Kinetic Resolutions by Means of Cycloaddition Reactions

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The principles and recent applications of kinetic resolutions of racemates by means of cycloaddition reactions (including Diels–Alder reactions, 1,3-dipolar cycloadditions and metal-mediated "cycloadditions") are discussed, with particular emphasis on examples based on the emerging concept of Parallel Kinetic Resolution.

Introduction

A kinetic resolution process, in general, is a chemical transformation of a racemic mixture in which one enantiomer is transformed into a product more rapidly than the other; i.e., one enantiomer reacts faster than the other in a certain reaction. Kinetic resolution is therefore based on a concept fundamentally linked to kinetics, all the kinetic aspects having been extensively analysed by Kagan and Fiaud in a landmark review.[1] The resolution of a racemic mixture relies on the possibility of recovering the unchanged substrate in a nonracemic form, and the efficiency of a resolution − that is, the enantiomeric excess of the unchanged starting material − depends on the relative reaction rate constants of the two enantiomers (the stereoselectivity factor),[1] on the extent of conversion and on the stoichiometric ratios of the reagents. This implies that, apart from cases with high stereoselectivity factors, a compromise always has to be made between the enantiomeric purity of the unchanged substrate and its chemical yield, since both of them cannot be maximized simultaneously.[1]

From the synthetic point of view, kinetic resolution is a method for obtaining optically active compounds from racemic mixtures. The first example of a kinetic resolution may be considered to be the fermentation of an aqueous solution of racemic ammonium tartrate by a *Penicillium glaucum* mould performed by Pasteur in 1858, from which he recovered optically active ammonium tartrate.[2] Nevertheless, kinetic resolutions have only recently become widely investigated and employed in organic synthesis. In addition

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Francesca Cardona (centre) was born in Firenze, Italy, in 1971. She studied at the University of Firenze, where she earned her Laurea in Chemistry in 1995 and her Doctoral degree in Chemistry in 1999, under the supervision of Prof. Alberto Brandi, working on syntheses and computational studies of glycosidase inhibitors. She joined the group of Prof. Vogel (University of Lausanne, Switzerland) during the third year of her PhD and continued as a Postdoctoral Fellow (1998, 1999), working on the syntheses of imino-C-disaccharides by cross-aldolization reactions. She was a C.N.R. Postdoctoral Fellow at the Consiglio Nazionale delle Ricerche, Centro di Studio sulla Chimica e la Struttura dei Composti Eterociclici e loro Applicazioni (CSCEA) in Firenze (2000). Her current research projects focus on the stereoselective syntheses of polyhydroxylated natural alkaloids and analogues based on 1,3-dipolar cycloaddition chemistry, new oxidation methods, and kinetic resolutions by 1,3-dipolar cycloaddition reactions.

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Alberto Brandi (left), born in 1951. Doctor in Chemistry 1975, University of Firenze. CNR fellowship from 1978. From 1980 Ricercatore Universitario at the Department of Organic Chemistry of University of Florence. From 1982 to 1984 NATO fellow with Professor Barry M. Trost at the University of Wisconsin, Madison. Associate Professor at the University of Basilicata, Potenza 1987, and in 1990 called back to the University of Florence, where he became Professor of Organic Chemistry in the Faculty of Science in 1994. Recent research deals with stereoselective 1,3-dipolar cycloadditions; enantiopure nitrones for syntheses of alkaloids and aza heterocycles; asymmetric synthesis of biologically active compounds; chemistry of strained small rings; synthesis of peptidomimetics; synthesis of new materials for molecular recognition. A. B. is the author of over 120 papers including 2 reviews in Topics on Current Chemistry and Chemical Reviews.

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to the earliest stoichiometric reactions (functional groups transformations, C−C bond-forming reactions), more recent catalytic methodologies such as organometal-catalysed or enzymatic reactions[3] have increasingly been introduced in order to achieve kinetic resolutions.

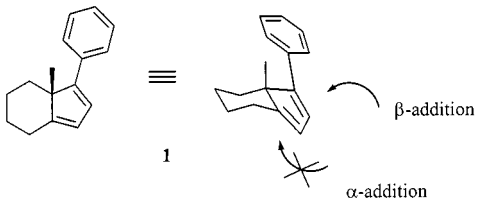
In the already rich panorama of kinetic resolutions, cycloaddition reactions have been examined only infrequently. The most comprehensive report regards enantioselective Diels−Alder reactions between enantiopure dienes and racemic α,β-unsaturated lactones and ketones.[4] However, an increasing number of examples of kinetic resolutions in cycloadditions have recently appeared in the literature, and the time is ripe for a complete review of the state of the art in this field.

Cycloaddition reactions are nicely suited for kinetic resolution, since they occur by way of a concerted mechanism through a highly organized transition state subjected to strict conditions. The reaction rate depends on the stability of the cyclic transition state, strongly governed by steric factors. This implies that transition states deriving from an enantiopure substrate and a racemic partner in a cycloaddition may, thanks to double asymmetric induction, differ significantly in terms of energy. Consequently, the cycloaddition reaction may result in an effective kinetic resolution of the racemate. The enantiopure reagent forms a "matched" pair with one enantiomer, which is consumed more quickly, and a "mismatched" pair with the other one. The racemic substrate can therefore be recovered in a nonracemic form enriched in the less reactive enantiomer. Of course, the higher the difference in energy contents of the two transition states, the more efficient the resolution.

Nowadays a number of cyclization processes which occur in a stepwise fashion (and therefore cannot be regarded as cycloaddition reactions) are often put forward as formal cycloadditions. Since this, to the best of our knowledge, is the first review of kinetic resolutions by means of cycloaddition reactions, resolutions achieved by way of these processes are also briefly reviewed. Finally, we also show how selectivities can be enhanced in parallel kinetic resolution experiments, a new, rapidly developing concept in the field of kinetic resolution processes.[5]

Kinetic Resolutions by Means of Diels−Alder Reactions

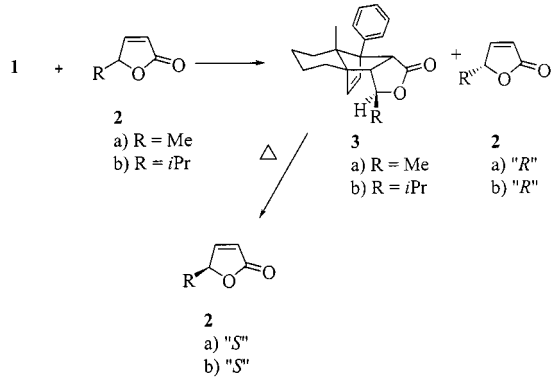
Winterfeldt and co-workers have widely exploited the possibility of performing kinetic resolutions by means of Diels−Alder reactions. Part of their work has been collected in a feature article,[4] and so only the most representative and recent examples are reported to illustrate their chemistry. Winterfeldt's idea was to mimic, in a purely chemical way, what happens in enzymatic reactions, which are capable of selecting a single enantiomer of a racemic mixture for a given transformation. The enantiomer selected is the one that fits better into the enzyme's chiral pocket. The Diels−Alder reaction has a great chance of manifesting a similar substrate specificity, since it proceeds through a concerted mechanism in which very rigid and constrained adducts are formed; and so steric discriminating effects should be relevant.



