Pergamon

Tetrahedron, Vol. 52, No. 46, pp. 14361-14384, 1996

0040-4020/96 $15.00 + 0.00

PII: S0040-4020(96)00888-5

TETRAHEDRON REPORT NUMBER 409

Enantioselective Desymmetrisation of Achiral Epoxides

David M. Hodgson,* Andrew R. Gibbs and Gary P. Lee

The Dyson Perrins Laboratory, University of Oxford, South Parks Road, Oxford OX1 3QY, UK

Contents

1.	Introduction	14361
2.	Desymmetrisation by Enantioselective Deprotonation	14362
3.	Desymmetrisation by Enantioselective Addition	14373
	3.1. Carbon and hydrogen nucleophiles	14373
	3.2. Sulphur nucleophiles	14374
	3.3. Nitrogen nucleophiles	14375
	3.4. Oxygen nucleophiles	14378
	3.5. Halogen nucleophiles	14379
	3.6. Metal nucleophile: enantioselective isomerisation	14379
4.	Concluding Remarks	14381

1. INTRODUCTION

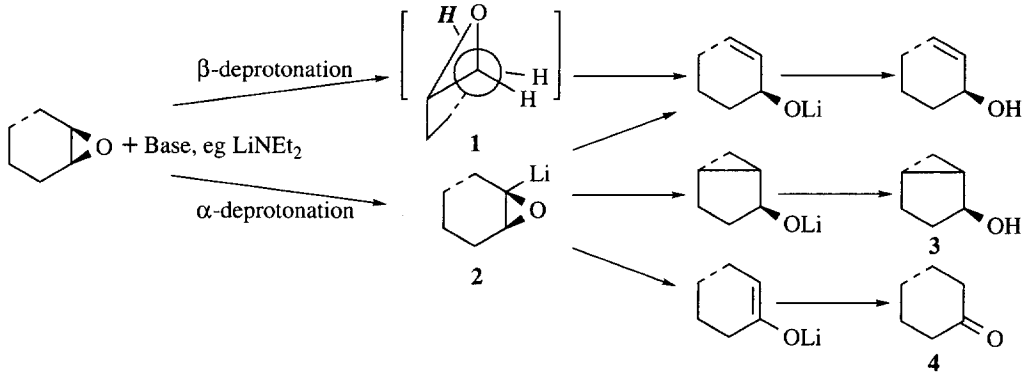
Enantioselective desymmetrisation of achiral materials is an attractive and extremely powerful concept in asymmetric synthesis. A number of strategies are already known which demonstrate its viability and application in targeted syntheses to provide compounds with high *ee* (enantiomeric excess).[1,2] This report reviews the methods which have been used to achieve enantioselective desymmetrisation by reaction of an epoxide functional group in an achiral substrate.[3] These methods are mainly asymmetric modifications of already known synthetically useful transformations of epoxides.[4] The strain in the three-membered epoxide ring, together with the polarisation of the C-O bonds (which can be enhanced through O-coordination to an electron-pair acceptor), impart reactivity to the epoxide functional group towards elimination reactions by bases and towards addition reactions by nucleophiles.

The importance of any (asymmetric) synthetic method not only relates to the products it provides access to, but also to the availability of the starting materials. Epoxides are predominantly prepared from alkenes, usually in one step by oxidation. There is a small class of alkenes which present homotopic faces to an epoxidising agent and thus lead to achiral epoxides. Epoxides derived from this class of alkenes have been used frequently in the development of enantioselective desymmetrisation methodology; these epoxides include those derived from cis disubstituted alkenes, in particular cyclic alkenes such as cyclohexene. Most alkenes present heterotopic faces (which may be enantio- or diastereotopic) to an epoxidising agent, and the bulk of these alkenes lead to chiral (racemic or non-racemic) epoxides. However, achiral alkenes which possess diastereotopic faces (eg 4-substituted cyclopentenes) also lead to achiral epoxides. Such epoxides have been

mainly used in applications of enantioselective desymmetrisation methods. An important feature in the preparation of such epoxides is that high and predictable diastereocontrol can often be exerted in the epoxidation step through steric effects and/or the directing effects of substituents present in the substrate alkene.[5] In addition, the more stereocentres that are present in the achiral epoxide, the greater the number of stereocentres in the enantioenriched product.

2. DESYMMETRISATION BY ENANTIOSELECTIVE DEPROTONATION

A brief overview of the reactions of epoxides with bases is given first in order to put the enantioselective transformations in perspective. Base-promoted non-enantioselective isomerisations of epoxides have been extensively studied.[6] The nature of the isomerisation depends principally upon the epoxide structure, but is also related to the base, solvent and temperature used (Scheme 1).



Scheme 1

β-Deprotonation (β-elimination) results in an allylic alcohol (Scheme 1). Syn, rather than anti, β-hydrogen removal was reported in 1970 by Thummel and Rickborn to generate allylic alcohols in a deuterium labelling study with *cis*- and *trans*-4-*tert*-butyl cyclohexene oxides using lithium diethylamide in ether.[7] β-Hydrogen removal was also observed in a recent deuterium labelling study by Morgan and Gajewski of the transformation of cyclohexene oxide to cyclohex-2-enol using LDA in ether.[8] Thus, this type of process is expected to be favoured with an epoxide which readily adopts conformations such as **1** with syn β-hydrogens (eg ***H***) accessible to the base. The earlier studies led to the acceptance of a 1:1 epoxide-base complex on the reaction pathway, where the base coordinates to a lone pair of electrons on the epoxide oxygen and thus mandates syn β-hydrogen removal (eg Figure 1).

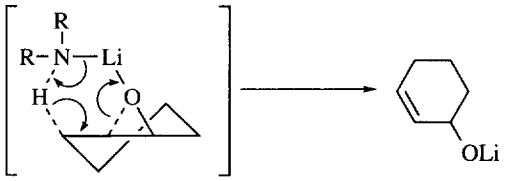
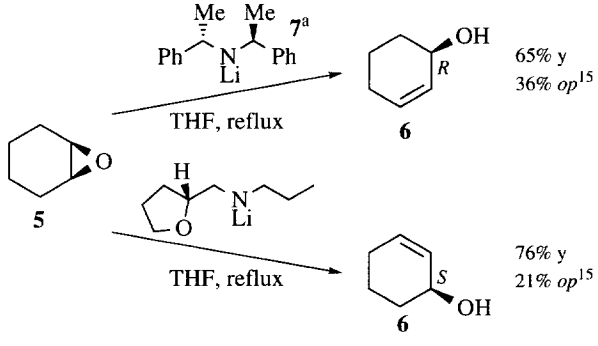


Figure 1

Application of the mechanism shown in Figure 1 often leads to useful models which aid examination of (enantio)selectivity in epoxide deprotonations. In reality, the systems will probably be composed of epoxide-base aggregates of varying complexity, several of which may provide pathways to product; the build-up of alkoxide as the reaction proceeds also serves to complicate the picture.[9]

Epoxides can also give products arising from α-deprotonation (Scheme 1). In certain cases the resulting carbenoid **2** can be trapped with electrophiles,[10] however the more common process is insertion into a nearby C-H bond. With epoxides derived from medium-sized cycloalkenes this occurs in a transannular manner to give bicyclic alcohols **3**. With epoxides derived from bicycloalkenes, ketones **4** are often produced. In the recent study by Morgan and Gajewski it was demonstrated that reaction of cyclopentene oxide with LDA in ether or benzene gave cyclopent-2-enol (along with cyclopentanone) by the α-deprotonation route.[8] Thus, an allylic alcohol could arise from an epoxide by either β- or α-deprotonation, or a mixture of the two pathways.

Deprotonations in achiral substrates which involve discrimination between enantiotopic protons have been achieved with chiral, non-racemic lithium amides,[11] and with organolithiums in the presence of chiral, non-racemic ligands.[12] Whitesell and Felman reported the first example of enantioselective deprotonation in 1980 in the reaction of cyclohexene oxide **5** with various lithium amides[13] to give cyclohex-2-enol **6** in modest optical purities (*op*s) (Scheme 2).[14]



[a] Base used contained approximately 20% of the meso isomer.

Scheme 2

The enantiotopic proton selection was explained by preferential reaction of the base with one of the rapidly equilibrating enantiomeric half-chair conformations of cyclohexene oxide **5** (Figure 2).

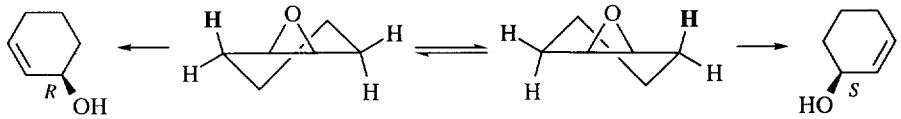
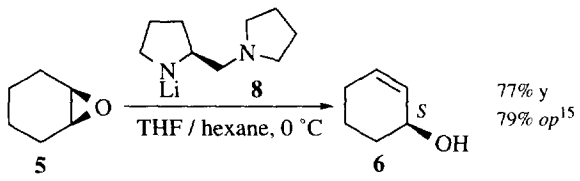


Figure 2

Good *op* levels for base-mediated desymmetrisation of achiral epoxides were first obtained by Asami in 1984 (Scheme 3).[16] Asami used proline-derived bases such as **8**; the corresponding amines had been previously used to effect a range of asymmetric transformations.[17] The amine precursor to lithium amide **8** is now commercially available.[18]



Scheme 3

Asami explained the good *ops* observed by developing further the amide-epoxide complex discussed earlier; deprotonation was suggested to occur preferentially through a complex where the steric interactions between the cyclohexane ring and the amide are minimised (Figure 3).

