Review

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Combined Enzyme and Transition-Metal Catalysis for Dynamic Kinetic Resolutions

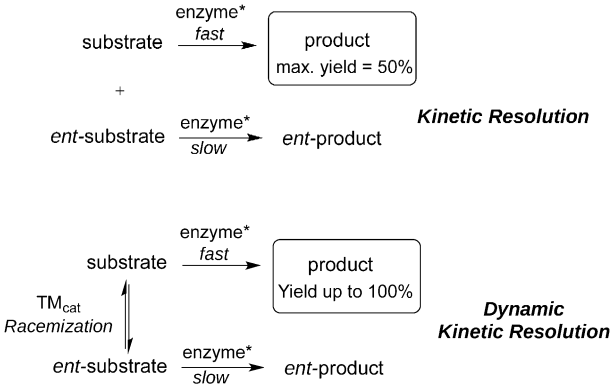
Rocío Marcos[a, b] and Belén Martín-Matute*[a, b]

Abstract: The preparation of optically pure alcohols, axially chiral allenes, and amine derivatives by using enzymes and transition-metal catalysts through dynamic kinetic resolution (DKR) is reviewed. After a general introduction into enzymatic kinetic resolutions and racemizations catalyzed by transition-metal complexes, selected examples of DKRs are presented, from early work to more recent outstanding contributions, and also applications of this approach.

Keywords: DKR · enzymes · kinetic resolution · racemization · transition metals

1. Introduction

Kinetic resolution (KR) is the achievement of partial or complete separation of the enantiomers in a racemate by virtue of unequal reaction rates with a homochiral agent (e.g., a chiral catalyst or reagent).[1] In KR, a maximum yield of 50% of an enantiomerically pure product can be obtained (Scheme 1). It also requires the separation of the product from the remaining unreacted enantiomer of the starting material. To overcome this limitation, KR can be combined with a racemization process. If the two enantiomers of the starting material are interconverted during KR, quantitative conversion of the racemate into enantiomerically pure product can be achieved. The enantiomers can be racemized with the aid of a catalyst, such as a transition metal, an enzyme, or a base. Processes that combine KR with simultaneous racemization are known as dynamic KRs (DKR; Scheme 1).[2]



Scheme 1.

Herein, we discuss DKRs of alcohols, axially chiral allenes, and amines involving enzymes as chiral resolving reagents and transition-metal complexes as racemization catalysts.

1.1. Enzyme-Catalyzed KR

Enzyme-catalyzed reactions are highly regio-, chemo-, and enantioselective for certain substrates.[3] The majority of enzymes used in transition-metal-catalyzed DKRs are lipases (EC 3.1.1.3). Lipases catalyze the hydrolysis of water-insoluble esters (e.g., triglycerides of long-chain fatty acids). Interestingly, they catalyze the hydrolysis of many non-natural esters as well, and many lipases are commercially available. For optimal activity, most of the enzymes require mild reaction conditions (physiological pH and temperature). Enzymes can also catalyze reactions in organic solvents.[4] This has resulted in the development of new enzyme-catalyzed reactions: in anhydrous media in the presence of nucleophiles such as alcohols, amines, or thiols, they catalyze transesterifications, aminolysis, or thiotransesterifications, respectively.

The reaction rates (v) of the enantiomers with the enzyme are different due to the diastereomeric character of the respective transition states. The degree of resolution achievable in a particular KR depends on the magnitude of the ratio of reaction rates ($v_s/v_{ent\text{-}s}$, in which s and *ent*-s are the enantiomeric substrates). The concentration of each of the enantiomers changes as the KR proceeds,

[a] R. Marcos, B. Martín-Matute
Department of Organic Chemistry
Arrhenius Laboratory
Stockholm University
SE-10691 Stockholm (Sweden)
fax: +46 8 15 49 08
e-mail: belen@organ.su.se

[b] R. Marcos, B. Martín-Matute
Berzelii Centre EXSELENT on Porous Materials
Stockholm University
SE-10691, Stockholm (Sweden)

and thus, the reaction rates do not remain constant.[5] As a consequence, the enantioselectivity obtained will depend on the conversion at which the reaction is terminated. In a KR where both enantiomers compete for the same active site of the enzyme, if there is no product inhibition and if the reaction is irreversible, the ratio v_s/v_{ent-s} can be expressed as shown in Equations (1), or (2) after integration. The E value[6] or enantiomeric ratio is a constant intrinsic to each KR. The E value is the ratio between the specificity constants (k_{cat}/K_M; K_M = Michaelis constant) for the catalytic conversion of enantiomeric substrates (s and *ent*-s) and expresses the relative rates of competing enzymatic reactions. Importantly, and in contrast to the enantiomeric excess (*ee*), E does not change with the conversion, but remains constant during a KR. Thus, the E value is an excellent tool for comparing the efficiency of different KRs.

$$v_s/v_{ent-s} = \frac{(v_{max/s}/K_{M,s} \cdot [s]}{(v_{max,ent-s}/K_{M,ent-s} \cdot [ent-s]} \quad (1)$$

$$\frac{\ln([s]/[s]_0)}{\ln([ent-s]/[ent-s]_0)} = \frac{v_{max,s}/K_M}{v_{max,ent-s}/K_{M,ent-s}} = E \quad (2)$$

From a practical point of view, E can be calculated by using the equations developed by Sih and co-workers[6] [Eqs. (3) and (4)] when two of the following three parameters in a KR are known: conversion (c), *ee* of the substrate (ee_S), and *ee* of the product (ee_P). Equation (4) is particularly useful because it allows an accurate calculation of E (enantiomeric purities can often be calculated more accurately than conversions), and it can be used at any value of conversion.

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

$$E = \frac{\ln \frac{[ee_P(1-ee_S)]}{(ee_P+ee_S)}}{\ln \frac{[ee_P(1+ee_S)]}{(ee_P+ee_S)}} \quad (4)$$

Highly selective KRs have E values greater than 200. Figure 1 shows the variation of ee_s and ee_p as the reaction proceeds in three KRs with different intrinsic selectivities (E = 5, 15, and >200).[7] If the KRs are stopped at 50% conversion, the product (p) is obtained with a mediocre ee_p when E = 5, moderate when E = 15, and very good when E > 200. It can be also concluded that, to obtain the product in high *ee* in a KR with E > 200, the reaction should be stopped before reaching 50% conversion. Alternatively, if we would like to recover the unreacted starting material in high *ee*, the reaction must be terminated after >50% conversion.

The majority of the DKR examples presented herein involve a lipase-catalyzed acylation.[8] The starting materials are either alcohols or amines, which in the presence of an acyl donor are converted into their corresponding acylated counterparts (Scheme 2).

The most commonly used enzymes in DKR mediated by transition-metal complexes are *Candida antartica* lipase B (CALB), *Candida rugosa* lipase, and *Pseudomonas cepacia* lipase (current name *Burkholderia cepacia*). The enantiopreference of CALB, *Pseudomonas cepacia* lipase, and *C. rugosa* lipase in the acylation of *sec*-alcohols can be predicted by applying the Kazlauskas rule[9] (Figure 2a). Proteases have also been used in DKR. They also catalyze acylation reactions of alcohols, but they usually show opposite enantiopreference (Figure 2b).

