Dynamic Resolutions in Asymmetric Synthesis

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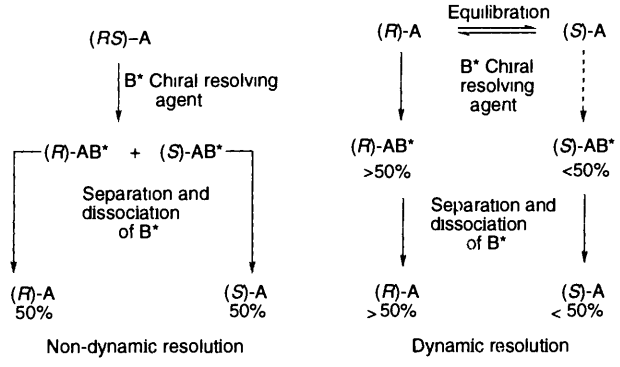
1 Introduction

The introduction of chirality into organic molecules is an increasingly important consideration when planning a route to targets of biological importance. Living systems are inherently chiral because many essential biomolecules exist in homochiral form. These include: carbohydrates which are involved in cell signalling and recognition processes and act as substrates in many key biochemical pathways; and also the amino acids which are important biochemical substrates and are the primary constituents of structural proteins, enzymes and receptors. It is not surprising therefore that biological activity is highly enantiomer dependent.

Synthesis of a racemic compound in which one enantiomeric form is poorly active or inactive is inefficient. The administration of a racemate as a pharmaceutical is undesirable as it usually requires a higher dose to elicit the desired response. Furthermore, the presence of the other enantiomer may have adverse side effects and indeed the commercialisation of racemic drugs is becoming increasingly difficult to justify. Thus, the demand for methods for the production of chiral non-racemic compounds has increased rapidly in response to these commercial considerations.

Most methods used for the preparation of enantiomerically enriched chiral organic molecules can be classified into two distinct strategies. The first involves the stereocontrolled formation of the new stereogenic centre, *i.e.* as the new chiral element is formed it is done so in a non-racemic fashion. This demands that the reactive centres experience some stereo-discriminating environment in the transition state. This can originate from an existing stereogenic centre in the substrate (chiral substrate or auxiliaries) or *via* a chiral reagent or catalyst (chemical or enzymatic). The second approach involves resolution; this utilises a stereoisomeric mixture and does not demand asymmetric induction in the formation of any new chiral element. Thus, preparation of a single stereoisomer by resolution of a stereoisomeric mixture may be achieved *via* a conventional separation procedure or by exploiting the difference in reactivity (kinetic resolution). The major drawback with the conventional resolution approach is that the yields will always be limited to 50%. However, this limitation can be overcome if the stereoisomers can interconvert; it may then be possible to selectively manipulate one of the isomers and hence effect a dynamic resolution with greater than 50% yield of the desired isomer (Scheme 1).

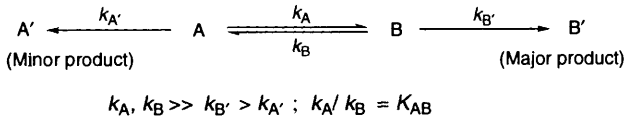


Scheme 1

2 Dynamic Kinetic Resolution (DKR)

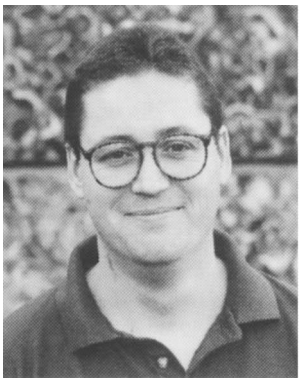
This area has recently been the subject of two excellent review articles by Noyori[1] and Ward.[2] It is our intention in this review to highlight examples of dynamic kinetic resolutions which have not previously been covered by these articles. In cases where we have felt compelled to include work already covered by these reviews we have referred to the appropriate review article(s).

It may be possible to effect a dynamic kinetic resolution (DKR) between rapidly equilibrating stereoisomers (A, B) by virtue of differential chemical reactivity. For a DKR to be successful the rate of epimerisation (k_A,k_B) must be a fast process relative to the rate of substrate transformation ($k_{A'}$,$k_{B'}$). Also the transformation itself should be essentially irreversible and the products formed need to be reasonably configurationally stable under the reaction conditions in order to avoid a thermodynamically derived product distribution. The difference in reactivity of the substrate stereoisomers leads to the bias in the product for one isomer over the other. As the rate differential (k_B/k_A) becomes more pronounced the stereochemical bias is increasingly reflected in the products (Scheme 2).

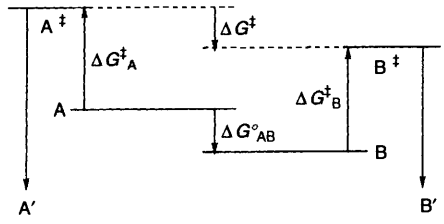


Scheme 2

Stephen Caddick received his undergraduate education at Paisley College of Technology and then part time at CCAT (Cambridge) whilst working in the laboratories of FBC Ltd (Saffron Walden). In 1989 he received a PhD degree from Southampton University working with P. J. Parsons and then spent two years at Imperial College as a postdoctoral assistant with W. B. Motherwell. In 1991 he was appointed to the staff at Birkbeck College in London and in 1993 moved to the University of Sussex.



Kerry Jenkins obtained his BSc from the University of Exeter (1989–1992). After spending 12 months in the Structural Chemistry department at Glaxo Group Research he returned to academia and obtained an MSc in Medicinal Chemistry from the University of Sussex (1993–1994). His research involved novel radical ipso substitution reactions of heteroaryl sulfones. He is currently a postgraduate student with Dr Stephen Caddick and is exploring dynamic resolution methodologies.



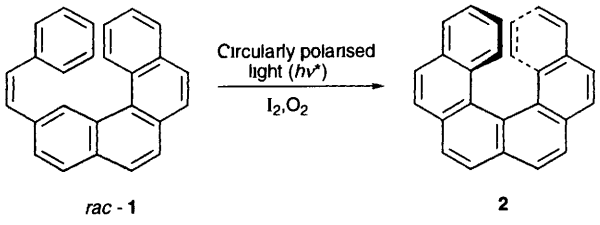
$[B']/[A'] = \exp[(-\Delta G^{\circ}_{AB} + \Delta G^{\ddagger}_{A} - \Delta G^{\ddagger}_{B})/RT]$
(first order/pseudo first-order reactions)

Scheme 3

This situation can be interpreted using Winstein–Holness and Curtin–Hammett kinetics The product distribution is related to the transformation rates (k_A ,k_B) and equilibrium constant (K_{AB}) by the equation $[B']/[A'] = k_B K_{AB}/k_A$ Expansion with Gibbs free energy and activation free energy parameters provides the equation given in Scheme 3 Where the substrate stereoisomers are related as enantiomers, chiral discrimination must occur *via* a chiral catalyst/promoter or by using a chiral reagent Since $\Delta G^{\circ}_{AB} = 0$, the relative transition state energies ($\Delta G^{\ddagger}$) solely determines the kinetic preference If the substrate stereoisomers are related as diastereoisomers the stereoselection arises as a function of the transition state energies ($A^{\ddagger}$, $B^{\ddagger}$) relative to the ground state energies (A, B) of the substrate isomers

2.1 Photochemical Promoted DKR

Circularly polarised light has been shown to effect chiral enrichment in the photochemical cyclisation of *rac*-**1** to the hexahelicene **2** (Scheme 4) [1,2] Both the substrate and product possess planes of chirality as a consequence of their restricted conformations



