Combination of Enzymes and Metal Catalysts. A Powerful Approach in Asymmetric Catalysis

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1. Introduction

Catalytic asymmetric synthesis is an important and expansive area in organic chemistry.[1] Catalytic enantioselective organic reactions can be achieved by either chemocatalysis or biocatalysis. The former field is dominated by metal catalysis, but recent work has also involved organocatalysis[2] and Lewis acid catalysis in enantioselective transformations. In biocatalysis, enzymes, in particular hydrolases, dominate. Yeast reductions have also found some use whereas catalytic antibodies have not yet found the broad practical use that enzymes have.

Triacylglycerol hydrolases (EC 3.1.1.3) are termed lipases and have become one of the most versatile classes of biocatalysts in organic synthesis.[3] This is because lipases can accept a wide range of organic substrates and they work very well in organic solvents. Lipases can be used as catalysts in either hydrolysis reactions or ester synthesis (acylation reactions). In both types of reactions, lipases usually react with high enantioselectivity.

Because of the fact that lipases have found applications in biotechnology as additives in detergents, some lipases are produced in hundreds of tons per year. Commercial manufacturing of such lipases is done by genetic engineering techniques. By gene expression in an appropriate microorganism such as a fungi, yeast or bacteria (e.g., *Escherichia coli*) large scale production of the lipase has been realized.

The majority of applications of lipases in catalytic asymmetric synthesis has involved kinetic resolution of racemates. The drawback with kinetic resolution is that a maximum of 50% of the starting material can be used to give product. One way to circumvent this problem is to employ *meso* substrates ("the *meso* trick") or prochiral substrates. With the use of these substrates, all of the starting material can be utilized. Now, because most of the substrates used for enzyme-catalyzed reactions do not have the symmetry element of a mirror plane (i.e., *meso* and prochiral compounds) but are chiral racemic compounds, kinetic resolution is still the major application of enzymes. Recently, methods to racemize the nonreacting enantiomer in kinetic resolution have been developed. If racemization is done continuously during the enzymatic resolution, this results in a dynamic kinetic resolution (DKR),[4] and in this way, all of the racemic starting material can be used for transformation into one enantiomer. This review will deal with the recent development of the combination of an enzymatic kinetic resolution and a metal-catalyzed racemization leading to a DKR process.

2. Chemoenzymatic DKR

2.1. Enzymatic Kinetic Resolution

Because of the chirality of the active site in enzymes, one enantiomer of the substrate is converted to the product at a higher rate than the other, resulting in a kinetic resolution of the starting racemate. Thus, in an ideal case, the enzymatic

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Jan-Erling Bäckvall was born in Malung, Sweden, in 1947. He received his Ph.D. from the Royal Institute of Technology, Stockholm, in 1975 under the guidance of Prof. B. Åkermark. After postdoctoral work (1975–1976) with Prof. K. B. Sharpless at Massachusetts Institute of Technology, he joined the faculty at the Royal Institute of Technology. He was appointed Professor of Organic Chemistry at Uppsala University in 1986. In 1997, he moved to Stockholm University where he is currently Professor of Organic Chemistry. He is a member of the Royal Swedish Academy of Sciences and the Finnish Academy of Science and Letters. His current research interests include the use of transition metals in selective organic transformations, enzyme chemistry, and development of new and mild oxidation methodology. Recently, efficient systems for dynamic kinetic resolution of alcohols based on combined ruthenium and enzyme catalysis were developed in his laboratory.

reaction will stop at 50% conversion when all of the reactive enantiomer has been converted to product. However, in many cases, the difference in reaction rate between the two enantiomers is not large enough, and to obtain good enantioselectivity of the product, it is necessary to stop the reaction at a lower conversion than 50%.[5]

Many enzymatic kinetic resolutions follow Michaelis−Menten kinetics.[6] In this case, the substrate (S) binds to the enzyme (E) in a reversible reaction to form the enzyme−substrate complex (ES), and from this complex, the product (P) is irreversibly formed (eq 1).

$$\mathrm{E} + \mathrm{S} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{ES} \xrightarrow{k_{cat}} \mathrm{E} + \mathrm{P}$$

$$\text{rate} = \frac{k_{cat} \cdot [\mathrm{E}]_t \cdot [\mathrm{S}]}{[\mathrm{S}] + K_M}$$

$$K = \frac{k_1}{k_{-1}};\ K_M = \frac{1}{K} \qquad (1)$$

The apparent second-order rate constant k_{cat}/K_M is often used to assess the overall efficiency and specificity of the enzyme reaction.[7] Usually, K_M is small (corresponding to a large K) because the substrate binds strongly to the enzyme and in this case the rate $\approx k_{cat} \cdot [\mathrm{E}]_t$.

In a kinetic resolution, the enantiomeric excess of both substrate (ee_S) and product (ee_P) varies with the degree of conversion. Therefore, a new dimensionless parameter, the enantiomeric ratio (E), was introduced to measure the ability of an enzyme to distinguish between enantiomers. The latter value is the ratio of the reactivity (ratio of rate constants) of the two enatiomers. As an empirical rule, reactions with E values lower than 15 are usually unsuitable for practical purposes.[3b]

2.1.1. Kinetic Resolution of Alcohols and Amines

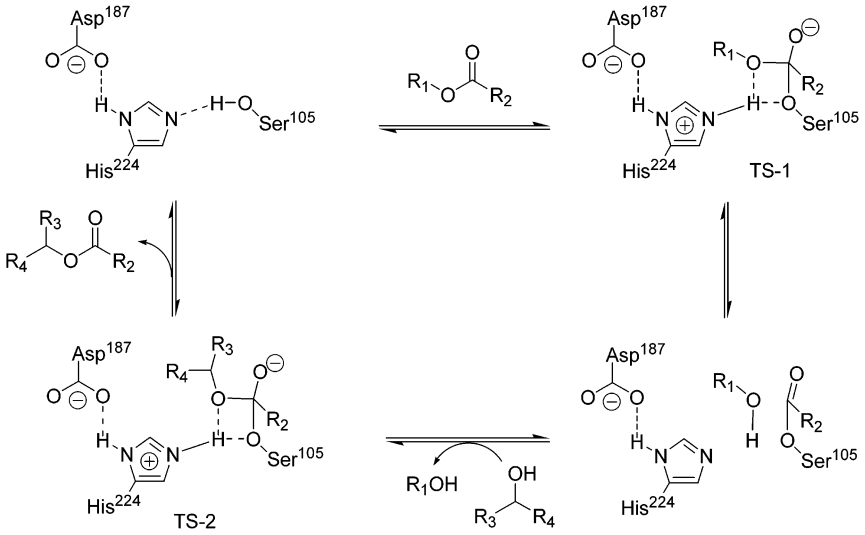
Alcohols, amines, and thioesters can be efficiently resolved using lipases.[3b,8] In particular, the kinetic resolution of secondary alcohols or their carboxylates via either esterification or hydrolysis has been extensively studied with different lipases.

From a mechanistic point of view, lipases, esterases, and proteases (when acting on esters) follow a similar mechanism.[3b,7] In general, a nucleophilic group from the active site of the enzyme attacks the carbonyl group of the ester. The nucleophilic group of lipases, esterases, and some proteases is the hydroxyl group of a serine.[9] For some proteases, it can also be either a carboxylic group of an aspartic acid or a thiol functionality of a cysteine.[3b]

The active site of many lipases is formed by residues of a serine, a histidine, and an aspartate (the so-called "catalytic triad"). The first X-ray structures of lipases reported in 1990[9,10] contributed significantly to the mechanistic understanding of these enzymes. The active site is usually covered by a lid, or flap, but in the presence of the substrate or an organic solvent, this flap moves away, and in this way, the active site becomes accessible to the substrate.[11] The mechanism for the esterification, and in the reverse way for the hydrolysis, can be characterized as bi-bi ping-pong (Scheme 1).[12] The special hydrogen-bonding rearrangement of the three amino acids increases the nucleophilicity of the serine residue, enabling attack at the carbonyl group of the acyl donor, to form the "acyl−enzyme intermediate". Subsequently, the substrate alcohol will attack the acyl−enzyme to give the product.

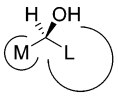
From an enantiodiscrimination point of view, almost all of the known lipases follow the Kazlauskas' rule.[13] This simple empirical model is based on the fact that the substituents at the sterocenter (one

Scheme 1. Reaction Mechanism of CALB



large and one medium) are placed in two different pockets according to their size (Scheme 2). This model, originally applied to secondary alcohols, has also proved valid for predicting the reactivity in the kinetic resolution of secondary amines.[3b]

Scheme 2. Empirical Model for Predicting the Faster Reacting Enantiomer of Secondary Alcohols



In recent years, the combination of X-ray crystallographic and molecular modeling studies has led to an understanding of the chiral recognition of secondary alcohols at the molecular level by studying the TS-2 as the key step in the enantiodiscrimination.[14] As an example, in Figure 1, we can see the productive docking TS-2 for (*R*)-2-pentanol in the active site of *Candida antarctica* lipase B (CALB). In accordance with the empiric Kazlauskas' rule, the methyl substituent is located in the medium-sized pocket (in green) pointing down and the large propyl substituent is pointing up. Thus, only the *R*-substrate with the medium-sized substituent pointing down and the large group pointing up has a productive docking and therefore can be acetylated.[14b]

2.2. Racemization

Despite great developments in asymmetric synthesis during the last two decades, kinetic resolution of racemates still has a dominant role. However, a major drawback of kinetic resolution is that the yield is limited to a maximum of 50%. Also, the product has to be separated from the unreactive enantiomer, which may cause separation problems. Therefore, the in situ racemization of the undesired enantiomer is important from both an economical and an environmental point of view. Thermodynamically, racemization is a favorable process. This is due to the increase of entropy caused by mixing the two enantiomers.