The majority of DKRs reviewed herein are performed in organic solvents, where transition-metal-catalyzed racemizations are most efficient. When an enzyme is lyophilized and then used in a KR in organic media, the selectivity obtained is usually similar to that obtained in the aqueous mixture from which it was lyophilized.[3b,c] However, enzymes usually show diminished activity in organic solvents. Furthermore, very often impurities, solvents, or the reactants themselves affect the stability and performance of an enzyme. The activity in organic solvents can be enhanced when the enzyme is lyophilized in the presence of additives that can form hydrogen bonds with the enzyme, and thus, act as replacements for the water molecules eliminated during lyophilization. Examples of such additives are surfactants such as sucrose, octyl β-D-gluco-

Belén Martín-Matute was born in Madrid and obtained her Ph.D. at the Universidad Autónoma de Madrid (UAM 2002) with Prof. A. M. Echavarren. After a postdoctoral stay at Stockholm University with Prof. J.-E. Bäckvall working on dynamic kinetic resolutions, she joined the UAM as an Assistant Professor (2005–2007) and worked with Prof. J. C. Carretero. She returned to Stockholm in 2007 and in 2011 became Associate Professor. She received the Sigma-Aldrich Young Chemist Award from the Spanish Royal Society of Chemistry in 2007.

Rocío Marcos was born in Palencia and obtained her Ph.D. at the Universidad Rovira i Virgili in Tarragona (ICIQ 2011) with Prof. M. A. Pericàs, working on the synthesis of supported ligands for metal-catalyzed reactions. She spent four months in the group of Prof. A. Pfaltz in Basel during her doctoral studies. Currently, she holds a postdoctoral position at Stockholm University, Sweden, with Prof. Belén Martín-Matute.

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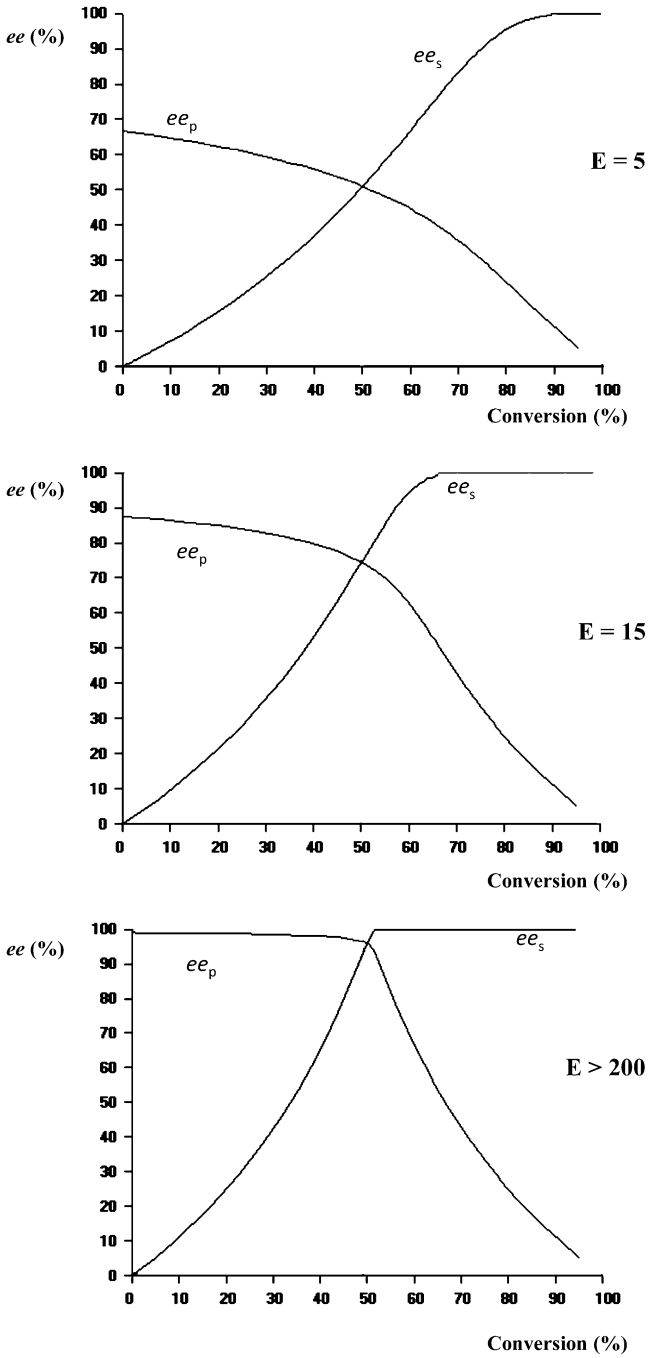
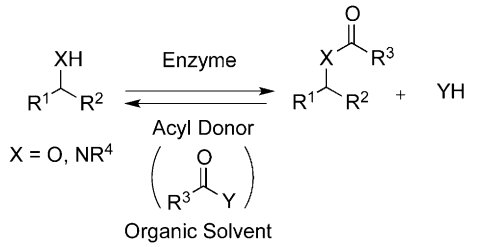


Figure 1. Variation of the enantiomeric excess of substrate (ee_s) and product (ee_p) with conversion in three KRs with E values of 5, 15, and >200.

pyranoside, or Brij-56 (polyethylene glycol hexadecyl ether).[10] Further stabilization is obtained by immobilization on inorganic supports (e.g., polymers, ceramic particles, Celite, mesoporous silica materials, etc.). For example, CALB shows excellent stability in organic solvents when adsorbed on cross-linked poly(methyl methacrylate). This immobilized preparation of CALB (Novozyme 435) is a product of Novozymes A/S. The outcome of an



Scheme 2.

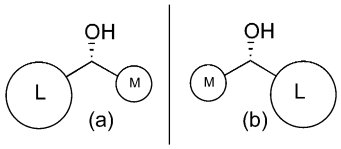


Figure 2. a) Enantiopreference of lipases. b) Enantiopreference of proteases.

enzymatic resolution is also dependent on the support of each enzyme, so a single enzyme can show variations in enantioselectivity and reactivity for a substrate as a result of the immobilization technique used.

Transesterifications (Scheme 2) are reversible reactions.[11] The equilibrium can be shifted towards the desired product by using an excess of the acyl donor or by distillation of the volatile residue (YH in Scheme 2).[12] Also, acyl donors that form byproducts (YH) of poor nucleophilicity can ensure irreversible transesterification. For example, phenyl or trichloroethyl esters (Figure 3) form phenol or trichloroethanol after the reaction, respectively. Also, enol esters (Figure 3), which form enols as byproducts that rapidly tautomerize to give the corresponding carbonyls, are excellent acyl donors for irreversible transesterifications.

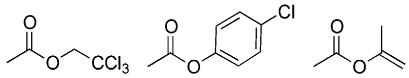


Figure 3. Acyl donors used in DKRs.

1.2. Transition-Metal-Catalyzed Racemizations

The transition metals used and the mechanism by which racemization is achieved depend on the substrate structure. Several complexes of ruthenium, palladium, rhodium, iridium, and other metals have been used in the racemization of alcohols and amines. However, only a few have been successfully employed in DKR in combination with enzymes. Some of these racemization complexes used in enzymatic DKRs are shown in Figure 4. Heterogeneous transition-metal complexes have also been reported (see below).

