Ruthenium-catalyzed redox reactions and lipase-catalyzed asymmetric transformations of alcohols

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Abstract

The major part of this thesis describes the synthesis of enantiopure alcohols and diols by combining ruthenium-catalyzed redox reactions that lead to racemization or epimerization and lipase-catalyzed asymmetric transformations in one-pot.

A mechanistic study of the unexpected facile formation of *meso*-diacetate products found in enzyme-catalyzed acetylations of alkanediols with *Candida antarctica* lipase B (CALB) was first performed. By deuterium labeling it was found that the formation of *meso*-diacetates proceeds via different mechanisms for 2,4-pentanediol and 2,5-hexanediol. Whereas the first reacts via an intramolecular acyl migration, the latter proceeds via a direct, anomalous *S*-acylation of the alcohol. The acyl migration occurring in the 2,4-pentanediol monoacetate was taken advantage of in asymmetric transformations of substituted 1,3-diols by combining it with a ruthenium-catalyzed epimerization and an enzymatic transesterification using CALB. The in situ coupling of these three processes results in de-epimerization and deracemization of acyclic, unsymmetrical 1,3-diols and constitutes a novel dynamic kinetic asymmetric transformation (DYKAT) concept.

Racemization of secondary alcohols effected by a new ruthenium complex was combined in one-pot with an enzyme-catalyzed transesterification, leading to a chemoenzymatic dynamic kinetic resolution (DKR) operating at room temperature. Aromatic, aliphatic, heterocyclic and functionalized alcohols were subjected to the procedure. A mechanism for racemization by this ruthenium complex has been proposed and experimental indications for hydrogen transfer within the coordination sphere of ruthenium were found. The same ruthenium catalyst was used for epimerization in DYKAT of 1,2-diols, and a very similar complex was employed in isomerization of allylic alcohols to saturated ketones. The former method is a substrate extension of the above principle applied for DYKAT of 1,3-diols. The combination of a lipase and an organocatalyst was demonstrated by linking a lipase-catalyzed transesterification to a proline-mediated aldol reaction for the production of enantiopure (*S*)-*β*-hydroxy ketones and acetylated (*R*)-aldols.

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List of publications

This thesis is based on the following papers, referred to in the text by their Roman numerals I–VII.

I **On the mechanism of the unexpected facile formation of *meso*-diacetate products in enzymatic acetylation of alkanediols**
Edin, M.; Bäckvall, J.-E.
J. Org. Chem. **2003**, *68*, 2216–2222.

II **One-pot synthesis of enantiopure *syn*-1,3-diacetates from racemic *syn*/*anti* mixtures of 1,3-diols by dynamic kinetic asymmetric transformation**
Edin, M.; Steinreiber, J.; Bäckvall, J.-E.
Proc. Natl. Acad. Sci. U.S.A. **2004**, *101*, 5761–5766.

III **Tandem enantioselective organo- and biocatalysis: a direct entry for the synthesis of enantiomerically pure aldols**
Edin, M.; Bäckvall, J.-E.; Córdova, A.
Tetrahedron Lett. **2004**, *45*, 7697–7701.

IV **Highly compatible metal and enzyme catalysts for efficient dynamic kinetic resolution of alcohols at ambient temperature**
Martín-Matute, B.; Edin, M.; Bogár, K.; Bäckvall, J.-E.
Angew. Chem. Int. Ed. **2004**, *43*, 6535–6539.

V **Combined ruthenium(II)- and lipase catalysis for efficient dynamic kinetic resolution of *sec*-alcohols. Insight into a new racemization mechanism**
Martín-Matute, B.; Edin, M.; Bogár, K.; Kaynak, F. B.; Bäckvall, J.-E.
J. Am. Chem. Soc. **2005**, in press.

VI **Dynamic kinetic asymmetric transformation of 1,2-diols: an enantioselective synthesis of *syn*-1,2-diacetates**
Edin, M.; Martín-Matute, B.; Bäckvall, J.-E. Manuscript.

VII **Highly efficient redox isomerization of allylic alcohols at ambient temperature catalyzed by novel ruthenium cyclopentadienyl complexes. New insight into the mechanism**
Martín-Matute, B.; Bogár, K.; Edin, M.; Kaynak, F. B.; Bäckvall, J.-E.
Submitted.

Abbreviations

Abbreviations and acronyms used are in agreement with the standards of the subject.[1] Only nonstandard and unconventional ones that appear in the thesis are listed here.

CALB	*Candida antarctica* lipase B
DKR	dynamic kinetic resolution
dr	diastereomeric ratio
DYKAT	dynamic kinetic asymmetric transformation
E	enantiomeric ratio
EC	enzyme commission
KAT	kinetic asymmetric transformation
KR	kinetic resolution
n.d.	not determined
on	over night
PCPA	*p*-chlorophenyl acetate
PCL	*Pseudomonas cepacia* lipase
Δ	heat

[1] (a) *J. Org. Chem.* **2005**, *70*, 26A–27A. (b) *The ACS Style Guide. A Manual for Authors and Editors*, 2nd ed.; Dodd, J. S., Ed.; American Chemical Society: Washington, DC, 1997; pp 107–141.

1 General introduction

This thesis brings together the world of transition metals and the world of enzymes by the common concept of catalysis. A catalyst lowers the activation energy for a chemical reaction and thereby acts as a rate accelerator. A transition-metal catalyst and a biocatalyst are very different in structure and origin and have different preferences concerning operating conditions. The challenge lies in making them both work efficiently under the same conditions, in a common reaction vessel, with the aim of preparing enantiomerically pure chiral compounds.

As stereochemistry in a drug molecule governs its biological activity, chirality is a key issue in pharmaceutical research. Ever since the tragedy associated with the chiral drug thalidomide in the 1960s, there has been an increasing demand for enantiopure compounds. The drug was prescribed as a racemate to pregnant women to cure morning sickness. While (*R*)-thalidomide has the desired effect, its *S* enantiomer is teratogenic and induces fetal malformations (Figure 1).[2,3] In nine of the top ten drugs of today, the active ingredients are chiral and six are small molecules supplied as single enantiomers.[4]

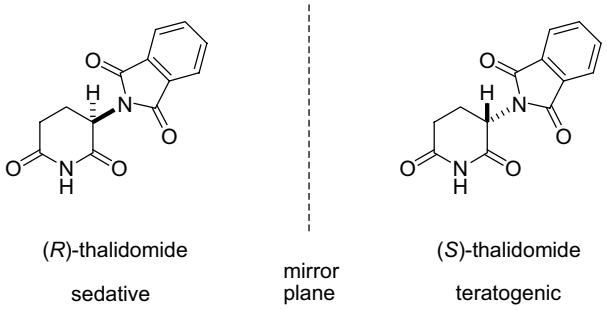

Figure 1. The two enantiomers of thalidomide.

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[2] Blaschke, V. G.; Kraft, H. P.; Fickentscher, K.; Köhler, F. *Arzneim.-Forsch.* **1979**, *29*, 1640–1642.

[3] This interpretation must be considered carefully, because the *R* enantiomer racemizes in vivo.

[4] Rouhi, A. M. *Chem. Eng. News* **2004**, *82*, 47–62.

There are three strategies for preparing enantiopure compounds. One way is to use naturally occurring enantiomerically pure and commercially available starting materials of defined absolute configuration, provided by nature's chiral pool. The second approach is to perform a resolution of a racemate. Thirdly, an asymmetric synthesis can be achieved in which one or more chiral centers are created in an achiral starting material. Asymmetric synthesis accomplished by the use of a chiral catalyst has been considered as the most refined strategy.

As will be clear from this thesis, the opposite of a resolution, i.e. the racemization of a chiral compound, can sometimes be highly desirable and be applicable in enantioselective synthesis. By combining a metal-catalyzed racemization with an enzyme-catalyzed resolution, a highly efficient asymmetric transformation to only one enantiomer can be obtained. Such dynamic kinetic resolutions with a theoretical yield of 100% represent a powerful approach to prepare enantiomerically pure molecules.

1.1 Enzymatic kinetic resolution

A resolution is defined as the separation of the enantiomers from a racemate with recovery of at least one of the enantiomers[5] and can be effected by several means. The very first kinetic resolution (KR) discovered was enzyme-catalyzed; in 1858 Pasteur resolved tartaric acid by fermenting yeast.[6] An enzymatic KR relies on an enzyme that reacts at a substantially higher rate with one enantiomer of a racemate than with the other. This phenomenon arises from the fact that diastereomeric transition-state structures (different in free energy) are formed when the enantiomers (equal in free energy) of the starting material bind to the chiral enantiopure enzyme. In the ideal case, the difference in reaction rates of the enantiomers is very large and one of the enantiomers is transformed quickly whereas the other is not converted at all.

In practice, most enzymatic KRs do not show this ideal behavior. The ratio of rates of conversion of the enantiomers is measurable, and to obtain high ee the yield will be lower than 50%. In a KR, the enantiomeric purity of the product and starting material varies as the reaction proceeds.[7] Thus, comparing enantiomeric purities for two KRs is meaningful only at the same extent of conversion. Sih et al. have developed equations to calculate the inherent enantioselectivity of a biocatalytic KR.[8] This enantioselectivity,

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5 Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; Wiley & Sons: New York, 1994; p 1206.

6 Pasteur, M. L. *C. R. Hebd, Seance Acad. Sci. Paris* **1858**, *46*, 615–618.

7 For a review, see: Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1988**, *18*, 249–330.

8 (a) For a review, see: Sih, C. J.; Wu, S.-H. *Top. Stereochem.* **1989**, *19*, 63–125. (b) Chen, C.-S.; Wu, S.-H. Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1987**, *109*, 2812–2817. (c)

called the enantiomeric ratio (*E*), measures the ability of the enzyme to distinguish between enantiomers. The *E* value remains constant throughout the reaction and offers a convenient way to easily compare the selectivity of KRs.[9] For an irreversible enzymatic KR the following three reactions may be used to experimentally determine *E* by measuring two of the three parameters conversion (c), ee of the product (ee_P) and ee of the starting material (ee_S) (Eq 1–3).

$$E = \frac{\ln[1-c(1+ee_P)]}{\ln[1-c(1-ee_P)]} \quad (1) \qquad E = \frac{\ln[(1-c)(1-ee_S)]}{\ln[(1-c)(1+ee_S)]} \quad (2) \qquad E = \frac{\ln \dfrac{[ee_P(1-ee_S)]}{(ee_P+ee_S)}}{\ln \dfrac{[ee_P(1+ee_S)]}{(ee_P+ee_S)}} \quad (3)$$

Equations 1–3.

As a rule of thumb, *E* values below 15 are unacceptable for practical purposes, in the range 15–30 regarded as moderate to good and above this value they are excellent.[10] Values of *E* >200 are difficult to measure accurately and require good analytical tools. Most enzymatic KRs follow Michaelis–Menten kinetics[11] and the *E* value may also be defined in terms of the rates of reaction of the competing enantiomer substrates (Eq 4), where k_{cat} and K_m denote the turnover number and Michaelis constant, respectively.

$$\frac{\left(\dfrac{k_{cat}}{K_m}\right)_R}{\left(\dfrac{k_{cat}}{K_m}\right)_S} = e^{-\Delta\Delta G^{\ddagger}/RT} = E$$

Equation 4.

Chen, C.-S.; Fujimoto, Y.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1982**, *104*, 7294–7299.

[9] The corresponding stereoselectivity factor used in chemocatalyzed KR is denoted *s*, see: (a) ref 7. (b) Martin, V.S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 6237–6240.

[10] Faber, K. *Biotransformations in Organic Chemistry*, 4th ed.; Springer-Verlag: Berlin, 2000; p 42.

[11] (a) Stryer, L. *Biochemistry*, 3rd ed.; W. H. Freeman and Company: New York, 1988; pp 187–191. (b) Michaelis, L.; Menten, M. L. *Biochem. Z.* **1913**, *49*, 333–369.

When the compound to be kinetically resolved exists as diastereomers, the definition of KR is not valid since it refers only to enantiomers.[12] Instead such a transformation should be called kinetic asymmetric transformation (KAT).

1.2 Lipases in organic synthesis

Lipases (EC 3.1.1.3) belong to the enzyme class hydrolases.[13,14] A hydrolase catalyzes hydrolysis, and a lipase preferentially catalyzes hydrolysis of water-insoluble esters such as triglycerides composed of long chain fatty acids (lipids). Hydrolases are the darlings among enzymes to the synthetic organic chemist for several reasons. First, the commercial availability and the fact that they do not need any cofactors to function make hydrolases popular. Further, they have the ability to hydrolyze many non-natural esters and they also work well in organic solvents,[15] where they catalyze the reverse reaction i.e. (trans)esterification.

Candida antarctica lipase B (CALB) and *Pseudomonas cepacia* lipase (PCL) are among the most enantioselective lipases toward secondary alcohols, and their substrate specificity is very broad. In hydrolysis/synthesis of esters (lipase substrate type III; the chirality resides at the alcoholic center) the enantiopreference of CALB and PCL is predicted by the Kazlauskas rule (Figure 2).[16] Due to the chirality of the enzyme's active site and the fact that the site has one large and one smaller pocket, an empirical model could be set up. Assuming the order of preference of the substituents agrees with large-small, Kazlauskas rule predicts an enantiopreference for the (*R*)-alcohol.

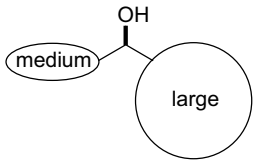

Figure 2. Empirical model for predicting the fast-reacting enantiomer of *sec*-alcohols.

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[12] Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; Wiley & Sons: New York, 1994; p 1201.

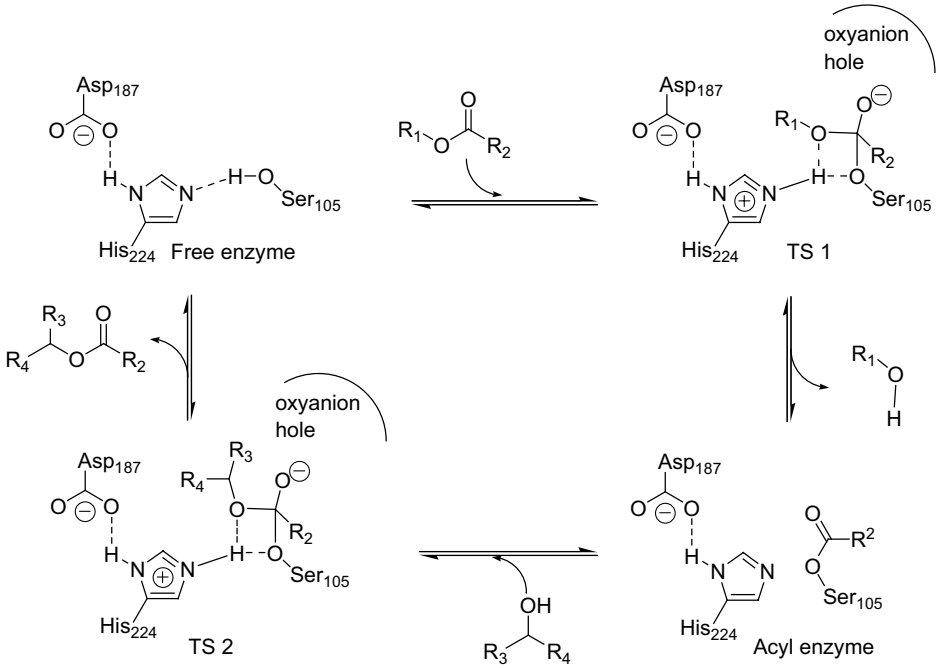
[13] Bornscheuer, U. T.; Kazlauskas, R. J. *Hydrolases in Organic Synthesis;* Wiley-VCH: Weinheim, 1999.

[14] *Enzyme Catalysis in Organic Synthesis: A Comprehensive Handbook*, 2nd ed.; Drauz, K.; Waldmann, H., Eds.; Wiley-VCH: Weinheim, 2002.

[15] (a) Klibanov, A. M. *Nature* **2001**, *409*, 241–246. (b) Halling, P. J. *Curr. Opin. Chem. Biol.* **2000**, *4*, 74–80. (c) Zaks, A.; Klibanov, A. M. *Proc. Natl. Acad. Sci. U.S.A.* **1985**, *82*, 3192–3196.

[16] Kazlauskas, R. J.; Weissfloch, A. N. E; Rappaport, A. T.; Cuccia, L. A. *J. Org. Chem.* **1991**, *56*, 2656–2665.

Funny enough, the thermostable CALB was isolated from the yeast *Candida antarctica* found in sediment from the bottom of an Antarctic lake.[17] CALB is not only active toward water-insoluble substrates but also toward water-soluble ones. Furthermore, CALB does not show the effect of interfacial activation[18] normally displayed by lipases.[19] Instead, CALB follows normal Michaelis–Menten kinetics.[11] This latter feature makes it an intermediate between an esterase and a lipase. CALB is widely used in both ester hydrolysis and esterification. Also, amino-, hydroperoxy- and thiol-groups can act as nucleophiles instead of water or alcohols in the catalytic cycle of CALB (Scheme 1). The application of CALB in organic synthesis has been reviewed.[20]



Scheme 1. Reaction mechanism of serine hydrolases. The esterification or trans-esterification involves two transition structures, TS 1 and TS 2, and one acyl enzyme intermediate.

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[17] (a) Patkar, S. A.; Bjørking, F.; Zundel, M.; Schulein, M.; Svendsen, A.; Heldt-Hansen, H. P.; Gormsen, E. *Indian J. Chem., Sect. B* **1993**, *32B*, 76–80. (b) Heldt-Hansen, H. P.; Ishii, M.; Patkar, S. A.; Hansen, T. T.; Eigtved, P. In *Biocatalysis in Agricultural Biotechnology*; Whitaker, J. R., Sonnet, P. E., Eds.; ACS Symposium Series 389; American Chemical Society: Washington, DC, 1989; pp 158–172.

[18] Martinelle, M; Holmquist, M.; Hult, K. *Biochim. Biophys. Acta* **1995**, *1258*, 272–276.

[19] For a review, see: Verger, R. *Trends Biotechnol.* **1997**, *15*, 32–38.

[20] (a) Rotticci, D.; Ottosson, J; Norin, T.; Hult, K. In *Methods in Biotechnology*; Vulfson, E. N.; Halling, P. J.; Holland, H. L., Eds.; Enzymes in Nonaqueous Solvents: Methods and Protocols, Vol. 15; Humana Press Inc.: Totowa, NJ, 2001; pp 261–276. (b) Anderson, E. M.; Larsson, K. M.; Kirk, O. *Biocatal. Biotransform.* **1998**, *16*, 181–204.

The crystal structures of CALB and of its complexes are well documented (Protein Data Bank[21] entries: 1LBS, 1LBT, 1TCA, 1TCB and 1TCC).[22] CALB is a serine hydrolase and the catalytic machinery is placed at the bottom of the funnel-shaped active site, and consists of the catalytic triad plus the oxyanion hole.[23] The triad involves aspartic acid-, histidine- and serine residues (Scheme 1).[24] The oxyanion hole stabilizes the oxyanion formed in the transition state.

Recently, two intriguing examples of genetic engineering of CALB were reported. The hydrolytic reaction specificity of CALB was engineered for catalysis of aldol reactions[25] and Michael additions.[26] Future applications of non-cofactor dependent and robust CALB in carbon-carbon bond formation might be of great value.

PCL, used to a lesser extent than CALB in this work, does show interfacial activation. PCL is also a serine hydrolase with a mechanism of action as depicted above (Scheme 1). X-Ray structures of PCL are available (Protein Data Bank entries: 1HQD, 1OIL, 2LIP, 3LIP, 4LIP and 5LIP).[27] The application of this lipase in organic synthesis has been reviewed.[28]

The enzymatic work presented in this thesis has been performed with the use of CALB as Novozyme® 435, manufactured by Novozymes (Denmark). This is a preparation of the enzyme immobilized on macroporous acrylic resin. Novozymes' commercial manufacturing of Novozyme® 435 is done by gene expression in an *Aspergillus* microorganism and provides amounts of tons per year, and the enzyme is supplied as an additive to detergents. The PCL employed is available from Amano Enzyme Inc. as PS-C "Amano" I and PS-C "Amano" II. Both of the latter are immobilized on ceramic particles.

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[21] Berman, H. M.; Westbrook, J.; Feng, Z.; Gilliland, G.; Bhat, T. N.; Weissig, H.; Shindyalov, I. N.; Bourne, P. E. *Nucleic Acids Res.* **2000**, *28*, 235–242.

[22] (a) Uppenberger, J.; Öhrner, N.; Norin, M.; Hult, K.; Kleywegt, G. J.; Patkar, S.; Waagen, V.; Anthonsen, T.; Jones, T. A. *Biochemistry* **1995**, *34*, 16838–16851. (b) Uppenberg, J.; Trier Hansen, M.; Patkar, S.; Jones, T. A. *Structure* **1994**, *2*, 293–308.

[23] Brady, L.; Brzozowski, A. M.; Derewenda, Z. S.; Dodson, E.; Dodson, G.; Tolley, S.; Turkenburg, J. P.; Christiansen, L.; Huge-Jensen, B.; Norskov, L.; Thim, L.; Menge, U. *Nature (London)* **1990**, *343*, 767–770.

[24] (a) Martinelle, M.; Hult, K. *Biochem. Biophys. Acta* **1995**, *1251*, 191–197. (b) Kraut, J. *Annu. Rev. Biochem.* **1977**, *46*, 331–358.

[25] (a) Branneby, C.; Carlqvist, P.; Magnusson, A.; Hult, K.; Brinck, T.; Berglund, P. *J. Am. Chem. Soc.* **2003**, *125*, 874–875.

[26] Carlqvist, P.; Svedendahl, M.; Branneby, C.; Hult, K.; Brinck, T.; Berglund, P. *ChemBioChem* **2005**, *6*, 331–336.

[27] (a) Luic. M.; Tomic, S.; Lescic, I.; Ljubovic, E.; Sepac, D.; Sunjic, V.; Vitale, L.; Saenger, W.; Kojic-Prodic, B. *Eur. J. Biochem.* **2001**, *268*, 3964–3973. (b) Schrag, J. D.; Li, Y.; Cygler, M.; Lang, D.; Burgdorf, T.; Hecht, H.-J.; Schmid, R.; Schomburg, D.; Rydel, T. J.; Oliver, J. D.; Strickland, L. C.; Dunaway, C. M.; Larson, S. B.; Day, J.; McPherson, A. *Structure*, **1997**, *5*, 187–202. (c) Kim, K. K.; Song, H. K.; Shin, D. H.; Hwang, K. Y.; Suh, S. W. *Structure*, **1997**, *5*, 173–185.

[28] Xie, Z.-F. *Tetrahedron: Asymmetry* **1991**, *2*, 733–750.

1.3 Ruthenium-catalyzed racemization of secondary alcohols

Racemization[29] of secondary alcohols can be accomplished by transition metal-catalyzed reactions. The mechanism of these reactions involves hydrogen transfer and has been extensively studied.[30] Whereas main group elements, e.g. aluminum as in the Meervein-Ponndorf-Verley/Oppenauer-reaction, react via direct hydrogen transfer (concerted process), it is generally assumed that the transition metal-catalyzed mechanism involves metal hydrides as key intermediates. A recent study indicates that two different hydridic pathways can be involved in these reactions: a metal monohydride mechanism or a metal dihydride mechanism.[31] The first mechanism operates for rhodium, iridium and most non-dihalide ruthenium complexes, whereas the latter mechanism applies to ruthenium dihalide catalyst precursors. Originally, it was suggested that metal hydrides were formed via metal alkoxides that underwent β-hydride elimination.[32] More recently however it was proposed that, for certain so-called metal-ligand bifunctional catalysts, hydrogen transfer proceeds in a concerted fashion without coordination of either alcohol or ketone to the metal.[33]

Although various rhodium, iridium and ruthenium complexes are known to catalyze rapid racemization of alcohols,[31,34] only few have proven compatible with an enzymatic resolution (Figure 3).[29a,35]

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[29] For reviews on racemizations, see: (a) Huerta, F. F.; Minidis, A. B. E.; Bäckvall, J.-E. *Chem Soc. Rev.* **2001**, *30*, 321–331. (b) Ebbers, E. J.; Ariaans, G. J. A.; Houbiers, J. P. M.; Bruggink, A.; Zwanenburg, B. *Tetrahedron* **1997**, *53*, 9417–9476.

