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Chemoenzymatic dynamic kinetic resolution

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During the past decade a new concept has appeared in asymmetric catalysis involving the combination of a biocatalyst and a chemocatalyst in one 'pot' leading to efficient deracemization via dynamic kinetic resolution (DKR). Here, we outline the different strategies that have been developed for efficient chemoenzymatic DKR, in particular the powerful combination of an enzyme and a metal catalyst.

During the past 30 years there has been an increasing demand for enantiomerically pure compounds for fine chemicals (i.e. agrochemicals and pharmaceuticals) and material science (i.e. liquid crystals and polymers). To date, the kinetic resolution of a racemate is still one of the major methods for the production of enantiomers on an industrial scale. However, the maximum theoretical yield of 50% in this method is too low to allow a positive economic and environmental balance for such transformations. To overcome this limitation different strategies have been developed that allow the transformation of both enantiomers of a racemate into a single enantiomer of the product. These strategies include the dynamic kinetic asymmetric transformation (DYKAT), stereoinversion, cyclic deracemization, enantioconvergent transformation and dynamic kinetic resolution (DKR) (reviewed in [1]). Of all these methods, DKR (Figure 1) is perhaps the one that has advanced most in recent years (for recent reviews see [2–5]). In this process the *R* and *S* enantiomers that react at different rates, k_R and k_S, are in equilibrium with one another and therefore the product P can be obtained optically pure in 100% yield. The obvious basic requirements for an efficient DKR are that an efficient kinetic resolution (KR) and an efficient racemization method have to be chosen. Moreover, the compatibility between both processes is crucial for the success of the DKR process.

In recent years the use of biocatalysis in organic synthesis has become an attractive alternative to conventional chemical methods. In particular, the use of enzymes in organic solvents [6] to promote an efficient KR of a racemate has been extensively applied [7]. Therefore, the number of examples of chemoenzymatic DKR that combine the enzymatic KR with an *in situ* racemization method has increased during the past few years. This review covers the most successful chemoenzymatic DKR strategies developed to date.

Chemoenzymatic DKR with classical racemization methods

Since the early 1990s, several non-metallic (classical) racemization methods have been combined with an enzymatic KR. The easiest and perhaps the most common approach is to combine an enzyme with an *in situ* base-catalyzed racemization. Because enzymes are usually stable at pH values close to 7, this strategy has been limited to substrates possessing a stereogenic center having an acidic proton (e.g. α-substituted carboxylic acid derivatives and α-substitued ketones). This approach has been extensively applied in combination with microbial reduction (for examples see [8–10]). However, in recent years successful chemoenzymatic DKRs have been obtained when combined with microbial oxidations and lipase-catalyzed transesterifications [11–14] (Figure 2).

An efficient DKR process has been developed for the deracemization of chemically labile secondary alcohols, thiols and amines (i.e. cyanohydrins, hemiacetals, hemiaminals and hemithioacetals) [15–16] (Figure 3a). This procedure takes advantage of the fact that these compounds are prone to racemization via dissociation-recombination under mild conditions.

More recently, a new 'classical' chemoenzymatic DKR approach has been developed by combining an enzyme with the *in situ* racemization via nucleophilic displacement [17–19]. This method is not yet widely used and is based on the nucleophilic substitution of a secondary organohalide by the same halide. Thus, this DKR procedure has been used for the deracemization of α-halo esters by enzymatic hydrolysis and aminolysis. A recent example is the efficient DKR of ethyl 2-chloropropionate [92% yield, 86% enantiomeric excess (ee)] achieved via

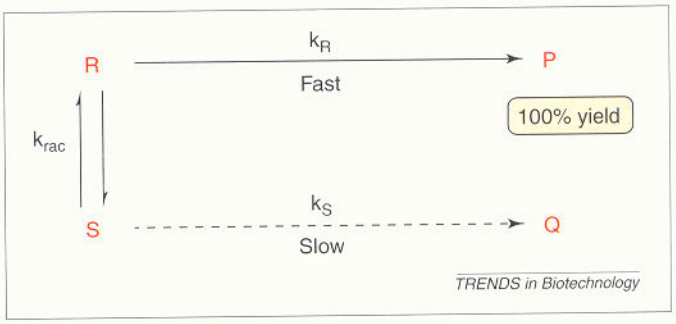

Figure 1. Schematic representation of a dynamic kinetic resolution (DKR). R and S represent the two enantiomers of the starting material; P and Q represent the two enantiomers of the product. Abbreviations: k_{rac}, rate constant for racemization; k_R, rate constant for reaction of R isomer; k_S, rate constant for reaction of S isomer.