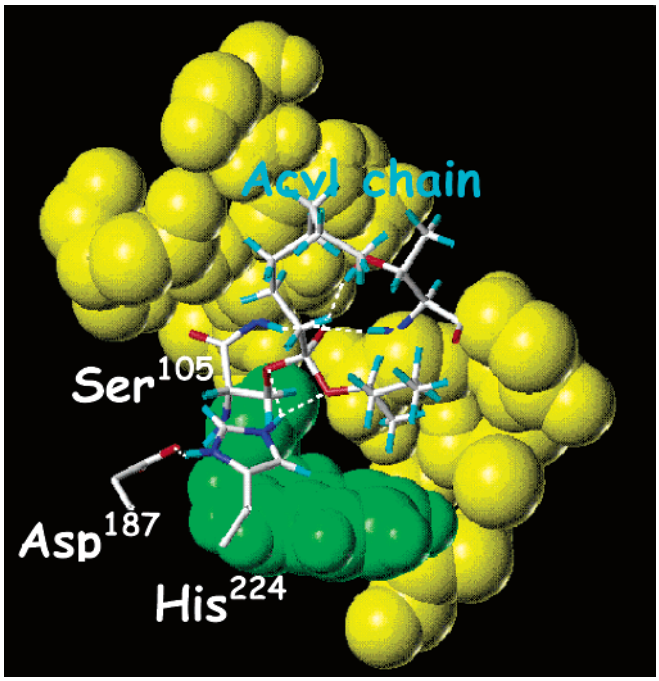


Figure 1. Productive docking for (*R*)-2-pentanol in the active site of CALB. Reprinted with permission from ref 14b. Copyright 1998 Taylor & Francis Ltd. (http://www.tandf.co.uk/journals).

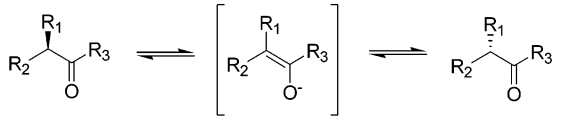
2.2.1. Examples of Racemization

Although the racemization technique depends to a large extent on the compound that is going to be racemized, Zwanenburg and co-workers[15] have classified the racemization methods in different categories: (i) base-catalyzed racemization, (ii) Schiff base-mediated racemization, (iii) thermal racemization, (iv) enzyme-catalyzed racemization, (v) acid-catalyzed racemization, and (vi) racemization via redox and radical reactions. Of all of these methods, the base-catalyzed, Schiff base-mediated, the thermal, and the enzyme-catalyzed racemization are those most commonly used.

The most widely applied method for racemization of optically pure compounds is the base-catalyzed

racemization. This method can be applied to almost all compounds bearing an acidic hydrogen at the chiral center. Thus, for instance, the racemization of keto compounds proceeds via an enolate intermediate (Scheme 3).

Scheme 3. Racemization Via Enolate Intermediate



Schiff base-mediated racemizations, although restricted to compounds bearing a free primary amino group at the chiral center, have been frequently utilized in the racemization of amino acids. For amino acids, the racemization proceeds via initial protonation of the imine, formed from reaction of a primary amino group with an aldehyde or ketone, followed by proton abstraction at the α-position of the acid (Scheme 4).

Many optically active compounds can be racemized by simply heating them to an appropriate temperature. A simple example is the racemization of biaryls by simple rotation around a single bond. Although this is an attractive cheap method for industrial and practical purposes, its scope is limited to substrates with high thermal stability.

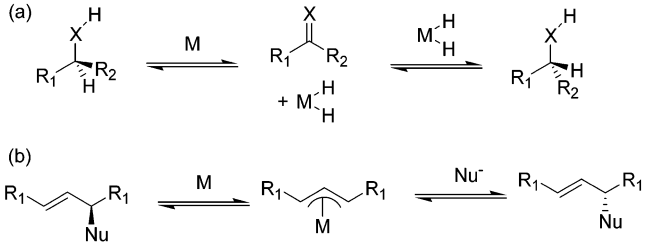
Enzyme racemases have also been used for the racemization of certain compounds under mild conditions. However, its scope is still limited to mainly amino acid derivatives and to α-hydroxy acid derivatives.

2.2.2. Transition Metal-Catalyzed Racemization

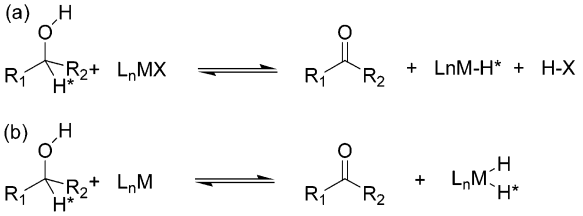
Although transition metals have been shown to catalyze many reactions under mild conditions,[1,16] their use for the racemization of different substrates has been almost neglected.[15] There are two general methods that have been used for the racemization using transition metal catalyst: (i) racemization via hydrogen transfer (Scheme 5a) and (ii) racemization via π-allyl formation (Scheme 5b).

Transition metal-catalyzed racemization via hydrogen transfer has been recently used for the racemization of secondary alcohols and amines.[17] The mechanisms of the transition metal-catalyzed hydrogen transfer reaction have been extensively studied.[18] It is generally assumed that the mechanism involves metal hydrides as key intermediates. However, a recent study indicates that two different hydridic pathways can be involved in these reactions: (i) a metal monohydride mechanism (Scheme 6a) and (ii) a metal dihydride mechanism (Scheme 6b).[19] This study indicates that the second mechanism operates for ruthenium dihalide catalyst precursors, whereas the first mechanism applies to rhodium, iridium, and most nondihalide ruthenium complexes.

Scheme 5. General Methods for Metal-Catalyzed Racemization



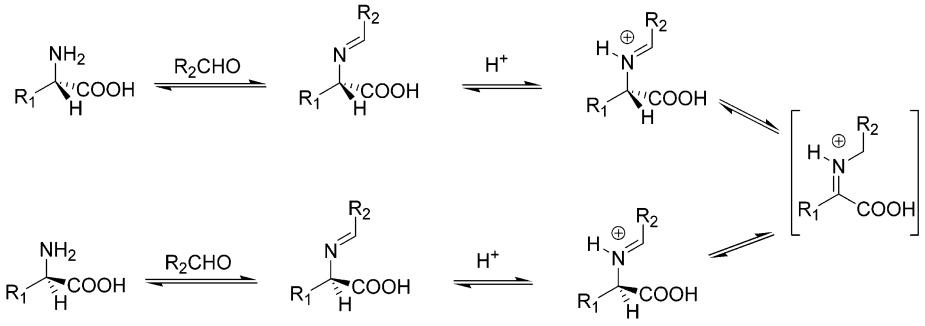
Scheme 6. Different Pathways for the Transfer Hydrogenation Reactions



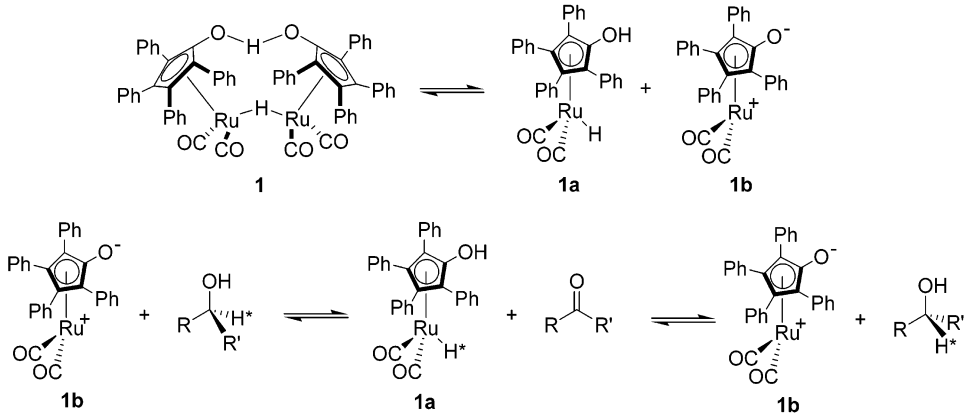
Scheme 7 shows the racemization mechanism for the Ru catalyst **1**. This catalyst has been chosen as an example since so far it is one of the few catalysts that has shown a broad substrate scope when combined with enzymatic kinetic resolution. An important feature of this complex is that no external base is needed as a cocatalyst, since one of the oxygens of the ligand acts as a basic center. Thus, the reaction of the basic oxygen with an alcohol results in proton abstraction followed by formation of the ruthenium hydride intermediate **1a**[20] and the ketone. The ketone generated is reduced by ruthenium intermediate **1a** to form the racemic alcohol and the ruthenium species **1b**. A similar mechanism but with the formation of ruthenium amine intermediates has been recently proposed for the dehydrogenation of amines to imines.[21]