[30] See for instance: (a) Clapham, S. E.; Hadzovic, A.; Morris, R. H. *Coord. Chem. Rev.* **2004**, *248*, 2201–2237. (b) Gladiali, S.; Alberico, E. In *Transition Metals for Organic Synthesis*, 2nd ed; Beller, M.; Bolm, C., Eds.; Wiley-VCH: Weinheim, 2004; Vol. 2, pp 145–166. (c) Bäckvall, J.-E. *J. Organomet. Chem.* **2002**, *652*, 105–111. (d) Wills, M.; Palmer, M.; Smith, A.; Kenny, J.; Walsgrove, T. *Molecules* **2000**, *5*, 4–18. (e) Palmer, M. J.; Wills, M. *Tetrahedron: Asymmetry* **1999**, *10*, 2045–2061. (f) Gladiali, S.; Mestroni, G. In *Transition Metals for Organic Synthesis*; Beller, M.; Bolm, C., Eds.; Wiley-VCH: Weinheim, 1998; Vol. 2, pp 97–119.

[31] Pàmies, O.; Bäckvall, J.-E. *Chem. Eur. J.* **2001**, *7*, 5052–5058.

[32] (a) Zassinovic, G.; Mestroni, G.; Gladiali, S. *Chem. Rev.* **1992**, *92*, 1051–1069. (b) Bäckvall, J.-E.; Chowdhury, R. L.; Karlsson, U.; Wang, G. Z. In *Perspectives in Coordination Chemistry*; Williams, A. F.; Floriani, C.; Merbach, A. E., Eds.; Helvetica Chimica Acta: Basel, 1992; pp 463–486.

[33] (a) Casey, C. P.; Johnson, J. B.; *J. Org. Chem.* **2003**, *68*, 1998–2001. (b) Casey, C. P.; Singer, S. W.; Powell, D. R.; Hayashi, R. K.; Kavana, M. *J. Am. Chem. Soc.* **2001**, *123*, 1090–1100. (c) Noyori, R.; Yamakawa, M.; Hashiguchi, S. *J. Org. Chem.* **2001**, *66*, 7931–7944. (d) Petra, D. G. I.; Reek, J. N. H.; Handgraaf, J.-W.; Meijer, E. J.; Dierkes, P.; Kamer, P. C. J.; Brussee, J.; Schoemaker, H. E.; van Leeuwen, P. W. N. M. *Chem. Eur. J.* **2000**, *6*, 2818–2829. (e) Yamakawa, M.; Ito, H.; Noyori, R. *J. Am. Chem. Soc.* **2000**, *122*, 1466–1478. (f) Alonso, D. A.; Brandt, P.; Nordin, S. J. M.; Andersson, P. G. *J. Am. Chem. Soc.* **1999**, *121*, 9580–9588. (g) Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 97–102.

[34] (a) Ito, M.; Osaku, A.; Kitahara, S.; Hirakawa, M.; Ikariya, T. *Tetrahedron Lett.* **2003**, *44*, 7521–7523. (b) Koh, J. H.; Jeong, H. M.; Park, J. *Tetrahedron Lett.* **1998**, *39*, 5545–5548.

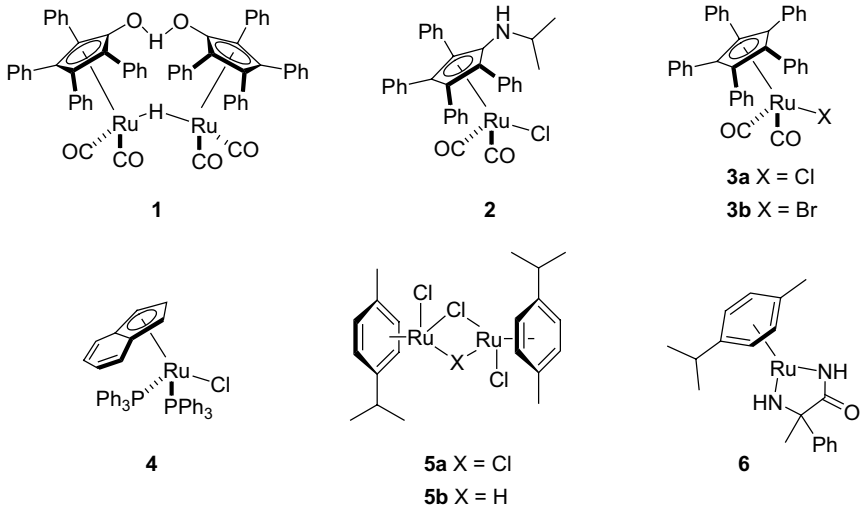

Figure 3. Transition metal racemization catalysts compatible with an enzymatic resolution.

The first practical catalyst applied in chemoenzymatic DKR of alcohols was reported by Bäckvall in 1997,[36] who used Shvo's diruthenium complex **1**.[37,38] This pre-catalyst is activated by heat and can, in 20–40 hours time at 70 °C, racemize simple alcohols (Scheme 2). The Shvo catalyst works also for many functionalized alcohols and it represented state-of-the-art until recently, when Kim and Park reported base-activated pre-catalyst **2** as a racemization catalyst effective at room temperature.[39] Shortly thereafter, our group identified catalysts **3** as highly efficient room-temperature racemization catalysts also after activation by base.[40] The applicability of these catalysts in DKR is demonstrated in this thesis. Kim and Park have applied catalyst **4** in DKR of alcohols[41] and complex **5b** for allylic alcohols.[42]

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[35] Dinh, P. M.; Howarth, J. A.; Hudnott, A. R.; Williams, J. M. J.; Harris, W. *Tetrahedron Lett.* **1996**, *37*, 7623–7626.

[36] Larsson, A. L. E.; Persson, B. A.; Bäckvall, J.-E. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1211–1212.

[37] (a) Shvo, Y.; Goldberg, I.; Czerkie, D.; Reshef, D.; Stein, Z. *Organometallics* **1997**, *16*, 133–138. (b) Menashe, N.; Salant, E.; Shvo, Y. *J. Organomet. Chem.* **1996**, *514*, 97–102. (c) Menashe, N.; Shvo, Y. *Organometallics* **1991**, *10*, 3885–3891. (d) Abed, M.; Goldberg, I.; Stein, Z.; Shvo, Y. *Organometallics* **1988**, *7*, 2054–2057. (e) Shvo, Y.; Czarkie, D.; Rahamim, Y. *J. Am. Chem. Soc.* **1986**, *108*, 7400–7402. (f) Blum, Y.; Czarkie, D.; Rahamim, Y.; Shvo, Y. *Organometallics* **1985**, *4*, 1459–1461.

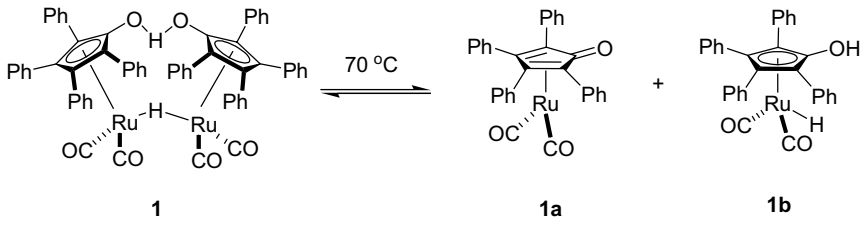
[38] Karvembu, R.; Prabhakaran, R.; Natarajan, K. *Coord. Chem. Rev.* **2005**, *249*, 911–918.

[39] (a) Choi, J. H.; Choi, Y. K.; Kim, Y. H.; Park, E. S.; Kim, E. J.; Kim, M.-J.; Park, J. *J. Org. Chem.* **2004**, *69*, 1972–1977. (b) Choi, J. H.; Kim, Y. H.; Nam, S. H.; Shin, S. T.; Kim, M.-J.; Park, J. *Angew. Chem. Int. Ed.* **2002**, *41*, 2373–2376.

[40] Csjernyik, G.; Bogár, K.; Bäckvall, J.-E. *Tetrahedron Lett.* **2004**, *45*, 6799–6802.

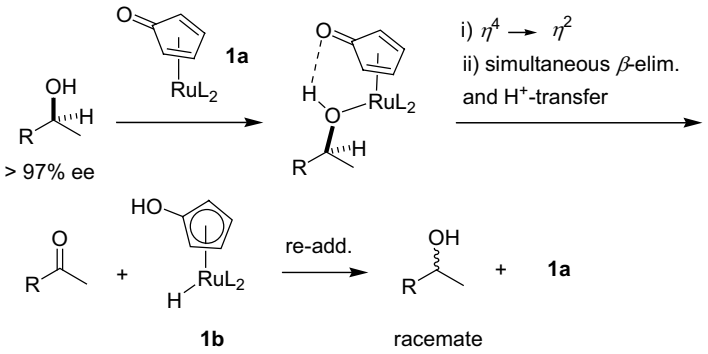
[41] Koh, J. H.; Jung, H. M.; Kim, M.-J.; Park, J. *Tetrahedron Lett.* **1999**, *40*, 6281–6284.

Noyori-type catalyst **6** is in use in a large scale process developed and run at DSM.[43]



Scheme 2. Activation of catalyst **1**.

Hydrogen transfer reactions by complex **1** proceed through metal monohydride species. Under thermal conditions **1** dissociates to species **1a**, in which the formal oxidation state is Ru(0),[44] and to 18-electron species **1b** (Scheme 2). Complexes **1a** and **1b** are both catalytically productive. Scheme 3 shows the mechanism we currently believe operates in the racemization of *sec*-alcohols. Complex **1a** coordinates the alcohol and oxidizes it through concerted β-elimination and proton transfer[45] to give an intermediate ketone and **1b**, which subsequently re-adds the hydrogens to the ketone.



Scheme 3. Mechanism of racemization of *sec*-alcohols via reversible dehydrogenation by the Shvo catalyst **1**. Phenyls omitted for clarity. L = CO.

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[42] Lee, D.; Huh, E. A.; Kim, M.-J.; Jung, H. M.; Koh, J. H.; Park, J. *Org. Lett.* **2000**, *2*, 2377–2379.

[43] Verzijl, G. K. M.; De Vries, J. G.; Broxterman, Q. B. Process for preparation of enantiomerically enriched esters and alcohols. PCT Int. Appl. 2001, WO 0190396 A1, November 29, 2001.

[44] A tautomeric form of **1a**, where two electrons have been moved to the ring to give a negatively charged ligand, is formally Ru(II).

[45] Johnson, J. B.; Bäckvall, J.-E. *J. Org. Chem.* **2003**, *68*, 7681–7684.

This mechanism has been studied in connection with either catalytic hydrogenation of aldehydes and ketones or hydrogen transfer reactions of ketones or alcohols, and several features of the mechanism have been discussed such as: (i) the presence and structure of an intermediate alcohol complex,[31,37b,d,46] (ii) a stepwise vs concerted mechanism for transfer of proton from the catalyst OH group to the aldehyde/ketone oxygen and hydride transfer from ruthenium to carbon[31,45,46c,33b] and (iii) the involvement of an $\eta^5 \rightarrow \eta^3$ ring slippage during β-hydride elimination from the alcohol.[47]

The Shvo catalyst has also been used in hydrogen transfer reactions of imines and amines by our group.[48] The mechanism of hydrogen transfer to imines and from amines has been studied by both Bäckvall[49] and Casey.[33b,50]

1.4 Acyl donors in enzymatic transesterification

Transesterifications are generally reversible in contrast to the irreversible nature of hydrolytic reactions. This leads to a slow reaction rate and can cause severe depletion of enantioselectivity.[51] To use an excess of the acyl donor would help shifting the equilibrium. A better approach however, is to choose acyl donors that ensure a more or less irreversible reaction.[52] For this purpose, activated esters such as trichloroethyl esters **7** have been used, which upon deacylation produce a weak nucleophile that does not compete with the substrate alcohol (Figure 4). An even more effective alternative is represented by enol esters **8**. In this case the equilibrium is shifted when aldehydes or ketones, completely inert under the reaction conditions, are formed by tautomerization of the acyl donor leaving groups. Another

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[46] (a) Casey, C. P.; Bikzhanova, G. A.; Bäckvall, J.-E.; Johansson, L.; Park, J.; Kim, Y. H. *Organometallics* **2002**, *21*, 1955–1959. (b) An alcohol complex was reported to be isolated, but later turned out to be in error (see ref 46a): Jung, H. M.; Shin, S. T.; Kim, Y. H.; Kim, M.-J.; Park, J. *Organometallics* **2001**, *20*, 3370–3372. (c) Laxmi, Y. R. S.; Bäckvall, J.-E. *Chem. Commun.* **2000**, 611–612. (d) Almeida, M. L. S.; Beller, M.; Wang, G.-Z.; Bäckvall, J.-E. *Chem. Eur. J.* **1996**, *2*, 1533–1536.

[47] (a) Csjernyik, G.; Éll, A. H.; Fadini, L.; Pugin, B.; Bäckvall, J.-E. *J. Org. Chem.* **2002**, *67*, 1657–1662. (b) Shvo proposed that the hydrogenation of alkynes proceeds through a ring-slip mechanism, see ref 37a.

[48] Transfer hydrogenation of imines: Samec, J. S. M.; Bäckvall, J.-E. *Chem. Eur. J.* **2002**, *8*, 2955–2961. Dehydrogenation of amines to imines: Éll, A. H.; Samec, J. S. M.; Brasse, C.; Bäckvall, J.-E. *Chem. Comm.* **2002**, 1144–1145. Aerobic oxidation of amines to imines: Samec, J. S. M.; Éll, A. H.; Bäckvall, J.-E. *Chem. Eur. J.* **2005**, *11*, 2327–2334. Racemization: Pámies, O.; Éll, A. H.; Samec, J. S. M.; Hermanns, N.; Bäckvall, J.-E. *Tetrahedron Lett.* **2002**, *43*, 4699–4702.

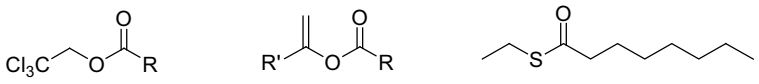
[49] Hydrogen transfer to ketimine: Samec, J. S. M.; Éll, A. H.; Bäckvall, J.-E. *Chem. Comm.* **2004**, 2748–2749. Dehydrogenation of amines: Éll, A. H.; Johnson, J. B.; Bäckvall, J.-E. *Chem. Comm.* **2003**, 1652–1652.

[50] Imine hydrogenation: Casey, C. P.; Johnson, J. B. *J. Am. Chem. Soc.* **2005**, *127*, 1883–1894.

[51] Hult, K.; Norin, T. *Pure Appl. Chem.* **1992**, *64*, 1129–1134.

[52] (a) Hanefeld, U. *Org. Biomol. Chem.* **2003**, *1*, 2405–2415. (b) see ref 10, pp 345–351. (c) see ref 13, pp 44–47.

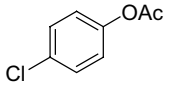
possibility is to employ thioesters such as (*S*)-ethyl thiooctanoate (**9**).[53] In this case the equilibrium is shifted because the thiol liberated is very volatile.



7 **8** **9**

Figure 4. Acyl donors in enzymatic transesterification.

The same requirements as for the KR also hold for the metalloenzymatic DKR. In addition, in a DKR it is crucial that the acyl donor and its remainder are compatible with the metal catalyst. From both an environmental and economic point of view, and also with respect to product purification, the use of enol esters **8** in DKR would be highly desirable. In Bäckvall's early work on DKR all activated esters bearing protons in the α-position to the oxygen and enol esters were dismissed because the alcohols and aldehydes/ketones produced, respectively, interfere with the ruthenium racemization catalyst. *p*-Chlorophenyl acetate (PCPA, **10**, Figure 5) was recognized as a specifically designed acyl donor; the *p*-chlorophenol produced is unable to tautomerize into a carbonyl compound, direct oxidation of the alcohol by ruthenium would disrupt the aromaticity and the reactivity in acylation was tuned by the chloro substituent.[54]



10

Figure 5. Specifically designed acyl donor for metalloenzymatic DKR.

1.5 Classification of asymmetric transformations

An asymmetric transformation is defined as a process where a mixture (usually 50:50) of stereoisomers is transformed into a single stereoisomer, or into a different mixture of stereoisomers, by an equilibrium process. Of great value in synthesis are the so-called asymmetric transformations of the second kind, which includes a concomitant separation of the stereoisomers.[55]

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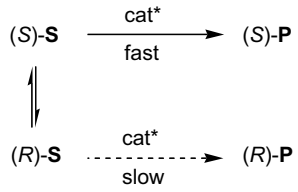
[53] (a) Orrenius, C.; Öhrner, N.; Rottici, D.; Mattson, A.; Hult, K.; Norin, T. *Tetrahedron: Asymmetry* **1995**, *6*, 1217–1220. (b) Öhrner, N.; Martinelle, M.; Mattson, A.; Norin, T.; Hult, K. *Biocatalysis*, **1994**, *9*, 105–114.

[54] B. A. Persson, A. L. E. Larsson, M. Le Ray, J.-E. Bäckvall, *J. Am. Chem. Soc.* **1999**, *121*, 1645–1650.

[55] Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; Wiley & Sons: New York, 1994; p. 364, pp 1192–1193.

The concept applies to both racemates[56] and diastereomeric mixtures.[57] The concept is very broad and includes a number of different transformations. A deracemization, for example, constitutes any process during which a racemate is converted into a non-racemic product in 100% theoretical yield without intermediate separation of materials. Analogously, a de-epimerization is the transformation of diastereomers into a single diastereomer, and takes place via epimerization.[58] It is important to note that since diastereomers are involved in the latter case, ΔH^0 of an epimerization does not equal zero, as in the case of a racemization. Hence, de-epimerization is more facile to affect than deracemization.

Dynamic kinetic resolution (DKR)[59] and dynamic kinetic asymmetric transformation (DYKAT)[60] are examples of deracemizations. Ward subdivided DKR into four categories: 1) DKR of enantiomers (Scheme 4), 2) DKR of diastereomers, 3) reagent controlled asymmetric synthesis involving DKR and 4) catalyst controlled asymmetric synthesis involving DKR. In the two latter cases an additional chiral center is created, but the interconversion of stereoisomers occurs before this event and is therefore a racemization. However, in subclass 2) the equilibrium involves epimerization, hence the mathematical treatment of DKR does not apply in this case.[59d,61] Therefore, we urge that this case be redefined as a DYKAT of diastereomers.[II]



Scheme 4. DKR of enantiomers by equilibrium involving racemization.

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[56] Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; Wiley & Sons: New York, 1994; pp 315–322.

[57] Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; Wiley & Sons: New York, 1994; pp 364–374.

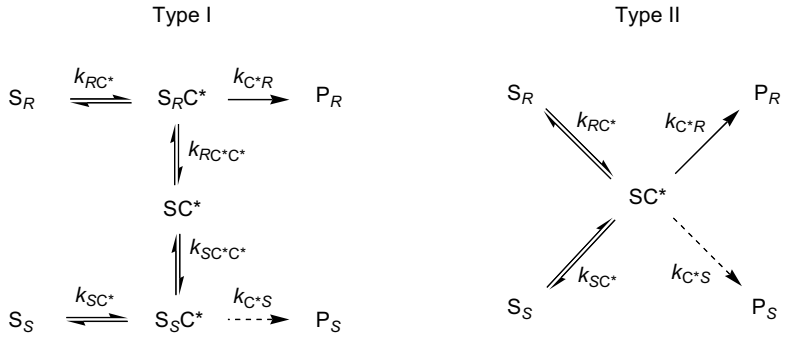
[58] For a treatise on asymmetric transformations of the second kind of a racemate, see Faber, K. *Chem. Eur. J.* **2001**, *7*, 5004–5010.

[59] (a) Pellissier, H. *Tetrahedron* **2003**, *59*, 8291–8327. Chemocatalyzed reviews: (b) Ratovelomanana-Vidal, V.; Genêt, J.-P. *Can. J. Chem.* **2000**, *78*, 846–851. (c) Ward, R. S. *Tetrahedron: Asymmetry* **1995**, *6*, 1475–1490. (d) Noyori, R.; Tokunaga, M.; Kitamura, M. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 36–56. Biocatalyzed review: (e) Schnell, B.; Faber, K.; Kroutil, W. *Adv. Synth. Catal.* **2003**, *345*, 653–666. For chemoenzymatic DKR, see references in chapter 1.6.

[60] Trost, B. M. *Chem. Pharm. Bull.* **2002**, *50*, 1–14.

[61] (a) Kitamura, M.; Tokunaga, M.; Noyori, R. *J. Am. Chem. Soc.* **1993**, *115*, 144–152. (b) Kitamura, M.; Tokunaga, M.; Noyori, R. *Tetrahedron* **1993**, *49*, 1853–1860.

To date, only two subtypes of DYKAT (apart from our own) have been presented in the literature, both by the group of Trost.[60] Both types start from a racemate, which is transformed into a single enantiomer product (Scheme 5). The equilibria involved in both types are epimerizations.



Scheme 5. Trost's two types of DYKAT, both equilibria involved are epimerizations. C* = chiral catalyst.

1.6 Coupled enzyme- and ruthenium catalysis

The purpose of combining an enzyme-catalyzed KR and a ruthenium-catalyzed equilibration is to circumvent the inherent limitation of a maximum of 50% yield in the KR. In theory, 100% yield is now possible. This not only increases the efficiency of the resolution, but also avoids the sometimes troublesome separation of product from unchanged starting material.

To the best of our knowledge, all coupled enzyme- and ruthenium-catalyzed asymmetric transformations reported before the work in this thesis are DKRs, except for one case.[62] The DKR of (symmetrical) diols reported in 1999 by our group does contain an epimerization rather than a racemization.[63] Although Ward has classified this type of transformation as a DKR, as mentioned above, we would like to reclassify it as a DYKAT of diastereomers.

The basic requirements for an efficient chemoenzymatic DKR can be summarized as follows: (i) an efficient KR has to be identified, (ii) an efficient racemization method has to be chosen, and (iii) the KR and the racemization method should be compatible with one another. To be efficient,

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[62] For recent reviews on chemoenzymatic DKR, see: (a) Turner, N. *Curr. Opin. Chem. Biol.* **2004**, *8*, 114–119. (b) Pàmies, O.; Bäckvall, J.-E. *Trends Biotechnol.* **2004**, *22*, 130–135. (c) Pàmies, O.; Bäckvall, J.-E. *Chem. Rev.* **2003**, *103*, 3247–3261. (d) Kim, M.-J.; Anh, Y.; Park, J. *Curr. Opin. Biotechnol.* **2002**, *13*, 578–587; Erratum: Kim, M.-J.; Anh, Y.; Park, J. *Curr. Opin. Biotechnol.* **2003**, *14*, 131.

[63] Persson, B. A.; Huerta, F. F.; Bäckvall, J.-E. *J. Org. Chem.* **1999**, *64*, 5237–5240.

a KR has to be irreversible to ensure high enantioselectivity. Further, the *E* value should be larger than 20. However, if the *E* value is greater than 200, the metal-catalyzed racemization may be slow compared to the enzymatic KR and a high enantioselectivity still be obtained. The ratio between the rate of racemization and the enzymatic transformation of the slow reacting enantiomer should, however, in all cases exceed 10. This can often be achieved by reducing the enzyme/metal ratio. Since enzymes and metal catalysts usually have different preferences for operating conditions, their combination in a one-pot reaction is not straightforward. The parameters solvent, acyl donor, metal-catalyst, and temperature have to be considered. For example, lipases work best in aprotic organic solvents like hexane or dialkyl ethers. In contrast, the metal-catalyst usually has a low solubility in these solvents, leading to a slow rate of racemization. The acyl donor has to be such that it, after acyl transfer, cannot interfere with the metal hydrogen transfer catalyst (Chapter 1.4). Most hydrogen transfer catalysts need a base as a co-catalyst. Enzymes, in turn, may be denaturated at a basic pH. Racemizations are faster at higher temperatures, but again, enzymes are denaturated at elevated temperatures, even in organic solvents.