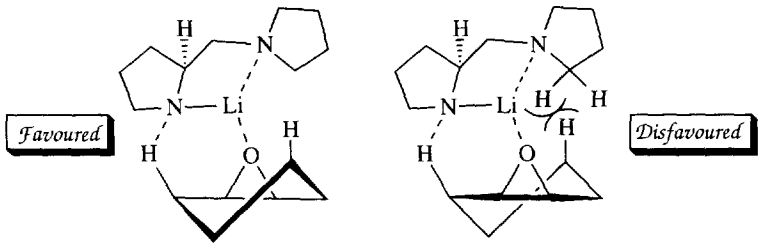
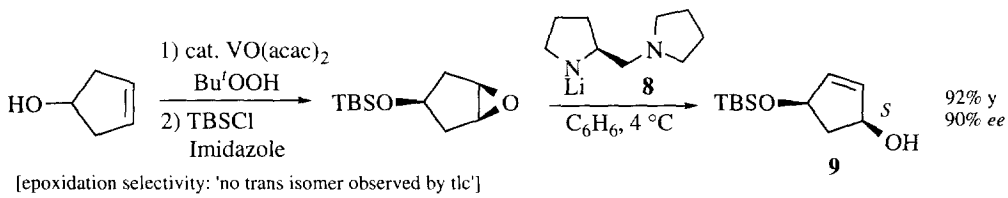


Figure 3

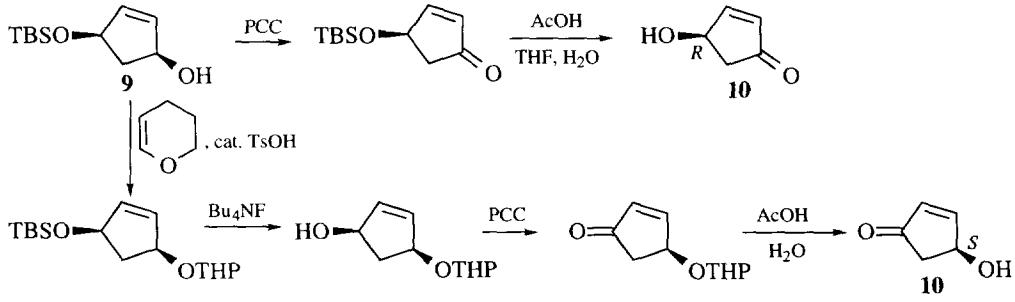
Asami also reported a useful application of this chemistry in 1985 (Scheme 4).[19]



[epoxidation selectivity: 'no trans isomer observed by tlc']

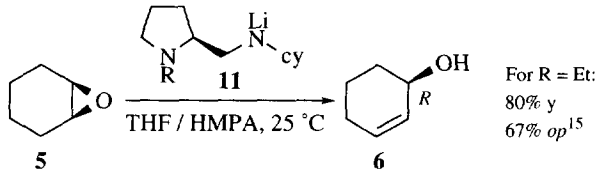
Scheme 4

The synthetic value of the allylic alcohol **9** was demonstrated by preparing the *R* and *S* enantiomers of 4-hydroxycyclopent-2-enone **10** (Scheme 5), which has been used in the synthesis of prostaglandins and various cyclopentanoid natural products.



Scheme 5

Proline is readily available only as the *S* enantiomer, thus the chemistry outlined above only provides direct access to *S* configured allylic alcohols. A solution to this problem has been reported by Asami and involves modification of the substituent R in the non-racemic lithium amide **11** (Scheme 6, cy = cyclohexyl).[20]



Scheme 6

With lithium amide **11** (R = Me or Et) predominantly (*R*)-cyclohex-2-enol **6** was obtained (Scheme 6). However, increasing the size of R (Me_2CHCH_2 or Me_3CCH_2) gave predominantly the opposite sense of asymmetric induction (34% *op* and 53% *op* respectively).[15] The dependance of enantioselection on the size of R was explained by Asami using four epoxide-base complexes (Figure 4).

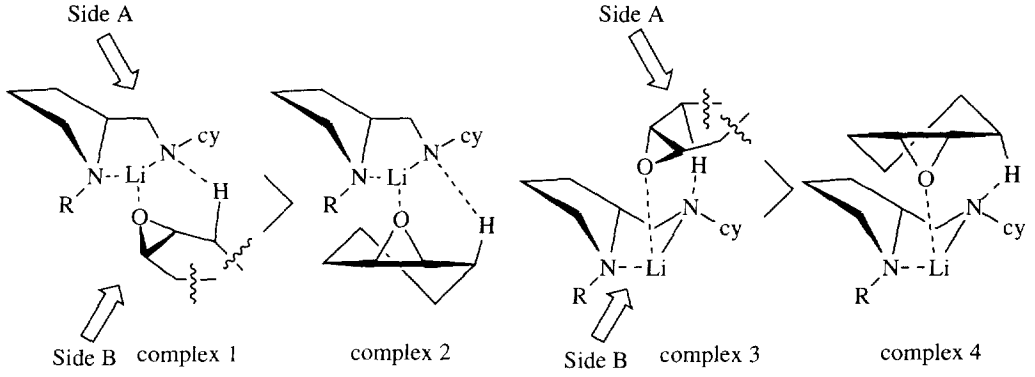


Figure 4

When R is small (< Me_2CHCH_2) complex 1 is favoured, which has fewer unfavourable steric interactions between the lithium amide and the cyclohexene ring than complex 2. The epoxide approaches from side B and (*R*)-cyclohex-2-enol **6** is obtained. When R is large (> Et) complex 3 is favoured, with the bulky R group away from the epoxide; less steric hindrance occurs when the epoxide approaches from side A and (*S*)-cyclohex-2-enol **6** is obtained.

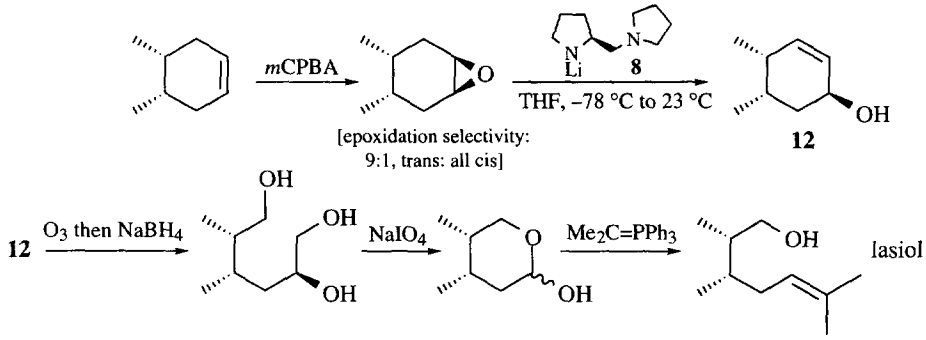
Various substrate epoxides were studied employing bases **8** and **11** (R = Et) in the presence of DBU as an additive in THF, including epoxides derived from acyclic alkenes and good *ees* were observed (Table 1).[16b,20] Although outside the scope of this review, base **8** has also been used in combination with DBU for the kinetic resolution of racemic epoxides.[21]

Epoxide	Base	Yield / %	*ee* / %[c]	Configuration
Cyclopentene oxide	**8**[a]	53[b]	41	*S*
Cyclopentene oxide	**11** (R = Et)	48[b]	15	*R*
Cyclooctene oxide	**8**[a]	84	50	*S*
Cyclooctene oxide	**11** (R = Et)[a]	61	34	*R*
(Z)-But-2-ene oxide	**8**	60[b]	72	*S*
(Z)-But-2-ene oxide	**11** (R = Et)	58[b]	62	*R*
(Z)-Oct-4-ene oxide	**8**	66	60	*S*
(Z)-Oct-4-ene oxide	**11** (R = Et)	66	59	*R*

[a] Reaction heated at reflux for 1.5-4 h. [b] Isolated after benzoylation. [c] Determined by ^{1}H-nmr of the acetate in the presence of Eu(hfbc)$_3$.

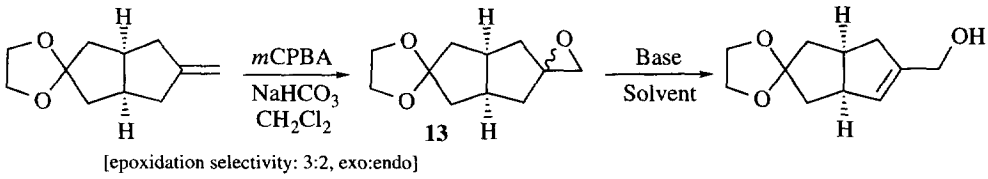
Table 1

Mori and co-workers used base **8** to prepare 4,5-dimethylcyclohex-2-enol **12** for the syntheses of the ant-derived terpenes lasiol (Scheme 7) and faranal.[22] Alcohol **12** was produced in good yield and in 73% *ee*; recrystallisation of the corresponding 3,5-dinitrobenzoate ester gave diastereo- and enantiomerically pure ester (32% from the epoxide) which, following hydrolysis, was used in the target syntheses.