The racemization via (π-allyl)palladium complexes is well-known, and the most common example of this method is the racemization of an allylic ester via

Scheme 4. Proposed Mechanism for the Racemization of Amino Acids Via Schiff Base

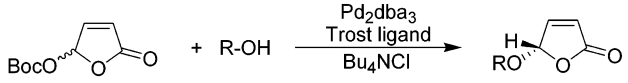


Scheme 7. Proposed Mechanism for the Racemization of Alcohols Catalyzed by 1



Pd(0) catalysis. This isomerization can proceed via different mechanisms.[22] Trost and co-workers have taken advantage of the rapid equilibration between (π-allyl)palladium intermediates for the synthesis of enantiomerically pure lactones via a dynamic kinetic asymmetric transformation (DYKAT) (Scheme 8).[23]

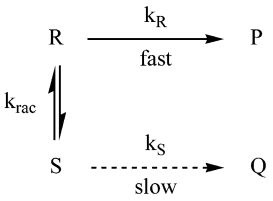
Scheme 8. Application of the Pd-π-Allyl Racemization to the DYKAT



2.3. Basic Requirements for Chemoenzymatic DKR

The principle for a DKR is shown in Scheme 9. In such a process, two enantiomers, *R* and *S*, that react with different rates, k_R and k_S, are in equilibrium with one another.[24] The basic requirements for an efficient DKR can be summarized as follows: (i) an efficient kinetic resolution has to be identified (i.e., $k_R \gg k_S$), (ii) an efficient racemization method has to be chosen, and (iii) the kinetic resolution and the racemization procedures should be compatible with one to another.

Scheme 9. General DKR



To be efficient, a kinetic resolution has to be irreversible to ensure high enantioselectivity. Moreover, the enantiomeric ratio ($E = k_R/k_S$) should be larger than 20.

It is obvious that the DKR process will be more efficient if the racemization is fast. However, usually in the case of chemoenzymatic DKR with enzyme and metal catalysts, the racemization is relatively slow as compared to the kinetic resolution. This does not represent a problem for the enantioselectivity of the product if the enzymatic kinetic resolution proceeds with excellent enantiodiscrimination (*E* value > 200) and as long as k_{rac} is substantially larger than k_S. A requirement is that the ratio between the racemization (k_{rac}) and the reaction of the slow enantiomer (k_S) should be larger than 10. This can often be achieved by reducing the enzyme/racemization catalyst ratio.

Because enzymes and chemical catalysts usually work in quite different environments, their combination in a one pot reaction is not straightforward. Because the commonly used enzymes usually work under relatively mild conditions at moderate temperature and pressure, the choice of racemization method is crucial. Thus, of all racemization methods known, only those taking place in a single step and under mild conditions are suitable for DKR. However, these considerations are not enough to ensure the compatibility between the enzymatic kinetic resolution and the racemization process. Thus, taking as example the combination of the lipase-catalyzed kinetic resolution via transesterification and the metal-catalyzed racemization via hydrogen transfer, other parameters such as solvent, metal catalyst, nature of acyl donor, and temperature have to be taken into account.

The solvent is an important parameter that has to be taken into consideration not just because of its influence in the lipase-catalyzed transesterification[3b,25] but also because of its effect on the racemization rate. Thus, for instance, the activity of lipases is usually increased in nonprotic solvents such as hexane and dialkyl ethers. However, usually the metal-catalyzed racemization proceeds slowly in these solvents mainly due to the low solubility of the catalyst. A recent example exemplifying this can be found in the DKR of azido alcohols.[26] Thus, despite the fact that the kinetic resolution of 2-azido-1-phenylethanol with CALB proceeds faster in diisopropyl ether and *tert*-butyl methyl ether than in toluene, the DKR process is faster in the latter solvent.

The choice of the acyl donor is crucial for the outcome of the DKR process as the early work of Bäckvall and co-workers has clearly shown.[27] Thus, for instance, the use of alkenyl acetates, widely used as acyl donors in the kinetic resolution, results in the formation of aldehydes and ketones after the acyl transfer process, which can interfere with the hydrogen transfer catalysts employed in the DKR. Also, the use of activated alkyl esters, like trifluoroethyl

esters, results in the formation of an alcohol that can compete with the substrate for the metal center. For this purpose, Bäckvall and co-workers turned their attention to the use of aryl esters. In particular, *p*-chlorophenyl acetate proved to be an excellent acyl donor for the DKR of different alcohols.

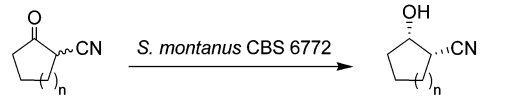
The choice of the catalyst is also important. Most hydrogen transfer catalysts need the addition of an external base as cocatalyst. The presence of base in the system can affect the performance of the enzyme and can also cause side reactions with the substrates and/or products of the DKR. For instance, when performing DKR of β-halo alcohols, the presence of base can cause epoxide formation. For this reason, the use of a catalyst that does not need the addition of external base, like ruthenium catalyst **1**, is advantageous.

The temperature is another important parameter to pay attention to when planning a DKR. Thus, whereas the racemization is usually faster at high temperatures, the enzymes can undergo denaturation at high temperatures. However, in recent years, it has been shown that the temperature resistance of enzymes, in particular that of lipases, can be increased by immobilization on certain supports. Therefore, the use of heterogenized lipases is preferred. Moreover, the heterogenization also favors the recovery and subsequent reuse of the lipase. Nevertheless, the "safe" upper temperature for the enzyme is usually set to about 60−80 °C.

2.4. Examples of Chemoenzymatic DKR with Nonmetallic (Classical) Racemization Methods

An efficient chemoenzymatic DKR can be performed when the enzymatic kinetic resolution is combined with nonmetallic racemization methods. However, this approach is mainly limited to substrates that possess a stereogenic center with an acidic proton.[28] Thus, the most common approach is to combine the enzyme with a base-catalyzed racemization via enol formation. This approach has been extensively applied in combination with the microbial reduction of α-substituted β-keto esters and nitriles.[29] In a recent example, the stereoselective reduction of 2-oxocycloalkanecarbonitriles to yield the corresponding *cis*-hydroxy nitriles in high chemical yields and enantioselectivity was achieved by the use of the yeast *Saccharomyces montanus* CBS 6772 (Scheme 10).[31c] Furstoss and co-workers have applied a similar

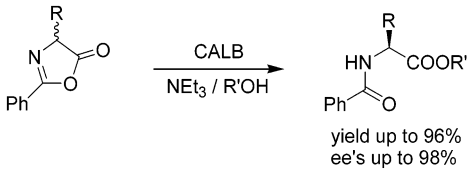
Scheme 10. Bioreduction of 2-Oxocycloalkanecarbonitriles



procedure for the preparation of lactones by combining the microbiologically mediated Baeyer−Villiger oxidation with a base-catalyzed racemization of the corresponding α-substituted cyclopentanone.[30]

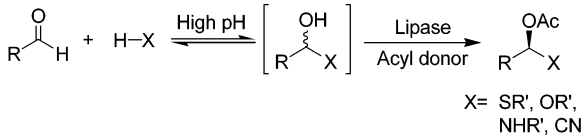
The base-catalyzed racemization has also been combined with the lipase-catalyzed kinetic resolution.[31] Thus, for instance, recently, various 5-oxazolones have been transformed into the corresponding enantiopure amino acid derivatives by combining CALB as the biocatalyst and triethylamine as the base (Scheme 11).[31c]

Scheme 11. DKR of 5-Oxazolones



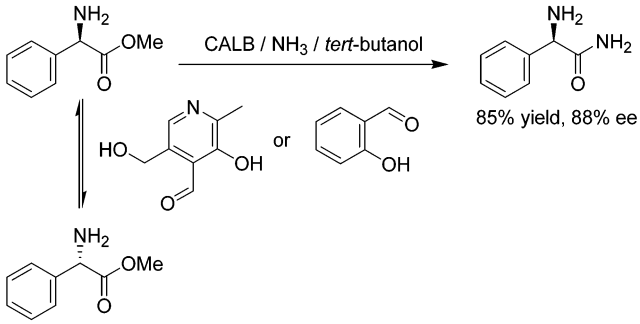
The DKR of cyanohydrins and hemiacetals and related derivatives has also been achieved by combining the lipase-catalyzed transesterification with the racemization via dissociation−recombination processes (Scheme 12).[32] A DKR procedure where the

Scheme 12. DKR of Cyanohydrins and Hemiacetals and Derivatives



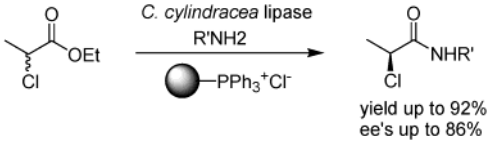
substrate is racemized via Schiff base formation has recently been reported.[33] Thus, in the CALB-catalyzed aminolysis of phenylglycine methyl ester, the unreactive enantiomer is in situ racemized via Schiff base formation with pyridoxal or salicylaldehyde (Scheme 13).