1.7 Objectives of the thesis

There is a constant need for new efficient methods to prepare enantiomerically pure compounds such as chiral alcohols. An important aim of the research in our group is to combine the powerful activity of metal-catalysis with the unbeatable selectivity of biocatalysis to obtain highly efficient transformations.

The first objective of the work presented was to find evidence in support of a mechanism for the unexpected formation of *meso*-diacetate products in enzyme-mediated acetylation of alkanediols at 70 °C. Such mechanistic insight would aid in future improvements of the low diastereoselectivity in existing protocols for KAT and DYKAT of these substrates, and in the development of new coupled CALB- and ruthenium-catalyzed methodology for enantio- and diastereoselective transformations of diols. The second objective, based on result from the first mechanistic study, was to develop a new type of DYKAT for de-epimerization and deracemization of 1,3-diols by combining an intramolecular acyl transfer, a ruthenium-catalyzed epimerization and a CALB-catalyzed transesterification. The third objective was to combine an organocatalyst with a lipase to prove their compatibility and use for preparation of enantiomerically pure aldols, important precursors to 1,3-diols.

The originally developed chemoenzymatic DKR can only be run at higher temperatures due to the racemization process. This limits the scope to the use of selective, thermostable enzymes. If a more active racemization catalyst

operating at lower temperatures would be compatible with the enzymatic process, also less selective and thermolabile enzymes would be applicable and the substrate variation would be significantly greater in future applications. The next objective was therefore to find reaction conditions to combine racemization by ruthenium complex **3a** with the enzymatic resolution in one-pot, to obtain a room temperature DKR. The racemization by complex **3a** is intriguing, and another objective was hence to elucidate the mechanism of this racemization. As a final objective, we wanted to explore the versatility of this catalyst by trying to apply the complex in a DYKAT of 1,2-diols, and in redox isomerization of allylic alcohols to saturated ketones.

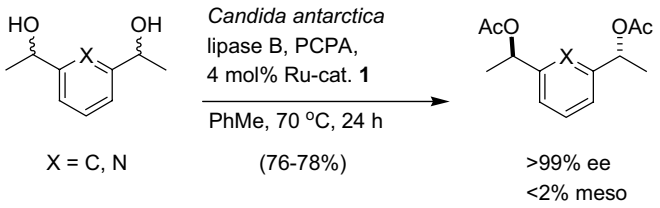
2 Mechanistic study of unexpected facile formation of *meso*-diacetates in CALB-catalyzed acetylation of alkanediols

(Paper I)

Investigations of a reaction mechanism can sometimes lead to great rewards for the synthetic organic chemist, since the new insight is often helpful in the development of new reactions. There are a number of kinds of experimental information that may be used in testing mechanisms.[64] This chapter describes how we used isotopic labeling to probe a reaction pathway and kinetic measurements to determine the relative rate constants for CALB-catalyzed KR. The relative rate constants in turn gave a measurement of the pseudo *E* value of the enzyme.

2.1 Introduction

As part of our ongoing program on the combined enzyme- and transition metal-catalyzed dynamic kinetic resolution (DKR) of various substrate classes,62 a procedure for symmetrical diols was previously reported.[63] All diols tested were transformed into diacetates in excellent enantiomeric excess. Several diacetates were also nearly diastereomerically pure (Scheme 6).



Scheme 6. DYKAT of diols giving products of high ee and dr.

In spite of the excellent enantiomeric excess obtained, this process showed moderate to low diastereoselectivity for certain diols, which gave also the *meso*-compound containing an *S*-acylated hydroxyl group (anti-Kazlauskas product) (Scheme 7).[63] This is unexpected since CALB-catalyzed acylations

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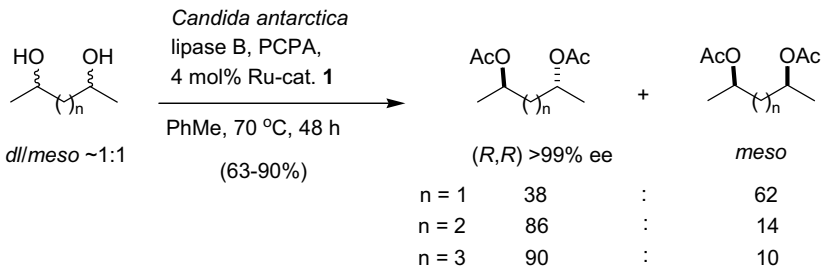
[64] (a) Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*, 3rd ed.; Harper & Row: New York, 1987. (b) Bernasconi, C. F. *Investigation of Rates and Mechanisms of Reactions*, 4th ed. (vol. 6 of Weissberger *Techniques of Chemistry*), 2 pts.; Wiley: New York, 1986.

normally lead to product formation in strict agreement with the Kazlauskas' rule.[16]



Scheme 7. DYKAT of diols diving low to moderate dr.

Also, in a report on enzymatic kinetic acylation of diols using the same enzyme, considerable amounts of the *meso*-diacetate were produced with 2,4-pentanediol as the substrate.[65] Two possible mechanisms have been proposed to account for the unexpected facile acylation of the (*S*)-alcohol function: (i) an intramolecular acyl transfer from the (*R*)-acetate to the (*S*)-alcohol in the (*R*)-monoacylated (*R*,*S*)-diol with subsequent enzyme-catalyzed acylation of the (*R*)-hydroxyl group released (cf. path A, Scheme 8) and (ii) direct acylation of the (*S*)-alcohol due to a lower enantioselectivity for the monoacylated diol (cf. path B, Scheme 8).

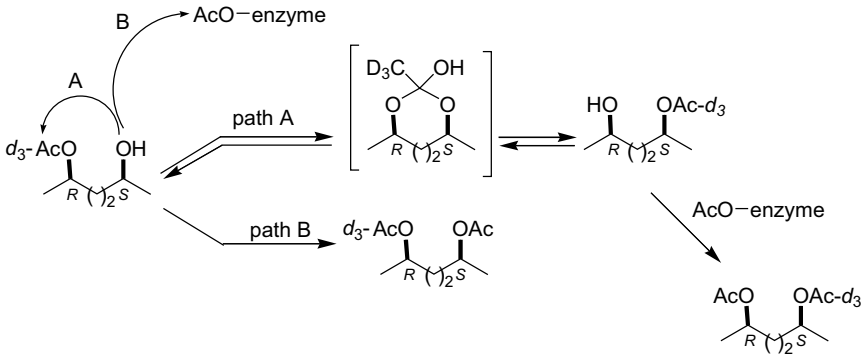
With the objective to explain why the dynamic kinetic asymmetric transformation (DYKAT) of acyclic diols gave such an unexpectedly large proportion of *meso*-diacetate and to perhaps in the future improve the diastereomeric ratios in the process, we studied the mechanism of the reaction.

2.2 Results and discussion

By deuterium labeling of the acetate group in (*R*)-monoacetate of the *meso*-diol it was possible to differentiate between the intramolecular acyl transfer pathway (path A, Scheme 8) and the direct acylation route (path B, Scheme 8). In the intramolecular pathway the deuterated acetoxy group would be transferred from the (*R*)-alcohol to the (*S*)-alcohol group via a cyclic intermediate (path A). The (*R*)-alcohol function released would be rapidly acylated via the enzyme and give diacetate deuterated in the *S*-position. The pathway via direct acylation would give a diacetate in which deuterium is retained in the *R*-position (path B). In a control experiment it was shown that

[65] Mattson, A.; Öhrner, N.; Hult, K.; Norin, T. *Tetrahedron: Asymmetry* **1993**, *4*, 925–930.

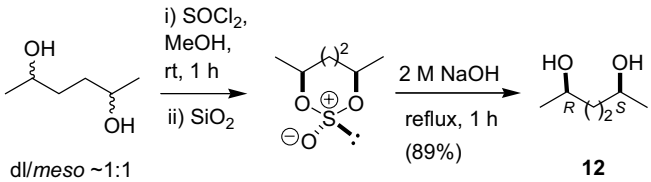
the formation of *meso*-diacetates/anti-Kazlauskas products in the DYKAT of symmetrical diols is not ruthenium-mediated.



Scheme 8. Deuterium labeling to distinguish between acyl transfer and direct enzymatic acylation.

2.2.1 Preparation of starting materials and reference compounds

Pure *meso*-2,4-pentanediol (**11**) was obtained by flash chromatography of the commercially available *dl*/*meso*-diol. Pure *meso*-hexanediol (**12**) was prepared from a commercially available *dl*/*meso*-diol (*dl*/*meso* ~1:1) by converting the isomers into cyclic sulfites,[66] followed by separation and hydrolysis (Scheme 9).



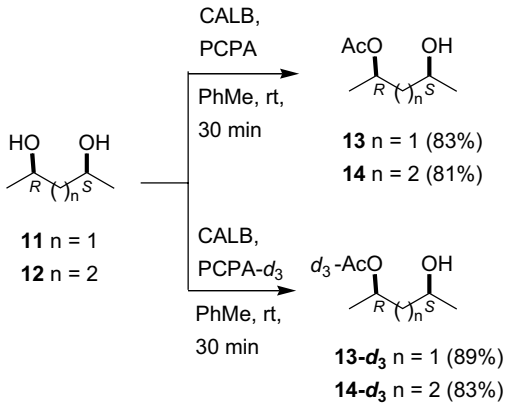
Scheme 9. Stereoselective preparation of *meso*-2,5-hexanediol.

Enzymatic acylation of **11** employing CALB and PCPA (**10**) at room temperature with careful monitoring of the reaction (TLC) gave monoacetate **13** in high selectivity. Analogously, stereoselective monoacylation of diol **11** by CALB and deuterium-labeled acyl donor PCPA-d_3 (**10-*d*$_3$**) afforded deuterated monoacetate **13-*d*$_3$** (Scheme 10).

The non-labeled and labeled (*R*)-monoacetates of *meso*-hexanediol were prepared in analogy with the pentanediol derivatives. CALB-catalyzed acylation of diol **12** with PCPA as acyl donor at room temperature gave

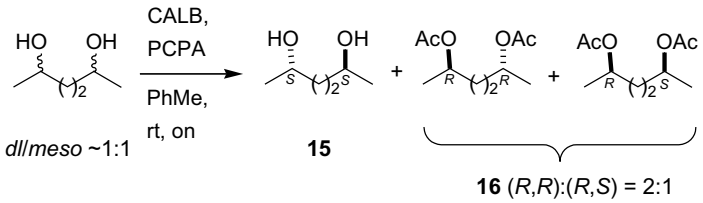
[66] Caron, G.; Kazlauskas, R. J. *Tetrahedron: Asymmetry* **1994**, *5*, 657–664.

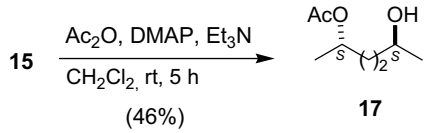
monoacetate **14**, while the same reaction employing labeled acyl donor PCPA-d_3 furnished monoacetate **14-d_3** (Scheme 10).



Scheme 10. Stereoselective preparation of (*R*)-monoacetates of *meso*-2,4-pentanediol and of *meso*-2,5-hexanediol.

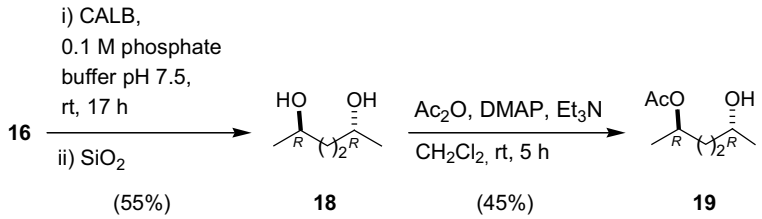
The stereoisomeric monoacetates **17** and **19** were also prepared from the commercially available *dl*/*meso*-2,5-hexanediol via diol **15** and diacetates **16**, respectively. Reaction of the commercial diol with enzyme and PCPA overnight afforded diacetates **16** and unchanged (*S*,*S*)-diol **15**, easily separable by flash chromatography. Diacetates **16** were isolated in a ratio of (*R*,*R*)/(*R*,*S*) ~ 2:1. The significant production of (*R*,*S*)-diacetate can be explained by the direct anomalous *S*-acylation found for monoacetates of 2,5-hexanediol (see section 2.2.3). This reaction gave also a monoacetate fraction containing mainly the (*R)*-monoacetate ((*R*,*S*)/(*S*,*S*) = 95:5). Since this fraction was not used for further studies, it was discarded and its structure omitted in Scheme 11.





Scheme 11. Enantioselective synthesis of monoacetate **17**.

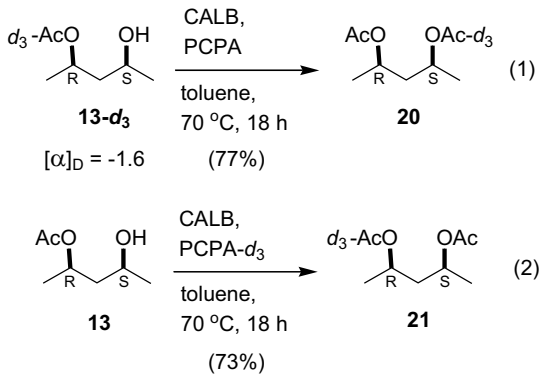
Chemical acetylation of **15** afforded monoacetate **17** (Scheme 11). Enzymatic hydrolysis of diacetate fraction **16** furnished after chromatography (*R*,*R*)-diol **18**, which was chemically transformed into monoacetate **19** (Scheme 12). The approach to combine enzymatic esterification and hydrolysis constitutes a novel approach toward these structures.



Scheme 12. Enantioselective synthesis of monoacetate **19**.

2.2.2 Studies of enzymatic acylation of the (*R*)-monoacetate of (*R*,*S*)-2,4-pentanediol

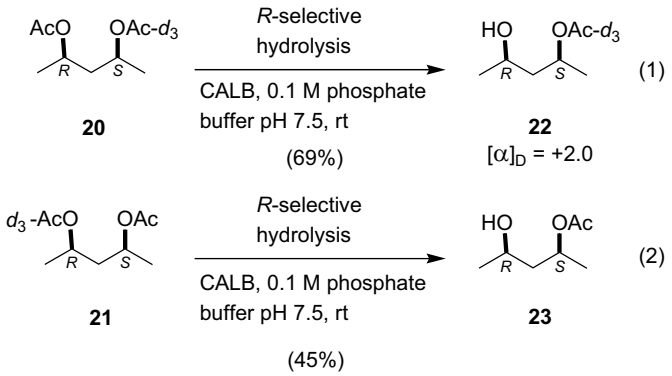
The two mechanisms outlined in Scheme 8 were distinguished by enzymatic acylation of specifically deuterated monoacetate **13-*d*$_3$** and non-deuterated monoacetate **13** with PCPA and PCPA-d_3, respectively. Enzyme-catalyzed acetylation of (*R*)-monoacetate **13-*d*$_3$**, specifically trideuterated in the acetyl group, with CALB and PCPA gave diacetate **20**, which now has the deuterium at the (*S*)-acetate and no deuterium in the original (*R*)-acetate (Scheme 13, eq 1). Analogously, enzymatic acetylation of non-deuterated (*R*)-monoacetate **13** with PCPA-d_3 afforded diacetate **21**, where the deuterated acetoxy group of the acyl donor ends up in the *R*-position (Scheme 13, eq 2).



Scheme 13. Results from enzymatic acylation of monoacetates.

These results unambiguously show that an intramolecular acetyl migration accounts for the formation of the (*S*)-acetate. Apparently, the acyl migration in the syn isomer (*R*,*S*) is relatively fast in this case, which is consistent with the observation[63] that there was more *meso*-diacetate than (*R*,*R*)-product in the combined ruthenium- and enzyme-catalyzed DYKAT of the *dl*/*meso*-diol (*dl*/*meso* ~1:1). In the latter study the relative amount of *meso* configuration in the product was higher than in that of the starting material, suggesting that the acyl migration is faster than the ruthenium-catalyzed epimerization.

The pseudo *meso*-diacetates **20** and **21** are formally enantiomers of one another and differ only in the deuterium labeling. To analyze these compounds we took advantage of the fact that lipases can hydrolyze *meso*-diacetates with high *R*-selectivity (Kazlauskas' rule considered). Enzymatic hydrolysis of diacetate **20** in a buffered aqueous solution afforded **22** (Scheme 14). It was found that the optical rotation of **22** had the opposite sign to that of its enantiomer **13-*d*$_3$**. The analogous enzymatic hydrolysis of **21** furnished **23**. Analysis of monoacetates **22** and **23** by ^{1}H NMR and MS showed that the former is deuterated in the acetoxy group whereas the latter is non-deuterated.



Scheme 14. Analysis of deuterated diacetates.

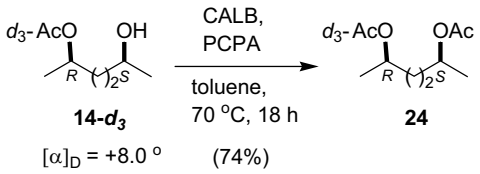
The presence of three deuteriums in the acetoxy group of compound **22** establishes that diacetate **20** has the d_3-acetate in the *S*-position (Scheme 14, eq 1). Furthermore, the lack of deuterium in product **23** shows that the isotope incorporation is at the (*R*)-acetate in diacetate **21** (Scheme 14, eq 2).

These results prove that the enzyme-catalyzed formation of the *meso*-diacetate from *meso*-2,4-pentanediol proceeds via mechanism A, where the second acylation is preceded by an intramolecular acyl transfer (Scheme 8). This acyl transfer releases the fast-reacting (*R*)-alcohol, which is subsequently rapidly acylated by the enzyme. A related acyl transfer has

been observed in lipase-catalyzed hydrolysis of diacetates of *meso*-1,3-diols (2-substituted 1,3-propane diols).[67]

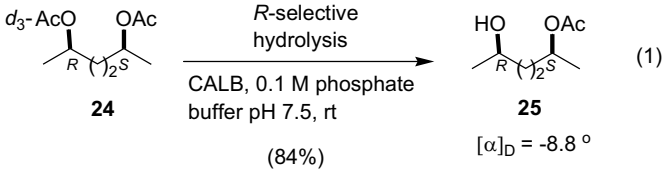
2.2.3 Studies of enzymatic acylation of the (*R*)-monoacetate of (*R*,*S*)-2,5-hexanediol

To make the analogous study of a corresponding 1,4-diol, deuterium-labeled monoacetate **14-d_3** of *meso*-hexanediol was acetylated in the presence of the enzyme. Interestingly, this substrate furnished diacetate **24**, which now has the labeling retained in the *R*-position (Scheme 15).



Scheme 15. Result from enzymatic acylation of monoacetate.

The diacetate was again analyzed by *R*-selective hydrolysis by the use of CALB in aqueous phosphate buffer (Scheme 16). The formation of (*S*)-monoacetate **25** was confirmed by optical rotation, which now had the opposite sign to that of the starting (*R*)-monoacetate **14-d_3**. This unambiguously confirms the *R*-selectivity of the enzyme hydrolysis. Analysis of monoacetate **25** by ^{1}H NMR and MS showed that it is non-deuterated. The lack of deuterium establishes that the label was in the *R*-position of diacetate **24**.



Scheme 16. Analysis of deuterated diacetate.

The corresponding study performed on monoacetate **14** was in accordance with this result. In this case acetylation using the deuterated acyl donor gave a diacetate in which the deuterated acetoxy group from the acyl donor is found in the *S*-position. Hydrolysis of this diacetate gave a deuterated (*S*)-monoacetate.

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[67] Liu, K. K.-C.; Nozaki, K.; Wong, C.-H. *Biocatalysis* **1990**, *3*, 169–177.

These results prove that mechanism B operates for the hexanediol and that the *meso*-diacetate is obtained through a direct enzymatic acylation of the (*S*)-alcohol. The possibility of a direct chemical acetylation was ruled out since no reaction was observed in the absence of enzyme, neither on the isomeric mixture of 2,5-hexanediols nor on the pure (*R*)-monoacetate. In addition, no acyl migration could be detected when monoacetate **14-d_3** was heated in toluene at 70 °C for 24 h in a control experiment.

2.2.4 Kinetic studies of enzymatic acylation of 2,5-hexanediol monoacetates

Because of the unexpected facile direct enzymatic acylation of the (*S*)-alcohol function of the (*R*)-monoacetate of *meso*-2,5-hexanediol the kinetics of the process were studied. The relatively easy enzymatic acylation of the (*S*)-alcohol of this monoacetate suggests that there is an additional interaction between the enzyme and the acetoxy group of the 5-acetoxy-2-hexanol. This interaction could facilitate acylation of the latter diol monoacetate and lead to a much lower rate ratio (pseudo *E* value) between the (*S*)-2-ol and the (*R*)-2-ol of the monoacetate, compared to that of the parent 2-hexanol. It was therefore of interest to determine the relative rate of the (2*R*)- and (2*S*)-alcohols when there is an acetate in the 5-position. Kinetic studies of the diastereomeric (2*R*,5*R*)-5-acetoxy-2-hexanol and (2*S*,5*R*)-5-acetoxy-2-hexanol were performed and the rates were compared for the approximate first-order acetylation reactions. This gave a pseudo *E* value of 25 for the enzyme (Scheme 17 and Figure 6, Left). This value is at least one order of magnitude smaller than that for 2-hexanol.[68] A related moderate enantioselectivity with CALB has been observed for *tert*-butyl 4-hydroxypentanoate ($E = 10$)[69] and ethyl 3-hydroxybutanoate ($E = 31$).[70]

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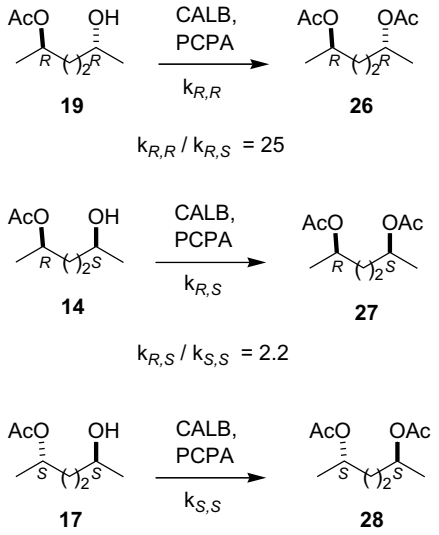
[68] Rotticci, D.; Hæffner, F.; Orrenius, C.; Norin, T,; Hult, K. *J. Mol. Catal. B: Enzym.* **1998**, *5*, 267–272.

[69] Runmo, A.-B. L.; Pàmies, O.; Faber, K.; Bäckvall, J.-E. *Tetrahedron Lett.* **2002**, *43*, 2983–2986.

[70] Magnusson, A.; Hult, K.; Holmquist, M. *J. Am. Chem. Soc.* **2001**, *123*, 4354–4355.



Scheme 17. Relative rates of stereoisomeric monoacetates.

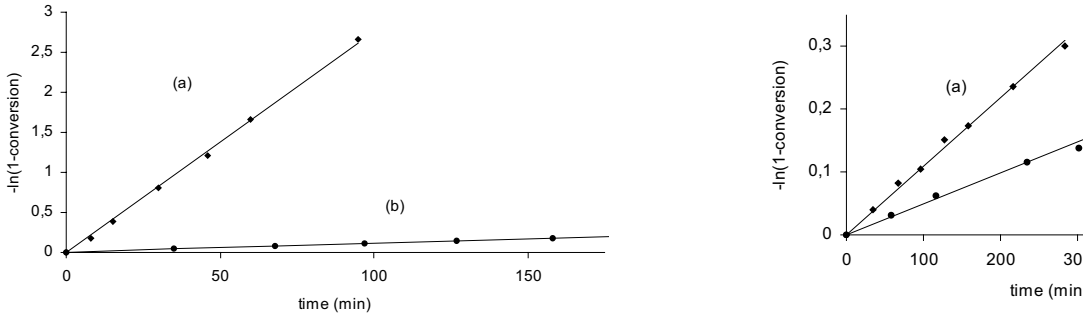


Figure 6. Left: Rate of acetylation of (a) alcohol **19** and (b) alcohol **14**. Right: Rate of acetylation of (a) alcohol **14** and (b) alcohol **17**.