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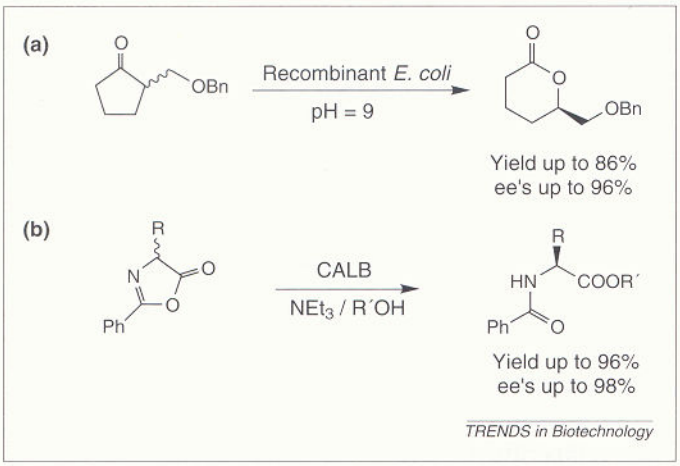


Figure 2. Recent examples of dynamic kinetic resolution (DKR) in which the base-catalyzed racemization is combined with **(a)** microbial Baeyer–Villiger oxidation and **(b)** lipase-catalyzed transesterification. Abbreviations: Bn, benzyl; CALB, *Candida antartica* lipase B; NEt_3, triethylamine; Ph, phenyl.

Candida cylindracea lipase aminolysis in the presence of supported triphenylphosphonium chloride [19].

A new approach for chemoenzymatic DKR has recently been reported by Sheldon *et al.* in the lipase-catalyzed aminolysis of phenylglycine methyl ester [20]. In this method the amino ester was racemized via Schiff base formation with pyridoxal- or salicylaldehyde.

Chemoenzymatic DKR with metal-catalyzed racemization

In recent years a new concept in chemoenzymatic DKR has been developed in which a racemate is deracemized by combining an enzymatic kinetic resolution and an *in situ* metal-catalyzed racemization. Although transition metals catalyze many reactions under mild conditions, their use for the racemization of different substrates has been almost neglected [21]. To date, there are two general metal-catalyzed racemization methods that have been applied in combination with the enzymatic KR: (i) racemization via hydrogen transfer and (ii) racemization via π-allyl complex formation (Figure 3b).

Racemization via hydrogen transfer

Transition metal-catalyzed racemization via hydrogen transfer has recently been used for the racemization of secondary alcohols and amines. The DKR of secondary alcohols based on this principle has become a powerful approach for the preparation of enantiomerically pure alcohols. Research in this area was initiated by the groups of Williams and Bäckvall [22–24]. Williams combined the alcohol racemization by different metal complexes as catalysts in the presence of stochiometric amounts of ketone and base with *Pseudomonas fluorescents* lipase-catalyzed transesterification of 2-phenylethanol using vinyl acetate as the acyl donor. Although the best results were moderate (60% yield with 98% ee), they demonstrated that the combination of both enzyme and metal catalyst is feasible [22].

Bäckvall and coworkers developed an efficient system for racemization based on the use of a ruthenium catalyst $[Ru_2(CO)_4(\mu\text{-}H)(C_4Ph_4COHOCC_4Ph_4)]$ and *p*-chlorophenyl acetate as acyl donor. Thus, an efficient DKR of secondary alcohols was obtained by combining the *Candida antarctica* lipase B (CALB) with the above mentioned acyl donor and ruthenium catalyst (78–92% yield with >99% ee) [23,24].

The main advantages of this system are:

(i) the acyl donor is fully compatible with the ruthenium catalyst. This is an important advantage over other acyl donors, such as alkenyl acetates, widely used in lipase-catalyzed transesterifications. The use of these acyl donors results in the formation of aldehydes or ketones after the acyl transfer process, which can interfere with the hydrogen transfer catalyst employed in the DKR. However, it has recently been shown that commercially available isopropenyl acetate can also be used, with similar results for the DKR of secondary alcohols, but an appropriate hydrogen source (H_2, formic acid or a secondary alcohol) for depressing the ketone formation is needed.