Scheme 13. Chemoenzymatic DKR of Phenylglycine Methyl Ester



Racemization via S_N2 displacement has also been used for the chemoenzymatic DKR of α-halo esters by enzymatic hydrolysis and aminolysis.[34] Thus, in a recent example, an efficient DKR of ethyl 2-chloropropionate was achieved via aminolysis catalyzed by encapsulated *Candida cylindracea* lipase in the presence of supported triphenylphosphonium chloride (Scheme 14).[34c]

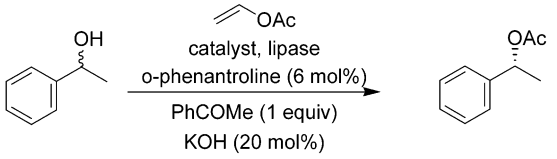
Scheme 14. Example of DKR Combining Enzyme and Racemization Via S_N2 Displacement



3. DKR of Alcohols

The combination of the enzymatic kinetic resolution with a metal-catalyzed racemization via hydrogen transfer for preparing enantiomerically pure alcohols was introduced by Williams[35] and Bäckvall.[27,36] Williams combined the alcohol racemization catalyzed by rhodium/phenantroline and iridium/phenantroline catalysts in the presence of stoichiometric quantities of ketone and base with the *Pseudomonas fluorescens* lipase-catalyzed transesterification using vinyl acetate as the acyl donor (Scheme 15).[35] Although the results were moderate

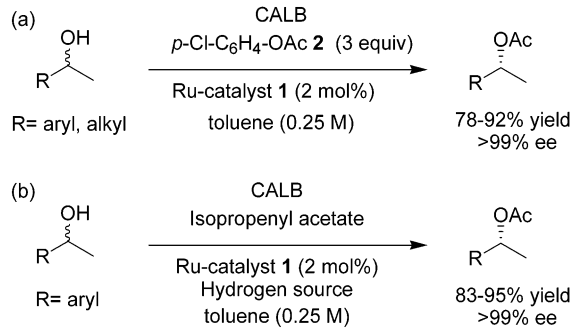
Scheme 15. DKR of 1-Phenylethanol



at best (76% conversion with 80% ee and 60% conversion with 98% ee), they showed that the combination in one pot of both metal and enzyme catalysis is possible.

Bäckvall and co-workers developed an efficient system based on the use of *p*-chlorophenyl acetate **2** as the acyl donor and the robust ruthenium catalyst **1** for the racemization.[27,36] The acyl donor is compatible with the ruthenium racemization catalyst **1**, and the latter does not need the addition of an external base or the addition of the corresponding ketone for the racemization.[36] Thus, an efficient DKR of secondary alcohols was obtained by combining immobilized CALB transesterification using **2** as acyl donor and ruthenium-catalyzed racemization (Scheme 16a).

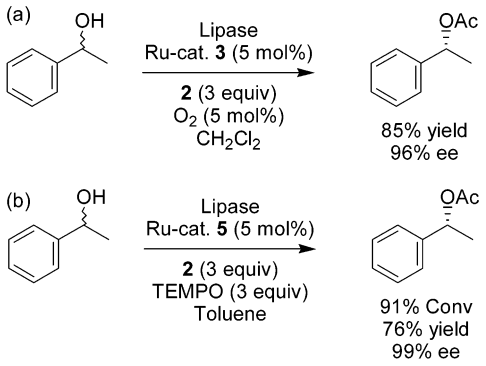
Scheme 16. DKR of Secondary Alcohols



Recently, Bäckvall and co-workers have developed a new protocol in which *p*-chlorophenyl acetate **2** has been replaced by commercially available isopropenyl acetate.[37,38] This has provided similar results, but the use of an appropriate hydrogen source is needed to prevent a drop in yield due to ketone formation (Scheme 16b).

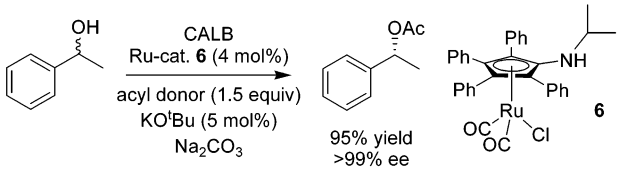
Other groups have also applied other ruthenium-catalyzed racemization catalysts using the Williams–Bäckvall methodology. Thus, Kim, Park, and co-workers also have performed a DKR using RuCl(η^5-indenyl)(PPh_3)$_2$ **3** as racemization catalysts in the presence of triethylamine and molecular oxygen (5 mol %) as the oxidant (Scheme 17a).[39] Park and co-workers have applied this methodology for the asymmetric reduction of ketones and enol acetates to enantiomerically pure acetates using ruthenium catalyst **1** and acyl donor **2**.[40] More recently, Sheldon and co-workers have studied the use of $RuCl_2(PPh_3)_3$ **4** and Ru(TsN(CH_2)$_2$NH)(*p*-cymene) **5** in combination with TEMPO as oxidant in the DKR of 1-phenylethanol with good conversions and enantioselectivity but with low selectivity with respect to formation of acetate (Scheme 17b).[41] Also, it should be mentioned that in 2002 a large scale industrial process for chemoenzymatic DKR of secondary alcohols was developed at DSM by Verzijl et al. in which they used a modified Ru–Noyori type catalyst together with immobilized CALB.[42]

Scheme 17



In a similar way, Park and co-workers have recently reported a novel ruthenium catalyst **6** that can racemize secondary alcohols at room temperature. When this racemization procedure is combined with the CALB-catalyzed transesterification using isopropenyl acetate as the acyl donor, an efficient DKR is obtained if sodium carbonate or molecular sieves are used as additives (Scheme 18).[43]

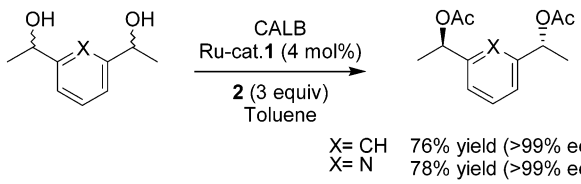
Scheme 18



4. DKR of Diols

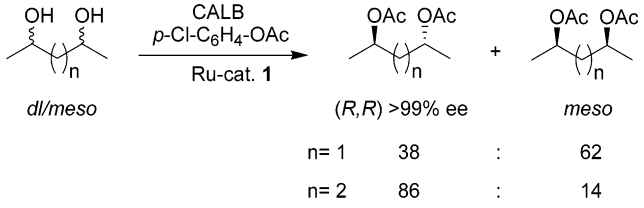
The combination of ruthenium and enzyme catalysis was also applied to the DKR of secondary symmetrical diols (as *meso*/*dl* mixtures).[44] The DKRs were carried out using ruthenium catalyst **1** (4 mol %), immobilized CALB (60 mg/mmol substrate) as the biocatalyst, and *p*-chlorophenyl acetate **2** (3 equiv) as the acyl donor in toluene at 70 °C (Scheme 19).

Scheme 19. Examples of DKR of Diols



In general, good yields (61−90%) of the corresponding diacetates with excellent enantioselectivity were obtained. However, for 1,3- and 1,4-diols, low to moderate diastereoselectivity was observed. Thus, the unexpected formation of *meso*-diacetate containing an *S*-acetylated hydroxyl group (anti-Kazlauskas product) was obtained (Scheme 20).[13] This is unexpected since CALB usually exhibits a high preference for (*R*)-alcohols.[3b,14b]

Scheme 20. DKR of 1,3- and 1,4-Diols



The mechanism for the formation of the unexpected *meso*-diacetate for 1,3- and 1,4-diols has been recently studied by deuterium labeling (Scheme 21).[45] The study indicates that for the 1,3-diol derivatives an intramolecular acyl transfer from the (*R*)-acetate to the (*S*)-alcohol is responsible for the formation of the *meso* product (path A). However, for the 1,4-diols, a neighboring group effect of the (*R*)-acetate reduces the substrate specificity of the enzyme and as a consequence the (*S*)-alcohol is enzymatically acetylated to some extent (path B).