The effect of neighboring acetate group was further studied by examining whether the configuration of the carbon bound to the acetate would influence the rate of the acylation of the alcohol. Remote recognition of a stereogenic carbon atom away from the reaction site has been reported for hydrolytic enzymes in enantioselective hydrolysis[71] and transesterification.[72] The

[71] (a) Mizuguchi, E.; Achiwa, K. *Tetrahedron: Asymmetry* **1993**, *4*, 2303–2306 and references therein. (b) Hughes, D. L.; Bergan, J. J.; Amato, J. S.; Bhupathy, M.; Leazer, J. L.; McNamara, J. M.; Sidler, D. R.; Reider, P. J.; Grabowski, E. J. J. *J. Org. Chem.* **1990**, *55*, 6252–6259.

[72] Ors, M.; Morcuende, A.; Jiménez-Vacas, M. I.; Valverde, S.; Herradón, B. *Synlett* **1996**, 449–451.

relative rates of (2*S*,5*R*)-alcohol **14** (vide supra) and (2*S*,5*S*)-alcohol **17** were compared and in this case the kinetic studies resulted in a pseudo *E* value of 2.2 (Scheme 17 and Figure 6, Right). Comparison of the pseudo $E_{R,R/R,S}$ = 25 with the pseudo $E_{R,S/S,S}$ = 2.2, indicates a small but significant influence of the configuration at the acetoxy-bearing carbon atom.

2.3 Conclusions

We have been able to distinguish between the two previously proposed mechanisms for the formation of anti-Kazlauskas products observed in CALB-catalyzed acylation of 2,4-pentanediol and 2,5-hexanediol. Deuterium-labeling studies show that the former diol gives a monoacetate that is prone to undergo intramolecular acyl transfer (Mechanism A, Scheme 8), whereas the latter substrate is diacylated in a direct enzymatic fashion (Mechanism B, Scheme 8). For the hexanediol monoacetates **14** and **14-d_3** a neighboring group effect of the acetate reduces the substrate specificity of the enzyme.

The elucidation of mechanisms made clear that (1) future improvements of the diastereoselectivity in (DY)KAT of 1,3-diols would require reaction conditions under which the rate of intramolecular acyl migration is suppressed with a maintained fast and selective enzymatic transesterification and (2) since 1,4-diol monoacetates do not suffer from intramolecular acyl transfer, future improvements of the (DY)KAT of 1,4-diols should focus on improving the enantioselectivity of CALB toward these intermediates.

3 DYKAT of 1,3-diols

(Paper II)

3.1 Introduction

1,3-Diols are recurring units in a variety of polyketide natural products[73] and polyene macrolide antibiotics.[74] Much work has been devoted to the development of enantio- and diastereoselective methods for the synthesis of *syn*- and *anti*-1,3-polyols.74[b,75] Isolated 1,3-diols can be prepared by stereocontrolled reductions of *β*-hydroxy ketones (aldols),[76] the aldol-Tishchenko reaction,[77] reductions of 1,3-diketones by catalytic hydrogenation[78] and enzymatic methods.[79]

In chapter 2 it was concluded that an intramolecular acyl migration takes place in 1,3-diol monoacetates (Path A, Scheme 8). The present chapter describes how we took advantage of the acyl transfer in a CALB/ruthenium system for the preparation of enantiomerically pure *syn*-1,3-diacetates. The products can be easily hydrolyzed affording enantiopure acyclic 1,3-diols. Our approach to couple the 1,3-acyl migration to a CALB/ruthenium system results in a new and highly enantioselective de-epimerization–deracemization transforming 1,3-diols **29** (L = large, S = small)[80] to enantiomerically pure *syn*-diacetates **30** (Scheme 18).

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[73] (a) *Comprehensive Natural Products Chemistry, Volume 1: Polyketides and Other Secondary Metabolites Including Fatty Acids and Their Derivatives*; Sankawa, U., Ed.; Elsevier: Amsterdam, 1999. (b) O'Hagan, D. *Nat. Prod. Rep.* **1995**, *12*, 1–32.

[74] (a) Omura, S.; Tanaka, H. In *Macrolide Antibiotics: Chemistry, Biology, and Practice*; Omura, S., Ed.; Academic Press: New York, 1984. (b) Rychnovsky, S. D. *Chem. Rev.* **1995**, *95*, 2021–2040.

[75] (a) Schneider, C. *Angew. Chem., Int. Ed. Engl*. **1998**, *37*, 1375–1378. (b) Oishi, T.; Nakata, T. *Synthesis* **1990**, 635–645.

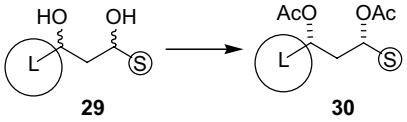
[76] See for instance: Vicario, J. L.; Badía, D.; Domínguez, E.; Rodríguez, M.; Carrillo, L. *J. Org. Chem.* **2000**, *65*, 3754–3760 and references therein.

[77] Mahrwald, R. *Curr. Org. Chem.* **2003**, *7*, 1713–1723.

[78] Kitamura, M.; Noyori, R. In *Ruthenium in Organic Synthesis*; Murahashi, S.-I., Ed.; Wiley-VCH: Weinheim, 2004; p 25.

[79] (a) Ahmad, K.; Koul, S.; Taneja, S. C.; Singh, A. P.; Kapoor, , M.; Hassan, R.; Verma, V.; Qazi, G. N. *Tetrahedron: Asymmetry* **2004**, *15*, 1685–1692. (b) Nakamura, K.; Yamanaka, R.; Matsuda, T.; Harada, T. *Tetrahedron: Asymmetry* **2003**, *14*, 2659–2681.

[80] CALB requires S < *i*-Pr and L > Et.

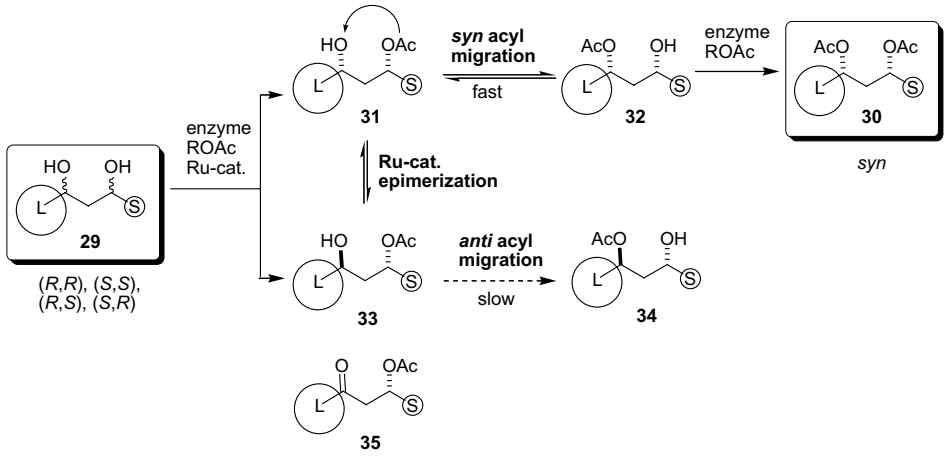


Scheme 18. One-pot de-epimerization and deracemization of unsymmetrical 1,3-diols containing one large group (L) and one small group (S) to enantiomerically pure *syn*-diacetates.

The large group prevents enzymatic acylation of the hydroxyl group next to it, regardless of its configuration. Instead, the acetate at this position must be delivered through an intramolecular acyl migration. The success of the method developed provides further experimental evidence in support of the acyl transfer mechanism (Chapter 2.2.2). To the best of our knowledge, this is the first example of a DYKAT of this kind in which a *syn*-selective acyl migration is coupled with a dynamic KAT.

3.2 Mechanistic considerations

The one-pot synthesis of enantiomerically pure *syn*-1,3-diacetates from racemic diastereomeric mixtures of 1,3-diols (Scheme 18) relies on the in situ coupling of three processes: (i) enzymatic transesterification of the secondary alcohol next to the small group, (ii) ruthenium-catalyzed epimerization of a secondary alcohol and (iii) intramolecular acyl migration in a *syn*-1,3-diol monoacetate. Scheme 19 shows the mechanism of the resulting, novel DYKAT concept. After an enzymatic esterification (in the presence of the Ru-cat.) of the alcohol next to the small substituent, all of the starting material should appear as either monoacetate **31** or **33**. Due to *anti*-acyl migration being slow, an epimerization of the remaining alcohol in **33** transforms *anti*-monoacetate **33** to *syn*-monoacetate **31**, in which acyl migration is fast. The enzyme can then acetylate the newly released alcohol to give enantiomerically pure product **30**. Scheme 20 shows also the more important oxidized intermediate acetoxyketone **35**.



Scheme 19. Mechanism of DYKAT combining (i) enzymatic transesterification, (ii) ruthenium-catalyzed epimerization and (iii) intramolecular acyl migration.

The cyclic intermediates formed during acyl migration in *syn*-diol monoacetates hold 1,3-bis-equatorial alkyl groups, whereas in the corresponding intermediate from *anti*-diol monoacetates one substituent must occupy an axial position (Figure 7).[81] The slow *anti*-acyl migration can take place to a lower extent, giving rise to the formation of diacetate **34**.

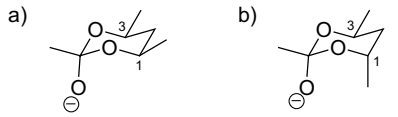
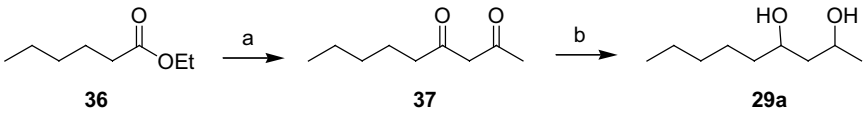


Figure 7. Intermediates in a) *syn*- and b) *anti*-acyl migration.

3.3 Preparation of starting materials

2,4-Nonanediol (**29a**) was prepared from ethyl ester **36**. Claisen acylation of **36** with acetone afforded **37**,[82] which was reduced to diol **29a** (Scheme 20).

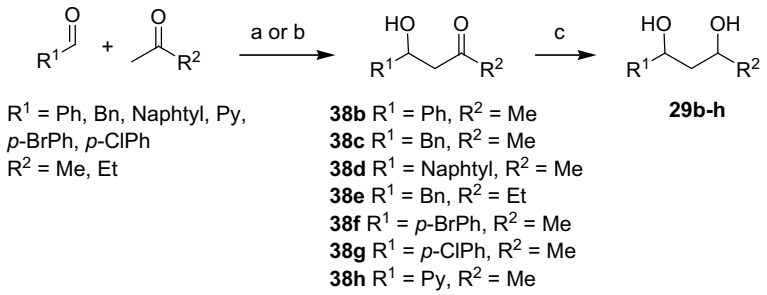


Scheme 20. Reagents: (a) NaH, acetone; (b) $NaBH_4$.

[81] $\Delta\Delta G^0$ in methyl cyclohexane (equatorial vs axial) is about 1.7 kcal/mol. Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; Wiley & Sons: New York, 1994; p 697.

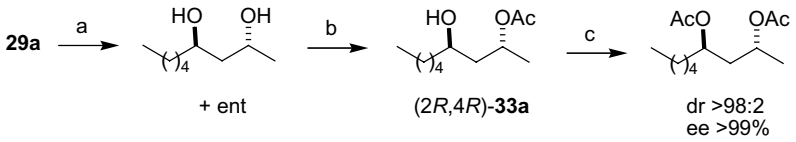
[82] Swamer, F. W.; Hauser, C. R. *J. Am. Chem. Soc.* **1950**, *72*, 1352–1356.

Diols **29b**–**29h** were prepared in two steps from commercial aldehydes and acetone or 2-butanone via hydroxyketones **38** (Scheme 21). Hydroxyketones **38b–38e** and **38h** were prepared by standard LDA-technique. **38f** and **38g** were synthesized by organocatalyzed aldol reactions.[83] Hydroxyketones **38** were subsequently reduced by $NaBH_4$.



Scheme 21. Reagents: (a) LDA; (b) 20 mol% DL-Pro, DMSO/acetone; (c) $NaBH_4$.

The diastereomers of diol **29a** were easily separated by preparative HPLC (Scheme 22). Kinetic resolution of the *anti*-diol thus obtained afforded monoacetate **33a**. The stereochemical purity of **33a** was analyzed after conversion to the corresponding diacetate.



Scheme 22. Reagents and conditions: (a) prep. HPLC; (b) CALB, PCPA, PhMe, rt, 30 min, 48%; (c) Ac_2O, Et_3N, DMAP, 70 °C, few secs, quant.

3.4 Results and discussion

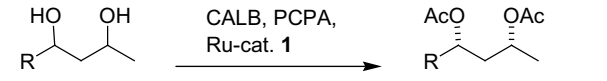
3.4.1 Investigations with *p*-chlorophenyl acetate as acyl donor

In the very first attempts to combine the intramolecular acyl migration with the enzyme-catalyzed transesterification and the ruthenium-catalyzed epimerization, we used CALB, PCPA and 4 mol% of Shvo's ruthenium catalyst **1**. At the time, complex **1** was the best racemization catalyst available for combination with the enzymatic reaction. Toluene was chosen as solvent as the efficiency of DKR is generally higher in toluene than in

[83] This experimentally convenient method was developed for asymmetric aldol reactions catalyzed by L-Pro: (a) List, B. *Tetrahedron* **2002**, *58*, 5573–5590. (b) Sakthivel, K.; Notz, W.; Bui, T.; Barbas, C. F. *J. Am. Chem. Soc.* **2001**, *123*, 5260–5267.

other solvents because of the good solubility of ruthenium catalyst **1** in toluene. When diol **29a** (racemic *syn*/*anti* mixture) was subjected to the DYKAT system at 70 °C, all starting material was consumed after 24 h. However, only 34% of diacetate **30a** had been formed and the remainder of the converted starting material was diol monoacetate and ketoacetate. Interestingly, the diacetate **30a** produced was enantiomerically pure (>99% ee) and was mainly of the *syn* form with a *syn*/*anti* ratio of 91:9 (Table 1, entry 1).

Table 1. *DYKAT with PCPA as acyl donor.*[a]



29a R = $CH_3(CH_2)_4$
29b R = Ph
29c R = Bn

30a R = $CH_3(CH_2)_4$
30b R = Ph
30c R = Bn

Entry	Diol	H-donor / Add. Time	Mol.sieves	Time (h)	Yield (%)[b]	dr[c]	ee (%)[d]
1	**29a**			24	34	91:9	>99
2	**29a**		Yes	24	43	93:7	>99
3	**29a**[e]	**40**[f] / 24	Yes	81	60	91:9	>99
4	**29a**	H_2 / 24	Yes	72	58	90:10	>99
5	**29b**	H_2 / 26	Yes	74	53	95:5	>99
6	**29c**			24	52	96:4	>99
				48	61	91:9	>99

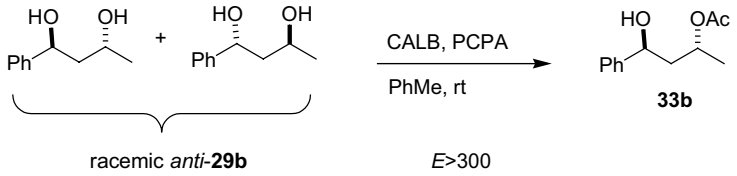
[a] Conditions: 0.188 mmol **29**, 11 mg CALB, 0.56 mmol PCPA and 4 mol% **1** in 1.5 mL toluene at 70 °C under argon or hydrogen as noted. [b] % Yield measured by GC. [c] Diasteremeric ratio measured by GC. [d] Enantiomeric excess determined by GC. [e] The concentration of diol was 0.25 M. [f] **40** = 2,6-dimethyl-4-heptanol.

The assignment of the *syn*- and *anti*-diacetates **30a** was done by transformation to acetonides and subsequent analysis by Rychnovsky's [^{13}C]acetonide method.[84] Despite the modest yield obtained, the result in entry 1, Table 1 shows that the principle of combining the acyl migration with the transesterification and the epimerization works since the yield of enantiomerically pure (>99% ee) **30** is larger than 23% (*syn*/*anti* ratio of starting material is 44/56). The results are consistent with acetyl migration being faster in the *syn*-diol monoacetate compared to the *anti*-diol monoacetate (see below).

The *E* value for the unsymmetrical diol was determined by studying the KR of racemic *anti*-diol **29b** (Scheme 23). Product **33b** was obtained in >99% ee at 33% conversion (20 minutes), which shows that the *E* value is

[84] Rychnovsky, S. D.; Rogers, B. N.; Richardson, T. I. *Acc. Chem Res.* **1998**, *31*, 9–17 and references therein.

>300. This explains why an excellent ee is obtained, even after prolonged reaction times in the DYKAT.



Scheme 23. Determination of the *E* value of *anti*-diol **29b**.

When the substrate concentration was varied in the interval 0.125–0.8 M, the yield of diacetate was essentially unaffected up to 0.5 M. At 0.8 M the reaction was less efficient and more of the starting material was oxidized to diketone. An increase of the acyl donor to 6 equivalents did not increase the yield. At prolonged reaction times the production of diacetate **30** ceased. The major byproduct was then acetoxyketone (**35** in Scheme 19). Traces of regioisomers and diastereomers of the monoacetylated diols (acetoxyalcohols) **33a** and **33b** were also detected.[85] In an attempt to get a faster epimerization by using twice as much ruthenium, 8 mol% **1** was used together with half the amount of CALB, but this gave only 14% diacetate after 24 hours. Addition of 2-octanol to the reaction when the diacetate production had stopped, afforded 2-octylacetate, which showed that the lower yield of diacetate was not caused by enzyme denaturation.

The "water effect"

It was observed that the presence of water, supposedly bound to the hygroscopic diol, had a negative effect on the reaction. To estimate this effect, three DYKAT experiments were run with the same batch of diol **29a**. To the first reaction 0.3 molar equivalents (to diol) of water were added. The second reaction was run under standard conditions (Table 1, entry 1) and the third was carried out in the presence of 4 Å molecular sieves (Table 1, entry 2). After 24 hours the yields of product were 24%, 34% and 43%, respectively, with the highest yield in the one with molecular sieves. This proved that there is a small but significant negative effect by water, which may reflect the reversibility of the enzymatic esterification, and led us to include molecular sieves in the reaction cocktail.

[85] Neither α,β-unsaturated ketones nor the corresponding saturated carbonyl compounds could be found. The first would be formed by acetate elimination from the acetoxyketone, and the latter by transfer hydrogenation of the first, followed by a ruthenium-catalyzed isomerization as reported in: Bäckvall, J.-E.; Andreasson, U. *Tetrahedron Lett.* **1993**, *34*, 5459–5462.

Hydrogen transfer using external H-sources

The major by-product consistently seemed to be acetoxyketone, which indicates problems with the hydrogen transfer. A plausible explanation for this is a hydrogen loss process. Such a process has been observed and discussed by our group during hydrogen transfer of 1,4-diols mediated by catalyst **1**.[86] Just recently, Casey reported mechanistic studies and calculations of elimination of hydrogen from the tolyl-substituted analogue of **1b**.[87] The formation of ketone can be partly overcome by the addition of a hydrogen source to the system, either as a sterically hindered alcohol that cannot be enzymatically acetylated such as 2,4-dimethyl-3-pentanol (**39**)69.[88] and 2,6-dimethyl-4-heptanol (**40**)[89] or hydrogen gas.[90] Several such PCPA-based systems have been reported for derivatized secondary alcohols.

Addition of **39** had no effect on the amount of diacetate produced, and addition of **40** as a hydrogen source gave a slightly higher yield (Table 1, entry 3). To run the reaction under hydrogen gas noticeably slowed down the rate of conversion. Instead, the reaction was run under argon for 24 hours, before the atmosphere was changed to hydrogen. This procedure gave, after a total reaction time of 72 hours, diacetates in 58 % yield for diol **29a** (entry 4) and 53% yield for diol **29b** (entry 5). It is plausible that the somewhat higher diastereoselectivity obtained for diol **29b** reflects its higher steric hindrance in the acyl migration.

The major by-products from diols **29a** and **29b** were either acetoxyketon **35** or acetoxyalcohol **33**. The nature of the byproduct depended on whether the reactions were run under argon (accumulation of acetoxyketones **35**, Figure 8) or hydrogen (accumulation of acetoxyalcohols **33**, Figure 8). The possibility of an unwanted diastereoselectivity in the hydrogen re-addition to acetoxyketone **35** to yield mainly *anti*-monoacetates was ruled out by a control experiment in which a diastereomeric ratio of *syn*/*anti* = 43:57 was obtained from transfer hydrogenation of acetoxyketone **35**. It is interesting to note that when the benzyl substituted diol **29c** was allowed to react under argon still no corresponding acetoxyketone could be detected, the major by-product being acetoxyalcohol (entry 6). This may be explained by a higher oxidation potential of the benzylic alcohol.

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[86] Martín-Matute, B.; Bäckvall, J.-E. *J. Org. Chem.* **2004**, *69*, 9191–9195.

[87] Casey, C. P.; Johnson, J. B.; Singer, S. W.; Cui, Q. *J. Am. Chem. Soc.* **2005**, *127*, 3100–3109.

[88] (a) Pámies, O.; Bäckvall, J.-E. *J. Org. Chem.* **2002**, *67*, 1261–1265. (b) Pàmies, O.; Bäckvall, J.-E. *Adv. Synth. Catal.* **2002**, *344*, 947–952. (c) Pàmies, O.; Bäckvall, J.-E. *Adv. Synth. Catal.* **2001**, *343*, 726–731.

[89] (a) Kim, M.-J.; Choi, Y. K.; Choi, M. Y.; Kim, M. J.; Park, J. *J. Org Chem.* **2001**, *66*, 4736–4738. (b) Jung, H. M.; Koh, J. H.; Kim, M.-J.; Park, J. *Org. Lett.* **2000**, *2*, 409–411.

[90] Steinreiber, J. (2003) Masters thesis (Stockholm University, Stockholm).

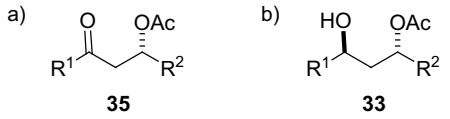
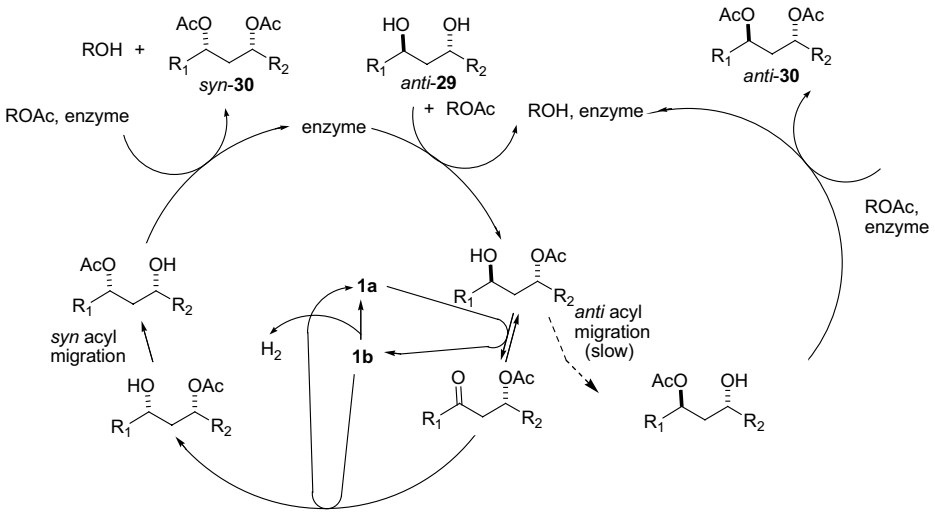


Figure 8. Major by-products under (a) argon and (b) hydrogen atmosphere.