1

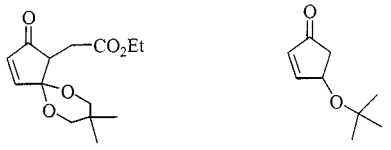
Cyclopentadiene **1**, available in both enantiomorphic forms,[6] was chosen in order to study the potential of chiral racemic dienophiles in effecting kinetic resolutions. Cycloadditions to **1** occurred with high diastereoselectivity, with dienophiles approaching the β-face − the convex side of the molecule − of the steroid-like diene, the recovered lactones being enantiomerically pure.[7]

Treatment of **1** with butenolides **2** was indeed highly diastereoselective, resulting exclusively in the formation of adducts **3**, and recovery of unchanged "*R*" **2a** or **2b**. The faster reacting enantiomers could also be recovered with the aid of thermal retro Diels−Alder processes, giving enantiomerically pure butenolides in very high chemical yields (Scheme 1).[8] As predicted, the reaction being totally regio- and *endo*-selective, only the enantiomeric lactones with the small hydrogen atom pointing toward the diene and the alkyl substituent pointing away from it reacted, leaving the "mismatched" enantiomers untouched. The racemic α,β-unsaturated cyclic ketones **4−6** could be efficiently resolved by use of the same methodology.[8,9] The resolution occurred even with oxo ester **6**, in which the stereogenic centre is in the homoallylic position rather than the allylic one, thus showing that, at least with cyclopentenones, a second possible location of the stereogenic centre is allowed.[8] In the case of the *tert*-butyl ether **7**, the Diels−Alder reaction was not as highly diastereoselective; two diastereomeric adducts were formed, showing that an oxygen atom, regardless of its substituent, can be accommodated in the "inside" position much more easily than a CH_2 group can.[9b]



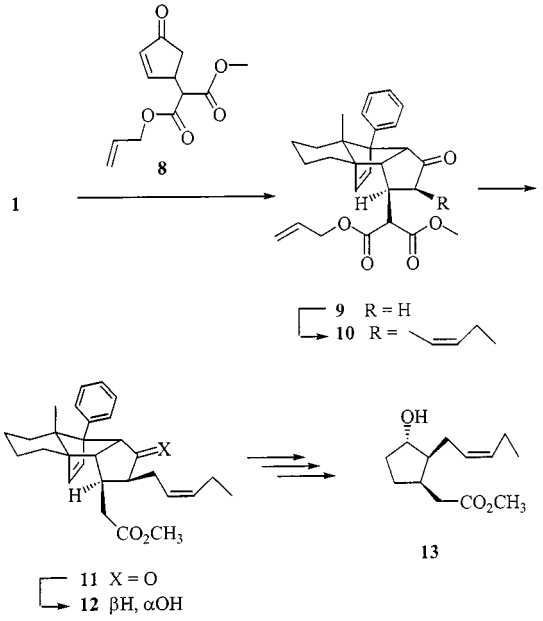
Scheme 1

rac-**4** rac-**5**



rac-**6** rac-**7**

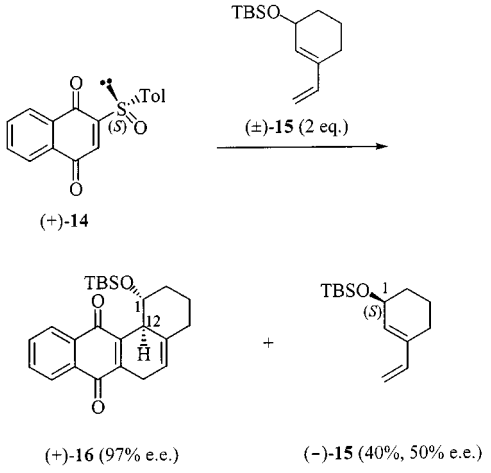
More recently, kinetic resolution of the malonate-substituted cyclopentenone **8** has been applied for the asymmetric synthesis of adduct **9**, a precursor of (−)-methyl cucurbate (**13**) (Scheme 2).[10] As expected, only the 4*R* enantiomer underwent cycloaddition, producing enantiopure **9**. Subsequent diastereoselective alkylation with (*Z*)-1-bromo-2-pentene, followed by palladium-catalysed cleavage of malonate and diastereoselective borohydride reduction of **11**, afforded **12**, which underwent thermal retro Diels−Alder reaction. Selective hydrogenation of the ring double bond with $Pd/CaCO_3$ yielded enantiomerically pure (−)-methyl cucurbate (**13**).[10]



Scheme 2

In a project aimed at the synthesis of angucyclinone antibiotics (natural products with a quinone structure, isolated from microbial sources[11] and displaying several forms of biological activity[12]) Carreño and co-workers have performed the asymmetric synthesis of the skeleton by using enantiopure dienophiles and taking advantage of efficient kinetic resolution of the diene partners in a Diels−Alder reaction.[13] Their extensive studies on the behaviour of sulfinylquinones as dienophiles in Diels−Alder cycloadditions have demonstrated the ability of these sulfoxides to dictate the regioselectivity, the *endo* selectivity and the π-facial selectivity with different kinds of dienes.[14] Thermal Diels−Alder cycloaddition, followed by sulfoxide elimination, turned out to be an efficient domino process for the creation of the tetracyclic skeleton of angucyclinones from a chiral dienophile.

Enantiopure sulfinylquinone (+)-**14**[15] was capable of discrimination between the two faces of racemic vinylcyclohexenes possessing bulky alkoxy substituents at the allylic positions. Of all the dienes employed, the best results were obtained with compound **15** (Scheme 3). Quinone (+)-**14** reacted with 2 equiv. of racemic **15** to afford highly enriched adduct (+)-**16** (97% *ee*), with a 40% yield of unchanged optically active diene (*S*)-**15** being recovered in 50% enantiomeric excess.[13a,13b] The effective kinetic resolution arises from a discriminating double asymmetric induction in the cycloaddition. On the premise that the *endo* mode of addition is favoured and that the quinone dienophile assumes the *s-cis* conformation, approach of the incoming diene at the *Si* face, shielded by the less encumbered sulfur electron pair, should be preferred. The "matched" interaction then occurred with diene (*R*)-**15**, which can dispose its bulky pseudoaxial substituent *anti* with respect to the direction of approach (Figure 1).



