Ruthenium-Catalyzed Hydrogen Transfer Reactions

Mechanistic Studies and Chemoenzymatic Dynamic Kinetic Resolutions

Madeleine Warner
“Organization is what you do before you do something, so that when you do it, it’s not all mixed up.”

[A. A. Milne]
Abstract

The main focus of this thesis lies on transition metal-catalyzed hydrogen transfer reactions. In the first part of the thesis, the mechanism for racemization of sec-alcohols with a ruthenium complex, Ru(CO)$_2$Cl($\eta^5$-C$_5$Ph$_3$) was studied.

The reaction between 5-hexen-2-ol and Ru(CO)$_2$(Ot-Bu)($\eta^5$-C$_5$Ph$_3$) was studied with the aim to elucidate the origin of the slow racemization observed for this sec-alcohol. Two diastereomers of an alkoxy carbonyl complex, which has the double bond coordinated to ruthenium, were characterized by NMR and in situ FT-IR spectroscopy. The observed inhibition of the rate of racemization for substrates with double bonds provided further confirmation of the importance of a free coordination site on ruthenium for $\beta$-hydride elimination. Furthermore, we observed that CO exchange, monitored by $^{13}$C NMR using $^{13}$CO, occurs with both the precatalyst, Ru(CO)$_2$Cl($\eta^5$-C$_5$Ph$_3$), and the active catalytic intermediate, Ru(CO)$_2$(Ot-Bu)($\eta^5$-C$_5$Ph$_3$). It was also found that added CO has an inhibitory effect on the rate of racemization of (S)-1-phenylethanol. Both these observations provide strong support for reversible CO dissociation as a key step in the racemization mechanism.

In the second part of this thesis, Ru(CO)$_2$Cl($\eta^5$-C$_5$Ph$_3$) was combined with an enzymatic resolution catalyzed by a lipase, leading to several efficient dynamic kinetic resolutions (DKR). DKR of exocyclic allylic alcohols afforded the corresponding acetates in high yields and with excellent enantiomeric excess (ee). The products were utilized as synthetic precursors for $\alpha$-substituted ketones and lactones. DKR of a wide range of homoallylic alcohols afforded the products in good to high yields and with high ee. The homoallylic acetates were transformed into 5,6-dihydropyran-2-ones in a short reaction sequence. Furthermore, DKR of a wide range of aromatic $\beta$-chloroalcohols afforded the products in high yields and with excellent ee. The $\beta$-chloro acetates were further transformed into chiral epoxides.
List of publications

This thesis is based on the following publications, referred to in the text by their Roman numerals I-VI. Reprints were made with kind permission from the publisher (Appendix A). The contribution by the author in each publication is clarified in Appendix B.

I. Unexpected Formation of a Cyclopentadienylruthenium Alkoxy carbonyl Complex with a Coordinated C=C Bond
Åberg, J. B.; Warner, M. C.; Bäckvall, J.-E.

Warner, M. C.; Bäckvall, J.-E.
*Manuscript*

III. CO Dissociation Mechanism in Racemization of Alcohols by a Cyclopentadienyl Ruthenium Dicarbonyl Catalyst
Warner, M. C.; Verho, O.; Bäckvall, J.-E.

IV. Enantioselective Route to Ketones and Lactones from Exocyclic Allylic Alcohols via Metal and Enzyme Catalysis
Warner, M. C.; Nagendiran, A.; Bogár, K.; Bäckvall, J.-E.

V. Dynamic Kinetic Resolution of Homoallylic Alcohols: Application in Synthesis of Enantiomerically Pure 5,6-Dihydropyran-2-ones and δ-Lactones
*Submitted for publication*
VI. Highly Efficient Route for Enantioselective Preparation of Chlorohydrins via Dynamic Kinetic Resolution
Träff, A.; Bogár, K.; Warner, M.; Bäckvall, J.-E.
*Org. Lett.*, **2008**, *10*, 4807-4810

Related papers by the author, but not included as part of this thesis:

**Shvo’s Catalyst in Hydrogen Transfer Reactions**
Warner, M. C.; Casey, C. P.; Bäckvall, J.-E.
(Book chapter)

**Mechanistic Aspects on Cyclopentadienylruthenium Complexes in Catalytic Racemization of Alcohols**
Warner, M. C.; Bäckvall, J.-E.
*Acc. Chem. Res.*, **2013**, *in press*
(Review article)
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Abbreviations

Abbreviations and acronyms are used in agreement with the standard of the subject. Only nonstandard and unconventional ones that appear in the thesis are listed here.

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>Asp</td>
<td>aspartic acid</td>
</tr>
<tr>
<td>Cat.</td>
<td>catalyst</td>
</tr>
<tr>
<td>CO</td>
<td>carbon monoxide</td>
</tr>
<tr>
<td>CALB</td>
<td>Candida antarctica lipase B</td>
</tr>
<tr>
<td>CNS</td>
<td>central nervous system</td>
</tr>
<tr>
<td>DFT</td>
<td>density functional theory</td>
</tr>
<tr>
<td>DYKAT</td>
<td>dynamic kinetic asymmetric transformation</td>
</tr>
<tr>
<td>DKR</td>
<td>dynamic kinetic resolution</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-dimethylaminopyridine</td>
</tr>
<tr>
<td>EC</td>
<td>enzyme class</td>
</tr>
<tr>
<td>ee</td>
<td>enantiomeric excess</td>
</tr>
<tr>
<td>FDA</td>
<td>food and drug administration</td>
</tr>
<tr>
<td>FT-IR</td>
<td>Fourier transform-infrared spectroscopy</td>
</tr>
<tr>
<td>Glu</td>
<td>glutamic acid</td>
</tr>
<tr>
<td>His</td>
<td>histidine</td>
</tr>
<tr>
<td>KR</td>
<td>kinetic resolution</td>
</tr>
<tr>
<td>m-CPBA</td>
<td>meta-chloroperoxybenzoic acid</td>
</tr>
<tr>
<td>RCM</td>
<td>ring-closing metathesis</td>
</tr>
<tr>
<td>Ser</td>
<td>serine</td>
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1. Introduction

This thesis covers two main topics; the first deals with mechanistic investigations of a ruthenium catalyst used in racemization reactions. The second topic concerns the synthesis of chiral building blocks by combining enzymatic and organometallic catalysis.

Substances with the same elementary composition but with different physical properties are denoted isomers. The existence of isomers was for many years a mystery to chemists and in particular the existence of optical isomers was puzzling. Optical isomers are substances that appear to be identical chemically and physically, except for their effect on polarized light. Louis Pasteur made a breakthrough when he managed to separate the two optical isomers of tartaric acid in 1848, but it took an additional 26 years before Van’t Hoff and Le Bel independently developed the theory of chirality in 1874. A chiral molecule is defined as a molecule that cannot be superimposed on its mirror image and each chiral compound can have one or more stereogenic centers. A molecule with one stereogenic center can exist in two different forms, which are mirror images of one another. These two forms are designated as enantiomers. A molecule with two stereogenic centers can exist in two different pairs of enantiomers and these are defined as diastereoisomers. Consequently, molecules become more and more complex with an increasing number of stereogenic centers.

Enantiomers have identical chemical and physical properties except for when they are in a chiral environment. This property can cause enantiomers to have different biological response when interacting with chiral receptors in our bodies. Thalidomide is an example of a chiral molecule where the two enantiomers show different pharmacological response (Figure 1). Thalidomide was administered in the late 1950’s as a racemate to prevent morning sickness during pregnancy, but was withdrawn from the market in the early 1960’s due to the discovery of its connection to babies born with birth defects. Later on, it was found that only one of the enantiomers, (S)-Thalidomide, had this teratogenic effect and that (R)-Thalidomide provided the desired therapeutic effect. It has more recently been shown that the two enantiomers can interconvert in vivo, thus administering the drug as pure (R)-Thalidomide will not prevent the teratogenic side effect.
In 1992 the US Food and Drug Administration (FDA) and the European Committee for Proprietary Medicinal Products decided that the physiological action of each enantiomer of a pharmaceutical product must be individually characterized. Furthermore, in 2004 it was reported that nine out of the top ten drugs on the market contained chiral compounds as their active ingredients, and that six of these were sold as single enantiomers. The increasing demand for enantiomerically pure substances provides a great challenge for chemists.

There are many techniques for the preparation of enantiomerically pure compounds, which can be divided into three different classes. The first class is asymmetric synthesis, which uses a chiral auxiliary or a catalyst to transform prochiral substrates into enantiomerically enriched compounds. A chiral auxiliary is used stochiometrically, whilst in a catalytic reaction the chiral source is used in substochiometric quantities. Another strategy uses naturally occurring chiral molecules, such as α-amino acids and carbohydrates as building blocks in the synthesis of more complex molecules. The third strategy is resolution of a racemic mixture using a chiral catalyst (e.g. an enzyme) to produce one of the enantiomers in its pure form. As this technique is based on separation of existing enantiomers it is limited to a theoretical yield of 50%.

1.1 Reactions and reaction mechanisms

The redistribution of the connectivity of atoms within a chemical structure or between two or more structures is defined as a reaction. Any given chemical transformation of one molecule into another, consists of one or several reactions. How the individual steps involved in a reaction happen at the molecular level is defined as the reaction mechanism. In other words a reaction mechanism describes in detail how the reaction takes place.

Knowledge of reaction mechanisms is an important tool in science. Once a reaction mechanism has been established, a chemist has the possibility to
modify the corresponding chemical transformation to his or her advantage. Improved chemical processes that are \textit{e.g.} cheaper, more environmentally friendly and/or more selective can be developed by choosing appropriate reaction conditions or by modifying the reactants. The power to manipulate nature in this way makes mechanistic investigations a basic goal of the science of chemistry.$^{13}$

1.2 Catalysis

A catalyst is a species that increases the rate of a reaction without undergoing any net chemical change itself. The catalyst acts by providing an alternative pathway for the reaction with lower activation energy, $E_a$ (Figure 2).$^{14}$ In the ideal case, the catalyst itself is not consumed during the reaction and theoretically it can be used in an infinite number of catalytic cycles. Naturally, this feature of catalysis provides a great advantage compared to traditional stochiometric reaction conditions and offers numerous possibilities for the development of more cost effective and environmentally friendly chemical processes. In reality, catalyst decomposition leading to loss of catalytic activity is common. Moreover, catalytic processes often need fine-tuned reaction conditions in order to give a high level of selectivity and good turnover numbers. There is an increasing demand in, for example, pharmaceutical industry for developing more robust catalytic systems for sustainable synthesis.$^{8,15-17}$ Owing to this demand, the field of catalysis has become a subject of extensive research for chemists of all disciplines.

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{gibbs_energy_diagram.png}
\caption{Simplified Gibbs free energy diagram for an uncatalyzed (red) and a catalyzed (blue) reaction.}
\end{figure}

Depending on the nature of the catalysis, it is classified to belong to one of four broadly defined subgroups, including \textit{transition metal catalysis},
organocatalysis, biocatalysis and Lewis-acid/base catalysis. All four subgroups can be further divided into homogeneous or heterogeneous catalysis, depending on whether the catalyst acts in the same or different phase as the reactants.

1.3 Enzymes as catalysts in organic reactions

Enzymes are proteins that catalyze chemical reactions and are used for the preparation of chiral compounds. Depending on the type of reaction catalyzed, enzymes can be divided into six different enzyme classes, which are oxidoreductases, transferases, hydrolases, lyases, isomerases and ligases. Lipases, which belong to the class of hydrolases are utilized in this thesis. They are also the enzymes most widely applied in organic synthetic reactions. The interest in lipases arises from their properties in terms of enantioselectivity, regioselectivity, and ability to function without a cofactor. Moreover, lipases accept a wide range of substrates, including alcohols, carboxylic acids, esters and amines.

The physiological role of lipases is to catalyze the hydrolysis of the ester bonds in triglycerides. In addition to their natural function, lipases can also catalyze the reverse reaction in nonaqueous media, i.e. formation of an ester from an alcohol in a transesterification reaction. The versatility of lipases makes them attractive catalysts in industrial applications, e.g. for preparation of pharmaceuticals, detergents and cosmetics.

Even though enzymes are widely used in industrial processes and academic research they do have limitations. The enantio- and regioselectivity is usually very dependent on the structure of the substrate. Also, enzymes are very specific in the reaction they catalyze and require optimal reaction conditions with respect to pH, solvent and temperature.

Lipases are classified as serine hydrolases, and Pseudomonas cepacia lipase and Candida antarctica lipase B are two members of this class. The reaction mechanism of hydrolysis/esterification involves a catalytic triad of three amino acid residues that are hydrogen bonded to one another. These residues are: serine (Ser), histidine (His) and glutamate (Glu)/aspartate (Asp) (Scheme 1). The amino acid residues are present in the enzyme’s active site, which is where the catalysis takes place. The transesterification can be described by using the ping-pong bi-bi mechanism (Scheme 1), which is a two-substrate, two-product (i.e. bi-bi) reaction. This mechanism begins with coordination of an ester (S1) to the enzyme (E). The altered enzyme (E’) then eliminates product (P1) before the alcohol (S2) binds. After reacting, the substrate leaves as product (P2) and at the same time regenerates the enzyme (E), allowing for the catalytic cycle to start again.
Kazlauskas’s rule can be used to predict the stereochemical outcome for the transesterification of sec-alcohols catalyzed by lipases. The size of the substituents at the stereocenter influences the enantioselectivity, due to the requirement of a “perfect fit” of the substrate in the active catalytic site of the enzyme. Kazlauskas’s rule states that if the large group has higher priority according to the Cahn-Ingold-Prelog classification than the medium/small group, the (R)-enantiomer will be favored (Figure 3). *Pseudomonas cepacia* lipase and *Candida antarctica* lipase B both follow this prediction.
Figure 3. The favored enantiomer for lipases according to Kazlauskas’s rule.

