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Review

Approaches based on enzyme mediated kinetic to dynamic kinetic resolutions: A versatile route for chiral intermediates

Ahmed Kamal *, M. Ameruddin Azhar, Tadiparthi Krishnaji, M. Shaheer Malik, Shaik Azeeza

Biotransformation Laboratory, Division of Organic Chemistry, Indian Institute of Chemical Technology, Hyderabad 500 007, India

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Contents

Abstract

The synthesis of enantiomerically pure compounds employing new and efficient methods has emerged as an active area of research in the recent past. In spite of the development of many asymmetric catalytic methods, the resolution of racemic mixtures i.e., kinetic resolutions are preferred industrially. The only drawback of kinetic resolution is that a maximum of fifty percent of starting material can be utilized, and the other enantiomer is usually not utilized. This limitation has been addressed in many cases by coupling the acylation of one enantiomer with a racemization reaction

* Corresponding author. Tel.: +91 40 27193157; fax: +91 40 27193189.
E-mail addresses: ahmedkamal@iict.res.in, ahmedkamal@iictnet.org (A. Kamal).

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for the *in situ* conversion of the undesired enantiomer to the desired products. Therefore a combination of lipases with transition metals or other related racemizing agents resulted in a single enantiomer. This process is termed 'dynamic kinetic resolution' and has been a focus of research in recent years towards asymmetric synthesis.

This review enlightens the changing trends from kinetic resolution to the development of dynamic kinetic resolution, with an emphasis on the chiral intermediates of biological significance and the type of catalysts used along with the enzymes in such processes.

Keywords: Enzymes; Dynamic kinetic resolution; Metal catalysts; Chirality; Enantiomeric excess

1. Introduction

Enantiomerically pure compounds have become the focus of research today. This may be attributed to an increasing demand of enantiomerically pure compounds for fine chemicals [1–3] (agrochemicals and pharmaceuticals) and material sciences (ligands and polymers). This has mainly been driven by the release of new FDA marketing guidelines [4]. In spite of a number of advances made in asymmetric synthesis, substrate driven or catalyst driven resolution of racemates emerged as a method of choice and remains so both in academia as well as in industry [5–8].

The resolution of racemates employing enzymes has become an important tool for obtaining chiral compounds of biological significance [9]. Lipases are amongst the most commonly used enzymes for kinetic resolution of racemates as they can be obtained commercially from an appropriate source on a required scale [10]. Further, combination of enzymes with metal catalysts is another important development for dynamic kinetic resolution strategies. Several reviews have appeared in the literature on lipase mediated resolution processes [9–14] including the combination of enzymes and metal catalysts as an approach for asymmetric synthesis [15–18]. However this review discusses the utilization of enzymes for chiral synthesis particularly the application of lipases with respect to the type of reactions which later lead to the development of dynamic kinetic resolution processes. Further, the recent observations that have taken place in this laboratory have also been included. Moreover an effort has also been made in the present review to highlight the recent trends particularly in the last decade that have taken place in this area.

1.1. Kinetic resolution

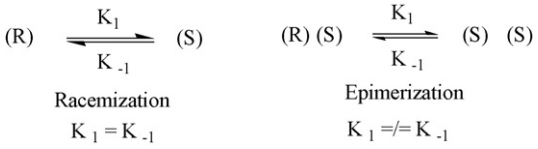
Kinetic resolution is a process in which one of the enantiomers of a racemic mixture is more readily transformed into a product than its mirror image. The main requirement of this process is that the $K_R \neq K_S$ where *R* and *S* are enantiomers of the given compound.

If the chiral catalyst of biological origin (usually enzymes) is used then the process is called as an enzymatic kinetic resolution or a biocatalytic resolution. In recent years extensive research has been carried out in this area of biocatalytic resolution processes. In enzymatic kinetic resolutions a racemic substrate undergoes an enzymatic reaction wherein chiral discrimination of enantiomers take place. In few cases, wherein the difference in the rate of reaction of enantiomers is very large, then only one enantiomer is transformed and the reaction when reaches around 50% conversion provides both the enantiomers in their optically pure forms. However in a number of cases this difference may not be that large as such the reaction further proceeds as a slow process, thereby decreasing the enantioselectivity.

Several kinetic resolution processes have been reported in the literature which utilize enzymes as the chiral catalysts. There are advantages for these processes such as higher reaction rates up to 10^{12} times (compared to chemical methods), improved efficiency, higher chemo-, regio- and enantioselectivity. Moreover, from the environmental context, biocatalytic processes are greener, less hazardous and least polluting. Amongst the very large collection of enzymes, lipases (triglycerol acyl hydrolases) have emerged as one of the most suitable enzymes for kinetic resolution processes in asymmetric synthesis. Some of the advantages of using lipases are that, they do not require cofactors, many lipases are available in free and immobilized form, and could be produced in large quantities. Most lipases can accept a broad range of non-natural substrates and are thus very versatile for applications in organic synthesis. Therefore, lipases have been used widely in a number of reactions for producing enantiomerically pure compounds. These processes could be broadly classified into two types that include asymmetrization of *meso*- and prochiral compounds and kinetic resolution of racemates. From a chemical point of view, lipases (also proteases) can be considered as mild and selective reagents that are able to activate a generic carboxylate and transfer it to a large number of nucleophiles in different organic solvents. Apart from the application of lipases in organic synthesis, there have been extensive studies on the improvement of selectivity as well as the rate of reaction by varying solvents, acyl donors, temperature etc. More recently the use of lipases in non-aqueous media has been extended to include supercritical fluids [19,20] and ionic liquids [21], which has been applied successfully in this laboratory towards the synthesis of enantiomerically pure 1,2-diols [22].

1.2. Dynamic kinetic resolution

Kinetic resolutions, in spite of their high utility possess an intrinsic limitation of maximum of 50% conversion. To overcome this limitation several approaches have been attempted, while dynamic kinetic resolution (DKR) involving a racemization reaction for the *in situ* conversion of undesired enantiomers has received considerable attention in the recent years. This process has been discussed in some recent reviews.



Scheme 1.

The following aspects are required for an efficient DKR process:

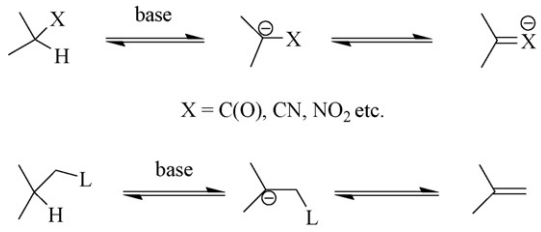
(i) The kinetic resolution step has to be irreversible.
(ii) *E* value has to be at least 30, preferably in the range of 50–100.
(iii) Apart from the *E*-values, K_{rac} has to be at least equal to K_R (rate of reaction of fast reacting enantiomer).

1.3. Racemization

Racemization therefore is one parameter, which needs to be optimized for successful DKR (Scheme 1).

If a kinetic resolution is accompanied by racemization, this process is called dynamic kinetic resolution. Moreover, racemization and resolution usually requires certain specific conditions (temperature, concentration, and pH) that are generally incompatible. Therefore, for an efficient DKR process a fine balance between these two aspects is desired. The driving force of the racemization process can be predominantly attributed to the increase of entropy caused by the mixing of the two enantiomers. The racemization methods have been classified on the basis of type of compounds and racemization methods [23]. The racemization could be catalyzed by a base, an acid or an enzyme, that may involve nucleophilic, photochemical, thermal or oxidative-reductive processes.

Base-catalyzed racemization is a well-known method and this has been extensively utilized. It is especially applicable to compounds with a stereo centre having an acidic proton. It involves the removal of hydrogen from the chiral centre to form a carbanion. This carbanion needs to be stabilized by an adjacent group such as keto, nitrile, nitro or other functionalities or by reversible formation of a β-substituent (Scheme 2). As an



Scheme 2.

Scheme 5.

example, racemization of an acidic proton neighboring to a carbonyl group where the carbonyl group stabilizes the generated carbanion is shown in Scheme 3.

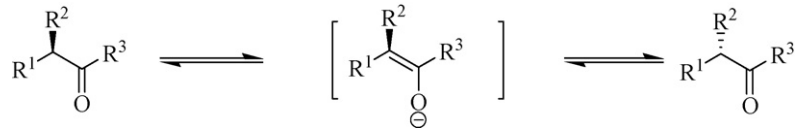
Oxidation and reduction reactions can be used to perform racemization. Oxidation removes H from an asymmetric carbon, generating an intermediate species with a planar geometry, reduction or hydrogenation restores the original hybridization state in a non-stereoselective manner thus generating a racemate (Scheme 4). The oxidation and reduction can be performed simultaneously in a single step or in two separate steps (with or without isolation of oxidized intermediate).

Racemization methods based on lability of certain molecules (e.g. organometallic species such as organolithium, organomagnesium or organopalladium compounds) and those involving sequential nucleophilic displacement over stereogenic centre are also known.

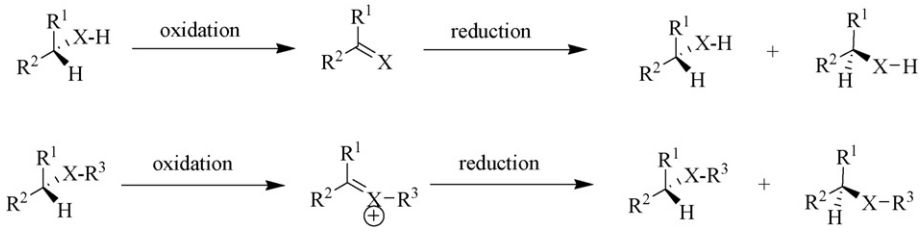
2. Enzymatic kinetic resolutions and dynamic kinetic resolutions (with metal catalysts)

2.1. Alcohols

Alcohols can be efficiently resolved using enzymes particularly lipases by either esterification or hydrolysis. The use of organic solvents for enzyme catalyzed reactions has revolutionized the esterification process by employing different lipases



Scheme 3.



Scheme 4.

Scheme 6.

[24–26]. Several studies have been carried out on solvent effects for enzyme catalysis including the effect of solvent on enantioselectivity in esterfication [27–31]. The enzyme-catalyzed transesterification in organic solvents has proven to be more effective in comparison with conventional esterification methods. The acylation of an alcohol could be performed with an ester like ethyl acetate [32], which can act both as solvent and acylating agent (Scheme 5).

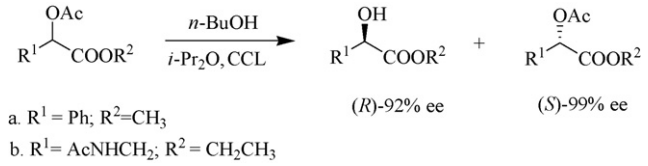
In the presence of a good leaving group on the acyl donor, the equilibrium is shifted towards product formation and for this purpose trichloroethyl or trifluoroesters or anhydrides can be used as acylating agents. When anhydrides are used as acylating agents enantioselectivity is enhanced by removing the acid co-product [33]. Studies indicate that the use of vinyl carboxylate provides the desired results (Scheme 6). In this process the reverse reaction is prevented by the tautomerization of alcohol to aldehyde in an irreversible manner [34].

2.1.1. Resolution of racemic secondary alcohols by transesterification

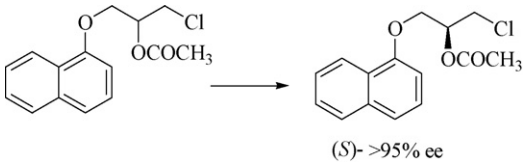
The process of transesterification, is discussed, based on the type of acylating agents, as the choice of these agents is important in the dynamic kinetic resolution process.

