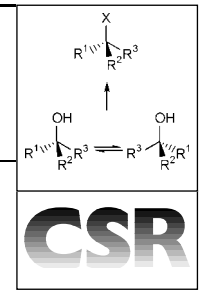
Racemisation in asymmetric synthesis. Dynamic kinetic resolution and related processes in enzyme and metal catalysis



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Received 21st June 2001
First published as an Advance Article on the web 10th October 2001

Dynamic kinetic resolution (DKR) has recently become not only an alternative to the traditional kinetic resolution, but also a new procedure for asymmetric synthesis. Enzymes are usually the tools to effect this methodology (DKR), although new techniques have emerged through the use of asymmetric transition metal catalysis. All of these methods need two supplementary steps: racemisation together with a consecutive asymmetric transformation. A breakthrough in this area appeared with the powerful combination of enzymatic resolution and transition metal-catalysed racemisation. Thus, new procedures for efficient dynamic kinetic resolution became available. This review covers the concept of dynamic kinetic resolutions emphasizing the most representative examples as well as new developments in this area. Special effort has been made to show the importance of the racemisation step in the whole asymmetric transformation process.

1 Introduction

Chiral, enantiomerically pure compounds are becoming more and more important. This is mainly due to the increasing interest and need for such compounds in pharmaceutical and agricultural industry. Although asymmetric catalysis has undergone a spectacular development during the last two decades, the most common way in industry today to obtain enantiomerically pure compounds is still *via* resolution of racemic mixtures. To obtain a single enantiomer from such a mixture, one can resolve it

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DOI: 10.1039/b105464n

either by conventional separation techniques or by using an existing difference in reactivity (kinetic resolution). In both cases, a major disadvantage is that only a maximum of 50% product yield can be obtained. In kinetic resolution (KR) the other 50% has to be separated and discarded or recycled in a more or less tedious fashion. Therefore, it is not surprising that dynamic kinetic resolution (DKR) has attracted an increasing amount of interest from both the industrial and the academic side over the past few years. DKR overcomes the drawback of classical resolution since it is theoretically possible to obtain 100% yield of the desired isomer.

For both reaction types, KR and DKR, a basic requirement has to be fulfilled. Thus, in order to obtain any resolution at all, the reaction rate (Scheme 1) of one enantiomer has to be much larger than that of the other, *i.e.* $k_F \gg k_S$ with the so-called *E* value, $E = k_F/k_S > 30$. The best results are achieved at $E > 50$–100; the higher *E* is, the better the resolution.[1] Probably the most common example of kinetic resolution is the reaction of a racemic alcohol with an acyl donor in the presence of an enzyme. In the ideal case one ends up with the expected 50% of the acylated alcohol of one enantiomer and 50% of the unreacted alcohol of the opposite enantiomer. To obtain DKR, the substrate itself has to undergo racemisation, and in this way the non-reacting enantiomer is transformed into the reacting one. In order for the DKR to be efficient, the rate constant for racemisation k_{rac} has to be equal to or greater than the rate constant k_F for converting substrate to product, *i.e.* $k_{rac} \geq k_F$. Alternatively, if the *E* value is very high, k_{rac} may be smaller than k_F. In all cases, k_{rac} has to be larger than k_S.

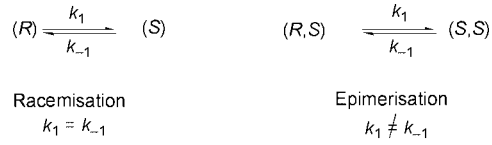
The question thus arises of how to efficiently a) resolve a substrate and b) racemise it. Our ongoing synthetic efforts in this field, together with developments in the literature over the past few years, prompted us to summarise and highlight some of the techniques used to obtain DKR by either enzymatic or non-enzymatic methods. For most examples dating from before 1996 the reader is directed to appropriate reviews from this time.[1a,2–5]

2 Racemisation

Despite the importance of an efficient resolution of a racemic mixture in order to get high ee's of both enantiomers, a dynamic kinetic resolution process is governed by the continuous equilibration of both enantiomers. Therefore, the racemisation is one parameter that has to be optimised. Recently, this topic has been the subject of a thorough review article by Zwanenburg *et al.*[6] Herein, we will point out some of the most significant and used examples of racemisation/epimerisation applied to dynamic processes (Scheme 2).

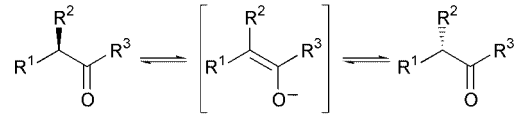
Thermodynamically, racemisation is a favourable process, which is due to the increase of entropy caused by the mixing of the two enantiomers. This entropy increase can be estimated (ignoring the enthalpy contribution due to the *R–R* or *S–S vs. R–S* interactions) as $\Delta G^\circ \approx RT\ln\frac{1}{2}$, which corresponds to −0.41 kcal mol^{-1} (−1.7 kJ mol^{-1}) at 25 °C.

Although the racemisation technique depends to a large extent on the compound that is going to be racemised,



Scheme 2

Zwanenburg *et al.* have classified the racemisation into different methods: i) thermal racemisation, ii) base-catalysed racemisation, iii) acid-catalysed racemisation, iv) racemisation *via* Schiff bases, v) enzyme-catalysed racemisation, vi) racemisation *via* redox and radical reactions.[6] Among these methods, only those taking place in a single step and under mild reaction conditions are suitable for a DKR. For compounds with a stereogenic centre bearing an acidic proton (*e.g.* adjacent to an electron withdrawing group, such as a ketone or ester), base-catalysed racemisation is the method of choice to equilibrate



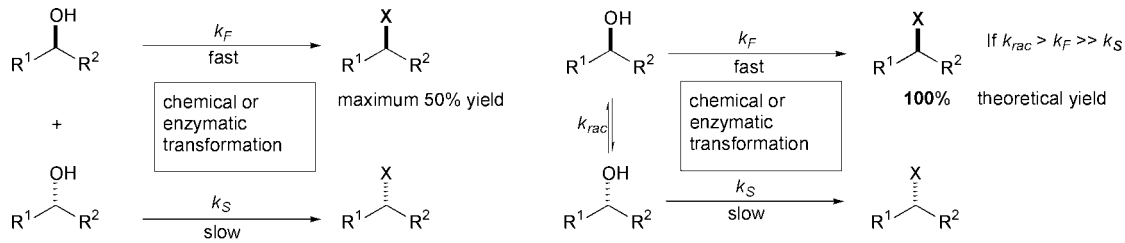
Scheme 3

enantiomers *via* an enolate intermediate (Scheme 3).

