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Otto Långvik

Bio and Chemocatalysis for Stereo and Regioselective One-Pot Reaction Applications

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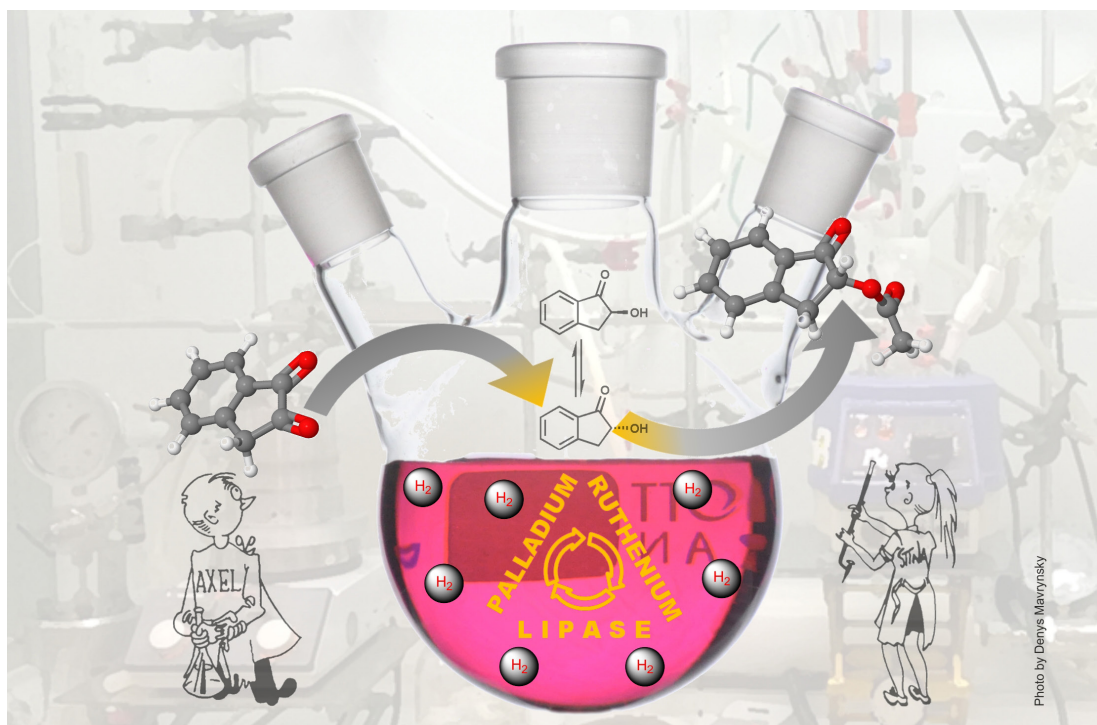
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Bio and Chemocatalysis for Stereo and Regioselective One-Pot Reaction Applications

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Finland
2015

Alice:

"have I gone mad?"

I'm afraid so, but let me tell you something, the best people usually are."

Lewis Carroll, Alice in Wonderland

Till min familj!

Katja, Erik, Ailo och Livia

Preface

I sincerely wish to thank my supervisor professor Reko Leino for giving me the opportunity to explore the beautiful field of Organic Chemistry. I think we both agree that the synthetic route to this particular PhD thesis has not been the shortest possible. I am anyhow very pleased for the interesting journey we have had together.

I am also very grateful to professor Ola Wendt and professor Martin Albrecht for reviewing my thesis and for all the valuable comments I have received. Furthermore, I wish to express my enthusiastic gratitude to professor Osmo Hormi for accepting to act as my opponent.

Acknowledgements and special thanks go to professor Dmitry Murzin, particularly for your exceptionally encouraging and kind attitude. Without your support I would not have started the PhD studies in the first place. Professor Liisa Kanerva is acknowledged for introducing me to the wonderful world of enzyme catalysis. It was fun and educational in many ways to visit your laboratory in PharmaCity. Great thanks are given to all my other co-authors Tiina Saloranta, Denys Mavrynsky, Päivi Mäki-Arvela, Thomas Sandberg, Alexey Kirilin, Arto Liljeblad, Atte Aho and Johan Wärnå. I am very grateful for your help and co-operation.

Exceptional thanks are given to Patrik Eklund. Without your positive smile and encouraging approach to my countless questions I would not have had the energy to drive my research work forward! All the other beautiful Organic Tigers at LOK are of course greatly and equally acknowledged. The time with you has been magic! Some of you I want to mention by name. Many thanks for the time with you Jenny-Maria Brozinski, Yury

Abstract

The development of cost efficient, selective and sustainable chemical processes for production of chiral building blocks is of great importance in synthetic and industrial organic chemistry. One way to reach these objectives is to carry out several reactions steps in one vessel at one time. Furthermore, when this kind of one-pot multi step reactions are catalyzed by heterogeneous chemo- and bio-catalysts, which can be separated from the reaction products by filtration, practical access to chiral small molecules for further utilization can be obtained.

The initial reactions studied in this thesis are the two step dynamic kinetic resolution of *rac*-2-hydroxy-1-indanone and the regioselective hydrogenation of 1,2-indanedione. These reactions are then combined in a new heterogeneously catalyzed one-pot reaction sequence enabling simple recovery of the catalysts by filtration, facilitating simple reaction product isolation. Conclusively, the readily available 1,2-indanedione is by the presented one-pot sequence, utilizing heterogeneous enzyme and transition metal based catalysts, transferred with high regio- and stereoselectivity to a useful chiral vicinal hydroxyl ketone structure.

Additional and complementary investigation of homogeneous half-sandwich ruthenium complexes for catalyzing the epimerization of chiral secondary alcohols of five natural products containing additional non-functionalized stereocenters was conducted. In principle, this kind of epimerization reactions of single stereocenters could be utilized for converting inexpensive starting materials, containing other stereogenic centers, into diastereomeric mixtures from which more valuable compounds can be isolated by traditional isolation techniques.

Sammanfattning

Utvecklandet av kostnadseffektiva och miljövänliga framställningsprocesser med hög selektivitet för framställningen av eftertraktade optiskt rena föreningar är av högsta prioritet inom industriell och syntetisk organisk kemi. Målsättningen med den ifrågavarande forskningen är att tillgodose dessa förväntningar genom att överföra enskilda reaktioner i ett och samma kärl och således utveckla ny syntesmetodik, s.k. reaktionskaskader. När olika flerstegsreaktioner förverkligas i ett kärl genom att utnyttja heterogena eller immobiliserade kemiska och enzymatiska katalysatorer underlättas upparbetningen och katalysatorerna kan isoleras enkelt med filtrering.

I det inledande skedet utvecklas en dynamisk kinetisk resolvering av *rac*-2-hydroxi-1-indanon och en regionselektiv hydrering av 1,2-indandion. I följande steg sammanförs de separata reaktionerna till ett kärl och en ny heterogent katalyserad reaktionskaskad med enkel upparbetning och produktisolering ur reaktionsblandningen förverkligas. Sammanfattningsvis, det lättillgängliga utgångsmaterialet, 1,2-indandion, kan med hjälp av den utvecklade reaktionskaskaden omvandlas med hög regio- och enantioselektivitet till en eftertraktad optiskt ren vicinal hydroxiketon genom att använda immobiliserade eller heterogena enzymatiska och metallbaserade katalysatorer.

En kompletterande studie av homogena rutenium baserade metallkomplex för att katalysera epimeriseringen av sekundära alkoholer har utförts för fem naturprodukter, alla innehållande ett flertal olika stereocentra. I princip kan denna typ av epimeriseringsreaktioner användas för att konvertera billiga och lätt tillgängliga utgångsmaterial till diastereomera blandningar från vilka dyrbara föreningar kan utvinnas med hjälp av traditionella isoleringsmetoder.

List of Publications

This thesis is based on four original articles and one minireview. Related work is also discussed in the appended pedagogical text.

I   Otto Långvik, Tiina Saloranta, Dmitry Yu. Murzin and Reko Leino **Heterogeneous Chemoenzymatic Catalyst Combinations for One-pot Dynamic Kinetic Resolution Applications** (minireview) *ChemCatChem* **2015**, DOI: 10.1002/cctc.201500459.

II   Otto Långvik, Tiina Saloranta, Alexey Kirilin, Arto Liljeblad, Päivi Mäki-Arvela, Liisa T. Kanerva, Dmitry Yu. Murzin and Reko Leino **Dynamic Kinetic Resolution of *rac*-2-Hydroxy-1-indanone by using a Heterogeneous Ru(OH)$_3$/Al$_2$O$_3$ Racemization Catalyst and Lipase** *ChemCatChem* **2010**, *2*, 1615–1621.

III   Otto Långvik, Päivi Mäki-Arvela, Atte Aho, Tiina Saloranta, Dmitry Yu. Murzin and Reko Leino **Regioselective Hydrogenation of 1,2-Indanedione over Heterogeneous Pd and Pt Catalysts** *Catal. Lett.* **2013**, *143*, 142–149.

IV   Otto Långvik, Thomas Sandberg, Johan Wärnå, Dmitry Yu. Murzin and Reko Leino **One-pot Synthesis of (*R*)-2-Acetoxy-1-indanone from 1,2-Indanedione Combining Metal Catalyzed Hydrogenation and Chemoenzymatic Dynamic Kinetic Resolution** *Catal. Sci. Technol.* **2015**, *5*, 150–160 (highlighted in back cover of the journal).

V   Otto Långvik, Denys Mavrynsky and Reko Leino **Selective Ruthenium-catalyzed Epimerization of Chiral *sec*-Alcohols** *Catal. Today* **2015**, 241, 255–259.

For a pedagogical text, see:

VI   Otto Långvik, Reko Leino and Tiina Saloranta **Lipase Catalyzed Kinetic Resolution of Racemic 1-Phenylethanol** Comprehensive Organic Chemistry Experiments for the Laboratory Classroom, Carlos A. M. Afonso (ed.), *Royal Society of Chemistry*, *Cambridge*, **2015**, accepted for publication.

CONTRIBUTION OF THE AUTHOR

This thesis is based on four original publications (II-V) and one minireview (I). In addition one pedagogical text (VI) for educational purpose is included as complementary material. The author of this thesis is the main author in all these six publications. The author is also responsible for the experimental work presented in this thesis, with the following exceptions:

- The preparation and characterization of the heterogeneous Ru catalyst in papers II and IV, Lewis acid catalysts in paper II and the Cu catalyst in paper II
- The TGA and SEM-EDXA analyses in paper III
- The preparation and analysis of the homogeneous Ru catalysts in publication V
- Operating the DFT calculations and the kinetic modeling presented in paper IV

However, for these exceptions apply that the author of this thesis has contributed in the planning of the parts mentioned and in the writing of the results.

Selected Conference and Seminar Contributions

C-I.   <u>Otto Långvik</u>, Tiina Saloranta, Reko Leino, Dmitry Yu. Murzin, Liisa Kanerva, Arto Liljeblad **Enzyme- and Chemocatalysts for Cascade and One-Pot Reaction Applications,** Poster presentation, *Summer School in Organic Chemistry, Tampere, Finland*, June 16-18, **2008**.

C-II.   <u>Otto Långvik</u>, Tiina Saloranta, Arto Liljeblad, Alexey Kirilin, Päivi Mäki-Arvela, Liisa T. Kanerva, Dmitry Yu. Murzin, Reko Leino **Towards Dynamic Kinetic Resolution of 2-Hydroxy-1-Indanone with Heterogeneous Catalysts**, Poster presentation, *COST Action D40, Innovation-III, Turku, Finland*, May 26-28, **2009**.

C-III.   <u>Otto Långvik</u>, Tiina Saloranta, Arto Liljeblad, Alexey Kirilin, Päivi Mäki-Arvela, Liisa T. Kanerva, Dmitry Yu. Murzin, Reko Leino **Dynamic Kinetic Resolution of rac-2-Hydroxy-1-indanone Using Heterogeneous Ru(OH)$_3$/Al$_2$O$_3$ Racemization Catalyst and Lipase**, Poster presentation, *The XI Spring Meeting of Synthetic Chemistry, Espoo, Finland*, June 8-9, **2009**.

C-IV.   <u>Otto Långvik</u>, Tiina Saloranta, Arto Liljeblad, Alexey Kirilin, Päivi Mäki-Arvela, Liisa T. Kanerva, Dmitry Yu. Murzin, Reko Leino **Dynamic Kinetic Resolution of 2-Hydroxy-1-Indanone with Heterogeneous Catalysts,** Poster presentation, *International Symposium on Relations Between Homogeneous and Heterogeneous Catalysis (ISHHC XIV), Stockholm, Sweden*, September 13-18, **2009**.

C-V.   <u>Otto Långvik</u>, Päivi Mäki-Arvela, Dmitry Yu. Murzin, Reko Leino **Regioselective Hydrogenation of 1,2- Indanedione over Supported Pd and Pt Catalysts**, Poster presentation, *17th European Symposium on Organic Chemistry, Crete, Greece*, July 10-15, **2011**.

C-VI.   Denys Mavrynsky, <u>Otto Långvik</u>, Reko Leino **Selective Ruthenium-catalyzed Epimerization of Chiral sec-Alcohols**, Oral presentation, *10th Congress on Catalysis Applied to Fine Chemicals (CAFC 10), Turku, Finland*, June 16-19, **2013**.

List of Abbreviations

BET	Brunauer-Emmet-Teller
tert-BuOK	Potassium *tert*-butoxide
CALA	*Candida antarctica* lipase A
CALB	*Candida antarctica* lipase B
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DIPE	diisopropyl ether
DKR	dynamic kinetic resolution
EA	ethyl acetate
ee	enantiomeric excess
HRTEM	high resolution transmission electron microscopy
ICP-OES	inductively coupled plasma optical emission spectrometry
KR	kinetic resolution
Lipase AK	*Pseudomonas fluorescens* lipase
MCF	meso cellular foam
MTBE	methyl *tert*-butyl ether
NMR	nuclear magnetic resonance
GC	gas chromatography
GC/MS	gas chromatography combined with mass spectrometry
RT	room temperature
SEM–EDXA	scanning electron microscope – energy dispersive X-ray analysis
THF	tetrahydrofuran
TLC	thin layer chromatography
TOF	turnover frequency
TON	turnover number
TPR	temperature programmed reduction
XPS	X-ray photoelectron spectroscopy

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1. Introduction

1.1 Background

The title "father of modern chemistry" is associated with Antoine-Laurent de Lavoisier.[1] Later, other well-known "heavy weight" scientist, such as Friedrich Wöhler and Hermann Kolbe, initiated the field of organic chemistry. Synthetic organic chemistry is traditionally divided in two domains: 1) The development of new synthetic methods or reactions; and 2) The synthesis of new target molecules. This doctoral thesis discusses the development of new one-pot type reaction applications and methods.

The modern industrialized society sets great expectations on products and applications, such as environmental impact and economic profitability. The total annual chemical sales of only the five biggest chemical enterprises exceeded $ 282 billion in 2013.[2] The globalized chemical companies aim to produce both bulk and fine chemicals efficiently in a sustainable manner in order to meet the market demands. The awareness of environmentally benign processes and sustainability has been a hot topic for some decades already. The famous 12 principles of green chemistry were published in the early 1990s.[3] The need to develop new synthetic reactions and methods for advancing the best available techniques has nevertheless not diminished. Many researchers are actively developing and discovering new environmentally sustainable reactions and processes with reduced time, costs, amount of starting materials, amount waste produced, energy consumed (in the form of heat, pressure or vacuum) and increased safety.[4]

From the industrial point of view, heterogeneously catalyzed processes are often preferred in large scale production due to potential recycling of the catalysts and generally more facile work-up of the reactions.[5,6] Heterogeneously catalyzed processes may also enable the appealing possibility to transfer the processes into flow type of operation.[7]

1.2 Stereoisomerism and Enantiomers

Isomerism represents in organic chemistry the different structural, chemical or physical properties molecules with the same empirical formula can have. Isomers are usually divided in two main subclasses, constitutional isomers and stereoisomers. Stereoisomers can then further be divided in diastereomers and enantiomers.

Chiral molecules contain at least one of the three chirality elements: 1) Chirality centre; 2) Chirality axis; 3) Chirality plane.[8] Stereoisomers and enantiomers in organic chemistry originate often from the carbon atom based chiral centers with the three dimensional structure of the sp^3-hybridized carbon atom, forming four bonds to four neighboring atoms. When all the four atoms, or groups of atoms, bonded to such an sp^3-hybridized carbon centered structure are different, the structure can exist in two non-superimposable mirror images and becomes chiral (Figure 1). These kinds of mirror image structures are called enantiomers. Enantiomeric structures have identical physical and chemical properties in an achiral environment, with a few exceptions. Enantiomers rotate plane polarized light in different directions and some enantiomeric structures crystallize in separate crystals, i.e., conglomerates. For more complex molecules, which for example include more than one chiral center, one observed situation is that two isomeric structures are non-superimposable yet not mirror images. Such structures are named diastereomers. Diastereomers have different physical and chemical properties also in an achiral environment and can therefore be separated by traditional isolation techniques.

The first researcher to separate the enantiomers of a racemic mixture was Louis Pasteur when he made the famous resolution experiments of the tartaric acid salts.[9,10] The experiments have gained much interest and are regarded as cornerstones in the development of isolation techniques of chiral compounds.[11,12] Pasteur was also the first to develop two other major methodological innovations, the classical resolution method using chiral reagents and the kinetic resolution (KR) using biocatalysis.[11,13] One important observation to note is that although enantiomers do not have different properties in an

achiral environment, they do have different properties in a chiral environment. Hence, since all living organisms are constructed of chiral building blocks, the optical isomerism needs to be taken into consideration very carefully when stereoisomers are utilized in biological context. In 1992 the U.S. Food and Drug administration agency published the guidelines for development of stereoisomeric drugs.[14] This guideline requires separate characterization data of enantiomeric structures for new drug candidates. FDA hereby established the importance of production of enantiopure compounds for use as drugs.
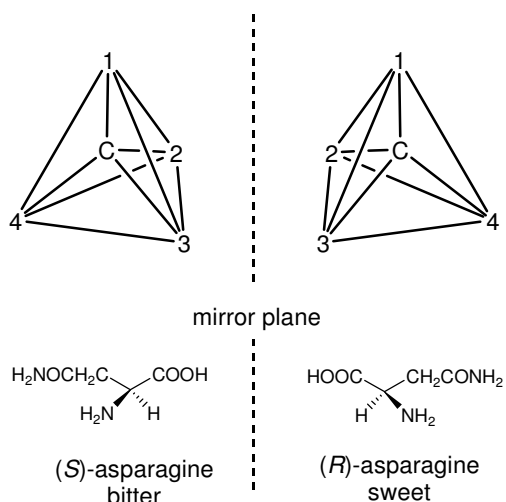
Figure 1. Mirror images of C-centered tetrahedral enantiomeric structures.