Scheme 7

Leonard and co-workers examined the enantioselective desymmetrisation of a diastereomeric mixture of the spiroepoxides **13** using bases **7**, lithium [(*R*)-1-phenylethyl](isopropyl)amide **7a** and **8** (Scheme 8).[23]



[epoxidation selectivity: 3:2, exo:endo]

Scheme 8

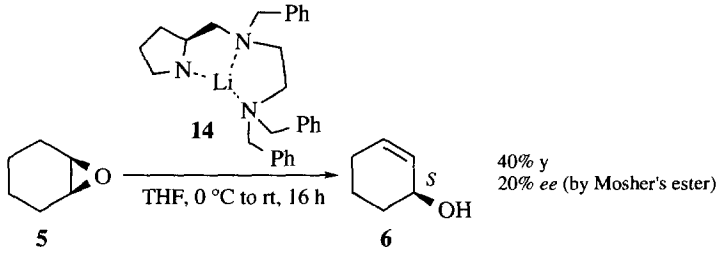
None of the reactions went to completion as the endo spiroepoxide **13** is less reactive than the exo isomer (Table 2).

Base	Solvent	Yield / %	Major enantiomer	*ee* / %
8	THF	58	(+)-	21
8	Benzene	35	(−)-	58
8	Et_2O	50	(+)-	23
7	THF	50	(+)-	76
7	Benzene	40	(+)-	21
7a	THF	55	(−)-	42

Table 2

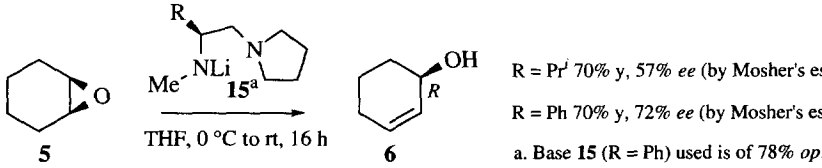
When a 1:9 exo:endo mixture of spiroepoxide **13** was used, the reactions only ran to approximately 15% completion, providing support for the unreactive nature of *endo*-**13**. This lack of reactivity of the endo form was thought to be due to the endo epoxide oxygen atom residing on the concave face of the molecule, hindering chelation of the base. The interesting reversal of enantioselectivity observed with benzene and THF when using base **8** is thought to be due to disruption/weakening of N-Li-N chelation in the polar solvent.

Singh and co-workers have examined other amino acid-derived bases for enantioselective epoxide desymmetrisation.[24] As lithium is normally tetracoordinate, one possibility to reduce aggregation and therefore improve enantioselectivity might be to prepare a base with three potentially ligating heteroatoms, eg base **14** (Scheme 9).[24a] Unfortunately, base **14** did not lead to high *ee*s.



Scheme 9

Singh and co-workers also developed bases for the preparation of *R* configured allylic alcohols, such as (*R*)-cyclohex-2-enol **6**, starting from readily available non-racemic precursors. The resulting bases **15** (R = Pr^i or Ph) derived from (*S*)-valine and (*S*)-phenylglycine respectively, gave reasonable levels of *ee* (eg Scheme 10).[24b] Recent advances in the syntheses of these bases which reduce or eliminate partial racemisation during their preparation, together with incorporation of a piperidine (rather than pyrrolidine) ring have led to improved *ee*s [using an (*R*)-phenylglycine/piperidine-derived base gave (*S*)-cyclohex-2-enol **6** in up to 80% *ee* (60% y) in THF; using the same base in benzene gave allylic alcohol **9** (cf Scheme 4) in up to 97% *ee* (66% y)].[24d]



Scheme 10

Singh and co-workers rationalised the enantioselectivity by invoking a cyclic six-membered transition state with the assumption that the sterically demanding R substituent of the base **15** would prefer to reside anti to the *N*-methyl group, thus reducing steric interactions within the base (Figure 5). Strong non-bonded interactions between the pyrrolidine ring and an out of plane cyclohexyl CH_2 are present in the disfavoured transition state.

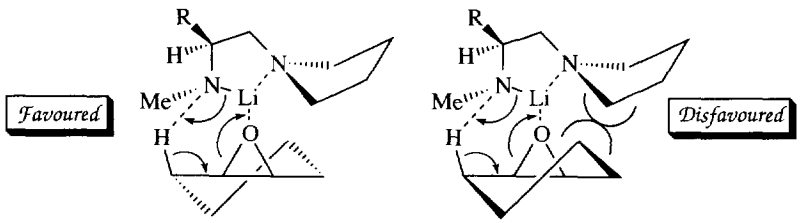


Figure 5

A significant advance in the field of base-mediated epoxide desymmetrisation was reported by Milne and Murphy in 1993.[25] Their work was influenced by the studies of Schlosser and co-workers who had observed rate accelerations for a variety of base-mediated reactions, including epoxide to allylic alcohol transformations,[26] when using LDA in the presence of potassium *tert*-butoxide. Schlosser and co-workers proposed possible transition states involving potassium *tert*-butoxide (Figure 6) and the increased reaction rates were explained by a push-pull mechanism.

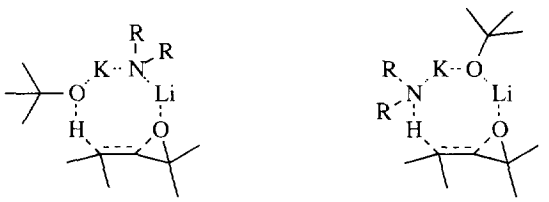
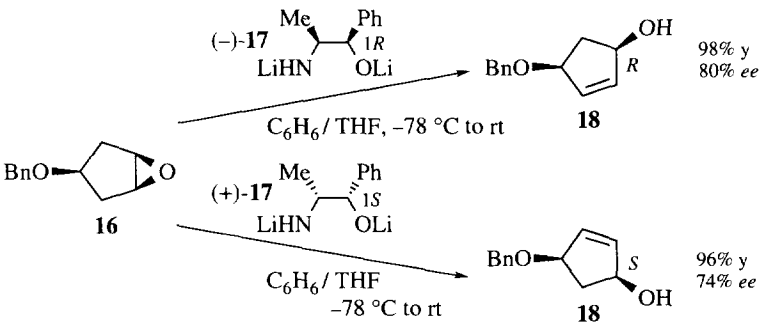


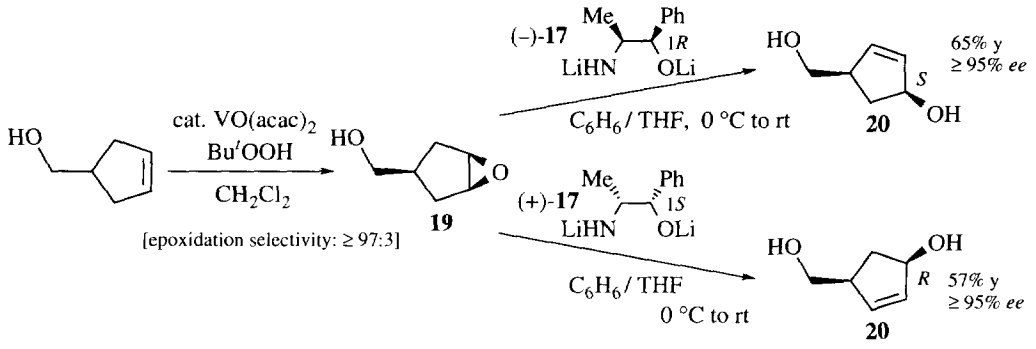
Figure 6

Consideration of these transition states led Milne and Murphy to attempt the rearrangement of epoxide **16** employing dilithiated amino alcohols of the ephedrine and norephedrine family which contain an alkoxide moiety covalently linked to the lithium amide. The dilithiated salts of norephedrine **17** proved to be the most successful of the amino alcohols examined to furnish allylic alcohol **18** (Scheme 11).



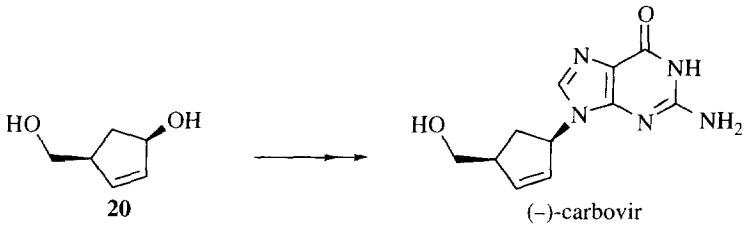
Scheme 11

The significance of Milne and Murphy's work is that it allows straightforward access to either enantiomeric allylic alcohol in good yields and *ee*s using commercially available amino alcohols. Hodgson and co-workers applied this methodology towards carbocyclic nucleosides using the epoxy alcohol **19** (Scheme 12).[27]