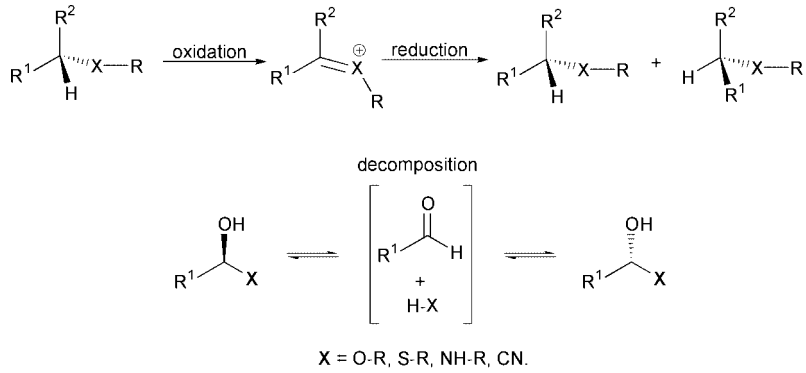
On the other hand, compounds without acidic protons at the stereogenic centre, but with a heteroatom such as O, S or N, can be racemised *via* a planar sp^2 hybridised intermediate, either by a redox process (*e.g.* alcohol → ketone → alcohol) or by elimination–readdition (such as the cleavage of hemithioacetals and cyanohydrins). Here, too, these processes have to be performed in a single step in order to achieve DKR (Scheme 4).

Racemisation *via* the formation of Schiff bases, as used *e.g.* for amino acid synthesis, has been less utilised in DKR. It is interesting to note that many enzymes themselves use this method to achieve racemisation *via* pyridoxal 5′-phosphate-dependent α-aminoacid racemases (Scheme 5). Condensation of amino acids with aldehydes under acidic conditions leads to the corresponding Schiff bases. In acidic media these can undergo a proton shift at the stereogenic centre resulting in the racemisation of the α-carbon in the amino acid moiety (Scheme 5).

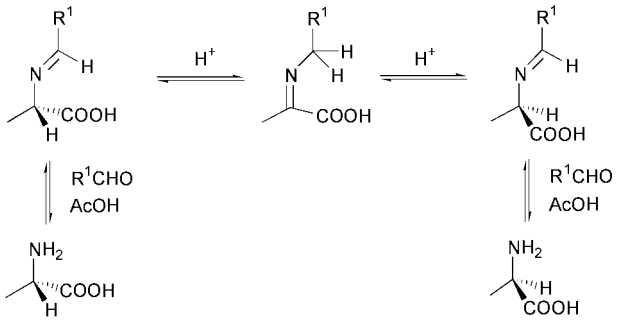
Finally, other common racemisation methods are those based on the lability of certain molecules (*e.g.* organometallic species such as organolithium, organomagnesium or organopalladium compounds) and those involving sequential nucleophilic displacement over the same stereogenic centre. DKRs using these racemisation techniques have been reported where the so-called resolution step should be considered rather as an asymmetric transformation. The narrow borderline between kinetic resolutions and asymmetric transformations makes it more difficult to classify these transformations correctly. Terms such as asymmetric transformation of the second kind, dynamic kinetic asymmetric transformation (DYKAT) and dynamic kinetic resolution (DKR) are often used ambiguously. Herein, we will refer to them as the authors did in the original articles.



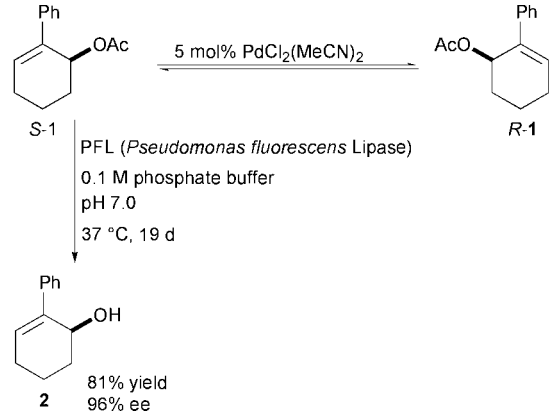
Scheme 1 Comparison of kinetic *vs.* dynamic kinetic resolution using alcohols as examples.



Scheme 4



Scheme 5



Scheme 6

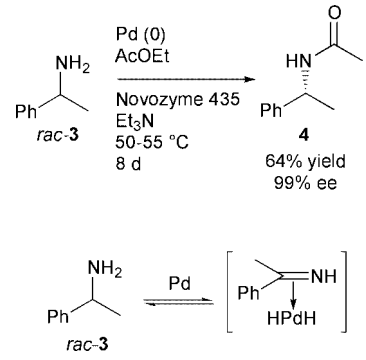
3 Enzymatic methods

In recent years, the use of biocatalysts for organic transformations has become an increasingly attractive alternative to conventional chemical methods. Especially in the resolution of enantiomers, the use of enzymes represents a major contribution to this type of transformation. In fact, lipases often display high applicability and efficiency in resolution processes. Furthermore, due to the fact that lipases can be used in organic solvents with improved chemo-, regio-, and enantioselectivity, their application has increased dramatically.[7] Combination of enzymatic resolution with *in situ* racemisation of the unreactive enantiomer leads to a dynamic kinetic resolution process. Faber *et al*. have reported on a biochemical DKR, in which the lability of a stereogenic centre is used in an efficient enzymatic resolution.[1] Herein, we would like to highlight those examples that have not been previously covered.

3.1 Transition metal-catalysed racemisation coupled with enzymatic resolution

Stürmer highlighted in 1997 a new concept for dynamic kinetic resolution: a tandem process with enzymes and transition metal complexes.[4] This combination has recently attracted much attention. Williams and Gihani demonstrated the compatibility of enzymes with metal complexes in one pot.[4,8] Palladium-catalysed racemisation of allylic acetates in the presence of a hydrolase illustrates this concept (Scheme 6). Hydrolysis of the cyclic α-substituted allylic acetate **1** by *Pseudomonas fluorescens* lipase (PFL) in a phosphate buffer in the presence of palladium-catalysed racemisation leads to the corresponding allylic alcohol **2** in 96% conversion (81% yield) and 96% ee.

The pioneering work by Reetz and Schimossek[9] in the DKR of 1-phenylethylamine (**3**) demonstrates the applicability of the lipase–transition metal combination to amines. Even though it has been mentioned in several previous reviews,[4,8] so far, it is the only dynamic kinetic resolution of an amine published to date (Scheme 7). Palladium on carbon as racemising agent together with an immobilised lipase (from *Candida antarctica*,

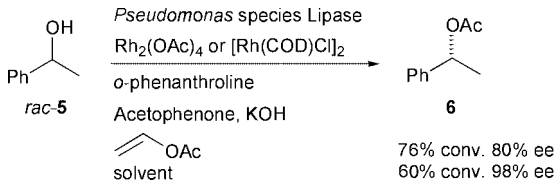


Scheme 7

Novozyme 435®) and ethyl acetate as an acyl donor in the presence of triethylamine led to the acylated 1-phenylethylamine (**4**) in 64% yield and 99% ee starting from **3**. The racemisation step, which proceeds *via* an amine–imine equilibrium promoted by palladium(0), is very slow and therefore the reaction takes 8 days.