Scheme 3

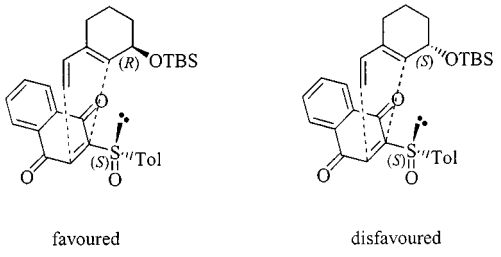
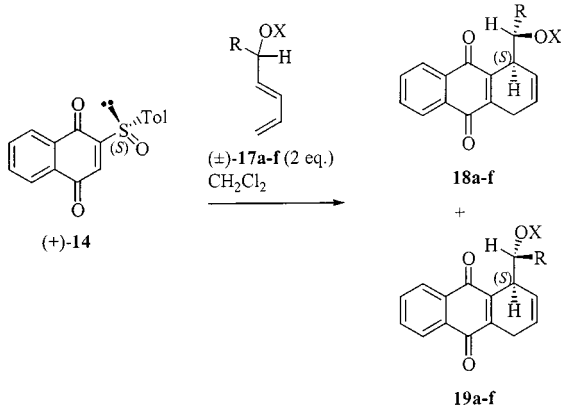


Figure 1. *endo* approaches for enantiopure sulfinylquinone (+)-**14** with racemic dienes **15**

The study has been successively extended to acyclic dienes bearing allylic stereogenic centres.[16] A series of chiral

racemic dienes **17** have been employed (Scheme 4), and in all cases the primary cycloadducts underwent pyrolytic elimination of the sulfinyl group. Two enantio-enriched diastereoisomers **18** and **19** were formed in a ca. 75:25 ratio. This indicates that a partial kinetic resolution of the diene had taken place (recovery of the unchanged optically active diene was possible in one case). Enantiopure sulfinyl quinone (+)-**14** was somehow able to discriminate slightly between the two enantiomers of the diene according to the two TSs depicted in Figure 2. Indeed, assuming preferred *endo* approach of the diene and *s-cis* conformation of the sulfinylnaphthoquinone, only one of the two enantiomers of the diene (the "matched" partner, approach mode A, Figure 2) can approach the dienophile while avoiding the *gauche* conformation between the bulky R group and the C^2-C^3 double bond in the transition state (approach mode B, Figure 2) when the allylic H atom is pointing towards the sulfinyl moiety.



diastereomeric ratio

	18 (% e.e.)	**19** (% e.e.)
a: R = Me, X = H	70 (70)	30 (74)
b: R = Me, X = MOM	75 (82)	25 (80)
c: R = Me, X = TBDMS	75 (68)	25 (72)
d: R = Ph, X = H	75 (74)	25 (68)
e: R = Ph, X = MOM	75 (68)	25 (68)
f: R = Ph, X = TBDMS	76 (68)	24 (72)

Scheme 4

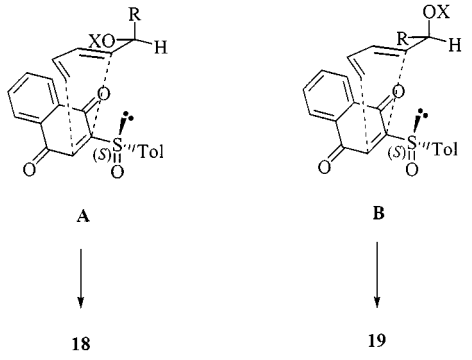
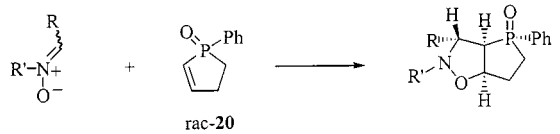


Figure 2. *endo* approaches for enantiopure sulfinylquinone (+)-**14** with racemic dienes **17**

Kinetic Resolutions by Means of 1,3-Dipolar Cycloadditions

Brandi and Pietrusiewicz have widely investigated the cycloadditions of nitrones to chiral vinylphosphane oxides, which regioselectively provided 5-phosphinyl-substituted isoxazolidines with high diastereoselectivity.[17] The facial selectivity was controlled by the phosphorus stereocentre, the major isomers resulting from a favoured *endo* approach in the transition state, with the stereogenic centre of the dipolarophile placing the largest group *anti* to the incoming dipole and the oxygen atom in the inside position ("inside heteroatom" transition state model analogous to Houk's "inside alkoxy" model).[18] The diastereoselectivity could be increased to 40:1 for the *endo* approach by matching interactions with chiral nitrones.[19]

Single and double asymmetric induction in the formation of 4-phosphinylisoxazolidines has been analysed using the chiral, racemic 2,3-dihydro-1-phenyl-1*H*-phosphole 1-oxide (**20**)[20] as a model substrate, because of its high regioselectivity and diastereoselectivity.[21] Cycloadditions between **20** and three achiral nitrones **21**−**23** resulted in the regioselective formation of the 4-phosphinyl adducts **24**−**26** as single diastereoisomers (Scheme 5).[22] The complete diastereoselection was due to the selective approach of the dipole to the less hindered face of the cyclic phospholene oxide, opposite from the phenyl ring, allowing complete control over four contiguous stereogenic centres in the final isoxazolidines.

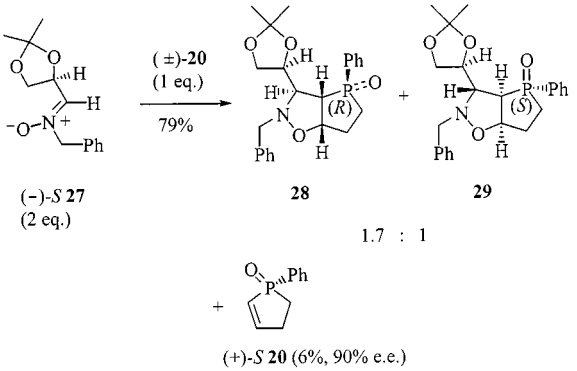


(*E*)-**21** R-R' = -$CH_2CH_2C(CH_3)_2$-
(*Z*/*E*)-**22** R = CO_2Me, R' = Me
(*Z*)-**23** R = Ph, R' = Me

24 65%
25 65%
26 72%

Scheme 5

This high diastereoselectivity prompted the study of double asymmetric induction with an optically active nitrone, such as the D-glyceraldehyde-derived (−)-**27** (Scheme 6). Two diastereomeric 4-phosphinylisoxazolidines,



Scheme 6

28 and **29**, were formed out of the eight possible ones. This was the result of a highly stereoselective *endo* approach of the enantiopure nitrone (with the largest methylene group of the dioxolane ring in an antiperiplanar relationship with the incoming dipolarophile) to each enantiomer of phospholene oxide **20** (Figure 3).[22]

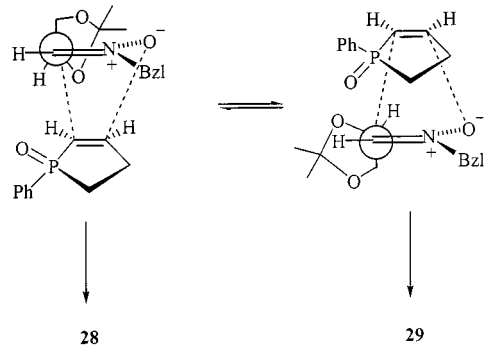


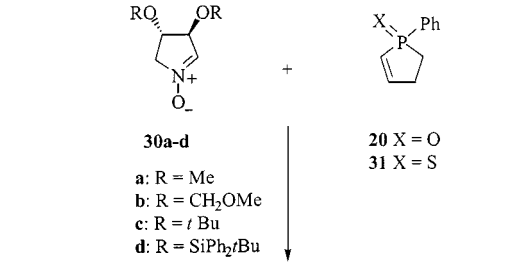
Figure 3. *endo* approaches for enantiopure nitrone (−)-**27** with racemic phospholene oxides **20**

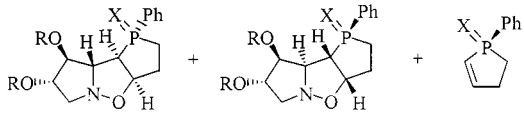
A slight difference in steric hindrance between the two transition states accounted for the observed small difference in reactivity between the two enantiomers of phospholene oxide, allowing partial kinetic resolution of racemic **20**. As a matter of fact, the unchanged phospholene oxide, although recovered in poor yield (6%), was enriched in the *S* enantiomer at the phosphorus stereogenic centre (90% *ee*).[22] This was the first example of a kinetic resolution by means of 1,3-dipolar cycloaddition reported in the literature.