2.1.1.1. Transesterification with non-activated esters. In enzymatic transesterifications with non-activated esters like methyl alkanoates, there is no requirement of additional solvent. Such processes have been employed for the enantioselective resolution of various secondary alcohols and diols [35,36]. The transesterification of the ester of a racemic alcohol with methanol or 1-butanol in the presence of lipase provides an efficient method for the preparation of chiral hydroxy compounds [37] as shown in Scheme 7. This process has also been extended to another important chiral intermediate [38] (Scheme 8).

2.1.1.2. Transesterification with activated esters. The enzymatic transesterifications with activated esters such as trichloro or trifluroethyl carboxylate is an efficient enzymatic procedure



Scheme 7.



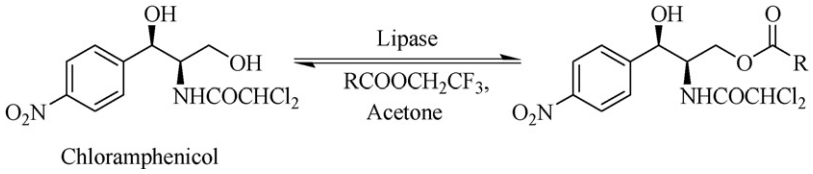
Scheme 8.

to achieve regioselective acylation of polyfunctional compounds of the type chloramphenicol [39] (Scheme 9).

This method of using activated esters has also been satisfactorily applied to the enantioselective synthesis of chiral esters or alcohols by the resolution of racemic allylic alcohol. Similarly 6-heptene-2-ol has been resolved with trifluoroethylbutyrate in the presence of porcine pancreatic lipase to enantiopure *R*-butyrate in good conversion (Scheme 10).

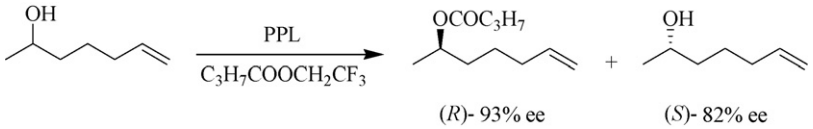
Further, resolution of secondary alcohols towards the synthesis of chiral intermediates for β-adrenergic blocking agents has been carried out in this laboratory by utilizing a similar protocol (Scheme 11) [40].

2.1.1.3. Irreversible transesterification. The typical procedure for an enzyme catalyzed irreversible transesterification utilizes vinyl carboxylate as an acylating agent [41,42]. As discussed earlier the vinyl alcohol tautomerizes to acetaldehyde, which makes the process irreversible and efficient. Primary alcohols possessing a 2-methyl group have been efficiently resolved by employing vinyl acetate in organic solvents with PFL to afford almost enantiomerically pure (*R*)-alcohols and their corresponding (*S*)-acetates (Scheme 12) [43–46]. Recently another intermediate, which is a precursor of thiolactomycin, has been

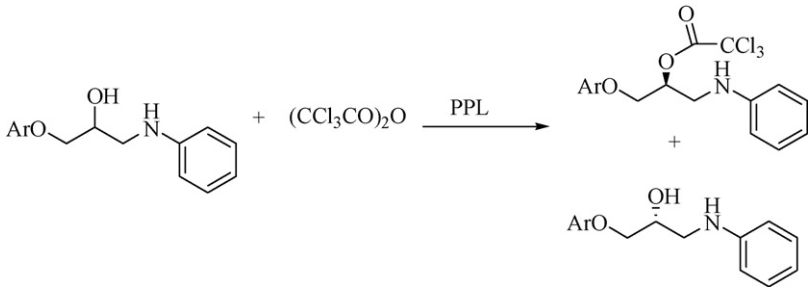


Chloramphenicol

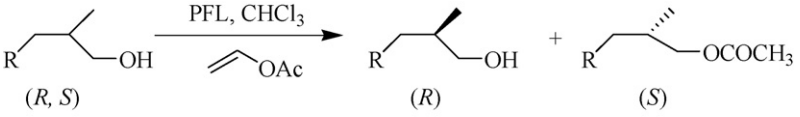
Scheme 9.



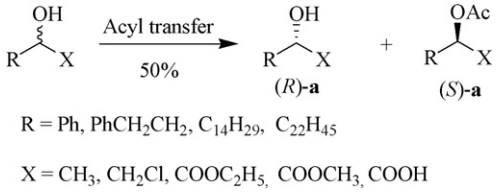
Scheme 10.



Scheme 11.



Scheme 12.



Scheme 13.

resolved in this laboratory by employing *Carica papaya* lipase [47].

Moreover, secondary alcohols have also been efficiently resolved (Scheme 13). The efficiency of the transesterification process using vinyl ester as an acyl donor along with lipases from different sources has been investigated with respect to the configuration. Interesting chiral compounds have been prepared by resolving their respective intermediates [48–56]. Various biologically active compounds have been prepared using this enzymatic procedure [9]. A few reviews [12,13] have emphasized the significance of this work. Substantial work has been carried out in this laboratory particularly towards the synthesis of intermediates of biologically important compounds like umbelactones [57], thiolactomycin [58], quinolone carboxylicacid [59], kavalactones [60], calcilytic agent NPS-2143 [61], β-adrenergic blocking agents [40,62], γ and δ lactones [63] and other related intermediates.

The generation of racemic secondary alcohols required for the resolution process is usually carried out by the reduction of corresponding carbonyl compounds. However, a one-pot reduction followed by lipase-mediated resolution has been developed in this laboratory [64]. For example, the reduction of acetophenones with sodium borohydride in the presence of neutral alumina in hexane followed by enantioselective acylation catalyzed by lipases is performed in one-pot (Scheme 14). This methodology has also been applied for the chemoenzyamtic synthesis of propanolol, sotalol [65] tembamide, aegiline, denopamine [66].

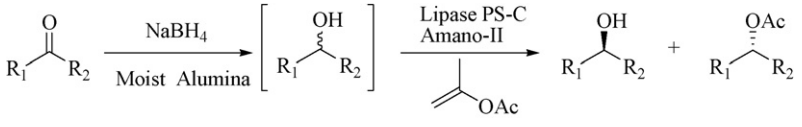
2.1.2. Resolution of allylic alcohols

Enantiomerically pure allylic alcohols represent an important structural motif and have attracted synthetic chemists for their wide range of applications in the synthesis of natural and non-natural compounds [67–72]. The chemoenzymatic synthesis of *R* and *S* verapamil [73] has been carried out employing such a chiral precursor (Scheme 15).

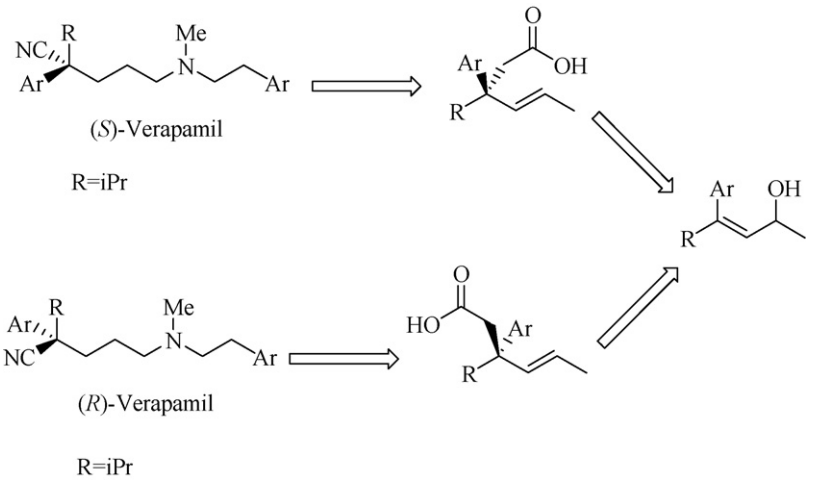
Kinetic resolution of allylic alcohols was first reported by Burgess and Jennings [74] as part of the study towards development of a simple active-site model for prediction of asymmetric induction and applied for the asymmetric synthesis of a statin analogue [75]. Schurig [76] have reported a kinetic resolution of *trans*-4-phenyl-3-butene-2-ol in high enantiomeric excess. The enantioselective transesterification as well as hydrolysis of its acetate has been studied (Scheme 16).

Itoh et al. [77] have demonstrated the kinetic resolution of some allylic alcohols in ionic liquid media under reduced pressure. An efficient enzymatic pathway has been developed for the synthesis of enantiopure allylic alcohols from corresponding α,β-unsaturated ketones in this laboratory by employing one-pot reduction followed by lipase-mediated resolution protocol in high enantiopurity (Scheme 17) [78].

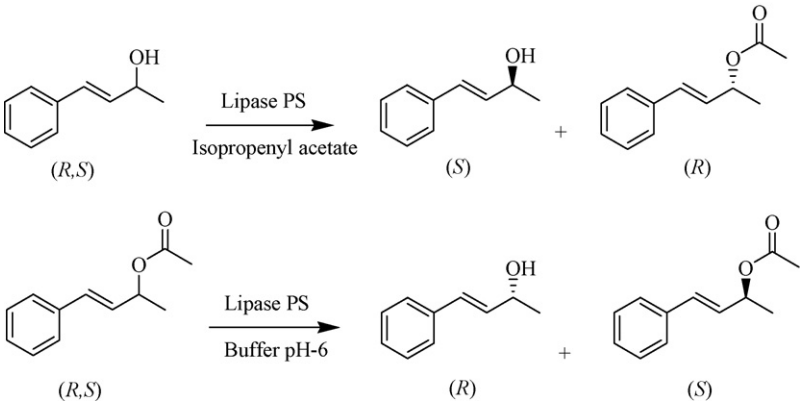
Chiral diamine (ether-phosphine) ruthenium(II) complexes have been used as highly active and selective catalysts in the



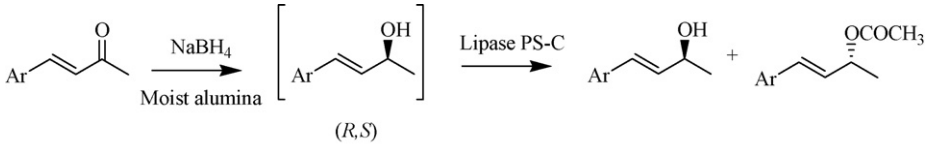
Scheme 14.



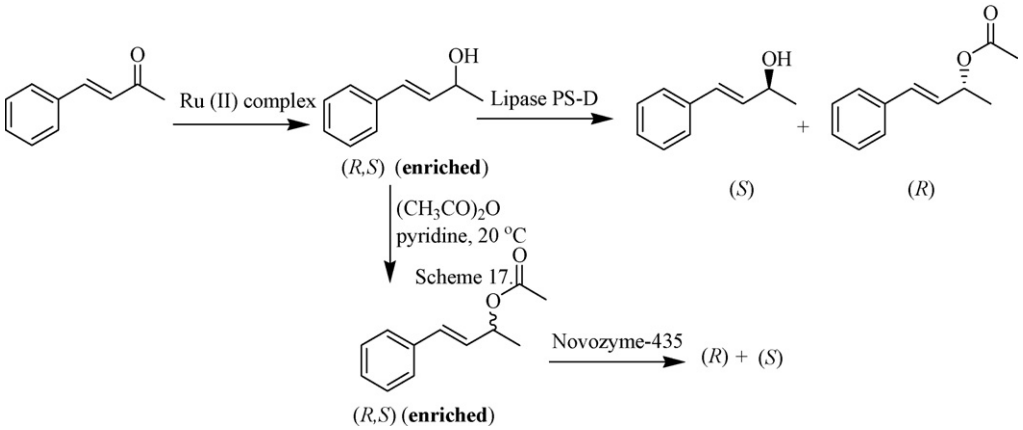
Scheme 15.