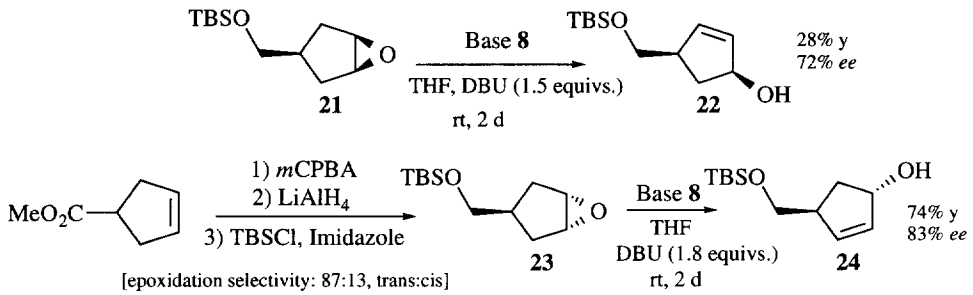
Scheme 12

Whilst the corresponding protected alcohols (TBS or benzyl) were inert to the dilithiated amino alcohol (or to refluxing LDA) the epoxy alcohol **19** smoothly rearranged to give the diol **20** with an excellent *ee*. Interestingly, the sense of asymmetric induction found with epoxy alcohol **19** was opposite to that observed by Milne and Murphy with epoxide **16**. Dilithiated (1*R*,2*R*)-norpseudoephedrine under the same reaction conditions with epoxy alcohol **19** gave predominantly the (1*R*)-diol **20** (63% yield, 86% *ee*).[28] These results demonstrate that the stereocentre bearing nitrogen in the amino alcohol dominates the enantioselection at least with epoxy alcohol **19**. The synthetic utility of the diol **20** was illustrated in a synthesis of the anti-HIV agent carbovir (Scheme 13).[27b]



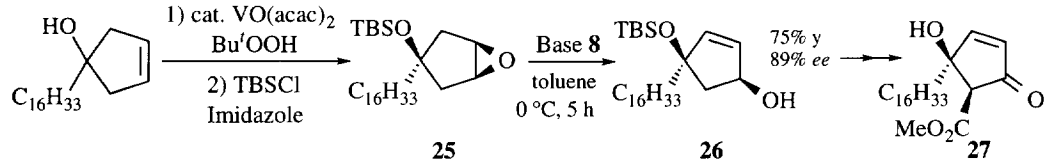
Scheme 13

Carbovir was also chosen by Asami as a target to demonstrate the potential of rearrangements employing non-racemic base **8**.[29] His first route involved the isomerisation of TBS-protected cis epoxide **21**, unfortunately this gave poor yields of the desired allylic alcohol **22** (Scheme 14). Use of the trans epoxide **23** in the rearrangement proved more successful, with allylic alcohol **24** obtained in good yield and *ee*. Trans allylic alcohol **24** was successfully converted to (–)-carbovir in three steps, however a Mitsunobu coupling with a purine base gave only low yields.



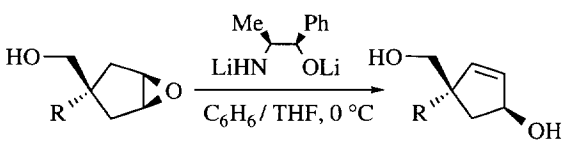
Scheme 14

Asami extended the desymmetrisation methodology to examine a tertiary alcohol-containing cyclopentene oxide **25**, to give the allylic alcohol **26** in good chemical yield and *ee*, in a total synthesis of (–)-untenone A **27** (Scheme 15).[30]



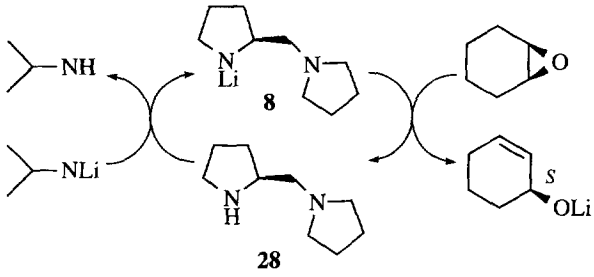
Scheme 15

The scope of cyclopentene epoxide rearrangements was further examined by Hodgson and Gibbs who recently investigated the isomerisation of epoxides containing quaternary carbon centres to generate allylic alcohols in high *ees* (Scheme 16).[31] These results, together with Asmai's work towards untenone, indicate that the introduction of a trans substituent in cyclopentene epoxides does not significantly alter the level of enantioselection in these rearrangements. Furthermore they suggest that, at least with the bases examined, these rearrangements proceed by a syn elimination mechanism. However, in the light of the recent study by Morgan and Gajewski (*vide supra*), rearrangement initiated by α-deprotonation cannot be strictly ruled out.



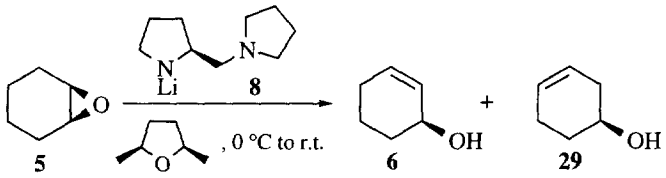
Scheme 16

A significant goal in lithium amide-mediated epoxide rearrangements is the use of the non-racemic base in catalytic quantities since the bases can be expensive or difficult to prepare (although sometimes recyclable). To date, only Asami has achieved this by employing a cheap achiral base and a catalytic quantity of non-racemic amine **28** (Scheme 17).[32] This work followed on from earlier observations that base **8** was more reactive towards epoxides than simple lithium amides such as LDA. The enantioselectivity observed by Asami is enhanced by the addition of 6 equivalents (equivs.) of DBU, which might reduce lithium salt aggregation to improve the rate of the proton transfer between amine **28** and LDA. (*S*)-Cyclohex-2-enol was obtained in 71% yield and 75% *ee* using LDA (1 equiv.), base **8** (0.2 equivs.) and DBU (6 equivs.) in THF.



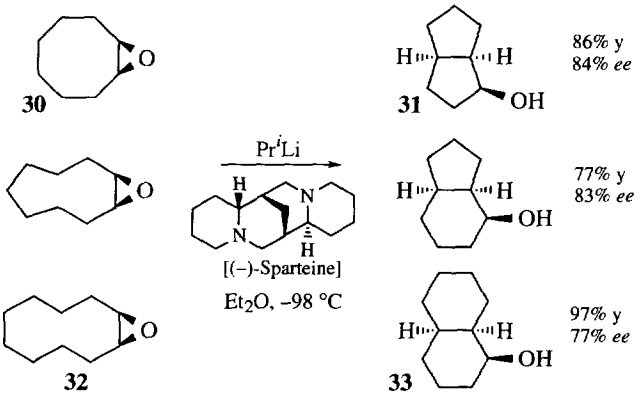
Scheme 17

Ahlberg and co-workers have reported that the products obtained from the reaction of cyclohexene oxide **5** with lithium amide **8** depend significantly on the solvent used (Scheme 18).[33] On changing the solvent from THF to *cis*-2,5-dimethyl-THF, the homoallylic alcohol cyclohex-3-enol **29** was obtained in up to 75% yield (5% *ee*) along with cyclohex-2-enol **6** (17%, 29% *ee*). Use of a mixed solvent of THF and *cis*-2,5-dimethyl-THF gave the homoallylic alcohol **29** in up to 51% yield (25% *ee*) and cyclohex-2-enol **6** (42%, 66% *ee*). It was established that racemic cyclohex-2-enol **6** could be isomerised to the homoallylic alcohol **29** in 74% yield when using lithium amide **8** in *cis*-2,5-dimethyl-THF.



Scheme 18

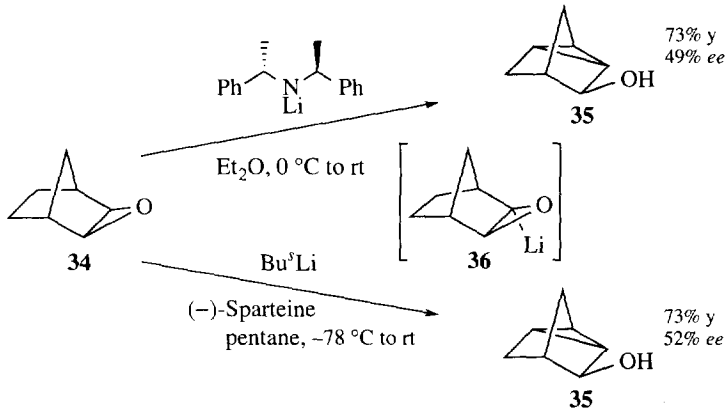
Enantioselective rearrangements which proceed specifically *via* metallation of an epoxide ring have recently been examined. Hodgson and Lee achieved enantioselective α-deprotonation-rearrangement of medium-sized (8-, 9- and 10-membered) cycloalkene-derived epoxides using organolithiums in the presence of (-)-sparteine to give bicyclic alcohols in good yields and *ees* (Scheme 19).[34]



Scheme 19

The work by Hodgson and Lee (Scheme 19) was the first study combining an organolithium with a non-racemic ligand for enantioselective epoxide desymmetrisation. The study followed earlier work by Hoppe and co-workers and by Boeckman. Hoppe and co-workers had found that highly enantioselective deprotonation α- to oxygen in carbamates was possible using Bu^{s}Li in combination with (–)-sparteine in ether.[35] Boeckman reported that the epoxides **30** and **32** (Scheme 18) rearranged cleanly to the bicyclic alcohols **31** and **33** respectively on treatment with BuLi in ether-hexane at –78 °C.[36] Importantly, Hodgson and Lee found that the combination of the diamine with the organolithium did not compromise yield or clean conversion of the medium-sized epoxides exclusively to the endo cis fused bicyclic alcohols. No cycloalk-2-enols were observed. It was also found possible to reduce the quantity of (–)-sparteine and still achieve good levels of asymmetric induction. Although Whitesell and White had observed clean rearrangement of cyclooctene epoxide **30** to bicyclic alcohol **31** using LDA in ether at reflux,[37] examination of lithium (*S,S*)-bis(1-phenyl)ethylamide **7** led to a mixture of bicyclic alcohol **31** (in low *ee*) and cyclooct-2-enol.[38]