Racemization of alcohols and amines can occur through hydrogen transfer. A simplified mechanism is

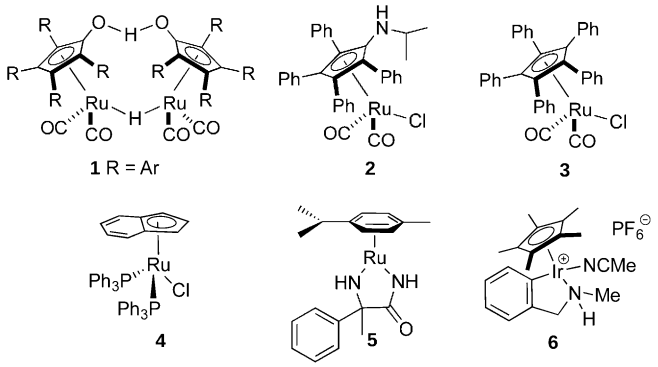
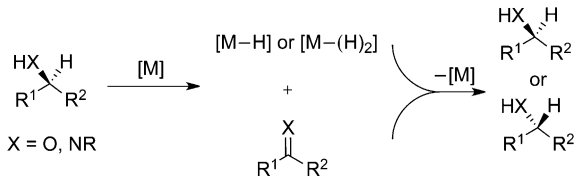


Figure 4. Some transition-metal complexes used in DKRs of alcohols and amines.

shown in Scheme 3. After abstraction of the α-hydrogen, a transition-metal hydride is formed. In the reverse step, the hydride is added to either of the two prochiral faces of the ketone or imine intermediate. Overall, this process results in racemization of the substrate. Depending on the transition-metal complex used, either metal monohydrides or metal dihydrides are formed. These two possibilities can be distinguished by racemizing α-deuterated alcohols or amines and analyzing the deuterium content in the racemized substrate.[13]



Scheme 3. Racemization of alcohols and amines.

Other mechanisms occur in the racemization of certain substrates or with certain metal complexes. For example, allylic acetates can be racemized with palladium via π-allyl Pd(II) intermediates, and allylic alcohols can be racemized through double migration of the oxygen atom (see below). These π-allyl Pd(II) intermediates have also been proposed in the racemization of axially chiral allenes. Racemization of benzylic *sec*-alcohols can occur through carbenium ion intermediates, and β-disubstituted primary allylic alcohols racemize through the enolization of aldehyde intermediates. These mechanisms are discussed in more detail in the next section.

1.3. Dynamic Kinetic Resolution

Due to the different nature of the catalysts, a major task when developing DKR is to find reaction conditions under which both racemization and KR work efficiently. Importantly, the enzyme must be highly selective for the desired transformation. Racemization must occur at a rate that is at least 10 times faster than that of acylation of the slow-reacting enantiomer in KR and this rate must be maintained throughout DKR. In this ideal situation, the maximum ee_p obtained in DKR will be that dictated by the E value (i.e., that of the KR when $t \rightarrow 0$ and $ee_s \approx 0$). For example, the acylated product would be obtained with a maximum *ee* of 66.6% when $E = 5$, 87.5% *ee* when $E = 15$, and 99.0% *ee* when $E = 200$; Scheme 1). To make the two processes compatible in one pot, several parameters usually need to be investigated, such as solvent, temperature, structure of the acyl donor and of the transition-metal complex, and even enzyme immobilization techniques.

1.3.1. Dynamic Kinetic Asymmetric Transformations

Resolution is defined as the separation of the enantiomers from a racemate. Therefore, if the starting material consists of a mixture of diastereomers, the term KR is not applicable. In these cases, the enzyme-catalyzed process is a kinetic asymmetric transformation (KAT). Similarly, the combination of a KAT with in situ epimerization is known as dynamic kinetic asymmetric transformation (DYKAT).[14]

In the next sections, we present the most outstanding examples of DKRs of alcohols, allenes, and amines by combining enzyme and transition-metal catalysis. Special attention is paid to efficiency, selectivity, and applications.

2. DKR of Alcohols

DKR of alcohols has achieved high levels of efficiency in the last decade. Several substrates with different electronic and steric properties have been successfully resolved through combined enzyme and transition-metal catalysis (Figures 5 and 6). Catalyst design has played a very important role. Also, much research effort has been put into achieving high levels of activity and selectivity in enzyme-catalyzed transformations in organic solvents, and even mutated variants have been used to achieve this goal.

DKR of *sec*-alcohols was reported for the first time by Williams and co-workers, who combined $[Rh_2(OAc)_4]$/*o*-phenanthroline with *P. fluorescens* lipase. A yield of 60% and 98% *ee* could be obtained in the DKR of 1-phenylethanol when 1 equiv. of acetophenone was added to the reaction mixture.[15] Shortly afterwards, Bäckvall and co-workers reported the use of Shvo's complex **1** and an immobilized lipase (CALB, Novzyme 435).[16a] The addition of acetophenone (1 equiv.) was also necessary in the first experiments, but was omitted in their second report.[16b] This was the first practical chemoenzymatic DKR of *sec*-alcohols (up to 92% yield, >99% *ee*) for a wide-ranging group of substrates studied (Scheme 4; R = aryl or alkyl).[16b] Some drawbacks of this methodology were that the Ru complex (**1**) required temperatures above 70 °C

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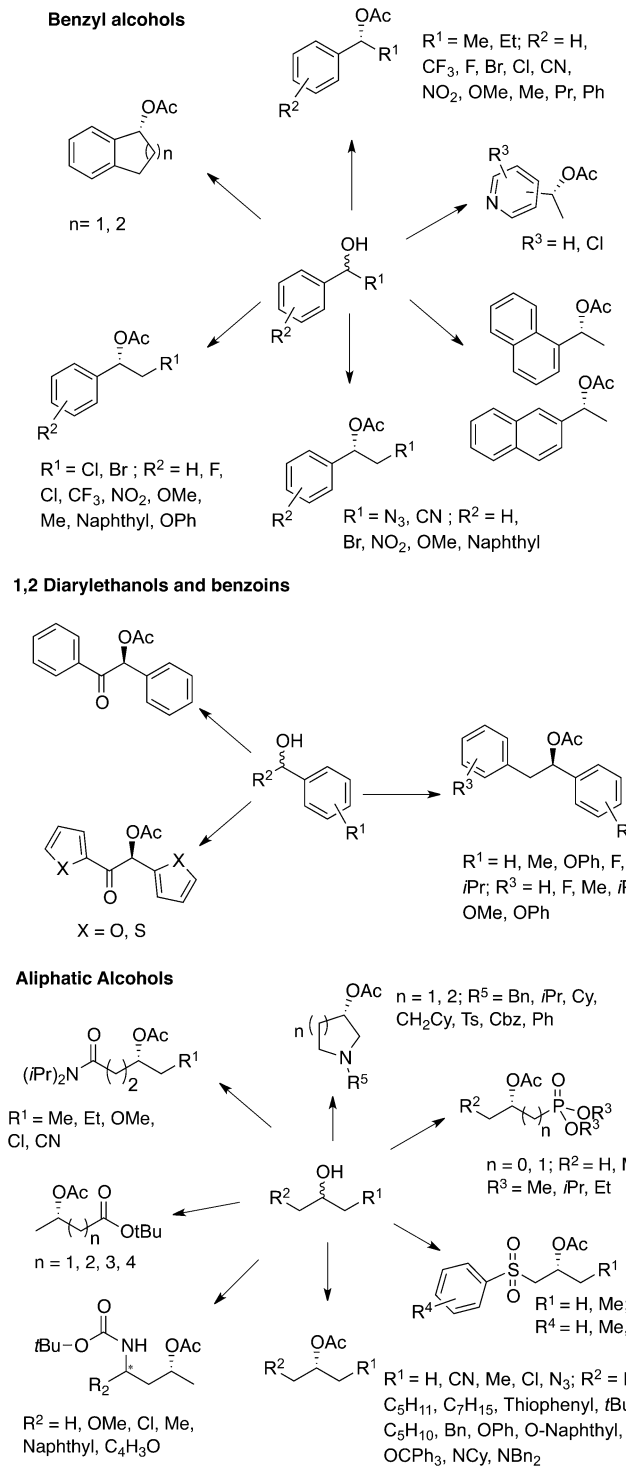


Figure 5. Alcohol scope in DKR.