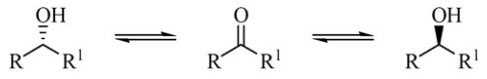
Scheme 16.



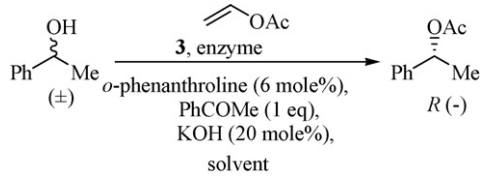
Scheme 17.



Scheme 18.



Scheme 19.



Scheme 20.

hydrogenation of α,β-unsaturated ketones to afford enantiomerically enriched unsaturated alcohols. Further, these have been subjected to the lipase-catalyzed kinetic resolution to obtain alcohols in high enantiomeric excess (Scheme 18) [79].

Nevertheless, several examples for the enzymatic kinetic resolutions have been investigated for the preparation of chiral intermediates; however the desired enantiomers could only be obtained in a maximum of 50% yield. Various attempts have been made to enhance this yield to more than 50% and the recent studies involving the dynamic kinetic resolution processes have provided encouraging results.

Several examples of dynamic kinetic resolutions are presently found in the literature while the trend which leads to the development of such processes is lacking. Therefore, different strategies that have been reported in the literature for the dynamic kinetic resolutions have been categorized systematically. These are being discussed in the present review not only to understand the recent trend but also to provide a useful direction in the future pursuit of this research.

2.1.3. Early period of dynamic kinetic resolution processes

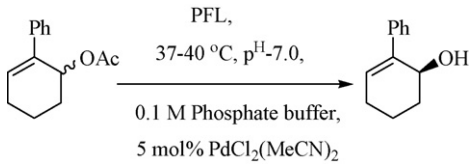
Dynamic kinetic resolution has been recognized as an important phenomenon in the early years of this decade [80]. This development has paved a way to the future endeavors in this area of research. In these investigations various enzymes and microorganisms have been utilized for the development of DKR processes.

2.1.4. Enzyme-metal combinations in dynamic kinetic resolutions: Application of this strategy for alcohols

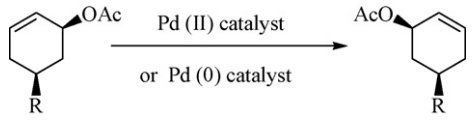
To address the limitations of enzymatic kinetic resolution such processes have been coupled with racemization reactions and given rise to DKR processes. Williams and co-workers [81] successfully attempted to racemize a single enantiomer of phenethyl alcohol (Scheme 19) with certain metals like rhodium [82], iridium [83], ruthenium [84], and aluminium [85] that are capable of catalyzing the transfer of hydrogen between ketones and alcohols.

Later, they were successful in demonstrating the application of this racemization process along with enzymatic resolution in a single pot (Scheme 20), which allows the production of more than 50% of the enantiomerically enriched products.

Further, they also [86] demonstrated the dynamic kinetic resolution of allylic alcohols with a palladium catalyst in combination with *Pseudomonas fluorescens* lipase (Scheme 21).



Scheme 21.



Scheme 22.

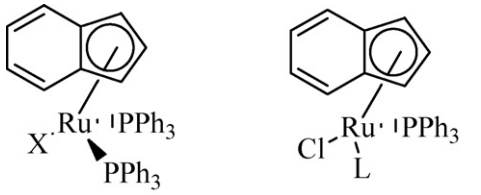
The palladium(II) catalyst [87] was chosen in comparison to the Pd(0) catalyst [88], as in this mechanism the acetate does not leave the substrate (Scheme 22). Moreover for the Pd(0) catalyzed racemization, an intermediate allyl palladium complex can be attacked by nucleophiles other than acetate.

Park and co-workers [89] have developed some racemizing catalysts (Fig. 1), like (η^5-indenyl)RuCl(PPh_3)$_2$ 1a that are found to rapidly racemize (*S*)-1-phenylethan-1-ol completely at room temperature in the presence of a base; the mechanism for which is depicted in (Scheme 23).

A detailed discussion is presented in this study on the rate of racemization by changing the halides, reaction conditions like solvents, bases and also by varying the triphenyl phosphine ligands along with the possible pathway for racemization.

Preliminary attempts to combine lipase-catalyzed acylation with the above catalytic racemization systems have not been fruitful due to predominant chemical acetylation of alkoxides. This problem has been overcome to a large extent by using weak bases like triethylamine [90], and catalytic amount of oxygen (Scheme 24). Trimethylamine N-oxide was also effective for racemization. Under these conditions triphenyl phosphine oxide was always formed as a by-product. This observation suggests that oxygen and trimethylamine N-oxide acted as activators, removing a phosphine ligand from the ruthenium center.

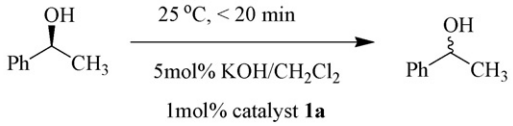
Mechanistically, the ruthenium complex is activated by oxygen and the racemization proceeds with weak bases. Under these conditions various alcohols have been transformed enantioselectively to the corresponding acetates without observable chemical



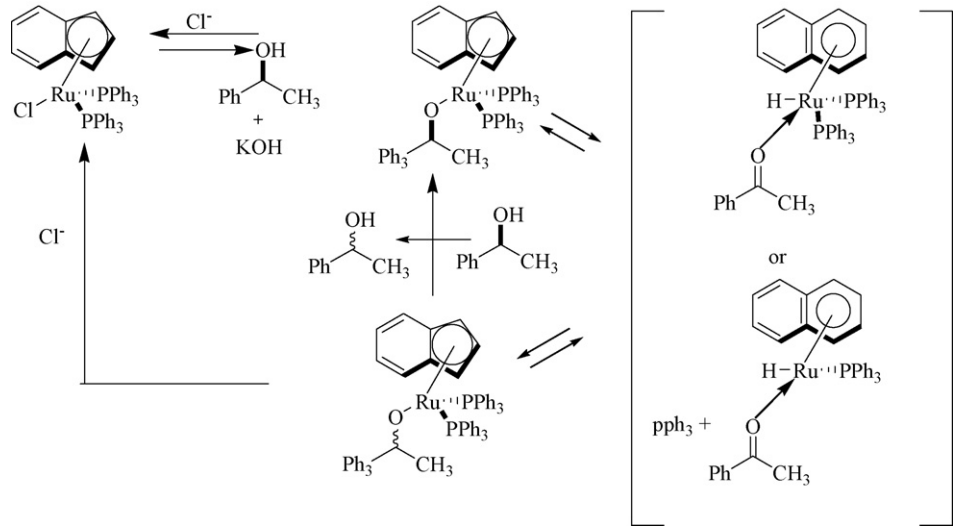
1a X = Cl
1b X = Br
1c X = I

2a L = P (OEt)$_3$
2b L = PMe_3

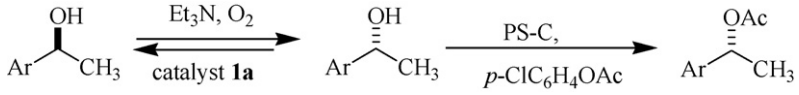
Fig. 1.



Mechanism



Scheme 23.



Scheme 24.

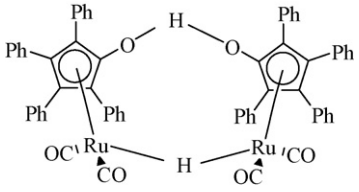


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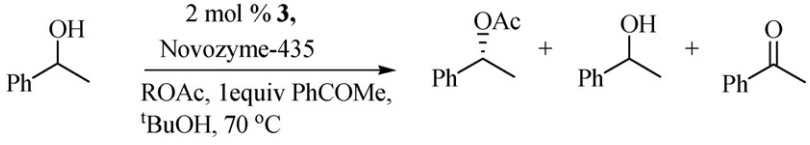
Fig. 2.

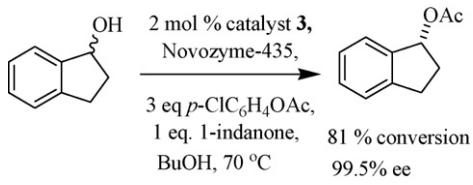
acetylation. Bäckvall and co-workers [91] have used a catalyst complex as shown in Fig. 2 as an *in situ* racemizing agent for the substrate, in combination with lipase-catalyzed esterification. The phenethylalcohol is completely racemized in the presence of this catalyst employing tertiary butanol. In this method 2% of this catalyst is used with respect to one equivalent of acetophenone required for the promotion of ruthenium catalyzed hydrogen transfer. This racemization has been combined with Novozyme-435 catalyzed transesterification process and the success of this process is largely governed by the type of acyl donors (ROAc). However, the aldehyde generated from the acyldonor acted as the hydrogen acceptor and oxidized the substrate alcohol to its corresponding ketone, thereby decreasing the overall yield in this process (Scheme 25).

In order to overcome the limitation of low yields, *p*-chlorophenylacetate has been used as an acyl donor in combination with an enzyme along with the racemizing catalyst. This change of the acyl donor allows the formation of the product in good yields and with high enantiomeric excess. This methodology has been extended for the resolution of racemic 1-indanol (Scheme 26).

The development of such racemization reagents has lead to the advent of a new era for DKR. However, there are some other limitations like longer reaction times and the use of inert atmosphere that needs to be addressed. Therefore, with a view to overcome such drawbacks extensive research has been carried



Scheme 25.



Scheme 26.

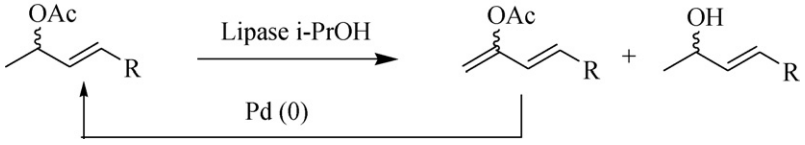
out by the same authors [91,92]. These studies include the use of Novozyme-435 along with the catalyst 3, in combination with some acyl donors. Activated esters such as trichloroethyl esters and trifluoroethyl esters have been used to shift the equilibrium of the enzyme catalyzed reaction towards acylation process. However, esters containing protons in the α-position to the oxygen are considered not suitable as the alcohol released in the process interferes with the ruthenium catalyst. In this context aryl esters have been found to be more suitable as acyl donors. The advantage of employing aryl esters is their higher reactivity in comparison to the alkyl esters and thus favoring the acylation of alcohol. Moreover, the reactivity could be tuned by the presence of electron withdrawing or electron donating substituents in the aryl esters. The studies indicated that 4-chlorophenylacetate is an excellent acyl donor for such a process. Interestingly, the variation of acyl donors does not have any effect on the selectivity by the enzyme. Extensive studies that have been carried out in the above DKR process reveal that the variation in acyldonors has a vital role in the enhancement of the rate of reaction apart from the solvents that have been examined. This investigation therefore allows one to explore further improvement of such processes by utilizing a variety of acyldonors that have been discussed earlier in many trans-esterification based resolutions. The related studies for trans-esterification processes have been discussed in the earlier part of this review.

Kim and co-workers [93] have carried out the DKR of acyclic substrates employing Pd(0) based racemization catalyst along with the lipase-catalyzed transesterification (Scheme 27).

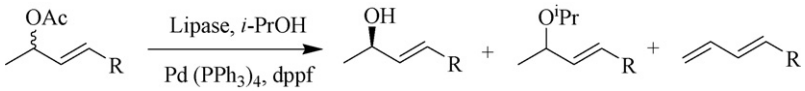
Further, tetrakis(triphenylphosphine) palladium(0) has been used along with bis(diphenylphosphino)ferrocene (dppf) as a racemization catalyst. However, the use of Pd catalyst alone gives the unwanted side reactions and therefore the use of dppf has suppressed the undesired side-reactions (Scheme 28).