1.3 Production of Chiral Compounds

The three main methodologies typically utilized for the preparation of chiral compounds are based on: 1) Racemate resolution; 2) Chiral pool; and 3) Asymmetric synthesis (Figure 2).[15-17] One drawback with traditional resolution by formation of diastereomeric salts is the requirement of equimolar amounts of resolving agents. Moreover, although many impressive improvements have been made in asymmetric synthesis, KR has remained as a widely utilized and convenient tool for the production of enantiopure molecules.
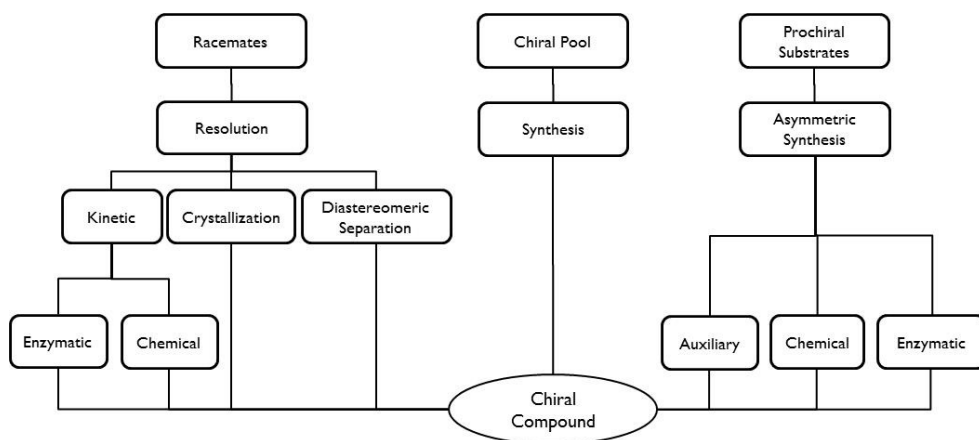
Figure 2. Illustration of the three typical routes used for the production or isolation of chiral compounds.

1.4 Catalysis

In 1836 Jöns Jacob Berzelius, a Swedish chemist, discussed his insights concerning interesting chemical processes he had observed. He defined the phenomenon as catalysis.[18]

> *"Accordingly, I shall designate it, thereby following a well known chemical etymology, the catalytic power of bodies; and the decomposition it produces I shall call catalysis ..."*

Later in the same paragraph it is indicated that a catalyst enables a reaction without being consumed itself. Berzelius addressed also the interesting phenomenon that catalysts can selectively enable certain reactions leaving other reactions uncatalyzed.

Wilhelm Ostwald carried out thorough studies of catalytic reactions in late 19th century. He was awarded the Nobel Prize in chemistry year 1909 in recognition of his work on catalysis and for his investigations into the fundamental principles governing chemical equilibria and rates of reaction.

Catalysts can be divided into two main types: 1) heterogeneous; and 2) homogeneous. In homogeneous catalysis all the reactants and catalysts are located in the same phase, quite often the liquid phase. Complementary to this, heterogeneous catalysis is considered

to be the situation where reactants and catalysts are not present in the same phase. Heterogeneous catalysis can be exemplified by the situation where the reactants and catalysts are located in a liquid and solid phase. Also other heterogeneous phase systems are in use, e.g. solid-gas and solid-liquid-gas.

Characterization of heterogeneous catalysts often includes determination of surface area, metal particle size, oxidation state of the metal and acidity of the support. Also *"turnover frequency"* (TOF) is often used when catalyst efficiency in terms of reaction rate is characterized. TOF is defined as the number of reactant molecules converted per time per catalytic site and was originally introduced by M. Boudart in 1966.[19] TOF is included in IUPAC's gold book and recognized by scientists in the field of catalysis.[20,21] Furthermore, *"turnover number"* (TON) is often used as a complement to TOF.[21] In the field of heterogeneous and homogeneous catalytic applications TON number describes the maximum number of molecular reactions or conversions that can be made under defined reaction conditions divided by the number of catalytic sites until the decay of catalytic activity takes place. Notably, chemists working in the field of catalysis need to be careful and aware of the fact that in the field of biochemistry the term TON is still used with the same meaning as TOF.[21]

Transition metals, typically Pd or Pt, are widely used as catalysts in the hydrogenation of ketones to secondary alcohols, for many structurally different starting materials.[22,23] In a regioselective reaction, one functional group of the starting material is transformed while other analogous functional groups in different positions of the same molecule are left intact. Such differences in reaction rates between similar chemical functionalities resulting in regioselectivity may be a consequence of the chemical and structural nature of the substrate itself, or be controlled by structure of the catalyst used for the desired transformation.[24-27] Under ideal conditions, hydrogenation of vicinal diketones may result in regioselective hydrogenation of only one of the carbonyl groups, thereby providing access to synthetically valuable α-hydroxy ketones (Scheme 1).
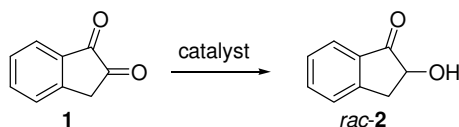
Scheme 1. Regioselective hydrogenation of 1,2-indanedione (**1**) yielding *rac*-2-hydroxy-1-indanone (*rac*-**2**).

1.4.1 Kinetic Resolution

Evolution has developed and tuned protein structures to catalyze preferred reactions over a period of millions of years. This development has resulted in enzymes that enable impressive reactions, essential for life, with high selectivity under mild conditions. Bio-catalysis and the quantitative treatment of biochemical kinetic resolution developed rapidly in the 1980s.[12,28] Also, the utilization of enzyme catalysis in non-aqueous solvents enables most of the unit operations and synthetic organic methodologies chemists are familiar with.[29,30] Furthermore, enzyme immobilization often enhances the enzyme's performance, e.g. thermal stability and recycling properties.[31] Kinetic resolution can be achieved by different methods, also non-enzymatic. In this work the focus is on enzyme catalyzed resolutions.
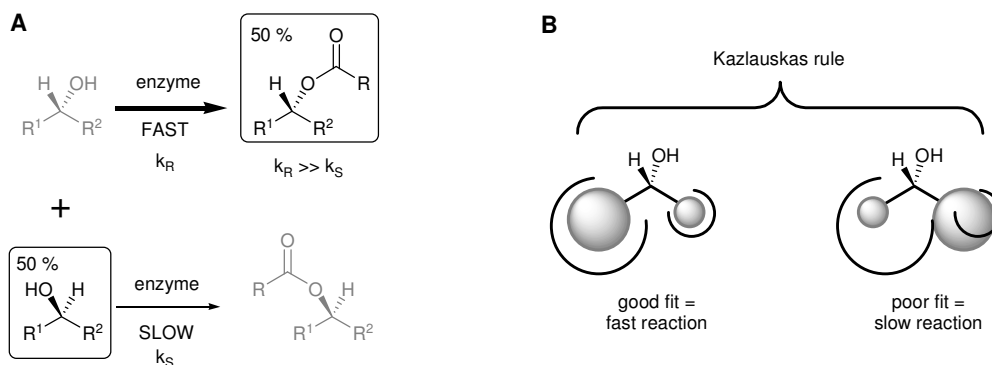
Scheme 2. A) The principle of enzyme catalyzed KR, and B) Representation of the empirical Kazlauskas rule.

In a KR one of the enantiomers in a racemic mixture reacts faster than the other one. Secondary alcohols can undergo KR utilizing the lipase catalyzed enantiospecific *O*-acylation (Scheme 2A). Kazlauskas and co-workers have described lipases ability to catalyze enantiospecific reactions of racemic secondary alcohols based on the sizes of the substituents at the stereocenter of the reacting secondary alcohol. This rule is called the Kazlauskas rule (Scheme 2B).[32] In an optimal case, the KR leaves the other enantiomer unreacted.[32] Consequently, the conventional enzyme-mediated KR possesses a major disadvantage of a maximum yield of 50 % for one specific enantiomer structure.[12]

The kinetic treatment of enzyme catalyzed reactions is most often done by applying Michaelis-Menten steady state conditions. The Michaelis-Menten constant is defined as $K_m = \frac{(k_{-1} + k_2)}{k_1}$ (Scheme 3). When the reversible association (k_1) and dissociation (k_{-1}) between substrate and enzyme is much faster than the acylation reaction k_2 ($k_2 << k_{-1}$), k_r equals k_2 ($k_r = k_2$) (Scheme 3). If the enzyme concentration is low enough and k_r equals k_2 the rate equation of enzyme catalyzed reaction can be simplified to $r = \frac{k_2}{K_m}[enzyme][substrate]$.

$$\text{Enz. + Substrate} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \left[\text{Enz.-Substrate}\right] \xrightarrow{k_2} \left[\text{Enz.-Prod}\right] \longrightarrow \text{Enz. + Product}$$
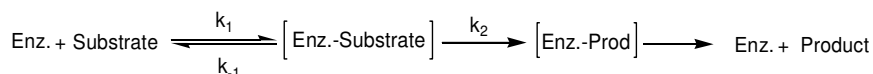
Scheme 3. Enzyme catalyzed reaction kinetics using Michaelis-Menten steady-state conditions gives the constant K_m.

The mathematical presentation of enzyme catalyzed KR reactions was further developed by Chen and co-workers by introducing the *E*-value.[28,33] The *E*-value is defined in Equation 1. The *E*-value describes how enantioselective the enzyme catalyzed KR is, i.e. the k_R/k_S ratio (Scheme 2).

Equations (2),(3) and (4) can be derived from (1), provided that the reaction k_R is irreversible.[34] Moreover, a reliable determination of the *E*-value, using Equations (2) and (3), should be made by plotting three, or several, data points in order to check the linearity

of the nominator/denominator values. For synthetic purpose the *E*-value should at least be 20 in order to get a sufficiently high *ee* (enantiomeric excess) of the product.

$$E = \frac{\left(k_R / K_m^{'}\right)_R}{\left(k_S / K_m^{''}\right)_S} \tag{1}$$

$$E = \ln\left[(1-c)(1-ee_{substrate})\right]/\ln\left[(1-c)(1+ee_{substrate})\right] \tag{2}$$

$$E = \ln\left[1 - c(1 + ee_{product})\right]/\ln\left[1 - c(1 - ee_{product})\right] \tag{3}$$

$$c = ee_{substrate} / \left(ee_{substrate} + ee_{product}\right) \tag{4}$$

$$ee = \left|\frac{[R]-[S]}{[R]+[S]}\right| \tag{5}$$

1.4.2 Dynamic Kinetic Resolution

Conventional enzyme-mediated KR limits the product enantiomer yield to 50%.[12,35] By using a racemization catalyst, the slower reacting starting material enantiomer may, however, be converted to the faster reacting one and the theoretical yield of one single enantiomer reaction product approach 100% (Scheme 4). A sufficiently high racemization rate is required to retain the *ee* of the starting material at a low level, thus ensuring the continuous feed of the reacting enantiomer to the enzyme catalyst.[36] An early Dynamic Kinetic Resolution (DKR) application was the hydrogenation of a 1,3-dione structure, reported by Noyori in 1989.[37]

The shifting from a lipase catalyzed KR to DKR is most conveniently performed by adding a suitable racemization catalyst to the reaction mixture. It is anyhow important to remember that for a viable chemoenzymatic DKR process, the enzyme and the racemization catalyst should be mutually compatible when applied in the same reaction vessel.
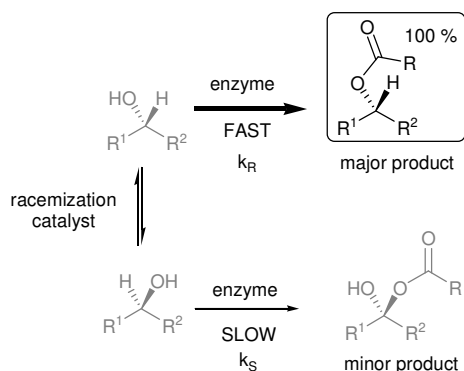
Scheme 4. Dynamic Kinetic Resolution of a secondary alcohol.

1.5 Racemization and Epimerization of Secondary Alcohols

Racemization is, by definition, the production of a racemate from a chiral starting material in which one enantiomer is present in excess.[8] When the racemization of a chiral secondary alcohol is achieved by an oxidation reduction sequence (Scheme 5) the intermediate is the planar, prochiral, sp^2 hybridized carbonyl structure. The equilibrium between two stereoisomers of a chiral secondary alcohol can hence also be achieved by traditional, stoichiometric, chemical methods, e.g. Oppenauer oxidation and subsequent Meerwein-Ponndorf-Verley reduction.[38,39]

An extensive review of catalytic racemization methods, including those for amines, is available.[40] In general, the catalytic racemization can occur by four conceptually different reactions: 1) Acid/Base catalyzed; 2) Enzyme catalyzed;[41] 3) Radical induced;[42] and, 4) Transition metal catalyzed.[43]
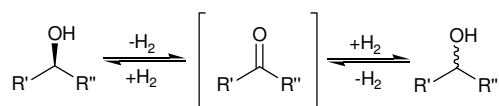
Scheme 5. Racemization of a secondary alcohol via an oxidation reduction sequence (R'≠R'').

Epimerization takes place by the configurational interconversion of one stereogenic center while leaving other stereocenters in the same molecule untouched. A secondary hydroxyl based stereocenter can principally interconvert selectively in the presence of a racemization catalyst although the molecule might possess several stereocenters. Some epimerization reactions have been reported for saccharides by homogeneous half-sandwich ruthenium complexes,[44] for terpenoids by heterogeneous and homogeneous catalyst systems[45,46] and for steroid structures by homogeneous half-sandwich rhenium catalysts.[46] This kind of single stereocenter equilibration in a chiral compound with multiple stereogenic centers can potentially be used for converting an inexpensive starting material into a diastereomeric mixture. A valuable compound from such a diastereomeric mixture can then be separated by traditional techniques provided that the equilibrium mixture contains a sufficient amount of the desired compound.

1.5.1 Homogeneous Ru-based Racemization Catalysts

Homogeneous catalysts often possess high activity and selectivity. Furthermore, the properties of homogeneous catalysts can often be developed and tailored for some specific reactions by chemically modifying the molecular structure of the catalyst itself. The modifications can enable some variation, e.g. electronic or steric, at the catalytically active center.

Epimerization of secondary alcohols using transition metal complexes was reported in the early 1990s by Gladysz and co-workers using homogeneous Re complexes.[46] Williams et al. also evaluated a set of different transition metal based catalysts (Ir, Rh and Ru) for racemization of secondary alcohol enantiomers.[47] Notably, they also reported the first chemoenzymatic DKR reactions utilizing the combination of a homogeneous transition metal catalyst for racemization and lipase.[47]

Since those first reports of Ru based racemization catalysts, much effort has been put on developing and screening different kinds of improved catalyst structures for secondary alcohol racemization.[48] One quite much utilized catalyst is the Shvo catalyst.[49] The Shvo

catalyst was successfully applied for in situ racemization of secondary alcohols in 1996 by Bäckvall and co-workers.[50] One important improvement in Ru based racemization catalysis was the development of the Bäckvall catalyst (**4**) (Figure 3).[51,52] Later Mavrynsky et al. have developed an analogue of the Bäckvall catalyst by replacing the phenyl substituents with benzyl groups (Figure 3).[53] Catalyst **5** was found to be more easily dissolved than catalyst **4** in conventional organic solvents, making the handling and operation using **5** more simple. Moreover, the synthesis of **5** is easier and cheaper compared to the synthesis of **4**.

Considerable effort has been made to study the catalytic racemization mechanisms.[53-56] The *sec*-alcohol racemization by homogeneous half-sandwich ruthenium catalysts has been shown to involve an oxidation-reduction (dehydrogenation-hydrogenation) sequence. Such racemization is initiated by β-hydride elimination of a *sec*-alcohol derived ruthenium alkoxide. The subsequent hydrogen transfer from ruthenium to a coordinated ketone takes place with equal probabilities from both enantiofaces of the C=O bond resulting in efficient configurational equilibration of the stereochemistry.
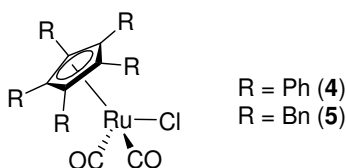
Figure 3. The structure of Ru based racemization catalysts: (η^5-pentaphenyl-cyclopentadienyl)RuCl(CO)$_2$ (**4**) and (η^5-pentabenzylcyclopentadienyl)RuCl(CO)$_2$ (**5**).

DKR of vicinal hydroxy ketones has recently been reported by Martín-Matute and co-workers using a ruthenium complex formed from commercially available [Ru(p-cymene)Cl$_2$]$_2$ and 1,4-bis(diphenylphosphino)butane.[57] The DKRs were performed in one-pot at room temperature (RT). The racemization at RT is fully compatible with an effective kinetic resolution catalyzed by a lipase from *Pseudomonas stutzeri*. The esterified products of the eleven structurally different vicinal hydroxy ketones studied were obtained in 73-93% yield and 94-99% *ee*.[57]

Ideally, also epimerization processes can be made dynamic (similar to DKRs) in the presence of a suitable enzyme catalyst. This has been demonstrated by Bäckvall and co-workers by epimerization of a non-anomeric stereogenic center in carbohydrates combined with an acylating enzyme.[58] An esterified secondary alcohol with equatorial configuration was obtained in 83% yield using *Candida antarctica* lipase B (CALB) and **4** starting from the corresponding axially configured starting material (4,6-*O*-benzylidene-D-allal).