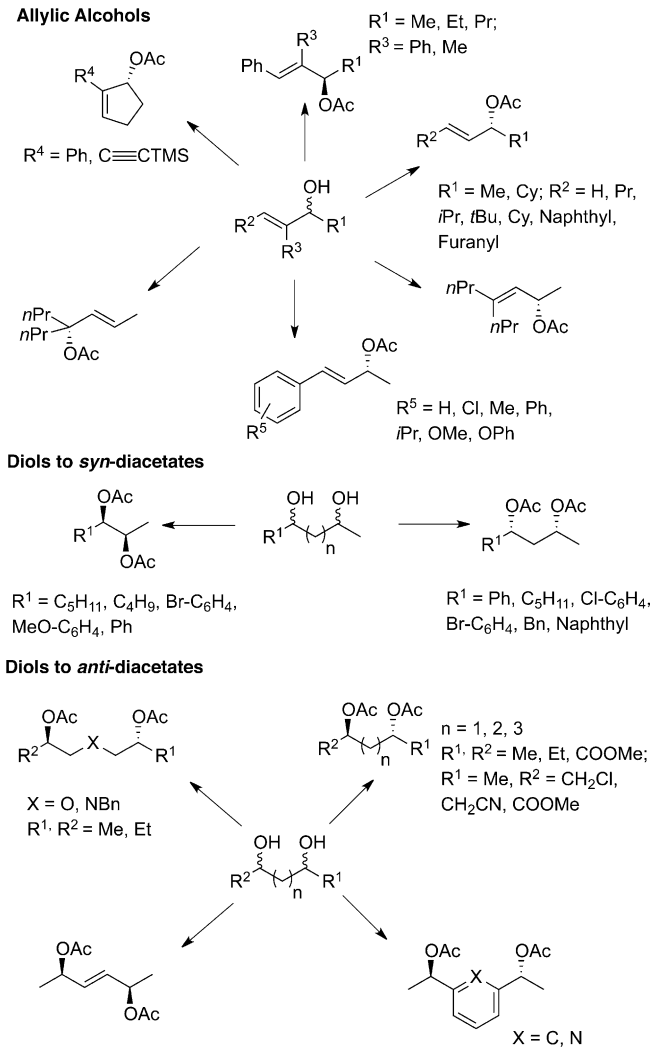
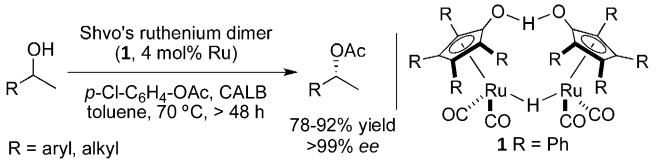


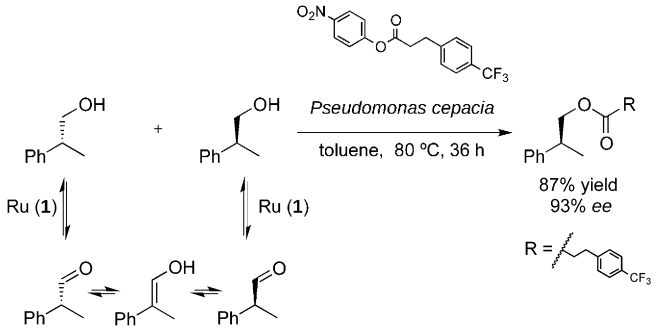
Figure 6. Alcohol scope in DKR.

for the racemization of *sec*-alcohols, which is incompatible with thermosensitive enzymes. Also, *p*-chlorophenyl acetate, which produced *p*-chlorophenol after acylation, was the optimal acyl donor, but this compound is less desirable from an environmental perspective. Other acylating reagents, such as isopropenyl acetate, could not be used because acetone produced after acylation interfered with the racemization process. Nevertheless, this process was successfully applied to a wide range of *sec*-alcohols, including hydroxy acids,[17a–c] β-azido alcohols,[17d] hydroxy esters,[17e] β-halo alcohols,[17f,g] β-hydroxy nitriles,[17h] β-hydroxy alkyl sulfones,[18] heteroaryl ethanols,[19] and diols.[14,20] DKR of primary alcohols mediated by Shvo's ruthenium complex has also been reported. Here, racemization occurs through enolization of the aldehyde intermediate derived from oxidation of the alcohol

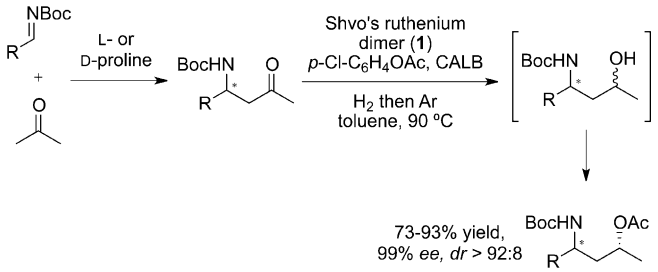


Scheme 4. DKR of *sec*-alcohols catalyzed by Shvo's complex and CALB.

(Scheme 5).[21] Recently, complex **1** was used in DYKAT of *sec*-alcohols functionalized with amino groups, providing a route to synthesize enantio- and diastereomerically pure 1,3-aminoalcohols, which were obtained with *ee* values exceeding 99% and in excellent yields of 73–93% (Scheme 6).[17i]



Scheme 5. Racemization mechanism in the DKR of primary alcohols.

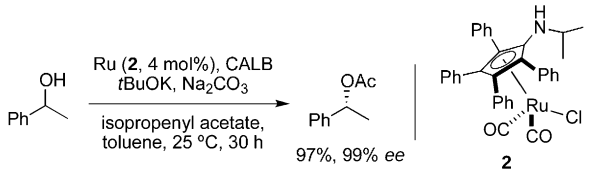


Scheme 6. DYKAT of γ-amino alcohols using Shvo's ruthenium complex.

The mechanism by which Shvo's complex racemizes *sec*-alcohols can be described in general terms as a dehydrogenation/hydrogenation sequence, such as that shown in Scheme 3. The mechanism has been studied in detail and reviewed recently by Warner, Bäckvall and Casey,[21] who discuss in detail possible mechanistic proposals, including inner- and outer-sphere pathways, based on experimental and theoretical evidence.