Further, Kim and co-workers [94] have reported an interesting asymmetric transformation that involves a one-pot process for the transformation of ketones or enol acetates to chiral acetates using lipase and catalyst 3 (Scheme 29). This process involves five steps that are deacetylation of enol acetate gives the corresponding enol and acylated lipase, which upon keto-enol tautomerization forms the ketone. Reduction of the ketone produces the racemic alcohol followed by the enantioselective acetylation of the *R*-alcohol with acetylated lipase to afford the *R*-acetate. Simultaneous reversible transformation between *S* and *R* alcohols, i.e. *in situ* racemization takes place.

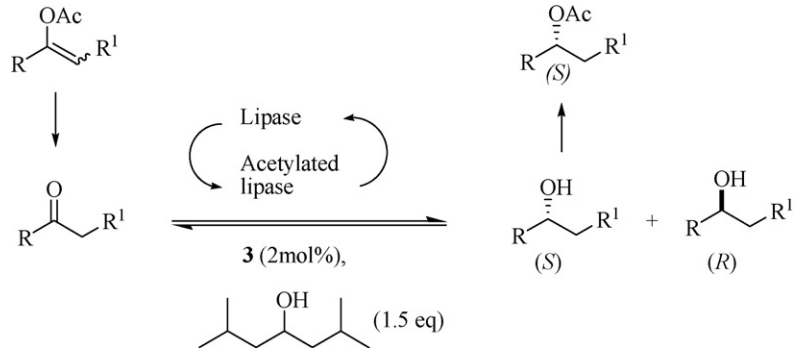
DKR of allylic alcohols has been reported by Park and co-workers [95] utilizing Ruthenium catalysts in combination with enzymatic resolution as shown in Fig. 3. Amongst the catalysts screened 4a and 4b gave and good results with respect to yields and enantioselectivity. Therefore, DKR has been carried out by using catalyst 4b. A number of allylic alcohols have been resolved using this protocol (Scheme 30). The DKR studies of allylic alcohols have generally utilized palladium and ruthenium catalysts such as 3. However it appears that there is ample scope



Scheme 27.



Scheme 28.



Scheme 29.

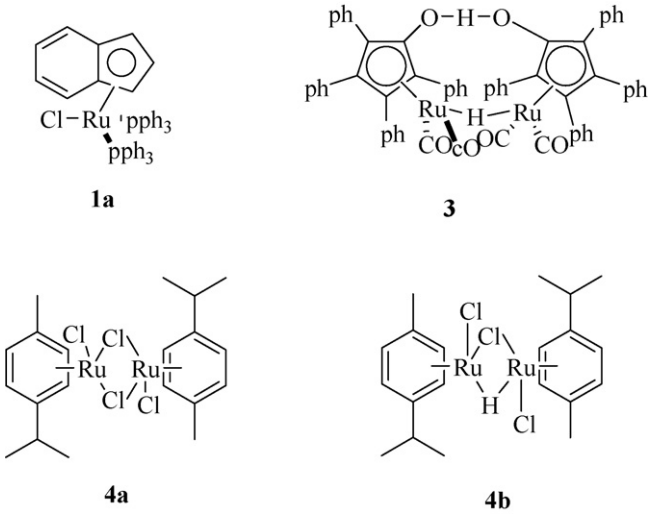


Fig. 3.

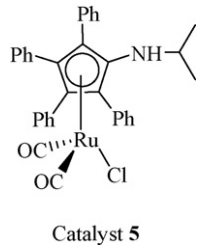


Fig. 4.

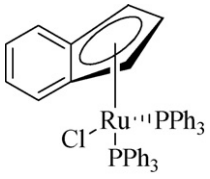


Fig. 5.

to employ other related ruthenium catalysts for broadening the applicability to different types of allylic alcohols with improved efficiency.

A one-pot method for reduction of ketones to alcohols as well as enol acetates to achiral acetates and simultaneous DKR to form chiral acetates has been developed by Park and co-workers [96] (Scheme 31).

Catalyst 3 is well known for the reduction of ketones and thus serves for this purpose along with the racemization of the alcohol. The solvent used itself acts as an acylating agent thereby decreasing the complexity of the process. A combination of different sources of hydrogen and various acyldonors have been studied to understand its compatibility with respect to the process. However there is potential to explore palladium as well as a variety of different ruthenium catalyst for this process.

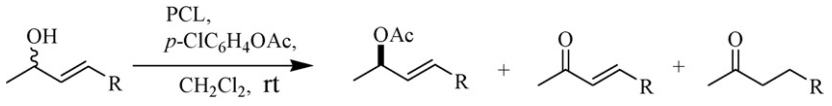
Later, Nakamura et al. [97] reported another ruthenium catalyst 5 (Fig. 4) that has been utilized for the DKR of secondary alcohols at ambient temperatures.

The mechanism of racemization is discussed in detail wherein it is proposed that the reversible transformation between a ruthenium–alcohol complex and a ruthenium–ketone is responsible for this racemization. Further the efficiency of this methodology has also been demonstrated by applying it to different substrates as shown in Scheme 32.

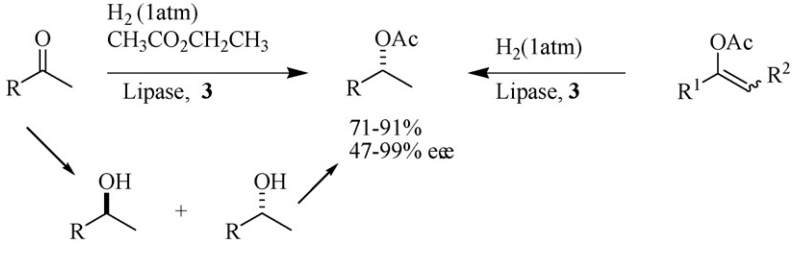
In another significant observation by Sheldon and co-workers [98], three new catalytic systems have been developed and examined for their racemization ability towards secondary alcohols. Moreover, an attempt has been made to overcome the requirement of the addition of one equivalent of acetophenone and three equivalents of triethylamine. In this context a catalyst system has been developed by combining catalyst 1a (Fig. 5), TEMPO and 1-phenylethanol which gives RuH_2L_3 (Scheme 33).

It is believed that ruthenium hydride which is generated in this process is responsible for the racemization of alcohols. However long reaction times and larger requirement of rather expensive TEMPO (3 mol%) limits this from practical applicability. Therefore, this necessitated the development of another catalytic system (Scheme 34).

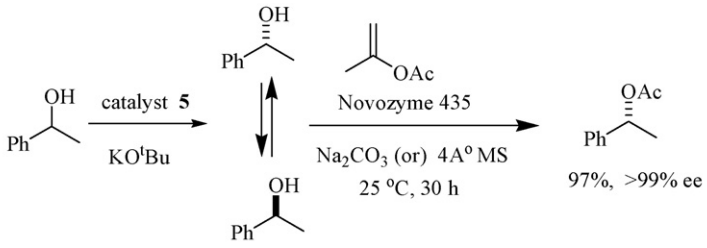
Addition of a base like potassium hydroxide leads to substantial increase in activity. A combination of catalyst 1a with TEMPO and catalyst 5a with potassium hydroxide did not provide the desired results. However the combination of catalyst



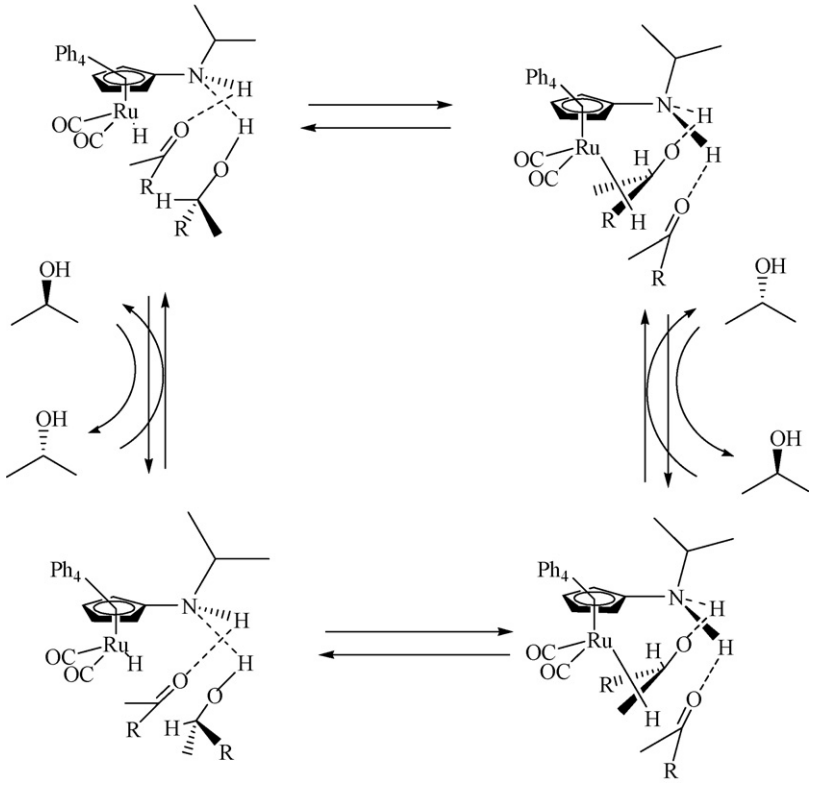
Scheme 30.



Scheme 31.



Mechanism

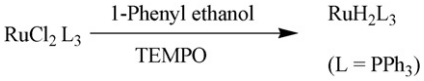


Scheme 32.

5 with TEMPO gives both *in situ* racemization and dynamic kinetic resolution.

Ikariya and co-workers [99] reported a catalyst system that shows rapid racemization of chiral non-racemizing secondary alcohols. The catalyst system used for racemization includes a combination of catalyst 6a: 2-diphenylphosphinoethyl amine: KO^{t}Bu in the ratio of 1:1:1. Mechanism of racemization is depicted in Scheme 35.

Bäckvall and co-workers [100] also reported that catalysts 8a and 8b (Fig. 6) racemize (*S*)-1-phenylethanol at room temperature with a half-life of about 2 min or less (Scheme 36). Extensive studies have been carried out with more catalysts of similar type.



Scheme 33.

Recently, Akai et al. [101] reported a DKR of allylic alcohols using a combination of lipases with a different metal catalyst [VO (OSiPh$_3$)$_3$] catalyst 9 (Scheme 37). Oxovanadium(V) compounds are known to catalyze the 1,3-transposition of allylic alcohols resulting in a thermodynamic equilibrium of two regioisomers, which undergoes a highly enantio and chemoselective esterification in presence of a lipase. This DKR protocol pro-

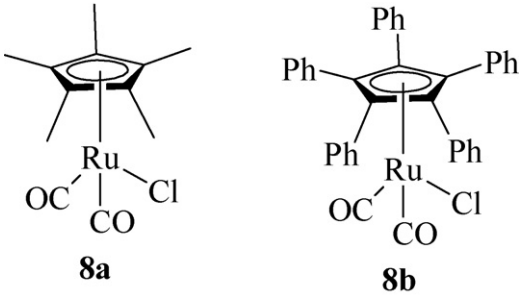
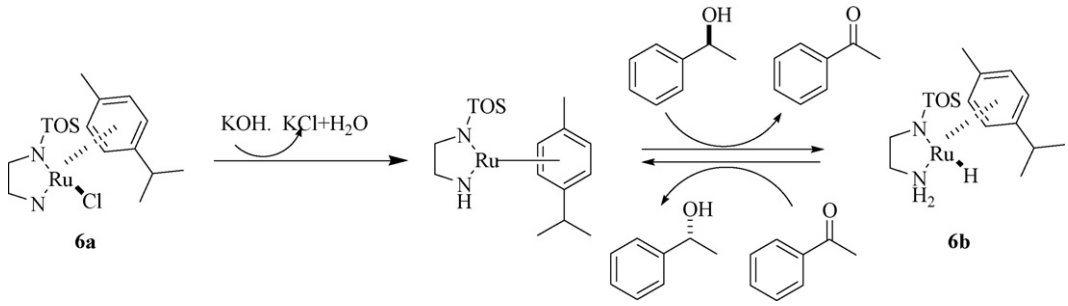
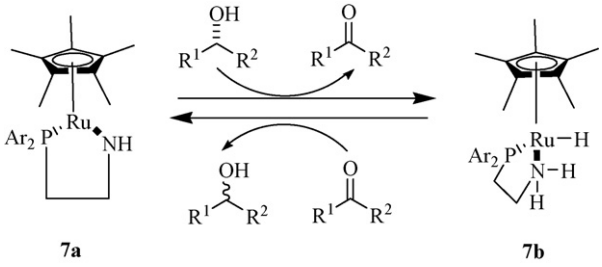


Fig. 6.