Serine proteases, e.g. Subtilisin Carlsberg, are another subclass of hydrolases that show the opposite enantiopreference compared to lipases, which is useful if the other enantiomer is the desired product. Subtilisin Carlsberg has been applied successfully in several dynamic kinetic resolution (DKR) protocols for sec-alcohols.

1.4 Hydrogen transfer

Transfer hydrogenation is defined as “the reduction of multiple bonds with the aid of a hydrogen donor in the presence of a catalyst”. The role of the catalyst is to transfer two hydrogens from the hydrogen donor (DH₂) to a hydrogen acceptor (e.g. a ketone) (Scheme 2).

Scheme 2. Concept of hydrogen transfer (DH₂ = hydrogen donor).

Hydrogen transfer reactions, in which hydrogen is transferred from an alcohol to a ketone, were first discovered in the 1920’s by Meerwein, Ponndorf and Verley. The original version uses aluminum isopropoxide to promote hydrogen transfer from isopropanol to a ketone, referred to as the MPV reduction after its discoverers (Scheme 3).


Later, Oppenauer discovered that the reaction could be run in the opposite direction, i.e. that secondary alcohols could be oxidized in the
presence of acetone (Scheme 3). In these reversible hydrogen transfer reactions, employing an excess of either isopropanol as alcohol or acetone as ketone, leads to MPV reduction or Oppenauer oxidation, respectively.\textsuperscript{32}

The major problem of the MPV-Oppenauer reactions is that the aluminum alkoxide is often required in stoichiometric amounts, which is a drawback for industrial applications where scaling up is often necessary.\textsuperscript{33} For this reason, interest in developing catalytic hydrogen transfer reactions was raised and transition metals were found to work in a catalytic manner. Henbest reported on the first example of transition metal-catalyzed hydrogen transfer in the 1960’s, using an iridium-based complex.\textsuperscript{32,34} The first ruthenium-catalyzed hydrogen transfer reaction was developed by Sasson and Blum in 1971.\textsuperscript{35} Drawbacks with these earlier systems include low turnover frequency and high temperatures. However, a major breakthrough was made when catalytic amounts of base were found to dramatically increase the rate of transfer hydrogenation.\textsuperscript{36,37} Since then many efficient catalytic systems have been developed that operate under milder conditions and that employ mainly ruthenium, iridium and rhodium complexes,\textsuperscript{38} and more recently iron complexes.\textsuperscript{39-41} Reduction by transfer hydrogenation can be applied successfully to both ketones and imines.\textsuperscript{38,42-44}

1.4.1 Mechanistic overview of hydrogen transfer reactions

The mechanism of hydrogen transfer reactions has been extensively studied and two main pathways have been proposed, depending on the type of metal used. For the main group metals direct hydrogen transfer is thought to be the main pathway, whereas a hydridic route has been proposed for transition metals.\textsuperscript{33,38}

Direct hydrogen transfer was originally proposed for the MPV reduction. It proceeds via a concerted process, which involves a six-membered transition state (Scheme 4). The hydrogen donor (isopropanol) and the hydrogen acceptor (ketone) are in close proximity to the metal center. The hydrogen is transferred directly to the hydrogen acceptor without the involvement of free metal hydride intermediates.\textsuperscript{35-47}

\[
\text{O} \quad \text{R}^1 \quad \text{R}^2 \quad \text{M} \quad \text{O} \quad \text{H} \quad \leftrightarrow \quad \begin{array}{c} \text{R}^1 \quad \text{O} \quad \text{M} \quad \text{O} \\ \text{R}^2 \quad \text{H} \quad \text{M} \end{array} 
\]

Scheme 4. The direct hydrogen transfer mechanism in the MPV reduction.

A common feature of the hydridic route is the involvement of a metal hydride as a key intermediate in the hydrogen transfer (Scheme 5). The hydridic route proceeds in a stepwise manner; a metal hydride is typically formed together with acetone via $\beta$-hydride elimination from the alkoxide.
The hydrogen is then transferred from the metal to the acceptor (Scheme 5).

\[
\begin{align*}
\text{Donor} & \quad + \quad \text{Accept} \quad \xrightleftharpoons{\text{[M]-cat.}} \quad \text{via [M]-H or H-[M]-H} \\
\text{H-O} & \quad + \quad \text{R^1R^2} \quad \xrightarrow{\text{[M]-cat.}} \quad \text{O} \quad + \quad \text{O}^*H
\end{align*}
\]

**Scheme 5.** The stepwise hydridic mechanism proposed for transition metals.

The hydridic route can be divided further into the monohydridic and the dihydridic route.\(^{46}\) In the monohydridic route only one of the hydrogens is transferred from the substrate to the metal (CHOH) (Scheme 6, path A), whereas in the dihydridic route both hydrogens (CHOH and CHO\(\text{H}\)) are transferred to the metal (Scheme 6, path B). The two mechanisms can be distinguished from each other by means of deuterium labeling, since the hydrogens will keep their identity throughout the reaction in the monohydridic route (Scheme 6, path A). In the dihydridic route the hydrogens will be scrambled between carbon and oxygen and therefore lose their identity (Scheme 6, path B).\(^{46}\)

\[
\begin{align*}
\text{Path A} & \quad : \quad \text{L}_n\text{MX} \quad \xrightarrow{\text{[M]-cat.}} \quad \text{O} \quad + \quad \text{L}_n\text{MH}^1 + \text{H}^3\text{X} \\
\text{Path B} & \quad : \quad \text{L}_n\text{M} \quad \xrightarrow{\text{[M]-cat.}} \quad \text{O} \quad + \quad \text{L}_n\text{MH}^1\text{H}^2
\end{align*}
\]

**Scheme 6.** Monohydridic (path A) versus dihydridic (path B) mechanism.

The monohydride mechanism can be further divided into two principally different pathways. In the *inner sphere* mechanism, formation of the metal monohydride from the hydrogen donor involves a transition metal alkoxide, which produces the M–H via \(\beta\)-hydride elimination (Scheme 7, path A). The hydride transfer occurs in the inner sphere of the metal. In the alternative *outer sphere* mechanism, the hydride transfer proceeds without coordination of the hydrogen donor to the metal (Scheme 7, path B). In both the inner sphere and outer sphere mechanisms the metal hydride migrates from the metal to the carbonyl carbon, producing the \(\alpha\)-CH. The two mechanistic pathways are further distinguished by the observation that the inner sphere mechanism involves a coordinated ketone, while the outer sphere mechanism does not.\(^{46}\)
1.5 Racemization

Racemization is often mentioned in the literature with the idea of avoiding it; however, racemization can also be essential for the preparation of enantiomerically enriched compounds, for example in DKR (vide infra). Racemization is defined as the irreversible formation of a racemate from an enantiomerically enriched compound, and always leads to loss of optical activity. The driving force of a racemization process can be attributed to the increase in entropy caused by mixing of the two enantiomers. There are several different techniques utilized for racemization, including: (i) thermal racemization; (ii) base-catalyzed racemization; (iii) acid-catalyzed racemization; (iv) racemization via Schiff bases; (v) enzyme-catalyzed racemization; (vi) racemization via oxidation-reduction and radical reactions. The focus of this thesis lies on transition metal-catalyzed racemization of secondary alcohols via redox reactions, with a ruthenium based catalyst. Shvo’s catalyst, [Ru₂(CO)₄(μ-H)(C₄Ph₄COHOC₄Ph₄)]₁ and Bäckvall’s catalyst, Ru(CO)₂Cl(η³-Ph₅C₃)₂ are two examples of ruthenium-based complexes often employed in hydrogen transfer reactions.

1.5.1 Shvo’s catalyst

Shvo’s catalyst 1 (Scheme 8) is a diruthenium complex which was first synthesized in 1984 by Shvo et al. This catalyst has found many applications in chemical reactions including oxidations, reductions and racemizations. The dimer 1 is activated by heat and dissociates into the two catalytically active monomers, one isolable Ru(II) 18 electron complex (1a) and one proposed Ru(0) 16 electron complex (1b) (Scheme 8). The 18 electron species acts as a hydrogenation catalyst, whereas the 16 electron species acts as a dehydrogenation catalyst. The two catalytically active species interconvert during the racemization (Scheme 8). Shvo’s catalyst 1 has successfully been used as a racemization catalyst in DKR protocols for sec-alcohols and amines. However, the thermal conditions needed for
activation of the racemization catalyst limit compatibility with enzymatic reactions, since thermostable enzymes are the only choice for the enzymatic resolution.

Scheme 8. Thermal activation of Shvo’s catalyst 1 into monomers 1a and 1b, and their mechanism of racemization via hydrogenation/dehydrogenation.

The mechanism for racemization by complex 1 has been extensively studied and it has been found that it is different for imines/amines compared to for alcohols/ketones. The hydrogenation of ketones and the dehydrogenation of alcohols have been proposed to operate through a concerted outer-sphere mechanism, i.e. the proton and the hydride are transferred to the substrate simultaneously.\(^\text{54,57}\) In contrast, it is thought that the hydrogenation of imines and the dehydrogenation of amines proceed in a stepwise manner, i.e. protonation of the substrate precedes the hydride transfer.\(^\text{58-60}\) These mechanistic insights are supported by studies on the kinetic isotope effects of each reaction\(^\text{54,57,58,60}\) and from DFT calculations.\(^\text{59}\) The hydrogenation of imines and the dehydrogenation of amines has been studied in more detail and some data support an inner-sphere mechanism,\(^\text{60,61}\) whereas other data support an outer-sphere mechanism.\(^\text{52,63}\)
1.5.2 Bäckvall’s catalyst

Bäckvall’s catalyst \(^2\)\(^{64}\) has been employed as a racemization catalyst for sec-alcohols in several DKR systems and can efficiently effect full racemization within 10 min at room temperature.\(^{64,65}\) The two possible mechanisms for racemization that were proposed when this work was initiated are shown in Scheme 9.\(^{65-67}\)

![Scheme 9. Proposed catalytic cycle for the racemization of sec-alcohols by 2.](image)

The proposed racemization mechanism begins with activation of ruthenium complex 2 by t-BuOK to produce ruthenium tert-butoxide complex 3 (Scheme 9, step i).\(^{65-67}\) Subsequent alcohol-alkoxide exchange produces a ruthenium sec-alkoxide complex 4 (Scheme 9, step ii). Racemization proceeds via \(\beta\)-hydride elimination, which requires a free coordination site on ruthenium, proposed to be either via \(\eta^5 \rightarrow \eta^3\) ring slippage producing complex 5\(^{66}\) or via CO dissociation forming complex 5\(^*\)\(^{68,69}\) (Scheme 9, step iii). Subsequent readdition of the hydride to either
side of the prochiral ketone in complex 5 or 5' causes racemization of the alcohol (Scheme 9, step iv), and most likely proceeds via the $\eta^2$-$\pi$-coordinated ketone (Equation 1). The racemic alcohol is released by another alcohol-alkoxide exchange, thus completing the catalytic racemization cycle (Scheme 9, step v).

\[
(S)-4 \rightleftharpoons [\text{Ru}]^{\bigg\rangle}_{R'} \text{Me} \rightleftharpoons 5'(S) \rightleftharpoons [\text{Ru}]^{\bigg\rangle}_{R} \rightleftharpoons (R)-4 \tag{1}
\]

1.6 Enzymatic kinetic resolution

Kinetic resolution is a common technique for separating enantiomers, and is based on the difference in reaction rate between the two enantiomers and a chiral catalyst.\textsuperscript{70,71} When the catalyst used is an enzyme, the process is termed an enzymatic kinetic resolution (Scheme 10).\textsuperscript{70} The basic requirement for an efficient kinetic resolution is that one of the enantiomers in a racemic mixture is transformed into the product much faster than the other, \textit{i.e.} $k_{\text{fast}} \gg k_{\text{slow}}$.\textsuperscript{70} In the ideal case, for a very selective enzyme, only one of the enantiomers will be transformed by the catalyst. This will cause the reaction to cease automatically at 50% conversion, thereby providing both the starting material and the product in their optically pure forms. However, this is rarely the case in practice and usually the reaction has to be stopped before reaching 50% conversion. Hence, kinetic resolution suffers from two major drawbacks, the first being a maximum theoretical yield of 50%. The other is the tedious separation of the remaining enantiomer from the desired product.\textsuperscript{72}

\[
\begin{array}{ccc}
\text{(R)-substrate} & \text{Enzyme} & \text{(R)-product} \\
& k_{\text{fast}} & \\
\text{(S)-substrate} & \text{Enzyme} & \text{(S)-product} \\
& k_{\text{slow}} & \\
\end{array}
\]

\textbf{Scheme 10. Principle for a (R)-selective enzymatic kinetic resolution (KR).}

Mathematical equations describing the efficiency (\textit{i.e.} the selectivity) of a kinetic resolution have been developed by Sih \textit{et al.}\textsuperscript{73} The “enantiomeric ratio” or the E-value can be calculated by either equation (2) or equation (3). The E-value is a dimensionless constant, useful for comparing the difference in enzyme selectivity. It can be calculated from any of the two following parameters: conversion (c), product \textit{ee} (\textit{ee}_p) or substrate \textit{ee} (\textit{ee}_s) as shown by equations (2) and (3).\textsuperscript{72,73} An E-value of 1 describes a completely nonselective transformation, \textit{i.e.} there is no discrimination between the two
enantiomers. E-values below 10 are insufficient for practical purposes, while E-values of between 15 and 30 are termed moderate to good.\textsuperscript{71,72} An E-value of > 100 is desired for a highly selective kinetic resolution.\textsuperscript{74}

\[
E = \frac{\ln [1 - c(1 + ee_p)]}{\ln [1 - c(1 - ee_p)]} = \frac{\ln [(1 - c)(1 - ee_s)]}{\ln [(1 - c)(1 + ee_s)]} \quad (2)
\]

\[
E = \frac{\ln \left[ \frac{ee_p(1 - ee_s)}{ee_p + ee_s} \right]}{\ln \left[ \frac{ee_p(1 + ee_s)}{ee_p + ee_s} \right]} \quad (3)
\]

1.7 Dynamic kinetic resolution

A kinetic resolution coupled to an in situ racemization of the two enantiomers is termed a dynamic kinetic resolution (DKR), and is a powerful tool for the preparation of enantiomerically pure compounds in high yields (Scheme 11). By constantly keeping the two enantiomers in equilibrium, the fast reacting enantiomer will never be depleted from the reaction mixture. This technique allows a maximum theoretical yield of 100% for the desired enantiomer, thereby overcoming the limitations of a traditional KR.\textsuperscript{71,72,75}

\[
\text{Scheme 11. Principle for a (R)-selective dynamic kinetic resolution (DKR).}
\]

There are several requirements for an efficient DKR protocol; (i) the KR must be irreversible, (ii) the KR must be selective enough (E > 100 is desired), (iii) the racemization should be fast enough to keep the two enantiomers in equilibrium and (iv) the enzymatic resolution and the racemization should be compatible with one another in a one-pot procedure.\textsuperscript{70,72,76} Most often, the compatibility of the two catalysts is the most difficult to accomplish, as the enzymatic resolution and the racemization both operate under very specific conditions.\textsuperscript{76}

A chemoenzymatic DKR employs an enzyme for the kinetic resolution and a transition-metal catalyst for the racemization.\textsuperscript{72} DKR protocols of this type have recently attracted substantial interest and several examples have been reported in the literature for e.g. secondary alcohols\textsuperscript{65}, amines\textsuperscript{78} and diols.\textsuperscript{79}
1.8 Objective and scope of this thesis

One objective of this thesis was to study the racemization of sec-alcohols catalyzed by a cyclopentadienylruthenium dicarbonyl complex, with the goal of developing a better understanding of the racemization mechanism. Another objective was to develop new DKR protocols for sec-alcohols.