Transition metal-catalysed hydrogen transfer reactions[10] involving reversible formation of a ketone from an alcohol opened up new racemisation pathways for secondary alcohols. The reaction between an optically pure alcohol and its corresponding ketone in the presence of transition metals leads to racemisation of the alcohol. The combination of this racemisation method with lipase-catalysed acetylation of one of the enantiomeric alcohols was a methodology introduced by the groups of Bäckvall[11] and Williams.[8,12] In the system used by Williams the racemisation of 1-phenylethanol (**5**) was performed by rhodium complexes, an inorganic base and *o*-phenanthroline as cocatalyst in the presence of 1 equiv. of acetophenone. The resolution was carried out by a *Pseudomonas* species lipase (PSL) using vinyl acetate as an acyl donor. The combined system leads to acetate **6** with 98% ee at 60% conversion, using a rhodium acetate complex in a vinyl acetate–

cyclohexane (2:1) mixture, or 80% ee at 76% conversion conducted with $[Rh(COD)Cl]_2$ in vinyl acetate–dichloromethane (3:1) (Scheme 8).



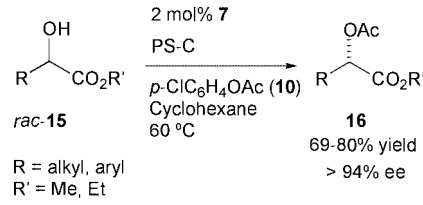
Scheme 8

Bäckvall and co-workers have developed a system that is based on a robust ruthenium complex and a specially designed acyl donor.[11,13] Ruthenium catalyst **7**[14] does not need an external base to perform the racemisation, therefore it does not interfere with the enzymatic activity and at the same time avoids direct base-catalysed transesterification. This is because complex **7** dissociates into a coordinatively saturated hydride complex **8** and complex **9**, with the latter acting as a base (Scheme 9).[15] The acyl donor **10** was chosen, because, after the acyl transfer, the resulting *p*-chlorophenol does not react with the ruthenium catalyst **7**, whereas other acyl donors, such as alkenyl acetates, generate carbonyl compounds that compete for the catalyst. The enzyme employed was a lipase from *Candida antarctica* (Novozym 435®). This new process allowed the synthesis of **6** starting from *rac*-**5** in quantitative yield and >99% ee.[11] The ruthenium–enzyme–catalysts combination was applied to the DKR of a variety of secondary alcohols[13] (**11**) and secondary diols[16] (**13**) (Scheme 10). It is worthy to remark that in compounds **13** (*dl*:*meso* ≈ 1:1) a traditional enzymatic resolution would lead to the diacetates **14** (*R*,*R*-form) in a maximum yield of 25%. The values obtained in this case (61–90% isolated yield, >99% ee) show an efficient double dynamic kinetic resolution (Scheme 10).

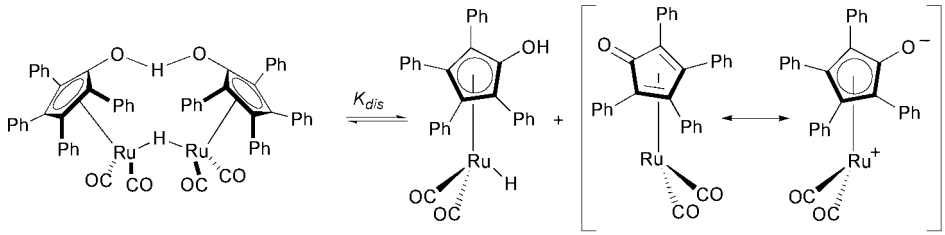
In the examples described above, the need for additional ketone to speed up the racemisation process has recently been the subject of a detailed investigation in our group. In principle, added ketone is not necessary to carry out the racemisation. The rate-accelerating effect of the added ketone can be explained by the faster readdition of the ruthenium hydride to the ketone, due to the higher concentration of ketone. Nevertheless, systems have been developed for the enzymatic resolution of secondary alcohols (**11**) coupled with ruthenium-catalysed racemisation without added ketone.[13,17]

Combined enzyme- and transition metal-catalysed reactions have been applied not only to simple secondary alcohols. It has been shown that this methodology is also compatible with other functionality in the molecule besides hydroxy groups. Racemic α-hydroxy acid esters (**15**) have been subjected to the aforementioned methodology giving α-hydroxy ester acetates (**16**) in high enantioselectivity and good yields (Scheme 11).[18] In the latter case, the formation of an *O*-acetylated α-hydroxyester increases the acidity of the α-proton. The presence of any base in the system would therefore lead to racemisation of the product by enolisation. Thus, employment of ruthenium catalysts that do not need activation by base is required. Among the different ruthenium catalysts used, catalyst **7** was crucial for the stereochemical outcome of the reaction. *Pseudomonas* species lipase (PS-C from Amano Ltd.) and **10** as an acyl donor were used in this case for the resolution of different α-hydroxyesters.

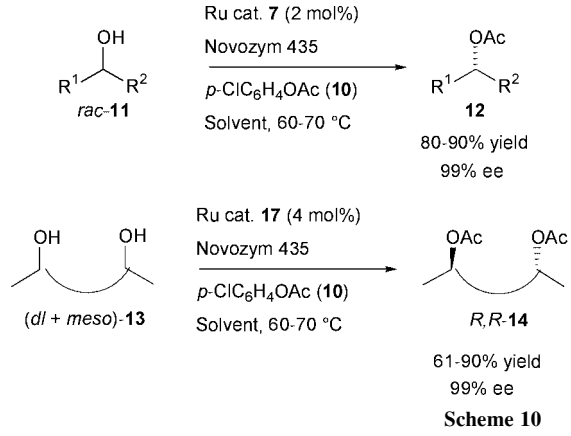
The same methodology was also applied to the dynamic kinetic resolution of β-hydroxyesters.[19] In the latter case, the reaction was carried out in tandem with an aldol reaction and the β-hydroxyester formed, after neutralisation, underwent DKR using the immobilised lipase from *Candida antarctica* (Novozym 435®) and catalyst **7** (Scheme 12).[19] The β-acetoxy esters



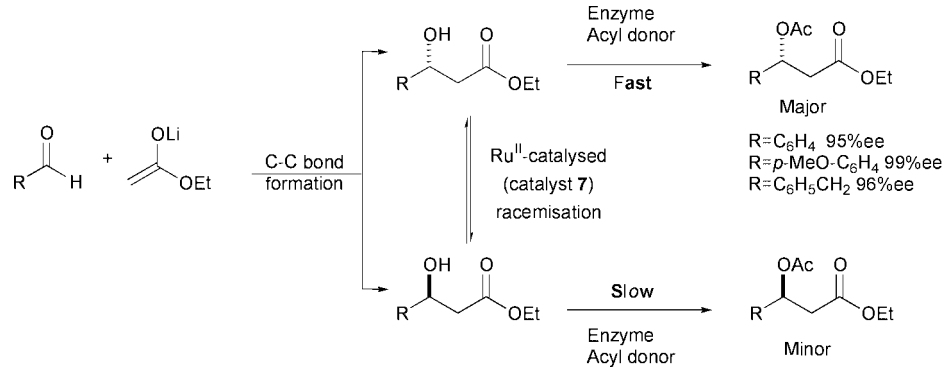
Scheme 11



Scheme 9



Scheme 10



Scheme 12

were obtained in yields over the range 69–75%, based on the aldehyde, and with high ee.

