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Dynamic Kinetic Resolution

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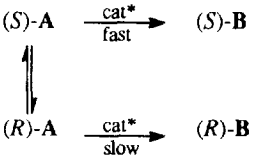
Abstract: The equilibration of a mixture of enantiomers or diastereoisomers prior to or during kinetic resolution permits the isolation of a single isomer of one product in >50% yield. Examples of such processes involving both enantioselective and diastereoselective reactions are discussed. In some cases highly efficient processes are available, yielding, for example, cyanohydrin acetates and α-substituted carboxylic acid derivatives in high yield and with high e.e. and d.e. respectively.

Contents

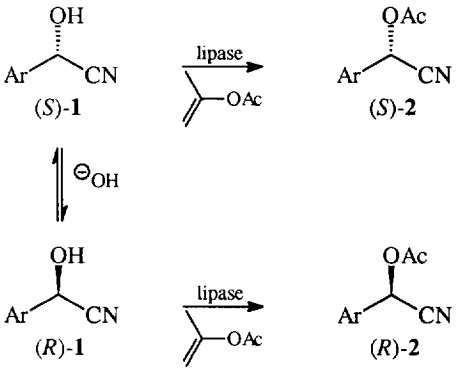
1. INTRODUCTION

Kinetic resolution has long been recognised as an effective tool for the preparation of enantiomerically enriched compounds.[1] Like conventional resolution processes, however, the maximum yield of one stereoisomer of the starting material or product which can be obtained is 50%. Therefore any procedure which allows *in situ* epimerisation of the substrate prior to the reaction has the advantage that it can in principle bring about quantitative conversion of the starting material into a single stereoisomer of the product.

The simplest process of this type is shown in scheme 1a, and is exemplified by the enzyme-catalysed acylation of a racemic cyanohydrin (Scheme 1b).[2] When this reaction is carried out in the presence of a basic anion exchange resin rapid interconversion of the (*R*)- and (*S*)-isomers of the cyanohydrin occurs leading to a high yield of one enantiomer of the product. In practice the parent aldehyde can be directly converted into the enantiomerically enriched cyanohydrin acetate in high yield. For example, benzaldehyde can be converted into its (*S*)-cyanohydrin acetate *(S)*-**2** in 96% isolated yield and 84% e.e..

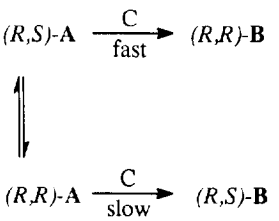


Scheme 1a

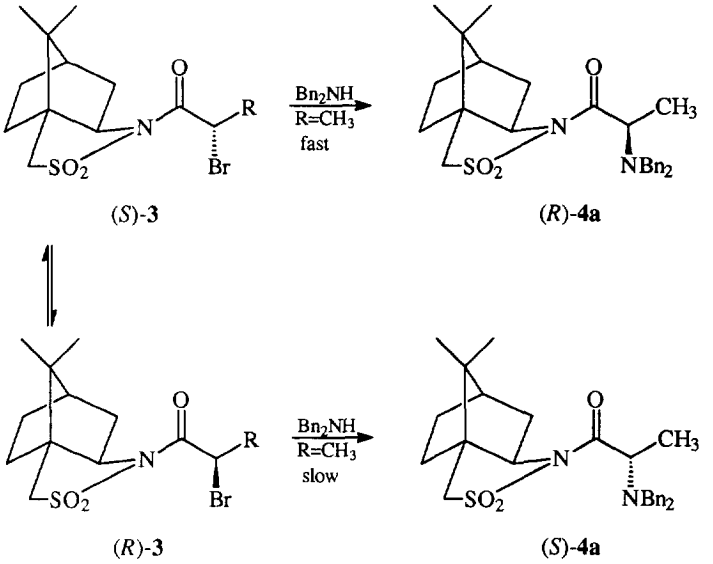


Scheme 1b

A number of other examples of this type of reaction are described in section 2. For dynamic kinetic resolution to be effective the reactant isomers must be in rapid equilibrium, making removal of one isomer the rate determining step. At least three other types of process involving rapid racemisation or epimerisation of the substrate prior to or during an enantioselective or diastereoselective reaction can be identified. One such process is the reaction of a mixture of equilibrating diastereoisomers with an achiral reagent (Scheme 2a). An example of this type of reaction is provided by our own work on the reactions of α-bromoamides with nucleophiles (Scheme 2b).[3] We have demonstrated that heating **3a** or **3b** in refluxing acetonitrile, or to 60°C in DMSO, causes epimerisation. Furthermore the process takes place more rapidly in the presence of additives such as KBr. Similar results were obtained with the α-bromo-3-phenylpropionyl derivative **3c**, although in DMSO elimination occurs to give the cinnamyl derivative. In the case of the α-bromophenylacetyl derivative **3d** a 50/50 mixture was obtained at equilibrium. Reaction of either diastereoisomer of **3a** with a soft, hindered nucleophile such as dibenzylamine allows equilibration to occur giving a single diastereoisomer of the product in quantitative yield. In contrast, when a hard, unhindered nucleophile such as azide is used displacement occurs without epimerisation giving the (*R*)-azide from the (*S*)-bromide and *vice versa*. Similar results were obtained with O and S nucleophiles.