This thesis is divided into two parts. The first part deals with studies of a cyclopentadienylruthenium dicarbonyl catalyst utilized for the racemization of sec-alcohols, using NMR spectroscopy and in situ FT-IR measurements.

In the second part of this thesis, this racemization catalyst is combined with a lipase in a one-pot procedure leading to the development of several efficient DKR protocols for sec-alcohols. DKR was applied to exocyclic allylic alcohols, homoallylic alcohols and β-chloroalcohols. The enantiomerically pure products are all versatile intermediates for further organic transformations and this was also demonstrated through synthetic applications.
2. The Mechanism of Racemization of sec-Alcohols Catalyzed by a Cyclopentadienyl Ruthenium Complex (Papers I-II)

2.1 Introduction

In recent years, mechanistic investigations of cyclopentadienyl ruthenium catalysts involved in hydrogen transfer reactions have attracted considerable interest.\textsuperscript{46,47,54,61,63,80-83} This is owing to the extensive applications of these catalysts in racemizations, (transfer) hydrogenations, and dehydrogenations.\textsuperscript{44,81,84,85} For example, ruthenium complexes 1-2 and 6-7 (Figure 4) have been employed as efficient racemization catalysts in combination with an in situ enzymatic kinetic resolution, leading to several successful DKR protocols.\textsuperscript{65,76,86-89}

\textbf{Figure 4.} Ruthenium complexes 1-2 and 6-7 employed as racemization catalysts.

Our group has developed an efficient DKR applicable to a wide range of sec-alcohols by utilizing ruthenium catalyst 2 in combination with a lipase and an acyl donor. The corresponding enantiomerically pure acetates are generally obtained in high yields and with excellent ee values.\textsuperscript{65,86,90} Furthermore, catalyst 2 has been employed in dynamic kinetic asymmetric transformations (DYKAT) of 1,2-,\textsuperscript{91} 1,3-,\textsuperscript{92-94} 1,4-,\textsuperscript{95} and 1,5-diols\textsuperscript{79,96} leading to enantiomerically and diastereomerically pure diacetates.

Previous work in our group has provided insight into the racemization mechanism of sec-alcohols catalyzed by highly efficient ruthenium complex 2. Catalyst activation by t-BuOK is proposed to form ruthenium tert-butoxide complex 3 (Scheme 12).\textsuperscript{86} The activation by t-BuOK is instantaneous and can be visually detected by a characteristic color change from yellow to orange/red.\textsuperscript{65} More recently it was shown that precatalyst activation takes place via CO assistance with the formation of an acyl
intermediate A. Acyl intermediate A was detected experimentally and thoroughly characterized by NMR spectroscopy and in situ FT-IR measurements. Full conversion from intermediate A to ruthenium tert-butoxide complex 3 proceeds within a few min at room temperature, via rapid alkoxide migration from carbon to ruthenium (Scheme 12). The existence of acyl intermediate A in the ligand exchange mechanism had previously been predicted by density functional theory (DFT) calculations.

Scheme 12. Precatalyst activation via acyl intermediate A.

Part of our research program focuses on the development of DKR protocols. In connection with our work on chiral diols, one approach aimed to synthesize enantiomerically pure piperidines and pyrrolidines by employing DKR of 5-hexen-2-ol (8) in the enantiodetermining step. However, DKR of this alcohol has yet to be successful (Scheme 13).

Scheme 13. Unsuccessful DKR of 5-hexen-2-ol (8).

2.2 Results and discussion

2.2.1 Unexpected formation of a cyclopentadienylruthenium alkoxycarbonyl complex with a coordinated C=C bond

Since the kinetic resolution of 5-hexen-2-ol (8) exhibits a good E-value (>200), the racemization of this substrate was investigated (Table 1). The results show that the rate of racemization for (S)-5-hexen-2-ol (S)-(8) is considerably slowed down compared to that of the corresponding saturated alcohol (S)-2-hexanol (S)-(10).
Table 1. Racemization study on (S)-8 and (S)-10.

<table>
<thead>
<tr>
<th>Entry&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Substrate</th>
<th>Time</th>
<th>ee 8, 10 (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(S)-8</td>
<td>270</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td></td>
<td>390</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>(S)-10</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reaction conditions: (S)-alcohol (1 mmol), Ru-cat. 2 (5 mol%), $t$-BuOK (10 mol%) and Na$_2$CO$_3$ (1 mmol) in dry toluene (2.0 mL) under argon atmosphere. <sup>b</sup> Determined by chiral GC.

The results in Table 1 suggest that the terminal double bond coordinates to ruthenium and interferes with the racemization. To prove this hypothesis, the reaction of ruthenium tert-butoxide complex 3 and 5-hexen-2-ol 8 was studied by NMR spectroscopy and in situ FT-IR measurements. Similarly to the $\beta$-hydride elimination, coordination of the double bond requires a free site on ruthenium (c.f. Scheme 9). Therefore, it was thought that this study could provide further insight into the racemization mechanism of $\text{sec}$-alcohols catalyzed by ruthenium complex 2.

The reaction was initially studied by letting pre-formed ruthenium tert-butoxide complex 3 react with 5-hexen-2-ol (8) in an NMR tube at room temperature. Analysis by $^1$H and $^{13}$C NMR spectroscopy showed the disappearance of complex 3, with concomitant formation of a 1:1 mixture of two diastereomers that had the double bond coordinated to ruthenium. Three plausible structures for these diastereomeric complexes were initially considered (Figure 5): 11a-b (complexes with only one CO ligand), 12a-b ($\eta^3$-C$_5$Ph$_5$), and 13a-b (acyl compounds similar to acyl intermediate A, c.f. Scheme 12). In the two diastereomers, the methyl group bound to the stereogenic $\alpha$-carbon of the alcohol points either up or down. For simplicity, the two diastereomers will from now on be designated as a and b.
When studying both the $^1$H and $^{13}$C NMR spectra it is clear that the double bond is coordinated to ruthenium. The proton at the internal carbon of the double bond (H5) is shifted upfield (1.2 – 1.5 ppm) from $\delta$ 5.74 ppm (free alcohol 8) to $\delta$ 4.52 and 4.28 ppm for a and b, respectively. The internal double bond carbon (C5) is also shifted upfield from $\delta$ 139.0 ppm (free alcohol 8) to $\delta$ 84.5 and 85.6 ppm for a and b, respectively. For the terminal double bond protons (H6 and H6$'$), an even bigger upfield shift (ca. 2.6 ppm) compared to the free alcohol 8 ($\delta$ 5.05 ppm) is observed, and these protons appear together as a multiplet for both diastereomers at $\delta$ 2.22 – 2.37 ppm. The terminal double bond carbon (C6) is shifted upfield from $\delta$ 114.5 ppm (free alcohol 8) to $\delta$ 19.4 and 21.9 ppm for a and b, respectively. These results are in good agreement with ruthenium complexes reported in the literature, which exhibit upfield shifts of similar magnitudes for the double bond protons.$^{98,99}$

A downfield shift was observed for the $\alpha$-CH protons (H2) of diastereomers a and b, which appeared at 4.21 and 3.90 ppm (relative to 3.49 ppm for free alcohol 8). This can be compared to the similar downfield shift of the $\alpha$-CH proton of the 1-phenylethoxide ligand of complex 4 (c.f. Scheme 9). A slight downfield shift was also observed for the $\alpha$-carbon (C2) from 67.1 ppm to 75.1 and 74.1 ppm for a and b, respectively. This initially led us to believe that the oxygen was coordinated to ruthenium, which would seem to support structures 11 and 12. However, it should be noted that structures 13 would also be expected to exhibit a downfield shift for the $\alpha$-CH protons.

Although the above results strongly support coordination of the double bond to ruthenium, none of the structures 11-13 had been ruled out by the $^1$H and $^{13}$C NMR experiments to this point. In the racemization of secondary alcohols, $\beta$-hydride elimination is proposed to occur via $\eta^5 \rightarrow \eta^3$ ring slippage or via CO dissociation (c.f. Scheme 9). Therefore, we were eager to find out whether the alkene complexes a and b had one or two coordinated CO ligands. In the CO region, the $^{13}$C NMR spectra showed three peaks between $\delta$ 203-204 ppm in a 1:1:2 ratio (Figure 6). Since this could be interpreted in different ways, the reaction was also repeated with $^{13}$CO-enriched ruthenium tert-butoxide complex 3 (55% $^{13}$CO content). The $^{13}$C NMR spectra showed

![Figure 5. Plausible structures for diastereomeric complexes a and b.](image-url)
doublets arising from coupling between two $^{13}$CO groups ($J_{CC} \approx 8.2$ Hz). In addition to this, singlets were observed from the $^{13}$CO groups with a neighboring $^{12}$CO ligand. Hence, the overall appearance of the signals was triplets and the resonance at $\delta$ 203.958 ppm corresponds to two overlapping CO signals (Figure 6). A HMBC spectrum was also recorded, clearly showing crosspeaks between the double bond protons and two CO groups each. These observations together with the fact that no free CO was observed at $\delta$ 184.7 ppm, rules out 11 as possible structures for diastereomeric complexes a and b.

![Figure 6. $^{13}$C NMR spectra of unlabeled (left) and $^{13}$C-labeled (right) diastereomeric complexes a and b.](image)

Of the two remaining possible structures, the acyl compounds 13 are expected to be more stable than $\eta^3$-coordinated complexes 12. The observation that only one signal ($\delta$ 108.0 ppm) is present in the $^{13}$C NMR spectra for the cyclopentadienyl carbon would suggest that the ligand is $\eta^5$-coordinated. Alternatively, the ligand could be $\eta^3$-coordinated if there is a rapid equilibrium between the five carbons on the cyclopentadienyl ring at room temperature, making them appear as equivalent. Therefore, we decided to study the reaction between complex 3 and alcohol 8 at lower temperature. An $\eta^3$-coordinated ligand would be expected to split into three peaks in a 1:2:2 ratio once the equilibrium is slowed down. At $-78^\circ$C, the peak at $\delta$ 108.0 ppm had split into two peaks in a 1:1 ratio, which appeared at $\delta$ 107.46 and 107.42 ppm (Figure 7). Exchange at this low temperature is ruled out since no line broadening of the peaks is observed and the best interpretation of these results is therefore that the two complexes a and b have $\eta^5$-coordinated ligands. These appear at the same shift for both complexes at room temperature, and then split into two peaks for a and b at lower temperature.
Figure 7. $^{13}$C NMR spectra of diastereomeric complexes a and b at 25 °C (left) and at −78 °C (right).

The only argument against acyl complexes 13 is that the $^{13}$C-signal for the acyl carbon appears more downfield than expected.$^{102-104}$ However, a similar downfield shift for the acyl carbon was recently also observed for acyl intermediate A$^{67}$ (c.f. Scheme 12). Therefore, the reaction between complex 3 and alcohol 8 was also studied by in situ FT-IR measurements (Figure 8).

Figure 8. FT-IR spectra before (grey) and after (black) the addition of 5-hexen-2-ol 8 to ruthenium tert-butoxide complex 3.

The peaks for complex 3 appear at 2021 cm$^{-1}$ (CO, symmetric stretch) and 1964 cm$^{-1}$ (CO, asymmetric stretch). Upon addition of alcohol 8 to the reaction, the peaks for complex 3 disappeared with concomitant formation of a new peak at 1982 cm$^{-1}$. It was also possible to detect a peak in the region where acyl peaks normally appear,$^{67,105,106}$ at 1644 cm$^{-1}$ (Figure 8). The reaction could not be followed to completion since severe decomposition
started after approximately 1 h. However, the detection of the acyl peak provides a consistent assignment of diastereomeric complexes \(a\) and \(b\) as alkoxy carbonyl complexes 13\textsuperscript{107}.