Very recently, efficient methods for dynamic kinetic resolution of β-azido alcohols[20] and β-hydroxy nitriles[21] were also developed.

Kim *et al*. have recently applied the same concept introduced by Williams (Scheme 6) for the dynamic resolution of acyclic allylic acetates (Scheme 13).[22] In this case a palladium(0) complex racemises allylic acetate **17** *via* a π-allylpalladium intermediate, which also gives rise to the side products **19** and **20** (Scheme 13). Immobilised lipases from *Pseudomonas cepacia* (PCL) and *Candida antarctica* (CAL) perform the resolution step with hydrolysis of the acetate completing the DKR process. It should be noted though that the authors in this case used a two-step, one-pot procedure (kinetic resolution and then racemisation *in situ* of the remaining enantiomer), thus rendering this process only formally a DKR process.[23]

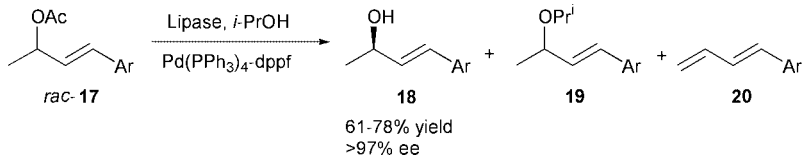
Park and Kim reported on the DKR of allylic alcohols **18** as a reverse reaction to the one depicted in Scheme 13. Racemisation of **18** was achieved using ruthenium catalysts **23** and **24**, whereas the enzymatic resolution was achieved with PCL using *p*-chlorophenyl acetate (**10**) as an acyl donor (*vide infra*). Thus, different alcohols were subjected to this procedure, leading to the corresponding allylic acetates (**17**) in 99% ee with 85% conversion (Scheme 14).[24]

3.2 Other types of racemisation in combination with enzyme catalysis

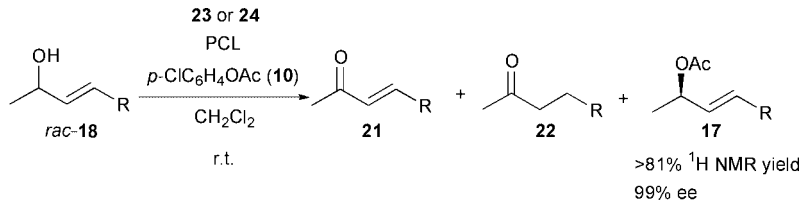
A new approach to dynamic kinetic resolution mediated by enzymes was reported by Sheldon *et al*. in the lipase-catalysed ammonolysis of phenylglycine ester **25**.[25] Thus, the amino ester **25** was racemised *via* Schiff base formation with pyridoxal or salicylaldehyde under the aforementioned ammonolysis conditions (Novozyme 435 in the presence of NH_3). The corresponding D-phenylglycine amide **26** was obtained in 88% ee with 85% conversion (Scheme 15).

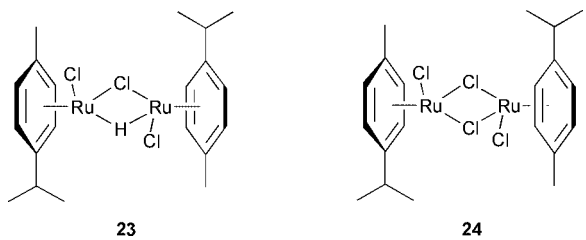
Racemisation *via* S_N2 displacement has been used for the dynamic kinetic resolution of the α-bromo ester **27** by enzymatic hydrolysis.[26] The product, an α-bromo acid (present in the reaction media as the corresponding carboxylate), is less reactive in the S_N2 process. Investigations of the bromide source and the lipase employed led to an optimised system where an immobilised phosphonium bromide was used together with cross-linked enzyme crystals from *Candida rugosa* lipase (CLEC-CRL) in water at pH 7 to afford the α-bromo carboxylic acid **28** in 79% ee at 80% conversion (78% yield) (Scheme 16). Very recently this procedure was extended to α-chloro esters.[26b]

Resolution of *in situ* formed hemithioacetals was investigated by Brand *et al*.[27] As shown in Scheme 17, different thiols and