With the high asymmetric induction furnished by phospholene oxide **20** established, increasing the efficiency of the kinetic resolution required nitrones displaying more pronounced facial diastereoselection. Enantiopure pyrroline *N*-oxides derived from L- or D-tartaric acid[23] and L- or D-malic acid,[24] used for highly stereoselective syntheses of natural and unnatural polyhydroxylated indolizidines[23c,23d,24a,25] and pyrrolizidines,[26] were the best candidates for this purpose. The enantiopure nitrones **30a**−**d**,[23a−23c] when treated with 1.8 equiv. of racemic **20** and sulfide **31**,[27] gave two diastereomeric products, **32** and **33**, in much better ratios (Scheme 7),[28] and enantio-enriched (*R*)-**20** and (*R*)-**31** were recovered.

On the premise that the dipolarophiles were approached by the nitrones exclusively from the face bearing the smaller P=X substituent and in an *exo* mode, the major adducts **32** must have resulted from "matched" interactions of the *S* dipolarophiles approaching the enantiopure nitrones *anti* with respect to the vicinal C^3 alkoxy or silyloxy group (approach mode A, Figure 4). "Mismatched" isomers **33** were obtained through the B approach mode.

A judicious choice of the size of the hydroxy protecting groups on the nitrone allowed a compromise between a good diastereoselectivity, the highest possible yields of cycloadducts and a reasonable yield of highly enantio-enriched dipolarophile. The best result was obtained when the





	ratio of **32**/**33**	yield% (% e.e.) of **20** or **31**
a: R = Me, X = O	3.3:1	45 (61)
b: R = CH_2OMe, X = O	5:1	45 (−)
c: R = *t* Bu, X = O	6.4:1	39 (49)
d: R = *t* Bu, X = S	8:1	46 (−)
e: R = $SiPh_2$*t*Bu, X = O	10:1	39 (59)

Scheme 7

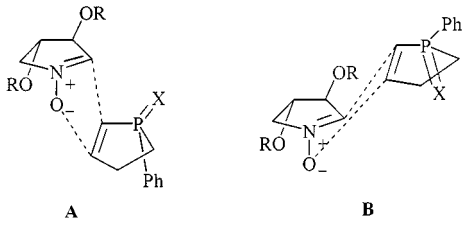
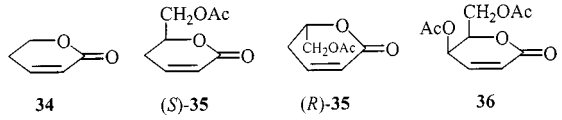


Figure 4. *exo* approaches for enantiopure nitrones **30** with racemic phospholene oxide **20** (X=O) and sulfide **31** (X=S)

tert-butoxy derivative **30c** and **20** were employed in 1:1.5 ratio; the desired cycloadducts were isolated in 91% yield and 2.9:1 ratio, and 27% of unchanged (*R*)-**20** (96% *ee*) was recovered.[28] A stereoselectivity factor of 14 for the cycloaddition between **30d** (possessing the bulkiest *tert*-butyldiphenylsilyl protecting groups) and **20** was calculated,[28] which compared favourably with many different reactions. More recently, the kinetic resolution has been extended, with analogous efficiency, to 1-phenyldihydrophosphole selenide, with similarly well differentiated faces of the dihydrophosphole ring.[29]

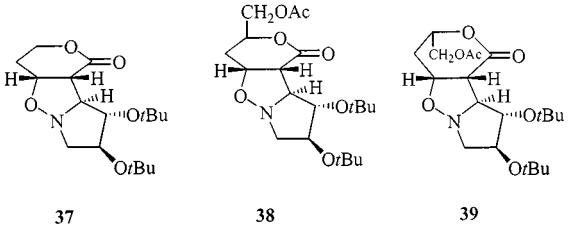
The efficiency of this kinetic resolution, due to the high facial selectivity of both nitrone and dipolarophile, is remarkable. Considering that both enantiomorphic forms of nitrones **30a**−**d** are available, this simple methodology allows both enantiomers of the dihydrophosphole derivatives **20** or **31** to be accessed easily. Moreover, the cycloadducts formed are immediate precursors, through N−O bond cleavage, to a new family of enantiopure aminophosphane ligands incorporating the 2,2′-linked pyrrolidinophospholane ring system in their structures.[30]

Double asymmetric induction in 1,3-dipolar cycloadditions of **30c** with sugar-derived α,β-unsaturated lactones has recently been investigated.[31] Hexopyranoid α,β-unsaturated lactones such as the readily available D-*glycero*-derived (*S*)-**35**[32] and D-*threo*-**36**[33] (Scheme 8) showed high facial diastereoselectivities towards conjugate additions of hydroxylamines[34] and hydrazines,[35] undergoing conjugate addition exclusively *anti* to the acetoxymethyl group. The high diastereoselectivity in the reactions of α,β-unsaturated cyclic ketones has been interpreted by invoking preferred axial approach of nucleophiles, resulting in more stable, chair-like enolate intermediates.[36] In addition, in 1,3-dipolar cycloadditions with acyclic (*Z*)-nitrones,[37] only *anti-endo* adducts were formed, suggesting the nucleophilic type of attack by the nitrone, with formation of the C−O bond prior to the C−C bond.[37]



Scheme 8

With cyclic nitrones, only an *exo* approach of the reactants is possible. Indeed, cycloaddition between **30c** and achiral lactone **34** occurred with almost total regio- and stereoselectivity, producing the *exo-anti* adduct **37** (Scheme 9)[31] and once more confirming the high facial diastereoselection of nitrone **30c**.