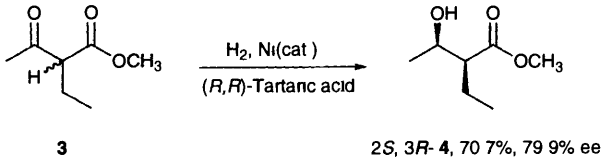
Scheme 4

Precursor, *rac*-**1**, rapidly equilibrates at ambient temperature The chiral influence of the circularly polarised light favours the formation of one enantiomer over the other as evidenced by a small but significant optical rotation (85%, *ca* 0 2% ee)

The ability of circularly polarised light to influence the stereochemical outcome of a reaction is an important observation in its own right but general application to chemical synthesis has yet to be demonstrated

2.2 Reduction of β-Keto Esters/Amides

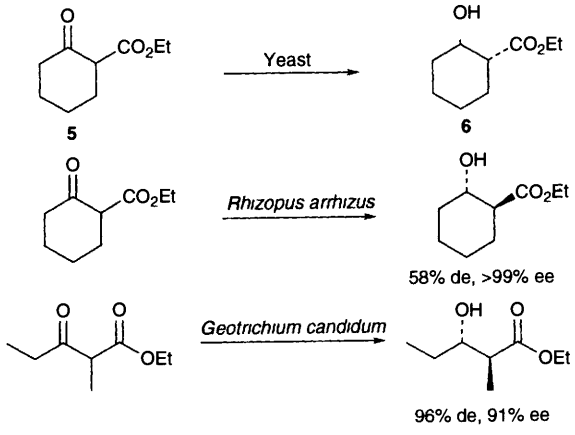
The propensity for α-substituted β-keto esters/amides to undergo enantiomerisation *via* keto–enol tautomerism has long been recognised This potentially undesirable property has been exploited to great effect in DKR by catalytic hydrogenation Tai[1,2] demonstrated a modified nickel catalysed heterogeneous hydrogenation of 2-alkyl-3-oxobutyrates using (*R,R*)-tartaric acid as a chiral modifying agent (Scheme 5) Addition of hydrogen from the catalyst surface (*Si* face) in the preferentially bound 2*S*-**3** complex furnishes the 2*S*,3*R*-**4** *syn* product



Scheme 5

The work by Noyori[1,2] and coworkers using the homogeneous Ru^{II}–BINAP catalytic system has greatly extended the synthetic utility of this methodology Very high levels of enantio and diastereo-control can be achieved and some examples have found industrial-scale application The DKR of acyclic β-keto esters generally affords *anti* selectivity when the C-2 substituent is alkyl Diastereoselectivity is often compromised but enantioselectivity can be excellent If the C 2 substituent can hydrogen bond to the ester moiety *syn* stereoselectivity is usually observed along with high enantioselection The sense and efficiency of diastereoselection is very substrate and solvent dependent whilst the enantio-selection seems to be less variable and is related to the absolute configuration of the BINAP ligand The C-2 geometry is fixed when hydride is delivered to the C-3 carbonyl Coordination of the ester carbonyl to the ruthenium acts as a trigger for the delivery of hydride The (*R*) BINAP ligand typically affords the *R* configuration at the C 3 hydroxy Very good levels of absolute and relative stereocontrol can be achieved when the C-2 alkyl substituent forms part of a ring due to constraints in the transition state As before the chirality of the BINAP ligand controls the ruthenium-carbonyl facial selectivity

Much attention has been focused on enzyme-mediated DKR of β-keto esters As early as 1976, Deol *et al* [1] had demonstrated that the yeast-mediated reduction of ethyl 2-oxocyclohexanecarboxylate (**5**) proceeded to give enantiomerically pure 1*R*,2*S*-ethyl 2 hydroxycyclohexanecarboxylate (**6**) as the sole product in 69% yield (88% based on conversion of **5**) Buisson and Azerad[1,2] have studied the reductions of β-keto esters using various fungal strains Excellent enantioselection (>95% ee) has been achieved along with moderate to excellent diastereoselection Perhaps most significantly they have shown that some organisms provide predominantly *anti*/*trans* diastereomers in contrast to yeasts (Scheme 6)



Scheme 6

Given the value of such DKR processes, the capability of having complementary approaches to different stereoisomers is extremely desirable To be able to generate a molecule with two chiral non racemic centres from a racemic compound in one step by DKR is particularly elegant The accessibility of racemic α-substituted-β-keto carboxylic acid derivatives coupled with the synthetic utility of chiral α-substituted β-hydroxy carboxyl compounds renders this technology an extremely powerful tool With the array of enzyme systems and chiral transition metal catalysts available the synthetic chemist has a variety of alternatives at his/her disposal, many of which are complementary in terms of their relative and/or absolute stereocontrol

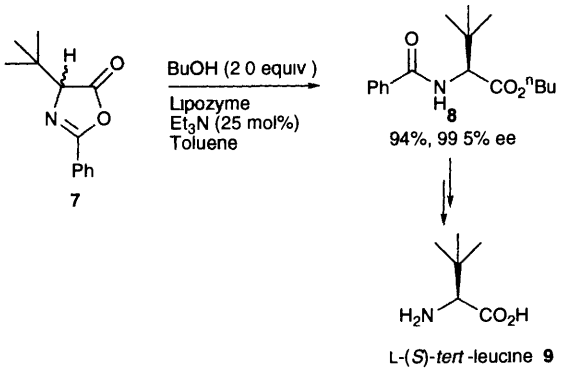
The complex nature of biocatalytic systems makes it difficult to propose accurate predictive models It is apparent that whole cell systems may utilise a range of oxidoreductase enzymes, some of which lead to opposing enantioselection Isolated enzymes can often produce higher enantio and diastereo-selectivities than the organism as a whole, however, isolated enzymes can suffer from reduced substrate compatibility Not surprisingly, the substrate structure has much influence on the diastereoselectivity and enzyme activity The nature of the C 2 substituent and the alkoxy group for example have

been shown to have significant effects in microbial reductions Seebach[3] has noted increased stereoselectivity in yeast-mediated reductions of β-ketoesters by using non-fermenting conditions

2.3 Other Enzyme-mediated DKR Transformations

Biotransformations have been recognised since the pioneering work on fermentation by Pasteur in the 1850s Historically, there has been a reluctance on the part of the synthetic organic chemist to employ biological processes routinely in organic syntheses As the impetus for chemists to synthesise enantiomerically pure molecules has increased over recent decades, biotransformations have begun to emerge as viable alternatives to traditional methods of asymmetric synthesis Much of the interest in biotransformations has been driven by the requirements of the chemical industry, in particular the pharmaceutical and agrochemical industries

The implication of azlactone formation in the racemisation mechanism of *N*-acylated peptides and amino acids has generated much interest in this class of heterocycle Condensation of activated *N*-acyl amino acids gives rise to the configurationally labile oxazolin-5(4*H*)-ones The acidity of the 4-proton is enhanced by the adjacent iminyl and carbonyl groups This chiral lability has recently been exploited in DKR processes Bevinakatti[2] has exploited this racemisation mechanism in the transformation of racemic azlactones into enantiomerically enriched amino acid derivatives *trans*-Acyl ring opening by nucleophiles in the presence of suitable lipase enzymes affords the enantiomerically enriched products with *in situ* racemisation of the azlactone