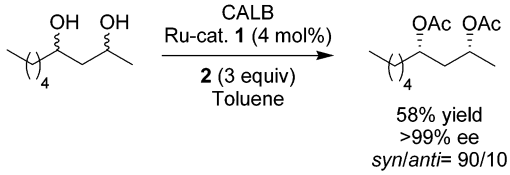
The facile acyl migration in monoacetylated *syn*-1,3-diols was applied to the preparation of enantiomerically pure *syn*-1,3-diacetates via DYKAT. The potential utility of this procedure was shown in the DYKAT of racemic (*syn*/*anti*) 2,4-nonanediol, employing ruthenium racemization catalyst **1**, immobilized CALB, and *p*-chlorophenyl acetate **2** as the acyl donor (Scheme 22).

Kim and co-workers have also applied the DKR for the deracemization of monoprotected 1,2-diols, in which the primary alcohol was protected with a trityl group.[46] The DKR reactions were performed using ruthenium catalyst **1** as the racemization catalyst, immobilized *Pseudomonas cepacia* lipase (PS-C) as the biocatalyst, and *p*-chlorophenyl acetate **2** as the acyl donor in toluene at 70 °C. The addition of 2,6-dimethyl-4-heptanol (0.5 equiv) was required to depress the formation of large amounts of the corresponding ketones. In all cases, high yields and enantioselectivity were obtained (Scheme 23).

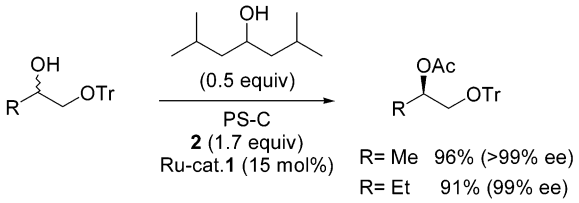
5. DKR of Functionalized Alcohols

The combination of enzyme- and transition metal-catalyzed reactions has not only been applied to simple secondary alcohols but has also been used for the DKR of functionalized alcohols that are useful building blocks for the synthesis of high-value compounds (e.g., pharmaceuticals, natural products, etc.).

Scheme 22. Chemoenzymatic DYKAT of 2,4-Nonanediol



Scheme 23. DKR of Monoprotected 1,2-Diols



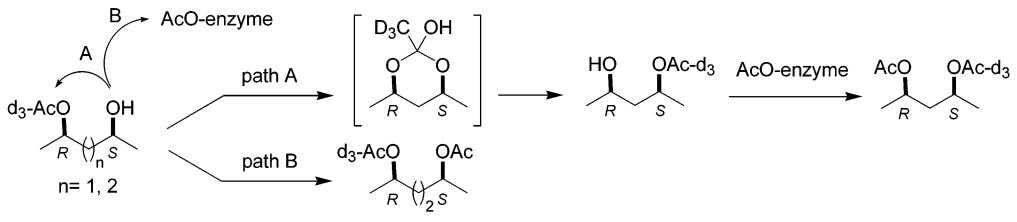
5.1. Hydroxy Acid Derivatives

The chemoenzymatic DKRs of hydroxy esters and amides have been extensively studied by Bäckvall and co-workers.[47] These compounds are important versatile building blocks in asymmetric synthesis. Thus, for instance, γ- and δ-hydroxy acid derivatives can be easily transformed into the corresponding lactones, which are present in a variety of natural products, especially in attractants and pheromones.[48] In addition, lactones are important building blocks for the synthesis of natural products, such as alkaloids and terpenoids and biologically active compounds.[49]

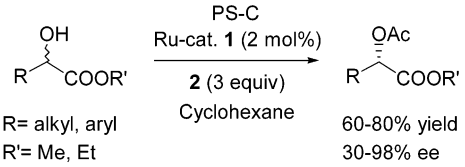
Racemic α-hydroxy esters were subjected to the chemoenzymatic DKR methodology. For this purpose, transesterification in cyclohexane using immobilized PS-C as the biocatalyst with *p*-chlorophenyl acetate **2** as the acyl donor was combined with the ruthenium-catalyzed racemization (Scheme 24).[47a] Under these conditions, various α-hydroxy esters were deracemized in moderate to good yields and enantioselectivity. The use of ruthenium catalysts **1** was advantageous since it does not need the presence of base as a cocatalyst. The presence of base could induce racemization of the formed acetates by enolization.

The same methodology was applied to the DKR of β-hydroxy esters.[47b] The reaction was carried out in tandem with an aldol reaction. The DKR of the formed β-hydroxy esters was performed after neutralization using immobilized PS-C as the biocatalyst, *p*-chlorophenyl acetate **2** as the acyl donor,

Scheme 21. Proposed Mechanisms for the Formation of *meso*-Diacetates from 1,3- and 1,4-Diols

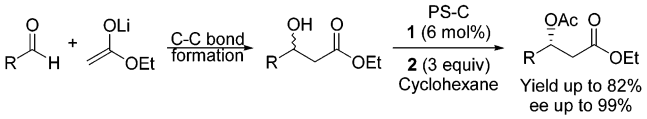


Scheme 24. DKR of Racemic α-Hydroxy Esters



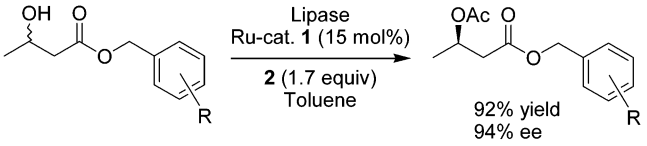
and ruthenium catalysts **1** as the racemization catalyst in toluene (Scheme 25). Under these conditions, various *β*-hydroxy esters were deracemized in moderate to good yields and enantioselectivity. Also, in this case, the absence of base is crucial since it can cause elimination of acetic acid from the product.

Scheme 25. Tandem Aldol Reaction and DKR of the Aldol Adduct



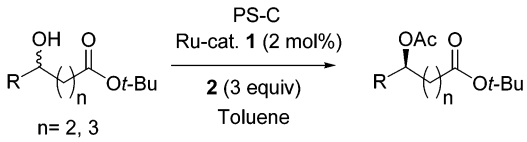
Kim and co-workers have studied the DKR of *β*-hydroxy esters under similar reaction conditions but with a much higher concentration of ruthenium catalyst (Scheme 26).[46] In this case, the carboxy functionality was protected by different bulky groups.

Scheme 26



Similarly, an efficient DKR of *γ*- and *δ*-hydroxy esters was performed by combining the PS-C lipase-catalyzed kinetic resolution with the ruthenium-catalyzed alcohol racemization (Scheme 27).[47c,d] Thus, under "standard" conditions (i.e., 70 °C, 50 mg lipase/mmol product, and 4 mol % of **1**) excellent ee's were obtained. However, substantial amounts of the corresponding ketones, formed during the hydrogen transfer process, were observed.

Scheme 27. DKR of Racemic *γ*- and *δ*-Hydroxy Esters



Several attempts to increase the efficiency of the process by reducing the amount of ketone have been carried out (Table 1). For this purpose, several hydrogen sources **7**−**10** were tested in the DKR of *tert*-butyl 5-hydroxyhexanoate (**11**) with the aim to push the equilibrium back to the alcohol.[47d,50]

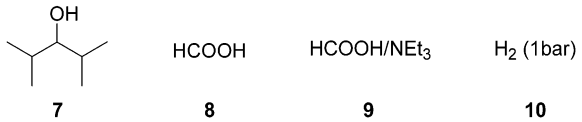
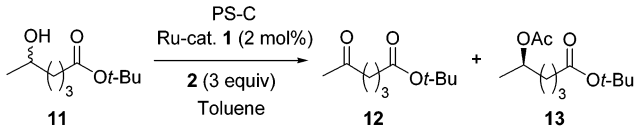


Table 1. Effect of Different Hydrogen Sources in the DKR of 11[a]



entry	H-donor	time (h)	% **11**[b]	% **12**[b]	% **13**[b]	% ee[c]
1		48	0	34	66	99
2	**7**[d]	48	10	25	65	98
3[e]	**7**[d]	72	1	7	92	98
4[e]	**8**[f]	48	21	2	50[g]	99
5[e]	**9**[f]	48	42	4	54	96
6	**10**	48	22		78	89
7[h]	**10**	92	11		89	98

[a] Reactions were performed on a 0.1 mmol scale with 5 mg of immobilized PS-C lipase, 4 mol % of **1**, and 3 equiv of **2** in 1 mL of toluene. [b] Determined by ^{1}H NMR. [c] % ee of **13** determined by HPLC. [d] A 0.5 equiv amount of H-donor used. [e] H-donor added after 24 h. [f] One equivalent of H-donor used. [g] A 27% amount of lactone formed. [h] One milligram of PS-C lipase and 6 mol % of **1** were used.

The addition of 0.5 equiv of 2,4-dimethyl-3-pentanol (**7**) to the reaction mixture reduced the amount of ketone **12** considerably (25%) but did not show an improvement in the formation of acetate **13** (entry 2). This can be attributed to the competition between alcohols **7** and **11** in the transfer hydrogenation process. To minimize this competitive reaction, **7** (0.5 equiv) was added after 24 h, when almost no alcohol **11** was present in the reaction mixture (entry 3). This significantly increased the efficiency of the process, and the desired acetate **13** was formed in 92% after 72 h of reaction in almost enantiomerically pure form (98% ee, entry 3).