Scheme 9

When racemic lactone **35**[38] was used, a nice double asymmetric induction was observed, with formation of the "matched" adduct **38** and the "mismatched" adduct **39** (Scheme 9, Figure 5) in a 91:9 ratio and lactone (*R*)-**35** being recovered in 77.4% *ee*.[31] The high facial differentiation of the double bond of the lactone is due to the presence of the C^6 acetoxymethyl group. Indeed, in the case of (*R*)-**35**, the *exo* approach of the dipolarophile proceeds *syn* with respect to the C^6 acetoxymethyl group (approach mode B, Figure 5) and it is therefore disfavoured, resulting in efficient kinetic resolution of the racemate. It is worth noting that the cycloadducts formed are putative precursors of (1→2)-joined pseudo-imino-*C*-disaccharides, a new class of imino-*C*-disaccharides[39] recently approached by cycloadditions to glycals.[40]

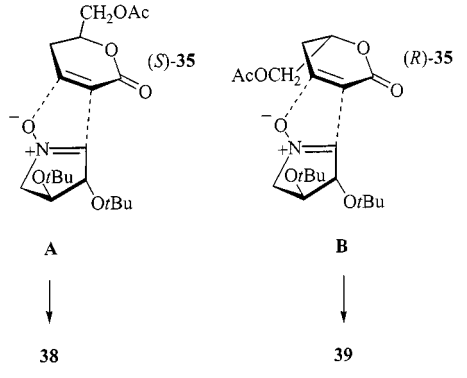
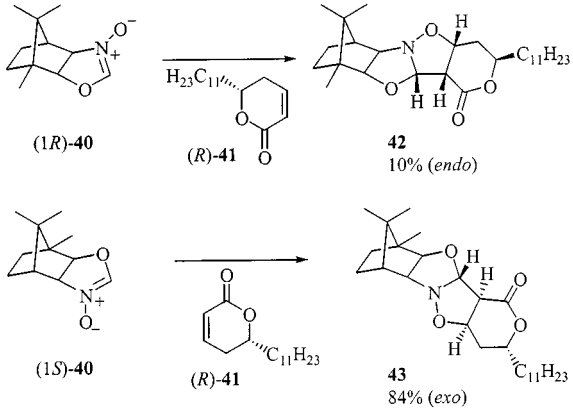


Figure 5. *exo* approaches for enantiopure nitrone **30c** with racemic lactones **35**

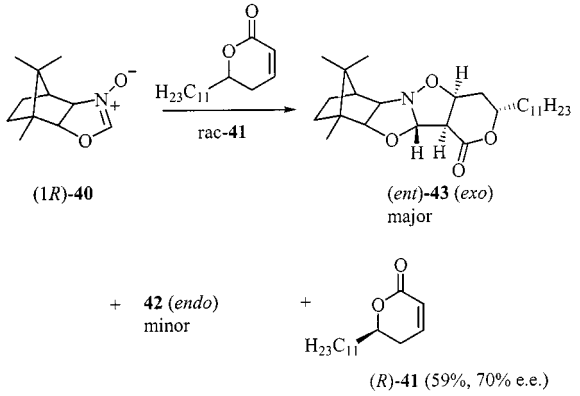
A similarly degree of double asymmetric induction has been recently reported by Langlois and co-workers in the cycloaddition between chiral isoxazolidine *N*-oxide **40** and an analogous α,β-unsaturated δ-lactone **41**.[41] The high regioselectivity and facial diastereoselection exhibited by the camphor-derived oxazoline *N*-oxide **40** in [3+2] asymmetric cycloadditions with several electron-deficient alkenes is well documented.[42] In a project involving the total synthesis of pancreatic lipase inhibitor tetrahydrolipstatin,[43] the cycloadditions between both enantiomers of **40** and (*R*)-**41** have been studied (Scheme 10). Although cycloadditions to **40** are usually *exo*-selective, the "mismatched" interactions occurring in a double differentiating reaction [in this case between (1*R*)-**40** and the lactone (*R*)-**41**] resulted in the favoured *exo* approach being completely inhibited, and only a small amount of the *endo* product was formed.



Scheme 10

The observed great difference in reactivities allowed kinetic resolution of racemic **41** when enantiopure oxazoline *N*-oxide (1*R*)-**40** was employed (Scheme 11, Figure 6).[41] The major *exo* adduct (*ent*)-**43** and the minor *endo* isomer **42** were formed and highly enriched (*R*)-lactone **41** was recovered (70% *ee* determined by proton-decoupled ^{13}C NMR analysis in a chiral liquid crystalline solvent).[44]

The high facial diastereoselection of lactone **41**, which is always approached by the nitrone *anti* to the equatorial aliphatic chain, has been interpreted by the authors by invoking stereoelectronic repulsion between the pseudo-axial hydrogen atom on C^4 and the negatively charged oxygen atom of the nitrone (Figure 7), rather than in terms of an axial approach[36] or of the steric hindrance of the aliphatic chain itself.



Scheme 11

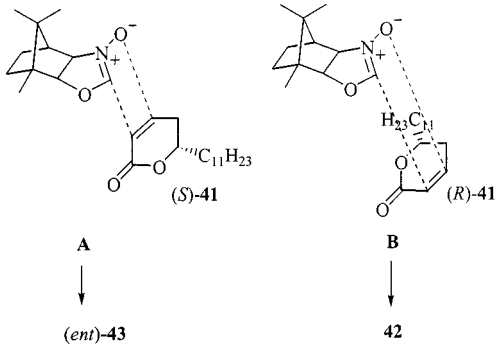


Figure 6. *exo* approaches for enantiopure nitrone (1*R*)-**40** with racemic lactones **41**

Other isolated examples of enantiodiscrimination in [3+2] nitrone cycloadditions using chiral enantiopure nitrones have been reported in the literature. In an investigation into asymmetric synthesis of β-lactam antibiotics by means of dipolar cycloadditions between nitrones and acyldiiron complexes, Gilbertson and Lopez found that enantiomerically pure nitrone (−)-**44**[45] was able to discriminate between the two enantiomers of racemic **45**. The reaction exclusively gave one isoxazolidine adduct, **46** or **47**, as a single diastereoisomer in 50% yield and optically active unchanged starting material was recovered (Scheme 12).[46] Assuming that the nitrone attacked the complex exclusively on the face opposite to the large *tert*-butyldimethylsilyl group and that the cycloaddition proceeded selectively through an $endo_{C=O}$ transition state, it is likely that the face of the olefin that was approached preferentially was the one opposite to the sulfur bridge. This double asymmetric induction resulted in kinetic resolution of the racemic starting material.

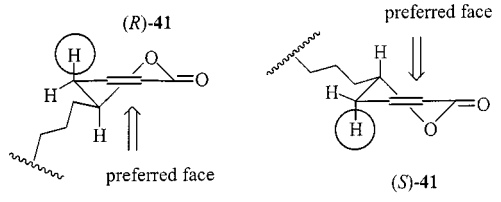
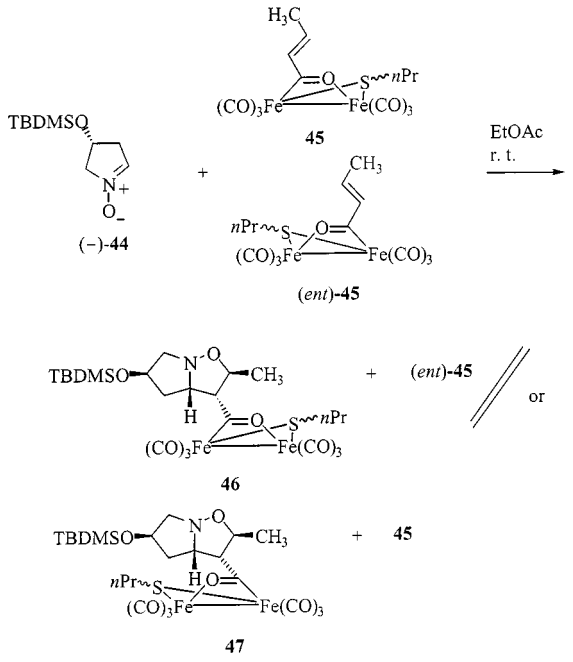
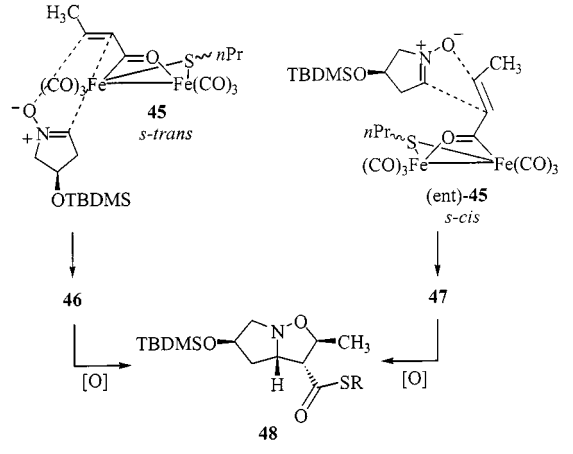