The enantioselective desymmetrisation of *exo*-norbornene oxide **34** has been examined by Hodgson and Wisedale (Scheme 20).[39]



Scheme 20

exo-Norbornene oxide **34** was originally isomerised to nortricyclanol **35** by Crandall using an achiral lithium amide.[40] Since *exo*-norbornene oxide **34** could not suffer from competing elimination to generate allylic alcohols, the enantioselective desymmetrisation was first examined using non-racemic lithium amides such as **7**, which gave nortricyclanol **35** in up to 52% *ee* (Scheme 20). Prior to this study, it was not clear that non-racemic lithium amides would be capable of enantioselective desymmetrisation by α-deprotonation since, unlike β-deprotonation (or α-deprotonation using organolithiums), this process has been demonstrated to be reversible using simple lithium amides.[6] Reversible α-deprotonations occur when the rate of reprotonation from the generated amine is competitive with the insertion step. From an asymmetric synthesis viewpoint, since enantioselectivity would be determined by kinetically controlled enantiotopic α-proton selection *via* diastereomeric transition states, reversible deprotonation could compromise *ee*. For example, in the presence of a non-racemic base, the lithiated epoxide **36** and its enantiomer could undergo C-H insertion (or protonation to return *exo*-norbornene oxide **34**) at different rates. Evaluation of RLi / (–)-sparteine indicated that it is also a viable reagent combination for the desymmetrisation of *exo*-norbornene oxide **34** (Scheme 20). The sense of asymmetric induction with RLi / (–)-sparteine parallels that observed in the earlier medium-ring study. Selective

removal of the *pro-R* hydrogen on the epoxide ring may be explained by considering a sparteine-RLi-epoxide complex, where the C-H bond on the epoxide *R* stereocentre is held closer to the organolithium than the *S* stereocentre, minimising non-bonded interactions between sparteine and the epoxide (Figure 7).

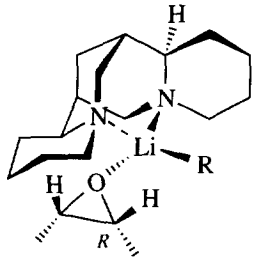
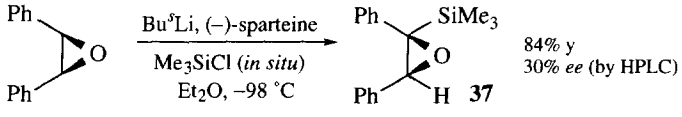


Figure 7

In certain cases the transient carbenoid arising from enantioselective α-deprotonation can be trapped with electrophiles (Scheme 21).[41] The absolute configuration of the predominant epoxysilane enantiomer **37** was tentatively assigned by analogy with other epoxides rearranged using (–)-sparteine.

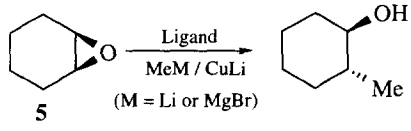


Scheme 21

3. DESYMMETRISATION BY ENANTIOSELECTIVE ADDITION[42]

3.1 Carbon and hydrogen nucleophiles

Davies and Wollowitz reported the desymmetrisation of an achiral epoxide by the enantioselective addition of a carbon nucleophile in 1980.[43] The reaction of cyclohexene oxide **5** with methylcuprates and Grignard reagents in the presence of non-racemic ligands such as (–)-ephedrine gives *trans*-2-methyl cyclohexanol (Scheme 22).

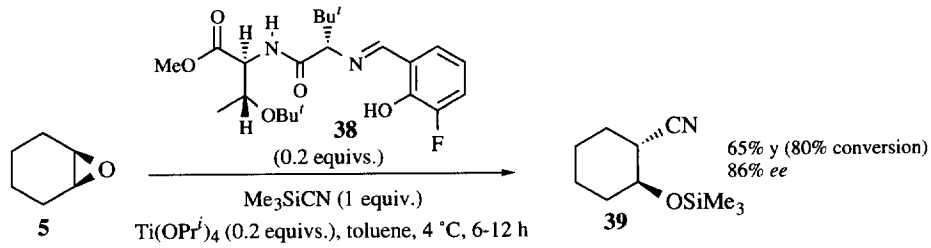


Scheme 22

Whilst the *ops* in these reactions were low (~3%), the principle of enantioselective addition had been demonstrated. The diastereoselective addition of chiral carbon nucleophiles, such as the lithium enolate derived from [(η^5-C_5H_5)Fe(CO)(PPh_3)$COCH_2Me$,[44] are not covered in this review.

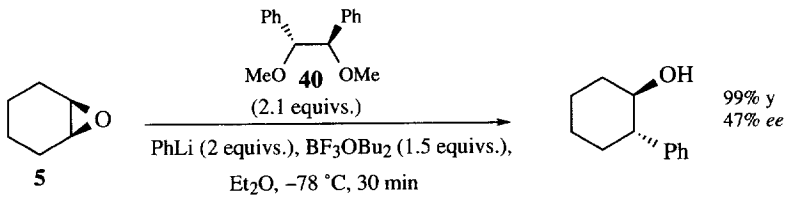
Snapper, Hoveyda and co-workers recently reported the catalytic enantioselective addition of trimethylsilyl cyanide to simple achiral epoxides (Scheme 23).[45] The study is notable not only for being the first to realise significant asymmetric induction in C-C bond formation by addition of an external nucleophile to achiral epoxides, but also for the application of rapid screening processes to evaluate potential ligands for the chiral catalyst. Oguni and co-workers had originally observed ligand-accelerated catalysis[46] in the reaction between

trimethylsilyl cyanide and cyclohexene oxide **5** using $Ti(OPr^i)_4$ in the presence of Schiff bases derived from aromatic hydroxy aldehydes and 2-aminoethanol.[47] Only small amounts of the corresponding isocyanide arising from the ambident nature of the cyanide nucleophile were observed. The recent enantioselective studies developed dipeptide Schiff bases such as **38** which gave nitrile **39** in up to 86% *ee*.



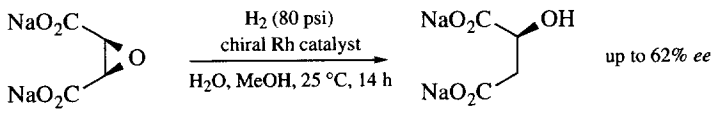
Scheme 23

Tomioka and co-workers have recently reported the enantioselective addition of phenyllithium to cyclohexene oxide **5** (and to an oxetane) using ligands such as **40** in the presence of a Lewis acid (Scheme 24).[48]



Scheme 24

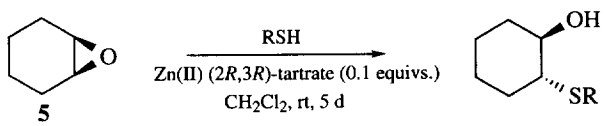
Chan and Coleman reported the enantioselective hydrogenolysis of sodium epoxysuccinate with rhodium catalysts containing chiral phosphine ligands (Scheme 25). A deuterium labelling study revealed that the hydrogenolysis proceeds by direct C-O bond cleavage.[49]



Scheme 25

3.2 Sulphur nucleophiles

The enantioselective ring opening of achiral epoxides [cyclohexene oxide **5**, cyclopentene oxide **41** and (*Z*)-but-2-ene oxide **42**] by thiols was reported by Yamashita and Mukaiyama in 1985 using zinc tartrate as a Lewis acid catalyst (Scheme 26).[50] This procedure gives β-hydroxy thioethers in moderate to good *ee* (Table 3).



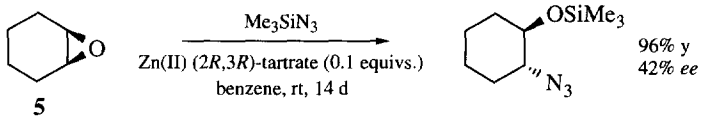
Scheme 26

Epoxide	R	Yield / %	*ee* / %
5	*p*-Tolyl	96	68
5	Benzyl	88	77
5	Bu	82	85
41	*p*-Tolyl	85	45
41	Benzyl	43	50
41	Bu	30	72
42	*p*-Tolyl	98	60
42	Benzyl	70	75
42	Bu	58	71

Table 3

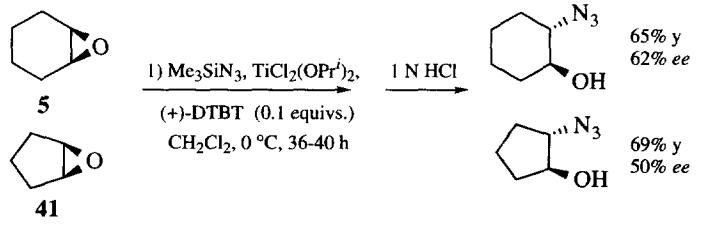
3.3 Nitrogen nucleophiles

Diastereoselective additions of chiral nitrogen nucleophiles to achiral epoxides, such as the reaction between cyclopentene oxide and the reagent formed from (*R*)-α-methylbenzylamine and trimethylaluminum,[51] are outside the scope of this review. The first examples of enantioselective ring opening of achiral epoxides by nitrogen nucleophiles were reported by Yamashita in 1987 (Scheme 27).[52,50b] Epoxides were opened with weakly basic nucleophiles such as aniline or (non-basic) trimethylsilyl azide in the presence of either zinc(II) or copper(II) tartrate to give trans *N*-phenyl β-aminoalcohols or trans *O*-trimethylsilyl-2-azido alcohols. The azido products can be converted into trans β-aminoalcohols by a two step procedure.