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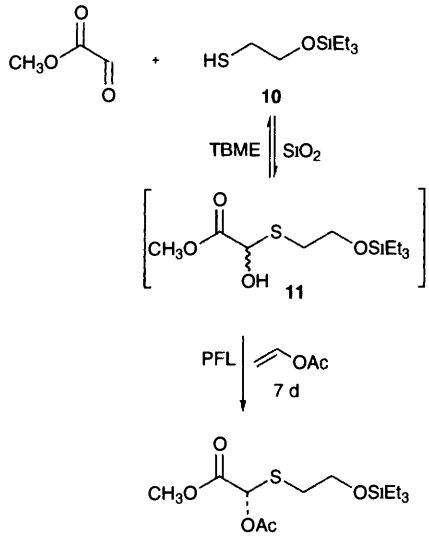
Scheme 7

An excellent example of this type of DKR has been developed by Turner *et al*[4] (Scheme 7) Treatment of *rac*-2-phenyl-4-*tert*-butyl-oxazolin-5(4*H*)-one (**7**) with butanol in the presence of the immobilised Lipozyme® (*Mucor miehei*) enzyme gave (*S*)-*N*-benzoyl *tert*-leucine butyl ester (**8**) in excellent yield and enantiomeric excess The process is amenable to scale-up and is a useful method for the preparation of the unnatural α-amino acid, L-(*S*)-*tert*-leucine (**9**) Some interesting (non-enzymatic) DKRs of azlactones have been studied by Weygand[5] and Miyazawa[1] using chiral amino acid ester nucleophiles

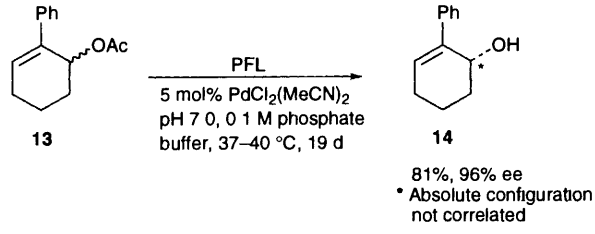
Enantiomerically enriched (*S*)-cyanohydrin acetates have been made *via* the DKR of racemic cyanohydrins using a lipase mediated acylation Oda and coworkers[1,2] have shown that cyanohydrins can be formed reversibly from aryl aldehydes under basic conditions and this provides a rapid racemisation process Dynamic kinetic resolution is effected by enantioselective acylation of the cyanohydrin by a lipase from *Pseudomonas sp*

Rayner *et al*[6] have employed a similar strategy for the enantioselective preparation of hemithioacetals They developed a DKR based on the observation that silica gel column chromatography of hemithioacetals promoted dissociation to the starting thiol and aldehyde Methyl glyoxalate was treated with thiol **10** in *tert*-butyl methyl ether (TBME) and the intermediate hemithioacetal **11** was kinetically resolved using *P fluorescens* lipase (PFL) and vinyl acetate in the presence of SiO_2 Hemithioacetal acetate (*S*)-**12** was obtained in 83% isolated yield with 90% ee (Scheme 8) A range of thiol/aldehyde combinations were similarly coupled with moderate to excellent chemical and enantiomeric yields (63—90%, 55—95% ee)



Scheme 8

Williams and Allen[7] have developed an intriguing DKR which uniquely combines a transition metal catalysed racemisation process with an enzymatic resolution The racemic phenyl substituted cyclohexenyl acetate **13** was enantiomerised *in situ* using 5mol% $PdCl_2(MeCN)_2$ to catalyse a [1,3]-sigmatropic acetate shift Enantioselective hydrolysis to the corresponding allylic alcohol, **14**, was achieved by *P fluorescens* lipase (PFL) in 81% yield and 96% ee (Scheme 9) In this strategy it is essential to identify a suitable enzyme to effect the kinetic resolution and which is not adversely affected by (or causes adverse effects on) the palladium catalyst

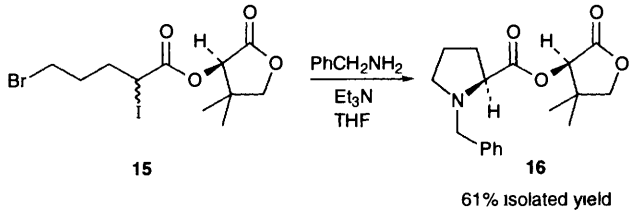


Scheme 9

2.4 Configurationally Labile Alkyl halides

Alkyl halides which have a halogen at the asymmetric centre are generally configurationally stable However, in certain cases epimerisation can be induced for example, many α-halo carboxyl compounds and anomeric glycosyl halides exhibit configurational lability, usually induced by additives such as polar solvents, base or halide sources

In 1993 Durst *et al*[8] made the observation that when a diastereomeric mixture of **15** (1 1 *S,R R,R*) was treated with benzylamine in THF the resulting proline derivative **16** was formed as a 7 1 diastereomeric mixture in which the *S,R* diastereomer predominated (Scheme 10) They concluded that the *R,R*-**15** diastereomer must react with benzylamine significantly faster than the *S,R*-**15**

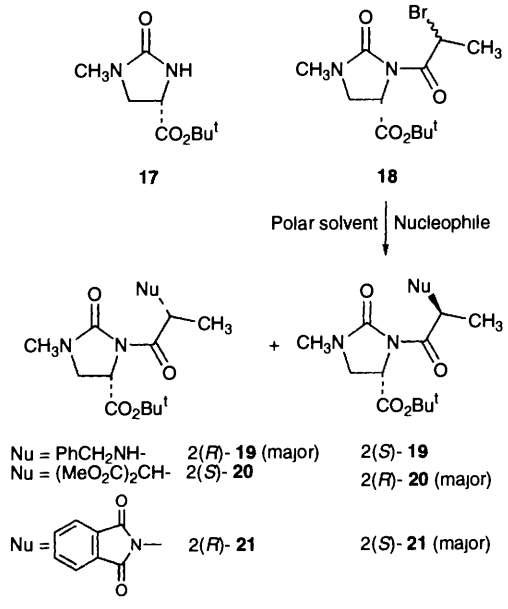


Scheme 10

diastereomer and that rapid epimerisation of the α-iodide, presumably catalysed by liberated halide, enabled conversion of the slower reacting diastereomer to the faster reacting diastereomer

Similarly impressive DKRs were performed on a variety of substrates with a range of amine nucleophiles It was found that α-bromo esters gave best results if a catalytic (0 2 equiv) amount of tetrahexylammonium iodide was added to facilitate epimerisation The generality of this DKR using the pantolactone auxiliary has since been extended to the preparation of α-hydroxy esters[9] and C_2 symmetric 2,5-disubstituted pyrrolidines [10]

Other chiral auxiliaries have been studied in related DKRs Nunami *et al* [11] introduced *tert*-butyl (4*S*)-1-methyl-2-oxoimidazolidin-4-carboxylate, **17** as an effective chiral auxiliary for this class of DKR High levels of stereocontrol were observed in nucleophilic displacements carried out on an epimeric mixture of **18** in polar solvents under conditions of base-catalysed epimerisation (Scheme 11) DKR of **18** with benzylamine gave 2(*R*)-**19** as the major