There are several possibilities for the mechanism for formation of alkoxy carbonyl complexes 13a-b (Scheme 14). Formation of sec-alkoxide complex 14 from ruthenium tert-butoxide complex 3 goes via an alcohol-alkoxide exchange (not shown, c.f. Scheme 9). Racemization via \(\beta\)-hydride elimination requires a free coordination site on ruthenium proposed to be formed by either \(\eta^5 \rightarrow \eta^3\) ring slippage or by loss of a CO ligand (Scheme 14, step \(i\)). Once the free coordination site has been formed, there are two competing reactions that may fill this coordination site on ruthenium. The first is \(\beta\)-hydride elimination (Scheme 14, step \(ii\)), which would cause racemization of the alcohol (Scheme 14, step \(iii\)). The second alternative is coordination of the terminal double bond of the alcohol to ruthenium (Scheme 14, step \(iv\)). Complexes 13a-b would then be formed via migratory insertion of the alkoxide to the CO ligand (Scheme 14, step \(v\)). Complexes 13a-b could also be formed via alkoxy migration from ruthenium to CO in complex 14 (Scheme 14, step \(vi\)), followed by subsequent coordination of the double bond to the free coordination site on ruthenium (Scheme 14, step \(vii\)). The formation of complexes 13a-b would inhibit the rate of racemization, since this ruthenium complex has been shown to be inactive\textsuperscript{108,109}.

![Scheme 14](image-url)
2.2.2 Racemization of substrates with carbon-carbon double bonds

The formation of diastereomeric complexes 13a-b raised interest in investigating the racemization of substrates with terminal double bonds at different distances from the alcohol moiety. Therefore, we compared the rate of racemization of (S)-4-penten-2-ol, (S)-15 (one carbon shorter) and (S)-6-hepten-2-ol, (S)-16 (one carbon longer) to that of (S)-hexen-2-ol, (S)-8 (Table 2). The reactions were performed on a 1 mmol scale of the (S)-alcohol with 5 mol% of ruthenium catalyst 2 at room temperature. As can be seen from the results, the terminal olefin inhibits the racemization reaction in all the cases. It can also be noted that (S)-5-hexen-2-ol, (S)-8 requires the longest reaction time, over 4.5 h to become fully racemic. The rates of racemization shown in Table 2 are all too slow for an efficient DKR.

### Table 2. Racemization study on substrates (S)-8, (S)-15 and (S)-16.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>n</th>
<th>Time (min)</th>
<th>ee 8, 15, 16 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(S)-15</td>
<td>1</td>
<td>120</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>240</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>(S)-8</td>
<td>2</td>
<td>270</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>390</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>(S)-16</td>
<td>3</td>
<td>10</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>30</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>60</td>
<td>8</td>
</tr>
</tbody>
</table>

a) Reaction conditions: (S)-alcohol (1 mmol), Ru-cat. 2 (5 mol%), t-BuOK (10 mol%) and Na₂CO₃ (1 mmol) in dry toluene (2.0 mL) under argon atmosphere. b) Determined by chiral GC.

Based on the slow racemization rates for substrates (S)-15 and (S)-16 we became curious about investigating whether or not they would form intermediates similar to that of diastereomeric complexes 13a-b with a coordinated double bond. This was done by adding either substrate 15 or 16 (1.1 equiv) to preformed ruthenium complex 3 (1 equiv) in an NMR tube. Double bond coordination to ruthenium would result in significant upfield shifts of these protons compared to the shifts for free alcohol. ¹H and ¹³C NMR recordings at room temperature have however failed to detect any such intermediates to this point.
Since racemization is known to be faster at higher temperature, the racemization of (S)-8 was also studied at 80 °C. The reaction was performed on a 1 mmol scale with 5 mol% of ruthenium catalyst 2 (Table 3). The elevated temperature considerably speeded up the rate of racemization and the substrate was almost fully racemic within 30 min.

Table 3. Racemization of (S)-8 at 80 °C.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Time (min)</th>
<th>ee 8 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>4</td>
</tr>
</tbody>
</table>

a) Reaction conditions: (S)-alcohol (1 mmol), Ru-cat. 2 (5 mol%), t-BuOK (10 mol%) and Na₂CO₃ (1 mmol) in dry toluene (2.0 mL) under argon atmosphere. b) Determined by chiral GC.

We also investigated the reaction between ruthenium tert-butoxide complex 3 and 5-hexen-2-ol (8) at elevated temperature by ¹H NMR. We were interested in whether or not diastereomeric complexes 13a-b would be formed and remain intact at higher temperature, since the racemization proceeds at an acceptable rate for this substrate at 80 °C. Since the racemization is speeded up, the double bond would be expected to equilibrate between being coordinated and uncoordinated in order to free the site needed for β-hydride elimination. This effect would be expected to result in line broadening or coalescence of the double bond protons. The ruthenium tert-butoxide complex 3 was formed in an NMR tube by reacting ruthenium chloride 2 (1 equiv) with t-BuOK (1.3 equiv) in dry toluene-d₈. Subsequent addition of alcohol rac-8 at room temperature revealed the formation of diastereomeric complexes 13a-b. The temperature was then raised in 10-15 degree increments and ¹H NMR spectra were recorded at 40, 55, 70, 80 and 90 °C. Interestingly, complexes 13a-b remained intact throughout the experiment. Furthermore, no line broadening or coalescence of the double bond protons was observed. The spectra obtained looked the same at elevated temperature but with slightly worse peak sharpness, most likely due to problems with shimming. The fact that no exchange of the double bond protons could be observed was ascribed to that the equilibrium between coordinated and uncoordinated double bond was too fast to be detected on the NMR time scale.
The effect on the rate of racemization for substrates with substituted double bonds was also studied. Three different enantiopure alcohols were synthesized for this purpose, one 6-methyl-substituted (S)-17a, one 6,6-dimethyl-substituted (S)-17b, and one 6-phenyl-substituted (S)-17c. All three substrates (S)-17a-c had the same number of carbons between the double bond and the alcohol moiety as 5-hexen-2-ol (8). Racemization reactions were performed on a 1 mmol scale with 5 mol% ruthenium catalyst 2 at room temperature (Table 4).

Table 4. Racemization study on substrates (S)-17a-c.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>R, R’</th>
<th>Time (min)</th>
<th>ee 17a-c (%)</th>
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<td>35</td>
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<td></td>
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<td></td>
<td>20</td>
<td>5</td>
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<td>2</td>
<td>(S)-17b</td>
<td>Me, Me</td>
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<td>35</td>
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</table>

a) Reaction conditions: (S)-alcohol (1 mmol), Ru-cat. 2 (5 mol%), t-BuOK (10 mol%) and Na₂CO₃ (1 mmol) in dry toluene (2.0 mL) under argon atmosphere. b) Determined by chiral GC.

As the results show, the racemization of all three substituted alcohol substrates (S)-17a-c is faster compared to (S)-8 (c.f. Table 1), most likely due to the sterical hindrance of the double bond in these substrates. However, the rates of racemization of (S)-17a-c are still lower compared to the saturated substrate (S)-10 (c.f. Table 1). This would indicate that there still is some coordination of the double bond to ruthenium. A slight trend that the most substituted bond shows the fastest racemization can also be noted, i.e. (S)-17c ≥ (S)-17b > (S)-17a (Table 4). This provides further support that double bond coordination inhibits the racemization by blocking the free site on ruthenium needed for β-hydride elimination.
2.3 Conclusion

During mechanistic investigations on Ru(CO)$_2$Cl($\eta^5$-C$_5$Ph$_3$), formation of two diastereomers of an alkoxy carbonyl complex which have the double bond coordinated to ruthenium were observed. The racemization of (S)-5-hexen-2-ol was found to be very slow at room temperature, which led us to study the reaction between this substrate and Ru(CO)$_2$(O$_3$Bu($\eta^5$-C$_5$Ph$_3$). We were able to thoroughly characterize these diastereomeric complexes by $^1$H NMR, $^{13}$C NMR and in situ FT-IR measurements at room temperature. Strong evidence for coordination of the double bond to ruthenium and for coordination of the alcohol oxygen to one of the CO ligands was provided. We also studied this reaction at elevated temperature by $^1$H NMR spectroscopy since the rate of racemization was considerably speeded up at 80 °C, and found that the diastereomeric complexes remained intact throughout the experiment.

Inhibition of the rate of racemization was also found for two additional sec-alcohols with terminal olefinic functionalities, (S)-4-penten-2-ol and (S)-6-hepten-2-ol. Interestingly, although the rate of racemization was slow for these substrates, no intermediates similar to the diastereomeric complexes have been observed by $^1$H NMR and $^{13}$C NMR spectroscopy. Furthermore, the racemization of three sec-alcohols with different substitution patterns on the double bond was investigated. It was found that racemization of these substrates proceeded faster than that for the substrates with terminal double bonds, but slower than for the corresponding saturated substrate, 2-hexanol. The inhibition effect observed on the rate of racemization in the presence of an olefin provides strong support for the hypothesis that a free coordination site is needed on ruthenium for $\beta$-hydride elimination.
3. CO Dissociation Mechanism in Racemization of Alcohols by a Cyclopentadienyl Ruthenium Dicarbonyl Catalyst (Paper III)

3.1 Introduction

As previously stated, mechanistic work performed in our group has provided insight into the mechanism for racemization of sec-alcohols by ruthenium catalyst 2. Catalyst activation by t-BuOK goes via the formation of an acyl intermediate A (Scheme 15, step i). The catalytically active species 3 has been characterized by $^{13}$C NMR. Immediate racemization of (S)-1-phenylethanol, (S)-18 upon addition to complex 3 provides strong support for complex 3 as an active intermediate in the catalytic cycle.  

Ruthenium sec-alkoxide complex 4 is formed after subsequent alcohol-alkoxide exchange (Scheme 15, step ii). Racemization proceeds via an inner-sphere mechanism that generates a ketone-hydride intermediate from $\beta$-hydride elimination. The participation of a free ruthenium hydride species, Ru(CO)$_2$H($\eta^5$-Ph$_4$C$_4$) has been ruled out as improbable by previous experimental observations.

Since ruthenium sec-alkoxide complex 4 is a coordinatively saturated 18-electron species, a free coordination site on ruthenium is required for racemization via $\beta$-hydride elimination. Although the mechanistic work to this point has provided a detailed picture of the racemization mechanism, there is still some doubt regarding the formation of this free coordination site. The two most plausible suggestions are $\eta^5$→$\eta^3$ ring slippage to form intermediate 5 or by CO dissociation which would produce intermediate 5' (Scheme 15, step iii or iv).

Based on the previous observation that CO exchange does not occur in the related Shvo hydride Ru(CO)$_2$H($\eta^5$-Ph$_4$C$_4$COH), CO exchange in complex 3 was considered to be unfavored and therefore the $\eta^5$→$\eta^3$ ring slippage pathway was originally proposed (Scheme 15, step iii). However, recent DFT calculations have shown that the potential energy barrier for the ring slippage mechanism was higher than expected, 42 kcal/mol. The potential energy barrier for the mechanism involving dissociation of a CO
ligand (Scheme 15, step iv) is lower and was calculated to be 22.6 kcal/mol. \textsuperscript{69,111}

Scheme 15. Simplified mechanism for racemization of (S)-18 by catalyst 2.

The computational studies suggest that CO dissociation is more favored compared to the $\eta^5 \rightarrow \eta^3$ ring slippage pathway. Based on these results, this project aimed to find experimental evidence that would either support or rule out the hypothesis that dissociation of a CO ligand is a key step in the racemization mechanism for sec-alcohols.

3.2 Results and discussion

3.2.1 Investigation of CO exchange

The idea for the preliminary experiments was to prepare $^{13}$CO enriched ruthenium catalyst 2 and thereafter study the CO exchange by following the release of free $^{13}$CO. The synthesis of $^{13}$CO enriched catalyst 2 was performed according to a literature procedure,\textsuperscript{112} and catalyst 2 was obtained in quantitative yield and with 44\% $^{13}$CO content. In the first attempt to study CO exchange, the $^{13}$CO enriched catalyst 2 (44\% $^{13}$CO content) was dissolved in toluene-d$_8$ and treated with t-BuOK (1.2 equiv) in an NMR tube.
Analysis was performed by $^{13}$C NMR after the addition of $^{12}$CO (g) (0.3 and 0.9 equiv) in two separate reactions. Unfortunately, no free CO was observed at 184.7 ppm$^{101}$ in either reaction after 12 h. This was ascribed to problems with detecting small amounts of dissociated CO by $^{13}$C NMR. Instead, monitoring the incorporation of $^{13}$CO over time for ruthenium catalyst 2 and ruthenium tert-butoxide complex 3 was considered to be a better approach.

The $^{13}$CO-incorporation was studied by the addition of gaseous $^{13}$CO (0.013 mmol, 0.3 equiv) to either ruthenium catalyst 2 or ruthenium tert-butoxide complex 3. Periodical aliquots from these reactions were withdrawn and analyzed by $^{13}$C NMR. The $^{13}$CO content was determined by comparison of the integrals for the peaks at $\delta$ 197.1 and 202.8 ppm (Figure 9) to those of reference spectra for complexes 2 and 3, respectively (1.1% $^{13}$C content). Under the chosen reaction conditions a theoretical maximum of 14% $^{13}$CO incorporation can be obtained.

![Figure 9. $^{13}$C NMR shifts for ruthenium complexes 2 and 3.](image)

For ruthenium catalyst 2, the CO exchange was fairly slow and samples were taken after 3, 6, 24 and 40 h (Figure 10a). The tert-butoxide complex 3 was found to exchange CO more rapidly (approximately 20 times faster than complex 2), and the $^{13}$CO content was determined after 30, 60 and 90 min (Figure 10b).

![Figure 10a: $^{13}$CO incorporation (%) for ruthenium chloride 2.](image)  
![Figure 10b: $^{13}$CO incorporation (%) for ruthenium tert-butoxide complex 3.](image)

The plotted results show that the $^{13}$CO incorporation slows down considerably after prolonged reaction times in both cases, which is expected
for this type of equilibrium reaction. The dramatic increase in rate for tert-butoxide complex 3 is most likely attributed to back-donation from the t-BuO group, which is expected to stabilize the transition state for losing a CO ligand, allowing for more facile CO dissociation from this intermediate.69,113,114

3.2.2 Formation of carboalkoxydicarbonylruthenium complex 19

The CO exchange study on ruthenium tert-butoxide complex 3 was complicated by the observed formation of a new complex with concomitant disappearance of the peaks for complex 3. The new complex was formed only after prolonged reaction times at low concentrations of CO (0.3 equiv). At higher CO concentrations (>1 equiv), significant amounts of the unknown complex were observed early in the reaction. The new complex was therefore first thought to be a decomposition product due to the instability of complex 3 towards moisture and air.