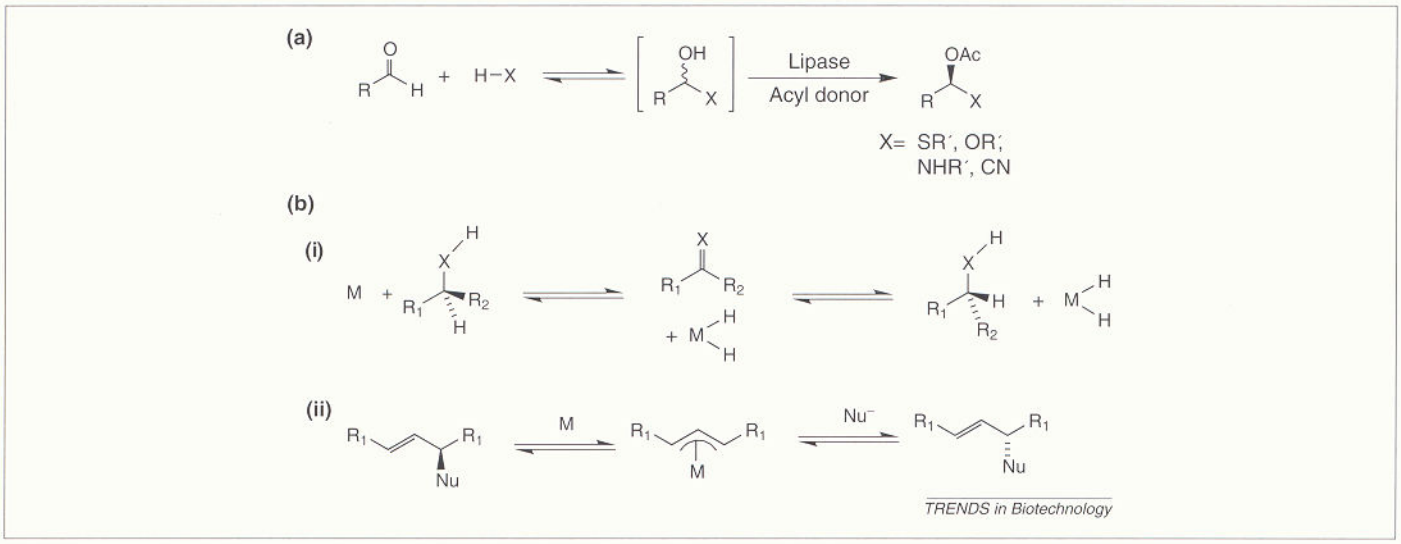


Figure 3. Combination of lipase-catalyzed transesterification with an *in situ* racemization via dissociation-recombination for an efficient dynamic kinetic resolution (DKR) process **(a)** and general metal-catalyzed racemization methods that have led to an efficient dynamic kinetic resolution (DKR) when combined with an enzyme **(b)**. Reaction (i) represents racemization of alcohols and amines (X=O or NH). Reaction (ii) represents racemization of allylic substrates (Nu can be an acetate or a nucleophile with a weak carbon–nucleophile bond in the allylic position. Abbreviations: AcO, acetate; M, metal; Nu, nucleophile.

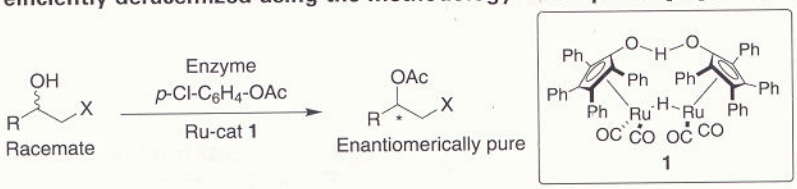
(ii) the ruthenium catalyst $[Ru_2(CO)_4(\mu\text{-}H)(C_4Ph_4COHOCC_4Ph_4)]$ does not require the addition of an external base because one of the oxygens of the catalyst acts as a basic center [25]. This is important for an efficient DKR because the presence of an external base can cause side reactions with the substrates and/or products [26,27] and affect the performance of the enzyme [7].
(iii) addition of the corresponding ketone for the racemization is not required. This is of great importance for the economy of the process.

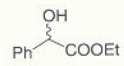
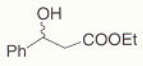
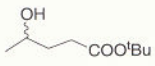
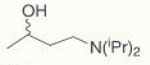
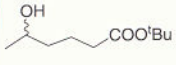
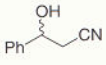
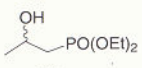
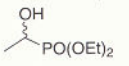
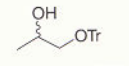
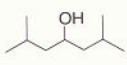
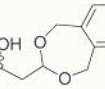
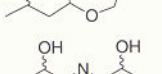
This method has also been applied to the DKR of different functionalized alcohols that are useful building blocks for asymmetric synthesis. Thus, efficient DKR protocols have been developed for hydroxyl-acid derivatives [27–31], hydroxy nitriles [32,33], halo alcohols [26], azido alcohols [34], hydroxy phosphonates [35] and protected 1,2-diols and hydroxy aldehydes [31] (Table 1). In general, good yields and excellent enantioselectivities were obtained. However, the addition of an appropriate hydrogen source was needed in some cases to prevent ketone formation. This usually resulted in an increase in yields of the corresponding acetates. Similarly, this protocol has also been applied to the DYKAT of secondary symmetrical diols (as a mixture of all isomers) with good yields and excellent diastereo- and enantio-selectivities [36,37].