Figure 7. Lactones **41** are always approached *anti* with respect to the equatorial aliphatic chain



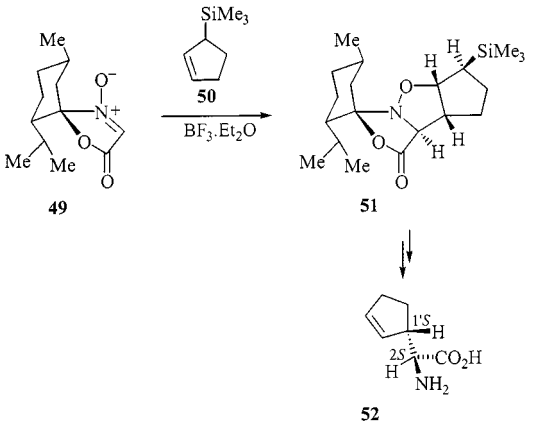
Scheme 12

However, since the same isoxazolidine thioester **48** was obtained after oxidation of the adduct, and the authors were not able to determine the absolute configuration at the metal centre, it remained uncertain which was the faster reacting enantiomer. Either enantiomer **45** reacted in the *s-trans* conformation or (*ent*)-**45** reacted in the *s-cis* conformation (Scheme 13). In any case, given the high diastereoselectivity of the cycloaddition, one conformational approach should predominate for each enantiomer, causing one of the two enantiomers of the racemic complex to react significantly faster.



Scheme 13

Lewis acid catalysed cycloaddition between spirocyclic enantiopure nitrone **49**[47] and 3-(trimethylsilyl)cyclopent-1-



Scheme 14

ene (**50**) has also been reported (Scheme 14).[48] The *S* enantiomer of the racemic dienophile, bearing the large $SiMe_3$ group *anti* (with respect to the direction of approach and to the coordinated BF_3) in the preferred *exo* transition state, was the only one to react, adding exclusively to the less hindered face of nitrone **49**, to afford adduct **51** (Figure 8). After removal of the chiral auxiliary from adduct **51** and further elaboration,[49] this highly efficient asymmetric dipolar cycloaddition of nitrone **49** resulted in enantiomerically pure (2*S*,1′*S*)-2-(cyclopent-2-enyl)glycine (2*S*,1′*S*)-**52** (Scheme 14).[48] Recovery of the unchanged, enantio-enriched dipolarophile **50**, however, was not reported by the authors, hampering appraisal of the efficiency of the kinetic resolution.

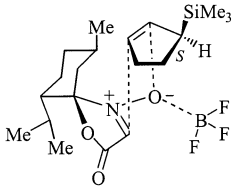
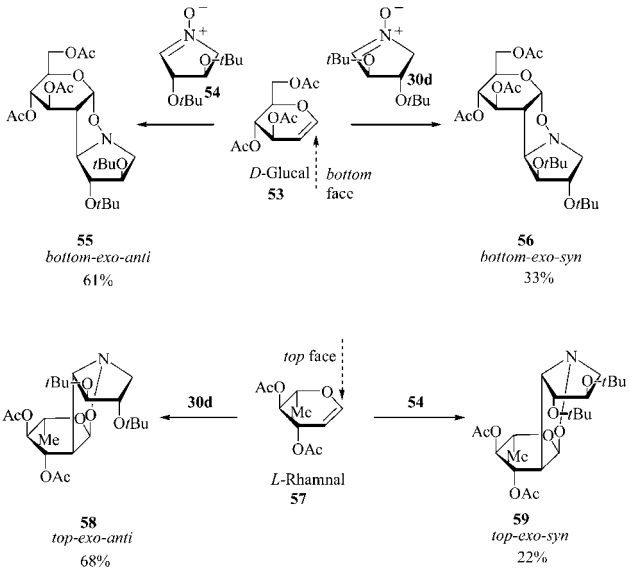


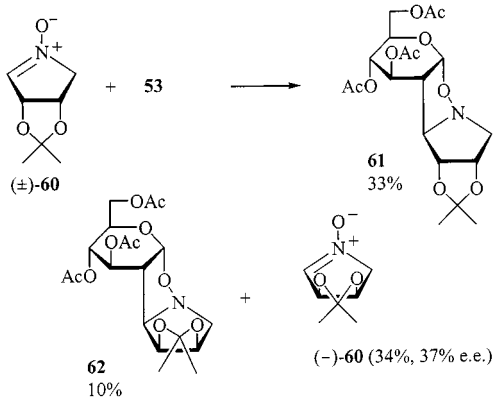
Figure 8. *exo* approach of enantiopure nitrone **49** with the *S* enantiomer of racemic cyclopentene **50**

The only kinetic resolution of a nitrone by means of a 1,3-dipolar cycloaddition has been recently reported by us, with use of 1,2-glycals as dipolarophiles.[50] The high level of stereocontrol provided by the pseudoequatorial group on C^3 of glycals has been widely demonstrated in many other cycloadditions, such as [2+2] addition to isocyanates[51] and hetero Diels−Alder additions.[52] The preferred addition, *anti* with respect to the substituent on C^3, determined the reactive face of the glycal (*bottom* or *top*). In 1,3-dipolar cycloadditions with hydroxylated pyrroline *N*-oxides, the single adduct isolated in each case also resulted from a preferred *exo* approach of the nitrone *anti* to the substituent on C^3.[40] With D- and L-tartaric acid derived enantiopure nitrones, "matched" and "mismatched" interactions arose from the enantiomorphic form of the nitrone employed, with "mismatched" interactions occurring when the nitrone was forced to react *syn* with respect to the vicinal bulky *O-tert*-butyl group (Scheme 15).[50]



Scheme 15

The high facial preference shown in this reaction with double asymmetric induction allowed the partial kinetic resolution of the *cis*-disubstituted racemic nitrone **60**.[26,53] D-Glucal **53** was able to discriminate slightly between the two enantiomers of racemic **60**, resulting in the formation of the *bottom-exo-anti* adduct **61** in higher yield (33%) and the recovery of enantio-enriched (37% *ee*) unchanged nitrone (−)-**60** (Scheme 16). Enantio-enriched (+)-**60** (43% *ee*) was obtained by performing an analogous experiment with L-rhamnal (**57**), which has the opposite facial diastereoselectivity. Unfortunately, the acetonide protecting group of the nitrone was not large enough to block the formation of smaller quantities of the "mismatched" adducts. This resulted in the recovery of nitrones with moderate *ee* values. However, an impressive increase in selectivity can be obtained by performing a parallel kinetic resolution experiment.