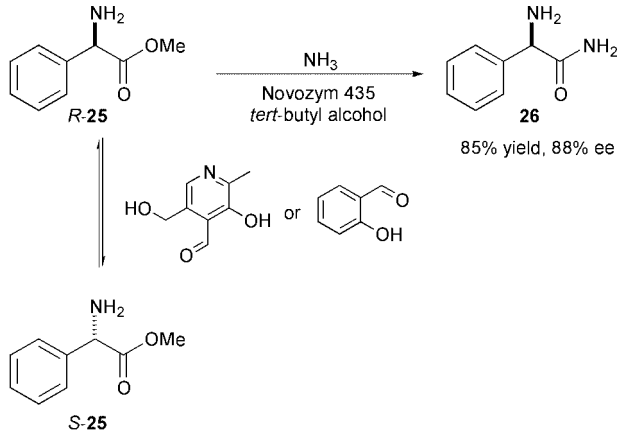


Scheme 13

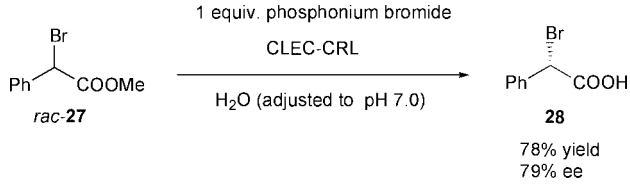


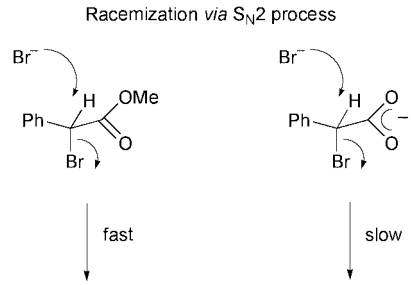


Scheme 14

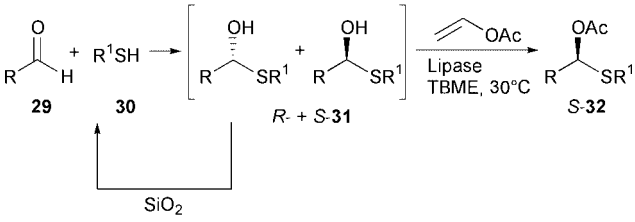


Scheme 15





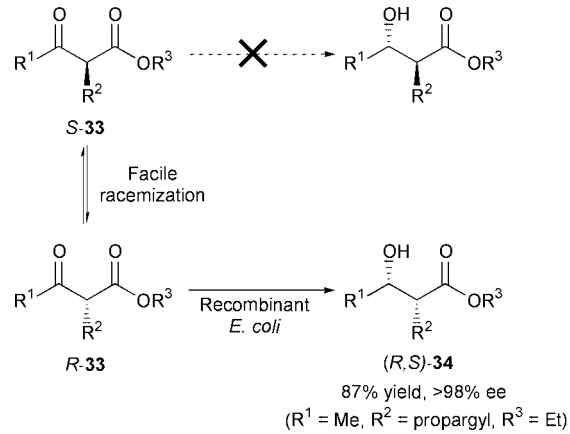
Scheme 16



Scheme 17

aldehydes were mixed together to form racemic hemithioacetals (**31**) of which essentially a single enantiomer was acylated by *Pseudomonas fluorescens* lipase under the reaction conditions. Racemisation of the unreactive hemithioacetal isomer was obtained by a dissociation–recombination process catalysed by silica gel. The best results, obtained with R = $AcOCH_2$ and R^1 = *n*-octyl, allowed the isolation of the acetylated (*S*)-hemithioacetal **32** in 85% yield and 95% ee. Quite remarkable is the fact that with this method it is possible to create a stereocentre from achiral precursors. This is also the case in the DKR of cyanohydrins.[1]

Microbial reduction of β-keto esters is a well-known biochemical transformation.[28] When applied to α-substituted β-keto esters, facile racemisation at the α-position *via* an enolisation equilibrium allows DKR. This transformation has been extensively studied and there are a number of publications dealing with this topic (for more information about this type of transformation see ref. 1). In a recent example, a recombinant *Escherichia coli* (*E. coli*) performs the stereoselective reduction of α-alkyl-β-keto esters (**33**), resulting in a dynamic resolution due to the enantiomeric equilibration of the starting material under the reaction conditions.[29] The best of the substrates gave 87% yield and >98% ee (Scheme 18).



Scheme 18

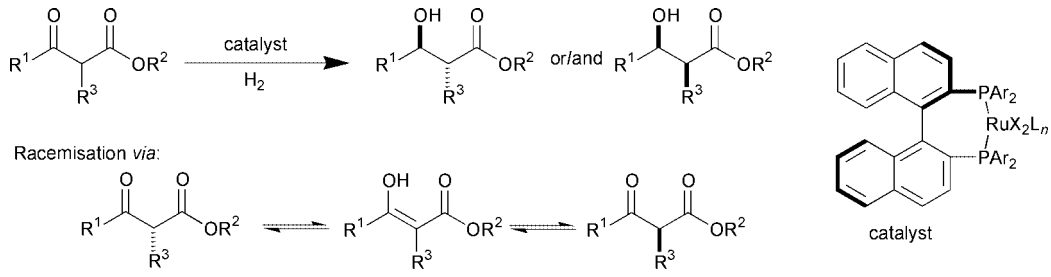
4 Non-enzymatic methods

There are certainly numerous ways of obtaining resolutions of chiral compounds by chemical means. The combination of these chemical kinetic resolutions with racemisation is, however, less obvious. Nevertheless, DKR processes can be exploited just as successfully for nonenzymatic reactions. Typically, chiral auxiliaries or chiral organometallic complexes are employed to achieve the desired resolution. An early example of a non-enzymatic dynamic process was described in 1979 by Tai and co-workers for the hydrogenation of an oxobutyrate with chiral nickel catalysts.[30] Even though the best results only gave a diastereomeric ratio of 70:30, with the highest enantiomeric excess around 80%, this result was nevertheless quite amazing at that time. The results implicated a moderate dynamic kinetic resolution and were the starting point for further research in this area as has been summarised in one of Noyori's latest reviews.[2,31]

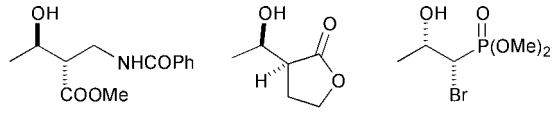
4.1 Chiral metal catalysts

Research done in this area often relies on the use of chiral metal complexes as catalysts (*cf.* the early findings of Tai and co-workers). In general, the most successful substrates usually contain a carbonyl function with an adjacent acidic C–H center. Ruthenium(II) catalysts together with a bidentate chiral ligand, usually of a phosphine type such as BINAP, under hydrogenation conditions give product yields of up to 90–100% with 90–100% ee (Scheme 19).[2,31] As described in Section 2, enolisation is the basis for the racemisation. Together with the highly selective, chiral metal complex only one major product is obtained as was demonstrated with a wide range of substrates. These can serve as useful precursors for drug or natural product synthesis (Scheme 20).

A recent example by Genêt and co-workers described the elegant synthesis of enantiomerically pure β-hydroxylysine, in which the key step was a ruthenium-catalysed asymmetric hydrogenation of **35**. They obtained compound **36** in quantitative yield and high stereochemical purity by this method (Scheme 21).[32] One is not limited to phosphine ligands as has been shown by Noyori and co-workers. By employing a diamino-type ruthenium(II) complex (**37**) in a transfer hydrogenation process, benzil was selectively reduced to 100% enantiomerically pure hydrobenzoin (Scheme 22).[33] The success of this asymmetric reduction is made possible due to the



Scheme 19



Scheme 20

stepwise reduction of **38** to **39** *via* benzoin (**40**). Compound **40** itself is configurationally labile and stereomutates rapidly. Computer aided analysis showed that in the case of catalyst **37**, (*S*)-benzoin reacted 55 times more slowly than the (*R*)-isomer.

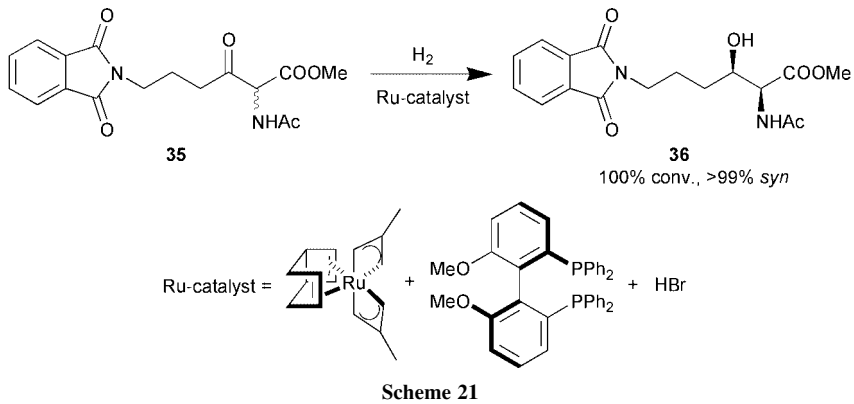
In connection with their work on chiral cobalt and chromium salen complexes Jacobsen and co-workers demonstrated DKR of epoxides (Scheme 23). With the Cr analogue **41** as catalyst they efficiently ring-opened epichlorohydrin with $TMSN_3$.[34] Quite remarkable is the possibility to ring-open epibromohydrin (but not the epichlorohydrin) using oxygen nucleophiles[35] with the cobalt complex **42**. The *in situ* racemisation of the substrates occurs in the presence of halide ions *via* a Payne-type rearrangement. Careful choice of solvent and catalyst (type of metal) is critical for suppression or enhancement of this effect.