1.5.2 Heterogeneous Racemization Catalysts

Homogeneous transition metal catalysts are often expensive, require oxygen and moisture free reaction conditions and are difficult to separate and recycle. Heterogeneous catalysts, on the other hand, often allow advantages over their homogeneous counterparts, such as easy separation by filtration and the consequently easier recycling.[5] Thus, several heterogeneous catalysts have been developed for racemization of secondary alcohols.[59] Examples of such heterogeneous catalysts include Brønsted acids[60] and bases,[61] Lewis and Brønsted acidic zeolites,[62-64] as well as various heterogeneous metal species including $VOSO_4$,[65] Cu/Al_2O_3,[66,67] and $Ru(OH)_3/Al_2O_3$.[68-72] Moreover, racemizations of primary amines have also developed, typically based on Pd as the active catalyst.[73-78] Notably, an early report on heterogeneous racemization catalysts is the Pd/C catalyzed racemization of primary amine enantiomer published in 1983 by Murahashi and co-workers.[79]

Also immobilizations of homogeneous half-sandwich ruthenium catalysts have been described. Park and co-workers have immobilized the homogeneous [Ph$_4$(η^4-C$_4$CO)]Ru(CO)$_3$ complex covalently on benzoyl chloride functionalized polystyrene. This covalently linked Ru-catalyst was successfully used in combination with CALB in DKR of secondary alcohols.[80,81] Moreover, Bäckvall and co-workers coupled an analogue of the Bäckvall catalyst covalently to a phosphonate inhibitor which in turn was anchored to some of the active sites of immobilized CALB. This protocol resulted in an immobilized CALB catalyst containing both Ru-species catalyzing the racemization of the substrate as well as accessible active sites of the enzyme catalyzing the kinetic resolution.[82]

Heterogeneous Brønsted and Lewis acids can be considered as simple and robust racemization catalysts. Bornscheuer and co-workers have described the racemization of an enantiopure vicinal hydroxy ketone by using the Brønsted acidic Amberlyst 15 catalyst.[60] In their work, a racemization mechanism involving keto-enol tautomerization was proposed and the racemization was found to be solvent dependent (Scheme 6).[60] Acidic zeolite materials are known to racemize unprotected secondary alcohols and have likewise been studied for the development of lipase catalyzed DKR processes.[38,62-64]
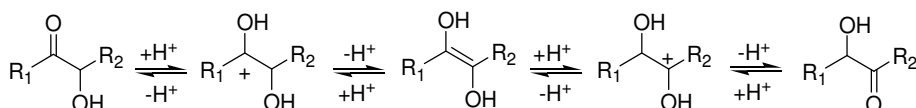
Scheme 6. Probable mechanism for a Brønsted acid catalyzed racemization of hydroxyl ketones.[60]

Inexpensive and readily available heterogeneous transition metal based catalysts would be preferred, at least in principle, in the development of industrial applications of DKR. In this context it is interesting that Ravasio and co-workers have utilized an easily available and low-cost copper based catalyst (Cu/Al_2O_3) for racemization of secondary alcohols.[66,67] Furthermore, Ravasio and co-workers have reported the use of Cu/Al_2O_3 to catalyze hydrogenation reactions of low value mint oils in the production of (−)-menthol.[83]

Heterogeneous Ru catalysts with different support materials have been developed for racemization of secondary alcohols. $Ru(OH)_3/Al_2O_3$ has also been used to catalyze oxidation of secondary alcohols to ketones and reduction of ketones to secondary alcohols.[69,84-87] Jacobs et al. reported in 2003 the use of Ru-hydroxyapatite for racemization of enantiopure secondary alcohols.[68] The Ru-hydroxyapatite catalyst was prepared by using an ion-exchange procedure of the initial Ca-hydroxyapatite catalyst providing the Ru catalyst with a surface area of 115 m^2/g Brunauer-Emmet-Teller (BET) method and Ru loading of 1.3 wt% (ICP).[68] Relatively fast (20 h) racemizations of both benzylic and aliphatic secondary alcohols were demonstrated using 3 mol% of Ru in toluene at elevated temperature (80 °C). Nevertheless, the functional group tolerance was found to be limited

since the racemization was inhibited seriously by carboxylic acids, primary, secondary and aromatic amines and to a lesser degree by esters.
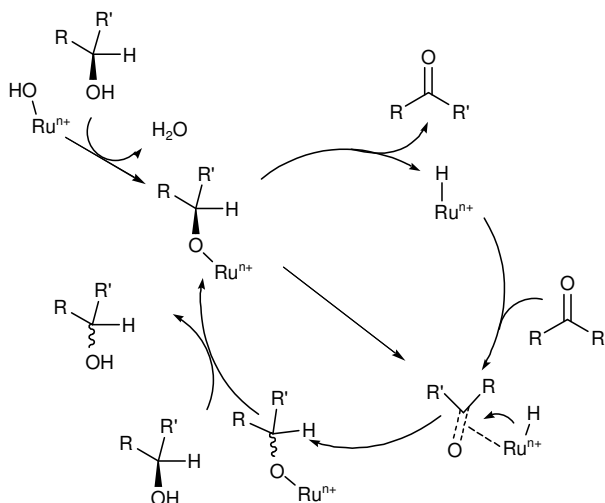
Heterogeneous Ru based racemization catalysts were further developed by using alumina as the support material.[69,72] Using $Ru(OH)_3/Al_2O_3$ complete racemization of both aliphatic and benzylic secondary alcohols was accomplished in 8 h in toluene with 3.6 mol% Ru at 70 °C.[72] Furthermore, the racemization was found to be faster in nonpolar solvents than in polar ones.

Mechanistic studies with $Ru(OH)_3/Al_2O_3$ catalyst were performed by Yamaguchi et al. for three different hydrogen transfer reactions, namely racemization of secondary alcohols, reduction of carbonyl compounds to alcohols, and isomerization of allylic alcohols to ketones.[69] The utilization of heterogeneous transition metal catalysts for the racemization of secondary alcohols is initiated with the adsorption of the chiral species to a metal surface followed by an oxidation reduction sequence. The proposed mechanism for the racemization of secondary alcohols using the $Ru(OH)_3/Al_2O_3$ catalyst includes a β-hydride elimination to afford the corresponding carbonyl compound and the subsequent re-addition of a hydride to the prochiral carbonyl carbon (Scheme 7).[69] The mechanistic studies including the determination of kinetic isotope effects suggested that the rate determining step is Ru-H bond cleavage (hydride transfer). Notably, the proposed catalytic cycle for the heterogeneous Ru catalysts resembles the mechanism derived for homogeneous half-sandwich Ru based racemization catalysts widely utilized in DKR applications.[54]

The heterogeneous Ru based racemization catalysts were also further developed by Mizuno and co-workers by screening TiO_2 based support materials.[70] The surface areas after grafting of Ru were determined for the two anatase and one rutile materials to be 298 m^2/g; 74 m^2/g and 7 m^2/g, respectively. The TOF of the three catalysts in racemization of (R)-1-phenylethanol were determined as 380 h^{-1}, 120 h^{-1} and 3 h^{-1}, respectively. $Ru(OH)_3/TiO_2$ with anatase as the support (298 m^2/g) exhibited the highest activity for racemization and was found to be approximately one order of magnitude faster than the corresponding $Ru(OH)_3/Al_2O_3$ catalysts. The same catalyst was also shown to exhibit high

activity in transfer hydrogenation reactions when ten different ketones or aldehydes were reduced to the corresponding alcohols using 2-propanol as the hydrogen donor.[70]

Scheme 7. Racemization mechanism proposed for the Ru(OH)$_3$/Al$_2$O$_3$ catalyst.[69] (Scheme adopted from reference 64 with permission from the publisher. Copyright 2005 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim)

1.6 Heterogeneously Catalyzed Dynamic Kinetic Resolution

Acid and Base Catalysts Combined with Lipases

For developing a viable chemoenzymatic DKR process, the enzyme and the racemization catalyst should be mutually compatible and preferably be applied in the same reaction vessel. Lipases are often highly enantiospecific and accept many structurally different secondary alcohols as substrates. The racemization step ensures the continuous feed of the reacting enantiomer to the immobilized enzyme catalyst. Furthermore, the product should be stable under the reaction conditions applied.

In the stereoselective hydrogenation via DKR, described by Noyori and co-workers, the starting material, a 1,3-diketone, undergoes fast racemization by keto-enol tautomerism.[37] The DKR process, utilizing asymmetric transfer hydrogenation as the kinetic resolution

step, provided only one of the four possible diastereomers in 98% *ee* and 100% conversion. The substrate scope of this approach is, however, limited to configurationally labile compounds.

An early report of enzymatic DKR was published in 1991 by Inagaki and co-workers combining a heterogeneous basic resin (Amberlite IRA-904) and a lipase for the production of cyanohydrin acetates (Scheme 8).[61] Further examples on the use of a heterogeneous basic resin or benzyltrimethylammonium hydroxide functionalized silica together with immobilized lipases have been reported in DKR applications producing enantiomerically pure *O*-acyl cyanohydrins.[88-90]
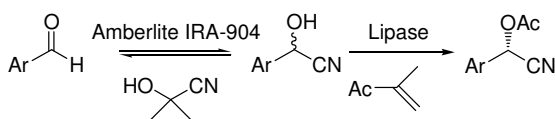
Scheme 8. DKR in the synthesis of optically active cyanohydrin acetates.

The strong acidic nature of both the Brønsted and Lewis acidic catalysts has often been concluded to be detrimental for the catalytic activity of lipases in one-pot applications. The physical separation of the acidic racemization catalyst and enzyme catalyst in two compartment reaction vessel has, therefore, often been a requirement for developing viable DKR processes.[60,64] Bornscheuer et al. have described the racemization of a vicinal hydroxy ketone by using the Brønsted acidic Amberlyst 15 catalyst.[60] The two-compartment DKR delivered the ester product with >91% *ee* at >91% conversion (Scheme 9, Figure 4).
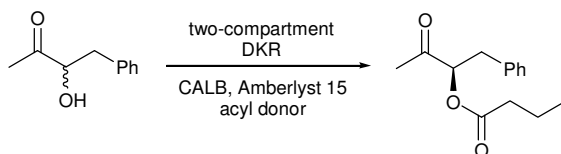
Scheme 9 Dynamic kinetic resolution of 3-hydroxy-4-phenylbutan-2-one combining CALB and Amberlyst 15 catalysts.[60]
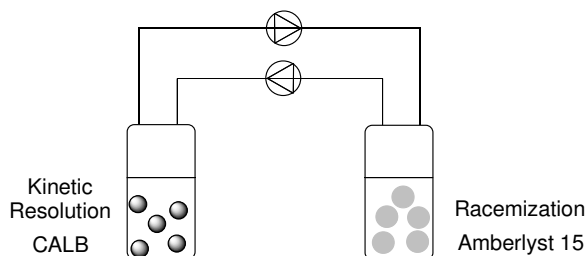
Figure 4. A two vessel set up for dynamic kinetic resolution combining CALB and Amberlyst 15 catalysts.[60]

Also Jacobs et al. have developed an interesting biphasic DKR.[64] The kinetic resolution was conducted with the immobilized CALB placed in the organic phase by mounting a basket made of inox gauze on the shaft of the mechanical stirrer.[64] Continuous racemization of the substrate was conducted by the zeolite catalyst located in the aqueous phase. The two phase reaction delivered yields up to 90% with >99% *ee*, using a large excess of the acyl donor (16 equivalents).[64]

A successful heterogeneously catalyzed DKR of benzoin was recently reported by Ansorge-Schumacher and co-workers.[91] The enantiospecific kinetic resolution was accomplished by using an immobilized lipase TL from *Pseudomonas stutzeri*. The racemization of (*R*)-benzoine was studied by incorporating different metals Zr and W in the meso-porous acidic silicate TUD-1. The best racemization result was achieved using Zr doped silicate (Si/Zr = 25) exhibiting full racemization of (*R*)-benzoine in 2 h and 4 h in toluene at 70 and 50 °C, respectively. The DKR of *rac*-benzoine in toluene at 50 °C gave after 20 h reaction time a yield >98% of the ester product in >98% *ee* at conversion >99%.[91]

Transition Metal Catalysts Combined with Lipases

The area of heterogeneously and homogeneously catalyzed DKR applications, combining transition metal and lipase catalysts, has been reviewed in literature by several authors.[36,43,59,92-98] Reetz and Schimossek have, already in 1996, reported a heterogeneous DKR of *rac*-phenylethylamine combining Pd/C and lipase cataysts.[75] The DKR provided

excellent *ee* values (99%) and moderate yields (75-77%) of the amide product after a long reaction time (8 days).

The use of immobilized homogeneous half-sandwich ruthenium catalysts in DKR applications have been described by both the groups of Park and Bäckvall. Park and co-workers have covalently immobilized a homogeneous Ru complex, [Ph$_4$(η^4-C$_4$CO)]Ru(CO)$_3$, on benzoyl chloride functionalized polystyrene. This immobilized Ru catalyst was then used in combination with CALB for the synthesis of seven benzylic and three aliphatic *sec*-alcohols under air athmosphere.[80] The DKR delivered the acylated products in 86-99% yield and 88-99% *ee*. The same catalyst combination was then further used in the asymmetric synthesis of rivastigmine, a compound with pharmaceutic importance, with the chemoenzymatic DKR as the key step (yield 96%, 99% *ee*) in the synthesis route.[81]

Wieczorek et al. made an interesting immobilization of a Bäckvall catalyst analogue. The Ru complex was covalently coupled to a phosphonate inhibitor, which in turn was anchored to some of the active sites of immobilized CALB.[82] Separate kinetic resolutions and racemizations were demonstrated using CALB and the catalyst material in question, but no DKR sequence was reported using this immobilized Bäckvall catalyst analogue.[82]

Park et al. have recently immobilized both the Shvo catalyst and [RuCl$_2$(pcymene)]$_2$ on phosphotungstic acid modified γ-alumina (Augustine's method).[99] A viable DKR of a model substrate, 1-phenylethanol, was developed using the combination of the immobilized Shvo catalyst (2 mol%) and CALB. The ester product was obtained, after a 5 h reaction time, in up to 89% yield and >99% *ee*.[99]

Although several heterogeneously catalyzed DKR processes have been reported, the combination of different types of catalyst materials, chemicals and solvent into a single reaction vessel often remains challenging. Only a few applications exist where Ru(OH)$_3$/Al$_2$O$_3$ and lipase catalysts for DKR of *sec*-alcohols are combined.[71,100] While the heterogeneous Ru catalyst may suffer from a diminished racemization rate in the presence of ester moieties, the catalyst appeared to be reasonably fast in the presence of ethyl acetate (EA), enabling a development of an efficient DKR processes.[100]

1.7 Cascade Approach

The production of chiral molecules for various purposes, e.g. pharmaceuticals, agrochemicals and other fine chemicals, is important in synthetic chemistry.[101] Different cascade reaction sequences, involving various types of tandem or multi-component reactions, are of high interest providing several advantages over conventional multi-step synthetic methods.[98,102-110] Sequential transformations are often atom-economical and avoid time-consuming protection/deprotection steps and isolation of intermediates.

Kroutil and Rueping have proposed a classification of different sequential reaction applications based on: 1) Mode of operation; 2) Number of reaction steps; 3) Type of catalyst.[111] Definitions and nomenclature of one-pot reactions are also discussed by Fogg and dos Santos.[112] Furthermore, Tietze has defined a domino reaction as: [113]

> *"… a process involving two or more bond-forming transformations (usually C-C bonds) which take place under the same reaction conditions without adding additional reagents and catalysts, and in which the subsequent reactions result as a consequence of the functionality formed in the previous step."*

For cascade reactions numerous reaction pathways are often possible simultaneously. These pathways can compete with the preferred reaction course by leading to undesired routes. Nevertheless, by careful selection of catalysts and reaction conditions, high levels of control can be achieved, promoting only a desired pathway, resulting in high selectivity for the overall transformation. Furthermore, it can be difficult to recycle catalyst material combinations in consecutive one-pot reactions. The overall reaction can be disadvantageously affected due to unfavorable catalyst-catalyst, catalyst-substrate or catalyst-product interactions. One approach to solve this kind of catalyst incompatibility issues is to co-immobilize the active catalyst materials on the same support material.

Heterogeneously catalyzed DKR processes have been developed by co-immobilizing both the racemization and kinetic resolution catalysts on the same carrier material. Bäckvall and co-workers have reported the immobilization of Pd nanoparticles and the subsequent co-immobilization of free CALB enzyme on the surface of a meso cellular foam (MCF), creating an artificial metalloenzyme used in the DKR of racemic primary amines.[76,114] The dimensions of the free CALB enzyme (approx. 3 x 4 x 5 nm) and Pd nanoparticles (1-2 nm) appear suitable for grafting them on the MCF surface. After functionalization the pore size of the MCF was determined to be 26 nm (specific pore volume 1.65 cm^3g^{-1}, BET surface area 380 m^2g^{-1}).[114] The typical size of the Pd clusters in the artificial metalloenzyme was found to be 1-2 nm (HAAF-STEM) and the Pd loading 4.8 wt% (ICP). Efficiency of the co-immobilized catalyst material was demonstrated by the DKR of *rac*-1-phenylethylamine (0.60 mmol) using ethylmethoxy acetate (1.20 mmol) as the acyl donor in toluene (4Å molecular sieves) under hydrogen atmosphere (1 atm.). For comparison, the same DKR sequence was carried out with two separate MCF based catalysts, one with the supported Pd nanoparticles and the other with immobilized CALB. The results demonstrated that by co-immobilizing both catalysts on the same support, the reaction time could be shortened from 20 to 16 hours and simultaneously the reaction yield increased from 89% to 99%, retaining the 99% *ee* of the amide.[76] Nevertheless, while the metalloenzyme catalyst delivers excellent efficiency, the recycling experiments showed enzyme inhibition to some degree already after the second recycling. Denaturation of the enzyme was found to be the major reason for the inhibition of the CALB enzyme. Leaching tests were conducted using ICPOES, concluding that less than 5% of the CALB had leached, which could not account for the deactivation observed.[76]

Synthetic applications of other co-immobilized catalyst materials and metalloenzymes have also been reported recently, e.g.: 1) Intracellular monoamine oxidase with Pd bound to the cell membrane for deracemization of a cyclic amine structure;[115] 2) Aminopeptidase in combination with Pt for cleaving amide bonds and subsequent reduction of a nitro group to an amine;[116] and, 3) Enzyme–metal (CALB–Pd) nanoparticle biohybrid catalyst utilized for DKR of *rac*-phenylethylamine.[117]

1.7.1 Combination of Hydrogenation and Dynamic Kinetic Resolution

Heterogeneously catalyzed one-pot reaction sequences enable most often fast and convenient operation. Heterogeneous transition metals, e.g. Pd or Pt, have been used extensively in catalytic hydrogenation reactions using H_2 as the hydrogen source. Also, examples of heterogeneous catalytic systems for DKRs of secondary alcohols have been reported in the literature. Nevertheless, one-pot operations combining both a hydrogenation and a DKR are rare, although a few examples for selected ketoxime and ketone compounds have been described.[83,100,118-124]

The first step in the production of chiral esters by chemo-enzymatic one-pot reaction involves a palladium catalyzed, non-stereoselective reduction of a ketone using H_2 as the hydrogen source to yield a secondary alcohol. Hydrogenation is then subsequently combined with a two-step DKR including racemization and KR of the non-isolated alcohol intermediate utilizing both Ru and lipase catalysis.