The use of formic acid (**8**) inhibited the formation of undesired ketone **12** but catalyzed the lactone formation via acid-catalyzed reaction (27% of lactone after 48 h, entry 4). The use of a mixture of formic acid/triethylamine (**9**) inhibited both ketone and lactone formation, but the activity and enantioselectivity were low (entry 5).

The use of hydrogen gas (1 bar) inhibited the formation of ketone completely. However, the DKR under these conditions gave the acetate in lower enantioselectivity (entry 6). This is mainly due to a decrease of the racemization rate under 1 bar of hydrogen gas. To obtain better enantioselectivity, the efficiency of the DKR was enhanced by increasing the ratio of the rate of racemization and the rate of enzymatic acetylation. Thus, by reducing the enzyme/ruthenium catalyst ratio, the relative rate of enzymatic acylation toward racemization decreased (cf. Scheme 1) and the enantioselectivity was substantially improved (entry 7).

Comparing the results with the different hydrogen sources, the authors concluded that although longer reaction times were needed, the use of molecular hydrogen is advantageous since no byproducts are formed. Under these conditions, a series of *γ*- and *δ*-hydroxy esters were deracemized in high enantiomeric excess (up to 99% ee) and good isolated yields (up to 81%).

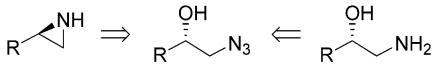
In a similar way, the DKR of *N*,*N*-diisopropyl-4-hydroxypentanamide was efficiently performed using

7 (0.5 equiv) as the hydrogen source. Thus, the corresponding acetate was obtained in 93% yield and 98% ee.[47c]

5.2. Azido Alcohols

Bäckvall and co-workers have studied DKR on β-azido alcohols.[26] The value of enantiopure azido alcohols lies in their utility as direct precursors for aziridines and vicinal amino alcohols (Scheme 28).[51]

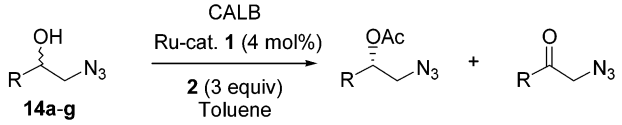
Scheme 28



The chemoenzymatic DKRs were carried out using ruthenium catalyst **1** as the racemization chemocatalyst, immobilized CALB as the biocatalyst, and *p*-chlorophenyl acetate **2** as the acyl donor in toluene at 80 °C (Table 2). In all cases, small amounts of the corresponding ketones, formed during the hydrogen transfer process, were observed. The DKR of various β-azido-α-phenethyl alcohols **14a**−**c** gave high yields with more than 99% ee (Table 2, entries 1−3). These results indicate that the presence of different substituents in the *para* position in the aromatic ring does not significantly influence the efficiency of the process.

For the benzyl (**14e**) and aryloxymethyl derivatives (**14f**,**g**), the DKR under the conditions used for **14a**−**d** (i.e., 120 mg N-435/mmol product, 80 °C, 4 mol % **1**) gave the acetates in moderate to low enantioselectivity (around 70% ee for **14e** and around 30% ee for **14f**,**g**). This is due to the lower enantioselectivity (*E*) of the enzyme for these substrates. To obtain better enantioselectivity, the efficiency of the DKR was enhanced by increasing the ratio of the rate of racemization and the rate of enzymatic acetylation. Thus, by reducing the enzyme/ruthenium catalyst ratio, the rate between enzymatic acylation of the slow-reacting enantiomer and racemization decreased (cf. Scheme 1) and the ee was therefore substantially improved from 30 (for **14f**,**g**) and 70% (for **14e**) to 85−86 and 96%, respectively (entries 5−7).

Table 2. DKR of 14a−g[a]



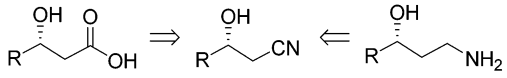
entry	sub-strate	R	% conv[b]	% yield[b]	% ee[c]
1	**14a**	Ph	100	94 (86)	>99 (+)
2	**14b**	*p*-Br-C_6H_4	100	98 (87)	>99 (+)
3	**14c**	*p*-MeO-C_6H_4	100	92 (84)	>99 (+)
4	**14d**	2-naphthyl	100	95 (85)	>99 (+)
5[d]	**14e**	benzyl	94	87 (80)	96 (−)
6[e]	**14f**	$PhOCH_2$	80	76 (70)	85 (+)
7[e]	**14g**	1-naphthyl-OCH_2	80	75 (71)	86 (+)

[a] Reactions were performed on a 0.6 mmol scale with 90 mg of immobilized CALB (Novozym 435), 4 mol % of 1 and 3 equiv of acyl donor **2** in 6 mL of solvent at 80 °C. [b] Determined by NMR. Isolated yields in parentheses. [c] % ee of **2** determined by HPLC. Optical rotation in parentheses. [d] N-435 (15 mg), 6 mol % of **1**, reaction time 48 h. [e] T = 60 °C, CALB (1.5 mg), 6 mol % of **1**, reaction time 72 h.

5.3. Hydroxy Nitriles

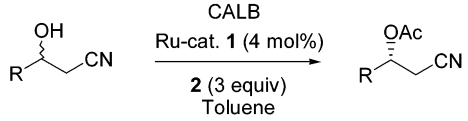
Bäckvall and co-workers have applied the combination of enzyme and metal catalysts for the deracemization of β-hydroxy nitriles.[52] Chiral β-hydroxy nitriles are direct precursors of γ-amino alcohols and β-hydroxy acid derivatives, which are versatile building blocks in both asymmetric synthesis and medicinal chemistry (Scheme 29).[48a,53]

Scheme 29



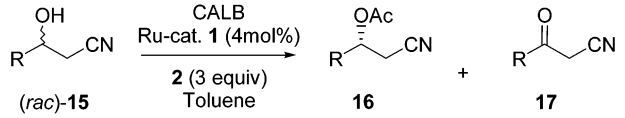
The chemoenzymatic DKRs were carried out using ruthenium catalyst **1** as the racemization chemocatalysts, immobilized CALB as the biocatalyst, and *p*-chlorophenyl acetate **2** as the acyl donor (Scheme 30). A special feature of this DKR process is that the reactions had to be performed at 100 °C, which is the upper temperature limit of the enzyme[3b]; at low temperature, the racemization does not occur. A possible explanation could be found in the coordinating properties of the nitrile group that favorably competes with the alcohol at low temperature.

Scheme 30



Under these conditions, the DKR of various alkyl-, aryl-, and naphthyl-substituted β-hydroxy nitriles gave the corresponding acetates in good yields and enantioselectivity (Table 3). However, the formation

Table 3. DKR of *rac*-15[a]



entry	R	time (h)	% of **16**[b]	% ee of **16**[c]	% of **17**[b]
1	Ph	36	74	97 (*R*)	23
2	*p*-MeO-C_6H_4	36	81	99 (*R*)	19
3	*p*-NO_2-C_6H_4	36	72	96 (*R*)	26
4	2-naphthyl	36	78	94 (*R*)	21
5	CH_3-$(CH_2)_7$-	36	93	92 (*S*)	4
6	$PhOCH_2$	36	98	36 (*R*)	2
7	1-naphthyl-OCH_2	36	95	44 (*R*)	3
8[d]	Ph	36	85	97 (*R*)	11
10[d]	*p*-MeO-C_6H_4	36	86	97 (*R*)	8
11[d]	*p*-NO_2-C_6H_4	36	80	94 (*R*)	13
12[d]	2-naphthyl	36	82	91 (*R*)	14
13[f]	$PhOCH_2$	36	73	74 (*R*)	1

[a] Conditions: 0.2 mmol of *rac*-**15**, 0.6 mmol of **2**, 20 mg of immobilized CALB (Novozym435), and 4 mol % of **1** in 2 mL of toluene at 100 °C. [b] Percent yield measured by NMR. [c] Optical purity measured by GC or HPLC. Absolute configuration shown in parentheses. [d] A 0.1 mmol amount of **7** added. [f] Five milligrams of immobilized enzyme was used.

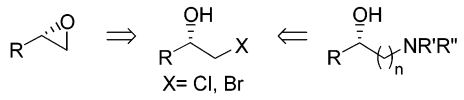
of large amounts of the corresponding ketones, formed during the hydrogen transfer process, was observed for the aryl and naphthyl derivatives. The efficiency of the DKR process was increased by adding **7** (0.5 equiv) as the hydrogen source. Thus, this did not only inhibit considerably the formation of ketone but, at the same time, increased the yield of the corresponding acetates.

For the aryloxymethyl derivatives, however, low enantioselectivity was obtained under the DKR conditions (Table 3). This was attributed to the low enantiopreference of the enzyme for this substrate at this temperature. The enantioselectivity was substantially improved (ee's up to 74%) by reducing the enzyme/ruthenium catalyst ratio.