Equilibration between π-allylpalladium complexes bearing chiral ligands has been and still is one of the most efficient ways to carry out dynamic kinetic asymmetric transformations (DYKAT) (Scheme 24).[2,5] Palladium-promoted allylic substitution is a widespread transformation in organic synthesis applicable to a great variety of substrates. Starting from racemic compounds different nucleophiles can be used yielding substitution products with high enantiomeric excess depending on the chiral ligand. In order to control both regio- and enantioselectivity many different ligands have been synthesised. Among the vast array of publications dealing with this topic, Trost and Toste have used this concept for the synthesis of enantiomerically pure lactones (Scheme 25) and applied it to the synthesis of the natural product (−)-aflatoxin B lactone (**47**).[36] After finding optimised reaction conditions, Trost and Toste[36] carried out a DYKAT of butenolide **43** in the presence of the sterically demanding coumarin **44** which yielded the intermediate **46** in good yield and in >95% ee. Further manipulation of this intermediate led to a known precursor of target **47**.

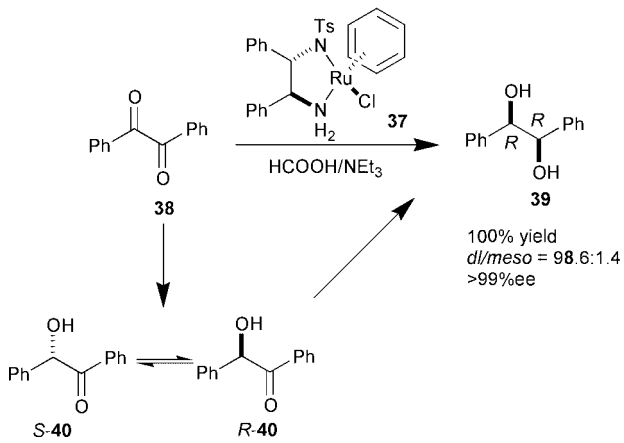
Thermal (spontaneous) racemisation is another basis for DKR, but examples of this approach are rare. When combined with (bio)chemical methods for further transformation, they are most often based on spontaneous racemisation taking place at room temperature or below. A recent example is described by Lloyd-Jones and Butts.[37] The authors used chiral nickel(II) complexes with phosphinooxazoline ligands such as **51** as pro-catalysts for Grignard cross-couplings (Scheme 26). As the Grignard reagent they employed the chiral racemic 1-phenylethylmagnesium chloride (**48**), which stereomutates spontaneously, and cross-coupled it with (*Z*)-β-bromostyrene (**49**). The authors' idea was that if this racemisation occurs faster than the rate of the cross-coupling reaction, then the process would become a dynamic kinetic resolution. At best, the enantioselectivity obtained was in the range of 40% (at 25 °C) with isolated yields of around 90%, which shows that a (moderate) dynamic kinetic resolution has taken place. A simplified mechanistic cycle is depicted in Scheme 27.

Azlactones (**52**) constitute an important class of compounds due to their straightforward transformation into amino acids. The lability of these compounds towards acid- or base-catalysed racemisation makes them useful substrates for DKR (Scheme 28). In general, amino acids and derivatives are often used as substrates for DKR *via* enzymatic transformations,[1] because of the many ways available to racemise these substrates.[6]

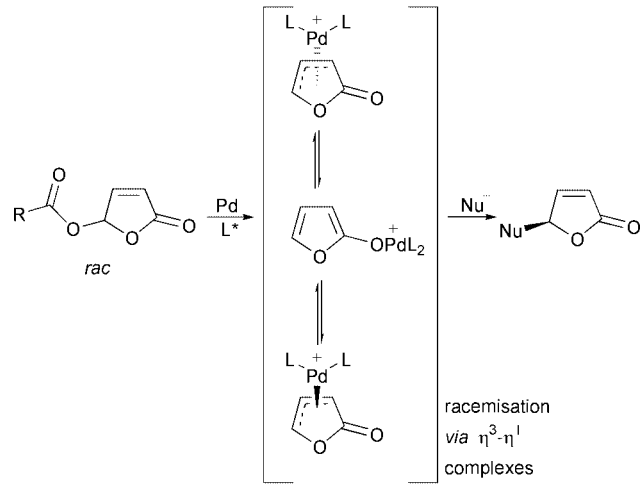
Fu *et al*. reported the synthesis of protected α-amino acids from racemic azlactones[38] (Scheme 29) employing DMAP derivative **54** as the catalyst for the ring opening of azlactones by alcohols. These alcohols participate in the *in situ* acid-catalysed racemisation generating protected α-amino acids in high yields and with ee's as a function of the alcohol employed as nucleophile. The stereoselectivity of the DKR of **53** increases as the steric demand of the alcohol increases, reaching 78% ee when *i*PrOH is used (Scheme 29). Unfortunately, ring opening under these conditions requires long reaction times ($t_{½} \approx 1$ week). This dependence of ee on the structure of the alcohols suggests that nucleophilic addition of catalyst **54** to the enantiomeric azlactone is not the stereochemically-determining step as it could be initially rationalised. Although the ee values



Scheme 21



Scheme 22



Scheme 24

are quite far from the final goal in DKR, it is worthwhile to note that these results represent the best selectivities reported to date for the deracemisation–ring opening of azlactones with non-enzymatic catalysts.

4.2 Chiral auxiliaries

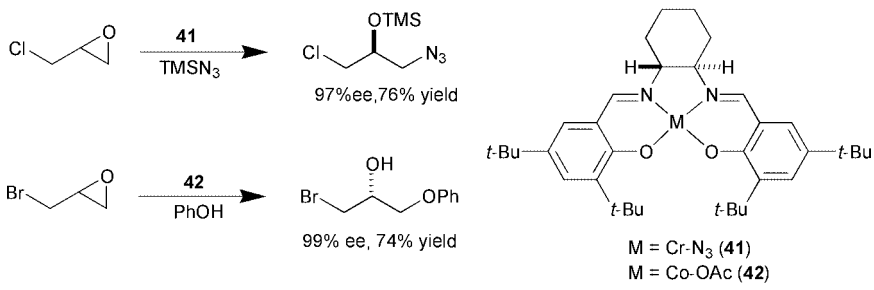
Besides metal complexes bearing chiral ligands there is also the possibility of using chiral auxiliaries for the asymmetric induction. Enders *et al*. used chiral auxiliaries such as SAMP (**55**) to produce chiral hydrazones in nucleophilic displacement reactions.[39] α-Substituted hydrazones play an important role here since they can easily epimerise at the α-position. This epimerisation stems from the stabilisation of a positive charge at this position. Thus, starting from an α-substituted aldehyde and transforming the latter to a chiral hydrazone it is possible to substitute at the α-position with several carbon, sulfur and oxygen nucleophiles. The a^2-reactivity (Umpolung) is achieved by using different kinds of Lewis acids for complexation. The reaction for the model compound **56** used by Enders *et al*.[39] is shown in Scheme 30.