However, it was possible to obtain quantitative conversion to the new complex by treating catalyst 2 dissolved in toluene with a slight excess of t-BuOK under CO atmosphere for 3 h at room temperature. After evaporation, a stable brown solid was obtained and the complex was assigned as carboalkoxydicarbonylruthenium complex 19,102,115 by $^{13}$C NMR spectroscopy (Figure 11). Complex 19 displayed three characteristic peaks in the $^{13}$C NMR spectra at $\delta$ 109.0 (cyclopentadienyl carbon), 186.5 (acyl) and 200.4 (CO) ppm. Characterization by IR was also possible and peaks were observed at 1654 cm$^{-1}$ (acyl), 1983 cm$^{-1}$ (CO, asymmetric stretch) and 2037 cm$^{-1}$ (CO, symmetric stretch). The assignments made were in good agreement with literature values for a similar complex Ru(CO)$_2$(COOr-Bu)(η$^5$-Me$_5$C$_5$), previously reported by Suzuki et al.102

![Figure 11. $^{13}$C NMR shifts for carboalkoxydicarbonylruthenium complex 19.](image)

The formation of carboalkoxydicarbonylruthenium complex 19 demonstrated that the mechanism of CO exchange was more complex than previously believed. Therefore, a new mechanistic model was created taking the involvement of complex 19 into account (Scheme 16). The model suggests that a free coordination site on ruthenium can be generated in two
ways, either by dissociation of one of the $^{12}$CO ligands (Scheme 16, path A), or by alkoxide migration from ruthenium to one of the CO ligands (Scheme 16, path B). Subsequent coordination of $^{13}$CO to intermediate 20 results in the formation of $^{13}$CO-enriched ruthenium tert-butoxide complex 3 (Scheme 16, path A). Both steps in this equilibrium CO exchange reaction are reversible. Intermediate 20 formed after dissociation of a CO ligand is the 16-electron complex suggested to be responsible for the racemization. In path B, complex 19 is formed irreversibly after coordination of CO to acyl intermediate 21 (Scheme 16, path B).

Scheme 16. Proposed mechanism for CO exchange on complex 3 (Path A) and formation of carboalkoxydicarbonylruthenium 19 (Path B).

The irreversible formation of complex 19 is based on the observations from the $^{13}$C NMR study. Also, complex 19 cannot be converted back into ruthenium tert-butoxide complex 3, even with heating under reduced pressure. Furthermore, it was found that complex 19 does not undergo exchange with $^{13}$CO, which is in accordance with its irreversible formation. Complex 19 was tested as a racemization catalyst for sec-alcohols but as expected, it showed no activity. The equilibrium between 3 and 21 (Scheme 16, step iii) was confirmed by first-order dependence of [CO] in the formation of complex 19 from complex 3.

3.2.3 CO inhibition study

The CO exchange study described above provides support for CO dissociation in the racemization mechanism for sec-alcohols. To further demonstrate this point, the effect on the rate of racemization upon addition of different concentrations of carbon monoxide was also investigated. The reactions were performed by adding $t$-BuOK (0.03 mmol, 3 mol%) to
ruthenium chloride 2 (0.01 mmol, 1 mol%) dissolved in dry toluene (2.0 mL). After stirring for 10 min to ensure formation of ruthenium tert-butoxide complex 3, gaseous CO (250, 300, 350, 400 μL; 1.1, 1.3, 1.5, 1.7 mol%) was quickly injected by a gas-tight Hamilton syringe. (S)-18 (1 mmol) was added to the reaction after an additional 10 min of stirring. Aliquots for GC analysis were withdrawn after 1, 3 and 10 min. For each CO concentration the experiment was reproduced twice and the mean ee values were plotted in a graph against the reaction time. A control experiment without any added CO in the racemization reaction was also performed as a reference.

![Figure 12. CO inhibition study on the racemization of (S)-18.](image)

As can be seen from the results (Figure 12), the rate of racemization was found to be highly dependent on the concentration of CO and a clear inhibition effect was observed. The control experiment with no added CO shows that a catalyst loading of 1 mol% produces an efficient system, capable of racemizing the substrate within 3 min at room temperature. Addition of 250 μL of CO had a negligible effect and the racemization rate was similar to that of the control experiment. The first sign of inhibition on the rate of racemization was observed when 300 μL of CO was added. This resulted in a dramatic decrease in rate to approximately half in comparison to the control experiment. Addition of 350 μL of CO showed similar results. An even more dramatic effect was observed when 400 μL of CO was added and the sample still exhibited 80% ee after 10 min of reaction time. At higher concentrations (≥500 μL) of added CO the racemization of (S)-18 was completely inhibited, and no racemization could be detected within 10 min. This was ascribed to the fact that irreversible formation of carboalkoxydicarbonylruthenium complex 19 or corresponding 19’ is
expected to be fast at these high concentrations of CO, as also previously demonstrated in the CO exchange study (c.f. Scheme 16).

The initial racemization experiments were performed with a three-fold excess of t-BuOK to ensure complete formation to ruthenium tert-butoxide complex 3. Another control experiment was therefore performed with 400 μL of CO and only 1 mol% of t-BuOK to prove that the concentration of base had no effect on the results. It was thought that a high concentration of t-BuOK could promote formation of complex 19, thereby resulting in a decrease of the racemization rate. However, as similar results were obtained, the concentration of t-BuOK was found to have a negligible effect on the rate of racemization.

The observed inhibition by carbon monoxide on the racemization of sec-alcohols strengthens the hypothesis that reversible CO dissociation is a key step in the racemization mechanism.

3.3 Conclusion

Mechanistic investigations on Ru(CO)$_2$Cl($\eta^5$-C$_5$Ph$_5$) have been conducted with the aim of providing a more detailed picture on the racemization of sec-alcohols. One question we wanted to answer concerned the formation of the free coordination site required for β-hydride elimination. Previous work pointed towards $\eta^5 \rightarrow \eta^3$ ring slippage as the most likely pathway, but recent density functional theory (DFT) calculations suggest that dissociation of CO is more energetically favored.

We have found experimental evidence for that CO exchange occurs with precatalyst Ru(CO)$_2$Cl($\eta^5$-C$_5$Ph$_5$) and active catalytic intermediate Ru(CO)$_2$(Ot-Bu)($\eta^5$-C$_5$Ph$_5$), monitored by $^{13}$C NMR and with the use of $^{13}$CO. This CO exchange reaction was found to be approximately 20 times faster for the active catalytic species, most likely due to back-donation from the tert-butoxide ligand which would stabilize the transition state for CO dissociation. If too high concentrations of $^{13}$CO were used, irreversible formation of a carboalkoxydicarbonylruthenium complex was observed. We also investigated the effect of adding CO to the racemization of (S)-1-phenylethanol and it was evident that larger concentrations of CO inhibited the rate of racemization. This observation together with the CO exchange study provides strong support for reversible CO dissociation as the likely pathway for formation of a free coordination site on ruthenium in the racemization mechanism of sec-alcohols.
4. Enantioselective Route to Ketones and Lactones from Exocyclic Allylic Alcohols via Metal and Enzyme Catalysis (Paper IV)

4.1 Introduction

Ketones and their corresponding lactone derivatives are important synthetic intermediates in organic transformations, and are also common structures in natural products. Considerable interest in many of these natural products arises from their potential biological and medicinal uses. Owing to these useful properties, many methods for the enantioselective synthesis of chiral lactones have been developed, including catalytic Baeyer-Villiger oxidations, 1,4-addition and 1,4-reduction reactions, metal-catalyzed cyclization reactions and enzymatic methods.

There are several examples of DKR of allylic alcohols reported in the literature, by our group and by others. In 2007, our group developed an efficient DKR for both cyclic and acyclic allylic alcohols, utilizing ruthenium catalyst for the racemization and CALB for the enzymatic resolution. The products obtained were also transformed into enantioenriched acyloin (α-hydroxy ketones) acetates via carbon-carbon double bond cleavage. The aim of the present project was to extend this methodology into a general and efficient route for the enantioselective synthesis of α-substituted ketones and their corresponding lactones.

Our planned synthetic strategy begins with the DKR of exocyclic allylic alcohols in the enantiodetermining step. By employing ruthenium catalyst for the racemization and CALB for the enzymatic resolution, the corresponding allylic esters are obtained. Alkenes are formed after Cu-catalyzed allylic substitution that proceeds with inversion of stereochemistry. Subsequent oxidative cleavage of the carbon-carbon double bond produces enantiomerically enriched α-substituted ketones. Finally, Baeyer-Villiger oxidation forms the corresponding lactones (Scheme 17).
Scheme 17. Synthetic route to enantiomerically pure α-substituted ketones (25) and lactones (26) via DKR and Cu-catalyzed allylic substitution.

4.1.1 Cu-catalyzed allylic substitution reactions

Cu-catalyzed allylic substitutions are a valuable type of C-C bond formation reaction, and Gilman reported on the first example in 1936.\textsuperscript{134} The allylic esters (23) formed after the DKR (c.f. Scheme 16), readily undergo this type of allylic substitution reaction.

The mechanistic aspects of Cu-catalyzed allylic substitution reactions with Grignard reagents are well studied. These reactions can proceed via two different mechanistic pathways, producing either the α-alkylated or the γ-alkylated product (Scheme 18).\textsuperscript{135-138} The oxidative addition to allylic esters by Cu(I) is generally accepted to proceed with high γ-regioselectivity and results in the formation of σ-allyl complex 27. This reaction is also well-known to proceed exclusively with \textit{anti} stereochemistry.\textsuperscript{136,139} Reductive elimination from complex 27 produces the γ-alkylated product 28 via an S\textsubscript{N}2′ reaction. Alternatively, rearrangement of copper complex 27 to σ-allyl copper complex 29 would result in the formation of α-alkylated product 24 via an S\textsubscript{N}2 pathway. Intermediate 27 will also be in equilibrium with its rotamer 27′ and depending on the rate of the equilibrium this could result in loss of stereocchemical information. Since products 24 and 24′ are diastereoisomers, the ratio between them will be determined by the Curtin-Hammet principle. In our synthetic approach, selective α-substitution producing product 24 with retained enantiomeric excess was desired (Scheme 18).
4.2 Results and discussion

4.2.1 Substrate synthesis

A straightforward two-step procedure providing high overall yields was applied for the preparation of cyclic allylic alcohols 22a and 22b (Scheme 19). A base-catalyzed crossed aldol condensation reaction using benzaldehyde and cyclopentanone (n = 1) or cyclohexanone (n = 2) as coupling partners was the first step. The products were obtained in moderate to high yields after purification by vacuum distillation. In the second step the keto-function was selectively reduced using NaBH₄. The reduction provided excellent yields of allylic alcohols 22a and 22b.

Scheme 18. Different mechanistic pathways for the Cu-catalyzed allylic substitution reaction.
Scheme 19. Two-step approach for the synthesis of cyclic allylic alcohols 22a-b.

4.2.2 DKR of allylic alcohols

As mentioned earlier, the DKR of allylic alcohol 22b, utilizing ruthenium catalyst 2 for the racemization and CALB for the enzymatic resolution has been published previously by our research group. These DKR conditions were found to be applicable for substrate 22a as well (Table 5). Both the acetylated products (R)-23a and (R)-23b were obtained in high isolated yields and with excellent enantiomeric excess (>99%).

Table 5. DKR of cyclic allylic alcohols 22a-b.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Conv. (%)</th>
<th>Yield (%)</th>
<th>ee (R)-23 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>22a</td>
<td>&gt;99</td>
<td>76</td>
<td>&gt;99</td>
</tr>
<tr>
<td>2</td>
<td>22b</td>
<td>&gt;99</td>
<td>84</td>
<td>&gt;99</td>
</tr>
</tbody>
</table>

a) Reaction conditions: rac-22 (2.0 mmol), Ru-cat 2 (64 mg, 5 mol%), CALB (12 mg), t-BuOK (5 mol%), Na2CO3 (2 mmol) and isopropenyl acetate (3.0 mmol) in dry toluene (4.0 mL) under argon for 48 h. b) Determined by 1H NMR spectroscopy. c) Isolated yield. d) Determined by chiral HPLC.

4.2.3 Cu-catalyzed allylic substitution

Using a previously published procedure, some different conditions for the Cu-catalyzed allylic substitution reaction were investigated. As a starting point, the reactions were performed on rac-23 with commercially available Grignard reagent MeMgBr. Using 1.5 equiv of MeMgBr and 20 mol% of CuCl in dry THF, 35% conversion to product 24 was observed. Under these conditions 15% of alcohol 22 was also formed, most likely due to attack of MeMgBr on the ester function. Furthermore, 50% of unreacted starting
material 23 was recovered. The same reaction conditions were evaluated using Et$_2$O as solvent instead of THF, but the reaction was much slower. Therefore, THF was chosen as the solvent for further optimization. Addition of 2.5 equiv of MeMgBr resulted in higher conversion but with a worse product to alcohol ratio. In the initial reactions the Grignard reagent was added to a mixture of the substrate and the copper salt in THF at 0 °C. After a closer look at the mechanism (Scheme 18), we thought that it would be better to first let the Grignard reagent react with the copper salt, to ensure formation of only dialkylcuprates, and then add the substrate. It was found that this method resulted in higher conversion and a better product to byproduct ratio.

Table 6. Cu-catalyzed allylic substitution reactions.