5.4. Halo Alcohols

The combination of enzymatic resolution with ruthenium-catalyzed alcohol isomerization was also studied for β-halo alcohols.[54] Chiral β-halo alcohols are important structural elements for asymmetric catalysis. The possible transformations include among others the formation of chiral epoxides and β- and γ-amino alcohols, widely used as adrenergic receptor blockers and immune stimulants (Scheme 31).[55]

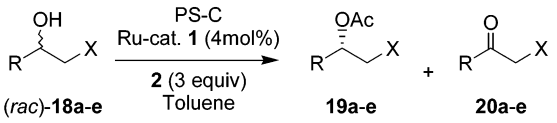
Scheme 31



The DKR reactions were carried out by combining the kinetic resolution of β-halo alcohols **18** using immobilized PS-C as the biocatalyst and **2** as the acyl donor with a ruthenium-catalyzed racemization process via hydrogen transfer with catalyst **1** at 70 °C (Table 4). In all cases, small amounts of the corresponding ketones **20** were observed. The DKRs of various β-chloro-α-phenethyl alcohols **18a**−**c** proceeded with excellent enantioselectivity. Moreover, the results indicate that the substituent in the *para* position of the aromatic ring affects the efficiency of the process. Thus, while the presence of a fluoro substituent in the *para* position has a slightly positive effect on the outcome of the reaction (entry 3), the introduction of a methoxy substituent in the *para* position of the phenyl ring has a negative effect on the efficiency of the process (entry 2). This is most likely due to the slower racemization of the latter substrate.

For the benzyl (**18f**) and aryloxymethyl derivatives (**18g**,**h**), good yields and moderate to good enantioselectivity were also obtained under these DKR conditions. The efficiency of the DKR is severely reduced when the chloro substituent is replaced by a bromo substituent (entries 1 and 5 vs 7 and 8). The authors discovered that the presence of the bromo substituent causes decomposition of the ruthenium catalysts, which triggers the progressive deactivation of the enzyme.

Table 4. DKR of *rac*-18[a]



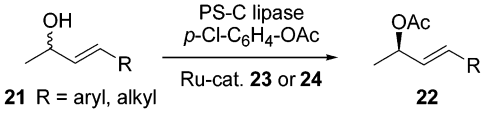
entry	sub-strate	R	X	% conv[b]	% yield of **19**[b]	% ee[c]
1	**18a**	Ph	Cl	96	93 (85)[d]	95
2	**18b**	*p*-OMe-C_6H_4	Cl	70	69 (58)[d]	96
3	**18c**	*p*-F-C_6H_4	Cl	100	>99 (91)[d]	93
4[f]	**18f**	benzyl	Cl	84	82 (74)[d]	91
5[g]	**18g**	$PhOCH_2$	Cl	87	87	85
6[g]	**18h**	1-naphthyl-OCH_2	Cl	98	98	87
7	**18d**	Ph	Br	72	63	97
8	**18e**	*p*-OMe-C_6H_4	Br	44	39[e]	95

[a] Conditions: 0.2 mmol of *rac*-**18**, 0.6 mmol of **2**, 4 mol % of **1**, 20 mg of immobilized PS-C lipase, and 2 mL of toluene. [b] Yield measured by NMR after 72 h. Isolated yields in parentheses. [c] Enantiomeric excess measured by GC or HPLC. [d] Reaction performed at 0.6 mmol scale. [e] 61% of unreacted starting material. [f] Five milligrams of enzyme was used. [g] A 2.5 mg amount of enzyme was used.

5.5. Allylic Alcohols

Enantiomerically pure allylic alcohols are important intermediates for asymmetric synthesis. Kim and co-workers combined the PS-C lipase-catalyzed transesterification with a ruthenium-catalyzed racemization via hydrogen transfer for the deracemization of allylic alcohols (Scheme 32).[56]

Scheme 32



A key choice in this procedure was ruthenium catalyst since it is known that ruthenium also catalyzes the isomerization of allylic alcohols to saturated ketones.[57] The authors found that $[RuCl_2(p\text{-cymene})]_2$ (**23**) and $[Ru_2Cl_2(\mu\text{-Cl})(\mu\text{-H})(p\text{-cymene})_2]$ (**24**) are able to racemize allylic alcohols in the presence of NEt_3 in CH_2Cl_2 at room temperature giving the lowest byproduct formation (for example, in the racemization of (*S*)-(*E*)-4-phenyl-3-buten-2-ol ketones, (*E*)-4-phenyl-3-buten-2-one and 4-phenylbutan-2-one were obtained in a combined yield of 25 and 18% using catalysts **23** and **24**, respectively). Using **24** as the racemization catalyst and PS-C lipase as the biocatalyst, a series of allylic alcohols **21** were deracemized in excellent enantioselectivity and good yields (Table 5).

Table 5. DKR of *rac*-21[a]

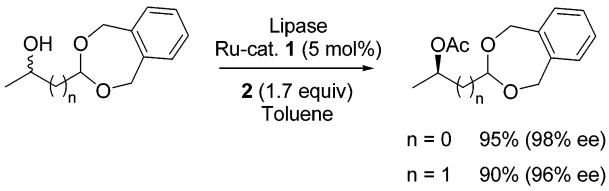
entry	sub-strate	R	% conv[b]	% yield of **22**[c]	% ee[d]
1	**21a**	Ph	>99	84 (83)	>99
2	**21b**	*p*-Cl-C_6H_4	>99	91 (88)	99
3	**21c**	*p*-OMe-C_6H_4	>99	85 (81)	99
4	**21f**	furyl	>99	92 (86)	99
5	**21g**	cyclohexyl	97	90 (84)	95
6	**21h**	isopropyl	>99	87 (83)	>99
7	**21d**	propyl	>99	86 (83)	95

[a] Conditions: 0.5−1.4 mmol of *rac*-**21**, 1.5−1.7 mmol of **2**, 4 mol % of **1**, 150 mg/mmol of immobilized PS-C lipase, 1 equiv of triethylamine, and 2−4 mL of dichloromethane. [b] Conversion measured by NMR after 48 h. Isolated yields in parentheses. [c] Yield measured by NMR. Isolated yields in parentheses. [d] Enantiomeric excess measured by GC or HPLC.

5.6. Protected Hydroxy Aldehydes

Kim and co-workers have studied the possibility to perform DKR on protected hydroxy aldehydes.[46] For this purpose, 2-hydroxypropanal and 3-hydroxybutanal were protected with 1,2-benzenedimethanol. For both substrates, good yields and high enantioselectivity were obtained when the ruthenium catalyst **1** was combined with a lipase (Scheme 33).

Scheme 33

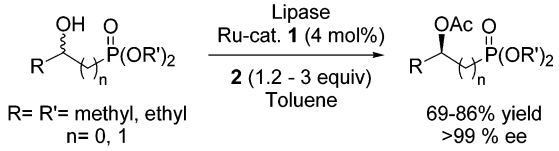


5.7. Hydroxyphosphonates

The combination of a lipase and a metal catalyst has also been applied for the deracemization of α- and *β*-hydroxyphosphonates.[58] Hydroxyphosphonates are an important class of substrates, with applications in medicinal chemistry (haptens of catalytic antibodies, phosphonic acid-based antiobiotics), biochemistry (enzyme inhibitors), and organic synthesis.[59]

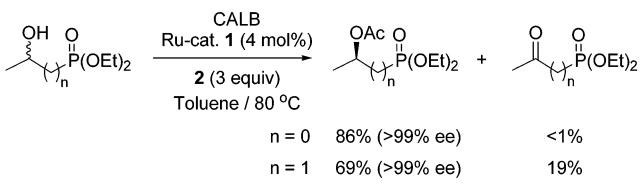
Under our typical conditions, the DKR of several dimethyl and diethyl-α-hydroxyphosphonates proceeded with excellent enantiomeric excess (>99%) and moderate to good yield (70−87%) after 24 h (Scheme 34). However, a decomposition of the ruthenium catalyst was observed at low alcohol concentration. This was attributed to the coordination of the phosphonate moiety to the ruthenium catalyst at a low alcohol concentration.

Scheme 34



This chemoenzymatic DKR procedure was also applied to the deracemization of diethyl *β*-hydroxyphosphonates. However, in contrast to the DKR results on α-hydroxyphosphonates, the formation of large amounts of the corresponding ketone was observed (Scheme 35).

Scheme 35

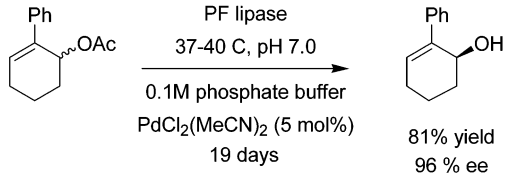


To increase the efficiency of the process by reducing the amount of ketone, the authors completely suppressed the ketone formation by adding **7** (0.5 equiv) as a hydrogen source after 24 h. Under these conditions, the DKR of *β*-hydroxyphosphonates proceeded with excellent enantiomeric excess (>99%) and moderate yields (64−69%) and without ketone formation.