Nucleophilic substitution on configurationally labile halides has been studied by several research groups.[3,40,41] All these studies were focused on compounds with a bromo or iodo atom in the α-position with respect to a carboxylic acid derivative (ester or amide), where the S_N2 is governed by a chiral auxiliary placed in the carboxylic moiety. Racemisation takes place by consecutive inversions at the labile centre induced by halide salts or any other additive. Except in one case (alkoxide was used as nucleophile, Devine *et al*.[42]), the use of amines as nucleophilic reagents is a common feature. Differences arise from the type of chiral auxiliary employed to achieve a high enantioselective asymmetric transformation (Scheme 31).[3,5]

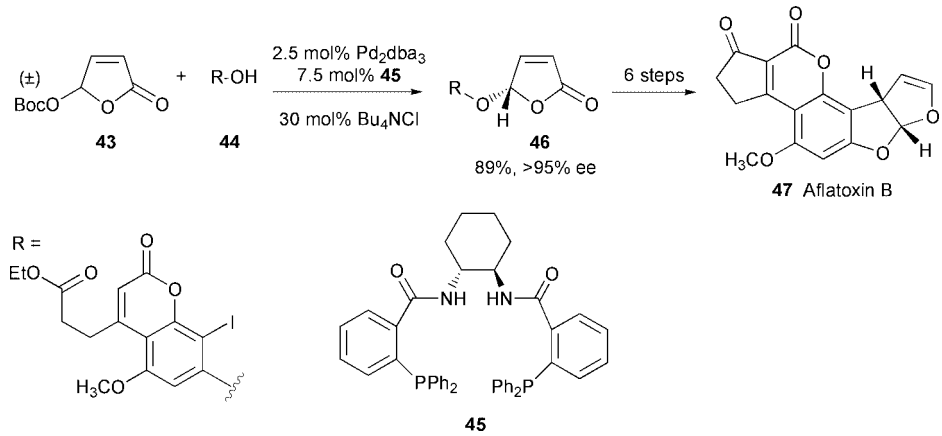
Norton *et al*. reported on the asymmetric formation of α-amino acid esters through a dynamic process (Scheme 32).[43] Addition of *N*-substituted amines to Cp_2ZrCl_2 gives configurationally labile zirconaaziridines **57**. Reaction of the latter with chiral cyclic carbonated CO_2 synthons [(*R*,*R*)-**61**] leads to enantioselection for one of the zirconaaziridines intermediates **57**. By controlling the CO_2 insertion rate by slow addition *via* syringe pump, high values of DKR were achieved. Alcoholysis of **58** would give the corresponding α-amino acid ester **59**, together with the C_2 symmetric diol **60** used as chiral auxiliary. This is a good example of how, by simple variation in the mode of addition, it is possible to control the rate of racemisation so that $k_{rac} \gg k_F$ (*vide supra*) in order to achieve a good DKR.

Configurationally labile anions are often utilised in asymmetric synthesis *via* DKR.[2,3,5] Asymmetric synthesis with organometallic bases to effect enantioselective deprotonation in the presence of a chiral complexing agent such as (−)-sparteine (**62**) is also an often-used procedure. However, there are examples where the enantioselection observed does not come from an asymmetric deprotonation to form a chiral anion, but from deprotonation and subsequent complexation of two diastereomeric salts in equilibrium. The latter asymmetric transformation can be achieved in two ways: (i) selective complexation of the ligand with one of the enantiomers, allowing the other enantiomer to racemise and finally form the favoured complex, which is then stereochemically trapped by reaction with an electrophile; (ii) the ligand may complex both enantiomers so that the two diastereomeric complexes exist in equilibrium; preferential reaction of the electrophile with one diastereomer accompanied by fast equilibration of unreacted complex will then lead to the asymmetric transformation. Although, in principle it might be difficult to distinguish the operating process, Beak *et al*. have shown how to differentiate between the three different reaction pathways.[44] Using as a model substrate *N*-Boc allylamine **63**, the mechanism of the asymmetric transformation could proceed *via* asymmetric deprotonation, dynamic thermodynamic resolution (*vide infra*) or dynamic kinetic resolution (formally a dynamic asymmetric transformation; DYKAT) (Scheme 33).

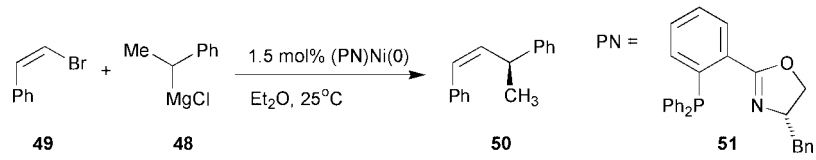
In a dynamic thermodynamic resolution, the dynamic step of equilibration to a thermodynamic ratio of isomers is slower than a subsequent product-forming step (that is, $k_{rac} < k_F$ in Scheme 1). Beak and co-workers have analysed these lithiation–