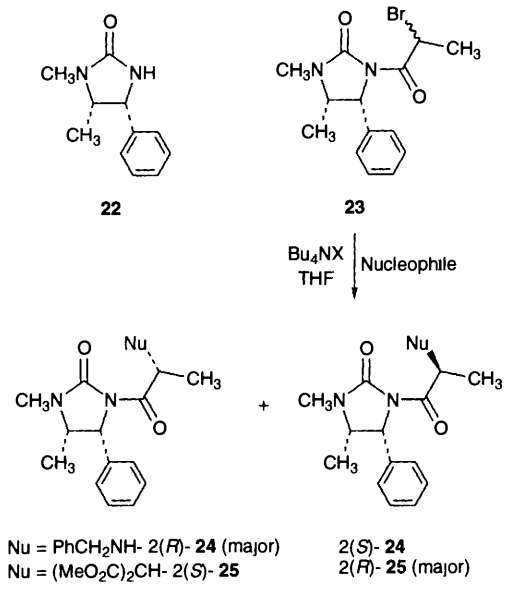


Scheme 11

product (96%, 88% de) whilst DKR with sodium dimethylmalonate[12] and potassium phthalimide[13] gave 2(*R*)-**20** (92%, 76% de) and 2(*S*)-**21** (90%, 94% de) respectively Durst *et al* [14] have reported aminations of α-bromo/iodo-acyl derivatives of the imidazolidinone, **17**, using catalytic tetrabutylammonium iodide to effect epimerisation The de values were generally greater than 98% with the *R* configuration[14] predominating at the site of substitution Yields for alkylation of benzylamine with a variety of substrates varied from 66—87%

An analogous DKR utilising an imidazolidinone chiral auxiliary has been developed by our group (see also section **3.4**) [15] (4*R*,5*S*)-1,5-Dimethyl-4-phenylimidazolidin-2-one (**22**) is readily prepared in one step *via* the thermal fusion of (−)-ephedrinium chloride and urea Treatment of a diastereomeric mixture (45 55 2*S* 2*R*) of **23** with benzylamine and catalytic tetrabutylammonium iodide resulted in the predominant formation of 2(*R*)-**24** in quantitative yield (74% de) Conversely, treatment of **23** with sodium dimethylmalonate[16] and tetrabutylammonium bromide gave 2(*R*)-**25** in 78% yield with 55—60% de (Scheme 12)

A striking feature of the DKRs so far reported with imidazolidinone derived chiral auxiliaries is the anomalous diastereoselectivity observed with amine nucleophiles It would be reasonable to assume that the substrates would preferentially adopt a ground state conformation whereby the imidazolidinone and acyl carbonyl groups are opposing one another and the alkyl substituent, R^3, would be expected to adopt the geometry shown The transition state energy for halide displacement is lowest when the α-halogen is perpendicular to the acyl carbonyl group One would expect the faster reacting substrate to be 2(*R*) whereby the nucleophile



Scheme 12

approaches from the least sterically hindered face as dictated by the auxiliary directing group(s) (Fig 1) However, the major products in all of the aminations have the 2(*R*) configuration which implies that the 2(*S*) substrates are the faster reacting diastereomers in S_N2 displacements with amine nucleophiles

Nunami[13 17] proposed a model to account for the unusual stereoselection observed with amine nucleophiles The model invokes a transition state in which the amine nucleophile hydrogen bonds to the ester carbonyl of the auxiliary (4*S*) *tert*-butyl carboxylate group thus guiding the amine to displace the halide from the sterically hindered face [Fig 2(*a*)] In an attempt to support this model the authors prepared the ether analogue **26** which was shown to be sig-

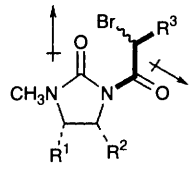


Figure 1 Predicted ground state geometry

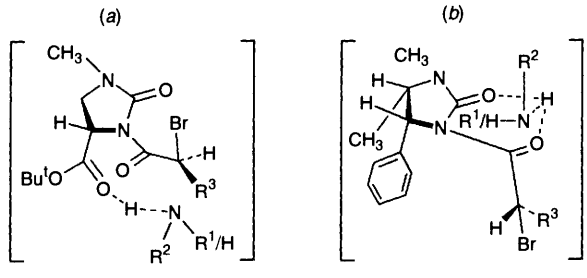
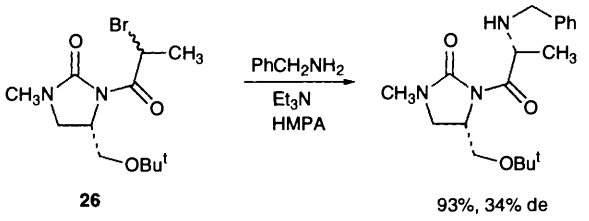


Figure 2 Predicted conformation for 2(S) diastereomers in amination DKR

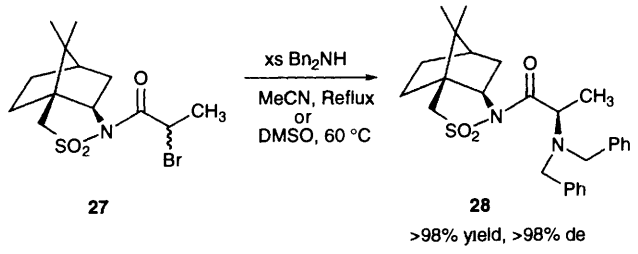
nificantly less stereoselective in the DKR (Scheme 13) Whilst the selectivity was undoubtedly reduced relative to the ester analogue **18**, the sense of stereoselection still results from preferential attack from the more hindered side Furthermore, in light of our results with the 1,5-dimethyl-4-phenylimidazolidin-2-one adduct, **23**, which is unable to participate in this 'amine guiding' process, this model does not adequately explain the anomalous stereoselection An alternative mechanism invokes a bifurcated hydrogen bond bridging the acyl carbonyl and the auxiliary carbonyl *via* a six membered chelate The amine nucleophile displaces the halide



Scheme 13

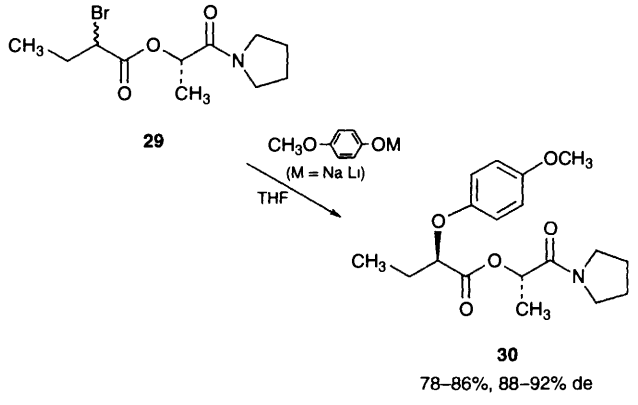
which occurs faster in the substrate in which the σ^* orbital of the C-Hal bond is least hindered [Fig 2(*b*)] At present this model is only supported by circumstantial evidence but may be useful in assisting the prediction of stereochemical outcome in these systems

Ward's group[18] have reported a highly efficient DKR of an α-bromopropanoic acid derivative using Oppolzer's chiral camphorsultam When a diastereomeric mixture of **27** was treated with dibenzylamine (10 equiv) in acetonitrile (reflux) or Me_2SO (60 °C) 2*R*-**28** was formed as the exclusive diastereomer in quantitative yield (Scheme 14)



Scheme 14

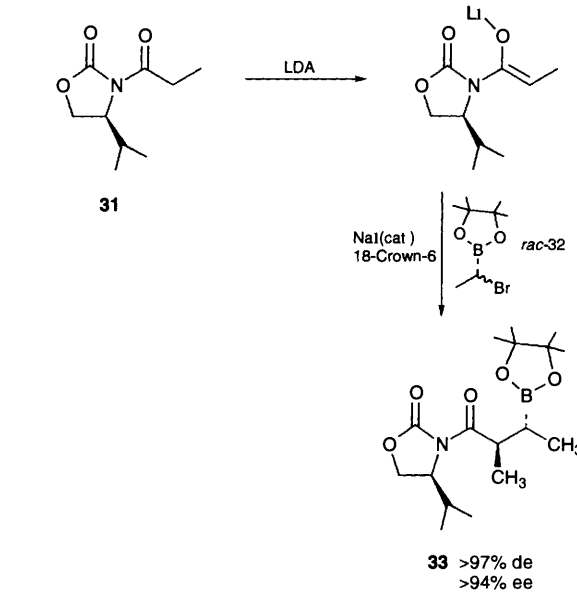
Devine *et al* [19] have used a DKR for the enantioselective preparation of 2-aryloxy carboxylic acids towards a synthesis of a potent endothelin antagonist The substrate **29** was treated with preformed sodium or lithium aryloxide in THF to furnish **30** in good to excellent yield (78%—86%) with excellent selectivity (88%—92% de, Scheme 15) The analogous substrate using ethyl lactate as a chiral auxiliary was found to react sluggishly and with diminished selectivity (60%—75% de)