Murzin and co-workers have reported the hydrogenation of acetophenone using heterogeneous Pd or bimetallic PdZn catalysts combined with a lipase and ruthenium catalyzed DKR.[100,121,122] Nevertheless, the reductive conditions applied by using H_2 at ambient pressure and mild temperatures in combination with the alumina supported noble metal catalysts promoted the significant formation of ethylbenzene by-product (Scheme 10).
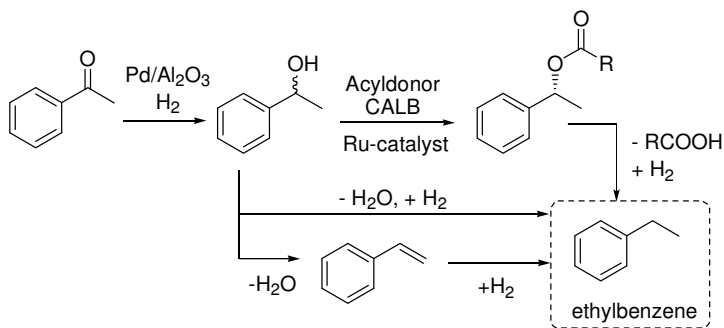
Scheme 10. Formation of ethylbenze by-product in the one-pot combination of hydrogenation and DKR using acetophenone as starting material.

Similar hydrogenation and DKR cascade reaction has also been demonstrated for different benzylic ketoxime starting materials utilizing the heterogeneous Pd/C catalyst in combination with immobilized CALB and EA as the acyl donor.[118] This synthetic methodology was further developed by replacing the Pd/C with Pd/AlO(OH) and EA with the activated acyl donor, ethyl methoxyacetate.[123] With these improvements the products were obtained in 85-88% yield 94-98% *ee*.

1.8 Objectives of this Thesis

The key objective of this thesis was to combine immobilized enzyme and heterogeneous chemo-catalysts and the transformations they enable into new cascade type one-pot reaction sequences.

The first objective was to combine racemization and kinetic resolution of a vicinal hydroxy ketone (*rac*-**2**) into a new, heterogeneously catalyzed, one-pot dynamic kinetic resolution (Scheme 11).
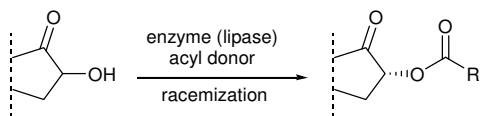
Scheme 11. DKR of a vicinal hydroxy ketone.

The second goal was to develop a practical highly regioselective hydrogenation of 1,2-indanedione (**1**) described in Scheme 12. The third objective was to combine the hydrogenation and DKR into a new heterogeneously catalyzed one-pot sequence to produce chiral (*R*)-2-acetoxy-1-indanone (*R*)-**3** directly from **1** (Scheme 13).
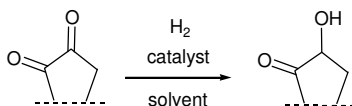
Scheme 12. Regioselective hydrogenation of a 1,2-dione structure.
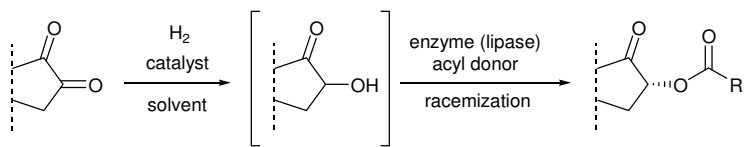
Scheme 13. One-pot combination of a regioselective hydrogenation and a DKR.

Also an additional and complementary investigation of homogeneous half-sandwich ruthenium catalyzed epimerization reactions of secondary alcohols, containing additional non-functionalized stereo-centers, was planned and made.

The results of this work are discussed in the following summary and in detail in the appended original publications II-V. During the course of this thesis a pedagogical text on CALB catalyzed KR of *rac*-1-phenylethanol, aimed at undergraduate laboratory teaching, was also produced and is appended as complementary material (publication VI).

2. Experimental

2.1 Materials

Chemicals

The chemicals were purchased from commercial sources and were used without further purification unless mentioned otherwise. The starting materials for the KR, racemization and DKR reactions were fully characterized with 1D ^{1}H and ^{13}C NMR spectroscopy using also 2D COSY, HSQC, and HMBC techniques.

The starting materials and reference compounds, 1,2-indanedione (**1**), *rac*-2-hydroxy-1-indanone (*rac*-**2**), *rac*-1-hydroxy-2-indanone, (*S*)-2-hydroxy-1-indanone [(*S*)-**2**], (S)-2-Acetoxy-1-indanone [(*S*)-**3**] were synthesized following known or slightly modified literature methods (Figure 5).[125-129]
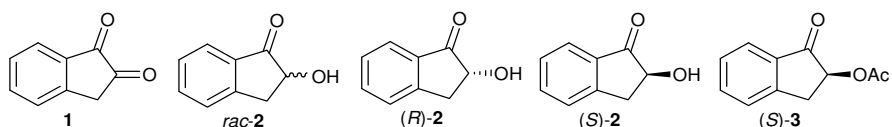
Figure 5. Structures of the compounds **1**, *rac*-**2**, (*R*)-**2**, (*S*)-**2** and (*S*)-**3**.

Enzymes

The commercially available immobilized lipases were used as delivered. The commercially available lyophilized lipases were immobilization on celite [10% (w/w) in the presence of sucrose 5% (w/w)] unless mentioned otherwise.[130] The commercially immobilized lipases CALB (Novozym 435) and lipozyme RM IM (from *Rhizomucor miehei*) were obtained from Novo Nordisk. The lyophilized CALB was obtained from Codexis and lyophilized *Candida antarctica* lipase A (CALA) was the product of Roche. The immobilized PS-CII and PS-D and lyophilized lipases PS SD (from *Burkholderia cepacia*) and AK (from *Pseudomonas fluorescens*) were purchased from Amano.

Cu/Al$_2$O$_3$

The heterogeneous copper catalyst was prepared starting from an aqueous ammonia and Cu(NO$_3$)$_2$ solution according to known literature procedure.[67] The alumina was added to the solution, the mixture was diluted and stirred. After filtration the filter cake was washed with water, dried overnight and calcined at 370 °C (3 h). The oxidized catalyst was obtained as a brown powder. Prior to each reaction the copper catalyst was reduced *in situ* at 270 °C for 30 min under flowing hydrogen.

Ru(OH)$_3$/Al$_2$O$_3$

The ruthenium catalyst was prepared according to the known literature procedure.[69,70] The calcined Al$_2$O$_3$ powder was applied in an aqueous solution of RuCl$_3$, the pH was adjusted to 13.2 with NaOH and the resulting slurry was stirred for 24 h. The solid was then filtered off, washed with a large amount of water, and dried in vacuum to yield a dark powder.

Bn$_5$CpRu(CO)$_2$Cl and Ph$_5$CpRu(CO)$_2$Cl

Catalysts **4** and **5** were prepared by co-author Denys Mavrynsky, or under his supervision, as described in the literature with spectroscopic data identical to those reported previously (Figure 6).[131,132]
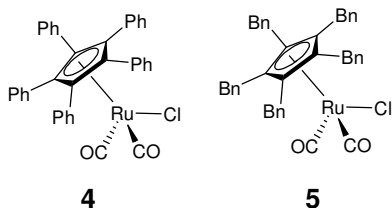
Figure 6. Structures of the half sandwich Ru complexes **4** and **5**.

Catalyst characterization

The solid Ru-catalyst samples for high resolution transmission electron spectroscopy (HRTEM) analyses were prepared from a suspension of ethanol. More than 100 particles were included for each sample when determining the metal particle diameters in the HRTEM images (in one or more pictures). The HRTEM measurements were performed with LEO 912 Omega, voltage 120 kV.

Temperature programmed reduction (TPR) of the $Ru(OH)_3/Al_2O_3$ catalyst was performed with an Auto Chem Micromeritics Auto-Chem 2900 apparatus by using the following temperature program: 10 °C/min to 400 °C.

The metal dispersion of the hydrogenation catalysts were determined using the Micromeritics apparatus by applying CO pulse chemisorption method. The Pd dispersion was calculated assuming an adsorption stoichiometry of 1/1 for CO/Pd.[133]

X-ray photoelectron spectroscopy (XPS) was conducted with Kartos Axis Ultra electron spectrometer equipped with a delay line detector. The binding energy scale was referenced to the C 1s first line of aliphatic carbon, set at 285.0 eV. The obtained spectra were processed with the Kratos software.

The ruthenium loading of the catalyst was determined by using an inductively coupled plasma optical emission spectrometer (ICP–OES; PerkinElmer, Optima 5300 DV) working at $\lambda=240.272$ nm. The ICP sample (16 mg) was applied in a teflon bomb together with aqua regia (2.5 mL) and HF (0.5 mL). The sample was digested in a microwave oven (Anton Paar, Multiwave 3000) and diluted to 100 mL with deionized water (18 MΩ) prior to analysis.

The specific surface area of the Pd/Al_2O_3 catalyst was measured by nitrogen physisorption using an automatic physisorption apparatus (Sorptomatic 1900, Carlo Erba Instruments). BET method was used for calculation of the surface area. The catalyst was degassed prior to the surface area measurement in vacuum at 150 °C.

The quantitative determination of Brønsted and Lewis acid sites of the catalyst support material was performed by using infrared spectroscopy (ATI Mattson FTIR) with pyridine as a probe molecule. The catalyst was pressed into thin wafers and evacuated at 450 °C for

60 min. The adsorption of pyridine was carried out at 100 °C for 30 min and desorption at 200 °C and spectra were recorded at 100 °C. The quantification of the adsorbed pyridine was based on the molar extinction coefficient for pyridine.[134]

2.2 Reaction Set Up

2.2.1 Heterogeneous Hydrogenation Reactions

The separate hydrogenation reactions of compounds **1, 6** and **7** (Figure 7) under atmospheric pressure were conducted in a five-necked 100 mL round-bottom flask equipped with a mechanical stirrer (gas tight adaptor), gas inlet (7 μm gas disperser merged in the solvent), in situ thermocouple, funnel (with degassing capability), rubber septa and condenser further connected to an oil bubbler for gas outlet. The catalysts used were Pd/Al$_2$O$_3$ (Aldrich; 5 wt% Pd), Pt/Al$_2$O$_3$ (Johnson–Matthey type 123; 5 wt% Pt) and Pt/Al$_2$O$_3$ (Johnson–Matthey type 5R94; 5 wt% Pt). The hydrogenation reactions were performed at 40 °C (oil bath) using hydrogen gas (Linde Gas–AGA, 99.999 %) under atmospheric pressure. The catalysts were pretreated under H$_2$ flow for 2 hours at elevated temperatures (250 °C for Pd and 400 °C for Pt) in order to ensure that all active metal is in metallic form.

6   **7**
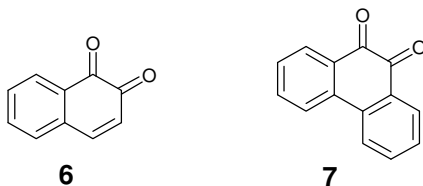
Figure 7. Structures of the compounds **6** and **7**.

For the hydrogenation of **1** (1.2 mmol,175 mg) both the starting material and the internal standard were dissolved in EA (60 mL) and deoxygenated by bubbling with H$_2$ (15 min) in the funnel directly connected to the hydrogenation vessel. The reaction was started by introducing the solution into the reaction vessel containing the activated catalyst. The

hydrogen flow rate during the reaction was 25–35 mL/min. Efficient stirring (500 rpm), small catalyst particle size (<63 μm) and metal loadings between 1 and 3 mol% were used for obtaining experimental data in the kinetic regime. For isolation of the product, the catalyst was removed by filtration through Celite. For collecting and recycling the catalyst material, the crude separation and washing were performed by removing the liquid phase from the top of the reaction vessel. The small-sized catalyst particles were allowed to sediment overnight in a tube shaped vessel after which the liquid was removed by using a syringe and needle. The catalyst particles could thereafter be transferred back to the reactor. Direct filtration of the catalyst was found unfeasible due to the fine powder-like character of the catalyst material sticking to all filter materials investigated.

2.2.2 Kinetic Resolution

The lipase (5–20 mg/mL) screenings of *rac*-**2** (0.02M) in organic solvents (2 mL) were carried out using a 4mL vial at RT. The reaction components were placed in the vials equipped with caps and the reactions were mixed using a linear shaker (170 rpm). Samples (0.1 mL) for the analyses were taken by filtering off the enzyme with 0.45 μm syringe filters.

2.2.3 Racemization Reactions

The racemization of the enantiopure (*S*)-**2** (0.01M) was conducted in three different reaction setups at 2–60 mL scale and DKR was performed on a 10 mL scale. The small scale (2 mL) reactions were performed by mixing with a linear shaker (170 rpm). For the transition metal-based racemizations, methyl *tert*-butyl ether (MTBE) or toluene (both HPLC grade) were deoxygenated by redistillation under Ar or by bubbling Ar through a 7 μm gas disperser merged in the solvent. The inert atmosphere was applied initially after 3 vacuum purge cycles with the solid catalyst material present in the Schlenk tube. Reactions in round bottom flask were stirred with a mechanical blade at 430 rpm and Schlenk tube reactions with a magnet at 750–1000 rpm. If the reaction was performed at elevated

temperatures, conventional oil bath was utilized for heating. Samples were filtered through a 0.2 µm syringe filter prior to derivatization and analysis.

2.2.4 Dynamic Kinetic Resolution Experiments

The DKRs were carried out under argon atmosphere using 10 mL (0.1 mmol *rac*-**2**) or 35 mL (3.5 mmol *rac*-**2**) solvent. The glassware used was oven dried and cooled in desiccator prior to use. For the larger scale reaction the *rac*-**2** (517 mg, 3.5 mmol) was placed in a deoxygenized (3 vacuum-argon cycles) 100 mL flask and dissolved in dry MTBE (35 mL). Trifluoroethyl butyrate (2113 µL, 14 mmol) and pentadecane (387 µL, 1.4 mmol) were added in the MTBE. The solid catalysts lipase AK (*Pseudomonas fluorescens* lipase) on celite (1756 mg), $Ru(OH)_3/Al_2O_3$ (990 mg), and dry 4 Å molecule sieves (170 mg) were placed in a Schlenk tube that was deoxygenated with several vacuum-argon cycles. Prior to reaction the tube was merged in an oil bath (41 °C). The reaction was started by adding the solution of the heterogeneous catalysts in the Schlenk tube. The reaction was stirred with a mechanical blade at 500 rpm. The sampling was conducted with a needle through gas tight septa. After the 5 h 10 min reaction, the catalysts were filtered using 0.2 µm syringe filters.

2.2.5 One-pot Reaction Application

The one-pot cascade type reactions were conducted in the same reaction vessel as the heterogeneous hydrogenation reactions and similar operation with the following minor modifications (see section 2.2.1). After Pd-catalyst pretreatment, the reaction vessel was cooled down and the degassed (three vacuum-argon cycles) mixture containing the $Ru(OH)_3/Al_2O_3$, lipase AK and 4 Å molecular sieves were introduced to the one-pot reaction vessel under Ar flow.

2.3 Homogeneous Ru-catalyzed Reactions

2.3.1 Epimerization Reactions

All glassware used in the epimerization reactions was oven dried and cooled in a desiccator over phosphorous pentoxide prior to use. Potassium *tert*-butoxide (*tert*-BuOK) was sublimated in vacuum prior to use. Tetrahydrofuran (THF) was distilled directly from sodium/benzophenone ketyl under argon. The chiral alcohols (−)-menthol, (−)-isopulegol, (+)-borneol, (+)-fenchol and (−)-cholesterol were all obtained from commercial sources. Of the starting materials, (−)-menthol was recrystallized from chloroform and (+)-borneol was predried over 4Å molecular sieves in stock solution (THF) for >24 h prior touse, (−)-isopulegol was redistilled under dry conditions (under Ar) and stored in a glovebox.

In a typical epimerization experiment, 20 µmol catalyst was dissolved in THF (2 mL) and transferred to a Schlenk tube. A magnetic stirring bar and 0.25 M solution of *tert*-BuOK in THF (100 µL, 25 µmol) were added. Activation time for the catalyst was >20 min, during which the tube was closed with a stopper and removed from the glovebox. Next, 2 mL of a 0.50 M stock solution of the starting material (1 mmol) was added to the Schlenk tube. The reaction mixture was stirred at 23 °C and samples were taken either through a rubber septa or counter gas flow using a degassed syringe and needle. Samples of the reactions were filtered through a small pad of silica in order to quench the reaction after which the sample was diluted and directly analyzed.

2.4 Analysis

Thin layer chromatography (TLC) analyses were performed by using silica gel F254 precoated aluminum sheets visualized with UV and sprayed with 25% H_2SO_4 in methanol prior to heating. Column chromatography was performed by using Merck silica gel 60 (0.040–0.063 mm). The heterogeneously catalyzed reactions were monitored by samples

from the reactor filtered using a syringe filter and diluted using the same solvent as in the reaction after which 1 μL of the solution was injected to the gas chromatograph. The main GC apparatus used was Agilent Technologies 6850 GC equipped with a Varian CP-7502 column (25.0 m x 250 μm x 0.25 μm), He as the carrier gas and FID detector. The NMR spectra were recorded by using a Bruker Avance 600 MHz spectrometer equipped with a BBI-5 mm-Zgrad-ATM probe operating at 600.13 MHz for ^{1}H and 150.92 MHz for ^{13}C. ^{1}H NMR spectra of (R)-1-oxoindan-2-yl butanoate was analyzed by using PERCH NMR software, with starting values and spectral parameters obtained from the NMR technique used.[135,136] The HRMS were recorded by using Bruker Micro Q-TOF with electrospray ionization (ESI) operated in positive mode. Melting points were determined in open capillars. The enantiomeric purity of the products was determined by chiral GC using a VARIAN, CP-Chirasil-Dex CB (25 m x 0.25 mm x 0.25 μm). The GC samples were diluted with the same solvent prior to analysis to reach low enough concentration (<1mg/ml). If applicable, the derivatization was done by 1 drop of acetic or propionic anhydride and 1 drop of pyridine containing 1% (w/w) of DMAP.