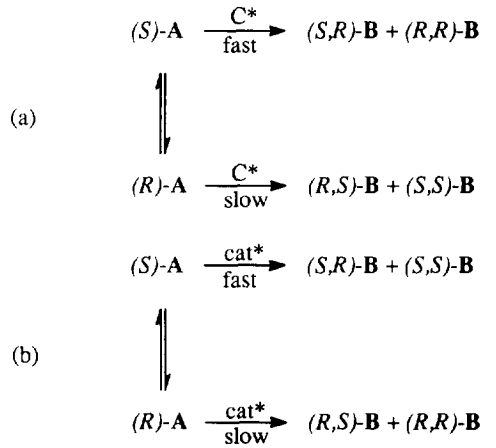
Scheme 2a



a R = CH_3; **b** R = C_2H_5; **c** R = CH_2Ph; **d** R = Ph

Scheme 2b

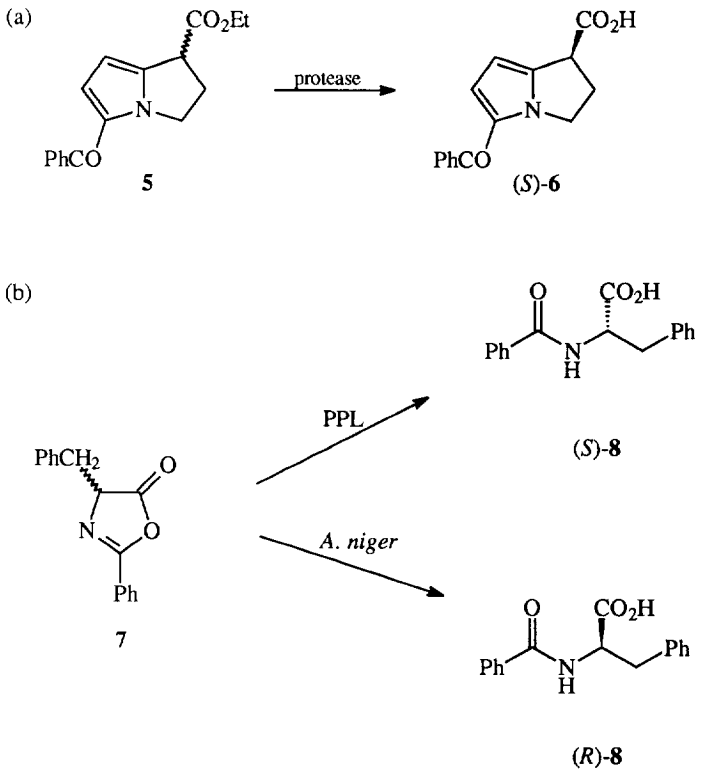
Other examples of this type of reaction are discussed in section 3. The two other types of process dealt with in this review are those in which an additional chiral centre is created, either by reaction with a homochiral reagent (section 4) or by the use of a chiral catalyst (section 5). The basic strategies involved in each case are shown in Schemes 3a and 3b respectively.



Scheme 3

2. DYNAMIC KINETIC RESOLUTION OF ENANTIOMERS

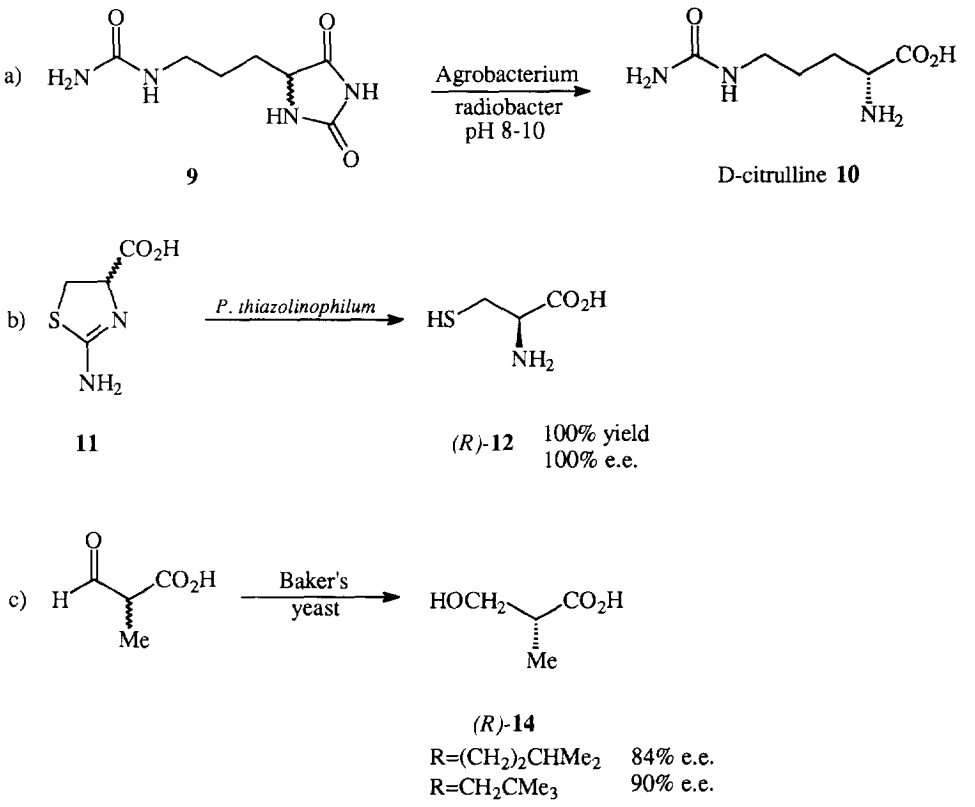
Two further examples of enzyme-catalysed reactions of the type depicted in Scheme 1a are shown in Scheme 4.[4-6] These reactions, like those dealt with in section 3, are characterised by the formation of no new chiral centres. Indeed, in the two examples shown in Scheme 4, like that in Scheme 1b, the configuration of the chiral centre is not altered by the reaction. Thus the carboxylic acid (*S*)-**6** can be obtained in 92% yield and 85% e.e. from the racemic ester **5** using a protease from *Streptomyces griseus* at pH 9.7. The N-benzoylphenylalanines (*R*)- and (*S*)-**8** can each be prepared in 100% yield and 99% e.e. from the racemic 2-phenyloxazolin-5-one **7** by using either the lipase from *Aspergillus niger* or porcine pancreatic lipase respectively.