Scheme 34.



Scheme 35.

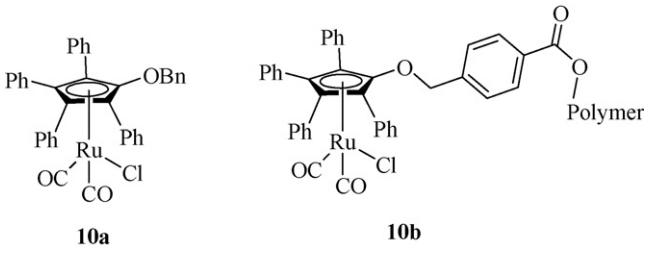
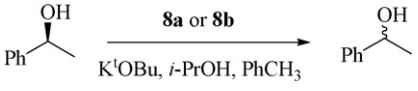


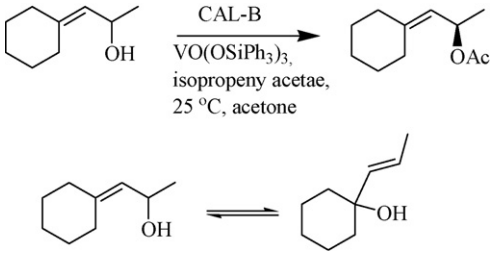
Fig. 7.



Scheme 36.

vides access to optically active esters of secondary alcohols from corresponding ketones via the readily available tertiary alcohols. Interestingly there is no need of an inert atmosphere in this DKR process.

A new racemization catalyst 10a, which is stable in atmosphere and recyclable has been developed by Park and co-workers along with its heterogeneous version 10b (Fig. 7)



Scheme 37.

[102]. DKR of different secondary alcohols has been performed using such catalysts. This is a fascinating study which employs a novel polymer supported catalyst for the aerobic DKR of alcohols. This approach could generate more practical catalyst systems for a variety of ruthenium catalysts for alcohol DKR.

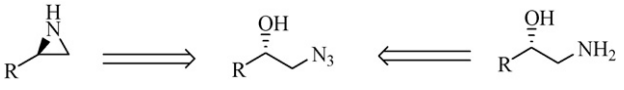
2.2. Azido alcohols

Chiral β-azido alcohols are of great significance as potential precursors for optically active aziridines and β-amino alcohols (Scheme 38) [103–108]. Chiral aziridines are attractive synthetic targets because of their increasing importance in organic synthesis and also due to their presence in bioactive molecules like leucomitomycin antibiotics e.g., mitomycin C, a DNA alkylating agent (Fig. 8) [109,110].

Chiral 1,2-amino alcohols can be synthesized by the reduction of 1,2-azido alcohols (Scheme 38) and are structural units of immense importance. Their presence in biologically active natural products, such as ephedrine and α- or β-adrenergic blockers and agonists reflects their importance [110]. Naturally occurring hydroxy amino acids containing a vicinal amino alcohol like serine or threonine are also of biological significance and useful members of the chiral pool [111]. Some other biologically important molecules like sphingosine and indinavir also contain vicinal amino alcohols (Fig. 8) [103,112]. Moreover, there are also some 1,2-amino alcohols that have found use in catalytic organic transformations [113].

2.2.1. Enzymatic kinetic resolution of azido alcohols

Owing to their high synthetic applicability, preparation of enantiopure azido alcohols is accomplished by enzymatic kinetic resolutions. The first enzymatic kinetic resolution of azido alcohol has been reported by Ader and Schneider on racemic 1-azido-3-phenoxy–2-propanol by *Pseudomonas cepacia* lipase-catalyzed acylation and hydrolysis of the acetate [114]. Similarly, 1-azido-3-(4-*tert*-octyl)phenoxy–2-propanol has been acetylated with moderate enantioselectivity [115]. Hönig and co-workers have also accomplished the lipase-catalyzed resolution of acyclic and cyclic 2-azido alcohols as



Scheme 38.

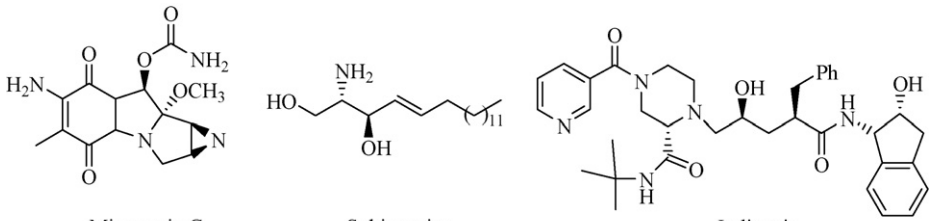
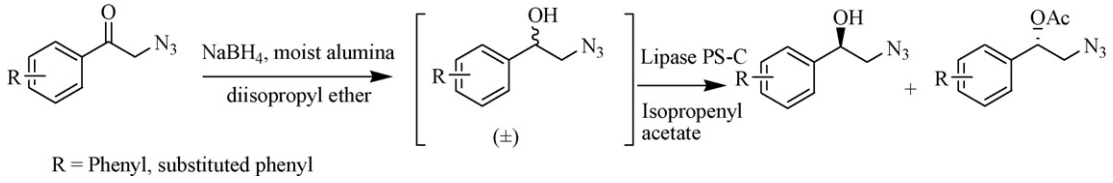
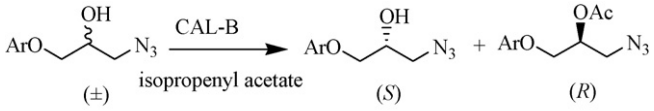


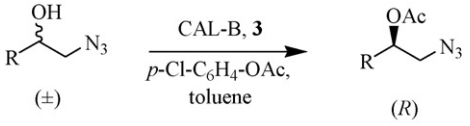
Fig. 8.



Scheme 40.



Scheme 39.



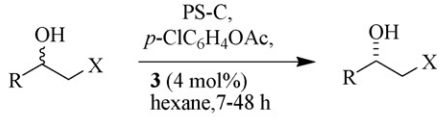
Scheme 41.

precursors of amino alcohols with good enantioselectivity [116]. Enantiopure 1-azido-3-aryloxy-2-propanol subunits present in numerous biologically active compounds such as β-adrenolytic drugs have been resolved by lipase-mediated trans-esterification to furnish the optically active (*S*)-alcohol and corresponding (*R*)-acetate [117,118] (Scheme 39).

A facile one-pot reduction, resolution protocol to provide access to enantiopure β-azido alcohols from their keto azides with high enantiomeric ratio has been developed in this laboratory [119] (Scheme 40). The synthetic utility of this procedure has been illustrated by its application in the synthesis of both the enantiomers of natural hydroxyamides like tembamide, aegeline and β-adrenoceptor agonist denopamine [70].

2.2.2. Dynamic kinetic resolution of azido alcohols

The DKR of different phenyl and aryloxymethyl substituted azido alcohol derivatives, has been accomplished by Pamies and Bäckvall employing enzymatic resolution in combination with ruthenium catalyzed alcohol isomerization [120] (Scheme 41). Enantiomerically pure acetates are obtained in high enantiomeric excess and conversion up to 98% employing this protocol on a variety of racemic β-azido alcohols using immobilized CAL-B with ruthenium catalyst 3 and *p*-



Scheme 42.

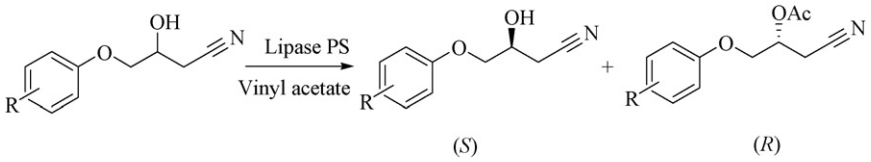
chlorophenyl acetate as acyl donor. This observation is likely to create more interest for exploring it on a wide spectrum of azido alcohol substrates that are building blocks for a number of biologically significant compounds, thus enhancing the practical utility of this protocol.

2.3. Halo alcohols

Chiral β-halo alcohols are important structural elements, as they are potential precursors of chiral epoxides and β-and γ-amino alcohols, widely used as adrenergic receptor blockers and immune stimulants [121]. The kinetic resolution of β-halo alcohols with *Candida antarctica* lipase B (CAL-B) proceeds with low selectivity. Pamies and Bäckvall [122] have accomplished DKR of different β-halo-α-phenethyl alcohols to provide acetate with excellent enantiomeric excess and conversions (Scheme 42).

2.4. Hydroxy nitriles

β-Hydroxy nitriles are a class of bifunctional compounds with importance both as reagents and as technical products in organic chemistry. These have been extensively investigated and employed in synthetic chemistry towards the preparation of various intermediates for naturally occurring bioactive compounds [123]. The cyano group can be easily transformed to different functional groups like β-hydroxy amides, β-hydroxy acids, β-hydroxy esters, diols, and aminoalcohols by using simple methods. Moreover, the stereogenicity at the hydroxyl group



R = H, 2-CH_3, 4-CH_3, 4-Cl, 4-Br, 2,3-(CH=CH-CH=CH)-, 3,4-(CH=CH-CH=CH)-

Scheme 43.

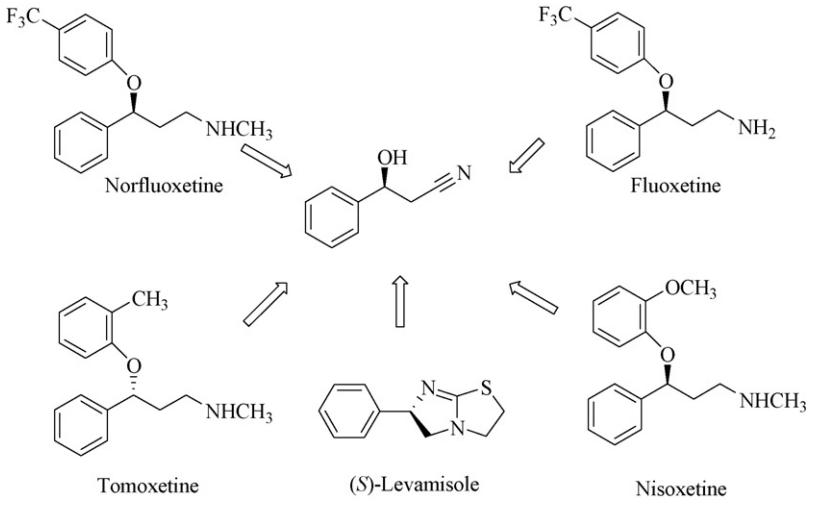


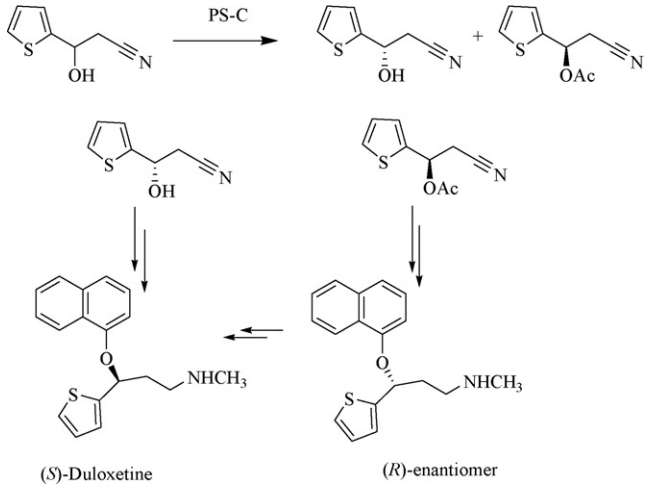
Fig. 9.

in these derived compounds has been used to control the generation of new stereocenters thus offering a potential route to diastereoselective 1,3-diols and 1,3-aminoalcohols intermediates for a large number of natural products, antibiotics and chiral auxiliaries.