2.5 Quantum Mechanical Calculations

The following computational set up was used for quantum mechanical calculations, also presented in publication IV. The TURBOMOLE program package[137,138] version 6.1 was utilized for determining the optimized structure of compound **1**. The calculations were performed by applying density functional theory[139] with the B3LYP hybrid exchange-correlation functional[140-142] in combination with the MARI-J approximation[143-145] and the TZVP basis set[146] for all atoms, as implemented in the TURBOMOLE program package. For determining the charge delocalization in the chemical structure **1**, the GAMESS software was applied using the Hartree–Fock (HF) theory with the basis set 6-31G*[147-149] obtaining corresponding electrostatic potential fit (ESP) charges.

2.6 Student Experiment

The laboratory experiments for educational purposes were made in 4 mL vials equipped with a small magnetic stirring bar and cap. The amount of CALB used was 10 mg, MTBE 1.7 mL, *rac*-1-phenylethanol 121 µL (1 mmol) and isopropenyl acetate 220 µL (2 mmol). Sampling was done after 30, 60 and 180 min and the diluted samples were analyzed by GC equipped with a chiral column. The students calculated the conversions, *ee* values for the starting material and the product for all samples and the E-value of the reaction using the given equations.

3 Results and Discussion

3.1 Development of a Heterogeneously Catalyzed Dynamic Kinetic Resolution

A DKR can be developed by combining a kinetic resolution with racemization of the starting material. To succeed with a one-pot DKR process the reaction conditions should not negatively influence the activity, selectivity, or stability of the catalysts involved. The development of the DKR of *rac*-**2** was made by first screening the conditions of the KR and racemization in separate steps before the two individual reactions were combined.

3.1.1 Kinetic Resolution

To develop a highly enantioselective kinetic resolution of *rac*-**2**, variations in type of lipase, solvent, residual water content and different acyl donors were studied.

Eight different lipases (CALA, CALB [Novo 435], CALB [lyophilized], lipase PS-CII, lipase PS-D, lipozyme RM-IM, lipase PS-SD and lipase AK) were screened in order to elucidate the potential of some lipases that were not included in the related earlier work of Saha–Möller and co-workers.[35] The focus of the present work was the utilization of immobilized enzymes in contrast to the free, not-immobilized, lipases used previously. In accordance with the earlier results, lipase AK adsorbed on Celite exhibited the highest performance.[35] *O*-acylation of *rac*-**2** by using vinyl butyrate in diisopropyl ether (DIPE) with lipase AK on celite provided (*R*)-**3** in 91% *ee* at 25% conversion (Table 1, entry 1).

In accordance with similar *O*-acylations,[150] apparent hydrolysis of the product, (*R*)-1-oxo-indan-2-yl-butanoate, back to the starting material was observed becoming more evident with increasing conversion and reaction time (Table 1, entries 1 and 2).

Table 1. Variations of solvent and reaction time for *O*-acylation of *rac*-**2** (0.02 M) with vinyl butyrate (0.04 M).

Entry	Solvent	time[h]	*ee* [%] substrate	*ee* [%] product	Conversion [%][a]
1	DIPE	1[b]	31[b]	91[b]	25[b]
2	DIPE	24[b]	35[b]	55[b]	38[b]
3	DPIE, dry[c]	2	10	95	9
4	DPIE, dry[c]	24	50	94	35
5	DPIE, dry[d]	24	50	92	35
6	MTBE, dry[c]	24	52	91	36
7	DEE, dry[c]	24	22	88	20
8	Toluene, dry[c]	168	16	93	15
9	THF, dry[c]	144	21	90	19
10	Acetone, dry[c]	144	9	95	9

[a] calculated from *ee* values; [b] loading of lipase AK catalyst= 20 mgmL[-1]; [c] dried with 4 Å molecular sieves; [d] dried with CaH$_2$.

For minimizing the influence of water originating from the immobilized enzyme on product hydrolysis, the enzyme loading was decreased from 20 mg/mL to 5 mg/mL. Likewise, all solvents were dried by using either 4 Å molecular sieves or CaH$_2$. As shown in Table 1, better results were obtained under dry conditions (Table 1, entries 2, 4, 5). Both DIPE and MTBE proved to be the good solvents for the KR of *rac*-**2**. MTBE was selected as the solvent for further experiments due to problems with solubility of *rac*-**2** in DIPE, especially at concentrations >0.02 M.

The *E*-value, expressing the enantioselectivity of the KR, becomes distorted because of the facile hydrolysis of the acylated product and is thus labeled *E**. Further, *E** is defined only in the beginning of the reaction at which time the influence of the product hydrolysis on enantioselectivity can be considered negligible.

The influence of four different acyl donors in the lipase AK catalyzed *O*-acylation of *rac*-**2** was studied. For all acyl donors used (vinyl butyrate, vinyl acetate, 2,2,2-trifluoroethyl butyrate and isopropenyl acetate), moderate enantioselectivities (*E**=20–30) were observed. Reactions with the vinyl esters gave higher conversions (36% and 45%) in

comparison with 2,2,2-trifluoroethyl butyrate (18%) and isopropenyl acetate (6%). Vinyl acetate provided, in some cases, higher enantioselectivities, but was replaced with vinyl butyrate to suppress the product hydrolysis.

Conclusively, lipase AK (5 mg/mL) as the catalyst using vinyl butyrate (2 equivalents) as the acyl donor and dry MTBE (4 Å molecular sieves) as the solvent, was the best combination for the resolution of *rac*-**2** (0.02M). Under these conditions, acceptable *ee* values (91%, E^*=34) of the product (*R*)-1-oxoindan-2-yl butanoate were obtained without any significant side reactions at 36% conversion after 24 h.

3.1.2 Heterogeneously Catalyzed Racemization of (*S*)-2-Hydroxy-1-indanone

In the present work the aim was to explore structurally simple heterogeneous racemization catalysts. The most apparent groups of potential catalysts were: 1) Brønsted or Lewis acids and bases; and 2) Transition metal catalysts.

The racemization of (*S*)-**2** (Scheme 14) was investigated by using one weak and three strong acidic resins (Amberlyst CG50, Dowex 508, Amberlyst 15, Smopex101) as well as five basic homogeneous or heterogeneous catalysts (Amberlite IRA 904, Duolite A-340, Proton sponge, 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU), Phosphazene base P4-tBu solution). The basic catalysts and weak carboxylic acid-based ion exchangers studied did not give satisfactory racemization. Nevertheless, by using strong, sulfonic acid based ion exchange based catalysts Amberlyst 15 and Smopex 101, reasonable racemization of the substrate (*S*)-**2** was achieved within 24 h. These observations are in line with the results of the earlier literature report.[60]
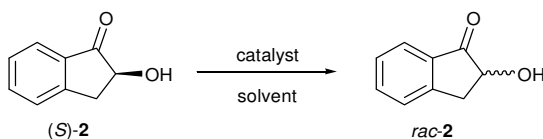
Scheme 14. Catalytic racemization of (*S*)-**2** to *rac*-**2**.

However, the use of strong sulfonic acid based catalyst included two main drawbacks. The first disadvantage was the inactivation of the lipases by Amberlyst 15, which was also reported earlier by Ödman et al.[60] The second, slightly surprising drawback, was the formation of 2-tert-butanoxy-1-indanone by-product in the presence of the MTBE solvent. More precisely, the cleavage of the *tert*-butanoyl-O bond in MTBE by strong Brønsted acids. The subsequent attack on the formed carbocation by the slightly nucleophilic OH group of 2-hydroxy-1-indanone then forms 2-tert-butanoyl-1-indanone and methanol (Scheme 15). The analytical data of the isolated 2-tert-butanoyl-1-indanone are consistent with those previously published.[151]
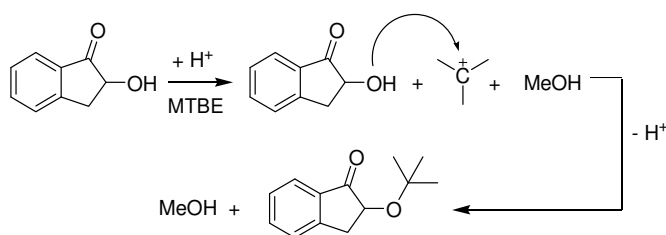
Scheme 15. Acid catalyzed formation of 2-tert-butanoyl-1-indanone in MTBE.

To avoid byproduct formation due to the solvent participation in the racemization experiments, the solvent was switched from MTBE to toluene. Pentadecane was used as an internal standard for comparing the relative concentrations of the components in the experiments. When studying the racemization reactions, a decrease in substrate/standard ratio with increasing catalyst concentration was observed. The data obtained suggest a process competing with racemization. Possible explanations could be dimerization of 2-hydroxy-1-indanone and/or substrate interference with the acidic functionalities of the catalyst.

It is known that also Lewis acidic materials, e.g. Zeolites and VOSO₄, catalyze the racemization of secondary alcohols.[65] Thus, attempts to racemize (S)-**2** with acidic mordenite (H-mor), ZSM 5, H-beta and VOSO₄ were made. The reaction conditions used were similar to those employed with Brønsted acidic catalysts. Racemization of (S)-**2** (0.02

M) at 40 °C using EA as the solvent in the presence of 0.02 M VOSO₄ proved unsuccessful. Conclusively, only modest racemization of (*S*)-**2** was observed using the Lewis acidic zeolites, possibly due to the substantially lower acid site concentration as compared to Amberlyst 15 and Smopex101.

Heterogeneous Cu-catalyst has also been reported to racemize secondary alcohols.[66] Characterization of the Cu/Al₂O₃ catalyst displayed low concentrations of Brønsted and Lewis acidic sites, 7 µmol/g and 156 µmol/g, respectively. The BET specific surface area of the support was 300 m²/g and the metal dispersion of Cu was, according to CO-pulse-chemisorption, close to 8 %. The trial racemization reactions of (*S*)-**2** using the Cu/Al₂O₃ seemed promising. Further racemization studies with 0.5 molar equivalents of (*S*)-**3** to mimic the DKR reaction product revealed a strong inhibition of the Cu-catalyst activity (Figure 8). The strong inhibition of the racemization may be due to coordination of the oxygen rich ester moiety in (*S*)-**3** to the active copper sites. Accordingly, further efforts to utilize a copper-based racemization catalyst for DKR were not pursued.
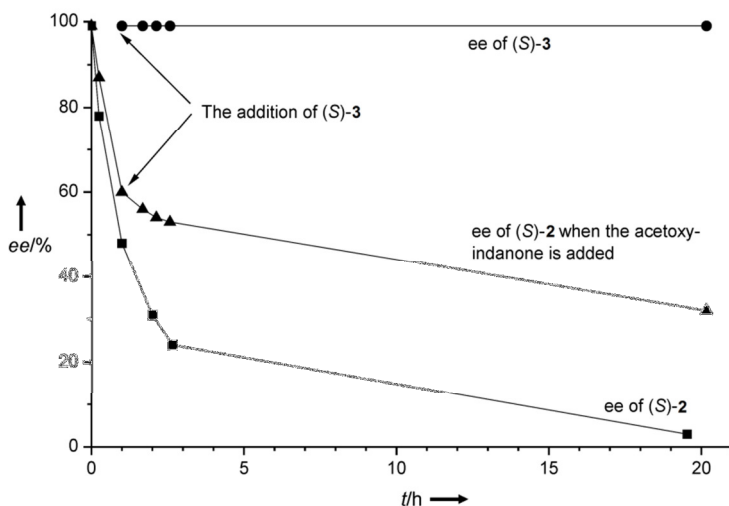

Figure 8. Racemization of (*S*)-2 (0.010 M) with 0.40 mg/ml Cu/Al₂O₃ catalyst in toluene at 70 °C. The first reaction (■) performed with only (*S*)-2 and catalyst. The second reaction (▲) was carried out analogously except for the addition of (*S*)-2-acetoxy-1-indanone (0.0050 M) after 60 min. The (●) describes the *ee* of (*S*)-2-acetoxy-1-indanone in the second reaction.

There are some reports in literature of secondary alcohol racemization using $Ru(OH)_3/Al_2O_3$ catalyst.[68-71] In this work the racemization of the vicinal hydroxyl ketone, (*S*)-**2**, a structurally more interesting molecule, catalyzed by $Ru(OH)_3/Al_2O_3$ was studied.

The heterogeneous Ru-catalyst prepared was characterized by means of HRTEM (particle size distribution), TPR (reduction temperature), and XPS (oxidation state). Based on ICP–OES results, the heterogeneous $Ru(OH)_3/Al_2O_3$ catalyst contained a 1.9% (w/w) metal loading. The mean particle size based on HRTEM was 1.3±0.4 nm. The sizes of species involved in the reactions are displayed in Figure 10. The TPR of the catalyst confirmed that no reduction took place at temperatures below 70 °C in H_2 atmosphere and the maxima for the H_2 uptake at 137, 244, and 338 °C (Figure 4A). The XPS data displayed binding energy peaks at 463.5 and 485.7 eV defining the oxidation state of the ruthenium species to +III (Figure 9B).
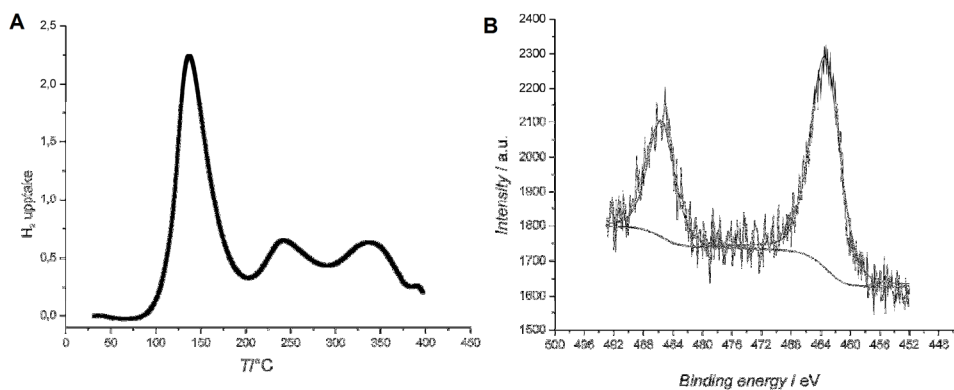
Figure 9. A) TPR of $Ru(OH)_3/Al_2O_3$ and B) XPS spectra of $Ru(OH)_3/Al_2O_3$ in the Ru 3p region.
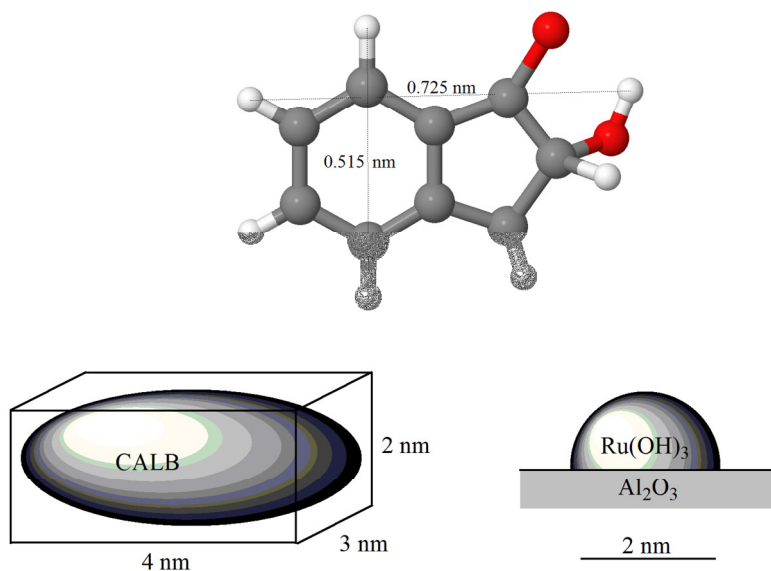
Figure 10. Display of the sizes (at different scales) for compound **2**, CALB and Ru metal particle on the $Ru(OH)_3/Al_2O_3$ catalyst.

To study the racemization reactions the *ee* values of (*S*)-**2** were plotted against the normalized time [(time)·(concentration of catalyst)]. When the racemization reactions are performed in the kinetic regime without external mass transfer limitations, with different concentrations of catalyst the normalized time data points should overlap. This was, however, not the case for (*S*)-**2** when 0.5 molar equivalents of **3** was present (Figure 11). The racemization rate accelerated more than expected when the catalyst concentration was increased. The poisoning at the lower Ru catalyst concentration, seemed to be a result of the higher [compound 3]:[Ru catalyst] ratio. Compound **3**, including the polar ester moiety, was probably more readily coordinating to the active sites on the Ru catalyst than (*S*)-**2**, thus inhibiting the racemization of (*S*)-**2**.
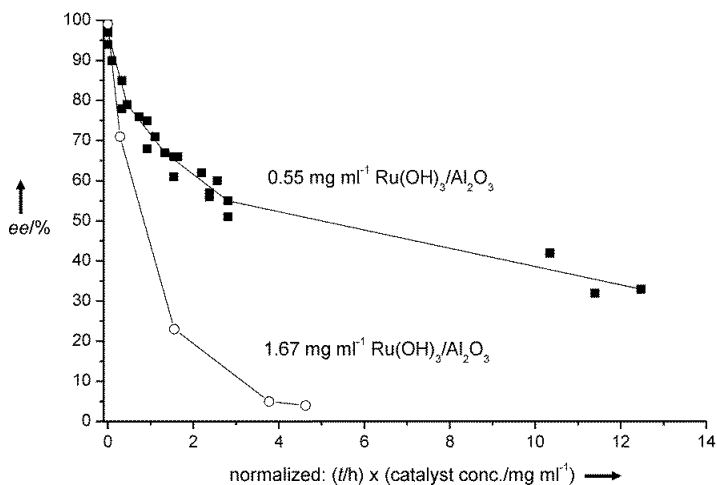
Figure 11. Racemization of (*S*)-**2** (0.01 M) under argon in the presence of 2-acetoxy-1-indanone (0.005 M) in MTBE at 25 °C. Two separate reactions were performed with different concentrations of Ru(OH)$_3$/Al$_2$O$_3$, (■) 0.55 mg ml^{-1} and (○) 1.67 mg ml^{-1}.