Other groups have also applied the Williams–Bäckvall method to test ruthenium-catalyzed racemization catalysts for the DKR of alcohols [38–42]. For example Kim and coworkers showed that the combination of $[Ru_2Cl_2(\mu\text{-}Cl)(\mu\text{-}H)(p\text{-cymene})_2]$ as racemization catalyst and *Pseudomonas* species lipase as biocatalyst can deracemize allylic alcohols (up to 88% yield and 99% ee) in the presence of triethylamine in dichloromethane at room temperature [39].

The recent work of Kim and coworkers [40] and Verzijl and coworkers [42] is particularly noteworthy. Kim's group recently reported a novel ruthenium catalyst, $[RuCl(CO)_2(C_4Ph_4NH^i_2Pr)]$ capable of racemizing secondary

Table 1. Various substrates efficiently deracemized using the methodology developed in [23] and [24][a]



Substrate	Enzyme	Additive	Yield	ee
	*Pseudomonas cepacia* lipase	–	74%	96% (*S*)
	*Pseudomonas cepacia* lipase	–	76%	95% (*R*)
	*Pseudomonas cepacia* lipase	H_2 (1 bar)	70%	94% (*R*)
	*Pseudomonas cepacia* lipase	–	93%	98% (*R*)
	*Pseudomonas cepacia* lipase		92%	98% (*R*)
	*Candida antarctica* lipase B		85%	97% (*R*)
	*Pseudomonas cepacia* lipase	–	93%	95% (*S*)
	*Candida antarctica* lipase B	–	94%	> 99% (*S*)
	*Candida antarctica* lipase B	–	69%	> 99% (*R*)
	*Candida antarctica* lipase B	–	86%	> 99% (*R*)
	*Pseudomonas cepacia* lipase		96%	> 99% (*R*)
	*Candida antarctica* lipase B	–	90%	96% (*R*)
	*Candida antarctica* lipase B	–	78%	99% (*R,R*)

[a]Abbreviations: AcO, acetate; ee, enantiomeric excess; Et, ethyl, ^{i}Pr, isopropyl, Ph, phenyl; ^{t}Bu, tertiary butyl; Tr, triphenylmethyl.

alcohols at room temperature, whereas Verzijl's group have developed the first large-scale DKR application for the preparation of enantiomerically pure acetates.

The combination of enzymes with a metal-catalyzed racemization via hydrogen transfer has also been successfully applied to deracemization of secondary amines. Research in this area was initiated by Reetz and coworkers [43]. The combination of immobilized CALB as the biocatalyst and palladium on carbon (Pd/C) as the racemization catalyst was used for the deracemization of 1-phenylethylamine. The racemization step, which proceeds via an amine–imine equilibrium promoted by palladium(0) is slow and therefore the reaction proceeds slowly (64% yield after eight days). Moreover, the formation of large amounts of by-products was observed.

Kim and coworkers improved the efficiency of the combined palladium–CALB DKR process by using ketoximes as starting materials in the presence of hydrogen, diisopropylamine and ethyl acetate in toluene at 60 °C. Under these conditions, a series of benzylic ketoximines were transformed into the corresponding optically active acetamides with good yields and high enantioselectivity after five days [44].

Bäckvall and coworkers recently reported an efficient ruthenium-catalyzed racemization of amines under hydrogen transfer conditions [45]. An important feature of this new procedure is that the ruthenium hydrogen transfer catalyst allows high functional group tolerance and that it proceeds with an unusually high recovery of razemized amine (95–99%). This procedure was applied for recycling the unreacted enantiomer after the enzymatic KR. Attempts to combine this racemization method with the *in situ* enzymatic resolution were unsuccessful because of the denaturation of the enzyme at the temperature required for an effective racemization.

Racemization via π-allyl formation

Racemization via π-allyl–palladium complexes is well known and the most common example of this method is the racemization of allylic esters with Pd(0) catalysts. The reaction mechanism can proceed via different mechanisms [46,47] and this approach has been used in combination with an enzyme for the deracemization of allylic acetates.