Scheme 4

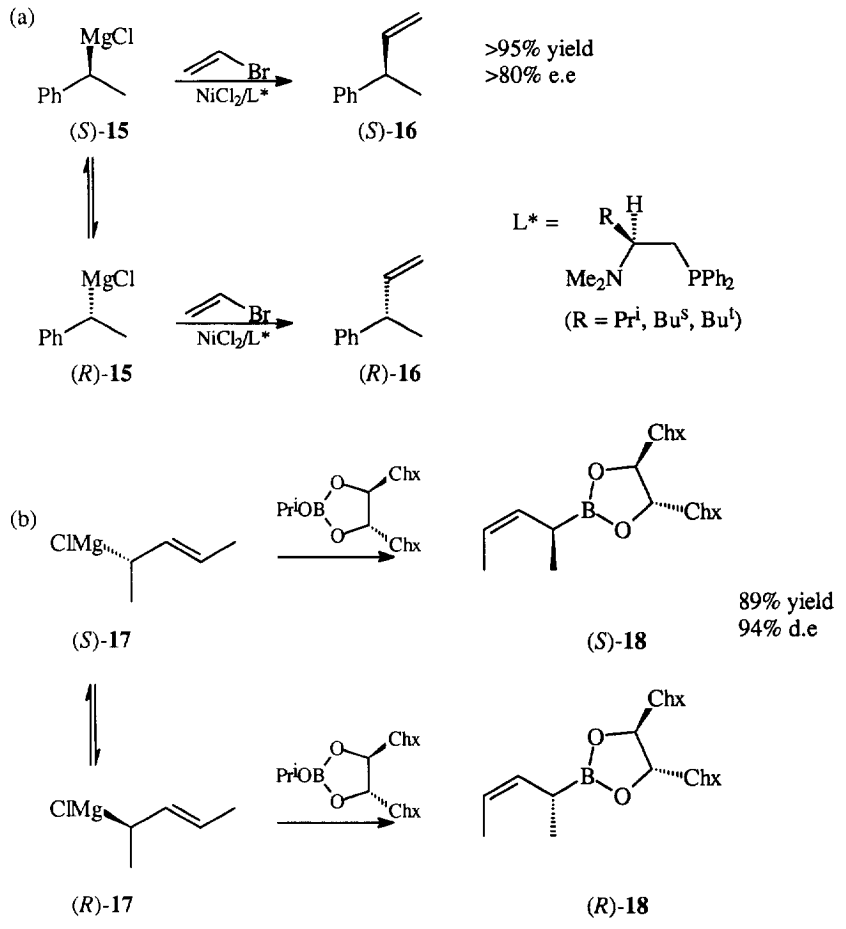
Racemic amino acid hydantoins can be converted almost quantitatively into D-amino acids by a system consisting of a D-hydantoinase and a carbamoylase. Thus D-citrulline **10** can be obtained in 79% yield and > 92% e.e. from the racemic hydantoin **9** (Scheme 5a).[7] The same method has also been used to produce

other D-amino acids. Racemic thiazoline **11** can also be converted into cysteine **12** in quantitative yield and with 100% e.e by *Pseudomonas thiazolinophilum* (Scheme 5b).[8] Reduction of alkyl 2-methyl-3-oxopropionates **13** by Baker's yeast (*cf.* section 5) affords the corresponding β-hydroxy ester **14** in 66-83% yield and 81-90% e.e. (Scheme 5c).[9,10]