6. DKR of Allylic Acetates

Williams and co-workers reported the first example of chemoenzymatic DKR of allylic acetates using a lipase as biocatalyst and a palladium(II) complex as the racemization catalyst.[60] In this procedure, a cyclic allylic acetate is deracemized via lipase-catalyzed hydrolysis in phosphate buffer at approximately 40 °C, and the unreactive enantiomer is racemized in situ with $PdCl_2(MeCN)_2$ (Scheme 36). Thus, 2-phenyl-

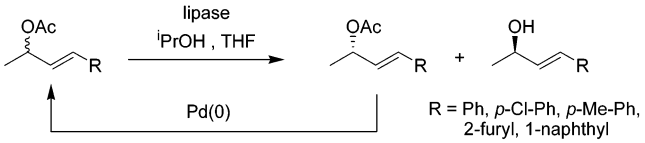
Scheme 36. DKR of 2-Phenyl-2-cyclohexenyl Acetate



2-cyclohexenyl acetate and methyl 5-(acetyloxy)-3-cyclohexene-1-carboxylate were satisfactorily deracemized using this procedure. However, the reaction time is very long (typically more than 2 weeks) due to the slow palladium racemization process.

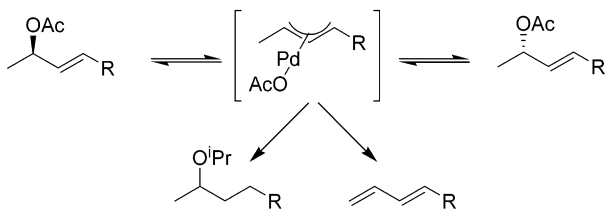
Kim and co-workers combined lipase-catalyzed transesterification with Pd(0)-catalyzed racemization in tetrahydrofuran (THF) (Scheme 37).[61] Although

Scheme 37



this idea at first glance is conceptually similar to Williams' approach, operationally they are different. As the acyl acceptor, the authors chose 2-propanol instead of H_2O because it and its acetate can be easily removed after the reaction is complete (Scheme 37). The unreacted enantiomer is racemized by $Pd(PPh_3)_4$ (with added dppf) via formation of a (*π*-allyl)palladium intermediate and subsequent *cis*-migration of acetate.[62] However, the palladium-catalyzed racemization in the presence of 2-propanol in THF is accompanied by elimination and substitution to form the corresponding diene and allylic isopropyl ether, respectively (Scheme 38). To minimize these side

Scheme 38



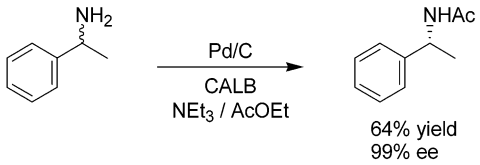
reactions, the palladium catalyst was added after the enzymatic kinetic resolution was done, but still 15−20% of byproducts were obtained. Under these condi-

tions, a series of linear allylic acetates were deracemized in high enantiomeric excess (97−99% ee) and moderate to good isolated yields (61−78%).

7. DKR of Amines

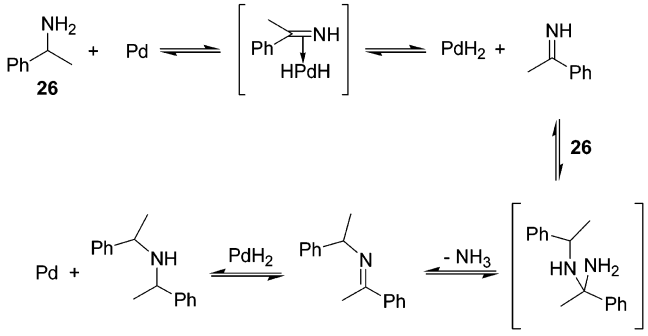
The chemoenzymatic DKR can also be used for the preparation of enantiomerically enriched amines, which are widely employed as building blocks for the synthesis of agrochemicals and pharmaceuticals. Reetz and co-workers demonstrated the first example of chemoenzymatic DKR for the preparation of enantiopure amines.[63] Thus, the combination of immobilized CALB as biocatalysts and palladium on carbon as racemization catalysts was used for the synthesis of (*R*)-*N*-(1-phenylethyl)acetamide (**25**) from 1-phenylethylamine (**26**) in moderate yield (64%) and enantiomerically pure form (Scheme 39).

Scheme 39. DKR of 26



The racemization step, which proceeds via an amine−imine equilibrium promoted by palladium(0), is very slow resulting in long reaction times (8 days). Moreover, acetophenone, *N*-(1-phenylethyl)-*N*-(1-phenylethylidene)amine, and *N*,*N*-di(1-phenylethyl)-amine were observed as byproducts. The formation of the latter products is best explained by reductive amination of the imine intermediate formed followed by elimination of ammonia (Scheme 40).[64]

Scheme 40



Kim and co-workers have recently improved the efficiency of the combined Pd/CALB DKR process by using ketoximes as starting materials under hydrogen atmosphere (Scheme 41).[65] In this way, the

Scheme 41. DKR of Ketoximes

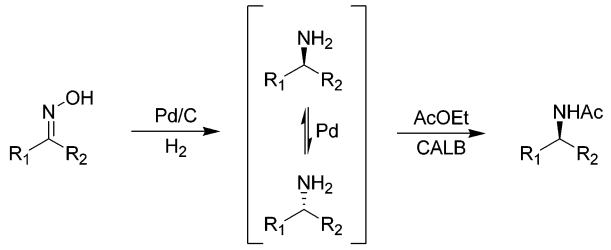


Table 6. DKR of Ketoximes[a]

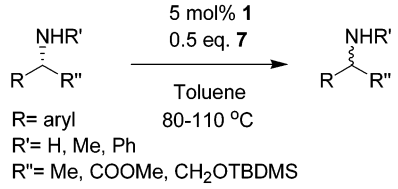
entry	R_1	R_2	% conv[b]	% yield[c]	% ee[d]
1	Me	Ph	>98	80	98
2	Me	*p*-Me-C_6H_4	>99	84	97
3	Me	*m*-Me-C_6H_4	>99	81	94
4	Me	*p*-OMe-C_6H_4	>99	82	96
5	Et	Ph	97	76	98

[a] Conditions: 0.5−1.4 mmol of *rac*-**21**, 1.5−1.7 mmol of **2**, 4 mol % of **1**, 150 mg/mmol of immobilized PS-C lipase, 1 equiv of triethylamine, and 2−4 mL of dichloromethane. [b] Conversion based on ^{1}H NMR. [c] Isolated yield. [d] Enantiomeric excess measured by HPLC.

concentration of amine is low and the formation of byproducts via reductive amination is less favored. Moreover, they also found that the use of diispropylamine as base inhibits the byproduct formation. Thus, a series of ketoximines were transformed into the corresponding optically active acetamides in good yields and enantioselectivity after 5 days (Table 6).

Bäckvall and co-workers have recently reported an efficient and mild ruthenium-catalyzed racemization of amines under hydrogen transfer conditions (Scheme 42).[66] An important feature of this new procedure is

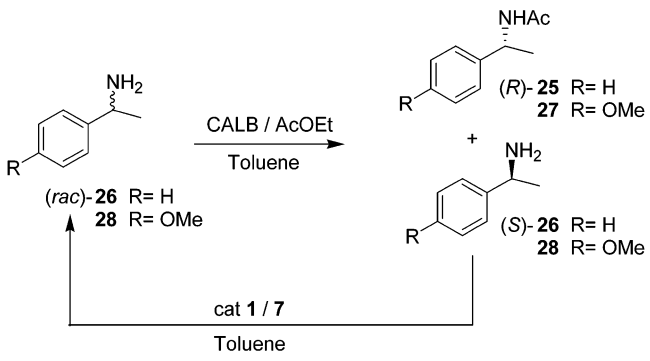
Scheme 42. Racemization of Primary and Secondary Amines Via Hydrogen Transfer



that the ruthenium hydrogen transfer catalyst allows high functional group tolerance.[18] It was also demonstrated that the reaction occurs with an unusually high recovery of amine (95−99%) after racemization even with primary amines.

This procedure was applied to the practical synthesis of enantiomerically pure **25** and (*R*)-*N*-((4-methoxyphenyl)ethyl)acetamide (**27**) from the corresponding racemic amines. For this purpose, the racemization procedure was combined with the CALB-catalyzed transesterification using ethyl acetate as acyl donor in a two step manner (Scheme 43). After two kinetic resolutions and one racemization, the corresponding acetamides were isolated in good combined yields (69% for **25** and 66% for **27**) in almost enantiomerically pure form (>98% ee).

Scheme 43



8. Concluding Remarks

Enzyme catalysis (for the resolution of a racemate) and metal catalysis (for the racemization of the slow-reacting enantiomer) is a powerful combination for obtaining successful DKR processes. The high efficiency of these processes makes them attractive alternatives to existing methods in asymmetric catalysis for obtaining highly functionalized chiral alcohols and amines in enantiomerically pure form.

9. Acknowledgments

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