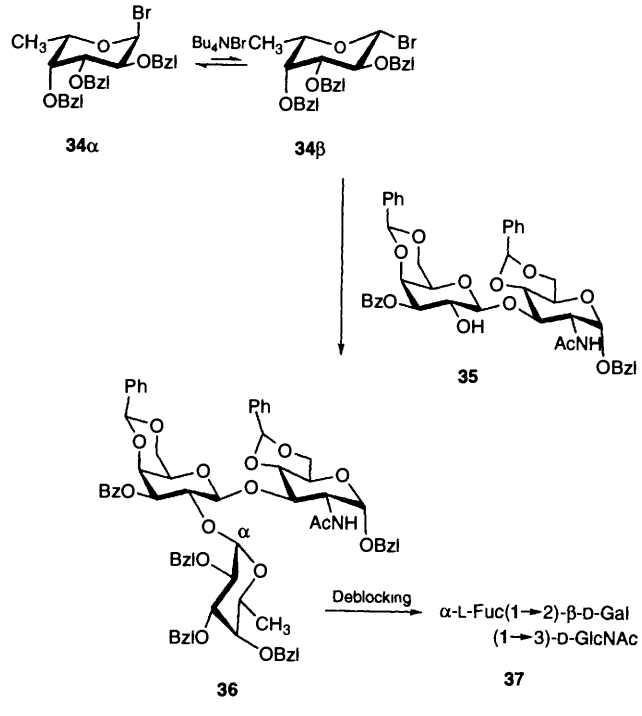
Scheme 15

Matteson and Man[2] have achieved a DKR of racemic (1-bromoalkyl)boronic esters by diastereocontrolled reaction with chiral *N*-acyloxazolidinone enolates under iodide catalysed racemisation (Scheme 16) Alkylation of the lithium enolate of (*S*)-4-(1-methylethyl)-3-propanoyloxazolidin-2-one, **31**, with *rac*-**32** in the presence of catalytic NaI and 18-crown-6 afforded **33** (100% conversion, >97% de, >94% ee)

The importance of carbohydrates in biomolecular recognition processes has driven the development of new methods for glycosidation Glycosyl halides represent one of the most widely used glycosyl acceptors and many variations of coupling glycosyl halides with donors exist One of the most appealing strategies was introduced by Lemieux[20] nearly three decades ago The formation of suitably protected β-glycopyranosides from α-haloglycopyranosyl precursors has been a long established procedure However the preparation of α-linked oligosaccharides from the β-haloglycopyranosides is marred by the thermodynamic instability of the β-halides over the α-halides by virtue of the strong α-anomeric effect Lemieux and coworkers[20] made the observation that glycosyl halides could be induced to anomerise in the presence of tetraalkylammonium halide Although the equilibrium lies heavily in favour of the thermodynamically more stable α-(axial) anomer a significant concentration of the kinetically more reactive β-(equatorial) anomer is maintained Reaction can proceed preferentially *via* the more reactive β-halide to give the α-glycoside linkage This process has been utilised in the stereoselective synthesis of the blood-group substance H (type 1),[21] **37**, from the L-fucosyl halide, **34** (Scheme 17) Other blood-group determinants have similarly been prepared



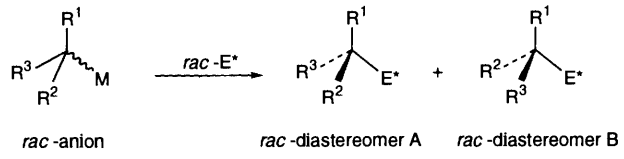
Scheme 16



Scheme 17

2.5 DKR of Configurationally Labile Anions

The configurational stability of carbanions in organometallic intermediates has received a great deal of attention in recent decades. The main emphasis has been concerned with methods of generating stable chiral anions from chiral, non-racemic precursors which can then be used in stereoselective reactions. There has been a gradual increase in the realisation that configurationally labile anions can be utilised in asymmetric synthesis by using principles of DKR. Hoffman has developed a useful test which enables the configurational stability of a carbanion to be evaluated *in relation to reaction with an electrophile*.[22] The test involves the generation of the anion as a racemate. Treatment of the racemic anion with a chiral, **racemic** electrophile will give a diastereomer ratio that reflects the kinetic difference of formation of the (racemic) product diastereomers (Scheme 18).

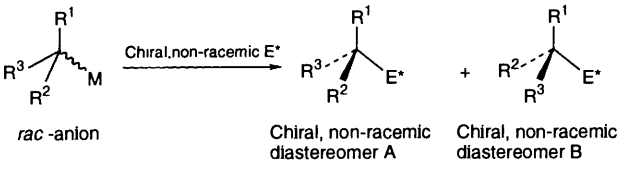


M = metal; E = electrophile
[*rac*-A]/[*rac*-B] $\propto k_A/k_B$
k_A = rate constant of formation of diastereomer A
k_B = rate constant of formation of diastereomer B

Scheme 18

Providing the diastereomeric ratio is significantly different from 1:1 (ideally 1.5—3.0) the electrophile is suitable for the test (if not, a different electrophile probe must be used). Treatment of the racemic anion with an equimolar amount of the chiral, **non-racemic** electrophile must result in the formation of the (enantiomerically pure) produce diastereomers in a 1:1 ratio *if the anion is stable on the reaction timescale* at 100% conversion (Scheme 19). If the

Provided that [*rac*-A]/[*rac*-B] ≠ 0

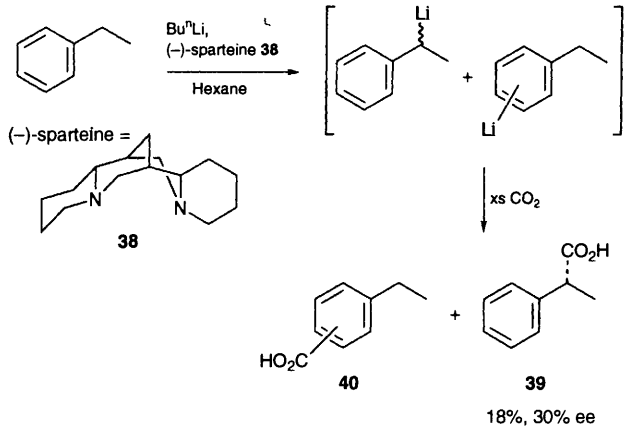


[A]/[B] = 1.0 if anion is *configurationally stable* on reaction timescale
[A]/[B] ≠ 1.0 if anion is *configurationally labile* on reaction timescale

Scheme 19

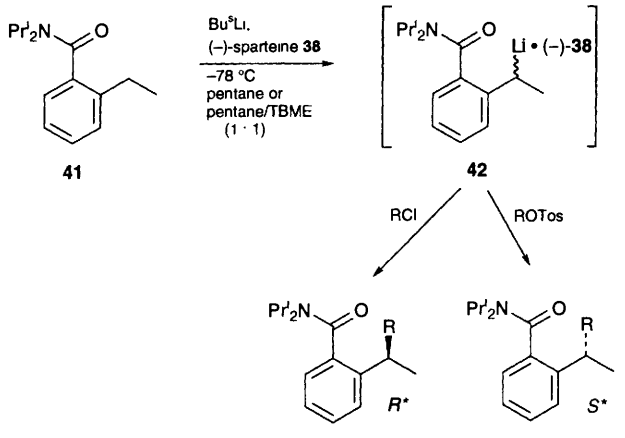
product diastereomer ratio differs from 1:1 then this is an indication that *the anion is configurationally labile on the reaction timescale* and that product formation is susceptible to a dynamic kinetic resolution by virtue of the difference in rates of formation of the product (as determined in the first experiment). The reactions must approach 100% conversion for the results to be meaningful otherwise, in the latter experiment, kinetic resolution may complicate the interpretation of the data.