The re-addition might simply be very slow because of steric hindrance or the diol monoacetate might lead to a substrate inhibition of the catalyst not seen for any of the simple alcohols whose racemization has previously been studied together with catalyst **1**. An experiment was performed where the reaction was started under argon, which was exchanged for hydrogen after 1 day. The change of atmosphere was repeated three more times over a period of 6 days. This gave 62% diacetate of a dr = 90:10.

Scheme 24 shows how an *anti*-diol (*anti*-**29**) would be transformed into the enantiomerically pure *syn*-diacetate *syn*-**30** in the DYKAT.

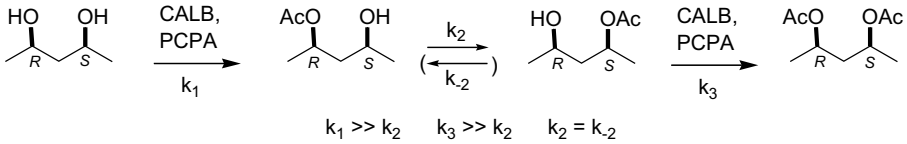


Scheme 24. Productive cooperation of enzyme- and ruthenium-catalysis and intramolecular acyl migration, transforming *anti*-1,3-diol into enantiomerically pure *syn*-diacetate. (R^1 = large- and R^2 = small substituent)

After acylation of the first alcohol, epimerization via hydrogen transfer by **1a** gives a chiral acetoxyketone along with **1b**, from which **1a** is regenerated after the successive transfer hydrogenation. In absence of complex **1b**, acetoxyketone will accumulate.[86] The Ru/enzyme catalytic cycle is closed by the acyl migration, which allows for the enzyme to again acetylate the newly released hydroxyl group next to the small substituent (R^2).

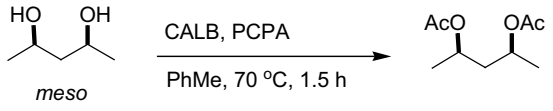
Rate of acyl migration

The rate of acyl migration was studied as a possible bottleneck in the DYKAT. Enzymatic acylation of *meso*-2,4-pentanediol at 70 °C to give the corresponding diacetate involves three reactions (Scheme 25).



Scheme 25. Enzymatic acylation of *meso*-2,4-pentanediol at 70 °C.

The first reaction is the stereoselective *R*-acylation to give the (*R*)-monoacetate. This is followed by an acyl migration to give the (*S*)-monoacetate, which is enzymatically acylated in the third step to produce the diacetate. In this reaction $k_2 = k_{-2}$, $k_1 >> k_2$, and $k_3 >> k_2$. The slow and rate-determining step will therefore be the acyl migration. Because $k_3 >> k_{-2}$ the back reaction of the acyl migration can be neglected. Therefore the rate of the formation of the diacetate will be a direct measurement of the rate of acyl migration. The kinetics is first-order where $t_{½}$ is 1h 45 min at 70 °C in toluene (Figure 9).



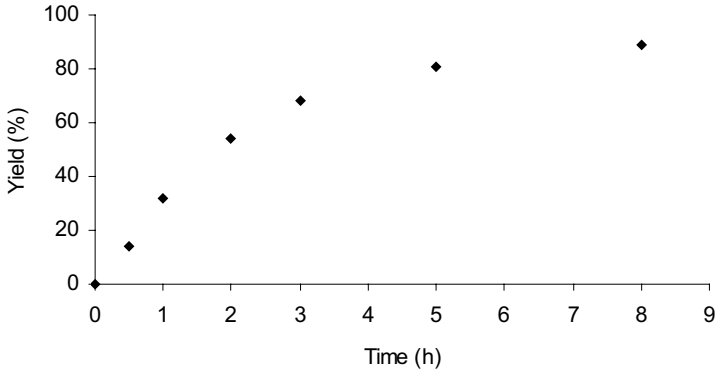
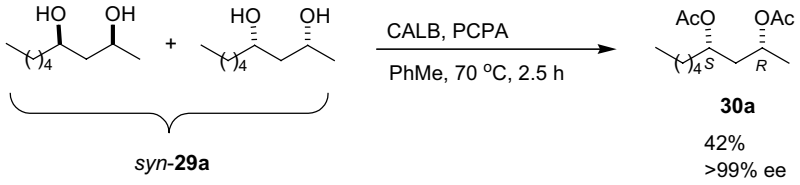


Figure 9. Rate of acyl migration in *meso*-2,4-pentanediol. Conditions: 0.2 mmol *meso*-diol, 12 mg CALB and 0.6 mmol PCPA in 0.6 mL toluene at 70 °C. Yield of diacetate was measured by GC.

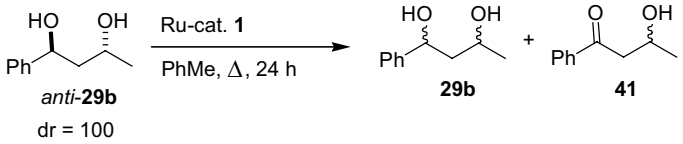
To estimate the rate of the acyl migration for the diol substituted with a large substituent, KR of racemic diol *syn*-**29a** was studied (Scheme 26). The presence of a more bulky substituent did not give a slower acyl migration and after 2.5 hours 42% enantiomerically pure *syn*-diacetate **30a** was observed. These experiments clearly show that the acyl migration cannot be the bottleneck in the DYKAT process, which is run at 70 °C in toluene for more than 24 h.



Scheme 26. KR of racemic *syn*-diol **1a** showing a fast acyl migration.

3.4.2 Rate of epimerization

The rate of epimerization was studied for *anti*-diol **29b** (Scheme 27). The diastereomers of diol **29b** are easily distinguished by ^{1}H NMR. Treatment with 4 mol% **1** at 70 °C for 24 hours gave after 24 hours *syn*-**29b**/*anti*-**29b**/**41** = 1:1:0.5 (^{1}H NMR). Raising the temperature to 80 °C furnished *syn*-**29b**/*anti*-**29b**/**41)** = 1:1:1 whereas the use of 8 mol% **1** also at 80 °C afforded *syn*-**29b**/*anti*-**29b**/**41** = 2:1.3:1. From these results it was concluded that the rate of epimerization is slow and is responsible (at least in part) for the moderate yield of diacetate in DYKAT. Epimerizations of (2*R*,4*S*)-2,4-nonanediol and (2*R*,4*R*)-2-acetoxy-4-nonanol (**33a**) were also performed and similar results were obtained.



Scheme 27. Epimerization studies of racemic *anti*-diol **29b**.

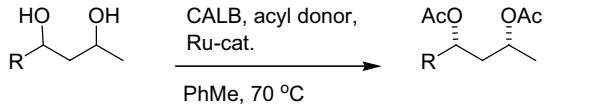
3.4.3 Investigations with isopropenyl acetate as acyl donor

In the original DKR study from 1997 it was demonstrated that isopropenyl acetate worked as acyl donor albeit giving only 72% yield.[36] At the time of the study on the 1,3-diols, a parallel investigation in our laboratory on the addition of hydrogen to the DKR of phenylethanol, employing the Shvo catalyst **1,** CALB and isopropenyl acetate, was very promising.90 Also about this time, Kim et al. reported on the use of ruthenium complex **2** (Figure 3, Chapter 1.3) as an efficient catalyst effecting racemization of secondary

alcohols at room temperature.[39] Catalyst **2** could be combined with CALB-catalyzed kinetic resolution employing isopropenyl acetate as the acyl donor in a DKR of secondary alcohols with no H-donor required.

When diol **29b** was exposed to Kim's procedure, a less efficient and less selective transformation was obtained (Table 2, entry 1). A breakthrough in our efforts was the use of ruthenium catalyst **1** in combination with isopropenyl acetate (**42**). After 12 hours under argon a not very impressive yield of 12% diacetate was obtained, but the diastereoselectivity was very high and when argon was changed to hydrogen the rate was increased and after 89 h 73% diacetate **30b** was obtained in a dr of 93:7 (entry 2). Running the reaction under hydrogen from the beginning resulted in a much faster initial rate, which however declined more quickly (entry 3). Introducing molecular sieves to this system did not result in the same improvement as with PCPA as the acyl donor. It was of interest to try H-donor **40** in this system. This gave a slower reaction that ceased at 35% (entry 4). However, when hydrogen was added after 50 h to the system, the production of diacetate started again and after 5 days the yield had reached 76%. It is interesting to note the favorable situation of combining two H-donors. To see whether the use of isopropyl acetate (**43**) would make the inclusion of any H-donor unnecessary, this acyl donor was applied to the reaction but the yield went down (entry 5). Also, attempts to combine acyl donors **42** and **43** were unsuccessful (entry 6).

Table 2. *DYKAT with isopropenyl acetate (**42**) and isopropyl acetate (**43**) as acyl donors.*[a]



29a R = $CH_3(CH_2)_4$ **30a** R = $CH_3(CH_2)_4$
29b R = Ph **30b** R = Ph

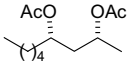
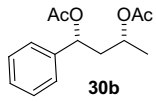
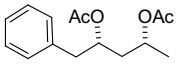
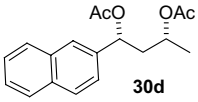
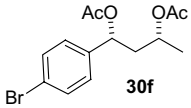
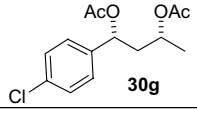
Entry	Diol	Ru-cat.	Acyl donor	H-donator / add.time (h)	Mol.sieves	Time (h)	Yield (%)[b]	dr[c]	ee (%)[d]
1	**29b**	**2**	**42**			37	15	83:17	[e]
2	**29b**	**1**	**42**	H_2 / 14		89	73	93:7	>99
3	**29b**	**1**	**42**	H_2 / 0		24	47	96:4	[e]
						45	52	93:7	[e]
4	**29a**[f]	**1**	**42**	**40**[g] / (0+25)	Yes	24	34	95:5	[e]
						48	35	94:6	[e]
				H_2 / 50		118	76	84:16	[e]
5	**29b**	**1**	**43**			23	19	97:3	[e]
6	**29b**	**1**	**42**+**43**			23	14	98:2	[e]

[a] Conditions: 0.188 mmol **29**, 11 mg CALB, 1.88 mmol mmol acyl donor and 4 mol% Ru-cat. in 1.5 mL toluene at 70 °C under argon or hydrogen as noted. [b] % Yield measured by GC. [c] Diastereomeric ratio measured by GC. [d] Enantiomeric excess determined by GC. [e] ee was assumed to be >99% and was not considered necessary to be determined in every attempt run to improve the yield in the process. [f] The concentration of diol was 0.25 M. [g] **40** = 2,6-dimethyl-4-heptanol.

3.4.4 Substrate study

A few diols were exposed to the DYKAT process developed. Four procedures (Methods A–D) have been investigated and applied to different diols (Table 3). Use of isopropenyl acetate as acyl donor in combination with hydrogen (and alcohol **40**) had proven to give the highest yields of diacetates **30** (Table 2, entry 4, 118 h). Hence, three of the methods include acyl donor **42** and hydrogen. Running the reaction under hydrogen from the start with a substrate concentration of 0.25 M and in the presence of molecular sieves, gave 69% diacetate **30a** after 72 hours (Method A). Diols **29b**–**29d** and **29f** were run at a substrate concentration of 0.125 M, without sieves, under argon the first 12 hours and thereafter under hydrogen (Method B). Benzylic diol **29c** did not give acetoxyketone **35c** when run under argon and higher yield was obtained with PCPA under an argon atmosphere (Method C, entry 4). Method D employs sequential KAT/DYKAT.

Table 3. *DYKAT of 1,3-diols.*[a]

Entry	Product	Method[b]	Time (h)	Yield (%)[c]	dr[c]	ee (%)[c]
1		A	72	69[d]	86:14[d]	>99[e]
2	**30a**	A[f]	81	60[d]	91:9[d]	>99[e]
3	 **30b**	B	89	73[d]	93:7[d]	>99[e]
4	 **30c**	C	72	63	88:12	>99
5	 **30d**	B	45	53	96:4	>99
6	 **30f**	B	72	62	92:8	>99
7	 **30g**	D	72	59	92:8	>99

[a] The reactions were carried out employing 60 mg CALB/mmol diol, 10 equiv isopropenyl acetate, 4 mol% Ru-catalyst **1** and the substrate diol as 0.125 M in dry toluene at 70 °C. [b] Method: A = DYKAT run under hydrogen 0–72 h, concentration of diol 0.25 M, 4 Å mol.sieves added to the reaction, B = DYKAT run under argon 0–12 h then hydrogen 12 h–end, C = 3.0 equiv of PCPA as acyl donor and DYKAT run under argon, D = Sequential KAT (0–2 h) and DYKAT (2–72 h) run under argon 0–10 h and hydrogen 10–72 h. [c] Measured by HPLC. [d] Measured by achiral GC. [e] Measured by chiral GC. [f] Reaction run under argon, 0.5 equiv **40 (**2,6-dimethyl-4-heptanol**)** added after 24 h.

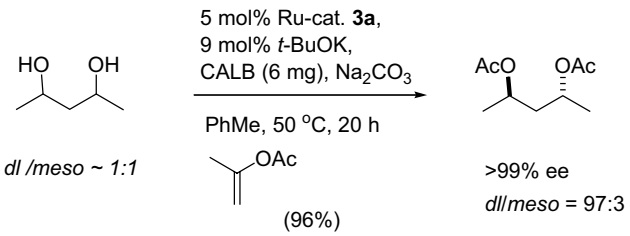
3.5 Efficient DYKAT of 2,4-pentanediol

Enantiomerically pure 2,4-pentanediol is an important intermediate in e.g. the preparation of useful chiral ligands for asymmetric synthesis. The most efficient literature procedure for stereoselective preparation of (*R*,*R*)-2,4-pentanediol is probably ruthenium-catalyzed hydrogenation of 2,4-pentanedione. Use of for example Noyori's (*R*)-BINAP ligand in this reaction gives the (*R*,*R*)-diol in 99% yield, 100% ee and a diastereomeric ratio of *dl*/*meso* = 99:1.[91]

In Bäckvall's previously reported DYKAT of symmetrical diols,[63] an unwanted acyl migration occurred and caused significant production of the

[91] Kitamura, M.; Ohkuma, T.; Inoue, S.; Sayo, N.; Kumobayashi, H.; Akutagawa, S.; Ohta, T.; Takaya, H.; Noyori, R. *J. Am. Chem. Soc.* **1988**, *110*, 629–631.

meso-diol byproduct (Scheme 7, Chapter 2.1). In that DYKAT the Shvo ruthenium catalyst was used for epimerization. With the new and more efficient transfer hydrogenation catalyst **3a** (Chapter 1.3 and 5) in hand, DYKAT of *meso*/*dl*-2,4-pentanediol was improved.[92] The reaction is analogous to the one described in Chapter 5, and extends the scope of that system. Scheme 28 shows the optimized conditions. At 50 °C the epimerization outruns the acyl migration and a commercial stereoisomeric mixture of the diol was transformed to 96% (*R*,*R*)-diacetate (measured by achiral GC) with an excellent ee (>99% as determined by chiral GC) and dr (achiral GC). To run the reaction at room temperature is not optimal.[93]



Scheme 28. Optimized DYKAT.

3.6 Conclusions

A novel DYKAT was developed in which readily accessible racemic diastereomeric mixtures of unsymmetrical, acyclic 1,3-diols are transformed to enantiomerically pure (ee >99%) *syn*-1,3-diacetates (dr ~90:10) in one pot. This new deracemization–de-epimerization of 1,3-diols relies on the fine-tuned cooperation of a lipase-catalyzed transesterification, a ruthenium-catalyzed epimerization and an intramolecular acyl migration. Interestingly, the choice of acyl donor was crucial for the efficiency of the DYKAT. The use of isopropenyl acetate surprisingly influenced the ruthenium-catalyzed epimerization and gave a significant improvement in yield. This acyl donor, together with the combined use of a bulky alcohol and/or hydrogen gas as H-donors, and in the presence of molecular sieves to reduce the amount of water in the system, gave the most efficient process.

Also another DYKAT was optimized, in which *meso*/*dl*-2,4-pentanediol was efficiently transformed into the corresponding (*R*,*R*)-2,4-diacetate. This procedure does not involve any acyl migration, but the use of ruthenium catalyst **3a**. The process is an improvement of the previously reported DYKAT employing the Shvo catalyst for epimerization, and expands the scope of the more efficient transfer hydrogenation catalyst described in chapter 5.

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[92] Edin, M. *Unpublished result*. See Appendix for experimental details.

[93] The best conditions found at room temperature gave after 40 hours 76% diacetate in > 99% ee and *dl*/*meso* = 94:6.

4 Combined organo- and biocatalysis as a direct entry to enantiopure aldols

(Paper III)

4.1 Introduction

The β-hydroxy ketone (aldol) is a commonly encountered structural motif in many molecular targets. Also, aldols are important synthetic building blocks to further manipulate into other structural patterns of biological interest, by for example stereo-controlled reduction to 1,3-diols (Chapter 3). The aldol reaction is one of the most powerful reactions available to the synthetic chemist.[94] Numerous impressive syntheses, employing the aldol reaction as a key transformation, of natural products of a formidable molecular architecture have been reported.[95]

Since the end of the twentieth century, important progress in catalytic asymmetric aldol methodology has been made.[96] Three different approaches have been taken: (1) biocatalysis by use of aldolase enzymes, catalytic antibodies or baker's yeast, (2) chemocatalysis by chiral Lewis acids or metal complexes that mimics class II aldolases and (3) organocatalysis.[97] In 2000 List et al. reported the first organocatalyzed direct intermolecular aldol reaction, in which proline works as a class I aldolase mimic.[98] This amazingly simple and robust catalytic asymmetric reaction has received much attention.

It is well known that by performing consecutive kinetic resolutions, less selective catalysts (most often enzymes) can be used while still yielding products of high optical purity.[99] A second advantage of such sequential resolutions is that the yield is increased relative to resolutions of racemic

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[94] Heathcock, C. H.; Kim, B. M.; Williams, S. F.; Masamune, S.; Rathke, M. W.; Weipert, P.; Paterson, I. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 2, pp 133–319.

[95] See for example Nicolau, K. C.; Snyder, S. A. *Classics in Total Synthesis II*; Wiley-VCH: Weinheim, 2003; pp 31–74.

[96] (a) Palomo, C.; Oiarbide, M; García, J. M. *Chem. Soc. Rev.* **2004**, *33*, 65–75. (b) Saito, S.; Yamamoto, H. *Acc. Chem. Res.* **2004**, *37*, 570–579. (c) Machajewski, T. D.; Wong, C.-H. *Angew. Chem. Int. Ed.* **2000**, *39*, 1352–1374. (d) Sawamura, M.; Ito, Y.; Carreira, E. M., In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I, Ed.; Wiley-VCH: New York, 2000; pp 493–541.

[97] (a) Dalko, P. I.; Moisan, L. *Angew. Chem. Int. Ed.* **2004**, *43*, 5138–5175. (b) Dalko, P. I.; Moisan, L. *Angew. Chem. Int. Ed.* **2001**, *40*, 3726–3748.

[98] List, B.; Lerner, R. A.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2000**, *122*, 2395–2396.

[99] (a) Guo, Z.-W.; Wu, S.-H.; Chen, C.-S.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1990**, *112*, 4942–4945. (b) Wang, Y.-F.; Chen, C.-S.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1984**, *106*, 3695–3696.

material. The same is true if an asymmetric synthesis is linked to a kinetic resolution. The latter concept has been less explored. One of the few drawbacks with the proline-catalyzed aldol reaction is that it affords aryl β-hydroxy ketones with an ee around 70%. Although the few lipase-catalyzed kinetic resolutions of aldols reported previously display a low activity,[100] the combination of proline and lipase catalysts for the preparation of enantiopure aldols or aldol adducts was envisioned.

4.2 Results and discussion

4.2.1 Kinetic resolution

A few commercially available lipases (PCL "Amano" I and II, CALB and *Candida cylindracea*), acyl donors (isopropenyl acetate and vinyl acetate) and solvents (toluene and chloroform) were screened in kinetic resolutions of aryl β-hydroxy ketone **38b** run at room temperature. The reaction is slow and the best result was obtained with "Amano" I (245 mg/mmol hydroxy ketone) in neat vinyl acetate in the presence of molecular sieves (Scheme 29). Under these conditions formation of the corresponding α,β-unsaturated ketone as a byproduct was completely suppressed, and the enzyme's $E >$ 200.

Scheme 29. Optimized kinetic resolution of **38b**.

4.2.2 (*R*)-Aldol adducts by sequential aldol reaction and kinetic resolution

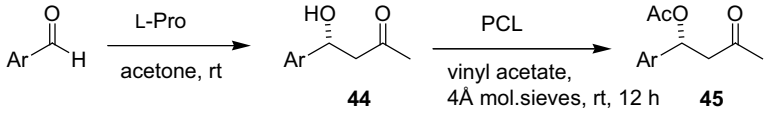
In the original procedure for the proline-catalyzed aldol reaction, DMSO is used as solvent.[98] With a one pot proline/lipase-catalyzed procedure in mind, aldol reactions were investigated in neat acetone. We were pleased to find that products were produced in comparable yields and enantioselectivities as compared to the reactions in DMSO, since this makes product isolation easier and the process more environmentally friendly.

The isolated, scalemic mixtures of aldols obtained in the L-proline-mediated reaction were then subjected to "Amano" I-catalyzed resolutions

[100] (a) Joly, S.; Nair, M. S. *J. Mol. Catal. B: Enzym.* **2003**, *22*, 151–160. (b) Nair, M. S.; Joly, S. *Tetrahedron: Asymmetry* **2000**, *11*, 2049–2052. (c) Khilevich, A.; Mar, A.; Flavin, M. T.; Rizzo, J. D.; Lin, L.; Dzekhtser, S.; Brankovic, D.; Zhang, H.; Chen, W.; Liao, S.; Zembower, D. E.; Xu, Z.-Q. *Tetrahedron: Asymmetry* **1996**, *7*, 3315–3326.

(Table 4). From ^{1}H NMR it was seen that all of the (*R*)-hydroxy ketone **44a** was acetylated by the enzyme in 12 hours, when 81% (*R*)-aldol adduct **45a** was detected (Table 4, entry 1). Also *p*-chloro substituted phenyl hydroxyketone **44b** (entry 2) and *p*-nitro substituted aldol **44c** (entry 3) gave enantiomerically pure aldol adducts with this aldol reaction–KR sequence.

Table 4. *Sequential direct catalytic aldol reactions and lipase-catalyzed KRs.*

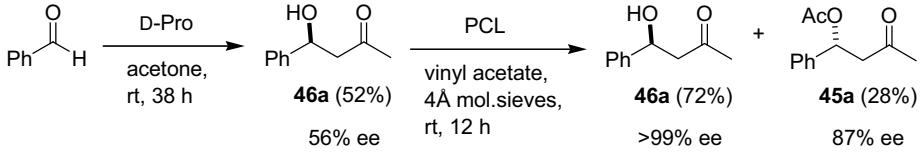


Entry	Ar	Prod. **44**	Time (aldol, h)	Yield[a] **44** (%)	ee[b] **44** (%)	Prod. **45**	Yield[c] **45** (%)	ee[b] **45** (%)
1	C_6H_5	**44a**	33	50	64	**45a**	81	>99
2	*p*-ClC_6H_4	**44b**	25	71	68	**45b**	65	>99
3	*p*-$NO_2C_6H_4$	**44c**	8	79	77	**45c**	76	>99

[a] Isolated yield. [b] Determined by chiral GC or HPLC. [c] Measured by NMR.