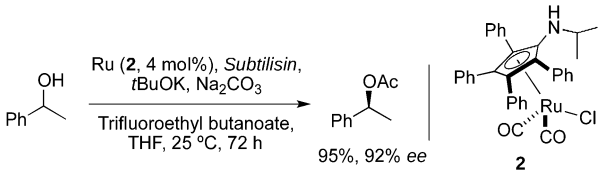
After the above-mentioned first successful reports on lipase- and ruthenium-catalyzed DKRs,[16] the process for the production of optically pure 1-phenylethanol was implemented industrially by DSM.[12]

To solve some of the drawbacks encountered in DKR mediated by Shvo's catalyst, Kim, Park and co-workers synthesized a novel aminocyclopentadienyl ruthenium chloride complex (**2**).[22] Remarkably, complex **2**, after its activation by potassium *tert*-butoxide, catalyzed the racemization of *sec*-alcohols at ambient temperature (Scheme 7). As a result, non-thermostable enzymes could also be used. Furthermore, acyl donors such as isopropenyl acetate were tolerated, since the acetone produced after acylation did not interfere with the racemization



Scheme 7. DKR of *sec*-alcohols at ambient temperature.

process at such mild temperatures (room temperature). Carbonate or molecular sieves were used to minimize the formation of acetic acid, produced by hydrolysis of the acyl donor. However, despite the high reaction rates of racemization (30 min) and KR (ca. 3 h) when performed independently, long reaction times were needed in the DKRs (from 31 h for 1-phenylethanol up to 7 days for other substrates). A plausible explanation is the poor compatibility of the two catalysts when combined in one pot. Nevertheless, catalyst **2** has been successfully used in a large number of DKRs of *sec*-alcohols,[23] including allylic alcohols, alkynyl alcohols, diols, hydroxy esters, and chlorohydrins. Furthermore, it was also used in combination with *Subtilisin*; a thermally labile protease that yields acylated products of the opposite configuration to those obtained with CALB (Scheme 8).[24] The performance of complex **2** in ionic liquids has been evaluated as well.[25a] Modifications of complex **2** by substituting the amine for oxygenated functional groups have resulted in several efficient new racemization complexes.[25b]



Scheme 8. DKR of *sec*-alcohols using a protease.

Aiming to improve the results obtained with the Shvo system (**1**), Bäckvall and co-workers synthesized a pentaphenylcyclopentadienyl ruthenium chloride (**3**).[26] The structure of this complex differed from that of **1** and **2** mainly in the nature of the substituents on the cyclopentadienyl ring: The last two catalysts contain a coordinating group (O or N, respectively) that can have an active role during the racemization mechanism (e.g., hydrogen bonding to the alcohol substrates),[21] whereas the cyclopentadienyl ligand in Bäckvall's catalyst (**3**) did not contain any heteroatom. As with complex **2**, Bäckvall's catalyst **3** required the addition of *t*BuOK to produce ruthenium alkoxides, which are the active catalytic species.[27] This Ru complex was the first catalyst that showed very high compatibility with the enzyme (Scheme 9). For instance, (*S*)-1-phenylethanol was racemized by **3** in less than 10 min and *rac*-1-phenylethanol was kinetically resolved

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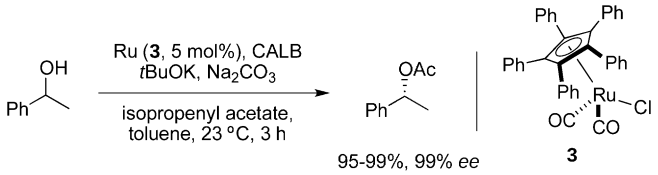
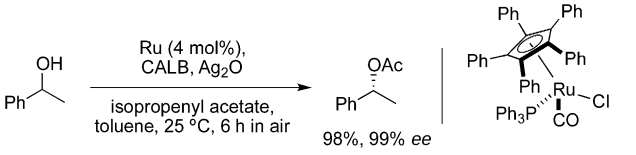


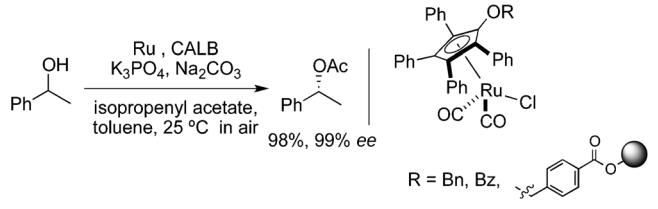
Scheme 9. DKR of *sec*-alcohols at ambient temperature in short reaction times.

by CALB in about 3 h. When the two processes were combined in one pot, DKR afforded the corresponding acetate in quantitative yield and >99% *ee* in only 3 h.[28] Complex **3** has been used with CALB and other enzymes in the DKR of several *sec*-alcohols,[28b,29,30] including β-hydroxynitriles,[28b] β-chloro alcohols[26a] (useful intermediates in the synthesis of several natural products, such as (*S*)-salbutamol[26b] or (*R*)-bufuralol[25c]), N-heterocyclic amino alcohols,[26c] aliphatic alcohols,[28,26a–e,30] allylic alcohols,[31] and diols[20d,28b,32] Also, it can be used in combination with a protease[10b,26c] and with a mutated variant of CALB[33] (see below). DKR of 1-phenylethanol was optimized to be applicable on a multigram scale by using only 0.05 mol% of Ru complex **3** (159 g of product obtained, 97% yield, 99% *ee*).[34]

Several modifications of this catalyst have been reported in recent years. By replacing one of the carbonyl groups in complex **3** with PPh_3, it was possible to carry out DKR of *sec*-alcohols at room temperature by using silver oxide instead of *t*BuOK as the activator under an air atmosphere (Scheme 10).[35] A ruthenacycle structurally related to **3** gave excellent results for DKR in the presence of K_3PO_4.[36] In addition, Kim, Park and co-workers designed and synthesized a series of ruthenium complexes that were stable under aerobic conditions, including an immobilized version[37] (Scheme 11), which was used in the synthesis of enantiopure (−)-rivastigmine.[38]

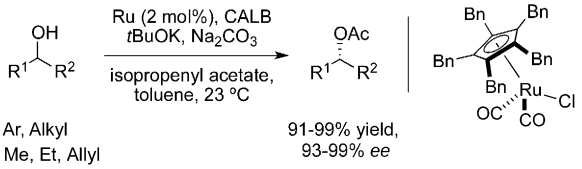


Scheme 10.



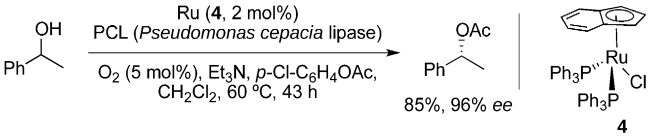
Scheme 11.

Leino, Kanerva and co-workers developed an analogous complex to **3** by replacing the phenyl substituents on the cyclopentadienyl ring with benzyl groups (Scheme 12).[39] This complex was an active racemization catalyst for the DKR of *sec*-alcohols, providing yields and enantioselectivities comparable to those obtained for the original complex **3**. It is noteworthy that this derivative could be prepared in a simple and high yielding manner. This catalyst was used in the synthesis of (*R*)-1-phenylethanol on a multigram scale (93% yield, 99% *ee*).[39c]



Scheme 12.

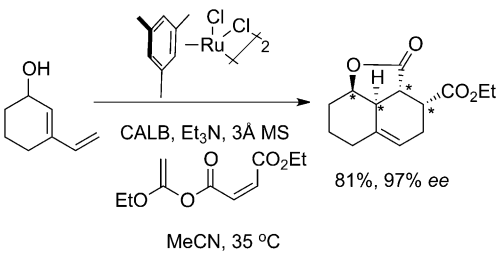
Another type of racemization catalyst, indenyl ruthenium complex **4**, was used with *Pseudomonas cepacia* lipase. Molecular oxygen was used to activate the ruthenium catalyst by oxidizing one of the phosphine ligands; thus facilitating the formation of the unsaturated 16-electron active catalyst (Scheme 13).[40]



Scheme 13.