2.4.1. Enzymatic kinetic resolution of β-hydroxy nitriles and their applications

A simple and efficient method for the preparation of a variety racemic β-hydroxy nitriles and its kinetic resolution using different lipases has been developed in this laboratory [124]. Optically pure β-hydroxy nitriles obtained have been utilized in the preparation of some β-adrenergic blocking agents (Scheme 43).

Lipase-catalyzed trans-esterification of racemic 3-hydroxy-3-phenylpropanenitrile using various lipases have been studied in this laboratory. Among all the lipases screened, lipase *Pseudomonas cepacia* adsorbed on ceramic particles (PS-C) in hydrophobic solvents like diisopropyl ether, toluene, and hexane enhanced the reaction rate drastically and gave optimal yields and high enantiomeric excess. Optically pure 3-hydroxy-3-phenylpropane nitrile has been utilized towards the preparation of fluoxetine, norfluoxetine, nisoxetine, tomoxetine and (*S*)-levamisole [125] (Fig. 9). An efficient and facile enantioconvergent synthesis of duloxetine by lipase-mediated resolution of 3-hydroxy-3-(2-thienyl)propanenitrile has been investigated in this laboratory [126] (Scheme 44). This lipase-catalyzed resolution process has also been extended for the chiral separation of 3-hydroxy-4-trityloxybutanenitrile, 3-hydroxy-4-tosyloxybutanenitrile, *N*-

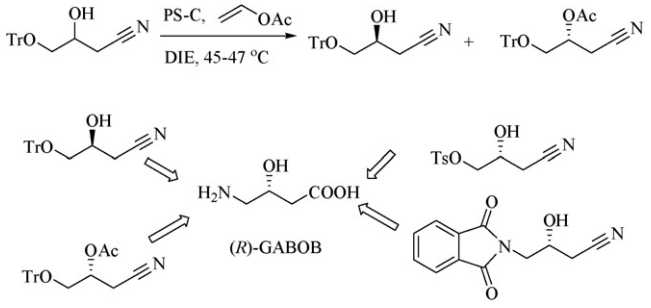


Scheme 44.

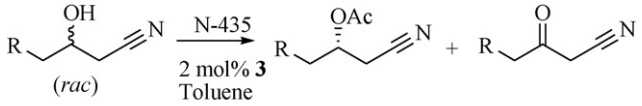
(3-cyano-2-hydroxypropan-1-yl)phthalimide in good enantioselectivity and conversions. These hydroxy nitrile intermediates are used as chiral building blocks in the preparation of numerous biologically significant compounds like β-adrenergic blocking agents, antimicrobials, oxazolidinones, GABOB, and carnitine [127,128] (Scheme 45).

2.4.2. Dynamic kinetic resolution of β-hydroxy nitriles

Pamies and Bäckvall [129] have reported the kinetic resolution of various alkyl, aryl and aryloxy methyl substituted β-hydroxy nitriles using *Candida antartica* (N-435) lipase in



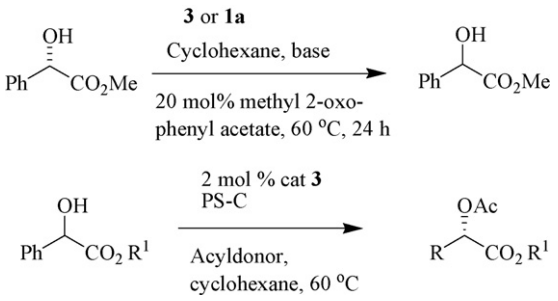
Scheme 45.



R = Ph, *p*-MeO-C_6H_4, *p*-NO_2-C_6H_4, 2-Naphtyl.

Scheme 46.

high enantiomeric purity. The combination of the enzymatic kinetic resolution along with a ruthenium-catalyzed alcohol racemization led to the dynamic kinetic resolution. This DKR process has also been carried out using ruthenium catalyst 3, Novozyme 435, and *p*-chlorophenylacetate as acyl donor. This study indicates that the efficiency of the process can be increased by using 2,4-dimethyl-1,3-pentanol as a mild hydrogen source to suppress ketone formation (Scheme 46).



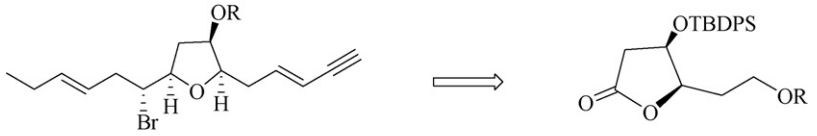
Scheme 49.

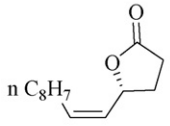
2.5. Hydroxy acid derivatives

γ-Hydroxy acids or γ-hydroxy lactones are of very high potential in the enantioselective synthesis of various chiral compounds like *trans*-Kumansyne and Beetle sex pheromone (Scheme 47).

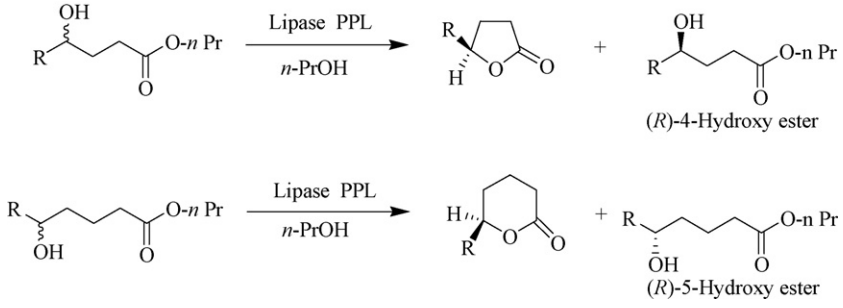
The catalytic potential of lipases towards the synthesis of macrocyclic lactones has been investigated. Hydroxy methyl esters gave enantiomerically pure macrolactones. A facile and highly stereoselective enzymatic intra molecular transesterification for preparation of γ-lactones is performed using PPL on different substrates (Scheme 48) [130]. In another significant development Japanese beetle pheromone was prepared by resolving γ-hydroxy carboxylic acid derivatives [131]. Kinetic resolutions using many other lipases have also been performed on these substrates [132].

Recently DKR of α-hydroxy esters has been reported by Bäckvall and co-workers [133] using enzymatic resolution in

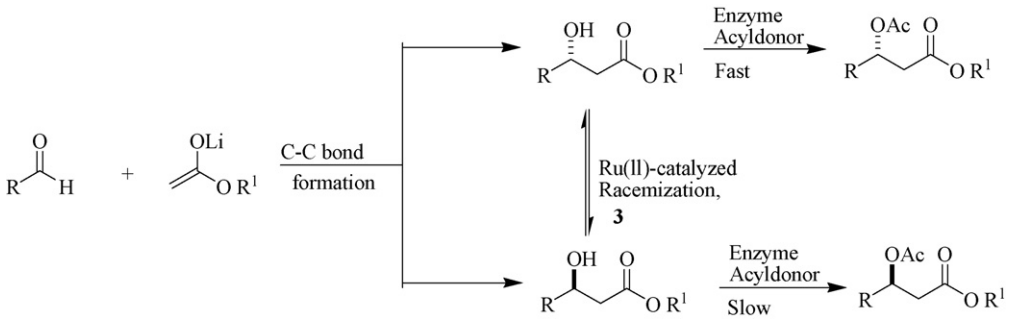




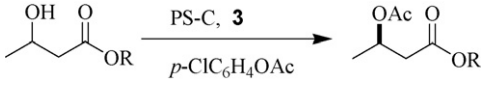
Scheme 47.



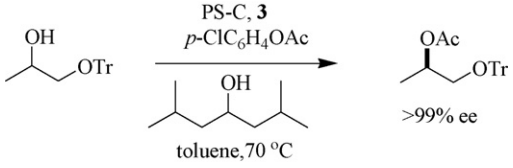
Scheme 48.



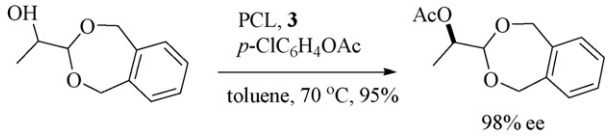
Scheme 50.



Scheme 51.



Scheme 52.



Scheme 53.

combination with ruthenium-catalyzed racemization. Different ruthenium based catalysts have been examined for their racemizing ability (Scheme 49).

A one pot aldol-reaction accompanied by simultaneous racemization and enzymatic resolution has been developed by Huerta and Bäckvall [134] (Scheme 50). A successful attempt has been made to combine two different types of reactions into one pot process.

This ruthenium and enzyme catalyzed DKR in tandem with C–C bond forming reactions like the aldol addition is a very valuable protocol for asymmetric synthesis. This methodology needs to be complemented to the previously reported procedures as enantiomerically pure aldol adducts lacking an α-substituent are usually difficult to prepare by catalytic asymmetric aldol reactions. Interestingly the applicability of this procedure could be further extended for the generation of C–C bonds using other type of reactions accompanied by DKR.

Park and co-workers [135] made another significant contribution to the field of DKR by applying DKR on three different functional secondary alcohols, which include β-hydroxy esters (Scheme 51), monoprotected 1,2-diols (Scheme 52) and hydroxyl aldehydes (Scheme 53).

Bäckvall and co-workers [136] have developed DKR of γ-hydroxy acid derivatives. Significant changes have been made in the substrate to avoid lactonization. A hydrogen source is used to reduce the ketone formation, a by-product (Scheme 54). Similarly, enzymatic kinetic resolution and dynamic kinetic resolution of δ-hydroxy esters has been reported by the same authors [137] (Scheme 55).

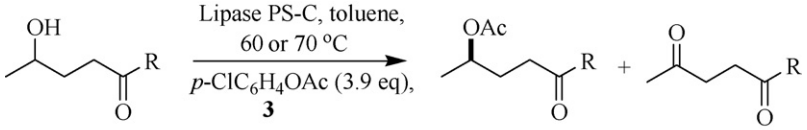
2.6. Amines

Enantiopure amines are used in the fine chemical industry as resolving agents, chiral auxiliaries and chiral synthetic building blocks for pharmaceuticals and agrochemicals. The recent literature on lipase-catalyzed resolution of amines and dynamic kinetic resolution approaches has been briefly discussed.

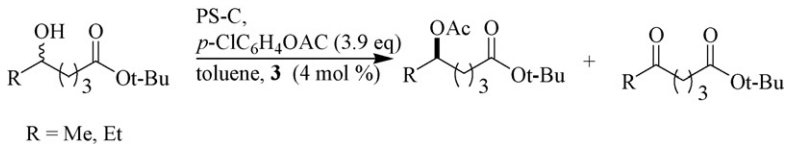
2.6.1. Enzymatic kinetic resolution of amines

Sheldon and co-workers [138] have reported the lipase-catalyzed resolution of α and β-aryl amines using penicillin acylase from *Alcaligenes faecalis* in organic and aqueous media (Scheme 56).