The use of organometallic bases to effect asymmetric deprotonations in the presence of chiral complexing agents such as (−)-sparteine (**38**) has been the focus of much attention in asymmetric synthesis. There are some notable examples in which it is apparent that enantioselection is achieved not by enantioselective deprotonation to form a stabilised chiral anion but by deprotonation and subsequent complexation of the interconverting anions by the chiral ligand. In principle there are two possibilities by which an asymmetric transformation can occur hereon. The ligand may selectively complex one of the anion enantiomers such that a single diastereomeric complex forms by virtue of the *in situ* enantiomerisation of the other uncomplexed anion. This complex is then trapped by rapid reaction with an electrophile. Alternatively the rapidly interconverting anion enantiomers may both form complexes with the chiral ligand such that both diastereomeric complexes exist in rapid equilibrium in solution. Diastereoselective reaction of one of the complexes with an electrophile accompanied by *in situ* equilibration of the unreacted complex could result in enantiomerically enriched products. In practice it may be difficult to establish which process is operating and it may not be possible to classify the examples included in this section. One of the first examples of this type of asymmetric transformation was illustrated by Nozaki and coworkers[23] in 1971. Lithiation of ethylbenzene in the presence of (−)-sparteine (**38**) followed by quenching with excess CO_2 gave a mixture of hydrotropic acid **39** and ethylbenzoic acids **40** which were isolated with 87% conversion. The mixture was optically active and based on the proportion of hydrotropic acid (18%) and the optical rotation it was estimated that (−)-(*R*)-hydrotropic acid was formed with 30% ee (Scheme 20).



Scheme 20

Beak[24] and coworkers have demonstrated that the intermediate sparteine complexes **42**·(−)-**38** derived from the lateral lithiation of **41** with BusLi/(−)-sparteine (**38**) are configurationally labile as evidenced by the Hoffman test.[22] The nature of the electrophile had a profound effect on the sense of stereoselection; chlorides such as allychloride gave the *R** products whereas tosylates such as allyltosylate gave the *S** products (Scheme 21). It is suggested that the



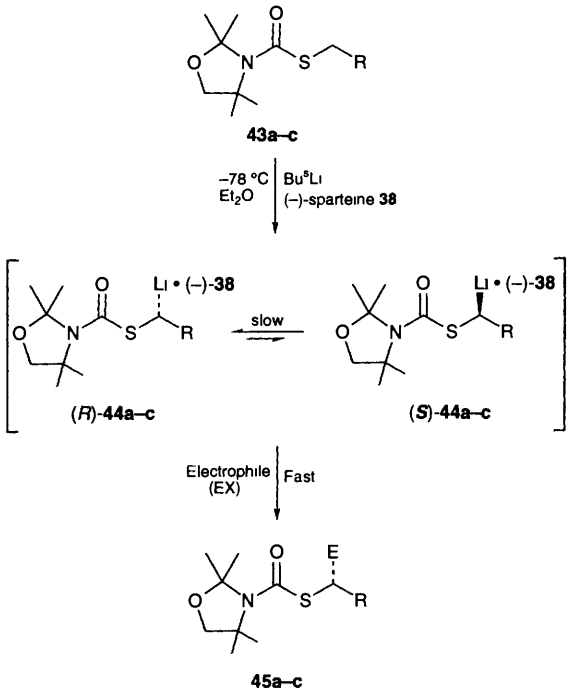
Scheme 21

enantioselection arises through the difference in transition state energy for electrophilic substitution between the two diastereomeric anion–sparteine complexes [*R*-**42**·(−)-**38**/*S*-**42**·(−)-**38**] and that the nature of the electrophile determines the preference for inversion or retention on electrophile trapping. This use of a non-covalently bound chiral auxiliary is particularly attractive as it allows the production of either enantiomer of a desired product from the same auxiliary.

An interesting warm–cool protocol has been introduced by Beak,[25] with similar types of substrate. The lability of

sparteine–anion complexes can be very temperature dependent Hence the mechanism of stereoselection can be affected depending on the specific protocol used to perform the reaction Beak has also suggested that the enantioselective electrophilic substitution of the *lithio* dianion of *N*-methyl-3-phenylpropionamide in the presence of (−)-sparteine may occur *via* DKR [26]

Hoppe *et al* [27] have demonstrated the lability of the α-thioalkyllithium sparteine complexes **44a—c** in contrast to their α-alkoxyllithium analogues Trapping of **44a—c**·(−)-**38** complexes with CO_2 or chlorotrimethylsilane gave the enantiomerically enriched products in good yield (77—95%) and with enantiomeric excesses between 40—60% (Scheme 22) The apparent independence of



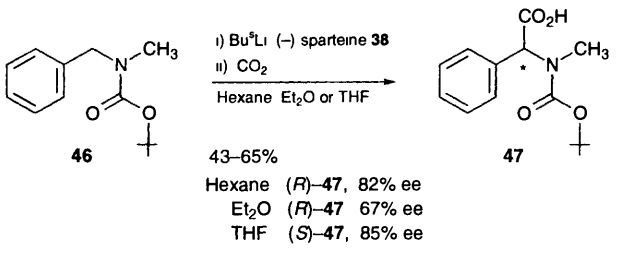
	R	EX	E[a]	Yield (%)	Ee (%)
a	Pr	CO_2	CO_2CH_3	91	47
		TMSCl	TMS	91	46
b	CH_3	CO_2	CO_2CH_3	89	40
		TMSCl	TMS	95	40
c	Pr^i	CO_2	CO_2CH_3	77	60

[a] Carboxylic acids converted to methyl esters using diazomethane

Scheme 22

enantiomeric excess on electrophile led the authors to suggest that the product ratio was a reflection of the thermodynamic ratio of the equilibrating diastereomeric complexes (*i e* the equilibration rate is slow compared to electrophilic trapping)

Schlosser and Limat[28] have shown that the configurationally labile (−)-sparteine (**38**) complex of the lithio anion of *N*-Boc-*N*-methylbenzylamine (**46**) gives rise to enantiomerically enriched products on reaction with electrophiles Intriguingly, the sense of enantioselection was dependent on the solvent used For example *N*-Boc-*N*-methylphenylalanine **47** was prepared by treatment of **46** with BusLi, (−)-sparteine and then CO_2 (Scheme 23) In hexane and