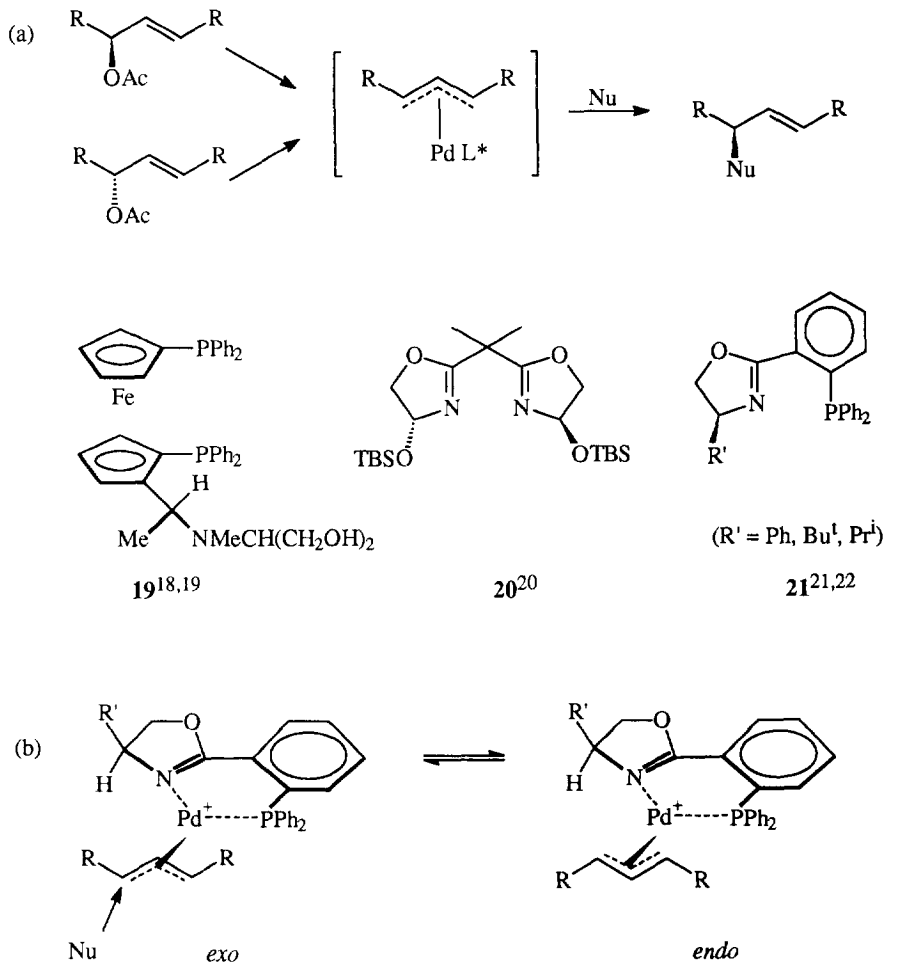
Scheme 5

A non-enzymic example of this type of process is illustrated by the reaction of secondary alkyl Grignard reagents with vinyl halides (Scheme 6a).[11-15] The reactions are catalysed by chiral ferrocenylphosphine-nickel and palladium complexes, and by chiral nickel or palladium complexes of β-aminoalkylphosphines. Optically active allylsilanes have also been prepared very efficiently using this methodology.[13] A related reaction is involved in the preparation of the pentenylboronic ester **18** by reacting the allyl Grignard reagent **17** with a chiral borate ester (Scheme 6b).[16] In this case a chiral reagent rather than a chiral catalyst is involved in the stereoselective step.



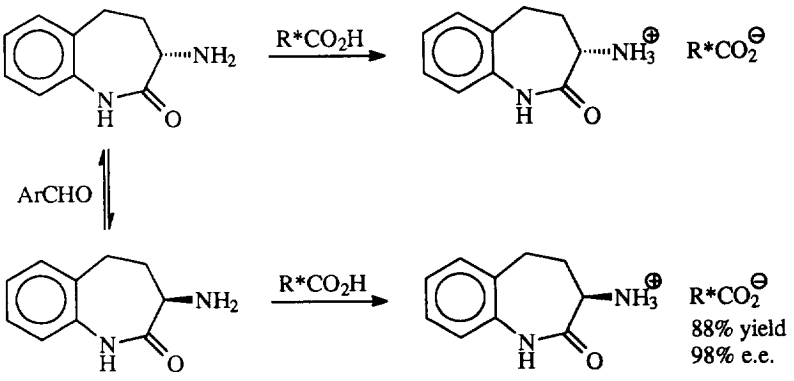
Scheme 6

Chiral palladium complexes have been used to catalyse the enantioselective alkylation and amination of racemic allyl acetates (Scheme 7a). A number of chiral ligands (e.g. **19-21**)[18-22] have been used and exceptionally high yields and e.e.s. have been obtained.[17-24] However in these reactions the two enantiomers of the substrate react with the catalyst to form a common chiral intermediate in which the chirality of the original substrate is lost, prior to reaction with the nucleophile. The outcome is therefore not dependent upon equilibration of the enantiomers of the starting material, but is determined by the regioselectivity of the subsequent step involving nucleophilic attack on the π-allyl complex (e.g. Scheme 7b).[21,22] These reactions are therefore conceptionally different from the other reactions discussed in this review.[25,26]