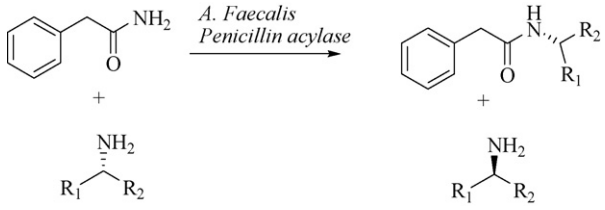
Irimescu and Kato [139] have reported lipase-catalyzed enantioselective acylation of 1-phenylethylamine and 2-phenyl-1-propylamine by the reaction of amines with carboxylic acids in a non-solvent system or in ionic liquids (Scheme 57). The reaction equilibrium has been shifted towards amide



Scheme 54.



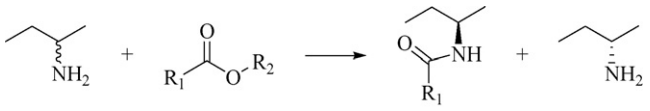
Scheme 55.



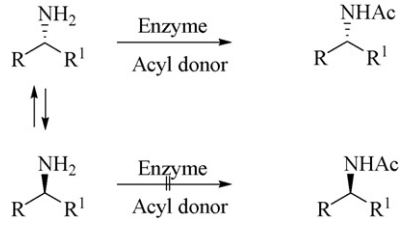
Scheme 56.

synthesis by the removal of water formed under reduced pressure.

Goswami et al. [140] reported *Candida antartica* lipase-catalyzed resolution of racemic *sec*-butylamine using ethyl esters of long chain fatty acids as acylating agents in various solvents (Scheme 58). Further subtilisin is also a promising resolution catalyst for amine [141].



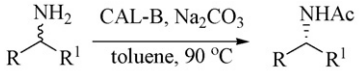
Scheme 58.



Scheme 59.

2.6.2. *Dynamic kinetic resolution of amines*

The chemoenzymatic DKR is also used for the preparation of enantiomerically enriched amines (Scheme 59). Paetzold and Bäckvall [142] reported for the first time an efficient protocol for DKR of unfunctionalized primary amines in high yield and enantioselectivity (Scheme 60). Overall, not much work has been carried out on the DKR for the preparation of enatiomerically pure amines and has the potential to be explored further.



R/R[1] Ph/Me, 3-Me-C_6H_4/Me, 4-F-C_6H_4/Me, 4-MeO/Me, 2-Naphtyl/Me, Ph/Et, 4-CF_3-C_6H_4/Me, *n*-C_6H_3/Me, $PhCH_2COO$/Me

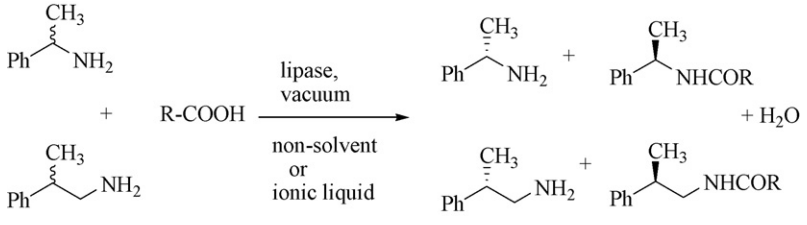
Scheme 60.

Kim and co-workers [143] have reported enantiomerically active amines in the acetylated forms by coupled lipase/palladium DKR catalysis in the presence of an acyl donor using ketoximes as starting materials under 1 atmosphere of hydrogen (Scheme 61). Recently Bäckvall and co-workers [144] have also developed an efficient and mild ruthenium-catalyzed racemization of amines under hydrogen transfer conditions (Scheme 62).

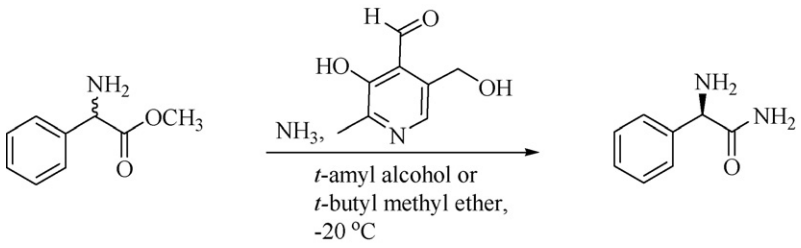
Reetz and Schimossek [145] have reported for the first time that the combination of CAL-B lipase and palladium on carbon for the synthesis of (*R*)-*N*-(1-phenylethyl)acetamide from 1-phenylethylamine in high ee (Scheme 63).

Blacker et al. [146] have reported a simple, efficient iridium based catalyst system for the dehydrogenation and racemization of a variety of amines. A process for the DKR of a secondary amine has been developed to give a product in good yield and high enantiopurity (Scheme 64).

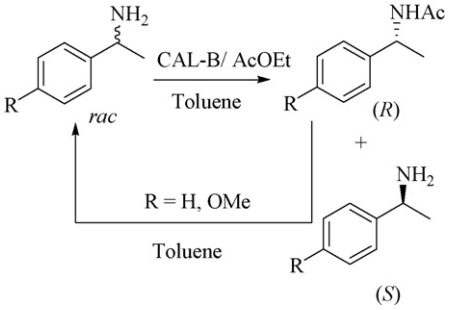
Enantiomerically enriched tertiary amines are commonly used as chiral auxiliaries, chiral bases, and catalysts in organic synthesis. Chiral tertiary amines are most important intermediates for the synthesis of pharmaceuticals and agrochemicals. Hu et al. [147] have reported an efficient and practical chemoenzymatic method for the preparation of chiral amines in addition to a variety of endo and exo cyclic alkyl–alkyl secondary amines (Scheme 65).



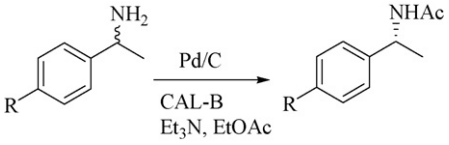
Scheme 57.



Scheme 61.

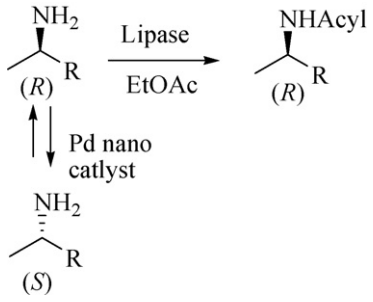


Scheme 62.



Scheme 63.

Recently Park and co-workers [148] have reported an efficient protocol for the DKR of primary amines. This protocol involves a palladium nanocatalyst as the racemization catalyst, lipase (Novozyme-435) and ethylacetate or ethylmethoxyacetate as the acyl donor (Scheme 66).

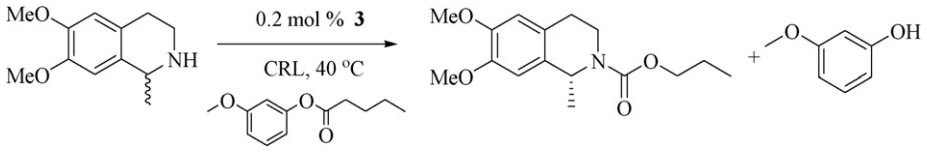


Scheme 66.

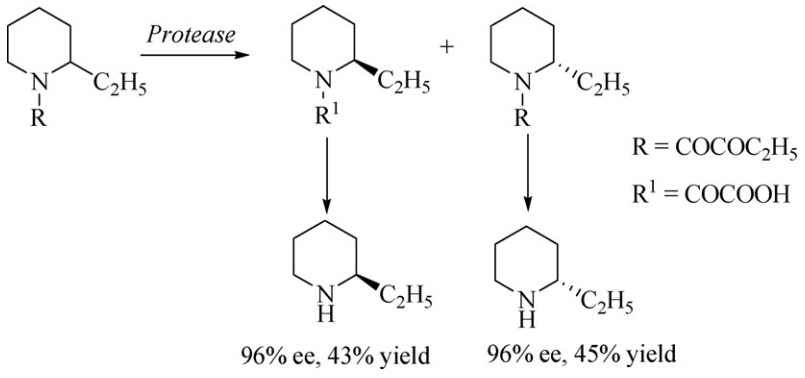
3. Enzymatic kinetic resolutions and dynamic kinetic resolutions (with out metal catalysts)

3.1. Thioesters

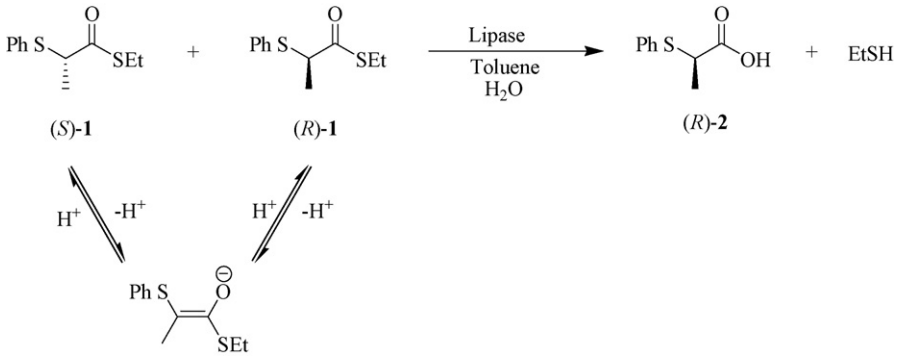
Generally enzymatic resolution processes have been carried out for esters and amides. However there are very few studies with regard to thioesters. In view of the high acidity of the α protons [149–152], Dreuckhammer and co-workers have developed the DKR of thioesters [153] which involves the mechanism as shown in Scheme 67. Extensive studies have been carried out to exploit the high acidic nature of α-hydrogen for development of a DKR process [152] (Scheme 68).



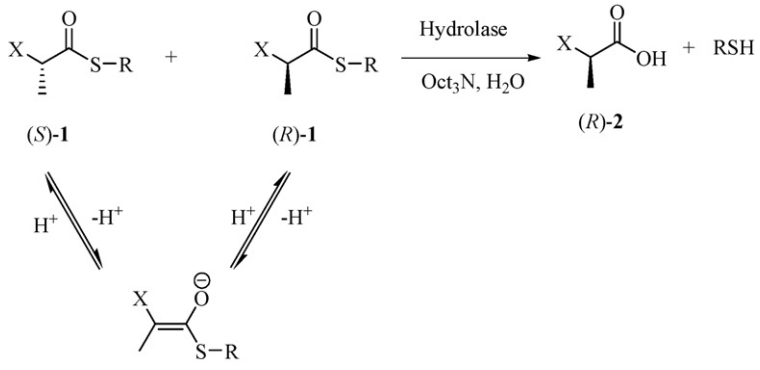
Scheme 64.



Scheme 65.

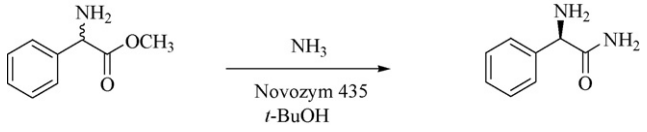


Scheme 67.



Scheme 68.

Another interesting example has been shown in Scheme 69, where a DKR process is accompanied by an enzymatic resolution to achieve high enantiomeric purity.