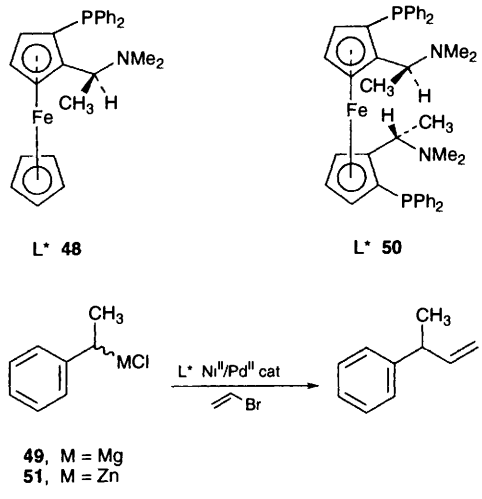


Scheme 23

diethyl ether the *R* enantiomer predominated (82% ee and 67% ee respectively) whilst in THF the *S* enantiomer was formed in excess (85% ee)

The solvent effect was ascribed to a mechanistic crossover from electrophile substitution on a contact species, with hexane and diethyl ether (retention), and a solvent separated ion pair, with THF (inversion) An interesting observation was made that in the case where THF was the solvent the ee increased slowly with increasing conversion until the point at which precipitation was observed At this point the enantiomeric excess rose rapidly Heterogeneity is another potential factor in what is already a mechanistically complex class of reaction (see section 3 2)

Kumada[1 2] utilised the configurational lability of secondary Grignard reagents in an asymmetric Grignard cross-coupling reaction catalysed by chiral transition metal complexes The chiral ferrocenyl ligand (*S*)-*N*,*N*-dimethyl-1-[(*R*)-2-(diphenylphosphino)-ferrocenyl]ethylamine (**48**) was used in conjunction with $NiCl_2$ to catalyse the coupling of racemic 1-phenylethylmagnesium chloride (**49**) with vinyl bromide This gave (*R*)-3-phenylbut-1-ene in >95% yield and 66% ee A number of variants on this cross-coupling reaction have since been developed Hayashi and Ito *et al* [1 2] have used the C_2 symmetric ligand (+)-**50** in a palladium catalysed coupling of 1-phenylethylzinc chloride **51** and vinyl bromide (*R*)-3-phenylbut-1-ene was obtained in quantitative yield and 93% ee (Scheme 24)



Scheme 24

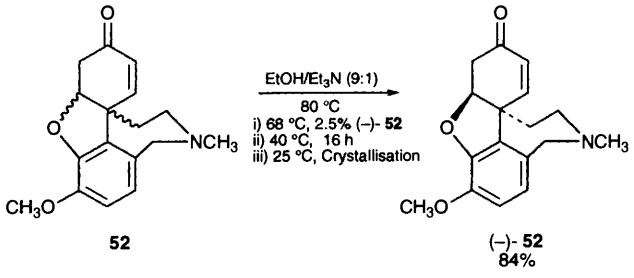
3 Crystallisation Induced Dynamic Resolution (CIDR)

A very practical and efficient method of asymmetric transformation is by dynamic resolution of chirally labile substrates by way of selective crystallisation This approach is of general synthetic appeal from small scale preparations (mg–g) to pilot and process scale production (kg–tonnes) The earliest example of CIDR was observed by Dubrunfaut[29] in 1846 who was studying crystallisation of glucose from solution There is great appeal in being able to transform a racemate (or epimeric mixture) to a pure isomer quantitatively by crystallisation from solution [30−32] A compound which is either spontaneously labile in solution or in which lability can be induced may be able to undergo CIDR through interaction with some stable chiral influence Some enantiomers can be resolved by crystallisation from solution by the action of a homochiral seed crystal which may be added or which may be the first enantiomer to randomly crystallise from the racemic solution Enantiomers may also be resolved by the formation of diastereomeric salts or complexes (non-covalently bound) with stable chiral resolving agents (CRAs) The CIDR of enantiomeric anions with chiral complexing agents is dealt with in a separate category in this review Substrates which are related as diastereomers *via* one labile stereocentre may be resolved by crystallisation The use of chiral auxiliaries covalently bound to a racemic substrate can be a viable method of achieving CIDR when the enantiomers are not suitable for direct

CIDR by seeding. Ideally, the chiral auxiliary should be inexpensive to prepare, should impart crystallinity to the substrate and should be readily cleaved and recovered. A distinct advantage of using chiral auxiliaries in a CIDR approach as opposed to controlling asymmetry in reactions is that the chiral framework does not need to be tailored for steric and electronic interactions. It is not even essential for the chiral auxiliary to be proximal to the labile stereocentre in CIDR since the chiral influence is largely directed intermolecularly in the crystal lattice and at the solution surface interface. However, if the auxiliary is too distant from the labile stereocentre the difference in physical properties of the diastereomers is likely to be reduced.

3.1 CIDR: Enantiomers

An impressive total resolution of racemic narwedine (**52**) has been carried out by Shieh and Carlson.[33] Under basic conditions narwedine can racemise *via* a retro-Michael reaction. Essentially pure (−)-**52** can be crystallised in 84% yield from racemic **52** in ethanol/Et_3N (9:1) using 2.5% (−)-**52** seed crystals (Scheme 25). It is generally accepted that such an approach is limited to conglomerates.[30,31]

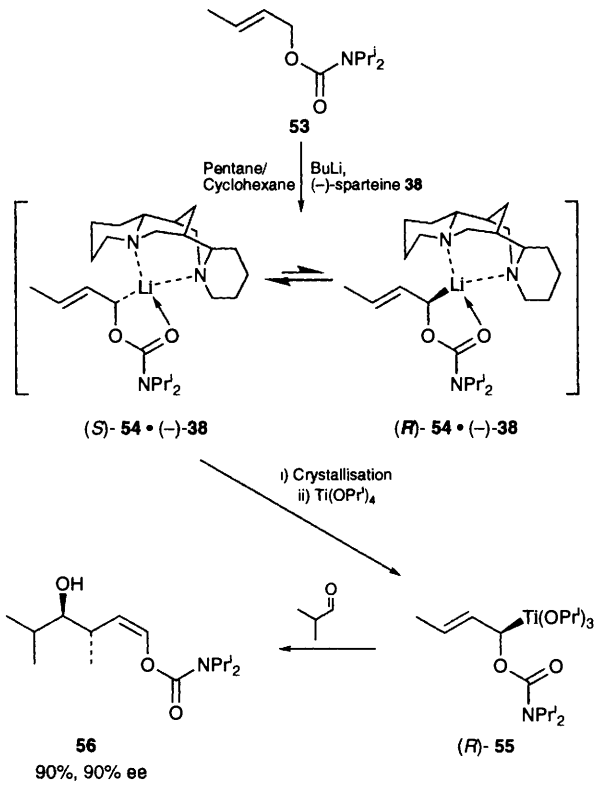


Scheme 25

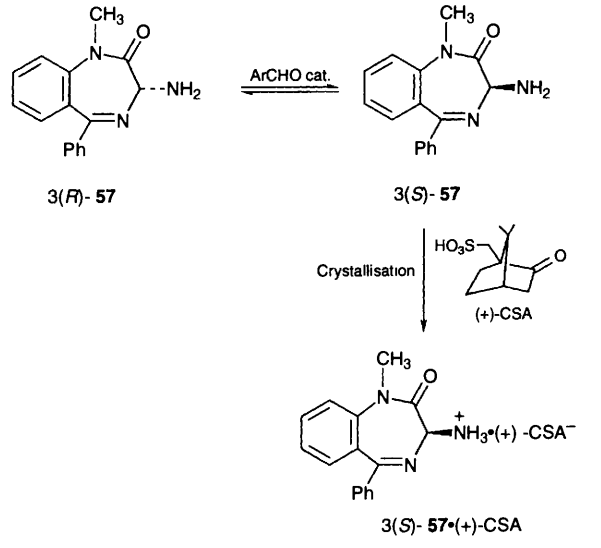
3.2 CIDR: Diastereomeric Organometallic Complexes

Dynamic kinetic resolutions utilising configurationally labile carbanions were reviewed in section 2.5. An interesting alternative asymmetric transformation has been described by Hoppe.[34] Deprotonation of the allyl carbamate **53** with BuLi/(−)-sparteine (**38**) gives rise to the configurationally labile diastereomeric complexes (*S*)-**54**·(−)-**38** and (*R*)-**54**·(−)-**38**. Preferential crystallisation of (*S*)-**54**·(−)-**38** can be achieved by addition of cyclohexane. The stable solid complex can be converted to the configurationally stable titanate (*R*)-**55** by rapid quenching with pre-cooled tetraisopropyltitanate (TIPT). The titanate (*R*)-**55** affords the homoaldol adduct **56** in 90% yield and 90% ee on treatment with isobutyraldehyde (Scheme 26).