However, complete racemization of (*S*)-**2** (0.01M) was observed in 5 h using 1.67 mg/mL^{-1} of the Ru(OH)$_3$/Al$_2$O$_3$ in the presence of 0.5 molar equivalents of (*S*)-**3**. When comparing the practical operation of the copper and ruthenium on alumina, the obvious advantage with the latter is that no reduction is required prior to its use, making the racemization over ruthenium simple to operate and thus viable for use in the context of DKR.

3.1.3 Dynamic Kinetic Resolution of *rac*-**2** Using Heterogeneous Catalysts

One of the objectives of this thesis was to develop a one-pot DKR of *rac*-**2**. The KR and racemization studies showed that best DKR results could be achieved by combining the heterogeneous Ru(OH)$_3$/Al$_2$O$_3$ racemization catalyst with the immobilized lipase AK.

When the KR was transformed into DKR the vinyl butyrate acyl donor was changed to trifluoroethyl butyrate to suppress possible coordination of the acyl donor to the ruthenium catalyst. The change of the acyl donor made it also possible to carry out the DKR under hydrogen atmosphere if needed. In addition, the amount of acyl donor was

increased from 2 to 4 molar equivalents. Furthermore, possibility for the product hydrolysis was decreased by addition of 4 Å molecular sieves to the reaction mixture.

When shifting from KR to DKR the conversion increased from 35 to 90 % while only marginally affecting the enantioselectivity 91-93% in KR versus 91-92% in DKR. The reaction was successfully scaled up using 0.5 g of substrate (0.1 mole/L) obtaining initial *ee* (91%) similar to those observed under lower substrate concentration. With longer reaction times, however, a slightly lower *ee* (86%) was obtained. After 5 h the conversion reached was similar to earlier values (85%). In the larger scale experiments, there was nevertheless a decrease in racemization activity resulting in higher *ee* of the starting material after 5 h (*ee* of (S)-**2**=40%) when compared to that observed under more diluted reaction conditions (*ee* of (S)-**2**=30 %).

Conclusively, although the racemization rate in the heterogeneously catalyzed DKR reactions is slightly inhibited by the esters present, the use of *rac*-2-hydroxy-1-indanone as the starting material provided the acylated product in 90% conversions and up to 92% *ee* of the acylated product (Scheme 16).
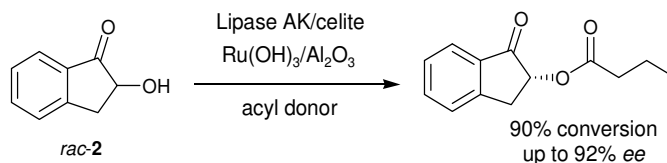
Scheme 16. DKR of *rac*-**2** using lipase AK/Celite and $Ru(OH)_3/Al_2O_3$.

The presence of compound **1** in low concentrations during the DKR experiments was confirmed by the GC and GCMS results. The formation of **1** should nevertheless be avoidable under reductive reaction conditions. Notably, Busygin et al. have reported the regioselective hydrogenation of **1** over Pt/Al_2O_3 catalyst to yield 2-hydroxy-1-indanone.[152]

Preliminary study on the kinetics indicates that the initial rate of the (S)-**1** racemization in the absence of acylation, using 0.5 molar equivalents of 2-acetoxy-1-indanone, is in the region of 0.08 mmol/(g_{cat} min). On the other hand the initial rate of the enzyme-catalyzed acylation of *rac*-**1** reaches 0.09 mmol/(g_{cat} min). Generally, in DKR, the racemization rate

should be higher than the rate of enzyme catalyzed acylation. However, in the reactions performed here, these rates were sufficiently similar to enable DKR. To produce a more efficient DKR, a higher racemization rate would be desirable. Kinetics of $Ru(OH)_3/Al_2O_3$ for racemization in DKR applications have been studied more carefully earlier for 1-phenylethanol by Kirilin et al.[100]

The gram scale DKR reaction was carried out in a similar but bigger schlenk vessel. The reaction solution was concentrated under vacuum and the product, (*R*)-1-oxoindan-2-yl butanoate, was purified twice by column chromatography using diethyl ether/hexane/MTBE 1:4:1 as the eluent and finally using the following gradient diethyl ether/hexane 0:1 →1:2. The product was received as a colorless oil [439 mg; 2.09 mmol; yield 60 %; *ee*=86%; α_D^{24}=-39.7 cm^{3}g^{-1}dm^{-1} (c=0.010 g/cm in CHCl$_3$)]. The isolated yield was lower than expected most likely as a result of the repeated column chromatography purifications and the formation of 1,2-indanedione by-product.

3.2 Regioselective Hydrogenation of 1,2-Indanedione

The utilization of **1** as a starting material for further synthetic applications is attractive due to the fact that it is easy to prepare and readily available. This is probably in part due to its minor use as a forensic fingerprint reagent.[153,154]

The initial hydrogenation experiments were made by using MTBE as solvent. However, when using **1** as starting material, MTBE was not sufficiently efficient as a solvent for reliable and practical operation. By switching the solvent to EA better reproducibility and more reliable results were obtained.

The hydrogenation studies were continued by hydrogenation experiments using three different catalyst concentrations, 1.0, 2.0 and 3.0 mol% Pd for determining the initial reaction rates. For this purpose the samples were withdrawn in the beginning of the reaction when the concentration of the starting material decreased linearly. Subsequently, when the calculated initial rates were plotted against the catalyst concentration, a linear

correlation was obtained confirming that the reaction proceeds without external (gas/liquid) mass transfer limitations.

The performances of both Pd and Pt catalysts were investigated in the hydrogenation of compound **1** (Pt/Al$_2$O$_3$ (type123), Pt/Al$_2$O$_3$ (type 5R94) and Pd/Al$_2$O$_3$). With both Pd and Pt catalysts **1** was converted to *rac-***2** in high selectivity (99 %) at up to 50 % conversion. While with increasing conversion the selectivity decreased, acceptable selectivities (92–94 %) were obtained with Pd/Al$_2$O$_3$ at 75–80 % conversion (Figure 12).
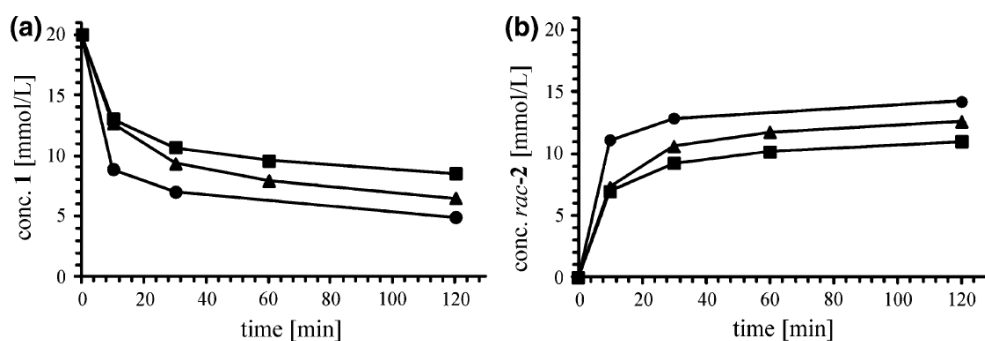
Figure 12. Kinetics of the hydrogenation of **1** using Pt/Al$_2$O$_3$ type 123 ■, Pt/Al$_2$O$_3$ type 5R94 ▲, Pd/Al$_2$O$_3$ ● displayed as a function of (a) concentration of **1**, and (b) concentration of *rac-***2**.

3.2.1 Deactivation of the Catalysts

The hydrogenation reaction was found to be very selective and all catalysts active during the initial stages of the reaction. After prolonged reaction time, the reaction rate declined. Retardation of the reaction rate was evident from analysis of the shapes of the reaction concentration profiles (Figure 12).

The observed inhibition of the reaction was assumed to be a consequence of catalyst deactivation. Performances of the Pd and Pt catalysts studied were similar, indicating that the deactivation is not caused by the catalyst material. Potential origins of the deactivation may include coking, metal leaching or strong poisoning by either impurities or reaction products.

Analysis of the BET specific surface area, thermogravimetric analysis and FTIR were made in order to determine if the origin of the deactivation would be coking. Nevertheless, no clear evidence clarifying the observed catalyst deactivation was found. In further analysis the elemental composition of the spent and deactivated Pd catalyst was investigated using scanning electron microscope – energy dispersive X-ray analysis (SEM–EDXA). The spent catalyst surface was found to contain 0.44 wt% sulfur and 0.16 wt% sodium. As it is generally known that these elements, especially sulfur, are often responsible for metal based catalyst poisoning the slow reaction rate observed at prolonged reaction times could, at least in part be attributed to sulfur deposited on the catalyst surface. Such deposition and poisoning could principally originate from the gas, solvent, catalyst or substrate of which the gas and the solvent can be ruled out based on the suppliers' quality assurance. Thus, the only source of sulfur contamination is the substrate, 1,2-indanedione.

Some attempts for elimination of the possible sulfur contamination in **1** were made. Initially, **1** was dissolved in acetone and the possible sulfur contamination removed by use of active carbon followed by recrystallization of **1** from acetone. This procedure did not, however, improve the results of the hydrogenation reaction.

The following attempt was modification of the synthetic procedure for preparation of **1**. The synthesis was modified by replacing the concentrated sulfuric acid used for hydrolysis of the 2-oxime-1-indanone precursor with concentrated HCl. The potential hazard in the use of HCl in turn is the possible formation of a toxic and carcinogenic by-product, bis(chloromethyl) ether, discussed earlier by Gupta and Marathe.[126] The hydrogenation of **1**, synthesized without the use of sulfuric acid, exhibited an apparent slightly increased reaction rate and conversion compared to the earlier experiments using **1** prepared by using the sulfuric acid based literature method. By using the improved synthesis of the starting material the average TOF value during 0-10 min increased slightly from 0.21 to 0.22 s^{-1} and the conversion at 120 min from 75–80 to 84 %. Furthermore, the spent Pd/Al$_2$O$_3$ catalyst was analyzed after the hydrogenation by same SEM–EXDA method verifying that no sulfur or chlorine was present on the catalyst surface when **1** was

prepared using HCl. Conclusively, these results suggest that the Pd catalyst in the hydrogenation of **1** could potentially be poisoned by sulfur originating from the concentrated H_2SO_4 used in the synthetic preparation of **1**. In addition, if the probable sulfur contamination originating from the sulfuric acid would sustain its acidity it could cause some leaching of Al from the Al_2O_3 structure creating additional porosity. This could in principle also account for the increase in the specific surface area of the Pd/Al_2O_3 catalyst analyzed before and after the hydrogenation reactions.

3.2.2 Selectivity

When comparing the Pd and Pt catalysts, the reactions over the Pd/Al_2O_3 catalyst gave after 120 min slightly higher conversions with selectivities similar to those observed for the two Pt catalysts (Table 2). The observed conversion of **1** over the Pt catalysts studied correlated with the metal dispersions of the catalyst materials so that the Pt catalyst with the somewhat higher metal dispersion also exhibited slightly higher conversion values. Due to the better overall performance and lower pretreatment temperature required, the Pd/Al_2O_3 catalyst was then selected for further studies.

Table 2. Conversion of **1** and selectivity towards *rac-***2** using Pd and Pt catalysts.

Entry	Catalyst[a]	Pretreatment temperature under H_2 flow	Conversion of **1**[b]	Selectivity for *rac-***2**
1	Pd/Al_2O_3	250	84	92
2	Pt/Al_2O_3 (type94)	400	68	93
3	Pt/Al_2O_3 (type123)	400	57(61)[c]	96

[a] 2 mol%; [b] At 120 min determined by GC; [c] Verified by NMR analysis

During the first 30 min of the hydrogenation reaction, the formation rate of indanediols was much lower (0.57 µmol/min) compared to the formation of *rac-***2** (24 µmol/min). In reactions with prolonged reaction time, the conversion of **1** exceeded 80 %

after 2 h and the concentration of *rac*-**2** started to decrease while the concentration of the isomeric indanediols increased from 1 mmol/L (2 h) to 10 mmol/L (18 h). To obtain a high yield of *rac*-**2** and low formation of indanediols, the reaction time of 120 min was found optimal with 2 mol% Pd, corresponding to 84 % conversion of **1** (Figure 13).
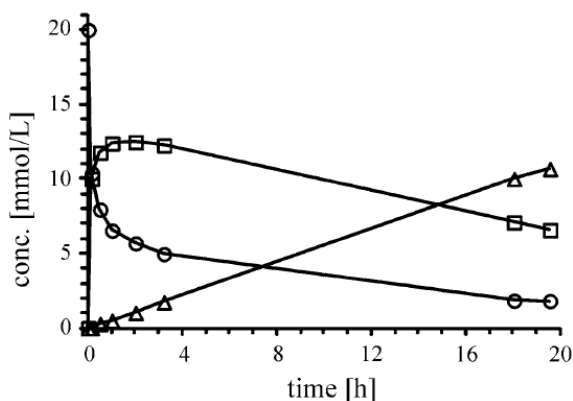
Figure 13. Concentration profile of **1** ○, *rac*-**2** □ and indanediols Δ during the hydrogenation reaction of **1** (1.2 mol) using 2 mol% Pd in EA (60 mL).

Only negligible amounts of the regioisomeric byproduct *rac*-1-hydroxy-2-indanone were detected in the hydrogenation of **1** to *rac*-**2**. Similar high regioisomeric selectivity towards *rac*-**2** has been reported earlier by Chiang et al. in a study of the kinetics and mechanism of acid catalyzed hydrolysis of the two related diazo compounds 1-diazo-2-indanone and 2-diazo-1-indanone (Scheme 17).[129] Chang et al. found the hydrolysis of 2-diazo-1-indanone, yielding *rac*-**2**, to be considerably faster than the hydrolysis of the corresponding regioisomer. The difference in the reactivity of the two diazo compounds was suggested to be a result of electron delocalization to the aromatic moiety when the diazo group is adjacent to an aromatic ring, decreasing the basic character of the diazo carbon in position 1.[129]
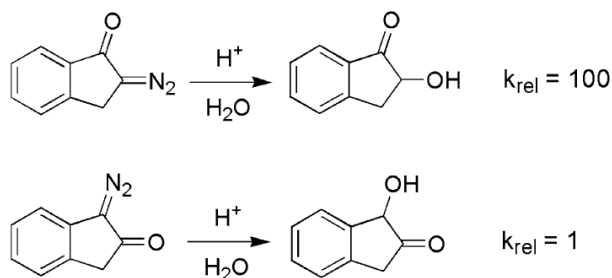
Scheme 17. Acid catalyzed hydrolysis of the regioisomeric diazoindanones.[129]

The high regioselectivity in the hydrogenation of **1** yielding *rac*-**2** is likely a result from the large reactivity difference between the two keto groups. This explanation is supported by the similar selectivities of both Pd and Pt catalysts towards *rac*-**2** in the hydrogenation of **1**. The adjacent aromatic ring remarkably decreases the reactivity of the carbonyl group in position 1.

Notably, the observed regioselectivity in the hydrogenation of 1,2-indanedione is reversed as compared to the regioselectivity in the heterogeneously catalyzed hydrogenation of the structurally more flexible analogue, 1-phenyl-1,2-propanedione.[155-157] For 1-phenyl-1,2-propanedione, the regioselectivity towards ketone moiety adjacent to the aromatic ring has been explained by the interactions between the substrate and the metal surface. Thus, while structurally related, the two substrates 1-phenyl-1,2-propanedione and 1,2-indanedione appear to exhibit different adsorption behavior on the catalyst surface thus resulting in opposite regioselectivities in hydrogenation reactions.

In order to verify that the hydrogenation reaction fully proceeds under heterogeneously catalyzed conditions without leaching of Pd to the liquid phase, ICP–OES analysis was used. According to the analysis, the amount of dissolved Pd is below the detection limit (2 ppm) thus indicating that the actual concentration of dissolved metal is likely to be even lower and does not influence the overall catalytic activity.

3.2.3 Product Isolations and *in situ* Derivatization

The primary objective of the hydrogenation of **1** was to develop a practical process for obtaining *rac*-**2** in high conversion and selectivity in sufficiently high isolated yield. Based on the conversion and selectivity, the expected yield should have been in the 70–77 % range. After filtration of the catalyst, removal of the solvent and chromatographic purification, the isolated yield of *rac*-**2** remained at 45 %. In order to improve the isolated yield, an in situ derivatization of the hydroxyl group in *rac*-**2** to the corresponding ester was attempted (Scheme 18). Disappointingly, only marginal improvement of the isolated yield to 48 % was obtained. Such high losses of isolated yield are evidently due to the small scale of operation investigated here.
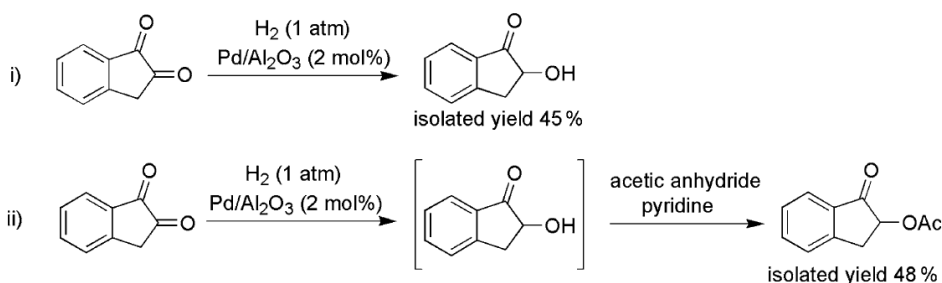
Scheme 18. i) Hydrogenation of **1** yielding *rac*-**2**, ii) Hydrogenation of **1** combined with in situ derivatization to 2-acetoxy-1-indanone.

In order to further develop and apply the regioselective hydrogenation of vicinal diketones to other potential structures, preliminary hydrogenation studies by using 1,2-naphthoquinone (**6**) and 9,10-phenanthrenequinone (**7**) as the starting materials were made. The hydrogenations of compounds **6** and **7** were initially carried out under similar reaction and pretreatment conditions as used for compound **1**. While investigating the hydrogenation of **6**, it became evident that the conditions used for **1** were not applicable for this compound. In the GC analysis, no product was observed although during the hydrogenation reaction a recognizable color change from bright yellow, distinctive for diones, to colorless was observed. The disappearance of the product was then discovered to be a result from back-oxidation of the product to starting material in air atmosphere prior

to analysis. Apparently, the reduction-oxidation equilibrium shifts rapidly towards the oxidized form upon exposure to air after venting of the hydrogenation reactor. In order to avoid the re-oxidation an in situ derivatization by acylation was applied. This was envisioned also to enable easier separation and to increase the isolated yield. This sequence provided for the two different starting materials the corresponding diacetates **8** and **9** in isolated yields of 85% and 78%, respectively (Schemes 19 and 20). The isolated diacetate products are likely formed by rearrangement of the hydroxy ketones by proton transfer and subsequent aromatization.