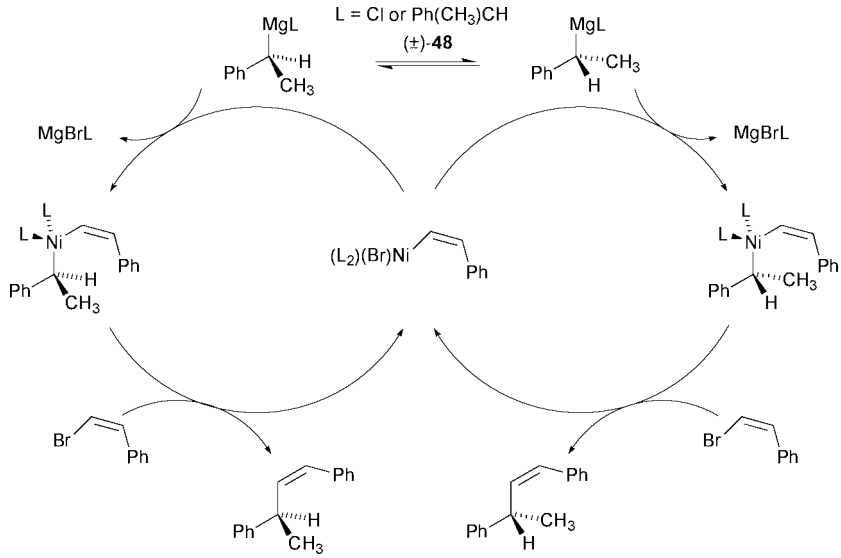
Scheme 23



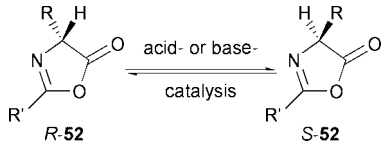
Scheme 25



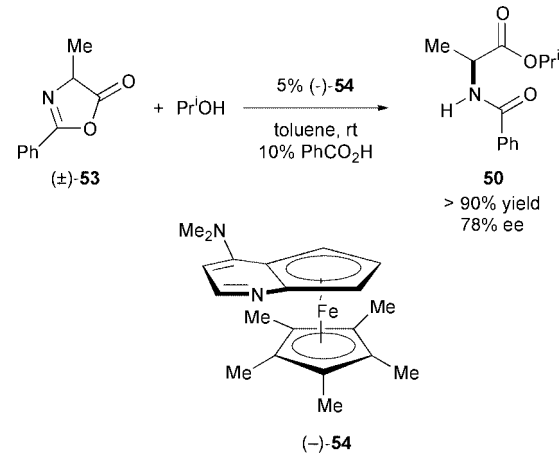
Scheme 26



Scheme 27



Scheme 28

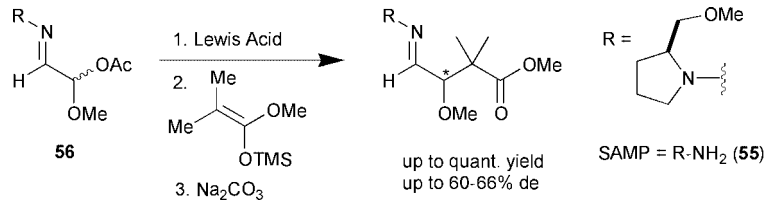


Scheme 29

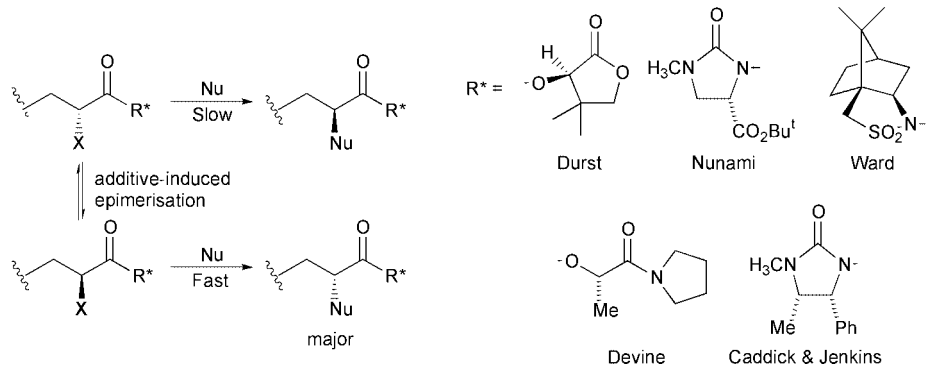
substitution pathways for reactions of (*E*)-**63** with *n*-BuLi–**62** to afford enecarbamate products **64**. The high enantio-enrichments achieved show that each of the three enantiodetermining processes can be operative, making it possible to select the reaction pathway by controlling the reaction conditions.

5 Conclusion

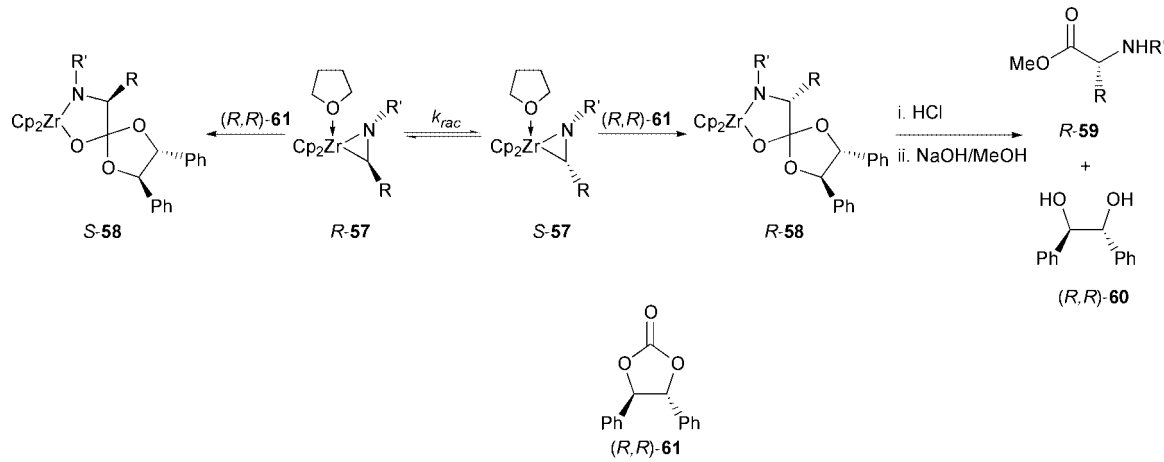
Racemisation and epimerisation of organic compounds have frequently been considered as undesirable reactions in organic chemistry. It is often desirable that a stereogenic centre is stable towards isomerisation in order to have control over the stereochemistry. However, as has been shown in this review, when coupled to a stereoselective transformation, there is an



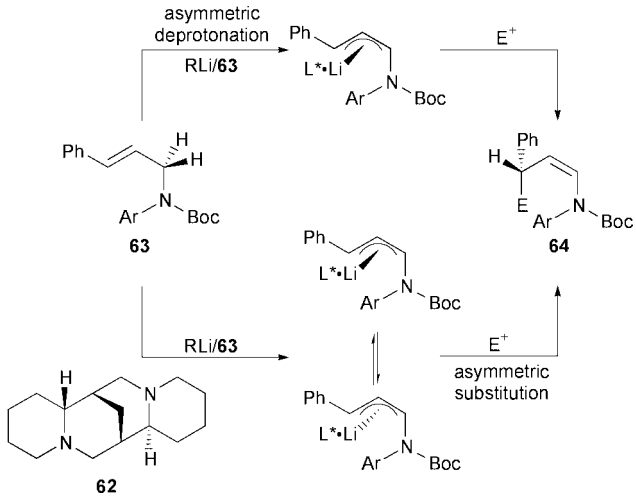
Scheme 30



Scheme 31



Scheme 32



Scheme 33

increased interest in developing techniques for controlled racemisation (or epimerisation). Thus, a racemisation coupled to a kinetic resolution is a powerful methodology for obtaining enantiomerically pure compounds *via* a dynamic process (DKR or DYKAT).

6 Acknowledgements

Financial support from the Swedish Foundation for Strategic Research, the Swedish Natural Science Research Council, and AstraZeneca R&D is gratefully acknowledged.

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