<table>
<thead>
<tr>
<th>Entry$^a$</th>
<th>Substrate</th>
<th>Product</th>
<th>R</th>
<th>Yield (%)$^b$</th>
<th>$\alpha:\gamma$(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(R)-23a</td>
<td>(S)-24a</td>
<td>Me</td>
<td>86</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>(R)-23a</td>
<td>(S)-24b</td>
<td>Et</td>
<td>64</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>(R)-23a</td>
<td>(S)-24c</td>
<td>Ph</td>
<td>88</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>(R)-23a</td>
<td>(S)-24d</td>
<td>4-MeOC$_6$H$_4$</td>
<td>86</td>
<td>90:10</td>
</tr>
<tr>
<td>5</td>
<td>(R)-23a</td>
<td>(S)-24e</td>
<td>CH$_3$(CH$_2$)$_4$</td>
<td>82</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>(R)-23a</td>
<td>(S)-24f</td>
<td>(CH$_3$)$_2$CH(CH$_2$)$_3$</td>
<td>76</td>
<td>81:19</td>
</tr>
<tr>
<td>7</td>
<td>(R)-23b</td>
<td>(S)-24g</td>
<td>Me</td>
<td>74</td>
<td>65:35</td>
</tr>
<tr>
<td>8</td>
<td>(R)-23b</td>
<td>(S)-24h</td>
<td>Ph</td>
<td>75</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>(R)-23b</td>
<td>(S)-24i</td>
<td>CH$_3$(CH$_2$)$_4$</td>
<td>76</td>
<td>74:26</td>
</tr>
<tr>
<td>10</td>
<td>(R)-23b</td>
<td>(R)-24j$^d$</td>
<td>(CH$_3$)$_2$CH(CH$_2$)$_3$</td>
<td>78</td>
<td>77:23</td>
</tr>
</tbody>
</table>

$^a$) Reaction conditions: (R)-23 (1 equiv) was added to a solution of RMgX (2.5 equiv) and CuCl (20 mol%) in dry THF at 0 °C. $^b$) Isolated yields. $^c$) The $\alpha:\gamma$ ratio was determined by $^1$H NMR spectroscopy. In the cases not indicated the reactions were $\alpha$-selective (>97% $\alpha$). $^d$) (S) changes to (R) because of the sequential rule.
DKR products \((R)-23a\) and \((R)-23b\) were subjected to Cu-catalyzed allylic substitution with a variety of different Grignard reagents (Table 6). The Grignard reagent (2.5 equiv) and CuCl (20 mol%) were stirred together in dry THF for 30 min. The substrate was thereafter added to the reaction dropwise at 0 °C. Using this methodology, the products were obtained with full inversion of stereochemistry in moderate to high isolated yields. In several cases the reaction was fully \(\alpha\)-selective (Table 6, Entries 1-3, 5 and 8). However, some of the \(\gamma\)-alkylated products were also formed when sterically hindered and more electron-rich Grignard reagents were employed (Table 6, Entries 4, 6-7, 9-10). The 5-membered ring substrate \((R)-23a\) was found to produce a slightly better \(\alpha:\gamma\) ratio.

4.2.4 Synthesis of ketone derivatives

Selected products from the Cu-catalyzed allylic substitution reaction (Table 6) were transformed into the corresponding \(\alpha\)-substituted ketone derivatives 25 (Table 7) by cleavage of the carbon-carbon double bond.

**Table 7. Oxidative cleavage of the carbon-carbon double bond.**

\[
\begin{array}{cccccc}
\text{Entry}\text{a} & \text{Substrate} & n & R & \text{Product} & \text{Yield} (\%)\text{b} & \text{ee} (\%) \\
1 & (S)-24a & 1 & \text{Me} & (S)-25a & 69^c & 94^d \\
2 & (S)-24b & 1 & \text{Et} & (S)-25b & 74 & >99^e \\
3 & (S)-24c & 1 & \text{Ph} & (R)-25c & 89 & 97^e \\
4 & (S)-24h & 2 & \text{Ph} & (R)-25d & 73 & 98^d \\
5 & (R)-24j & 2 & (\text{CH}_3)_2\text{CH(CH}_2)_2 & (R)-25e & 82 & >99^f \\
\end{array}
\]

a) NaIO\(_4\) (5 equiv) and RuCl\(_3\)\(x\)H\(_2\)O (ca. 1 mol%) was added to \((S)-24\) (1 equiv) dissolved in a 1:1:2 DCM/CH\(_3\)CN/H\(_2\)O mixture at room temperature. b) Isolated yields except for entry 1. c) Yield determined by GC using decane as internal standard. d) Determined by chiral GC. e) Determined by chiral HPLC. f) Determined by chiral GC after transformation to the lactone derivative.

Oxidative cleavage of the carbon-carbon double bond was performed using the established Sharpless procedure.\(^{140}\) The ketone derivatives 25 were obtained by employing RuCl\(_3\)\(x\)H\(_2\)O (1 mol%) as catalyst and NaIO\(_4\) (5
equiv) as oxidant. Purification by flash chromatography afforded the ketones 25 in moderate to high isolated yields. In some cases racemization of the stereogenic center was observed, especially for the substrates with aromatic substituents in the α-position. However, the products could be obtained with almost retained enantiomeric excess by carefully controlling the reaction times. These reactions were quenched near full conversion affording the products (R)-25c and (R)-25d with 97 and 98% ee, respectively (Table 7, Entries 3-4). No racemization was observed for substrates (S)-25b and (R)-25e (Table 7, Entries 2 and 5).

4.2.5 Synthetic application

The corresponding lactone derivatives of the ketones from Table 7 are easily accessed by employing meta-chloroperoxybenzoic acid (m-CPBA) in a Baeyer-Villiger oxidation. As a synthetic application, ketone (R)-25e was used in natural product synthesis of (R)-10-methyl-6-undecanolide, (R)-26. The latter compound is a caprolactone recently isolated from a marine streptomycete.141 This caprolactone has shown promising activity against several human cancer cell lines, with concomitant low general cytotoxicity.141 After oxidation with m-CPBA (2 equiv), lactone (R)-26 was isolated by flash chromatography in 90% yield and with excellent enantiomeric excess (>99% ee) (Scheme 20).

![Scheme 20. Synthesis of (R)-10-methyl-6-undecanolide, (R)-26.](image-url)
4.3 Conclusion

As ketones and lactones are useful building blocks in organic synthesis and occur as structural elements in many natural products, methods for their enantioselective preparation are highly desired. In this project, we have developed a highly efficient and general method for the synthesis of enantioenriched $\alpha$-substituted ketones and their corresponding lactone derivatives, utilizing dynamic kinetic resolution (DKR) and Cu-catalyzed $\alpha$-allylic substitution as the key steps.

In the enantiodetermining step, DKR of exocyclic allylic alcohols was performed with $\text{Ru(CO)}_2\text{Cl} (\eta^5\text{C}_5\text{Ph}_5)$ for the racemization and *Candida antarctica* lipase B (CALB) for the enzymatic resolution. The DKR protocol afforded the corresponding exocyclic allylic acetates in high yields and with excellent enantiomeric excess (>99% ee). Subsequent Cu(I)-catalyzed allylic substitution was performed with different Grignard reagents. High yields of the products were obtained (64-86%) with complete inversion of stereochemistry. Selective $\alpha$-substitution was generally obtained, except for in the reactions with sterically hindered and electron-rich Grignard reagents, where some $\gamma$-alkylation was also observed. The products obtained in the substitution reaction were further transformed into the ketone derivatives by oxidative cleavage of the carbon-carbon double bond with $\text{RuCl}_3 \cdot \text{xH}_2\text{O}$ (1 mol%) and $\text{NaIO}_4$. High yields of the $\alpha$-substituted ketone derivatives (69-89%) were obtained and with retained or nearly retained enantiomeric excess. One of the ketone derivatives was also subjected to Baeyer-Villiger oxidation with *meta*-chloroperoxybenzoic acid, which provided a high yield (90%) and excellent ee (>99%) of (R)-10-methyl-6-undecanolide, a natural product which has shown promising activity against several human cancer cell lines.
5. Dynamic Kinetic Resolution of Homoallylic Alcohols: Application to the Synthesis of Enantiomerically Pure 5,6-Dihydropyran-2-ones and δ-Lactones (Paper V)

5.1 Introduction

Homoallylic alcohols are useful as intermediates for further organic synthesis, hence methods to prepare them in their enantiomerically pure form are highly desired. Various techniques for synthesizing enantiopure homoallylic alcohols include asymmetric allylation of aldehydes, asymmetric reduction, enzymatic kinetic resolution and dynamic kinetic resolution.

In 2011, the groups of Kanerva and Leino reported on a DKR of 1-phenyl-3-buten-1-ol that afforded the corresponding acetate in 96% yield and with 95% ee, but the reaction required 168 h to reach completion. Kim and Park developed a DKR utilizing an ionic-surfactant-coated Burkholderia cepacia lipase (ISCBCL) in 2011, applicable to a few homoallylic alcohol substrates, providing the products in 95-98% ee.

Chiral homoallylic alcohols are valuable precursors for the synthesis of enantiomerically pure 5,6-dihydropyran-2-ones and δ-lactones. These structural elements are abundant in many natural products and have been shown to have various important biological and pharmaceutical effects (Figure 13).

![Figure 13. Some examples of naturally occurring 5,6-dihydropyran-2-ones and δ-lactones.](image)

The aim of this project was to develop an efficient DKR protocol, applicable to a wide range of homoallylic alcohol substrates, utilizing ruthenium catalyst 2 for the racemization and a lipase for the enzymatic
resolution. Furthermore, we aimed to utilize the DKR products as precursors to obtain enantiomerically pure 5,6-dihydropyran-2-ones and their corresponding \( \delta \)-lactones via a general and short synthetic sequence (Scheme 21).

\[
\begin{array}{ccc}
\text{R} & \text{OH} & \text{DKR} \\
& & \text{Ru-cat. 2/CALB} \\
\text{30} & \text{OAc} & \text{Base} \\
& \text{R} & \text{OH} \\
\text{31} & \text{30} & \\
\end{array}
\]

\[
\begin{array}{ccc}
\text{Cl} & \text{O} & \text{O} \\
& \text{R} & \text{RCM} \\
\text{32} & \text{Grubbs Ru-cat.} & \\
& \text{O} & \text{Reduction} \\
\text{33} & \text{34} & \\
\end{array}
\]

**Scheme 21.** Synthetic strategy towards enantioenriched 5,6-dihydropyran-2-ones, 33 and \( \delta \)-lactones, 34.

5.2 Results and discussion

5.2.1 Synthesis of homoallylic alcohols

The racemic homoallylic alcohol substrates 30a-n were prepared by the Grignard addition of allylmagnesium chloride (1.2 equiv) to commercially available aldehydes (1 equiv) (Scheme 22). The products were obtained in good to high yields after purification by flash chromatography.

**Scheme 22.** Synthesis of racemic homoallylic alcohols 30a-n.

5.2.2 Racemization of homoallylic alcohols

First, the racemization of substrate (\( \delta \))-30a catalyzed by ruthenium catalyst 2 was investigated. Since the racemization of substrates with carbon-carbon double bonds is previously known to be inhibited by coordination of the double bond to ruthenium,\(^{110}\) the reaction was also studied at elevated temperature. Racemization reactions were performed at 20, 40 and 70 °C in dry toluene, using 5 mol% of catalyst 2 (Table 8). At room temperature the
racemization was much too slow, as (S)-30a still exhibits an ee value of 81% after 2 h of reaction time (Table 8, entry 1). When the temperature was raised to 40 °C, the racemization reaction was faster (Table 8, entry 2). At 70 °C the substrate was almost fully racemized within 10 min (Table 8, entry 3), which should be sufficient for a successful DKR.

**Table 8. Racemization study on (S)-30a at 20, 40 and 70 °C.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temp (°C)</th>
<th>Time (min)</th>
<th>ee 30a (%)</th>
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<tbody>
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</tr>
<tr>
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<td>120</td>
<td>81</td>
</tr>
<tr>
<td>2</td>
<td>40</td>
<td>30</td>
<td>64</td>
</tr>
<tr>
<td></td>
<td></td>
<td>60</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td></td>
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<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>60</td>
<td>3</td>
</tr>
</tbody>
</table>

a) Reaction conditions: (S)-30a (1.0 mmol), Ru-cat. 2 (0.05 mmol), t-BuOK (0.5 M solution in THF, 0.05 mmol) in dry toluene (2 mL). b) Determined by chiral GC after derivatization to the acetate rac-31 with Ac₂O, Et₃N and cat. DMAP.

5.2.3 Enzymatic kinetic resolution of homoallylic alcohols

Next, a few commercially available lipases were investigated for the enzymatic reaction. Out of the enzymes tested, *Candida antarctica* lipase B (CALB) showed the highest activity in the transesterification reaction, which reached 50% conversion in 22 h at 70 °C. Following the results from the racemization study, we also determined the E-value for a few of the substrates with CALB at 70 °C (Table 9). High E-values were obtained for the substrates tested, indicating a highly selective enzymatic reaction.
Table 9. Enzymatic kinetic resolution of homoallylic alcohols with CALB.

\[
\text{OH} \quad \text{CALB, Na}_2\text{CO}_3 \quad \text{isopropenyl acetate} \quad \text{toluene, 70 °C} \rightarrow \quad \text{OH} \\
(rac-30) \quad \text{R} \quad (S)-30 \quad \text{OAc} \\
\quad \text{R} \quad (R)-31
\]

<table>
<thead>
<tr>
<th>Entry(^a)</th>
<th>Substrate</th>
<th>Time (h)</th>
<th>(R)-31 (%)(^b)</th>
<th>ee (R)-31 (%)(^c)</th>
<th>E(^d)</th>
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<td>47</td>
<td>&gt;99</td>
<td>&gt;200 (581)</td>
</tr>
<tr>
<td>2</td>
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<td>46</td>
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<td>183</td>
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<tr>
<td>3</td>
<td><img src="image3.png" alt="Substrate" /></td>
<td>2.5</td>
<td>42</td>
<td>98</td>
<td>&gt;200 (211)</td>
</tr>
</tbody>
</table>

\(^a\) Reaction conditions: rac-30 (0.2 mmol), Na\(_2\)CO\(_3\) (0.2 mmol), CALB (16 mg) and isopropenyl acetate (0.32 mmol) in dry toluene (0.4 mL) at 70 °C. \(^b\) Determined by \(^1\)H NMR spectroscopy. \(^c\) Determined by chiral GC. \(^d\) Calculated E-value.