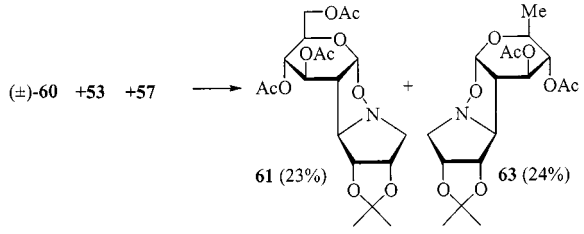


Scheme 16

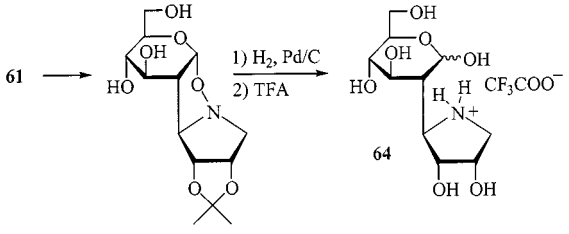
Parallel Kinetic Resolutions

The main disadvantage of a kinetic resolution is that the selectivity factor (the ratio of the reaction rates between the two enantiomers and the chiral enantiopure resolving reagent) to recover the unchanged starting material in 100% *ee* must be greater than 200.[1] The requirement for such a high difference in rates reaction is based on kinetic laws. Indeed, as the reaction proceeds, the concentration of the less reactive enantiomer increases, and so its reaction rate increases. At the end of the reaction, both enantiomers react, due to balance being reached between the inherent rate and the available concentration.[1] Nevertheless, if the less reactive enantiomer is removed during the course of the resolution by means of a different reaction occurring at a similar rate, this concentration bias is not effective and higher selectivities can be achieved. This concept, envisaged theoretically by Ugi,[54] has resulted in a new strategy, named Parallel Kinetic Resolution (PKR),[5,55] and this has been applied successfully in the intramolecular cyclopropanation of racemic secondary diazoacetates,[56] in the alkaline hydrolysis of a racemic epoxide,[57] and in the parallel esterification of a racemic alcohol.[55]

In the first reported example of PKR by 1,3-dipolar cycloaddition,[50] the racemic nitrone **60** was treated with quasienantiomeric D-glucal **53** and L-rhamnal **57** to yield diastereomeric *exo-anti* adducts **61** and **63** exclusively, in a 1:1 ratio. Formation of the disfavoured cycloadducts was avoided completely (Scheme 17). Since the two competing reactions had similar rates, the intrinsic maximum selectivity was maintained throughout the parallel resolution. Compounds such as **61** and **63** can be considered as synthons of pseudo-iminodisaccharides **64**, potential new selective inhibitors of glycosidases (Scheme 18).[40,50]

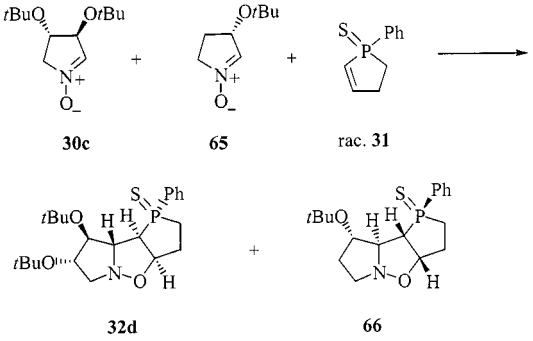


Scheme 17



Scheme 18

The same strategy has been applied by Brandi and Pietrusiewicz to the resolution of racemic dihydrophosphole derivative **31**, which was treated with L-tartaric acid derived nitrone **30c** and L-malic acid derived nitrone **65**, giving rise to two distinct, easily separable adducts, each derived from a different nitrone and a single enantiomer of the dihydrophosphole derivative (Scheme 19).[29] These examples demonstrate that the PKR strategy permits the best use of a racemic substrate for the synthesis of two different chiral products in enantiomerically pure forms, with better selectivities than obtained in simple kinetic resolutions.



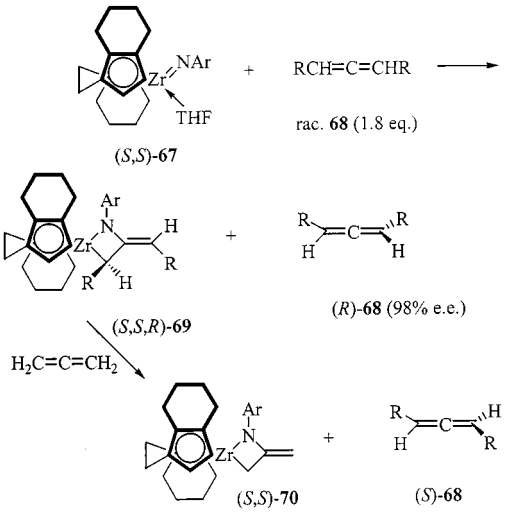
Scheme 19

Kinetic Resolutions in Metal-Mediated Cycloaddition Reactions

This last section is devoted to reactions that give, or occur through, formal cycloadducts involving organometallic species with M=X double bonds. It should be pointed out that these reactions proceed mainly through stepwise mechanisms, even in those cases in which stereospecificity is observed.[58] Although they are not classical pericyclic reactions, the products formed are formally the results of [2+2] cycloaddition reactions and so are considered in this review for this reason.

Bergman and co-workers have widely investigated the reactivities of stable and isolable imidozirconocene complexes in cyclization reactions. The highly reactive metal−nitrogen double bond underwent addition with a wide variety of unsaturated organic molecules, including alkynes,[59] imines[60] and certain alkenes.[61] More recently, the authors have extended this investigation to systems capable of undergoing highly enantioselective reactions, such as the chiral imido complex **67**, possessing the C_2-symmetric EBTHI [bis(tetrahydroindenyl)ethane] ligand.[62] Reactions between (*S*,*S*)-**67** and a variety of both symmetrically and unsymmetrically 1,3-disubstituted racemic allenes showed excellent diastereoselectivity. When (*S*,*S*)-**67** was treated at room temperature with 1.8 equiv. of racemic disubstituted allene **68**, consumption of approximately 50% of the allene and formation of one major diastereoisomer (*S*,*S*,*R*)-**69** was observed, with recovery of the highly enriched (*R*)-allene (*ee* up to 98%) (Scheme 20). Making this process even more interesting, it was possible to regenerate the faster reacting allene enantiomer from the metallacycle by treatment with an excess of 1,2-propadiene (Scheme 20). Thus, both enantiomers of the allene racemates could be recovered; the slower reacting one directly from the reaction mixture and the faster reacting one by displacement from the cyclization

product. Such a high degree of enantioselectivity is the result of mutually reinforcing stereocontrol imposed by the EBTHI ligand and the bulky imido substituent (Figure 9); "matched" interactions occur for the *S* enantiomer of the allene, capable of approaching the imidozirconocene complex in such a way as to minimize steric interactions between the R groups of the allene, the EBTHI ligand and the imido substituent (approach mode D, Figure 9).



