lactones is discussed. An intriguing switch from S- to R-selectivity was observed upon going from small (ring sizes < 8) to larger lactones (ring sizes > 7). This was attributed to the transition from a cisoid to a transoid conformational preference of the ester bond. The larger, transoid lactones could be polymerized, without exception, by straightforward kinetic resolution polymerization (KRP), yielding the enantiopure R-polyester with good degree of polymerization and excellent ee.

The Concluding remarks of this thesis focus on the scope and potential of ITC.
Samenvatting

Tandemkatalyse is het gecombineerd uitvoeren van meerdere katalytische reacties zonder opwerking van tussenproducten. Tandemkatalyse wordt, zowel in de academische wereld als in de chemische industrie, in toenemende mate gezien als een veelbelovend alternatief voor klassieke organische meerstapssyntheses. Inmiddels is een groot aantal toepassingen van tandemkatalyse in de organische synthese beschreven, waarvan de dynamische kinetische resolutie (DKR) het meest in het oog springt. In de zeer succesvolle DKR van secundaire alcoholen zorgt de combinatie van lipase-gekatalyseerde omestering met ruthenium-gekatalyseerde racemisatie via transfer-hydrogenering voor de volledige omzetting van een racemisch mengsel van een alcohol in de overeenkomstige $R$-ester. In tegenstelling tot de vele voorbeelden uit de organische synthese, bestaan er maar weinig toepassingen van tandemkatalyse voor de bereiding van polymeren. Bovendien zijn de katalytische processen in de meeste gevallen niet complementair en kan de reactie ook in twee stappen uitgevoerd worden. In dit proefschrift wordt een nieuwe, op tandemkatalyse gebaseerde polymerisatiemethode geïntroduceerd. Daarnaast worden de synthese en de karakterisering van een reeks nieuwe katalysatoren voor racemisatie beschreven. Deze katalysatoren bleken uitstekend te presteren in de DKR van secundaire alcoholen.

De synthese en structuuronderzoek van een reeks rutheniumcomplexen met tetrafluorsuccinaat- en fosfine-liganden (zie figuur) zijn beschreven in hoofdstuk 2. Deze complexen zijn uitstekende katalysatoren voor de acceptorvrije dehydrogenering van 1-fenylethanol onder
vorming van acetofenon en waterstof. De reactie verloopt onder relatief milde condities en de goede opbrengsten gaan gepaard met een uitstekende selectiviteit, zonder dat zuur of base nodig zijn. Daarnaast zijn deze katalysatoren toegepast als racemisatiekatalysator in de DKR van secundaire alcohole, waarbij uitstekende resultaten zijn behaald met slechts 0.10 mol% van de rutheniumkatalysator, zie hoofdstuk 3. Novozym 435 (*Candida Antarctica* Lipase B geadsorbeerd op een macroporeuze hars) is hierbij gebruikt als omesteringskatalysator.

In hoofdstuk 4 is iteratieve tandemkatalyse (ITC) geïntroduceerd als nieuwe polymerisatie methode. ITC is gedefinieerd als een polymerisatie waarbij de ketengroei wordt bewerkstelligd door een combinatie van twee (of meer) intrinsiek verschillende katalytische processen die zowel compatibel als complementair zijn. Het grote voordeel van een dergelijke polymerisatie is dat de coöperatieve werking van de katalytische processen een hoge mate van controle over de chemische structuur van het polymer mogelijk maakt. Dit is aangetoond met de oligomerisatie van (S)-6-methyl-ε-caprolacton (6-MeCL), waarbij als product oligo-(R)-6-MeCL gevormd wordt. Als katalysatoren werden Novozym 435 voor de omestering en een ruthenium complex voor de katalytische racemisatie toegepast. Compatibiliteit bleek het grootste probleem te zijn, zowel van de katalysatoren onderling als met de reactiecondities. Optimalisatie van het systeem maakte de volledige omzetting van racemisch 6-MeCL in het optisch zuivere poly-(R)-6-MeCL mogelijk, zie hoofdstuk 5. De gevormde polymeren hadden moleculgewichten tot 25.0 kDa ($M_n$) en enantiomere overmaten (ee's) tot 96%. Daarnaast is 6-ethyl-ε-caprolacton (6-EtCL) omgezet in poly-(R)-6-EtCL. In de ITC experimenten is de conversiesnelheid doorgaans niet significant afhankelijk van de substraatconcentratie. Een verklaring voor dit nulde orde gedrag in substraat volgt uit een kinetische analyse van het tandemkatalytische systeem.
Hoofdstuk 6 behandelde de Novozym 435-gekatalyseerde ring-opening van andere \(\omega\)-gemethyleerde lactonen dan 6-MeCL. Hierbij bleek de overgang van kleine (ringgrootte < 8) naar grotere lactonen (ringgrootte > 7) gepaard te gaan met een fascinerende overgang van \(S\)- naar \(R\)-selectiviteit. Een verklaring voor deze opmerkelijke overgang volgt uit de voorkeur van de esterbinding voor een cisoide conformatie in het geval van de kleine ringen en een voorkeur voor de transoide conformatie in het geval van de grote ringen. De grotere, transoide lactonen konden door middel van kinetische resolutiepolymerisatie (KRP) eenvoudig worden omgezet in de corresponderende enantiomeerzuivere \(R\)-polyester. Hierbij werden goede molecuulgewichten en uitstekende ee’s behaald.

De epiloog van dit proefschrift gaat in op de belofte van ITC als nieuwe polymerisatiemethode en plaatst de aanpak in perspectief.
Curriculum Vitae

Jeroen van Buijtenen was born on October 28, 1977 in Eindhoven, the Netherlands. After secondary education at the Eckart College in Eindhoven, he started studying Chemical Engineering at the Eindhoven University of Technology in 1996. He obtained his master degree in 2002 with a graduation project at the Laboratory of Homogeneous Catalysis and Coordination Chemistry under guidance of prof. dr. D. Vogt. He started his Ph.D. research in September 2002 at the laboratory of Macromolecular and Organic Chemistry under guidance of prof. dr. L. A. Hulshof and prof. dr. E. W. Meijer. The most important results of this research are described in this thesis.
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