Scheme 27

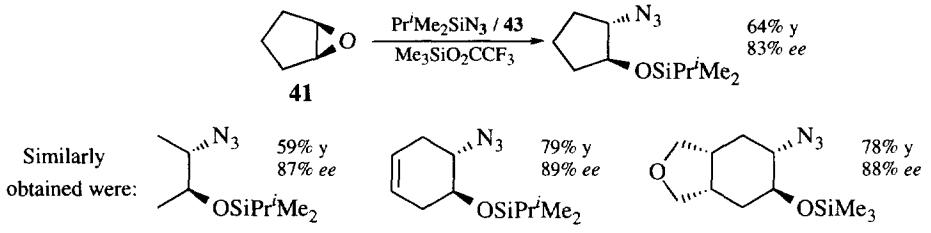
Sinou and co-workers reported the reaction of cyclohexene oxide **5** with trimethylsilyl azide using titanium tetraisopropoxide in the presence of chiral diols or aminoalcohols, to give *trans*-2-azidocyclohexanol in up to 24% *ee*.[53] Oguni and co-workers reported that titanium complexes of dialkyl tartrates, such as the complex formed from $TiCl_2(OPr^i)_2$ and di-*tert*-butyl tartrate (DTBT), can be used for the enantioselective addition of trimethylsilyl azide to achiral epoxides (Scheme 28).[54]



Scheme 28

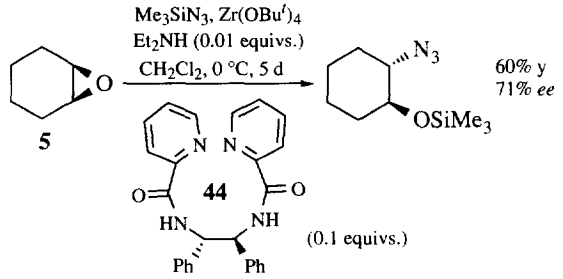
A significant advance in the enantioselective addition of nitrogen nucleophiles to epoxides was reported by

Nugent in 1992 using a zirconium catalyst **43** prepared from $Zr(OBu^t)_4$ and the tetradentate C_3 symmetric ligand (*S,S,S*)-triisopropanolamine.[55] Reaction of cyclohexene oxide **5** with trimethylsilyl azide, catalyst **43** (0.1 equivs.) and a trace of trimethylsilyl trifluoroacetate in 1,2-dichlorobutane at 25 °C for 18 h gave the corresponding *O*-trimethylsilylazido alcohol in 86% *ee*. Enantioselectivity could be improved (up to 93% for cyclohexene oxide) with lower temperatures and the bulkier azide reagent $Pr^iMe_2SiN_3$. High *ee*s were observed with several epoxides (Scheme 29).



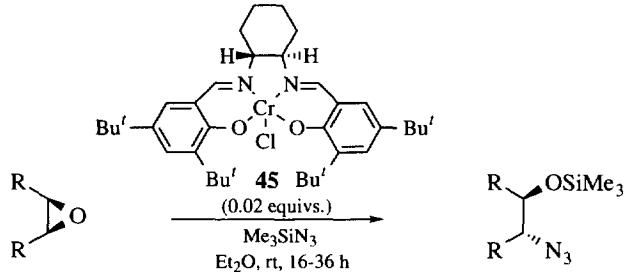
Scheme 29

Adolfsson and Moberg applied titanium and zirconium complexes of bis-picolinic amides to the ring opening of cyclohexene oxide **5** with trimethylsilyl azide.[56] The best conditions used a catalyst prepared from ligand **44**, $Zr(OBu^t)_4$ and a small amount of secondary amine (Scheme 30).



Scheme 30

The best procedure to date for the enantioselective ring opening of achiral epoxides involves (salen)Cr(III) complexes such as **45** developed by Jacobsen and co-workers (Scheme 31).[57] Aside from the good yields (65-90%) and good to excellent *ee*s (81-98%), the method is noteworthy for its efficiency as a catalytic process.



Scheme 31

The methodology developed by Jacobsen *et al.* was used on the achiral epoxides shown in Table 4.

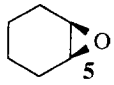
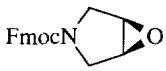
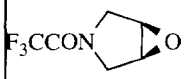
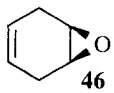
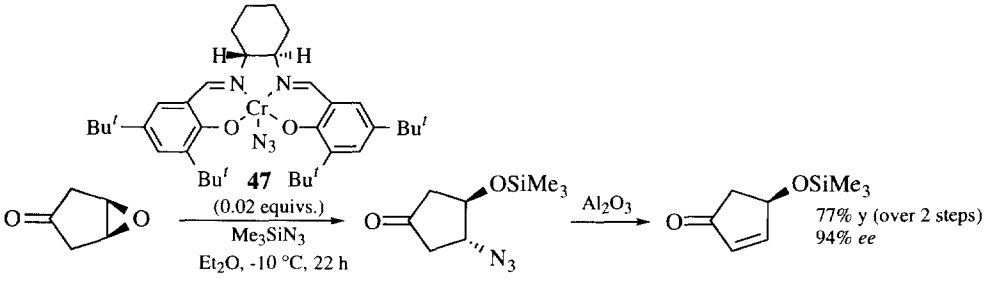
Epoxide	Time / h	Yield / % (after desilylation)	*ee* / %
 **5**	18	80	88
 **41**	28	80	94
	18	80	98
	36	80	95
	16	90	95
 **46**	46	72	81
 **42**	30	65	82

Table 4

Jacobsen and co-workers have also shown that the catalyst **45** can be recycled quantitatively in a solvent-free process (Table 5). Following distillation of the product the residual catalyst can be treated with additional portions of trimethylsilyl azide and an epoxide and the process repeated through several cycles. This is an excellent example of a catalytic asymmetric process which is also environmentally benign.

Cycle	Epoxide	Time / h	Yield / %	*ee* / %
1	**5**	18	86	84
2	**5**	21	88	87
3	**5**	20	91	88
4	**37**	4	81	94
5	**46**	18	75	83

Table 5

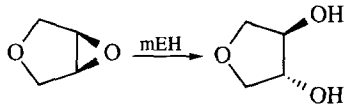


Scheme 32

Jacobsen and Leighton have used a (salen)Cr(III) complex to prepare an important precursor for prostaglandin synthesis (Scheme 32).[58] The (salen)CrN_3 complex (*S,S*)-**47** was used in this process rather than the corresponding chloride **45**, since mechanistic studies indicate that **45** is a precatalyst to **47** and **45** leads to trace chloride addition side products. Excellent kinetic resolution of terminal epoxides is also possible using the the (salen)CrN_3 complex **47**.[59]

3.4 Oxygen nucleophiles[60]

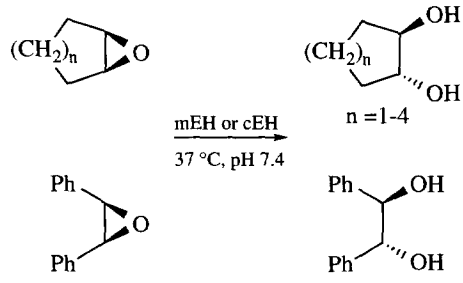
Epoxides can be biotransformed to the corresponding vicinal diols by epoxide hydrolase catalysed trans addition of water.[2,61] The microsomal epoxide hydrolase (mEH) exhibits low substrate specificity and has been examined with a variety of achiral and chiral epoxides. Chiral recognition can be very high with preferential ring opening usually at the *S* configured oxirane carbon (eg Scheme 33, V_s = rate of hydrolysis under enzyme saturation conditions). This procedure can be used to converge enantiomers of a racemic epoxide, such as (±)-3,4-epoxytetrahydropyran, to a single diol enantiomer.



quant. y (V_s = 26±0.8 nmole min^{-1} mg^{-1} protein)
96.5% *ee*

Scheme 33[61b]

A comparison of mEH with cytostolic epoxide hydrolase (cEH) indicated that the former enzyme is more active and gives higher *ee*s with several achiral epoxides (Scheme 34, Table 6).[62]



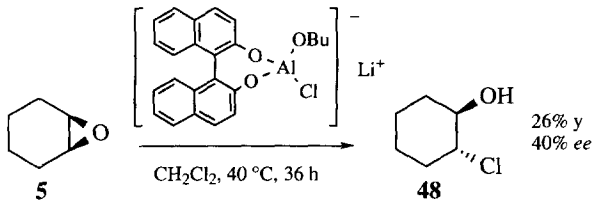
Scheme 34

	mEH			cEH		
Epoxide	V_s / nmol min^{-1} mg^{-1} protein	*ee* / %	Config.	V_s / nmol min^{-1} mg^{-1} protein	*ee* / %	Config.
cyclopentene oxide	23.0 ± 0.2	90	*R,R*	0.45 ± 0.1	60	*R,R*
cyclohexene oxide	14.5 ± 1.0	76	*R,R*	1.00 ± 0.1	20	*R,R*
cycloheptene oxide	31.5 ± 0.5	40	*R,R*	0.65 ± 0.1	30	*R,R*
cyclooctene oxide	1.1 ± 0.1	70	*R,R*	no hydrolysis seen	—	—
cis-stilbene oxide	17.0 ± 1.0	88	*R,R*	1.00 ± 0.1	70	*R,R*