4.2.3 (*S*)-Aldols by sequential aldol reaction and kinetic resolution

By the change from L-proline to D-proline, the sequential reactions were also successfully used for the preparation of enantiomerically pure (*S*)-*β*-hydroxy ketones (Scheme 30). The D-proline-catalyzed aldol reaction of benzaldehyde gave (*S*)-*β*-hydroxy ketone **46a** in 52% isolated yield. In this case, a high *E* value of the enzyme for the substrate is required for successive, exclusive acetylation of the minor enantiomer in the scalemic mixture of aldols. Again, the "Amano" I-catalyzed resolution was completed in 12 hours and 72% of unchanged, enantiopure aldol **46a** was detected (by NMR), along with 28% of acetylated aldol **45a** adduct in the resolution.

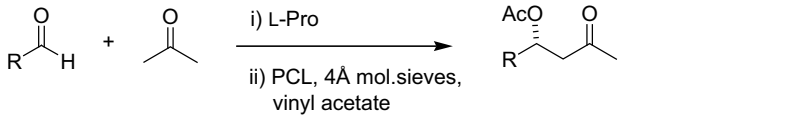


Scheme 30. Sequential asymmetric synthesis of (*S*)-aldol **46a**.

4.2.4 Tandem reactions in one pot

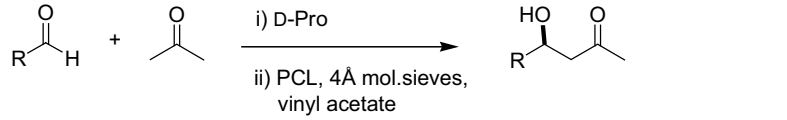
The compatibility of the two catalysts was explored when the tandem reactions were performed in one-pot. Scheme 31 shows how (*R*)-aldol adducts were obtained, and in Scheme 32 the synthesis of the corresponding (*S*)-aldols is depicted. In these procedures excess acetone from the first step

was evaporated before introduction of enzyme and acyl donor into the reaction vessel.



45a R = C_6H_5 (31%, >99% ee)
45b R = *p*-$NO_2C_6H_4$ (37%, >99% ee)

Scheme 31. One-pot tandem aldol reaction and KR to give (*R*)-aldol adducts.



46a R = C_6H_5 (37%, >99% ee)
46b R = *p*-$NO_2C_6H_4$ (51%, >99% ee)

Scheme 32. One-pot tandem aldol reaction and KR to give (*S*)-aldols.

Importantly, the optical purity of the products was not affected by the one-pot procedure. The yields however decreased ca. 10% as compared to when the intermediate hydroxy ketones were isolated.

4.3 Conclusions

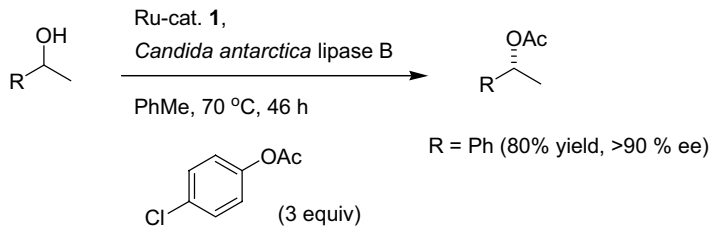
The novel combination of organocatalytic aldol reactions and enzyme-catalyzed kinetic resolutions developed allows a mild and nontoxic preparation of enantiomerically pure aryl *β*-hydroxy ketones, or adducts thereof, with complementary configurations.

5 DKR of alcohols

(Paper IV and V)

5.1 Introduction

Chiral alcohols are abundant in nature, and functionalized alcohols are important building blocks in enantioselective synthesis. Consequently, much effort has been made to develop efficient methods for their preparation. Several approaches are available today, such as asymmetric transfer hydrogenation,[30] catalytic hydrogenation[101] and CBS-reduction[102] of ketones, and metal-catalyzed alkylation of aldehydes.[103] In industry, KR of racemic alcohols plays a dominant role.[104] In recent years, chemoenzymatic DKR of secondary alcohols has been a rapidly evolving field of research.[62] The first example was reported in 1996 by Williams who combined a rhodium catalyst and a lipase to obtain a DKR of *sec*-alcohols with moderate efficiency.[35] In 1997 our group reported the first practical DKR process for the synthesis of enantiopure alcohols by use of the Shvo catalyst **1** (Chapter 1.3) in combination with immobilized CALB (Scheme 33).[36,54]



Scheme 33. First practical chemoenzymatic DKR of alcohols.

This method and slightly modified procedures have been applied by us and by Kim and Park to a variety of functionalized alcohols (Scheme 34).[42,62,89a]

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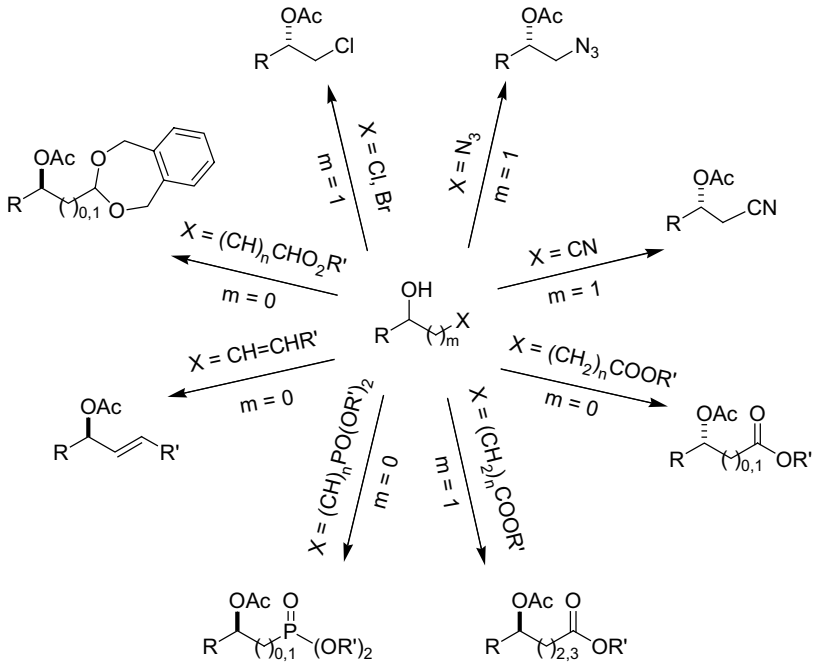
[101] Ohkuma, T.; Noyori, R. In *Transition Metals for Organic Synthesis*, 2nd ed; Beller, M.; Bolm, C., Eds.; Wiley-VCH: Weinheim, 2004; Vol. 2, pp 29–113.
[102] Corey, E. J.; Helal, C. J. *Angew. Chem. Int. Ed.* **1998**, *37*, 1986–2012.
[103] Lin, G.-Q.; Li, Y.-M.; Chan, A. S. C. *Principles and Applications of Asymmetric Synthesis*; John Wiley & Sons: New York, 2001; pp 107–118.
[104] Breuer, M.; Ditrich, K.; Habicher, T.; Hauer, B.; Keβeler, M.; Stürmer, R.; Zelinski, T. *Angew. Chem. Int. Ed.* **2004**, *43*, 788–824.



Scheme 34. Alcohol derivatives obtained by ruthenium- and lipase-catalyzed DKR.

The strength of the previously developed DKR system is its robustness and excellent enantioselectivity. The drawbacks are that an elevated temperature is required to activate the ruthenium pre-catalyst, that PCPA is required as a specifically designed acyl donor (Chapter 1.4), and that long reaction times (several days) are needed.

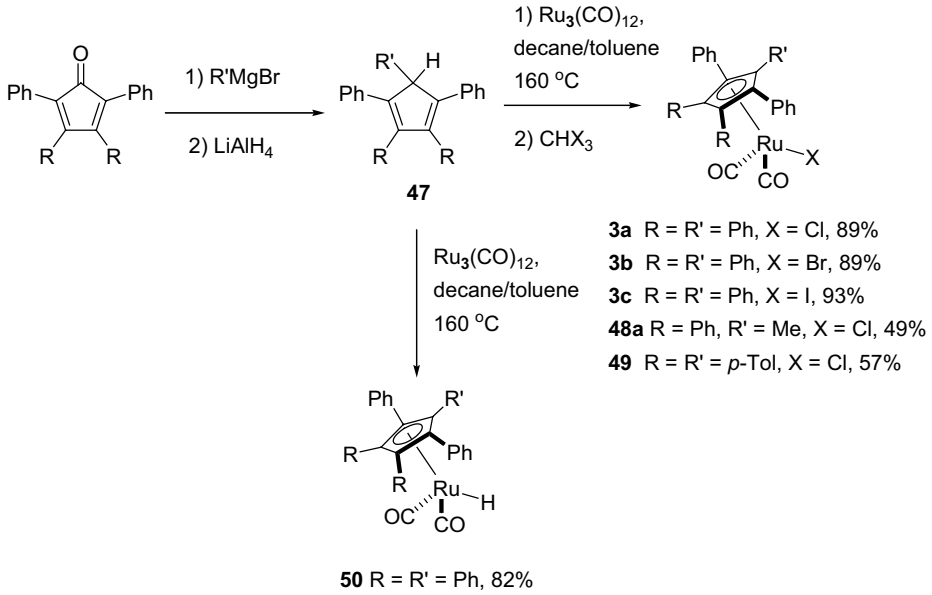
An improvement was made when Kim and Park recently reported the use of base-activated ruthenium complex **2** (Chapter 1.3) in combination with isopropenyl acetate as acyl donor in a room temperature DKR. A limitation with their system is the very long reaction time (1.3 to 7 days), caused by compatibility problems of the metal and enzyme catalysts.

Very recently our group found that complexes **3a** and **3b** (Figure 3, Chapter 1.3), after activation by potassium *tert*-butoxide, are capable of racemizing chiral alcohols within minutes at room temperature.[40] Initial attempts to combine racemization by catalysts **3a** or **3b** with an enzymatic resolution were unsuccessful and gave either no DKR or led to very long reaction times for the DKR (several days). This was frustrating, as the isolated reactions (enzymatic resolution, racemization) are very fast. Finally, we were able to find reaction conditions under which the DKR has almost the same rate as the KR. This chapter describes the development of a room temperature DKR that is more than two orders of magnitude faster than our

previous procedures[36,54,62] and one order of magnitude faster than the hitherto fastest procedure reported.[39]

5.2 Syntheses of catalysts

In the early stages of the project, we prepared ruthenium complexes **3a** and **3b** by a literature procedure in which C_5Ph_5X (X = Cl,[105] Br) was treated with $Ru_3(CO)_{12}$ in toluene under reflux.[IV] A new method was later developed that also allowed the preparation of **3c**, **48** and **49** (Scheme 35). Ruthenium hydride **50** was also accessible from **47** by reaction with $Ru_3(CO)_{12}$.[106]



Scheme 35. Novel route to ruthenium complexes.

The structures of **3a**, **3c** and hydride **50** were confirmed by X-ray diffraction analysis. The structure of hydride **50** is shown in Figure 10.

[105] Conelly, N. G.; Manners, I. *J. Chem. Soc. Dalton Trans.* **1989**, 283–288.

[106] The low yield of **48a** is due to simultaneous formation of the dimerized complex (45%). The dimer is easily transformed to the corresponding Ru-Br (**48b**) and Ru-I (**48c**) monomers by treatment with Br_2 or I_2 respectively.

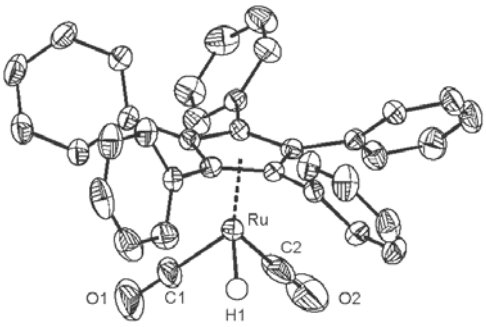


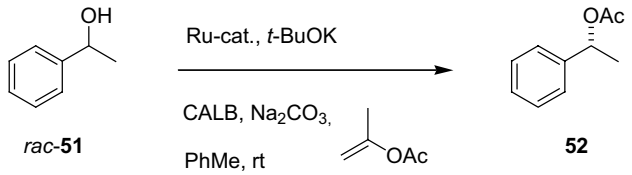
Figure 10. X-ray crystal structure of ruthenium hydride **50**. Thermal ellipsoids are drawn at 50% probability. Selected bond lengths (Å): Ru(1)-C(1) 1.795(5), Ru(1)-C(2) 1.811(5), Ru(1)-Cp carbons: Ru(1)-C(3) 2.270(3), Ru(1)-C(4) 2.268(3), Ru(1)-C(5) 2.267(3), Ru(1)-C(6) 2.251(3), Ru(1)-C(7) 2.286(3). Selected angles (°): C(1)-Ru(1)-C(2) 89.3(2).

5.4 Results and discussion

5.4.1 Combining racemization and resolution

Racemizations studies catalyzed by complexes **3a**–**3c**, **48a** and **49** showed that the rate is affected by the substituents on the Cp ring; pentaaryl substituted catalysts were superior in racemization of (*S*)-phenylethanol. Pre-catalysts **3a**–**c** were applied in attempts to combine the ruthenium- and lipase-catalyzed processes, to achieve a DKR of phenylethanol chosen as a model substrate (Table 5).

Table 5. *DKR of phenylethanol.*[a]



Entry	Ru-catalyst	Time (h)	% Yield[b]	% ee[b]
1[c]	**3b**	4	55	>99
2[d]	**3b**	4	99 (97)[e]	>99
3	**3b**	3	98	>99
4[f]	**3a**	3	95 (92)[e]	>99
5[f]	**3c**	3	60	93
6[f]	**3c**	7.5	66	93
7[f,g]	**3c**	3	86	35
8[h]	**3b**	15	60	>99

[a] Unless otherwise noted, Ru-catalyst (4 mol%), CALB (6 mg), Na_2CO_3 (1 mmol), and *t*-BuOK (5 mol%) were stirred in toluene (2 mL) for 6 min before adding **51** (1 mmol). After 4 min, isopropenyl acetate (1.5 mmol) was added and the mixture was stirred under an argon atmosphere. [b] Determined by chiral GC [c] A solution of **51** in toluene (3.3 mL) was added to a mixture of Ru catalyst and *t*-BuOK, and after stirring (6 min) CALB, Na_2CO_3 and isopropenyl acetate were added. [d] 3.3 mL of toluene. [e] Isolated yield. [f] 5 mol% of catalyst **3c**. [g] 6 mol% of *t*-BuOK. [h] Under an air atmosphere.

The order of mixing the substrate, pre-catalyst **3b** and *t*-BuOK in toluene turned out to be crucial. When 1-phenylethanol was present in this mixture from the start, only 55% yield of enantiopure acetate was obtained after 4 h (Table 5, entry 1). In contrast, when the mixture of potassium *t*-butoxide and complex **3b** was stirred for 6 min in toluene before addition of **51**, acetate **52** was formed in 99% yield and >99% ee in 4 h (entry 2). When the substrate concentration was increased, the DKR was complete in only 3 h (entry 3). A similar result was obtained with pre-catalyst **3a** (entry 4). The combination of catalysts **3a** and **3b** with the enzyme is so efficient that the starting alcohol stays racemic throughout the reaction (Figure 11). Unexpectedly, iodide complex **3c** was unsuccessful in the DKR (entry 5). A plausible explanation for this is the higher solubility of KI, as compared to KBr and KCl, which leads to the presence of **3c** and *t*-BuOK in the mixture; *t*-BuOK causing chemical acylation. The yield did not increase with time (entry 6), and use of more base gave more chemically acetylated product (entry 7). It was observed that the system is very sensitive to molecular oxygen. This is clear from the result obtained when the reaction was run under air (entry 8).

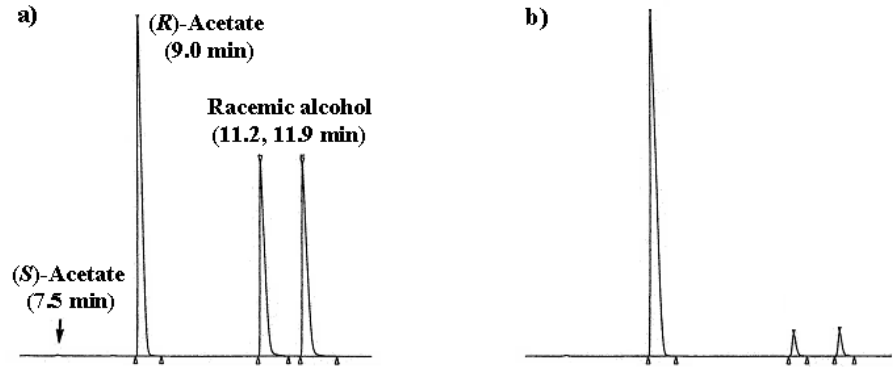
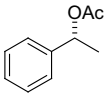
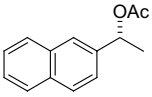
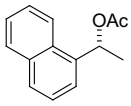
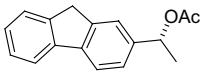
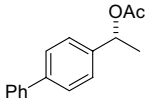
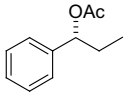
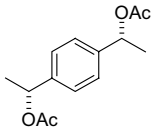
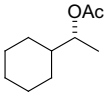
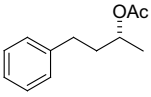
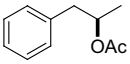


Figure 11. GC chromatogram from DKR of 1-phenylethanol catalyzed by ruthenium complex **3b** at a) 42% conversion and at b) 91% conversion.

5.4.2 Scope and limitations of the DKR

Of the two most successful racemization catalysts **3a** and **3b** in the DKR of phenylethanol, we considered **3a** to be the most readily available one. Hence, **3a** was used when the scope and limitations of the room temperature DKR were studied. The amount of base required to activate the catalyst depends on the substrate and on the amount of enzyme employed. The required amount of enzyme, in turn, depends on the substrate. Therefore, the quantity of potassium *tert*-butoxide was optimized for each case. Table 6 shows the results from DKR of aromatic and aliphatic alcohols. 2-Naphthyl ethanol gave a high yield in short time (Table 6, entry 2), whereas the more sterically congested 1-naphthyl derivative reacted substantially slower (entry 3). The long reaction times required for 2-fluorenyl (entry 4) and biphenyl (entry 5) substituted alcohols were ascribed to the poorer solubility of these substrates in toluene. CALB-catalyzed KR of the ethyl carbinol is significantly slower than for phenyl ethanol, but by use of more enzyme 92% yield was obtained in 17 hours (entry 6). Diols also work in this DKR (entry 7). We were very pleased to find that aliphatic alcohols gave acetates in high yields and selectivities (entries 8–11), since both asymmetric catalytic hydrogenation and transfer hydrogenation of aliphatic substrates proceed with lower selectivity than of aromatic substrates. In general, CALB is highly active and selective toward aliphatic alcohols. However, for 1-phenyl-2-propanol a lower selectivity (E = 70) was observed. By use of much enzyme relative to the other aliphatic substrates studied, this alcohol gave full conversion and a product with 91% ee (entry 11).

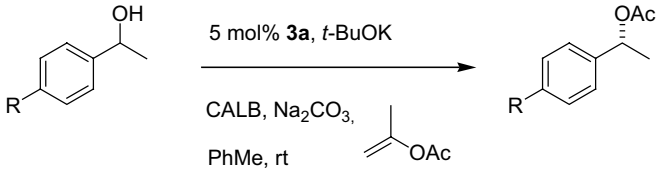
Table 6. *DKR of aromatic and aliphatic alcohols.*[a]

Entry	*t*-BuOK (mol%)	Time (h)	Product	Yield[b,c] (%)	ee[b] (%)
1	5	3		95 (92)	>99
2	6.25	3		93	>99
3[d]	5	24		>97 (97)	>99
4[e]	5	24		>97[f] (97)	>99[f]
5	5	24		>96[f] (96)	>99[f]
6[g]	8	17		92 (90)	>99
7[h]	6	10		94 (90)	>99 (97% de)
8	7	17		98[i]	>99
9[j]	7	20		93	>98
10[k]	5	12		91	96
11[g]	8	6		99	91

[a] Unless otherwise noted, Ru-catalyst **3a** (5 mol%), CALB (6 mg), Na_2CO_3 (1 mmol), and *t*-BuOK were stirred in toluene (2 mL) for 6 min before adding the alcohol (1 mmol). After 4 min, isopropenyl acetate (1.5 mmol) was added and the mixture was stirred under an argon atmosphere at ambient temperature. [b] Determined by chiral GC. [c] Isolated yield in parenthesis. [d] 3 mL of toluene. [e] CALB: 12 mg, 5 mL of toluene and 40 °C. [f] Determined by chiral HPLC. [g] CALB: 40 mg. [h] 50 °C, 3 equiv of isopropenyl acetate. [i] Yield determined by ^{1}H NMR spectroscopy. [j] CALB: 2 mg. [k] CALB: 0.5 mg.

The influence from variations in electronic properties of the substrate was studied. It was found that alcohols bearing electron-donating substituents (Table 7, entries 2 and 3) or a weakly electron-withdrawing substituent (entry 4) work very well. Alcohols with more electron-withdrawing substituents gave close to quantitative yields and excellent enantioselectivities, but the reaction time was significantly longer (entries 5–7).

Table 7. *DKR of aromatic alcohols with different electronic properties.*[a]

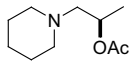
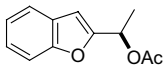
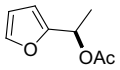
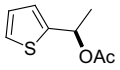
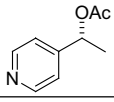


Entry	R	*t*-BuOK (mol%)	Time (h)	Yield[b,c] (%)	ee[b] (%)
1	H	5	3	95 (92)	>99
2	OMe	7.5	6	96 (94)	>99
3	*n*-Pr	5	6	96 (95)	99
4	Cl	5	6	93 (91)	>99
5	NO_2	5	20	99 (97)	>99
6	CN	5	20	98 (95)	>99
7	CF_3	5	24	>98 (98)	>99

[a] Unless otherwise noted, Ru-catalyst **3a** (5 mol%), CALB (6 mg), Na_2CO_3 (1 mmol), and *t*-BuOK were stirred in toluene (2 mL) for 6 min before adding the alcohol (1 mmol). After 4 min, isopropenyl acetate (1.5 mmol) was added and the mixture was stirred under an argon atmosphere at ambient temperature. [b] Determined by chiral GC. [c] Isolated yield in parenthesis.

A few heterocyclic alcohols were subjected to this DKR, and the results are collected in Table 8.

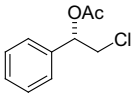
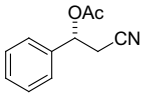
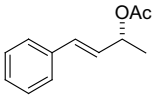
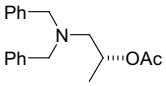
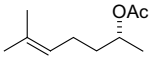
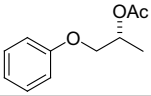
Table 8. *DKR of heterocyclic alcohols.*[a]

Entry	*t*-BuOK (mol%)	Time (h)	Product	Yield[b,c] (%)	ee[b] (%)
1	5	5		>99	99
2	7	6		98 (92)	96
3[d]	8	6		93	96
4	5	6		>98 (98)	>99
5[e]	5	20		97 (96)	99

[a] Unless otherwise noted, Ru-catalyst **3a** (5 mol%), CALB (6 mg), Na_2CO_3 (1 mmol), and *t*-BuOK were stirred in toluene (2 mL) for 6 min before adding the alcohol (1 mmol). After 4 min, isopropenyl acetate (1.5 mmol) was added and the mixture was stirred under an argon atmosphere at ambient temperature. [b] Determined by chiral GC. [c] Isolated yield in parenthesis. [d] THF was not evaporated from the base solution. [e] 50 °C.