5.2.4 Dynamic kinetic resolution of homoallylic alcohols

The combination of the enzymatic resolution and the racemization in DKR looked promising based on the results from the separate investigations of these parameters. The DKR reactions were performed on various different homoallylic alcohol substrates 30a-n (1 mmol scale) with ruthenium catalyst 2 (5.0 mol%) at 70 °C. In many of the cases, the acylated products were obtained in high yields after 12-48 h, and with good to excellent ee values (Table 10).
Table 10. Dynamic kinetic resolution of homoallylic alcohols.

<table>
<thead>
<tr>
<th>Entry&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Substrate</th>
<th>Time (h)</th>
<th>Yield (R)-31 (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>ee (R)-31 (%)&lt;sup&gt;c&lt;/sup&gt;</th>
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<td>12</td>
<td>99 (84)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>&gt;99</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="Substrate 30b" /></td>
<td>24</td>
<td>99 (74)</td>
<td>98</td>
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<td><img src="image" alt="Substrate 30d" /></td>
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<td>99 (83)</td>
<td>&gt;99</td>
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<td>5</td>
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<td>99 (86)</td>
<td>&gt;99</td>
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<td><img src="image" alt="Substrate 30f" /></td>
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<td>99 (88)</td>
<td>&gt;99</td>
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<td>9</td>
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<td>92 (88)</td>
<td>96</td>
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<tr>
<td>10</td>
<td><img src="image" alt="Substrate 30j" /></td>
<td>18</td>
<td>99 (92)</td>
<td>90</td>
</tr>
</tbody>
</table>
a) Reaction conditions: rac-(30) (1 mmol), Ru-cat. 2 (0.050 mmol), t-BuOK (0.050 mmol), CALB (10-100 mg), Na$_2$CO$_3$ (1 mmol) and isopropenyl acetate (1.5 mmol) in dry toluene (2 mL) at 70 °C under argon. b) Determined by $^1$H NMR spectroscopy. Isolated yield after chromatography in parentheses. c) Determined by chiral GC or HPLC. d) 5 mmol scale. e) The reaction was run at room temperature. f) 4-oxo-6-phenyl-1-hexene was obtained. g) (R) changes to (S) because of the sequential rule.

DKR of the model substrate 30a afforded (R)-1-acetoxy-1-phenyl-3-butenene ((R)-31a) in 79% isolated yield and with 99% ee after 24 h. This reaction was also performed on a 5 mmol scale, which afforded an 84% yield of the enantiopure product (R)-31a (Table 10, entry 1). Substrates with electron-withdrawing substituents on the aromatic ring were shown to give excellent results (Table 10, entries 4-6) but electron-deficient substituents were moderately tolerated (Table 10, entry 3). Substituents in the para-position on the aromatic ring were compatible with this catalytic system (Table 10, entries 2-6), whereas ortho-substituted aromatic rings gave very poor results, most probably due to steric factors (Table 10, entries 7-8). The 2-naphthyl aromatic system was favoured over the 1-naphtyl, and the DKR of the former substrate afforded a 72% yield of the product (R)-31i with 96% ee (Table 10, entry 9). Two heterocyclic substrates also provided good results in the DKR reaction (Table 10, entries 10-11). Furthermore, the benzylic homoallylic alcohol 30l was shown to be compatible with the DKR conditions (Table 10, entry 12), affording the product (R)-31l in 86% yield and with 96% ee. For the homoallylic alcohol 30m that also contained an allylic functionality, the isomerized ketone was obtained as the only product (Table 10, entry 13). Aliphatic substrates where the small group is larger than ethyl and/or functionalized are not usually tolerated by this procedure, so we were pleased to find that a good result was obtained for aliphatic substrate 30n (Table 10, entry 14).
5.2.5 Synthetic application

As a synthetic application we devised a short reaction sequence to obtain enantioenriched 5,6-dihydropyran-2-ones and their corresponding δ-lactone derivatives (Scheme 23).

Scheme 23. Synthetic application.

Hydrolysis of (R)-1-acetoxy-1-phenyl-3-butene ((R)-31a) with K₂CO₃ at room temperature afforded the corresponding enantiopure homoallylic alcohol (R)-30a in nearly quantitative yield. Subsequent DMAP-catalyzed acylation with acryloyl chloride and Et₃N provided a moderate yield of the ring-closing metathesis (RCM) precursor (R)-32a after purification by flash chromatography. Both Grubbs 1st and 2nd generation ruthenium catalysts were investigated in the RCM reactions, which were performed with 10 mol% of catalyst in dry DCM at 55 °C. Since equal results were obtained with both catalysts, the cheaper 1st generation catalyst was employed for further reactions. The 5,6-dihydropyran-2-one (R)-33a was obtained in 86% yield and with 97% ee after purification by flash chromatography. Wilkinson’s rhodium catalyst, RhCl(PPh₃)₃ was found to be highly selective in the reduction of the carbon-carbon double bond. The reaction was performed with 2.5 mol% of catalyst in benzene under H₂ atmosphere (1 atm). The δ-lactone (R)-34a was obtained after purification through a short pad of silica in 85% yield and with 97% ee.
5.3 Conclusion

Enantioselective synthesis of 5,6-dihydropyran-2-ones and their corresponding δ-lactones has attracted considerable interest due to the natural abundance of these structures and their biological and medicinal properties. Homoallylic alcohols are common synthetic precursors to obtain these compounds.

In this project, we have developed an efficient and general dynamic kinetic resolution (DKR) for a wide range of homoallylic alcohol substrates. The protocol utilized Ru(CO)$_2$Cl($\eta^5$-C$_5$Ph$_5$) for the racemization and Candida antarctica lipase B (CALB) for the enzymatic resolution. It was found to be applicable to a wide range of aromatic homoallylic alcohols, with both activating and deactivating groups on the aromatic ring. para-Substituted aromatic systems were highly favored over ortho-substituted ones, most likely due to steric factors. Heterocyclic substrates were found to be compatible with this catalytic system, as well as one aliphatic substrate. The acetylated products were obtained in high yields and with high to excellent enantiomeric excess (90-99% ee) within 48 h.

A short reaction sequence was also applied to the model substrate (R)-1-acetoxy-1-phenyl-3-butene. Deprotection by basic hydrolysis and subsequent acylation with acryloyl chloride afforded the ring-closing metathesis (RCM) precursor. RCM catalyzed by Grubbs 1st generation catalyst afforded (R)-6-phenyl-5,6-dihydro-2H-pyran-2-one in 86% yield and with 97% ee. After selective reduction of the carbon-carbon double bond with Wilkinson’s catalyst, the corresponding (R)-6-phenyltetrahydro-2H-pyran-2-one was obtained in 85% yield and with 97% ee.
6. Highly Efficient Route for Enantioselective Preparation of Chlorohydrins via Dynamic Kinetic Resolution (Paper VI)

6.1 Introduction

Enantiomerically enriched β-chlorohydrins are versatile synthetic precursors that can be employed in the asymmetric synthesis of epoxides, β-aminoalcohols, pyrrolidines, and functionalized cyclopropanes. Epoxides are highly reactive synthetic precursors which in turn can be converted into a wide range of products, for example β-aminoalcohols. Two examples of the latter are Propranolol and Norepinephrine, both pharmaceutically important compounds that target the adrenergic receptors in our bodies. The former compound is used for treatment of cardiovascular diseases, while the latter compound is an important neurotransmitter acting in the central nervous system (CNS) (Figure 14).

Other methods reported for the synthesis of chiral β-chlorohydrins that provide high enantiomeric excess include asymmetric hydroboration, (transfer) hydrogenation, and biocatalytic reduction of α-chloroketones. Furthermore, kinetic resolution and dynamic kinetic resolution of β-halohydrins has been studied previously. In 2002, our group reported on a DKR protocol effective for a few β-chlorohydrins utilizing Shvo’s catalyst combined with Pseudomonas cepacia lipase (PS-C II). Since the development of ruthenium catalyst has greatly improved the racemization of sec-alcohols, making it highly efficient at ambient temperature, the aim of this project was to improve the DKR for β-chloroalcohols and apply it to a wider range of substrates than previously reported. Our suggested synthetic
route allows for enantiomerically pure epoxides and β-aminoalcohols to be easily synthesized in a few steps from the corresponding racemic β-chloroalcohols, utilizing DKR in the enantiodetermining step (Scheme 24).

**Scheme 24.** Suggested synthetic route towards epoxides and β-aminoalcohols utilizing DKR of β-chloroalcohols in the enantiodetermining step.

6.2 Results and discussion

6.2.1 Substrate synthesis

The simplest chlorohydrin, 2-chloro-1-phenylethanol (35a) was commercially available. The rest of the racemic β-chlorohydrins were prepared according to different methods depending on the accessible starting materials. Simple reduction of the corresponding ketone with NaBH₄ gave high yields, and was used to prepare substrates 35b-d (Scheme 25).

**Scheme 25.** NaBH₄ reduction of α-chloro ketones.

Cu-catalyzed ring-opening of the corresponding commercially available epoxide precursors was another straightforward method, which afforded chlorohydrins 35e-f in high yields (Scheme 26).

**Scheme 26.** Cu-catalyzed ring-opening of epoxides.
Another synthetic method used was the Friedel-Crafts acylation\textsuperscript{165} (Scheme 27). The selectivity of this reaction is dependant on the directing effect of the substituents already present on the aromatic ring. In this case, moderate selectivity for the desired \textit{para}-substituted product over the \textit{ortho}-substituted product was observed with the former as the major product. The small amounts of \textit{ortho}-substituted product that were formed could be separated by flash chromatography and were not investigated further in this study. The ketones obtained by Friedel-Crafts acylation were subsequently reduced by NaBH\textsubscript{4}, to give chlorohydrins 35g-h (Scheme 27).

\begin{scheme}
\centering
\includegraphics[width=\textwidth]{scheme27}
\caption{Friedel-Crafts acylation followed by NaBH\textsubscript{4} reduction.}
\end{scheme}

Some commercially available substituted acetophenones were subjected to direct \textit{\alpha}-chlorination using \textit{N}-chlorosuccinimide (NCS).\textsuperscript{166} Low to moderate yields of the products were obtained due to incomplete conversion and byproduct formation. The byproduct was identified as the bis-chlorinated ketone. However, isolation of the desired mono-chlorinated product was possible by flash chromatography. Again, reduction of the obtained ketones by NaBH\textsubscript{4} afforded the \textit{\beta}-chlorohydrins 35i-k (Scheme 28).

\begin{scheme}
\centering
\includegraphics[width=\textwidth]{scheme28}
\caption{Direct chlorination of with NCS followed by NaBH\textsubscript{4} reduction.}
\end{scheme}

In order to circumvent the problem with the bis-chlorinated byproducts, an alternative synthetic method was devised. The two-step approach began with oxytosylation\textsuperscript{167} at the \textit{\alpha}-position of the ketone with Koser’s reagent (hydroxyl(tosyloxy)iodobenzene),\textsuperscript{168} and subsequent \textit{S}_\text{N}2 displacement of the oxytosylate group was performed using MgCl\textsubscript{2}\textsuperscript{169} (Scheme 29). The \textit{\alpha}-chloro ketone formed was then reduced using the standard method with NaBH\textsubscript{4}. This revised approach provided high yields for all the steps and none of the bis-chlorinated byproduct was observed. Also, no workup or purification was needed between the oxytosylation and the chlorination steps.

53
Scheme 29. Oxytosylation and chlorination followed by NaBH₄ reduction.

6.2.2 Kinetic resolution of β-chlorohydrins

According to previous work on β-chlorohydrins performed in our group, two lipases, *Pseudomonas cepacia* lipase and *Candida antarctica* lipase B (CALB) have shown to be selective in the kinetic resolution. The former lipase was chosen for this project since CALB displayed a much slower reaction. Utilizing PS-C “Amano” II, the selectivity of the enzymatic transformation, i.e. the E-value, was determined for a few of the β-chlorohydrins at room temperature (Table 11). The E-values were calculated from the ee of the product and the ee of the remaining alcohol substrate, according to equation 3 (Section 1.6).

Excellent selectivity was observed for the substrates with aromatic groups (Table 11, entries 1 and 3-6). The presence of both electron-donating and electron-withdrawing groups on the aromatic ring was tolerated and did not influence the selectivity. For the aliphatic substrate rac-35f (Table 11, entry 2) poor selectivity was observed. Two other lipases, PS-C “Amano” I and PS-D “Amano” II were also evaluated for this substrate, but showed no improvement of the selectivity.

The E-value of substrate 35e was also determined at higher temperature (Table 11, entry 1) since the racemization of this substrate is slow at room temperature (*vide infra*). A dramatic decrease in E-value to 81 was observed for the enzymatic resolution at 80 °C. However, this selectivity factor should be sufficient for an efficient DKR, provided that the racemization is fast enough."
Table 11. Kinetic resolution of a few β-chlorohydrins.

<table>
<thead>
<tr>
<th>Entry&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Substrate</th>
<th>Time (h)</th>
<th>Conv (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>ee (S)-36 (%)&lt;sup&gt;c&lt;/sup&gt;</th>
<th>ee (R)-35 (%)&lt;sup&gt;c&lt;/sup&gt;</th>
<th>E&lt;sup&gt;b&lt;/sup&gt;</th>
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<tr>
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<td>&gt;300</td>
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<td>46</td>
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<td>(80 °C)&lt;sup&gt;e&lt;/sup&gt;</td>
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<td>3</td>
<td>40</td>
<td>&gt;99</td>
<td>65</td>
<td>&gt;300</td>
</tr>
</tbody>
</table>

a) Reaction conditions: rac-35 (0.5 mmol), Na₂CO₃ (0.5 mmol), PS-C “Amano” II (25 mg) and isopropenyl acetate (1.0 mmol) in dry toluene (1 mL). b) Calculated from the values of enantiomeric excess for the (S)-acetate and the (R)-alcohol. c) Determined by chiral GC. d) Determined by chiral HPLC. e) PS-C “Amano” II (2.5 mg/mmol) at 80 °C.