Williams and coworkers reported the first example of the chemoenzymatic DKR of allylic acetates using a lipase as biocatalyst and a palladium(II) complex as the racemization catalyst [48]. In this procedure a cyclic allylic acetate is deracemized via lipase-catalyzed hydrolysis in phosphate buffer at ~40 °C, and the unreactive enantiomer is racemized with a $PdCl_2(MeCN)_2$ complex (Figure 4a). This approach proved to be limited because only 2-phenyl-2-cyclohexenyl acetate and methyl 5-(acetoxy)-3-cyclohexene-1-carboxylate were properly deracemized. Moreover, the reaction time is long (typically more than two weeks) because of the slow palladium racemization process.

Kim and coworkers improved the DKR of allylic acetates by introducing a conceptually similar but chemically different strategy to that developed by Williams and coworkers. They combined the lipase-catalyzed transesterification with the Pd(0)-catalyzed racemization in tetrahydrofuran (Figure 4b) [49]. For this purpose, they used 2-propanol as the acyl acceptor and the unreactive enantiomer was racemized by $Pd(PPh_3)_4$ (with added diphosphine) at room temperature. Under these conditions, a series of linear allylic acetates were deracemized in high enantiomeric excess (97–99% ee) and with moderate to good isolated yields (61–78%).

With the methodology discussed in this review the enzyme transforms one enantiomer (the reactive enantiomer) while the non-reacting enantiomer is isomerized to the reactive one. With this principle the absolute configuration of the product (*R* or *S* configuration) will depend on the selectivity of the enzyme. All known lipases used in transesterification favour the same enantiomer (usually the *R*-enantiomer) and this would seem to limit the DKR for preparation of this isomer. However, Kim and Park recently reported DKR with the use of a protease for transesterification (subtilisin) that transforms the opposite enantiomer (*S*-enantiomer) to that transformed by lipases (*R*-enantiomer) [50] so either enantiomer is accessible with chemoenzymatic DKR.

Concluding remarks

The combination of enzyme catalysis (for the resolution of a racemate) and chemo catalysis (for the racemization of the slow-reacting enantiomer) is powerful for obtaining

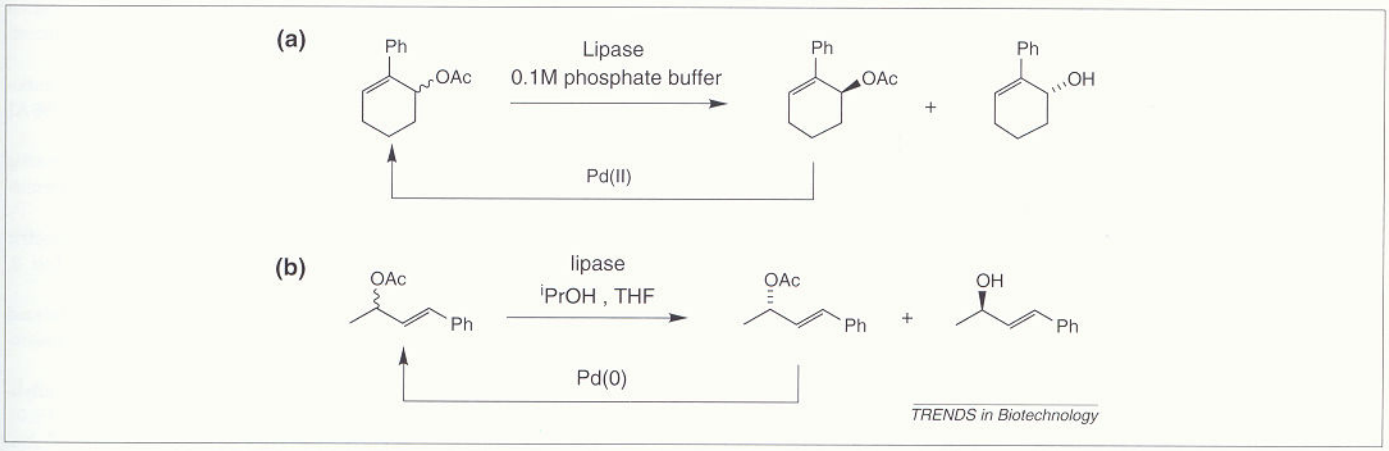


Figure 4. Different approaches for the dynamic kinetic resolution (DKR) of allylic acetates. Abbreviations: AcO, acetate; ^{i}Pr, isopropyl; Ph, phenyl; THF, tetrahydrofuran.

successful DKR processes. The high efficiency of these processes makes them an attractive alternative to existing methods in asymmetric catalysis.

Acknowledgements
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