Hoppe[35] has used a similar CIDR approach to selectively crystallise the (*R*)-lithio·(−)–sparteine complex derived from 1-methylindene. Electrophilic quenching of the crystal suspension led to 1,1-disubstituted indenes in moderate to good yields (52—79%) and excellent enantiomer excesses (>95% ee).



Scheme 26



Scheme 27

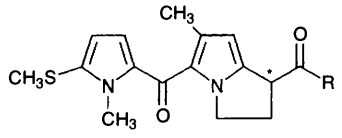
3.3 CIDR: Diastereomeric Salts

Reider *et al.*[2] used a highly efficient CIDR approach to the non-peptidal CCK antagonist L-364,718 developed at the laboratories of Merck (MSD). The amine precursor 3(*RS*)-**57** could be readily racemised in the presence of a catalytic amount of aryl aldehyde. This promoted the racemisation process *via* the more acidic intermediate imine. Hence the spontaneous total resolution of 3(*RS*)-**57** was effected by the addition of catalytic 3,5-dichlorosalicaldehyde (3 mol%) and then (1*S*)-(+)-10-camphorsulfonic acid [(+)-CSA, 92 mol%]. It was important to add less than a full equivalent of (+)-CSA in order to maintain a concentration of free amine **57** which catalyses the racemisation of the imine. The diastereomeric salt 3(*S*)-**57**·(+)-CSA was obtained in 91% yield and >98% optical purity (Scheme 27). *N*-Acylation with the indole-2-carboxylic acid moiety provided L-364,178 in 79% yield and 99.8% ee. This preparation could be carried out on a 10 kg scale.

Toda and Tanaka[36] observed higher than theoretical yields in the resolution of racemic cyanohydrins with the basic alkaloid, brucine. The cyanohydrins can racemise *via* base induced reversible dissociation to hydrogen cyanide and prochiral ketone. Controlled evaporation of the solvent allowed the formation of diastereomerically pure salts in up to 100% yield.

3.4 CIDR: Epimers

Ethyl 5-(1′-methyl-5′-methylthiopyrrol-2-ylcarbonyl)-1,2-dihydro-6-methyl-3*H*-pyrrolo[1,2-*a*]pyrrole-1-carboxylate **58c** is a potent antiinflammatory analgesic compound of the 5-aroyl-1,2-dihydro-3*H*-pyrrolo[1,2-*a*]pyrrole-1-carboxylic acid class (Fig. 3).[37] Esterification of the racemic parent acid **58a** with (*R*)-(+)-α-methylbenzyl alcohol gave rise to a diastereomeric mixture **58b** which could be epimerised in the presence of a catalytic amount of



58a, R = OH CH_3

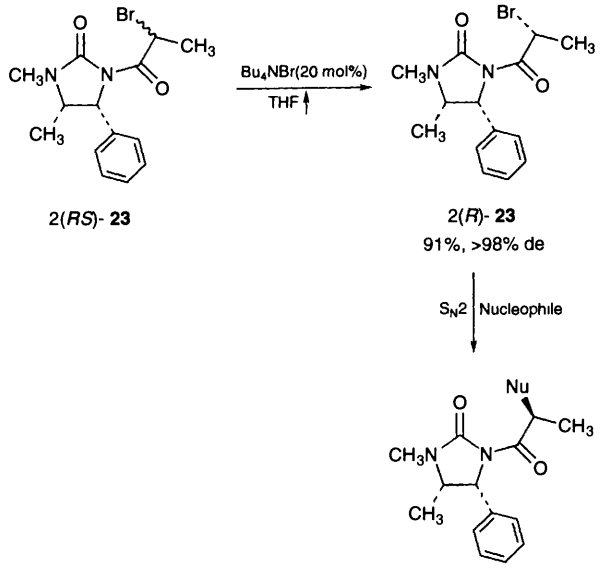
b, R = O Ph

c, R = OEt

Figure 3

1,5-diazabicyclo[4 3 0]non-5-ene (DBN) Crystallisation of the diastereomeric mixture from hot ethyl acetate–hexane (1 3) with catalytic DBN (*ca* 10 mol%) gave essentially one diastereomer (86% yield) This preparation has been carried out on >150 g scale

In our group[15] we have shown that 2*RS*-**23** can be transformed to 2*R*-**23** in 91% yield by crystallisation from THF in the presence of catalytic tetrabutylammonium bromide (Scheme 28)



Scheme 28

The bromide source induced epimerisation and with slow evaporation of the solvent the less soluble 2*R*-**23** was selectively deposited The tetrabutylammonium bromide can be removed from the precipitate by aqueous extraction leaving the stable 2*R*-**23** diastereomer which can undergo nucleophilic displacement with amines to give amino acid derivatives of the opposite configuration to those derived from the DKR of the same substrate (section **2.4**) The principle of being able to transform a racemate to either enantiomeric form of a product *via* complementary dynamic resolution processes using one chiral form of the auxiliary is quite appealing We are currently exploring the generality of such complementary dynamic resolutions During our study we have attempted DKRs and CIDRs on analogous substrates using Evans' oxazolidinone We have observed[16] that the oxazolidinones are more prone to *trans* acyl ring cleavage and, whilst CIDR was shown (85% de), the increased chiral lability compromised stereoselectivity during work-up and subsequent S_N2 reactions *Induced* configurational lability is the key to effective CIDR

4 Concluding remarks

Amongst the existing armoury of asymmetric synthetic strategies dynamic resolutions are gaining increasing recognition There is a certain elegance in being able to utilise configurational lability at a chiral centre in the efficient transformation to isomerically enriched or pure products Traditionally, the presence of potentially labile stereocentres in intermediates along a synthetic pathway would present cause for concern but given consideration they may provide access to enantiomerically enriched products Although dynamic resolutions are confined to suitably labile substrates this review illustrates the diversity of useful products that can be obtained, often with unsurpassed efficiency and from relatively accessible substrates The variety of approaches that have been employed in both dynamic kinetic resolutions and in crystallisation induced dynamic resolutions has also been shown to be wide-ranging Many of the examples included in this article have been developed with a view to industrial-process scale or for large-scale laboratory preparation of important research chemicals, hence, cost, efficiency, practical and environmental considerations are of paramount importance Resolution of stereoisomers has always been a reliable method of obtaining enantiomerically pure compounds but the fundamental limitation of yield has made it thoroughly unfashionable The use of dynamic resolutions in asymmetric synthesis seems to be increasing and it would appear that chemists are considering these resolution strategies as a serious alternative to conventional methods for asymmetric synthesis

Added in proof Recently a CIDR of dipeptide-derived oxazolones has been described H T Stock and N J Turner, *Tetrahedron Lett* , 1996, **37**, 6575

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