6.2.3 Racemization of β-chlorohydrins

For a few of the β-chlorohydrin substrates the rate of racemization was also investigated (Table 12). Using 5 mol% of ruthenium catalyst 2, 2-chloro-1-phenylethanol (R)-35a was fully racemized within 5 min at room temperature (Table 12, entry 1). For substrate (R)-35b with the presence of an electron-withdrawing substituent on the aromatic ring, the racemization was found to be equally efficient (Table 12, entry 2). However, electron-rich
substrate (R)-35e exhibited a much slower racemization. An ee value of 30% was measured after 120 min at ambient temperature (Table 12, entry 3). The combination of this racemization with an enzymatic resolution in DKR would give very poor results. As elevated temperature is known to speed up the rate of racemization, the same reaction was also evaluated at 60 and 80 °C. Indeed, at 80 °C, the substrate was almost fully racemized within 5 min.

**Table 12. Racemization study on a few β-chloroalcohols.**

<table>
<thead>
<tr>
<th>Entry&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Substrate</th>
<th>Time (min)</th>
<th>Temp. (°C)</th>
<th>ee (R)-35 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(R)-35a</td>
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<td>(R)-35b</td>
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<td>25</td>
<td>0&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>3</td>
<td>(R)-35e</td>
<td>120</td>
<td>25</td>
<td>30&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
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<td></td>
<td></td>
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<td>60</td>
<td>5&lt;sup&gt;c&lt;/sup&gt;</td>
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<td></td>
<td></td>
<td>5</td>
<td>80</td>
<td>5&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reaction conditions: (R)-35 (0.3 mmol), Ru-cat 2 (0.015 mmol), t-BuOK (0.03 mmol) and Na₂CO₃ (0.3 mmol) in dry toluene (0.6 mL). <sup>b</sup> Determined by chiral GC. <sup>c</sup> Determined by chiral HPLC.

6.2.4 Dynamic kinetic resolution of β-chlorohydrins

The separate investigations on the enzymatic resolution and the racemization showed promising results for combination in a successful DKR. After some further optimization of the one-pot reaction conditions, DKR of 2-chloro-1-phenylethanol 35a reached full conversion within 24 h at ambient temperature. (S)-36a was obtained in 95% isolated yield and with >99% ee (Table 13, entry 1). Using the same optimized DKR conditions, a variety of different β-chlorohydrins were investigated (Table 13).
Table 13. Dynamic kinetic resolution of β-chloroalcohols.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Time (h)</th>
<th>Yield (%)&lt;sup&gt;b,c&lt;/sup&gt;</th>
<th>ee (S)-36 (%)&lt;sup&gt;b&lt;/sup&gt;</th>
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</thead>
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<td>&gt;99 (95)</td>
<td>&gt;99</td>
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<td>4&lt;sup&gt;d&lt;/sup&gt;</td>
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<td>99 (86) (80 °C)</td>
<td>98</td>
</tr>
<tr>
<td>5&lt;sup&gt;e&lt;/sup&gt;</td>
<td>35e</td>
<td>48</td>
<td>84</td>
<td>92&lt;sup&gt;f&lt;/sup&gt; (90 °C)</td>
</tr>
<tr>
<td>6</td>
<td>35g</td>
<td>24</td>
<td>97 (90)</td>
<td>&gt;99</td>
</tr>
<tr>
<td>7</td>
<td>35h</td>
<td>22</td>
<td>&gt;99</td>
<td>&gt;99</td>
</tr>
<tr>
<td>8</td>
<td>35i</td>
<td>48</td>
<td>&gt;99</td>
<td>98</td>
</tr>
<tr>
<td>9</td>
<td>35j</td>
<td>24</td>
<td>&gt;99</td>
<td>98</td>
</tr>
</tbody>
</table>
a) Conditions: rac-35 (0.5 mmol), Na₂CO₃ (0.5 mmol), PS-C “Amano” II (25 mg), Ru-cat 2 (0.025 mmol), t-BuOK (0.05 mmol) and isopropenyl acetate (1.0 mmol) in dry toluene (1.0 mL). b) Determined by chiral GC. c) Isolated yield in parenthesis. d) rac-35d (10 mmol), Na₂CO₃ (2 mmol), PS-C “Amano” II (120 mg), Ru-cat 2 (0.05 mmol), t-BuOK (0.05 mmol) and isopropenyl acetate (15 mmol) in dry toluene (5.0 mL). e) PS-C “Amano” II (2.5 mg/mmoll). f) Determined by chiral HPLC.

The DKR was very effective for different aromatic β-chlorohydrins with both activating and deactivating groups on the aromatic moiety. The products were obtained in high yields and with excellent ee values (>99%) in many cases (Table 13, entries 1-3, 6-7 and 11-12). Elevated temperature was required in order to speed up the racemization for the substrates with highly electron-withdrawing groups on the aromatic ring. However, the selectivity of the enzyme at 60-80 °C is still high and the products were obtained with 98% ee (Table 13, entries 4 and 8-10). For 1-chloro-3-phenoxypropan-2-ol 35e, the racemization was too slow compared to the enzymatic resolution at room temperature (vide supra). The reaction was performed at elevated temperature and it was found that the best results concerning yield and ee value were obtained at 90 °C (Table 13, entry 5).

6.2.5 Synthetic applications

All the products from Table 13 are important precursors for chiral epoxides. To prove the synthetic utility of the DKR method, a few of the chiral β-chloro acetates were transformed to the corresponding epoxides 37. With the halogen readily acting as a leaving group, the epoxides were obtained after short reaction times (5-30 min) by treatment of acetates (S)-36 with LiOH in EtOH at room temperature. The products were isolated by flash chromatography in high yields and with retained or nearly retained enantiomeric excess (Table 14).
Table 14. Base-induced epoxide formation.

\[
\text{(S)-36} \rightarrow \text{(S)-37}
\]

<table>
<thead>
<tr>
<th>Entry (^a)</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield (^b) (%)</th>
<th>ee (S)-37 (^c) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>((\text{S)-36a}))</td>
<td>((\text{S)-37a}))</td>
<td>87</td>
<td>&gt;98</td>
</tr>
<tr>
<td>2</td>
<td>((\text{S)-36b}))</td>
<td>((\text{S)-37b}))</td>
<td>97</td>
<td>&gt;98</td>
</tr>
<tr>
<td>3</td>
<td>((\text{S)-36g}))</td>
<td>((\text{S)-37g}))</td>
<td>96</td>
<td>99</td>
</tr>
<tr>
<td>4</td>
<td>((\text{S)-36m}))</td>
<td>((\text{S)-37m}))</td>
<td>95</td>
<td>&gt;95</td>
</tr>
</tbody>
</table>

a) Conditions: (S)-36 (1.0 mmol) and LiOH (3.0 mmol) in 95% EtOH (10 mL). The reactions were quenched by addition of NaHCO\(_3\) (6.0 mmol). b) Isolated yields after purification by flash chromatography. c) Determined by chiral HPLC.

As another synthetic application, a large scale DKR (10 mmol) of 2-chloro-1-(3,4-difluorophenyl)ethanol 35d with only 0.5 mol% of Ru-cat 2 was performed. This procedure afforded synthetic intermediate (S)-36d in 99% yield and with 98% ee (Table 13, entry 4). (S)-36d has previously been transformed into pharmaceutically important cyclopropanes (38)\(^{170,171}\) (Scheme 30).

\[
\text{rac-35d} \rightarrow \text{(S)-36d} \rightarrow \text{ref. 170, 171} \rightarrow \text{38}
\]

\(R = \text{CONH}_2\) (ref 170)
\(R = \text{NH}_2\) (ref 171)

Scheme 30. Large scale DKR of 35d and synthetic application of (S)-36d.
6.3 Conclusion

As β-chloroalcohols are useful building blocks in organic synthesis, methods for their enantioselective preparation are highly desired. β-Chloroalcohols are precursors for e.g. epoxides and β-aminoalcohols, the latter compounds being pharmaceutically important motifs.

A general dynamic kinetic resolution (DKR) protocol for β-chlorohydrins has been developed utilizing Pseudomonas cepacia lipase for the enzymatic resolution in combination with highly efficient racemization catalyst Ru(CO)$_2$Cl(η$^5$-C$_5$H$_5$)$_2$. The protocol was found to be successful for a wide range of aromatic β-chlorohydrins, with both activating and deactivating groups on the aromatic ring. The corresponding enantiomerically pure acetates were obtained in high yields (83-99%) and excellent ee values (>99% ee in many cases). For substrates with strongly electron-withdrawing groups, an elevated temperature was needed to speed up the racemization but high selectivity in the enzymatic resolution was still observed.

The synthetic utility of the DKR products was demonstrated by base-induced ring-closure to form epoxides in high yields (87-97%) and with retained or nearly retained enantiomeric excess. Furthermore, a large scale DKR (10 mmol scale) affording a pharmaceutically interesting synthetic intermediate could be performed with only 0.5 mol% loading of racemization catalyst Ru(CO)$_2$Cl(η$^5$-C$_5$H$_5$)$_2$. 
7. Concluding Remarks

An important tool in chemical science is to develop an understanding of reaction mechanisms, as this knowledge gives us power to modify the corresponding chemical transformation to our advantage. Our mechanistic investigations on a cyclopentadienyl ruthenium dicarbonyl catalyst, Ru(CO)$_2$Cl($\eta^5$-C$_5$Ph$_5$) have provided insight into the mechanism for racemization of sec-alcohols. We have also combined this racemization catalyst with an enzymatic resolution leading to several efficient dynamic kinetic resolution (DKR) protocols for a wide range of different sec-alcohols.

We have characterized two diastereomers of an alkoxy carbonyl ruthenium complex by $^1$H NMR, $^{13}$C NMR and in situ FT-IR measurements that had the double bond coordinated to ruthenium and the alcohol oxygen coordinated to one of the CO ligands. The observed inhibition on the rate of racemization for substrates with double bonds provided further confirmation of the importance of a free coordination site on ruthenium for $\beta$-hydride elimination. We have also monitored CO exchange with $^{13}$CO by $^{13}$C NMR spectroscopy for Ru(CO)$_2$Cl($\eta^5$-C$_5$Ph$_5$) and Ru(CO)$_2$(Ot-Bu)($\eta^5$-C$_5$Ph$_5$).

Furthermore, we observed an inhibition effect on the rate of racemization upon addition of CO to the racemization of (S)-1-phenylethanol. Both these experimental observations provide strong support for reversible CO dissociation as a key step in the racemization mechanism for sec-alcohols.

DKR is an important tool for the preparation of enantiomerically pure compounds. We have developed three efficient DKR protocols for different sec-alcohols utilizing Ru(CO)$_2$Cl($\eta^5$-C$_5$Ph$_5$) for the racemization and a lipase for the enzymatic resolution. First, DKR of exocyclic allylic alcohols coupled to a tandem Cu-catalyzed allylic substitution provided a general and efficient route to prepare enantiomerically pure $\alpha$-substituted ketones and their corresponding lactone derivatives. Second, DKR of a wide range of homoallylic alcohols afforded homoallylic acetates in high yields and with high ee values. The enantiopure products were applied to the synthesis of 5,6-dihydropyran-2-ones and their corresponding $\delta$-lactones. Finally, DKR of a wide variety of aromatic $\beta$-chboroalcohols afforded the corresponding $\beta$-chloro acetates in high yields and with excellent ee values. The enantiopure products were further applied to the synthesis of chiral epoxides, which in turn are valuable synthetic intermediates for the preparation of pharmaceutically interesting $\beta$-aminoalcohols.
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*Org. Lett.*, **2008**, *10* (21), pp 4807-4810
Appendix B – Contribution to publications I-VI

**Paper I**  
Performed half of the experimental work. Took a small part in writing the paper.

**Paper II**  
Performed all the experimental work and wrote the article.

**Paper III**  
Performed the major part of the experimental work. Wrote most of the article and the supporting information.

**Paper IV**  
Performed the major part of the synthetic work. Supervised the work performed by diploma worker Anuja Nagendiran. Wrote most of the article and the supporting information.

**Paper V**  
Performed the major part of the synthetic work. Took a small part in supervising diploma workers Suzan Jouda and Grigory Shevchenko. Wrote parts of the article and supporting information.

**Paper VI**  
Performed a minor part of the experimental work
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This thesis is dedicated to the loving memory of my dear father, Gunnar (†2007). You were taken from us too soon but will live on forever in our hearts. Will miss you always and love you forever ♥
References


(2) Pasteur, L. Ann. Ch. Phys. 1848, 24, 442.


(72) Stecher, H.; Faber, K. *Synthesis* **1997**, *1*.
(97) Only two out of the four possible diastereomers were observed [there are three stereogenic centers: the ruthenium, the α-carbon of the alcohol (C2), and one of the coordinated carbons of the alkene (C5)]
(100) Heteronuclear multiple bond correlation spectrum; shows crosspeaks for long-range couplings between protons and carbons.
(107) Only two of the possible four diastereomers were observed. DFT-calculations indicate that the change of the configuration at C5 relative to the configuration at Ru leads a significant energy change. This means that for a given Ru configuration it is energetically favorable to coordinate one face of the alkene whereas coordination of the other face is very unfavored. The two diastereoisomers observed will therefore have the same or opposite absolute configuration at C2 and C5 (2R,5R-2S,5S, or 2R,5S-2S,5R) (Nyhlén, J. unpublished results).

(108) This conclusion is based on the assumption that racemization proceeds via β-hydride elimination. However, other racemization mechanisms are also possible, for example pathways involving CO participation. These include a formyl intermediate, an acyloxy intermediate and a hydroxyl carbene intermediate. In all these alternative mechanisms, the formation of complexes 13a-b would also be expected to inhibit the rate of racemization.

(109) Possible racemization mechanisms involving CO participation:

These pathways have been ruled out on the basis of DFT calculations (Nyhlén, J. Unpublished results)


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