Notably, because of the symmetric structure of **7** the hydrogenation cannot proceed in a regioselective manner. Nevertheless, the successful in situ derivatizations of the reaction products indicate that the envisioned conceptually related one-pot hydrogenation and esterification sequences should be feasible.
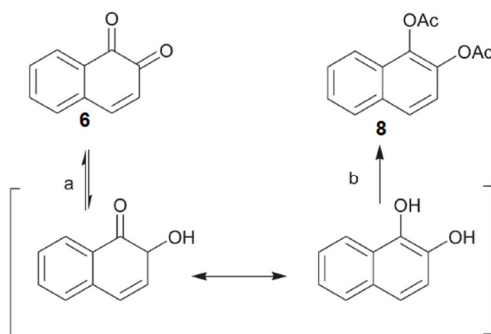
Scheme 19. Hydrogenation (a) and subsequent esterification (b) of **6** to **8** with H_2 (1 atm.) and Pd/Al$_2$O$_3$ as catalyst.
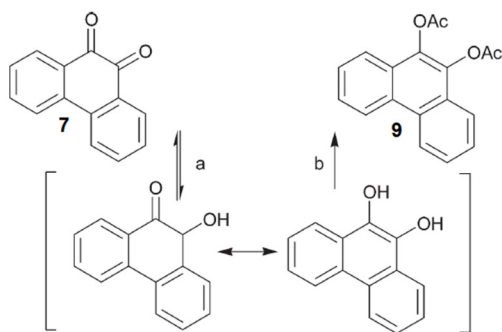
Scheme 20. Hydrogenation (a) and subsequent esterification (b) of compound **7** to **9** with H_2 (1 atm.) and Pd/Al_2O_3 as catalyst.

3.3. Development of a New One-pot Reaction Cascade

The primary aim of this thesis was to combine the regioselective hydrogenation of **1** with DKR of *rac*-**2** thus providing, if successful, a rapid access to (*R*)-**3** from 1,2-indanedione directly.

3.3.1 Antiaromatic Character of 1,2-Indanedione

Quantum mechanical calculations were carried out in order to elucidate the potentially antiaromatic character of compound **1** to clarify if some eventual incompatibilities could emerge with the catalysts or reaction conditions used.

By definition antiaromatic compounds contain 4n (n ≠ 0) π-electrons in a cyclic and planar or nearly planar system consisting of alternating single and double bonds.[20] Three additional characteristics possessed by antiaromatic compounds are: 1) Decreased thermodynamic stability; 2) Tendency to alternation of bond lengths; and 3) Small energy gap between the highest occupied (HOMO) and the lowest unoccupied molecular orbitals (LUMO).[20] Tyutyulkov and coworkers have earlier performed quantum chemical calculations for the enolic anion form of **1**, with results supporting the antiaromatic

character of the anionic structure with Jahn–Teller distortion and spectroscopic data supporting the proposal of a small band gap between the HOMO–LUMO.[158] Furthermore, compound **1** and the related reactive radical structures have been studied using electron spin resonance by other investigators.[159-161]

As the tendency to alternation of bond lengths is one of the characteristics possessed by antiaromatic compounds, the bond lengths of **1** were evaluated here using quantum mechanical calculations. The calculations performed clearly indicate the unmodified structure of **1** to be less antiaromatic compared to its enolic counterpart with the calculated bond lengths of **1** not significantly differing from the expected ones, also not indicating any significant Jahn–Teller distortions (Figure 14).
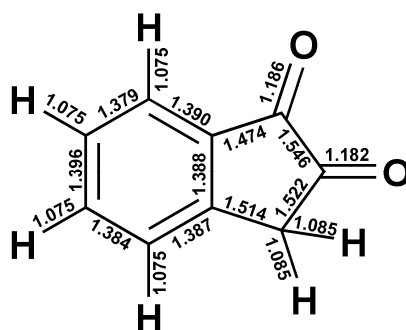
Figure 14. The interatomic distances (in Ångström) for the 1,2-indanedione obtained from the quantum mechanical calculations.

As the benzylic charge delocalization likely results in different atomic charges on the carbonyl groups in position 1 and 2, and could influence the chemical behavior of **1**, the atomic charges were calculated. While the difference between the atomic charges of the two carbonyl carbons is moderate (C-1 +0.45; C-2 +0.56), the results obtained support the earlier suggested property of delocalization of the benzylic C=O double bond to the aromatic region and thus resulting in the relatively higher reactivity of the carbonyl group in position 2.[129]

Conclusively, in order to fully explain the behavior of **1** in the heterogeneously catalyzed hydrogenation reactions, more thorough calculations would be needed, including calculations of the different adsorption modes of the substrate to the different

catalyst surfaces. As indicated by the results obtained herein, the non-ionized form of **1** shows only one antiaromatic feature, namely the small band gap between the HOMO and LUMO, -0.246 E_h and -0.110 E_h, respectively.

3.3.2 One-pot Reaction Combining Hydrogenation and Dynamic Kinetic Resolution

The minor formation of compound **1**, an undesired by-product, was observed during the development of the DKR. As shown, by selecting suitable reaction conditions it is possible to achieve a regioselective catalytic hydrogenation of compound **1** producing *rac*-**2**. The one-pot combination of the regioselective hydrogenation of **1** and DKR of *rac*-**2** would produce a beneficial and efficient reaction sequence.

The initial one-pot experiments combining the hydrogenation and DKR were conducted by switching the reaction atmosphere from hydrogen gas to argon during the reaction. This was also made in a conceptually similar and related one-pot type reaction sequence reported by Bäckvall and co-workers.[119] In the first one-pot experiments performed, the gas feed was therefore changed from hydrogen to argon after two hours of reaction. When comparing the reactions where the atmosphere was changed from H_2 to Ar with those reactions where only H_2 was used, it was evident that the introduction of argon did not enhance the outcome of the one-pot reaction sequence. Therefore further one-pot experiments were conducted using only hydrogen gas.

For selecting a suitable solvent for the one-pot reactions both MTBE and EA were considered. The MTBE required a long time to dissolve **1** at the desired concentrations and at higher concentrations resulted even in slightly hazy solutions, also observed earlier in the development of the regioselective hydrogenation. For this reason EA was chosen as the solvent for further one-pot experiments.

In the one-pot sequence reactions where EA was used as solvent and trifluoroethyl butyrate as acyl donor, not surprisingly, both the acetate and butanoate products were observed in a 1.7:1 ratio. In previous lipase catalyzed esterification reactions, Park and co-workers have reported the use of EA in a dual role, both as an acetyl donor and a

solvent.[77,162] Generally, when the solvent also acts as the acetyl donor, the overwhelming molar excess of solvent compared to the molar amount of substrate drives the reaction equilibrium heavily to the right. In the one-pot sequence reactions investigated here, the use of EA as both the solvent and acetyl donor also proved feasible at first, retaining the high product *ee* (>90% after 21 h) value throughout the whole reaction (Table 3, entry 2). An activated acetyl donor was needed for increasing the conversion and yield. By carrying out one-pot reactions with increasing amounts of activated acyl donor, trifluoroethyl acetate, the yield consequently increased as expected (Table 3, entries 3–5).

Table 3. One-pot sequence combining hydrogenation and DKR producing (*R*)-**3** from **1** (1.2 mmol) over Pd/Al$_2$O$_3$ (2.0 mol%) using a 21 h reaction time.

| Entry	Solvent	Acyl donor[a] (equivalents)	Yield[b] [%]	ee[b,c]
1	MTBE	8 (3.7)	52	28
2	EA	-	34	90
3	EA	9 (1)	33	91
4	EA	9 (2.5)	40	86
5	EA	9 (4)	51	86

[a] Equivalents acyl donor related to the amount starting material; [b] Based on GC analysis; [c] *ee* = 100·([*R*-**3**]-[*S*-**3**])/([*R*-**3**]+[*S*-**3**]); [d] Added in portions.

To further study how the reaction properties influence the outcome of the one-pot reaction sequence, reactions with different enzyme amounts (93, 130, and 163 mg) were performed. Changes in the enzyme amount were expected to influence the reaction rate of the KR part of the one-pot sequence (Figure 15). Consequently, the change in the acetylation rate was assumed to influence the (*R*)-**2**:(*S*)-**2** ratio. The rate by which the acetylated end product was formed (k_A) was, nevertheless, influenced only slightly by the variation of the enzyme amount (Scheme 21). Subsequently, the concentrations of the components in the three separate one-pot reactions are similar. One example of the kinetic curves obtained from a one-pot process is shown in Figure 16. Conclusively, these results demonstrate that the enzyme catalyzed KR in the one-pot sequence is not the rate limiting step.
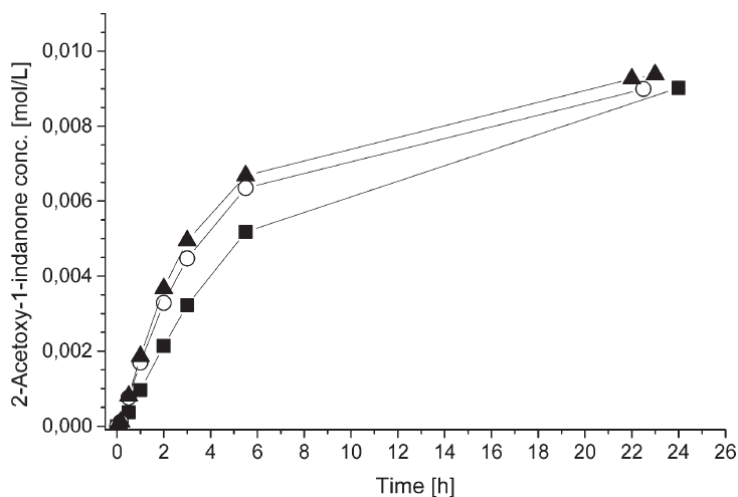
Figure 15. Concentration of 2-Acetoxy-1-indanone for one-pot reactions using ■ 93 mg, ○ 130 mg and ▲ 163 mg of lipase AK together with 51.6–51.9 mg Pd/Al$_2$O$_3$, 89.5–90.1 mg Ru(OH)$_3$/Al$_2$O$_3$ and 4 equivalents (550 µL) of the acetyl donor at 40 °C.
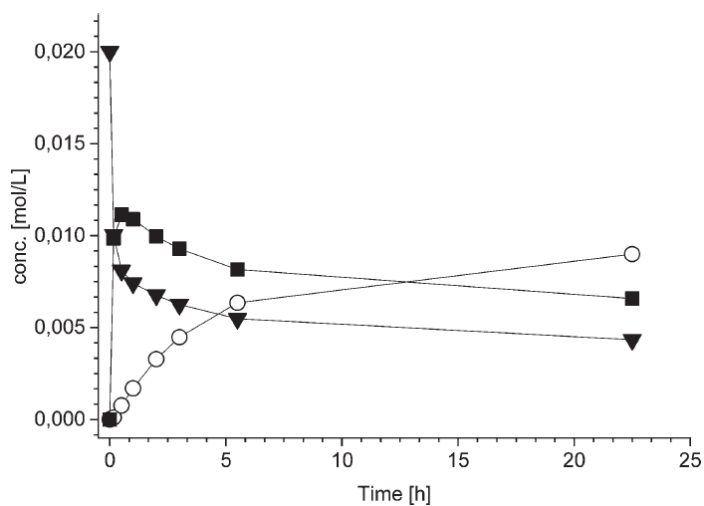
Figure 16. Concentration profiles of compound 1 ▼, compound 2 ■ and compound 3 ○ for a one-pot reaction using 51.6 mg Pd/Al$_2$O$_3$, 89.5 mg Ru(OH)$_3$/Al$_2$O$_3$, 130 mg lipase AK and 4 equivalents (550 µL) of activated acetyl donor at 40 °C.
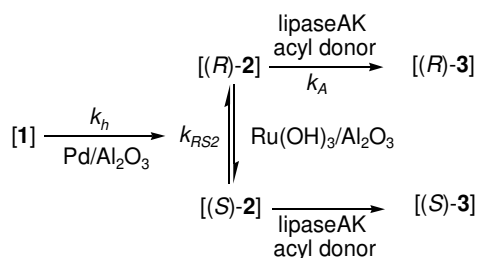
Scheme 21. One-pot reaction sequence including: *i*) hydrogenation of **1**; *ii*) racemization of (*S*)-**2** and (*R*)-**2**; *iii*) acylation of the (*R*)-**2** with acyl donor forming (*R*)-**3**.

The limiting step in the one-pot reaction appears to be, at least partially, the hydrogenation of compound **1** to *rac*-**2**. This was somewhat unexpected, as a long reaction time (20 h) in the hydrogenation reaction, without combining it with the DKR process, resulted in high (>85%) conversion of **1** (See section 3.2). Conversion above 85% in turn resulted in significantly decreased selectivity (less than 40%) due to the consecutive hydrogenation of *rac*-**2** to diols. During the development of the one-pot reaction sequence described here, the 2 mol% loading of Pd was considered to be sufficiently high for obtaining satisfactory reaction rates while avoiding the diol formation from overhydrogenation. Avoiding the consecutive hydrogenation to diols is particularly essential in the one-pot approach, when the lipase catalyzed acetylation of the isomeric alcohols would result in undesired mixtures of acetylated products.

Additionally, also the racemization rate (r_{RS2}) appears to be lower than expected under the applied one-pot reaction conditions resulting in increased *ee* of the 2-hydroxy-1-indanone (section 3.1.2). Particularly the esterified product appears to inhibit the $Ru(OH)_3/Al_2O_3$ racemization catalyst as shown in Figure 17, where *ee* of the intermediate compound 2 versus the concentration of the 2-acetoxy-1-indanone end product exhibits linear dependence. Moreover, variations in the amount of lipaseAK catalyst applied does not seem to influence the racemization rate (Figure 17).

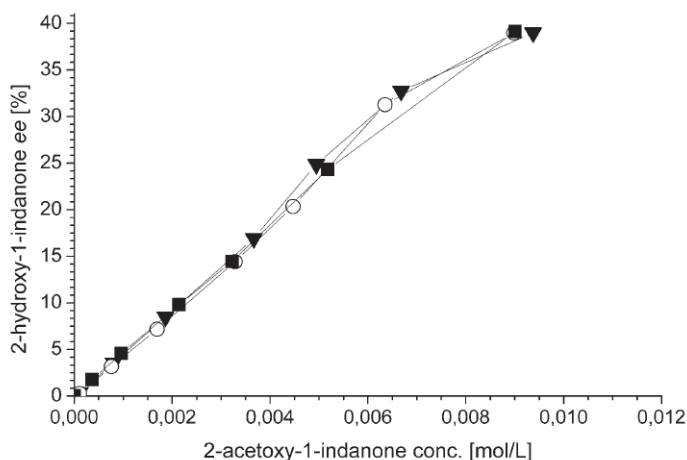**Figure 17.** Enantiomeric excess ($ee = 100 \cdot ([(R)\text{-}\mathbf{3}]\text{-}[(S)\text{-}\mathbf{3}])/([(R)\text{-}\mathbf{3}] + [(S)\text{-}\mathbf{3}]))$ of 2-hydroxy-1-indanone versus concentration of 2-acetoxy-1-indanone in one-pot reactions using ■ 93 mg, ○130 mg and ▼163 mg lipase AK.

Hence, in order to improve the conversion and yield and to decrease the influence of the acyl donor on the racemization catalyst activity, the acetyl donor was added in five portions during the first two hours of the reaction, providing the end product in 51% yield (according to GC). The stepwise addition of the acyl donor also further enhanced the efficiency of the racemization catalyst to some degree. Despite of this, the intermediate product **2** in the one-pot sequence did not remain fully racemic throughout the reaction. Thus, after the modifications mentioned the one-pot reaction sequence provided acceptable yields and high *ee* values of the product (*R*)-**3**.

Overall, the combination of the regioselective hydrogenation of **1** yielding *rac*-**2** with the subsequent DKR producing (*R*)-**3** enables an efficient reaction operation without the need for separation of the intermediate hydrogenation product. Furthermore, the reductive reaction conditions employed here enhance the efficiency of the DKR of *rac*-**2**, eliminating the formation of the oxidized DKR byproduct reported previously.

3.3.3 Kinetic Modelling of the One-pot Reaction Sequence

For better understanding the cascade reaction network and for elucidateing eventual inhibition of catalysts, kinetic modelling of the one–pot process was performed. The kinetic modelling was performed of those three reactions where the amount of enzyme catalyst was varied.