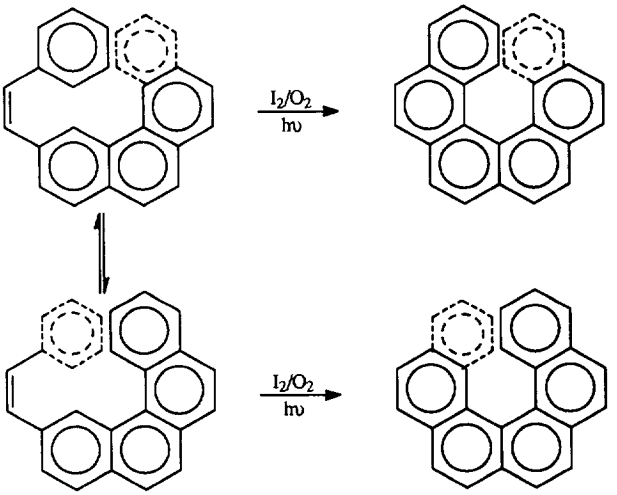
Scheme 7

The reactions discussed in this section should also be clearly distinguished from simple racemisation/resolution processes, including second order asymmetric transformations,[27] since the latter normally depend upon differences in solubility rather than reaction rate and involve, for example, salt formation rather than a stereoselective reaction (e.g. Scheme 8)[28].



Scheme 8

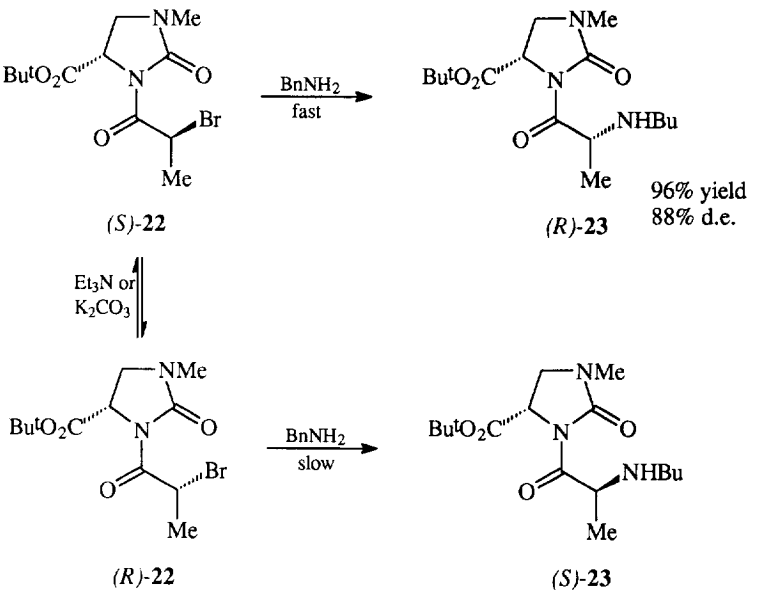
An intriguing example of dynamic kinetic resolution is involved in the photochemical cyclisation of various stilbene derivatives to hexahelicenes using circularly polarised light (Scheme 9).[29,30] Alternative explanations for the enantioselectivity of these reactions, such as selective destruction of one enantiomer of the product, have apparently been excluded. A high yield of the enantiomerically enriched product is obtained but the enantiomeric excess is, however, very low.



Scheme 9

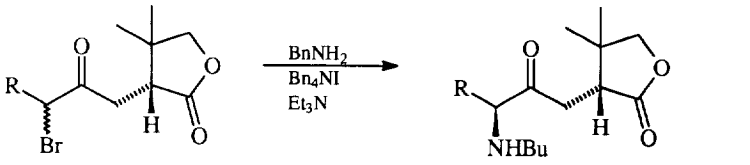
3. DYNAMIC KINETIC RESOLUTION OF DIASTEREOISOMERS

The equilibration of diastereomeric α-bromoamides prior to reaction with a nucleophile (Scheme 2b) has also been reported by Nunami *et al.*[31] They studied the reaction of the *tert*-butyl 1-methyl-2-oxoimidazolidine-4-carboxylate **22** with benzylamine in HMPA in the presence of potassium carbonate or triethylamine, and found that one diastereoisomer of the product **23** was predominantly formed in nearly quantitative yield (Scheme 10). In dichloromethane kinetic resolution without epimerisation occurred.



Scheme 10

In a closely related study Durst *et al.* have shown that esters of (*R*)-pantolactone with racemic α-bromo acids react with amines to give α-amino esters (Scheme 11).[32] The same methodology has also been extended to the synthesis of α-phenoxy esters.[33]