Some functionalized alcohols that are suitable for further transformations, or are themselves important intermediates to valuable compounds, were also exposed in this reaction (Table 9). *β*-Chlorophenylethanol is best resolved by *Pseudomonas cepacia* lipase. The optimized DKR gave enantiopure acetate in good yield (Table 9, entry 1). To obtain the *β*-cyanoderivative in higher than 91% ee and in short time, the temperature had to be raised to 100 °C (entry 2). This result proves that the catalyst does not decompose at high temperature. Importantly, allylic alcohols are tolerated, and only a small amount of the saturated ketone was formed by ruthenium-catalyzed redox isomerization (see Chapter 7). Applications to the syntheses of an aminoalcohol (entry 4), the pheromone sulcatol (entry 5) and a bactericide intermediate (entry 6) were also found.

Table 9. *DKR of miscellaneous alcohols.*[a]

Entry	*t*-BuOK (mol%)	Time (h)	Product	Yield[b,c] (%)	ee[b] (%)
1[d]	10	13		83[e]	>99
2[f]	8	6		85[g]	97
3	6	18		89[h]	>99
4[i]	5	5		97[e] (94)	>97[j]
5[k]	5	72		92 (90)	98
6[i]	5	24		>98 (96)	>92

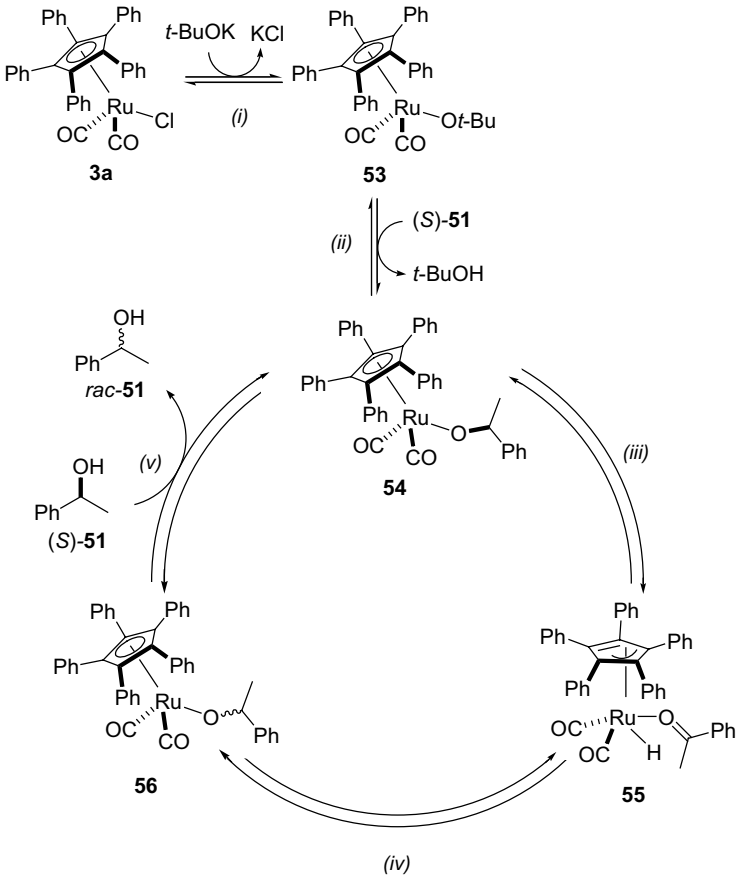
[a] Unless otherwise noted, Ru-catalyst **3a** (5 mol%), CALB (6 mg), Na_2CO_3 (1 mmol), and *t*-BuOK were stirred in toluene (2 mL) for 6 min before adding the alcohol (1 mmol). After 4 min, isopropenyl acetate (1.5 mmol) was added and the mixture was stirred under an argon atmosphere at ambient temperature. [b] Determined by chiral GC. [c] Isolated yield in parenthesis. [d] Enzyme: PS-C "Amano" II, THF was not evaporated from the base solution. [e] Yield determined by ^{1}H NMR spectroscopy. [f] 100 °C, CALB: 100 mg. [g] Yield determined by ^{1}H NMR spectroscopy, 9% of cinnamonitrile was also produced. [h] 11% of 4-phenyl-2-butanone was also formed. [i] 35 °C. [j] Determined by chiral HPLC. [k] CALB: 1 mg. [l] CALB: 1 mg, 40 °C.

One limitation was observed for 1-phenylpropargyl alcohol. Racemization of this substrate could not be effected by use of either pre-catalyst **3a** or **49**.

5.4.3 Mechanism of racemization

Based on the fact that it was necessary to premix the ruthenium complex and potassium *t*-butoxide in toluene, and on the basis of a few mechanistic studies (vide infra), we propose the following catalytic cycle for racemization of chiral alcohols (Scheme 36). Ruthenium halide pre-catalyst **3a** is activated by potassium *tert*-butoxide with concomitant formation of ruthenium *t*-butoxide **53** (step *i*, Scheme 36). Ligand substitution of **53** by enantiomerically pure alcohol *(ii)* affords another ruthenium alkoxide **54**.

Complex **54** undergoes β-hydride elimination *(iii)* to give η^3-coordinated cyclopentadienylruthenium hydride **55**, with the ketone produced still in the coordination sphere of the metal. In this hydride ketone complex (**55**) free rotation around the ruthenium oxygen bond occurs. Hydride addition to either face of the coordinated ketone *(iv)* produces alkoxide complex **56**. Subsequent ligand substitution with (*S*)-alcohol *(v)* releases the racemic alcohol and regenerates intermediate **54**.



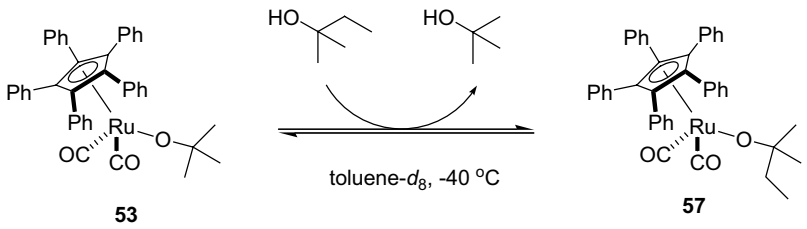
Scheme 36. Proposed catalytic cycle for racemization of (*S*)-phenylethanol.

Because pre-catalyst **3a** and the proposed ruthenium alkoxides both are 18-electron complexes, the mechanisms of each one of the fundamental reactions steps in the proposed cycle are non-trivial and of mechanistic interest. There are two principal mechanisms by which ligand substitution can take place, either an associative or a dissociative. Ligand substitution on 18-electron complexes normally follows the dissociative pathway, unless the metal holds another ligand capable of changing its hapticity. To us, a change

in hapticity of the Cp ligand seems most likely for two reasons. Firstly, it is known that dissociation of CO requires elevated temperature[107] and secondly, dissociation of alkoxides would, in the presence of isopropenyl acetate, lead to chemical acylation and enantiomerically pure acetates would not be obtained in the DKR. *β*-Hydride elimination requires a free coordination site, while migratory insertion opens up a coordination site, and both these events can be accounted for by Cp ring slippage. We performed separate mechanistic studies on steps *(i)* and *(ii)* by NMR, and on step *(iv)* by other experiments.

When complex **3a** is mixed with *t*-BuOK in toluene (step *i*, Scheme 36), a new complex is formed. The reaction is supported by a color change from yellow to red within a few minutes. When we performed this reaction in deuterated toluene in an NMR tube, a fine precipitate of KCl was formed and ruthenium alkoxide **56** was observed by ^{13}C NMR. The resonances of **56** differ from those of **3a**, potassium *t*-butoxide and *t*-butanol in toluene-d_8. Further, when (*S*)-phenylethanol was added to the NMR tube containing alkoxide **53**, racemization occurred within five minutes as confirmed by chiral GC.

The alkoxide ligand substitution (step *ii*) was studied by addition of *t*-amyl alcohol (3 equiv) to ruthenium alkoxide **53** in toluene-d_8 at low temperature (Scheme 37). We chose to use another tertiary alcohol in the exchange to avoid *β*-elimination also in the new complex. After less than 10 minutes at −40 °C the formation of a new ruthenium alkoxide complex **57** was observed by ^{13}C NMR (ca. 20%). In another experiment in which one molar equivalent of *t*-amyl alcohol was added, equilibrium was quickly established between the two alkoxide complexes at 10 °C. The mechanism of this alkoxide exchange remains unknown.



53 **57**

Scheme 37. Alkoxide substitution reaction *(ii)*.

To investigate whether ruthenium hydride **50** is an active catalytic species or not, (*S*)-phenylethanol was subjected to 5 mol% **50** (available by independent synthesis, Chapter 5.2) and 5 mol% acetophenone in toluene at room temperature. The racemization was followed by chiral GC. It was

[107] (a) Guari, Y.; Sabo-Etienne, S.; Chaudret, B. *J. Am. Chem. Soc.* **1998**, *120*, 4228–4229. (b) Guari, Y.; Sabo-Etienne, S.; Chaudret, B. *Eur. J. Inorg. Chem.* **1999**, 1047–1055.

found that **50** can effect fast catalysis, but only after an induction period of 2.5 h (Figure 12). During the first two hours, the reaction mixture remained yellowish (**50** is a light brown powder) then it turned orange and finally dark red, indicating the formation of Ru-alkoxides. (Complex **53** in toluene is a red solution.) The result shows that reaction of hydride **50** with acetophenone is slow, but once the active species is formed racemization proceeds fast. We interpreted this as although ruthenium hydride intermediates most likely are involved in racemization, η^5-ruthenium hydride **50** is not abundant in the catalytic cycle. We suggested the η^3-coordinated complex **55**, with the ketone coordinated, as the more active species (Scheme 36).

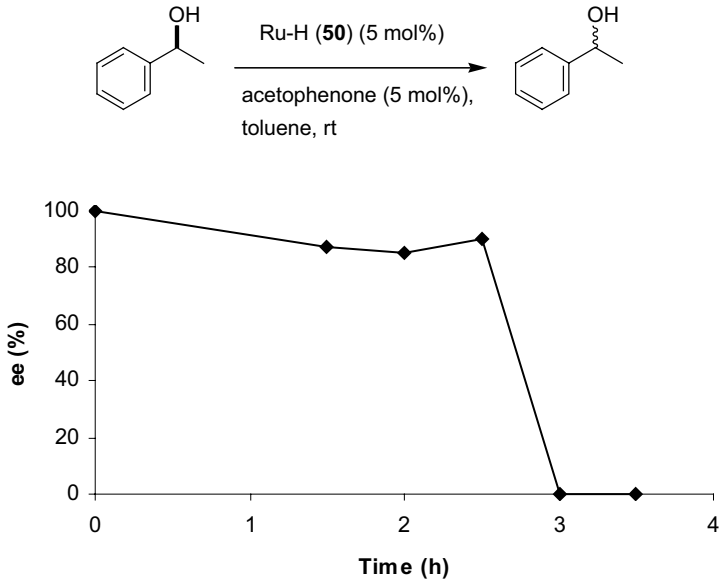
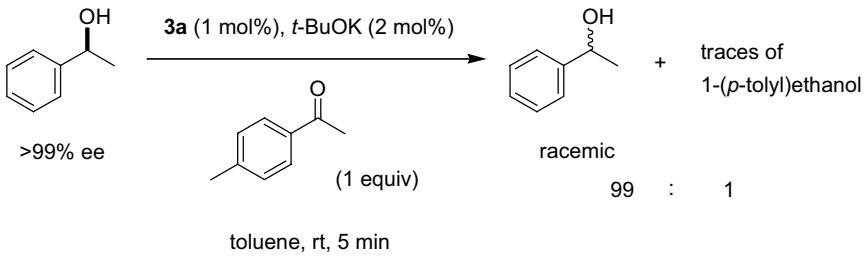


Figure 12. Racemization of (*S*)-phenylethanol catalyzed by η^5-ruthenium hydride **50**.

To obtain further support for the proposed η^3-ruthenium hydride **55** and the suggested inner-sphere insertion, racemization of (*S*)-phenylethanol catalyzed by 1 mol% **3a** activated by 2 mol% base was carried out in the presence of an equimolar amount of *p*-methylacetophenone. We reasoned that if the intermediate acetophenone produced would leave the coordination sphere of ruthenium before re-insertion into the hydride, then insertion of the added similar ketone into the Ru–H bond would also occur. Indeed, after only five minutes the reaction was complete while only about 1% of the added ketone had been reduced (Scheme 38).



Scheme 38. Crossover experiment: racemization in the presence of 1 equiv *p*-methylacetophenone.

Further evidence for the proposal that the substrate stays coordinated to ruthenium is found in the fact that acetone, which is produced from isopropenyl acetate upon deacylation, does not interfere with the ruthenium hydride.

5.5 Conclusions

The method described in this chapter is the fastest DKR of alcohols ever reported. A vast substrate tolerance has been demonstrated, including aliphatic and heterocyclic alcohols. For most substrates the process works at room temperature, which makes the use of thermolabile enzymes possible in future applications. The highly efficient ruthenium catalyst used for racemization represents a new class of hydrogen transfer catalysts, without any ligand on the metal that interacts with the substrate. Mechanistic studies led to the proposal of a catalytic cycle that involves β-elimination from a ruthenium alkoxide to give an η^3-hydride ketone complex. Experimental evidence that the latter complex undergoes reversible insertion with the ketone kept within the coordination sphere was found.

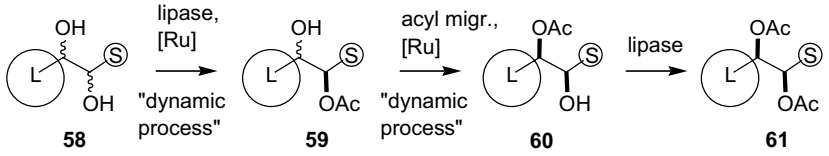
6 DYKAT of 1,2-diols: a case study

(Paper VI)

6.1 Introduction

Chiral *vic*-diols are important building blocks in enantioselective synthesis. Enantiopure *syn*-1,2-diols are readily available by Sharpless asymmetric dihydroxylation.[108] Alternative "greener" protocols that use environmentally benign terminal oxidants such as hydrogen peroxide are available, e.g. the triple-catalytic system developed in our laboratories.[109] Another entry to enantioenriched diols is provided by lipase-catalyzed resolution of racemic diols. Neither normal nor sequential resolutions of unsymmetrical acyclic *vic*-diols with two stereogenic centers seem to have been much explored.

An efficient approach toward enantiopure *syn*-diols would be to combine a lipase-catalyzed transesterification, a ruthenium-catalyzed epimerization and an intramolecular acyl migration. Analogously to the DYKAT in Chapter 3, unsymmetrical diol **58** would be acylated by the enzyme exclusively at the hydroxyl group closest to the small substituent (Scheme 39). In the presence of ruthenium epimerization should occur and all of **58** would be transformed to **59**, in which one stereocenter is defined. If acyl migration in **59** is favored in *syn*-diol monoacetates over *anti*-diol monoacetates, the acetate migrates to give, under dynamic conditions, only **60**. Next, **60** would be acylated again by the enzyme at the released alcohol next to the small substituent to give enantiopure *syn*-diacetate **61**.



Scheme 39. Productive cooperation of three processes in a one-pot de-epimerization and deracemization of unsymmetrical, acyclic 1,2-diols. L = large, S = small group.

[108] Kolb, H. C.; VanNieuwenhenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483–2547.

[109] (a) Jonsson, S. Y.; Adolfsson, H.; Bäckvall, J.-E. *Chem. Eur. J.* **2003**, *9*, 2783–2788. (b) Jonsson, S. Y.; Färnegårdh, K.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **2001**, *123*, 1365–1371.

Acyl migration in 1,2-diol monoacetates has been identified to occur e.g. during deacylation of terminal diesters[110] and in mono- and diglycerides.[111] This chapter describes studies toward a DYKAT of 1,2-diols. A case study on 1-phenyl-1,3-propanediol (**58a**) is presented, in which the three processes have been examined separately and in one-pot to obtain a DYKAT. KRs of two more diols are discussed.

6.2 Preparation of starting materials

The 1,2-diols used in this study (**58**) are most readily available as either their *syn*- or *anti*-racemates from osmium-catalyzed dihydroxylation[112] or epoxidation followed by alkaline hydrolysis[113,114] of the corresponding *trans*-olefins. Regioisomeric and diastereomeric monoacetates, needed in control experiments, were obtained by monoacetylation of **58a** and flash column chromatography to separate the regioisomers.

6.3 Results and discussion

6.3.1 KR and KAT of racemic *syn*-diols

To the best of our knowledge, there are only two reports on kinetic resolution (KR) of 1-phenyl-1,2-propanediol and neither uses CALB. Kim et al. performed transesterification of *anti*-**58a** using *Pseudomonas cepacia* lipase to obtain at 53% conversion one major monoacetate and one minor diacetate.[115] More recently, Ley et al. screened seven lipases (CALB not included) for regioselective protection of the inner alcohol in *syn*-**58a**.[116]

When racemic *syn*-diol **58a** was subjected to CALB and isopropenyl acetate in toluene at 50 °C, mono- and diacylation occurred (Scheme 40). Regioisomeric monoacetates **59a** and **60a** were formed in a ca. 3:1 ratio. Because CALB does not catalyze acyl migration (Chapter 6.3.3), it was concluded that **60a** was formed via direct enzymatic acylation of the inner alcohol. The selectivity of this acylation is high and follows Kazlauskas' rule. For example, at 42% conversion (60 minutes) **60a** was obtained in 11% yield and 96% ee. At this stage, no diacetate **61a** was yet formed.

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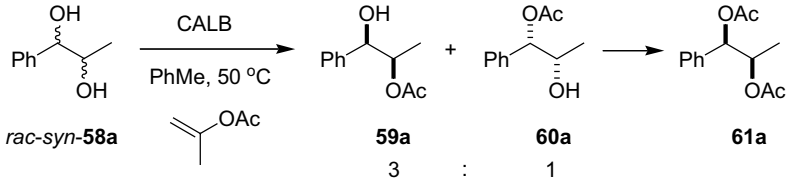
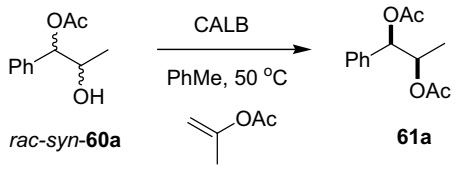
[110] Bisht, K. S.; Kumar, A.; Kumar, N.; Parmar, V. S. *Pure Appl. Chem.* **1996**, *68*, 749–752.
[111] Bornscheuer, U. T.; Kazlauskas, R. J. *Hydrolases in Organic Synthesis*; Wiley-VCH: Weinheim, 1999; pp 163–164.
[112] VanRheenen, V.; Kelly. R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, *17*, 1973–1976.
[113] Ley, S. V.; Mitchell, C.; Pears, D.; Ramarao, C.; Yu, J.-Q.; Zhou, W. *Org. Lett.* **2003**, *5*, 4665–4668.
[114] (a) Zioudrou, C.; Chrysochou, P.; Karabatsos, G. J.; Herlem, D.; Nipe, R. N. *Tetrahedron Lett.* **1972**, *13*, 5293–5296. (b) Berti, G.; Macchia, B.; Macchia, F. *Tetrahedron Lett.* **1965**, *6*, 3421–3427.
[115] Kim, M.-J.; Choi, G.-B.; Kim, J.-Y.; Kim, H.-J. *Tetrahedron Lett.* **1995**, *36*, 6253–6256.
[116] Lee, A.-L.; Ley, S. V. *Org. Biomol. Chem.* **2003**, *1*, 3957–3966.



Scheme 40. Kinetic asymmetric transformation of racemic *rac-syn*-**58a**.

In contrast, the formation of the major monoacetate **59a** is less selective. At 13% conversion (24 minutes), **59a** was obtained in 10% yield and ~86% ee (along with 3% yield of **60a**), which corresponds to *E* ~15.

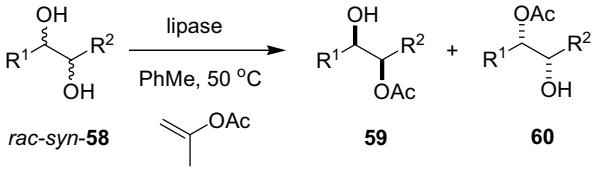
Prolonged reaction time was required for consecutive acetylations to occur. The transformation to diacetate is a KAT. After 21 h, 7% of **61a** was produced. The same reaction performed in the presence of Na_2CO_3 gave, again after 21 h, 28% diacetate **61a**. From a control experiment, in which racemic *syn*-monoacetate **60a** was subjected to KR, it was concluded that the second acylation is somewhat slower than the first acylation (29% diacetate in 70 minutes, Scheme 41). Hence, the reason for the slow transformation to diacetate in KAT is due to a combination of slow acyl migration and a slower second acylation.



Scheme 41. KR of racemic *syn*-monoacetate **60a**.

KRs of two more *syn*-1,2-diols were performed. Table 10 shows the results.

Table 10. *KR of syn-diols.*[a]

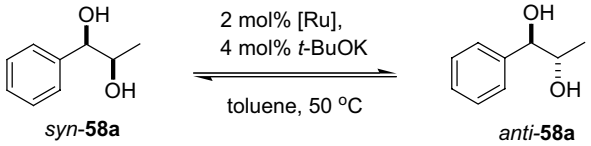


Entry	Diol	R^1	R^2	Time (min)	Yield (%)[b]		ee (%)[c]		~E[d]	
					59	**60**	**59**	**60**	**59**	**60**
1	**58a**	Ph	Me	24	10	3	86	96	15	n.c.[e]
2	**58b**	*n*-Pentyl	Me	7	20	3.8	96	n.d.	61	n.c.[e]
3[d]	**58c**	Ph	CO_2Me	210	26	3.4	n.d.	n.d.	n.d.	n.d.

[a] Isopropenyl acetate (3 equiv) was added to a mixture of diol and CALB (20 mg/mmol **58**) in toluene (2 mL/mmol **58**) and the reaction was stirred at 50 °C under argon. [b] Determined by NMR. [c] ee measured by chiral GC after separation by flash column chromatography and chemical acetylation to diacetate. [d] PCL "Amano" II (80 mg/mmol **58**) was used. Since this is a parallel kinetic resolution the *E* values are not readily calculated from the data. For the larger component the *E* value was estimated as if it were an ordinary kinetic resolution. [e] n.c. = not calculated.

6.3.2 Combining three processes in one-pot

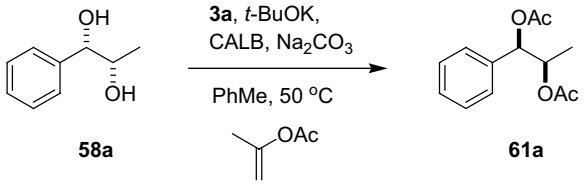
Epimerization of racemic *syn*-**58a** was studied by use of 2 mol% ruthenium complex **3a**, activated by 4 mol% *t*-BuOK (Scheme 42). A diastereomeric ratio of *syn*/*anti* ~2:1 was detected after 1 h, and this ratio remained constant. The *syn* (or *threo*) isomer is the thermodynamically most stable one.



Scheme 42. Epimerization of racemic *syn*-diol.

DYKAT was studied with 5 mol% **3a** and 5 mol% *t*-BuOK and in the presence of Na_2CO_3. After 24 hours all diol was consumed and ~38% diacetate (of *syn*/*anti* ~2:1) was obtained (Table 11, entry 1). The reaction went to completion after prolonged time (entry 2). An increased amount of enzyme gave a faster reaction (entries 3 and 4). That the system is sensitive to water is clearly demonstrated in entries 5 and 6 where even more enzyme was used, hence more water in the system, and a slow reaction with lower ee was obtained. The higher dr of **61a** is further evidence that epimerization was inhibited, as the starting material was pure *syn*-diol.

Table 11. *DYKAT of 1-phenyl-1,2-propanediol.*[a]

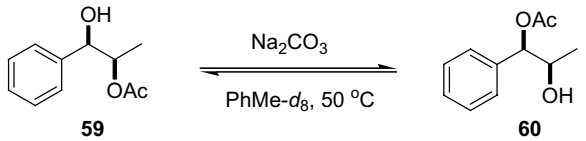


Entry	Enzyme (mg/mmol)	*t*-BuOK (mol%)	Time (h)	% Conv.[b]	% **61a**[b]	dr[b] (*syn*:*anti*)	% ee[c] (*syn*, *anti*)
1	6	5	24	100	~38	2:1	n.d.
2	6	5	12 d	100	100	2:1	99, >99
3	20	8	24	100	~67	2:1	n.d.
4	20	8	72	100	100	2:1	98, 99
5	60	5	20	100	<50	6:1	n.d.
6	60	5	44	100	~60	3:1	72, n.d.