The following rate equations were used in the kinetic modelling:

$$r^{(h)} = \frac{k_h K_1 C_1}{1 + K_1 C_1 + K_{AD} C_{AD}} \rho_{Pd} \tag{6}$$

$$r^{(R2 \rightarrow R3)} = \frac{k_{R3} K_{R2} K_{AD}^E C_{R2} C_{AD}}{1 + K_{R2} C_{R2} + K_{S2} C_{S2} + K_{AD}^E C_{AD}} \rho_{En} \tag{7}$$

$$r^{(S2 \rightarrow S3)} = \frac{k_{S3} K_{S2} K_{AD}^E C_{S2} C_{AD}}{1 + K_{R2} C_{R2} + K_{S2} C_{S2} + K_{AD}^E C_{AD}} \rho_{En} \tag{8}$$

$$r^{(S2 \rightarrow R2)} = \frac{k_{RSA} K_{S2} C_{S2}}{1 + K_{AD}^{Ru} C_{AD}} \rho_{Ru} \tag{9}$$

$$r^{(R2 \rightarrow S2)} = \frac{k_{RSA} K_{R2} C_{R2}}{1 + K_{AD}^{Ru} C_{AD}} \rho_{Ru} \tag{10}$$

In equation (1) k_h is a lumped constant containing also the hydrogen concentration. Further, in equation (1) C_1 and K_1 denote concentrations of compound **1** and its adsorption coefficient on Pt. K_{AD} denotes the adsorption of the acyl donor to the Pd surface. K_{AD} was added to the model due to a possible blocking of the catalyst active sites on the surface, thereby decreasing the catalyst activity. The enzymatic reactions $r^{(R2 \rightarrow R3)}$ and $r^{(S2 \rightarrow S3)}$ were assumed to proceed by a sequential bisubstrate mechanism. Finally, for the racemization reactions, adsorptions of (R)-**2** and (S)-**2** were considered to be inferior to the much stronger adsorption of the acyl donor. In eqn (6)–(10) ρ_{Ru}, ρ_{Pd} and ρ_{En} correspond to

the bulk densities of ruthenium, palladium and lipase, respectively. The generation rates for the compounds can be written the following way:

$$-\frac{dC_1}{dt} = r^{(h)}, \; \frac{dC_{R3}}{dt} = r^{(R2 \to R3)}, \; \frac{dC_{S3}}{dt} = r^{(S2 \to S3)},$$

$$\frac{dC_{R2}}{dt} = 0.5r^{(h)} - r^{(R2 \to R3)} - r^{(R2 \to S2)} + r^{(S2 \to R2)}, \quad\quad (11)$$

$$\frac{dC_{S2}}{dt} = 0.5r^{(h)} - r^{(S2 \to S3)} + r^{(R2 \to S2)} - r^{(S2 \to R2)}$$

The kinetic modelling was performed for all reaction rates in the three reactions where enzyme amount was varied. For the parameter estimation, a set of differential equations describing the changes in the concentration profiles of the reagents and products with time was solved by means of ModEst software.[163] Using Levenberg–Marquardt simplex method, the target function, which was defined as incompliance between the experimental and calculated values of concentrations was used to solve the system. The sum of the residual squares between the model and the experimental data was minimized. The quality of the fit and accuracy of the model description was defined by the degree of explanation R^2; which reflects comparison between the residuals given by the model to the residuals of the simplest model one may think of, i.e., the average value of all the data points.

Preliminary calculations demonstrated that the description of the hydrogenation reaction is mediocre due to strong catalyst deactivation, which could not be sufficiently well described assuming only adsorption of the acyl donor on Pd surface acting as a catalyst poison. In previous work,[120] where also hydrogenation and chemoenzymatic DKR were combined in a one-pot fashion, the hydrogenation of acetophenone on palladium was found to undergo strong deactivation, similar to the current case where palladium is inhibited in the hydrogenation of compound **1**. For the sake of modelling, an empirical time dependent function for the catalyst activity was proposed.[120] Since a physical meaning in such dependence is unclear, a more mechanistically based assumption was used.

The expression for hydrogenation was modified to the following form (12):

$$r^{(h)} = \frac{k_h K_1 C_1}{1 + K_1 C_1 + K_{AD} C_{AD}} \rho_{Pd} q_{deact} \tag{12}$$

by including the following deactivation function (13)

$$q_{deact} = \frac{C_1 - C_{1,\infty}}{C^0_1 - C_{1,\infty}} \tag{13}$$

where C_1 is the concentration of **1**, C^0_1 is the initial concentration of the substrate **1**, $C_{1,\infty}$ is the concentration at infinite time, which was also considered as an adjustable parameter in the data fitting. The deactivation function has been used in earlier work[164] to explain the activity profile in the hydrogenation reactions and is based on the assumption that a decline in catalyst activity is proportional to the amount of product formed. Calculations made with eqations (2)–(5) and (7) allowed further simplifications neglecting adsorption terms in denominators of all rate expressions. The final expressions for the reaction rates used are the following:

$$r^{(h)} = k_h K_1 C_1 \rho_{Pd} \frac{C_1 - C_{1,\infty}}{C^0_1 - C_{1,\infty}} = k'_h \rho_{Pd} \frac{C_1 - C_{1,\infty}}{C^0_1 - C_{1,\infty}} \tag{14}$$

$$r^{(R2 \rightarrow R3)} = k_{R3} K_{R2} K^E_{AD} C_{R2} C_{AD} \rho_{En} = k'_{R3} C_{R2} C_{AD} \rho_{En} \tag{15}$$

$$r^{(S2 \rightarrow S3)} = -k_{S3} K_{S2} K^E_{AD} C_{S2} C_{AD} \rho_{En} = k'_{S3} C_{S2} C_{AD} \rho_{En} \tag{16}$$

$$r^{(S2 \rightarrow R2)} = k_{RSA} K_{S2} C_{S2} \rho_{Ru} = k'_{RSA} C_{S2} \rho_{Ru} \tag{17}$$

$$r^{(R2 \rightarrow S2)} = k_{RSA} K_{R2} C_{R2} \rho_{Ru} = k'_{RSA} C_{R2} \rho_{Ru} \tag{18}$$

The calculations gave the estimated values of the parameters as well as the relative standard errors (in %) which are presented in Table 4. To demonstrate how well the kinetic model matches the experimental data the result for one reaction is displayed in Figure 18.

Table 4. Estimated parameter values and the corresponding relative standard error.

Parameter	Value	Relative standard error [%]
k'_h [h^{-1}]	3.22	8.1
k'_{R3} [h^{-1}]	2.09·10^{-3}	7.0
k'_{RSA} [h^{-1}]	2.56·10^{-2}	17.2
k'_{S3} [h^{-1}]	3.52·10^{-5}	50.9
$C'_{1,\infty}$ [mol L^{-1}]	6.37·10^{-3}	2.5
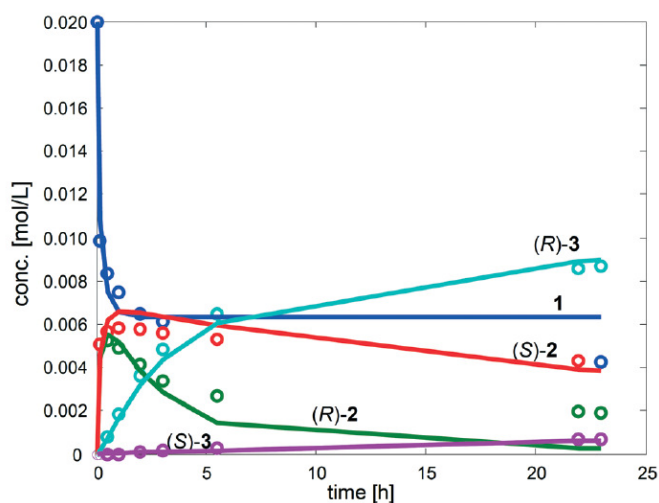
Figure 18. Comparison of the experimental data and the prediction from the kinetic model for the reactants and product in the one-pot reaction where 163 mg lipase AK was used. Solid lines represent the estimated data and circles the experimental data. The degree of explanation is 92.94%.

Conclusively a new, simple to operate one-pot reaction sequence was developed here provideing the valuable building block (*R*)-2-acetoxy-1-indanone in 86–92% *ee* using a 20 h reaction time enabling simple recovery of the catalysts by filtration facilitating easy product isolation. The yield obtained in this one-pot synthesis is in the same range as with

the traditional sequential reactions approach but the time and effort used, at least in lab scale, is decreased.

3.4. Selective Epimerization of Secondary Alcohols

Also the potential extension of *sec*-alcohol racemization catalyzed by homogeneous half-sandwich ruthenium complexes to the epimerization of *sec*-alcohol natural products containing additional non-functionalized chiral carbon atoms was studied in this work. In such cases, only the sec-alcohol stereocenter is expected to interconvert, making the epimerization processes essentially analogous to racemization.
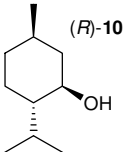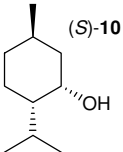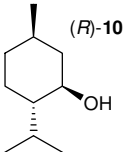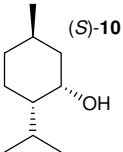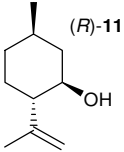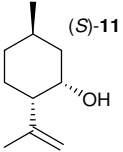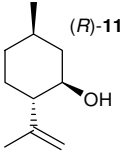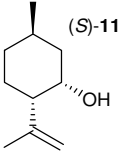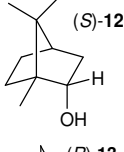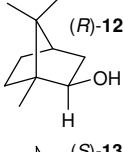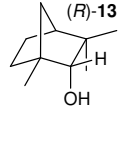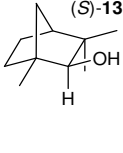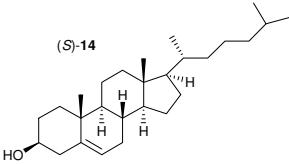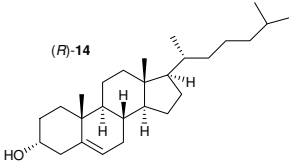
The test epimerizations of (−)-menthol [(*R*)-**10**] and (−)-isopulegol [(*R*)-**11**] were performed using the two homogeneous ruthenium catalysts **4** and **5**. Further reactions using three other structurally different natural products, (+)-borneol [(*S*)-**12**], (+)-fenchol [(*R*)-**13**] and (−)-cholesterol [(*S*)-**14**] were epimerized using catalyst **5**. All starting materials used in the epimerization study are interesting because of their biological activity or various uses in fine chemicals and pharma industries.

The configurational inversion of the secondary alcohol based stereocenter in the readily available natural products (−)-menthol and (−)-isopulegol under mild reaction conditions and low catalyst loadings (2 mol%) provides ideally rapid catalytic access to the rare diastereomeric terpenoids. In the initial epimerization of (−)-menthol and (−)-isopulegol using **5** as the catalyst, diastereomeric mixtures of (*R*)-**10**:(*S*)-**10** and (*R*)-**11**:(*S*)-**11** were obtained within a few hours in 3:1 and 6:1 ratios, respectively. These first experiments were carried out at ambient temperature in a glove box ensuring high quality of inert (water and oxygen free) reaction conditions. When comparing the catalysts **4** and **5** for epimerization, the former was found to be less efficient, providing with both starting materials (*R*)-**10** and (*R*)-**11** diastereomeric mixtures of (*R*)-**10**:(*S*)-**10** and (*R*)-**11**:(*S*)-**11** in 89/11 and 93/7 ratios, respectively, after 23 h (Table 5, entries 2 and 4). Furthermore, the longer reaction times with catalyst **4** for starting materials (*R*)-**10** and (*R*)-**11** resulted in cloudy reaction

mixtures, likely due to the poor overall solubility of catalyst **4** in common organic solvents as compared to **5**. Thus, for further experiments, catalyst **5** was selected, providing in all cases fast and selective epimerizations.

Table 5. Epimerization reactions of the naturally occurring chiral alcohols 3–7 in the presence of ruthenium catalyst 1 or 2 (2 mol%) and *tert*-BuOK (2.5 mol%) in THF at 23 ∘C.

Entry	Catalyst	Starting material	Epimeric structure	Diastereomer ratio
1	4	(R)-**10**	(S)-**10**	(R)-**10**/(S)-**10** 75/25[a]
2	5			(R)-**10**/(S)-**10** 89/11[a]
3	4	(R)-**11**	(S)-**11**	(R)-**11**/(S)-**11** 84/16[a]
4	5			(R)-**11**/(S)-**11** 93/7[a]
5	4	(S)-**12**	(R)-**12**	(S)-**12**/(R)-**12** 71/29[b]
6	4	(R)-**13**	(S)-**13**	(R)-**13**/(S)-**13** 82/18[b]
7	4	(S)-**14**	(R)-**14**	(S)-**14**/(R)-**14** 78/22[b]

[a]Reaction time 23 h; [b]Reaction time 21 h; [c]Catalyst loading 7 mol%.

For demonstration of the proof-of-concept, the more expensive, minor diastereomers were then separated and purified by conventional column chromatography in 40–80% yields, based on their concentrations in the reaction mixtures. Isolation of the products was performed by column chromatography using CH_2Cl_2-hexane mixture as the eluent.

The isolated yields of reaction products (+)-neomenthol [(S)-**10**] and (+)-neoisopulegol [(S)-**11**] were 32 mg and 10 mg, respectively.

4. Concluding Discussion

4.1 Summary and Conclusions

The kinetic resolution of *rac*-**2**, using immobilized lipase AK in MTBE, yields (*R*)-**3** in 91% *ee* at 36% conversion. During the screening of reaction conditions and catalysts, observations of a hydrolysis of the esterified resolution product back to the starting material were made. This undesired hydrolysis was minimized by the use of dry reaction conditions. The best activity and selectivity for racemization of (*S*)-**2**, using a heterogeneous catalyst, was obtained with $Ru(OH)_3/Al_2O_3$. Practically complete racemization of (*S*)-**2** (0.01 M) was observed in 5 h by using 1.67 mg/mL of the supported ruthenium catalysts in the presence of 0.5 molar equivalents of (*S*)-2-acetoxy-1-indanone. Small scale DKR experiments with *rac*-**1** (0.01 M) were performed providing 85–90% conversions and 90–92% *ee* values enabling a scale up to 0.5 g and 0.1M. The utilization of heterogeneous catalysts in one-pot DKR facilitates the operation by enabling the separation of the catalysts by filtration. It was shown that after careful screening of the reaction parameters, a practical DKR producing (*R*)-**3** with promising enantioselectivity and by utilization of heterogeneous catalysts can be developed.

Highly regioselective hydrogenation of compound **1** producing *rac*-**2** was also investigated. Three different heterogeneous Pd and Pt catalysts and two different solvents were evaluated. Five consecutive experiments were also carried out for studying the performance of Pd/Al_2O_3. The removal of sulfur contamination responsible for the inhibition was investigated and the yield of hydrogenation could be slightly improved by replacing the H_2SO_4 used in the synthetic preparation of **1** with HCl. Hydrogenation of **1** (0.02 M) in EA under atmospheric pressure of H_2 produced, according to GC-analysis, *rac*-**2** in 77 % yield using 120 min reaction time and 2 mol% of Pd/Al_2O_3.

Overall, the combination of the Pd catalyzed regioselective hydrogenation of **1** yielding *rac*-**2** with the subsequent lipase AK and Ru catalyzed DKR producing (*R*)-**3** enables an

efficient reaction operation without the need for separation of the intermediate hydrogenation product. Furthermore, the reductive reaction conditions employed here enhance the efficiency of the DKR of *rac*-**2**. A new, simple to operate one-pot reaction sequence provides the valuable building block (*R*)-**3** in moderate enantiopurity (86–92%) in a reasonable reaction time (20 h). In contrast to a multi-step reaction approach in separate reactors, the one-pot, heterogeneously catalyzed reaction sequence ideally enables simple recovery of the catalysts by filtration facilitating product isolation.

Overall, the readily available 1,2-indanedione can be transferred to a useful chiral building block with high regioselectivity and moderate stereoselectivity using economically viable heterogeneous catalysts in a practical catalytic operation.

Also the extension of secondary alcohol racemization catalyzed by homogeneous half-sandwich ruthenium complexes to the epimerization of natural products including additional non-functionalized stereo-centers was developed. The use of catalyst **5** enables the epimerization of the *sec*-alcohols (−)-menthol, (−)-isopulegol, (+)-borneol, (+)-fenchol and (−)-cholesterol under mild reaction conditions. The catalytic epimerization provides rapid access to mixtures of the less abundant diastereoisomers (+)-neomenthol, (+)-neoisopulegol, isoborneol, *β*-fenchol and epicholesterol with the parent diastereomers in ratios ranging from 1:4.9 to 1:2.4 (epimer:parent). The more expensive, minor diastereomers can then be separated and purified by conventional separation techniques in good yields.

One of the objectives of this PhD thesis was to develop heterogeneous reactions with simple operation. Homogeneous transition metal catalyzed catalytic transformations require often oxygen and moisture free reaction conditions. The heterogeneously catalyzed KR and DKR are sometimes more easy to operate and do not require time consuming preparations of dry solvents or protective atmosphere. To demonstrate this, a heterogeneously catalyzed KR experiment for educational purpose for undergraduate students was developed and implemented. This experiment can be made by the students themselves using the guidelines given without any need of specialized training.

The new heterogeneously catalyzed one-pot reactions studied here, combining individual reaction steps into sequences, potentially enhance the efficiencies of overall chemical processes by reducing costs, time and labor efforts. These and similar concepts can, at least in theory, be used for enhancing the sustainability and effectiveness of various synthetic manufacturing processes in the future.

4.2 Future Perspectives

Deeper understanding of all phenomena related to various catalytic reactions combined in one-pot reactions will in the future require cross-disciplinary knowledge. The different fields involved in such cascade type operations include synthetic chemistry, computer simulations, reactor design, reaction and protein engineering as well as industrial and large scale production aspects. For example, different epimerizations can principally be combined with enzyme catalyzed stereoselective reactions. This type of combinations enable dynamic kinetic asymmetric transformations, thus obtaining stereoselective transformations of diastereomeric structures possibly yielding rare, expensive or otherwise desired stereoisomeric structures.

The field of bio-catalysis is also undergoing a rapid development. Using different protein engineering techniques available naturally existing protein end enzyme structures can be modified and reproduced. These kinds of target-oriented randomized protein engineering methods are known as directed evolution. Thus, enzyme catalyst structures can be designed for a specific substrate or target molecule, enhancing the selectivity or reaction rate by modifying the catalytically active center. The development of protein engineering methods allows dramatic improvements in enzyme and bio-catalysis. This enables bio-catalysis to become an increasingly important tool in organic synthesis.

Moreover, applications using flow chemistry are receiving significant and increasing attention from both the academia and industry. Different reactions that are difficult to separate spatially in batch reactors can be effectively implemented using flow reactors by

applying compartmentalization, i.e., separating different types of catalysts in the reactor space. Further, the application of small scale flow reactors, microreactors, in the laboratory can sometimes offer considerable advantages over batch reactors. The advantages are nevertheless dependent on the type of chemical transformations and reactor designs available. Different flow reactors become particularly important when reaction times are fast and the heat and mass transport limitations become critical. Also a reduced contact in flow mode when handling hazardous reactants, products or waste can produce safer synthesis.

The merge of different disciplines such as synthetic organic chemistry, material technology and chemical reaction engineering will certainly provide sustainable production of chemicals required by the modern society. A fruitful combination of individual reactions with suitable catalysts constructing multistep cascade type one-pot reaction applications will have several advantages compared to traditional isolated single step synthesis.

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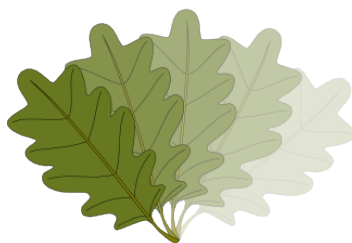
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