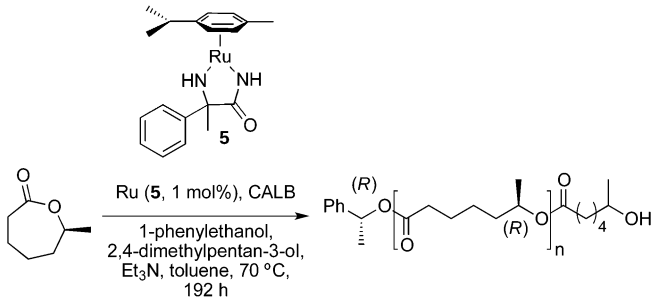
Arene–ruthenium derivatives were also active catalysts for racemizing *sec*-alcohols, including allylic alcohols, under mild conditions.[25a,41] For example, Kita and coworkers reported the first domino process that combined DKR of *sec*-alcohols with a Diels–Alder cycloaddition.[41b] This remarkable transformation affords tricyclic molecules with four stereogenic centers in excellent yields and enantioselectivities (Scheme 14).

In addition, Ru complexes formed from [{$RuCl_2$(*p*-cymene)}$_2$] and diamine ligands in combination with



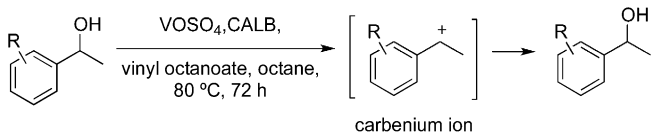
Scheme 14. Domino DKR/Diels-Alder.

2,2,6,6,-tetramethylpiperidine N-oxyl (TEMPO) as the co-catalyst have been successfully used in DKR of benzylic alcohols.[42] A [Ru(*p*-cymene)(diamide)] complex (**5**) was used to prepare enantioenriched oligoesters by DKR (Scheme 15).[43] The enzymatic ring opening of 6-methyl-ε-caprolactone was combined with a racemization step catalyzed by **5** using triethylamine as a base and 2,4-dimethylpentan-3-ol as an additive. The same catalyst system was used to synthesize optically active polyesters.[44]



Scheme 15. Iterative DKR to produce enantioenriched oligoesters.

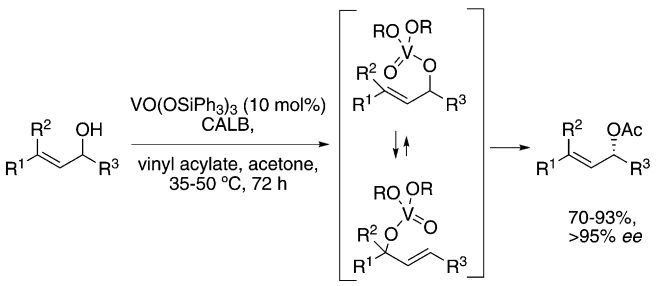
Complexes of other transition metals have been combined with KR of *sec*-alcohols catalyzed by CALB in a number of instances. For example, cyclopentadienyl iridium complexes with N-heterocyclic carbenes, [Cp*$Ir^{(III)}$-(NHC)], are effective catalysts in CALB-catalyzed DKR of *sec*-alcohols without the necessity for an additional base.[45,46] Also, vanadium complexes ($VOSO_4$ and V_2O_4) were used as racemization catalysts in DKR of benzylic alcohols,[47] using CALB and vinyl octanoate as the acyl donor (Scheme 16). The racemization occurred through carbenium ion intermediates.



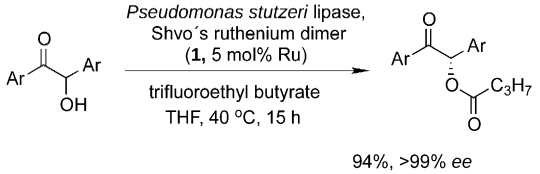
Scheme 16. DKR of alcohols using $VOSO_4$.

Oxovanadium(V) complexes [$VO(OR)_3$] and immobilized CALB for the DKR of allylic alcohols were used by Akai and co-workers.[48a,b] They proposed a mechanism involving the formation of allyl vanadate intermediates that undergo reversible 1,3-transposition, resulting in racemization.[48] The enzyme effects esterification to give optically active allyl esters (Scheme 17).

With a few exceptions, CALB is the enzyme used in most DKRs of *sec*-alcohols in combination with transition-metal catalysts. However, CALB is able to resolve only *sec*-alcohols carrying one small substituent (most often CH_3, CH_2CH_3) and one larger substituent (i.e., Ph, long aliphatic chains) at the hydroxymethine center (see also Figure 2). To perform DKR of alcohols with other substitution patterns, other enzymes have been used. For example, *Pseudomonas stutzeri* lipase efficiently catalyzes the KR of benzoins,[49] and works efficiently with Shvo's ruthenium complex **1** in DKR (Scheme 18). The same

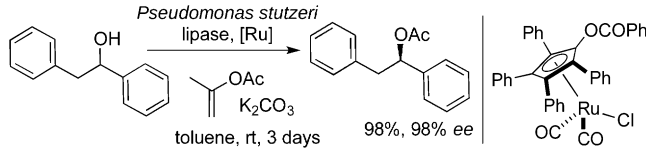


Scheme 17. Racemization through reversible 1,3-transposition in the DKR of allylic alcohols.

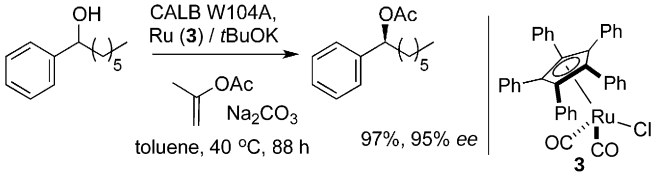


Scheme 18.

enzyme has been used in the DKR of 1,2-diarylethanols (Scheme 19).[37b] Also, a variant of CALB has been created by mutation in one of the residues that limits the size of the stereoselectivity pocket (CALB W104A). This mutant catalyzes the acylation of larger substrates than those tolerated by wild-type CALB. Interestingly, this mutated variant is (*S*)-selective in the acylation of *sec*-alcohols, including 1-phenylethanol (Scheme 20).[33] Another enzyme that acylates large substrates is *Pseudomonas cepacia* lipase (*Burkholderia cepacia* lipase), which was recently used with cyclopentadienyl ruthenium(II) complexes in DKRs of *sec*-alcohols.[50]



Scheme 19.



Scheme 20.

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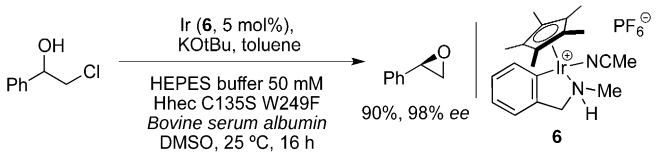
A different approach to deracemize *sec*-alcohols was used by Feringa, De Vries and co-workers, who employed haloalcohol dehalogenases to produce enantioenriched chiral epoxides from *rac*-β-haloalcohols.[51] The key to the success of this methodology was the use of a cationic half-sandwich iridacycle that catalyzed the racemization of *sec*-alcohols under the aqueous conditions needed for KR. A doubly mutated haloalcohol dehalogenase was used (Hhec C153S W249F). The mutations provided increased stability towards oxidation (Cys153Ser) and increased enantioselectivity for aromatic substrates (Trp249Phe; Scheme 21).