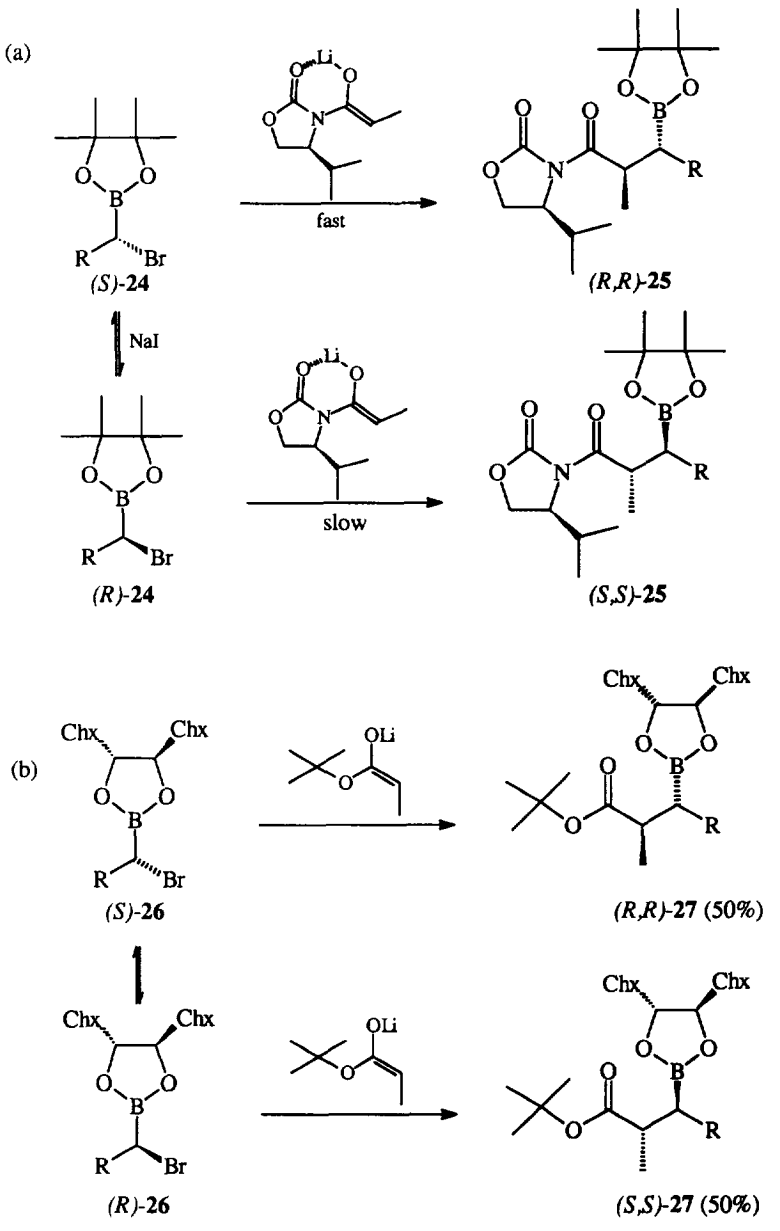


R = Ph 77% yield, 82% d.e.
R = Et 70% yield, 75% d.e

Scheme 11

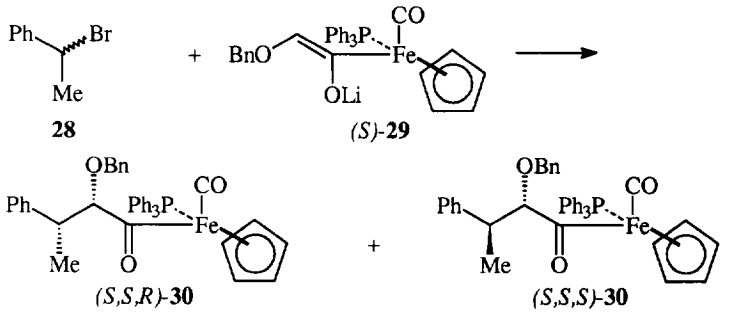
4. REAGENT CONTROLLED ASYMMETRIC SYNTHESES INVOLVING DYNAMIC KINETIC RESOLUTION

Matteson has shown that chiral α-bromoboronic esters undergo iodide-catalysed equilibration prior to reaction with a chiral enolate leading to complete utilisation of both enantiomers to produce a single product in high diastereomeric and enantiomeric purity (Scheme 12a).[34] Matteson describes the process as involving "enantioselective capture with retroracemisation". However the corresponding reaction starting with a mixture of diastereoisomeric α-bromoboronic esters and involving reaction with an achiral enolate gave only a 50/50 mixture of the diastereoisomeric products (Scheme 12b).