[a] Ru-catalyst **3a** (5 mol%), CALB, Na_2CO_3 (1 mmol), and *t*-BuOK were stirred in toluene (1 mL) for 6 min before adding the alcohol (1 mmol) in toluene (1 mL). After 4 min, isopropenyl acetate (3 mmol) was added and the mixture was stirred under an argon atmosphere at 50 °C. [b] Determined by NMR. [c] Measured by chiral GC.

6.3.3 Acyl migration

When *syn*-diol monoacetate **59a** was heated in deuterated toluene at 50 °C, no acyl migration took place. (Samples were withdrawn and analyzed by NMR up to 28 h.) Acyl transfer was however observed in a similar experiment where Na_2CO_3 (1 equiv) was added (Scheme 43).[117] Also pyridine (10 mol%) was attempted to catalyze acyl transfer, but did not show any effect. That CALB does not catalyze migration was concluded from a control experiment run in the presence of the enzyme.[118]

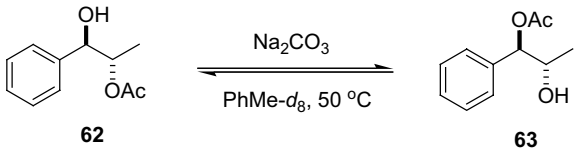


Scheme 43. Acyl migration in racemic *syn*-diol monoacetate.

When *anti*-diol monoacetate **62** was heated in the presence of sodium carbonate (1 equiv) acyl transfer was also observed (Scheme 44). The ratio of *anti*-regioisomers **63**/**62** was measured at different times. This plot was compared to the corresponding plot for migration in the *syn*-derivatives

[117] After 4 h **59**/**60** = 57:43. This ratio remained constant.
[118] After 2 h <5% migration was observed. After prolonged time a mixture of monoacetates, diol and diacetate was formed.

60/**59**. Figure 13 shows that the rate of acyl transfer in the *syn*-monoacetate is almost three times faster than the one in the *anti*-derivative under these conditions.



62 **63**

Scheme 44. Acyl migration in racemic *anti*-diol monoacetate.

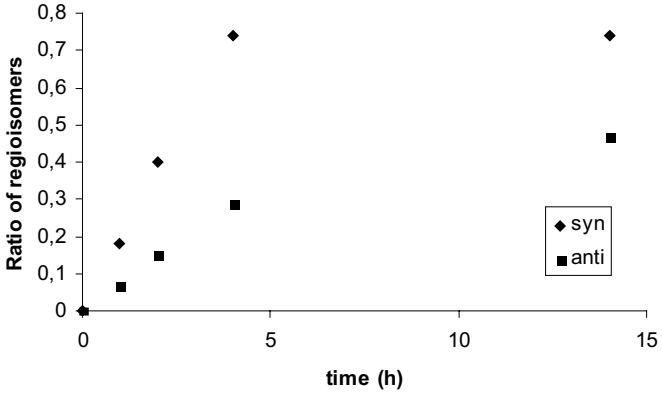


Figure 13. Acyl migration in *syn*- and *anti*-diol monoacetates.

The long reaction time required for quantitative formation of diacetetate in KAT and DYKAT seems to be due to a combination of a slow acyl transfer and a not very fast second acylation. The low dr obtained in DYKAT is ascribed to acyl migration in the *anti*-diol monoacetate (obtained from epimerization of **59a**) and to formation of monoacetate at the benzylic position (**60a**) with the (*S*)-configuration.

6.4 Conclusions

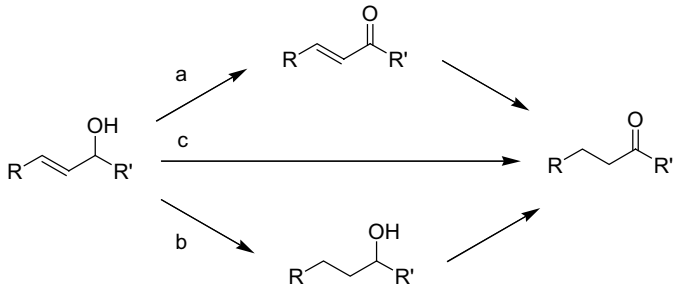
Studies toward a DYKAT of unsymmetrical, acyclic 1,2-diols were performed on 1-phenyl-1,2-propanediol as a model substance. CALB was used for the first time to catalyze KR of this substrate. An efficient, but not highly selective, resolution was developed. By use of ruthenium complex **3a** efficient epimerization was attained. In combination with two consecutive KRs and an intervening intramolecular acyl transfer an enantioselective DYKAT analogous to the one in Chapter 3 was achieved.

7 A mild ruthenium-catalyzed redox isomerization of allylic alcohols

(Paper VII)

7.1 Introduction

Transition metal-catalyzed isomerization of allylic alcohols to saturated ketones is a transformation of potential use in organic synthesis. The process constitutes an internal redox reaction, and offers a more atom-economic[119] approach than the corresponding classical, sequential redox transformations (Scheme 45).



Scheme 45. Classical (paths a and b) and transition metal-catalyzed (path c) redox transformations of allylic alcohols to saturated ketones.

Various transition metals have been explored for such redox reactions.[120] Several reports on the use of ruthenium have appeared. Early examples suffer from poor selectivity leading to complex product mixtures, while more recent examples still require elevated temperatures and tolerate only a limited substitution pattern on the substrate. The first Cp ruthenium(II) complex used in this isomerization was reported by Trost, who employed $RuClCp(PPh_3)_2$ in combination with Et_3NHPF_6 at 100 °C.[121] Bäckvall has previously developed a procedure based on Shvo catalyst **1** at 65 °C.[85]

During our work on DKR of an allylic alcohol, traces of ketone byproduct formation caused by isomerization was observed (Chapter 5). In efforts

[119] (a) Trost, B. M. *Acc. Chem. Res.* **2002**, *35*, 695–705. (b) Trost, B. M. *Science* **1991**, *254*, 1471–1477.

[120] (a) Suzuki, H.; Takao, T. In *Ruthenium in Organic Synthesis*; Murahashi, S.-I., Ed.; Wiley-VCH: Weinheim, 2004; pp 309–331. (b) Uma, R.; Crévisy, C.; Grée, R. *Chem. Rev.* **2003**, *103*, 27–51. (c) van der Drift, R. C.; Bouwman, E.; Drent, E. *J. Organomet. Chem.* **2002**, *650*, 1–24.

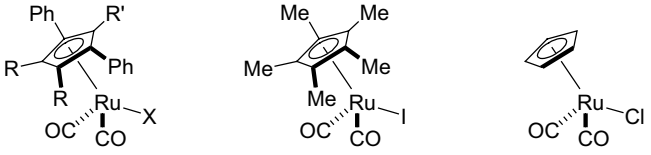
[121] Trost, B. M.; Kulawiec, R. J. *J. Am. Chem. Soc.* **1993**, *115*, 2027–2036.

made to suppress the byproduct formation, ruthenium complexes **3a** and **48a** were tried and were found to give different amounts of ketone. In this chapter, the development of a mild (room temperature) and efficient ruthenium-catalyzed redox isomerization of allylic alcohols is described.

7.2 Results and discussion

7.2.1 Choosing the catalyst

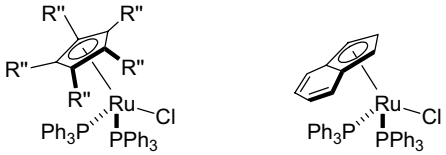
Cp ruthenium complexes **3a**, **48a** and **48b**, described in chapter 5, along with five more ruthenium half-sandwich complexes shown in Figure 14 were tried as catalysts in the isomerization of allylic alcohol **68a**.[122] The structure of **48b** was confirmed by X-ray diffraction analysis.



3a R = R' = Ph, X = Cl
48a R = Ph, R' = Me, X = Cl
48b R = Ph, R' = Me, X = Br

64

65



66 R" = Me
67 R" = H

4

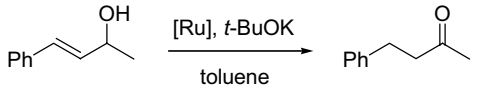
Figure 14. Ruthenium complexes tested in redox isomerization.

Because of the efficient activation of catalysts by *t*-BuOK as described in chapter 5, the complexes were treated with a slight excess of the base in toluene, before addition of the substrate. Thus activated catalyst **48b** successfully effected isomerization even at ambient temperature (Table 12, entry 1). At higher temperatures, the catalyst loading could be decreased

[122] The complexes were prepared according to literature procedures. **64**: Nelson, G. O.; Sumner, C. E. *Organometallics* **1986**, *5*, 1983–1990. **65**: Nagashima, H.; Mukai, K.; Shiota, Y.; Yamaguchi, K.; Ara, K. I.; Fukahori, T.; Suzuki, H.; Akita, M.; Moro-oka, Y.; Itoh, K. *Organometallics* **1990**, *9,* 799–807. **66**: Chinn, M. S.; Heinekey, D. M. *J. Am. Chem. Soc.* **1990**, *112*, 5166–5175. **67**: Bruce, M. I.; Mameister, C.; Swinger, A. G.; Wallis, R. C. *Inorg. Synth.* **1990**, *28*, 270–272. Complex **4** is commercially available.

(entries 2–4). Sodium carbonate, a component in DKR, is an unnecessary additive in isomerization (cf. entries 1 and 5). The comparable results obtained with different halide atoms in the pre-catalyst indicate that the same active intermediate is generated (entries 5 and 6). The substitution pattern on the Cp ligand affects the reaction rate. The fact that **3a**, **64** and **65** all gave significantly slower isomerization than **48** (entries 7–9), suggests that both steric and electronic effects influence the activity of the catalyst. A change from carbonyl ligands to phosphines on ruthenium gave slower reaction rates at room temperature (entries 10–11). However, these catalysts work at a higher temperature (entry 12). Although indenyl complex **4** is a less efficient catalyst than **48** at room temperature, it is noteworthy that **4** still operates at low temperature when activated by *t*-BuOK, instead of Et_3NHPF_6.[121]

Table 12. *Izomerization of allylic alcohol **68a** catalyzed by various Ru complexes.*[a]



68a **69a**

Entry	[Ru] (mol%)	*t*-BuOK (mol%)	Temp (°C)	Time (h)	Yield (%)[b]
1[c]	**48b** (5)	7	rt	1.5	96
2[c]	**48b** (3)	6	45	1	96
3	**48a** (2)	2.8	60	0.16	98
4	**48a** (1)	1.4	60	0.5	98
5	**48b** (5)	7	rt	1.5	96
6	**48a** (5)	7	rt	1.5	93
7[d]	**3a** (5)	7	rt	1.5	58
8[e]	**64** (5)	7	rt	3	52
9	**65** (5)	7	rt	17	14
10	**66** (5)	7	rt	17	26
11	**67** (5)	7	rt	17	14
12	**67** (5)	7	50	17	91
13[f]	**4** (5)	7	30	1.5	40

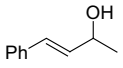
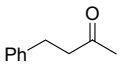
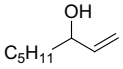
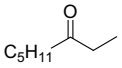
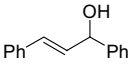
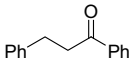
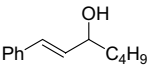
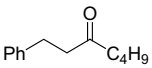
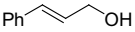
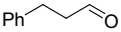
[a] Unless otherwise noted, *t*-BuOK (0.5 M in THF) was added to a solution of Ru-catalyst (5 mol%) in toluene (substrate concentration: 0.5 M) under an argon atmosphere. The mixture was stirred for 4 min before adding the alcohol. [b] Determined by GC or ^{1}H NMR. [c] 1 equiv of Na_2CO_3 added. [d] 91% yield of **69a** and 9% of benzylideneacetone after 18h. [e] 92% yield of **69a** and 8% of benzylideneacetone after 24h. [f] 90% yield after 17 h.

7.2.2 Substrate study

Ruthenium complex **48a** was used when the substrate tolerance was investigated. Allyl alcohols **68a**–**b** isomerized to **69a**–**b** quickly and in near quantitative yields (Table 13, entries 1 and 2), as did also aliphatic alcohol **68c** (entry 3). Also conjugated allylic alcohol **68d** was smoothly transformed

to saturated ketone (entry 4). The more sterically demanding alcohol **68e** did however require higher temperature (entry 5). Unfortunately, primary allylic alcohol **68f** failed to isomerize. Surprisingly, also at higher temperatures only smaller amounts of saturated aldehyde **69f** were formed (entry 6). We believe a plausible explanation to be a much faster 1,2-hydride addition than 1,4-hydride addition to the intermediate α,β-unsaturated aldehyde. Evidence for that reversible 1,2-hydride addition occurs before irreversible 1,4-addition takes place was provided by the observation that **68a** racemized before it underwent rearrangement.

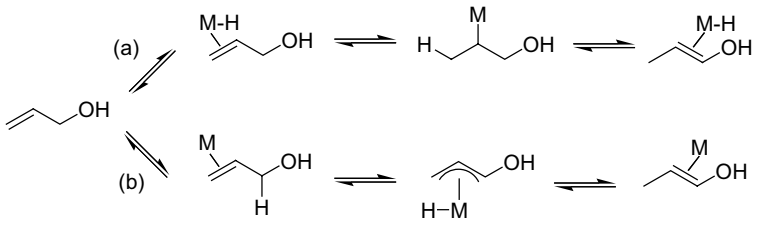
Table 13. *Isomerization of allylic alcohols catalyzed by **48a**.*[a]

Entry	Substrate	Time (h)	Temp (°C)	Product	Yield (%)[b]
1	 **68a**	1.5	rt	 **69a**	95
2	 **68b**	2.5	rt	 **69b**	99
3	 **68c**	3	rt	 **69c**	97
4	 **68d**	2.5	rt	 **69d**	95
5	 **68e**	3	80	 **69e**	92
6	 **68f**	23	80	 **69f**	22

[a] Unless otherwise noted, *t*-BuOK (0.5 M in THF) was added to a solution of Ru-catalyst (5 mol%) in toluene (substrate concentration: 0.5 M) under an argon atmosphere. The mixture was stirred for 4 min before adding the alcohol. [b] Determined by GC or ^{1}H NMR.

7.2.3 Mechanistic considerations

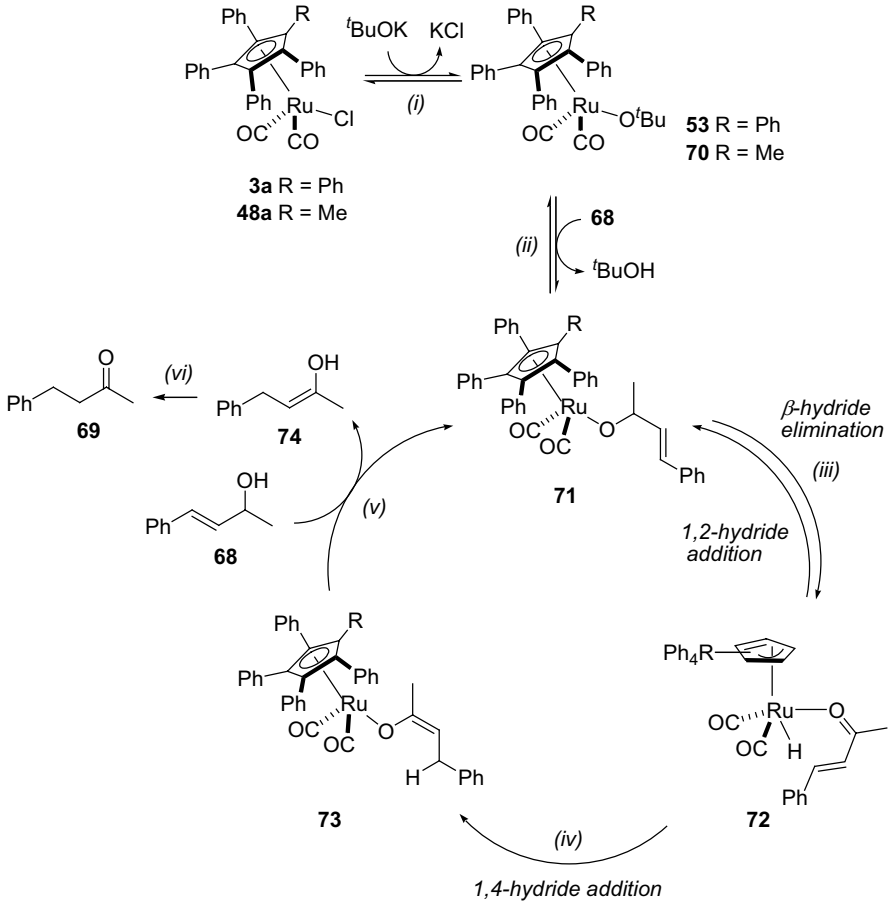
Two main mechanisms have been proposed for transition metal-catalyzed isomerization, or transposition, of allylic alcohols. The first one is thought to operate when the catalyst is a metal hydride (Path a, Scheme 46). The metal hydride coordinates to the C–C double bond and migratory insertion of the olefin into the M–H bond gives a metal alkyl intermediate. *β*-Hydride elimination produces an enol and regenerates the metal hydride. The enol tautomerizes into a saturated carbonyl compound. This metal hydride addition-elimination proceeds in an intermolecular fashion and involves a 1,2-hydrogen shift. The second mechanism operates for other metal complexes than hydrides (Path b, Scheme 46). Again, the metal coordinates to the C–C double bond. Oxidative addition of a C–H bond gives a π-allyl metal hydride. Subsequent reductive elimination leads to the enol and the regenerated metal catalyst. This mechanism involves an intramolecular 1,3-hydrogen shift. A few alternative mechanisms, involving coordination of the substrate oxygen, have appeared.[32b,85,121,123]



Scheme 46. (a) Mechanism via metal alkyl intermediates and (b) mechanism via π-allyl intermediates.

We propose the following catalytic cycle for isomerization of allylic alcohols catalyzed by Cp ruthenium complexes (Scheme 47). Activation of e.g. pre-catalyst **48a** by *t*-BuOK gives ruthenium alkoxide **70** and KCl (step *i*, Scheme 47). Ligand substitution of **70** by allylic alcohol **68** *(ii)* affords another ruthenium alkoxide **71**. Complex **71** undergoes *β*-hydride elimination *(iii)* to give η^3-coordinated Cp ruthenium hydride **72**. The microscopic reverse of this is a migratory insertion or a 1,2-hydride addition, which may well compete with the 1,4-hydride addition (both of them proposed to be accompanied by ring slippage) leading to enol intermediate **73** (step *iv*). Subsequent ligand substitution with substrate **68** (step *v*) releases enol **74** and regenerates intermediate **71**. The enol tautomerizes to ketone **69**.

[123] Markó, I. E.; Gautier, A.; Tsukazaki, M.; Llobet, A. ; Plantalech-Mir, E.; Urch, C. J.; Brown, S. M. *Angew. Chem. Int. Ed.* **1999**, *38*, 1960–1962.



Scheme 47. Proposed catalytic cycle for isomerization of allylic alcohols.

The suggested formation of **70** was based on two observations. First, a color change from yellow to red when pre-catalyst **48a** is treated with *t*-BuOK indicates the presence of alkoxides and second, the nature of the halide atom on the pre-catalyst did not significantly affect the isomerization indicating a common active intermediate (see above). Evidence for that the α,β-unsaturated ketone stays coordinated after β-elimination (step *iii*) was provided by the fact that no exchange occurred with an externally added α,β-unsaturated ketone. Further, evidence for ruthenium enolate **73** was found when isomerization in the presence of benzaldehyde gave the corresponding aldol product. When hydride **50** (cf. Scheme 35) was used, an isomerization of **68a** occurred that was only slightly slower than by use of complex **48a**. We believe that a mechanism involving metal alkyl intermediates (path a, Scheme 46) operates simultaneously for the ruthenium hydride.

7.3 Conclusions

By use of ruthenium complex **48a**, a mild and highly efficient catalytic redox isomerization of allylic alcohols was developed. The method tolerates relatively hindered substrates. A mechanism involving ruthenium alkoxides and ruthenium enolates has been proposed. Evidence in support of this was found, along with indications of hydrogen transfer inside the coordination sphere of ruthenium. However, another mechanism involving metal alkyl intermediates seems likely to operate simultaneously.

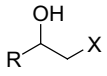
After the completion of this work, a communication appeared describing the use of a $Cp^*Ru(PN)$ complex.[124] This catalyst isomerized allylic alcohols to the corresponding ketones at 30 °C within 1 h.

[124] Ito, M.; Kitahara, S.; Ikariya, T. *J. Am. Chem. Soc.* **2005**, *127*, 6172–6173.

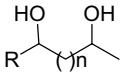
8 Concluding remarks

The main body of the work presented deals with the combination of ruthenium-catalyzed racemization or epimerization and lipase-catalyzed transesterification of alcohols. When this work was initiated, Bäckvall had already developed a protocol for such combo-catalyzed transformations. The present studies have significantly improved the previous DKR of alcohols to make it more than two orders of magnitude faster. By making a new type of Cp ruthenium half-sandwich complex compatible with the lipase, DKR of 1-phenylethanol can now be completed in 3 hours at room temperature. The substrate scope of the DKR has been expanded to include also heterocyclic alcohols (Figure 15). The mechanism for racemization by the present ruthenium complex is intriguing, and indications of hydrogen transfer within the coordination sphere of ruthenium were found. Because the new system operates at ambient temperature, many more enzymes can be used in future applications, and because the racemization is extremely fast, also less selective enzymes may be employed. A closely related ruthenium half-sandwich complex was efficiently used to catalyze redox isomerization of allylic alcohols at room temperature.

For 2,4-pentanediol a deuterium-labeling study showed that an intramolecular acyl migration occurs, which explains the poor diastereoselectivity in the previous protocol. This acyl transfer could be outrun by a fast epimerization and this led to a greatly improved DYKAT of this substrate (Figure 15). The same acyl migration was taken advantage of and was coupled to a ruthenium-catalyzed epimerization and a lipase-catalyzed transesterification of unsymmetrical diols to obtain a novel type of DYKAT of 1,3-diols and a 1,2-diol (Figure 15).



R = Ar, Alk, Het, X= H, Me, Cl, CN



R = Me, n = 1
R = Ar, Alk, n = 1
R = Ph, n = 0

Figure 15. Structures subjected to ruthenium–enzyme combo catalysis.

A brief study of the combination of lipase and proline catalysts showed that synthesis of enantiopure aldols can be realized by linking either L- or D-proline-mediated aldol reactions to lipase-catalyzed acetylation.

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♦ My wonderful and supportive family: Gun, Hasse and Andreas.

♥ Kalle for bringing me so much happiness.

Appendix

Supplementary material to Chapter 3.5

DYKAT of 2,4-pentanediol. Ruthenium complex **3a** (32 mg, 0.05 mmol), CALB (6 mg) and Na_2CO_3 (0.106 g, 1 mmol) were placed in a Schlenk flask. The flask was evacuated and filled with argon and then toluene (2 mL) was added. Addition of *t*-BuOK (0.5 M in THF, 180 μL, 0.09 mmol) to the yellow suspension resulted in a color change to orange. The mixture was stirred for 6 min, and then 2,4-pentanediol (110 μL, 1 mmol) was added. On the addition of the diol the mixture turned red. After 4 min isopropenyl acetate (332 μL, 3 mmol) was added and the flask was placed in an oil bath of 50 °C. After 20 h the reaction mixture was filtered and analyzed: 96% yield, *anti*/*meso* = 97:3 (achiral GC, CP-Sil 8 CB column), >99% ee (chiral GC, CP-Chirasil-Dex column).