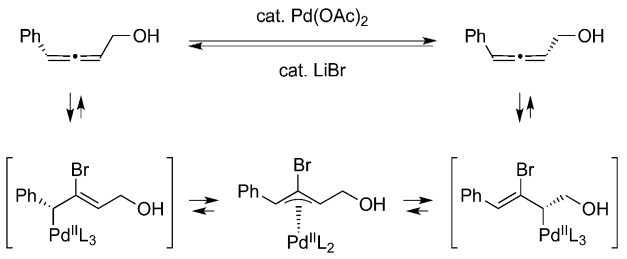


Scheme 21. DKR of β-haloalcohols.

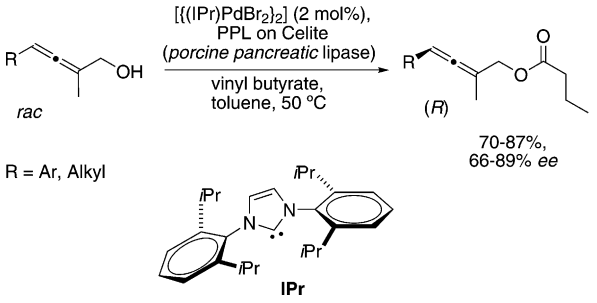
Although not catalyzed by transition-metal complexes, other metals such as aluminum have been used in successful DKRs of *sec*-alcohols.[52] Also, zeolites mediate the racemization of benzylic alcohols via carbenium ions.[53] This protocol was performed in a continuous reaction system using ionic liquids and supercritical CO_2.[53d]

3. DKR of Allenes

DKR of allenes is conceptually different. Allenes are an important class of axially chiral compounds. In 2004, Bäckvall and Horváth reported an efficient method to racemize this kind of compound.[54] The mechanism proposed involves a bromopalladation–debromopalladation sequence, in which π-allyl Pd(II) intermediates are key intermediates (Scheme 22). A few reports exist on the KR of axially chiral racemic allenic alcohols using enzymes such as porcine pancreatic lipase (PPL).[55] However, only a single example of DKR has been reported by Bäckvall and co-workers, who elegantly achieved this transformation by using NHC–palladium(II) complexes.[56] In combination with PPL, allenyl butyrates



Scheme 22.



Scheme 23. DKR of axially chiral allenes with NHC–palladium catalysts.

were synthesized in good to high yields and enantioselectivities of up to 89% *ee* (Scheme 23).

4. DKR of Amines

Enantiomerically pure amines are widely used as building blocks in synthetic organic chemistry and they are commonly encountered in a large number of pharmaceuticals. There are numerous examples of chiral amine syntheses by KRs. Despite this, only a few examples of successful amine DKRs have been reported, most of them during the last few years.[2] This is partly due to more difficult and less efficient racemization of this type of substrates compared with that of alcohols. Racemization of amines usually requires high temperatures. This limits the number of enzymes that can be used in DKR, since most of them only work at physiological temperature and may undergo thermal denaturing at higher temperatures. Additionally, in some cases, acidic media are used to protonate the imine intermediates formed during racemization,[57] and this can affect the enzyme activity. Nevertheless, several substituted chiral amines have been prepared by DKR mediated by enzyme and metal catalysis. Figure 7 shows the structure of benzylic, aliphatic, and cyclic amines that have been successfully subjected to DKR.

Early examples of the DKR of amines were developed through the use of palladium-based catalysts in 1996.[58] CALB was used in the presence of ethyl acetate as the acyl donor with moderate results. KR and racemization were performed in successive steps. In 2002, Bäckvall and co-workers improved these first results for primary amines by using Shvo's ruthenium complex (**1** in Figure 4; R = Ph) as the catalyst.[59] This process was also carried out in a two-step manner. A few years later, a breakthrough was reported by Bäckvall and Paetzold, who achieved the DKR of primary unfunctionalized amines by combining KR and racemization in the same pot (Scheme 24).[60] The key to success was the use of a Shvo-based ruthenium catalyst with electron-donating substituents on the cyclopentadienyl rings (**1**; R = *p*-MeO-

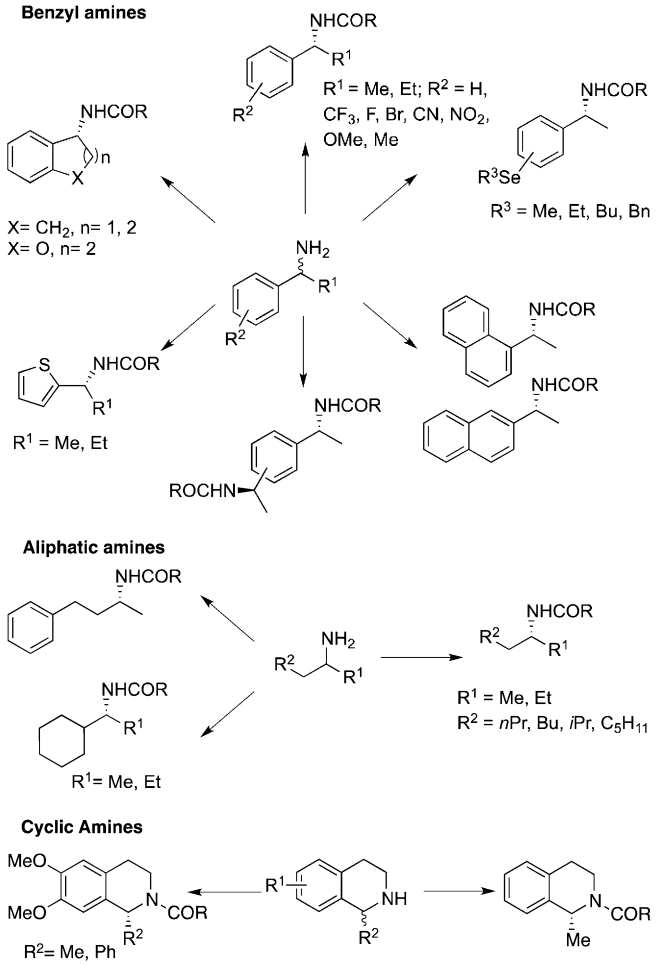
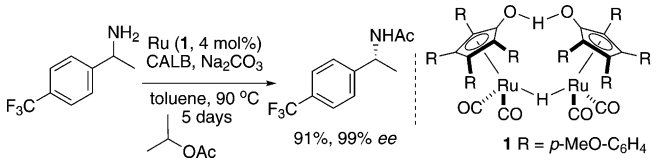
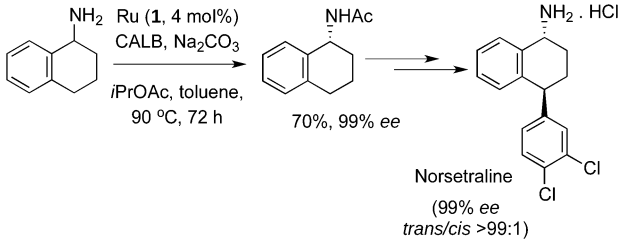


Figure 7. Substrate scope in the DKR of amines.



Scheme 24.