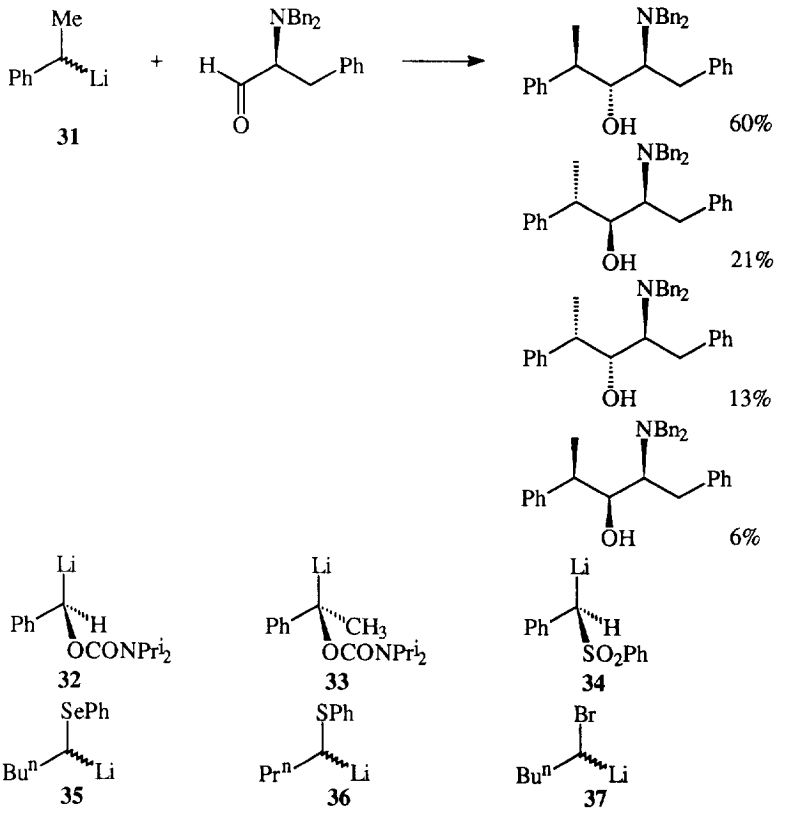
Scheme 12

A similar situation is involved in the reaction of racemic 1-phenylethyl bromide (**28**) with the chiral enolate **29** (Scheme 13).[35] The (S,S,R) and (S,S,S) diastereoisomers of **30** were obtained in a 30:1 ratio and in 71% yield, and the residual bromide was recovered in racemic form.



Scheme 13

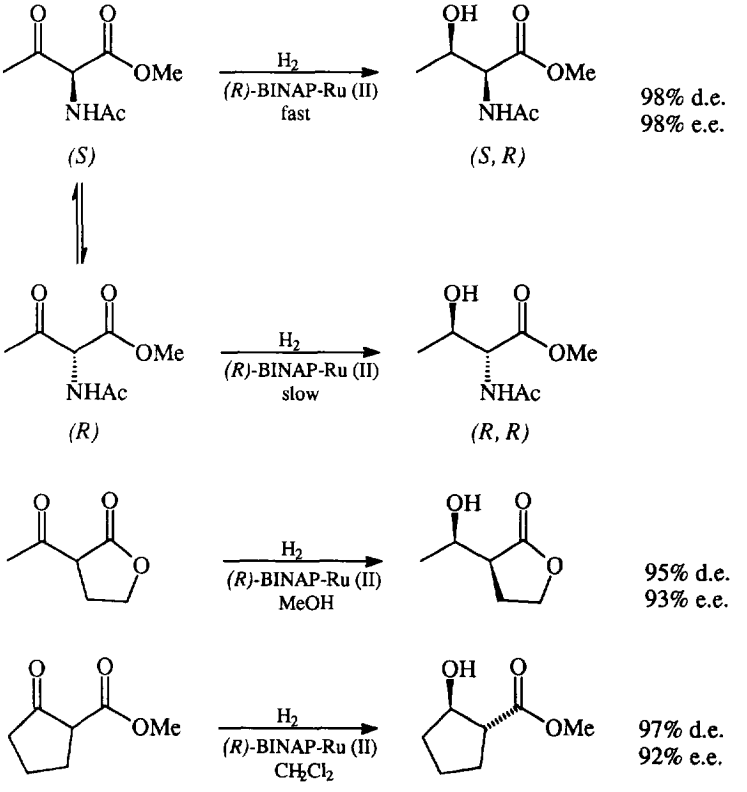
Hoffmann *et al.* have shown that α-methylbenzyllithium **31** racemises faster than it undergoes addition to aldehydes and ketones.[36] This is demonstrated by the fact that the same ratio of products is obtained irrespective of whether the racemic or enantiomerically pure aldehyde or ketone is used (Scheme 14). In contrast the carbamoyloxy and phenylsulphenyl derivatives (**32** - **34**) were shown to be configurationally stable under the same reaction conditions.[37] Other alkyllithium compounds (**35** - **37**) bearing α-phenylseleno, α-phenylthio or α-bromo groups also add more rapidly to the chiral aldehyde than they racemise.[38]