Scheme 20

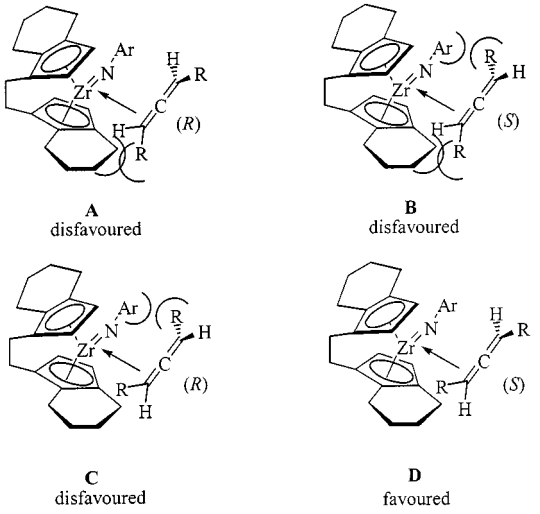
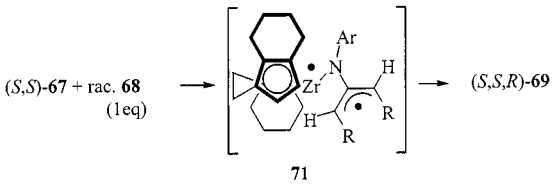


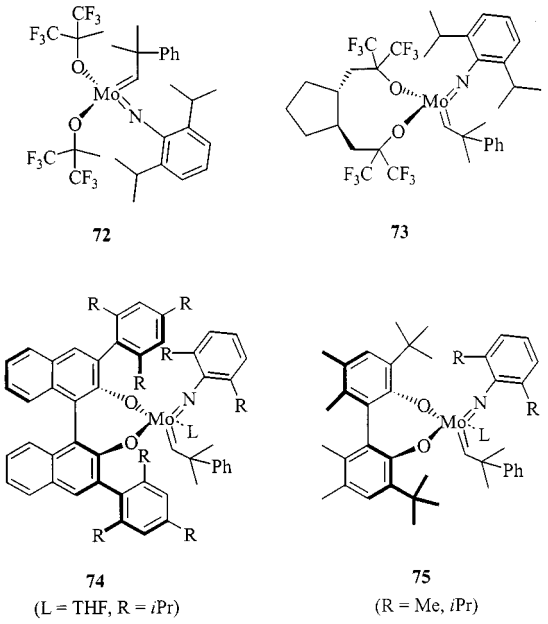
Figure 9. Approaches of enantiopure imidozirconocene complex (*S*,*S*)-**67** with racemic allenes **68**

Surprisingly, if the enantiopure imidozirconocene complex was treated with only 1 equiv. of a racemic disubstituted allene, no unchanged allene was recovered and only one diastereomeric metallacycle was obtained. By displacement with an excess of 1,2-propadiene, highly enriched (85% *ee*) (*S*)-allene was recovered. This is a nice example of dynamic kinetic resolution (DKR):[63] when the slower reacting (*R*)-allene adds to (*S*,*S*)-**67**, its configuration is inverted, allowing quantitative conversion of racemic allene into a material that is highly enriched in the *S* enantiomer. It should be stressed, however, that this DKR is possible only because the imido−allene cycloadditions are not pericyclic reactions and the processes are not concerted: involvement of a diradical intermediate **71**, as suggested by the authors,[62] explains the results (Scheme 21).



Scheme 21

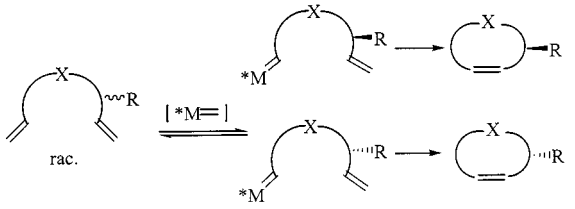
Although its relation to cycloaddition reactions is even weaker, alkene metathesis is probably the most important reaction worth mentioning in the field of metal-mediated "cycloaddition" processes. Here, formation of formal [2+2] cycloadducts only refers to transient reactive metallacyclobutane intermediates from carbenemetal compounds, according to the generally accepted "Chauvin mechanism".[64] Its extensive recent application to organic synthesis also includes a number of nice examples of kinetic resolutions of alkenes,[65] achieved by the use of Mo-catalysed ring-closing metathesis. Hoveyda and Schrock have already reviewed this subject,[66] and so we will confine ourselves here to illustrating the principle on which the process is based.



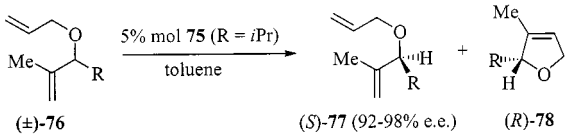
Schrock and co-workers have introduced and widely investigated the potential of molybdenum- and tungsten-based catalysts of general formula [M(=CHCMe$_2$Ph)(=NAr)(OR)$_2$] in metathesis reactions.[67] Among these, commercially available **72** showed pronounced reactivity. Chiral versions of this catalyst, readily prepared by introduction of chiral ligands around the molybdenum centre,

have opened the way to different kinds of asymmetric metathesis reactions.

Indeed, the ring-closing metathesis (RCM) reaction (Scheme 22) is well suited for asymmetric induction when a chiral alkylidene complex is used, since the two diastereoisomeric cyclic transition states may be different in terms of energy, and therefore the rates of cyclization of the enantiomers in the presence of the chiral catalyst can be different. This, in principle, can produce kinetic resolution of the racemic starting material. The pioneering experiments used the simplest complex **73**.[68] More recently, the use of Mo-based catalysts bearing the BINOL- or BIPHEN-derived ligands **74** and **75** has afforded excellent results in terms of asymmetric induction.[69] For instance, the ARCM (asymmetric ring-closing metathesis) of racemic allylic ethers (±)-**76** for the Mo-catalysed asymmetric synthesis of dihydrofurans (*R*)-**78** permitted recovery of highly enantio-enriched allylic ethers (*S*)-**77** (*ee* values 92−98%) (Scheme 23).[69b]



Scheme 22



R = pentyl, isobutyl, cyclohexyl

Scheme 23

Conclusions

Chemical kinetic resolution processes have long been known. However, only in the last few years have they been widely applied for resolving racemic compounds. In principle, a kinetic resolution process represents a good alternative to classic resolution procedures, since it can produce the substrate directly in a nonracemic form. To make kinetic resolution an efficient approach to enantiomer discrimination, a proper choice of structural requisites of reagents, based on knowledge of the mechanistic details of the reactions, has to be made. The examples discussed above demonstrate that cycloaddition reactions, with their strict mechanistic requisites and rigidly ordered transition states, are particularly well suited for design of efficient kinetic resolutions. On this basis, it may be anticipated that many more racemic compounds will be resolved in the near future by way of stereoselective cycloaddition reactions.

Acknowledgments

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