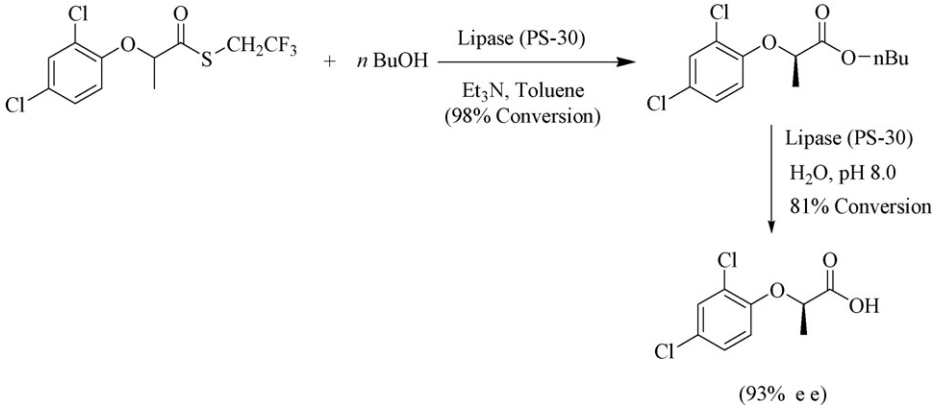


Scheme 70.

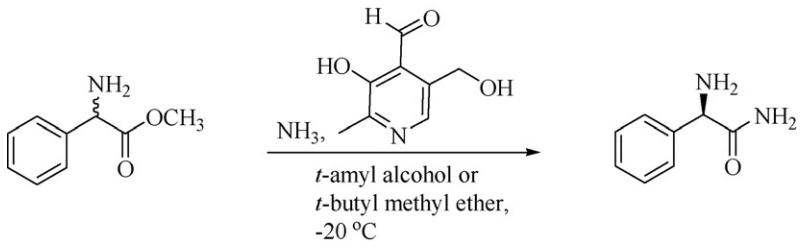
3.2. Phenyl glycine ester (ammonolysis)

Sheldon and co-workers have reported the lipase (Novozyme 435) catalyzed ammonolysis of racemic phenylglycine methylester to D-phenylglycineamide [154] (Scheme 70). The synthetic utility of this has been demonstrated in synthesis of penicillin and cephalosporin antibiotics.

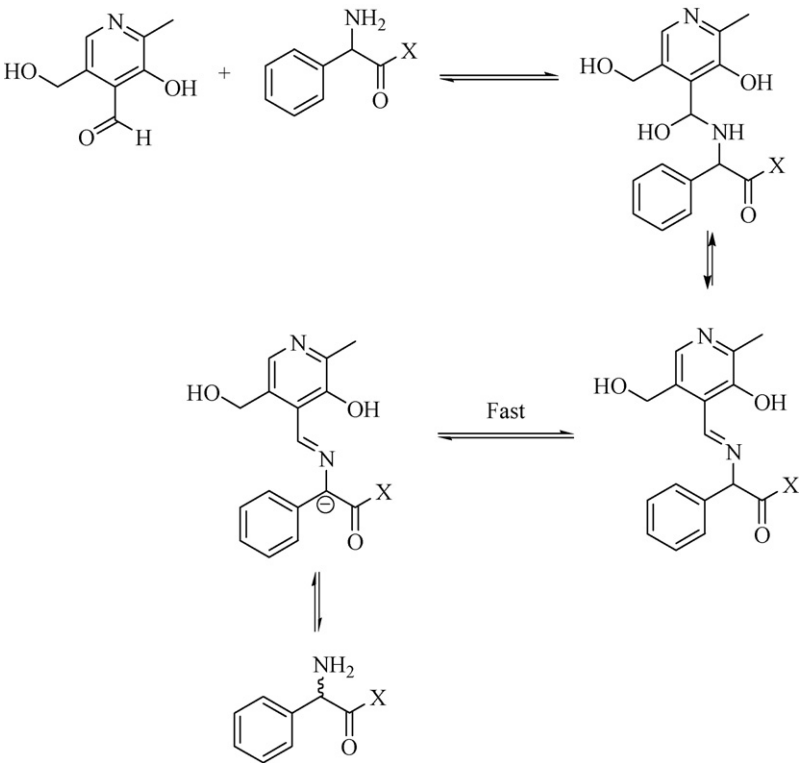
Recent efforts have lead to the development of DKR process for glycineamide by employing efficient racemizing agents like salicylaldehyde and pyridoxal along with lipase-catalyzed transesterification (Scheme 71). The proposed mechanism for this process is shown in Scheme 72.



Scheme 69.



Scheme 71.



Scheme 72.

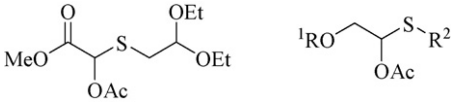
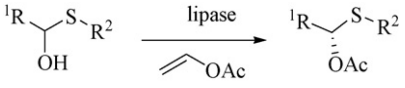


Fig. 10.

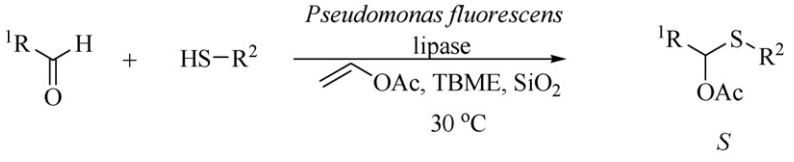


Scheme 73.

3.3. Hemiacetal

Rayner and co-workers [155] used the lipase for the resolution of α-acetoxy sulfides (Fig. 10) (Scheme 73). These α-acetoxy sulfides are useful in the synthesis of lamivudine a promising drug candidate for HIV.

Further studies on this molecule towards development of a DKR process have been performed (Scheme 74). A model very nearest to this type is that of cyanohydrins. So, the racemizing agents used in DKR of cyanohydrins have been applied for α-acetoxy sulfides, but with disappointing results. Finally, SiO_2 proved to be the racemizing agent for either enantiomer. A DKR process using *pseudomonas fluorescens* lipase



Scheme 74.

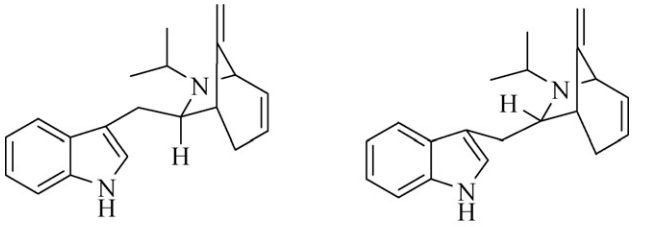
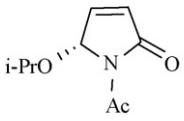


Fig. 11.



pyrrolinone dienophile

Fig. 12.

and SiO_2 as racemizing agent has been developed. A detailed study has been performed by same authors, where in the ee and yield with different substituents and conditions has been described.

3.4. Furanone and pyrrolidinones

5-(Acyloxy)-2-5*H*-furanone and pyrrolinone synthons are a class of heterocycles that are of proven potential as chiral synthons [156,157] (Fig. 11). (*R*)-1-Acetoxy-5-isopropoxy-3-pyrrolinone is used as versatile chiral dienophile for Diels–Alder reaction to demonstrate its synthetic utility [158] (Fig. 12).

Lignans based on structural moiety (Fig. 13), possessing properties like anti tumour activity, platelet activating factor (PAF) antagonists, sodium selective diuretic properties, inhibitory effect on microsomal monooxygenases in insects, etc. can be synthesized.

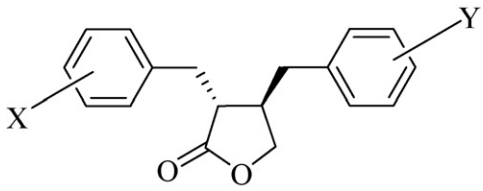


Fig. 13.

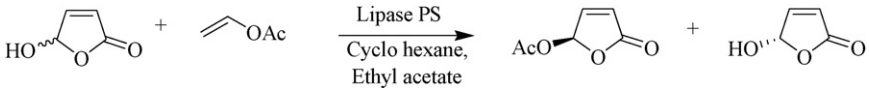
Keeping in view the high potential of these synthons in enantioselective synthesis, lipase-catalyzed resolution and second order asymmetric transformation is developed. 5-(Acyloxy)-2-(5*H)*-furanones1 and pyrrrolidines 2 have been synthesized in enantiomerically pure form by exploiting the property of spontaneous *in situ* racemization leading to complete resolution by coupling the kinetic resolution to an asymmetric transformation [159] (second order asymmetric transformation). Racemization occurs spontaneously under the reaction conditions (Scheme 75).

6-Acetoxy-2*H*-pyran-3(6*H*)-one is obtained in enantiomerically enriched form [160] by exploiting its ability to undergo facile racemization on its own with the aldehyde (Scheme 76).

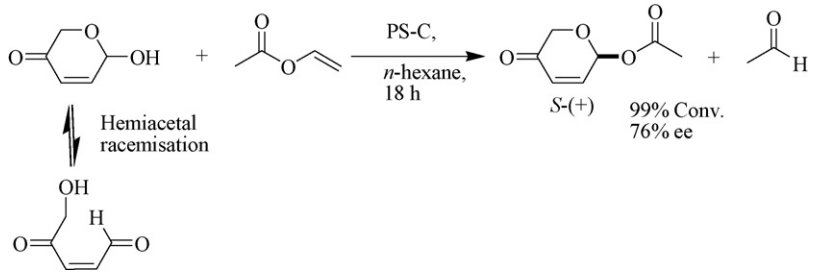
Enantiomerically pure (acyloxy) pyrrolidinones are obtained by kinetic resolution [160] employing CAL-B in *n*-hexane/*n*-BuOH (Scheme 77).

An intensive study was done by employing different substrates and a possible racemization of substrate may occur under certain conditions, probably owing to ring opening at C_5 (Scheme 78).

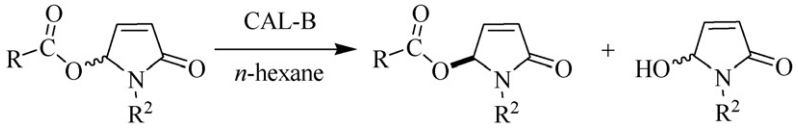
This concept has been exploited and different solvents are tested by raising temperature (Scheme 79).



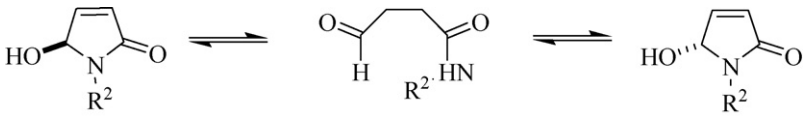
Scheme 75.



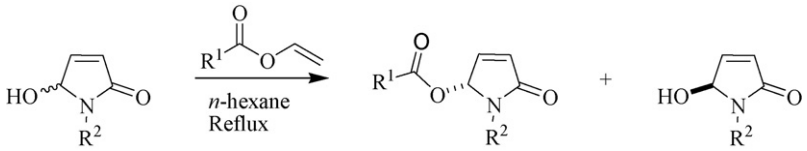
Scheme 76.



Scheme 77.



Scheme 78.



Scheme 79.

4. Conclusion and outlook

Biocatalysis has been one of the challenging areas of research towards the development of asymmetric synthetic methodologies. Recent technological developments in this area which has a relatively greener perspective have made these processes industrially more viable. Lipases are the biocatalysts of choice with remarkable enantioselectivity for practical purposes. In the last decade a reasonably good understanding has been achieved to resolve substrates of different types, thus demonstrating the wide applicability of lipases for enantioselective synthesis. Recent investigations on the combination of enzyme catalysis and metal catalysis for achieving several DKR processes are highly commendable. It is felt that this approach based on the existing knowledge in asymmetric synthesis could provide highly useful chiral intermediates for academic as well as industrial purposes.

Acknowledgement

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