Scheme 14

5. CATALYST CONTROLLED ASYMMETRIC SYNTHESES INVOLVING DYNAMIC KINETIC RESOLUTION

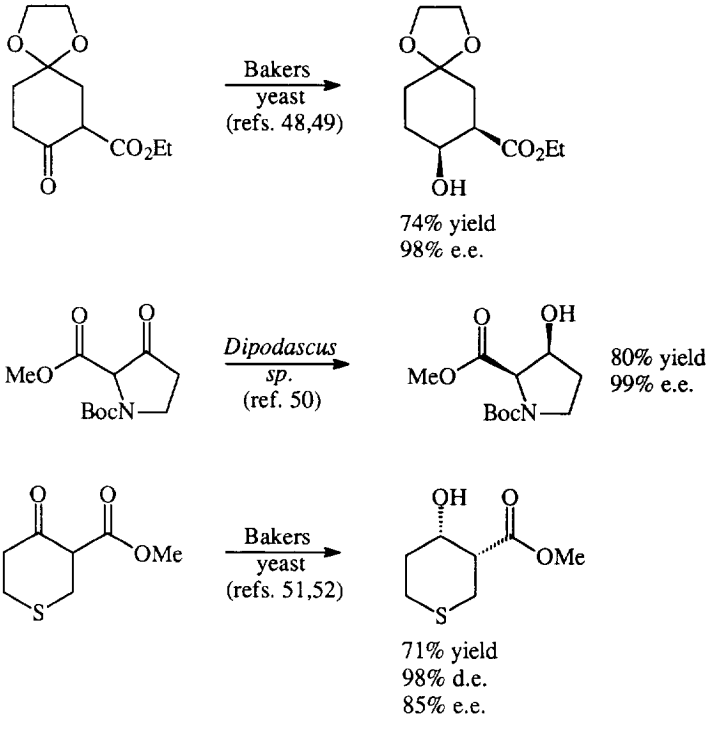
Some of the earliest examples of dynamic kinetic resolution involve the stereoselective hydrogenation of α-substituted β-keto esters using modified nickel or ruthenium catalysts (Scheme 15).[39-41] In each of the examples shown one of four possible stereoisomeric β-hydroxy esters is obtained in > 90% yield. A mathematical analysis of the reaction kinetics involved in this process has been reported,[42-44] and the factors upon which the selectivity depends have been reviewed.[45,46] Thus the absolute configuration at C-3 is determined by the configuration of the catalyst. However the *syn/anti* selectivity depends upon the substituent at C-2 and is also strongly dependent on the solvent. For example, an amide group at C-2 which is capable of intramolecular hydrogen bonding favours the formation of the *syn* product.



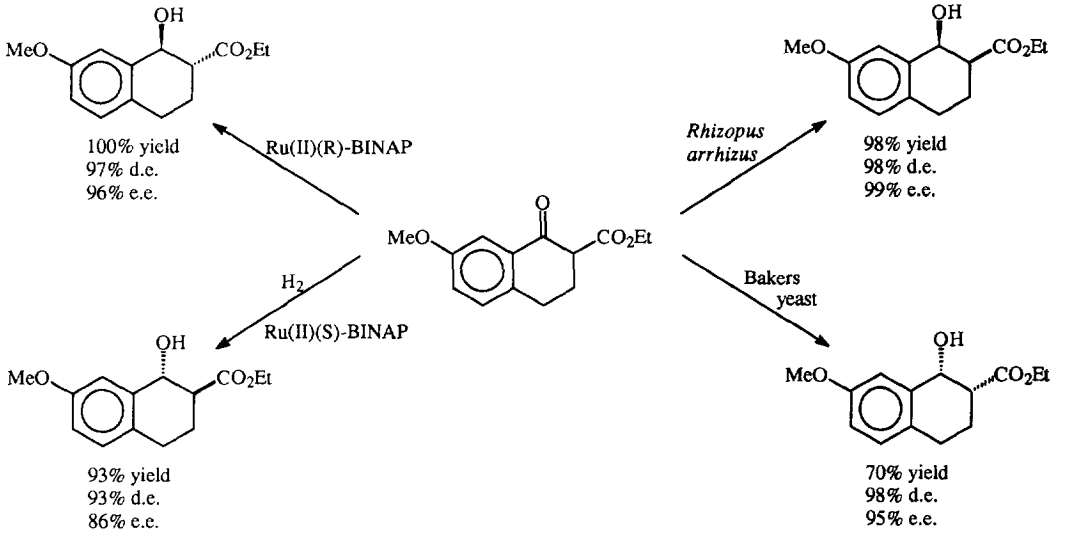
Scheme 15

The reduction of β-keto esters (and α-keto esters[47]) can also be accomplished using Baker's yeast and other microorganisms, and a wide range of applications of this methodology have been reported.[48-55] Enhanced diastereoselectivity can often be achieved by using isolated enzymes rather than intact microorganisms, since in Baker's yeast, for example, several competing enzymes may be operative. Furthermore the preferred diastereoselectivity frequently depends upon the detailed structure of the substrate. Nevertheless the process is accompanied by dynamic kinetic resolution and it provides an alternative method for obtaining high yields of enantiomerically enriched β-hydroxy esters. Some representative examples are shown in Scheme 16.[56-60]

The reactions discussed in this section illustrate the power of dynamic kinetic resolution as an adjunct to asymmetric synthesis. Indeed by careful judgement it is possible to obtain any of the four possible isomeric β-hydroxy esters from a given β-keto ester (Scheme 17).[61-62]



Scheme 16



Scheme 17

6. CONCLUSIONS

While it is clear that dynamic kinetic resolution is not a widespread phenomenon it is equally clear that the cases reported are more than isolated instances. By collecting together and categorising the known examples it is possible that trends will be recognised which can act as a pointer for future work. Thus α-bromo amides and α-bromo esters, including boronic esters, would seem to provide suitable substrates for a number of such reactions and are clearly worthy of further study.

Whatever type of substrate is employed the advantages of this approach are that it is possible to obtain a single stereoisomer of a product in high yield (> 50%) starting from a mixture of stereoisomers of the starting material. Examples of such reactions will always be worthy of note.

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