C_6H_4). It was proposed that this electron-rich complex increased the rate of hydrogenation of the imine intermediates. As in DKR of alcohols, the addition of base (Na_2CO_3) was necessary. The first examples were performed by using *i*PrOAc as the acyl donor. Later, this was replaced by dibenzyl carbonate, which improved the enantioselectivity and provided a method to prepare free amines, since the benzyloxy carbonyl group in the product can be easily removed under mild reaction conditions.[61] The highly efficient methodology was applied to a broad family of primary benzylic amines containing various functional groups (F, Cl, Br, NO_2, CF_3) and also to aliphatic amines.[62] The efficiency of the process was demonstrated in a multigram experiment, in which *rac*-1-phenylethylamine (5.45 g) was transformed into (*R*)-2-methoxy-*N*-1-phenylethyl acetamide (83% isolated yield and 98% *ee*) by using low ruthenium loadings (1.25 mol% of **1**; R = *p*-MeO-C_6H_4).[63] DKR under similar reaction conditions (CALB and **1**; R = *p*-MeO-C_6H_4) was used as the key step in the synthesis of norsetraline, which is a selective serotonin reuptake inhibitor (Scheme 25).



Scheme 25.

Several examples exist where heterogeneous transition-metal complexes are used in the DKR of amines. In 2005, Jacobs and co-workers reported the use of palladium supported on alkaline earth salts together with CALB in the DKR of a wide range of primary amines (Scheme 26),[64a] including aliphatic[64b] and selenium-containing amines.[64c] To improve the racemization reaction, microwave irradiation was used as a heating source.[64d] The same group also reported the DKR of 1-phenylethylamine (93% yield, 99% *ee*) using palladium supported on amine-functionalized silica and CALB.[64e]

Scheme 26.

Kim, Park and co-workers used palladium nanoparticles entrapped in an AlO(OH) matrix as a highly active racemization catalyst in amine DKR.[65a,b] It was possible to recycle both the enzyme and metal catalysts ten times without significant loss in their activities.

De Vos and co-workers reported that heterogeneous Raney nickel and CALB afforded good results in the DKR of aliphatic amines.[64f]

While there are several examples of DKR protocols for primary amines, there are few examples of the DKR of secondary amines. Page and co-workers reported an efficient protocol for these substrates under mild reaction conditions (40 °C) by using *Candida rugosa* lipase and a pentamethylcyclopentadienyl iridium iodide dimer as the racemization catalyst.[66a] A 10 g scale reaction was

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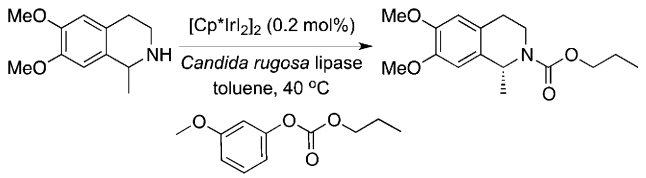


Scheme 27.

carried out with only 0.2 mol% of Ir complex (Scheme 27).[66b]

Amino acid derivatives are easily racemized and have been resolved through DKR processes (Figure 8).

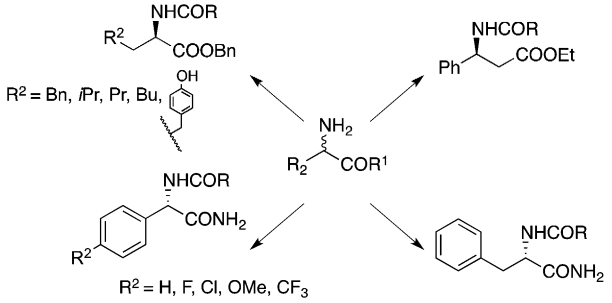
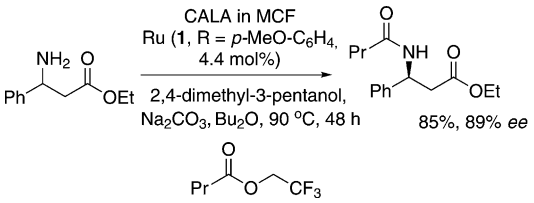


Figure 8. DKR of amino acid derivatives.

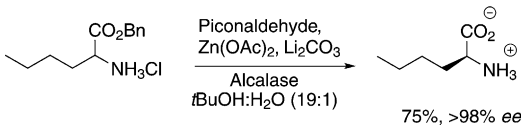
Bäckvall and co-workers applied the Shvo's complex in combination with CALB to the DKR of β-amino acid esters with good results.[67] The enantioselectivity of this procedure was dramatically improved when using CALA immobilized in mesocellular foam (MCF). Immobilization significantly enhanced the stability of the enzyme at high temperatures (Scheme 28).



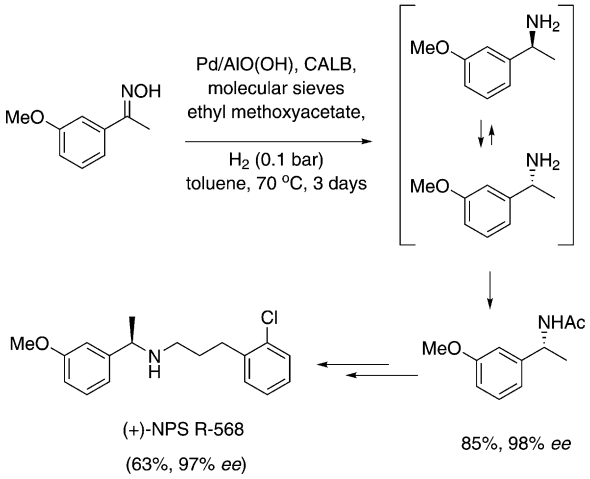
Scheme 28.

Aron and co-workers used zinc complexes of piconaldehyde in combination with alcalase in the DKR of amino acid esters. Lithium carbonate was added to maintain the enzyme activity.[68] Aromatic and aliphatic γ-branched compounds were resolved with enantioselectivities of up to 98% *ee* (Scheme 29).

Amino acid amines were converted into optically active amino acid derivatives by using Pd nanoparticles/AlO(OH) and CALB by Kim, Park and co-workers.[65c] The same system, Pd/AlO(OH), was also effective in the DKR of benzyl ketoximes,[65d] and this methodology



Scheme 29.



Scheme 30. Synthesis of (+)-NPS R-568 using Pd/AlO(OH) and CALB.

could be applied to the synthesis of calcimimetic compound (+)-NPS R-568 (Scheme 30).[65e]

5. Summary

DKR catalyzed by enzymes and transition-metal complexes as a method to prepare optical pure alcohols and amines has been discussed. Several transition-metal complexes have been used in combination with a variety of enzymes. Great efforts have been made to increase the compatibility of the two catalysts in one pot. The majority of early examples focused on DKRs of *sec*-alcohols, which were usually performed under mild reaction conditions. In general, the racemization of amines requires higher reaction temperatures and the number of enzymes that can be used is rather limited. However, in recent years, excellent catalytic systems applied to the DKR of amines have been discovered, and many of them use heterogeneous catalysts. Furthermore, transition-metal- and enzyme-catalyzed DKRs have been employed in the synthesis of a variety of natural products and large-scale examples have shown the applicability of this methodology. The great advances achieved recently in enzyme engineering will enable the scope of DKRs to be broadened, in particular, helping the resolution of highly substituted molecules. Also, as demonstrated in one example, enzyme engineering can help to reverse the enantioselectivity of a particular enzyme; thus providing a method to access both enantiomers of the product. Finally, the use

of environmentally friendly transition-metal complexes, such as iron, would make DKRs highly attractive from an industrial perspective.

Acknowledgments

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