Table 6

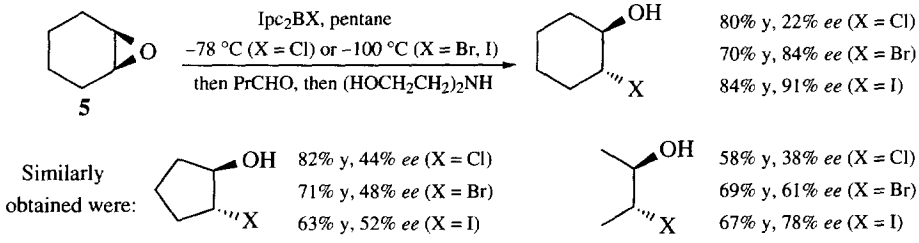
3.5 Halogen nucleophiles

In 1988 Yamamoto and co-workers reported that aluminum reagents prepared from (–)-menthol or (*R*)-binaphthol could generate the chlorohydrin **48** from cyclohexene oxide **5** with modest *ee*.[63] The best *ee* with menthol (34%) was obtained using the ate complex formed between (–)-menthoxyaluminum dichloride and Bu^{s}Li. Addition of BuOLi to binapthol and diethylaluminum chloride gave a reagent which produced the chlorohydrin **48** in 40% *ee* (Scheme 35).



Scheme 35

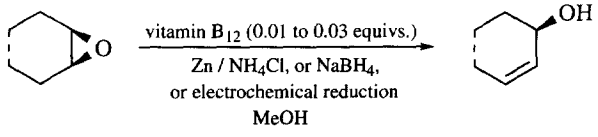
In 1988 Brown and co-workers reported that *B*-halodiisopinocamphenylboranes (Ipc_2BX, X = Cl, Br or I) could be used to generate halohydrins in good yield and *ee*.[64] Simple cyclic and acyclic epoxides were both found to be suitable substrates (Scheme 36).



Scheme 36[64b]

3.6 Metal nucleophile: enantioselective isomerisation

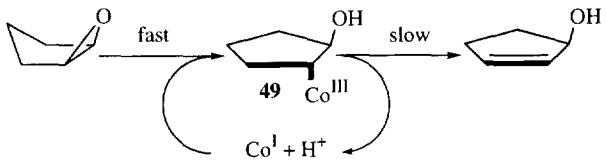
In 1988 Scheffold and co-workers reported the enantioselective isomerisation of achiral epoxides to allylic alcohols using reduced vitamin B_{12} as a catalyst (Scheme 37).[65]



Scheme 37

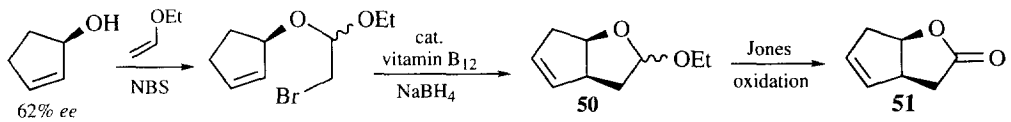
Cyclopentene oxide was converted to (*R*)-cyclopent-2-enol in 50% *ee* (68% yield) after 7 h at 45 °C using 0.03 equivs. of the catalyst in methanol. Using 0.01 equivs. of catalyst at 22 °C for 168 h gave the alcohol in 65% *ee* (64% yield). Cyclohexene oxide and (*Z*)-but-2-ene oxide also gave the corresponding *R*-allylic alcohols in up to 42% and 26% *ee* respectively. Cyclooctene oxide failed to undergo isomerisation.

Bonhôte and Scheffold conducted a detailed mechanistic study of the isomerisation of cyclopentene oxide to cyclopentenol.[66] This study concluded that the isomerisation proceeded *via* two steps. Firstly, an irreversible proton-assisted nucleophilic attack of the chiral Co(I) catalyst at the epoxide gives (diastereomeric) Co(III) intermediates (Scheme 38, corrin omitted for clarity) which are the dominant species in the steady state. These intermediates decompose in a rate limiting step to the allylic alcohol and recycled catalyst. A deuterium labelling study established that the hydrocobalt elimination is non-stereoselective. The process occurs *via* reversible Co-C bond homolysis to a free radical from which stereoelectronically controlled H atom abstraction by Co(II) takes place. The major byproducts in this reaction are cyclopentene (30%) by fragmentation of intermediate **49** under reducing conditions, and lesser amounts of cyclopentanone.



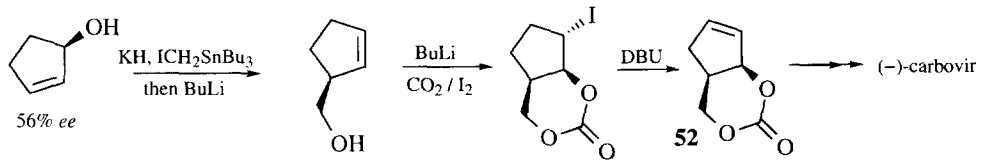
Scheme 38

The power of vitamin B_{12} in synthesis was elegantly demonstrated in a preparation of the prostaglandin intermediate **51** using cyclopentenol prepared by the above procedure (Scheme 39).[67] The lactone could be recrystallised to > 99 *ee* (45% yield from the lactol **50**).



Scheme 39

Cyclopentenol prepared by cobalt catalysis has also been used in a short route to (–)-carbovir (Scheme 40).[68] The route involves a [2,3]-sigmatropic Wittig rearrangement, and palladium catalysed coupling of a purine and an allylic carbonate **52**.



Scheme 40

The potential of vitamin B_{12} catalysis has been demonstrated in other enantioselective desymmetrisation processes: the isomerisation of 1,4-epiperoxides to 4-hydroxycycloalk-2-enones (in 17% *ee*);[69] achiral aziridines to *N*-acyl allylic amines (in up to 95% *ee*),[70] and activated cyclopropanes to alkenes (in up to 86% *ee*).[71]

4. CONCLUDING REMARKS

This review has surveyed reactions where achiral epoxides are converted into enantioenriched materials. The epoxide to allylic alcohol transformation is the most developed of these and has been applied to a number of important targets. As this process is an isomerisation, the ultimate goal in this area must be to achieve the transformation cleanly in good *ee* with a range of epoxides using a chiral catalyst for which both enantiomers are readily available and with the consumption of no other reagents in the reaction. Conceptually, Scheffold's work using vitamin B_{12} comes closest to this goal (see Section 3.6). In practice however, Scheffold's method suffers from modest *ee*s, substrate limitations, the formation of byproducts, long reaction times and access to only one enantiomer. At the strategy level, since epoxides are usually prepared from alkenes, the two-step alkene to allylic alcohol transformation is equivalent to allylic transposition of the unsaturation with allylic hydroxylation at the carbon atom which was part of the original C=C bond. Methods for direct catalytic enantioselective allylic oxidation (allylic acyloxylation) are being developed; these methods provide access to allylic alcohols following hydrolysis or reduction.[72] However, enantioselective desymmetrisation by allylic acyloxylation using achiral alkenes bearing stereogenic centres has yet to be demonstrated.

Desymmetrisation by catalytic enantioselective addition to an achiral epoxide has been studied most for azide addition; the most efficient method to date is that of Jacobsen and co-workers (see Section 3.3). The combination of the epoxidation and enantioselective addition steps are equivalent to asymmetric trans vicinal addition of oxygen and another heteroatom to an achiral alkene. Efforts to effect similar processes in one step are being made, a significant recent development being catalytic enantioselective cis aminohydroxylation.[73]

It might seem from the preceding discussion that enantioselective transformations on achiral epoxides will be superseded by asymmetric proceses on the precursor alkenes. However, in functionalised molecules desymmetrisation can give diastereomers as well as enantiomers. Proceeding intially through a (predictable) diastereoselective epoxidation step can remove an element of diastereoselective ambiguity in the enantioselective transformation. Also, as has been pointed out before,[42] with the development of asymmetric epoxidation of unfunctionalised alkenes,[74] methods are required to transform these materials further. Low diastereoselectivity would be expected in transformations where strong directing elements are absent in the enantioenriched epoxides. Methods developed for the enantioselective desymmetrisation of achiral epoxides may be of use in these cases.

5. ACKNOWLEDGEMENTS

We thank the EPSRC (Research Grant GR/K22587), AgrEvo UK, the LINK Asymmetric Synthesis Programme, The Royal Society and Zeneca (Strategic Research Fund) for supporting our work in the field of enantioselective desymmetrisation described in this review. Prof. E. L. Eliel and Dr. R. E. Marriott are thanked for useful discussions.

6. REFERENCES AND NOTES

1. Ho, T.-L. *Symmetry: A Basis For Synthesis Design*; Wiley: New York, 1995; Ward, R. S. *Chem. Soc. Rev.* **1990**, *19*, 1-19.
2. Schoffers, E.; Golebiowski, A.; Johnson, C. R. *Tetrahedron* **1996**, *52*, 3769-3826.
3. Gorzynski Smith, J. *Synthesis* **1984**, 629-656.
4. In order to describe as a group all of the epoxides discussed in this review, the term achiral is used in preference to the term meso. For example, cyclopentene oxide could not strictly be described as meso

since, unlike *cis*-cyclooctene oxide for example, cyclopentene oxide does not belong to a set of diastereomers that also includes at least one chiral member. For a full discussion see: Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994.

5. Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307-1370.
6. Crandall, J. K.; Apparu, M. *Org. React. (N. Y.)* **1983**, *29*, 345-443.
7. Thummel, R. P.; Rickborn, B. *J. Am. Chem. Soc.* **1970**, *92*, 2064-2067.
8. Morgan, K. M.; Gajewski, J. J. *J. Org. Chem.* **1996**, *61*, 820-821.
9. Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624-1654; Collum, D. B. *Acc. Chem. Res.* **1993**, *26*, 227-234.
10. Eisch, J. J.; Galle, J. E. *J. Org. Chem.* **1990**, *55*, 4835-4840.
11. Cox, P. J.; Simpkins, N. S. *Tetrahedron: Asymmetry* **1991**, *2*, 1-26.
12. Knochel, P. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1459-1461.
13. The amine precursor to **7** is commercially available (Aldrich Chemical Co, Oxford Asymmetry Ltd).
14. Whitesell, J. K.; Felman, S. W. *J. Org. Chem.* **1980**, *45*, 755-756.
15. To aid comparisons in the present review, cyclohex-2-enol **6** optical purities (*ops*) shown have been adjusted from the originally published values by using $[\alpha]_D$ +130.6 (*c* 1.21, $CHCl_3$) for > 99% *ee* of (*R*)-cyclohex-2-enol (note 3 in ref. 32 below, see also refs. 24a and 19b).
16. (a) Asami, M. *Chem. Lett.* **1984**, 829-832; (b) *idem. Bull. Chem. Soc. Jpn.* **1990**, *63*, 721-727.
17. Asami, M.; Mukaiyama, T. *Top. Curr. Chem.* **1985**, *127*, 133-167.
18. Aldrich Chemical Co.
19. (a) Asami, M. *Tetrahedron Lett.* **1985**, *26*, 5803-5806; Asami, M. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 1402-1408; see also: Hendrie, S. K.; Leonard, J. *Tetrahedron* **1987**, *43*, 3289-3294; Asami, M.; Inoue, S. *Tetrahedron* **1995**, *51*, 11725-11730; (b) Review: Asami, M. *J. Synth. Org. Chem. Jpn.* **1996**, *54*, 188-199.
20. Asami, M.; Kirihara, H. *Chem. Lett.* **1987**, 389-392.
21. Asami, M; Kanemaki, N. *Tetrahedron Lett.* **1989**, 30, 2125-2128.
22. Lasiol: Kasai, T.; Wantanabe, H.; Mori, K. *Bioorg. Med. Chem.* **1993**, *1*, 67-70. Faranal: Mori, K.; Murata, N. *Liebigs Ann.* **1995**, 2089-2092.
23. Leonard, J.; Hewitt, J. D.; Ouali, D.; Simpson, S. J.; Newton, R. F. *Tetrahedron Lett.* **1990**, 31, 6703-6706.
24. (a) Bhuniya, D.; Singh, V. K. *Synth. Commun.* **1994**, *24*, 375-385; (b) Bhuniya, D.; Singh, V. K. *Synth. Commun.* **1994**, *24*, 1475-1481; (c) Bhuniya, D.; DattaGupta, A.; Singh, V. K. *Tetrahedron Lett.* **1995**, *36*, 2847-2850; (d) *idem. J. Org. Chem.* **1996**, *61*, 6108-6113.
25. Milne, D.; Murphy, P. J. *J. Chem. Soc., Chem. Commun.* **1993**, 884-886; *corrigendum*, **1994**, 675.
26. Mordini, E.; Ben Rayana, E.; Margot, C.; Schlosser, M. *Tetrahedron* **1990**, 46, 2401-2410.
27. (a) Hodgson, D. M.; Witherington, J.; Moloney, B. A. *Tetrahedron: Asymmetry* **1994**, *5*, 337-338; (b) Hodgson, D. M.; Witherington, J.; Moloney, B. A. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3373-3378.
28. Hodgson, D. M.; Gibbs. A. R. unpublished work.
29. Asami, M.; Takahashi, J.; Inoue, S. *Tetrahedron: Asymmetry* **1994**, *5*, 1649-1652.
30. Asami, M.; Ishizaki, T.; Inoue, S. *Tetrahedron Lett.* **1995**, *36*, 1893-1894.
31. Hodgson, D. M.; Gibbs, A. R. *Tetrahedron: Asymmetry* **1996**, *7*, 407-408.

32. Asami, M.; Ishizaki, T.; Inoue, S. *Tetrahedron: Asymmetry* **1994**, *5*, 793-796.
33. Zul-Qarnian Khan, A.; Arvidsson, P. I.; Ahlberg, P. *Tetrahedron: Asymmetry* **1996**, *7*, 399-402.
34. Hodgson, D. M.; Lee, G. P. *Chem. Commun.* **1996**, 1015-1016.
35. (a) Hoppe, D.; Hintze, F.; Tebben, P. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1422-1424; (b) Review: Hoppe, D. ; Hintze, F.; Tebben, P.; Paetow, M.; Ahrens, H.; Schwerdtfeger, J.; Sommerfeld, P.; Haller, J.; Guarnieri, W. ; Kolczewski, S.; Hense, T.; Hoppe, I. *Pure Appl. Chem.* **1994**, *66*, 1479-1486.
36. Boeckman, Jr. R. K. *Tetrahedron Lett.* **1977**, 4281-4284.
37. Whitesell, J. K.; White, P. D. *Synthesis* **1975**, 602-603.
38. Hodgson, D. M.; Lee, G. P. unpublished work.
39. Hodgson, D. M.; Wisedale, R. *Tetrahedron: Asymmetry* **1996**, *7*, 1275-1276.
40. Crandall, J. K. *J. Org. Chem.* **1964**, *29*, 2830-2833.
41. Witherington, J. PhD Thesis, University of Reading, **1994**.
42. For a brief review see: Paterson, I; Berrisford, D. J. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1179-1180.
43. Davies, S. G.; Wollowitz, S. *Tetrahedron Lett.* **1980**, *21*, 4175-4178.
44. Davies, S. G.; Warner, P. *Tetrahedron Lett.* **1985**, *26*, 4815-4818.
45. Cole, B. M.; Shimizu, K. D.; Krueger, C. A.; Harrity, J. P. A.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1668-1671.
46. Berrisford, D. J.; Bolm, C.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1059-1070.
47. Hayashi, M.; Tamura, M.; Oguni, N. *Synlett* **1992**, 663-664.
48. Mizuno, M.; Kanai, M.; Iida, A.; Tomioka, K. *Tetrahedron: Asymmetry* **1996**, *7*, 2483-2484.
49. Chan, A. S. C.; Coleman, J. P. *J. Chem. Soc., Chem. Commun.* **1991**, 535-536.
50. (a) Yamashita, H.; Mukaiyama, T. *Chem. Lett.* **1985**, 1643-1646; (b) Yamashita, H. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 1213-1220.
51. Overman, L. E.; Sugai, S.; *J. Org. Chem.* **1985**, *50*, 4154-4155.
52. Yamashita, H. *Chem. Lett.* **1987**, 525-528;
53. Emziane, M.; Sutowardoyo, K. I.; Sinou, D. *J. Orgmet. Chem.* **1988**, *346*, C7-C10.
54. Hayashi, M.; Kohmura, K.; Oguni, N. *Synlett* **1991**, 774-776.
55. Nugent, W. A. *J. Am. Chem. Soc.* **1992**, *114*, 2768-2769.
56. Adolfsson, H.; Moberg, C. *Tetrahedron: Asymmetry* **1995**, *6*, 2023-2031.
57. Martínez, L. E.; Leighton, J. L.; Carsten, D. H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1995**, *117*, 5897-5898.
58. Leighton, J. L.; Jacobsen, E. N. *J. Org. Chem.* **1996**, *61*, 389-390.
59. Larrow, J. F.; Schaus, S. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1996**, *118*, 7420-7421.
60. Diastereoselective additions of selenium-containing binaphthyls to cyclohexene oxide have also been reported: Tomoda, S.; Iwaoka, M. *J. Chem. Soc., Chem. Commun.* **1988**, 1283-1284.
61. (a) *Enzyme Catalysis Organic Synthesis*; Drauz, K.; Waldmann, H. Eds.; VCH: Weinheim. 1995, pp. 271-278; (b) Barili, P. L.; Berti, G.; Mastrorilli, E. *Tetrahedron* **1993**, *49*, 6263-6276.
62. Bellucci, G.; Capitani, I.; Chiappe, C.; Marioni, F. *J. Chem. Soc., Chem. Commun.* **1989**, 1170-1171.
63. Naruse, Y.; Esaki, T.; Yamamoto, H. *Tetrahedron* **1988**, *44*, 4747-4756.
64. (a) Joshi, N. N.; Srebnik, M.; Brown, H. C. *J. Am. Chem. Soc.* **1988**, *110*, 6246-6248; (b) Srebnik,

M.; Joshi, N. N.; Brown, H. C. *Isr. J. Chem.* **1989**, *29*, 229-237.
65. Su, H.; Walder, L.; Zhang, Z.; Scheffold, R. *Helv. Chim. Acta* **1988**, *71*, 1073-1078.
66. Bonhôte, P.; Scheffold, R. *Helv. Chim. Acta* **1991**, *74*, 1425-1444.
67. Busato, S.; Tinembart, O.; Zhang, Z.; Scheffold, R. *Tetrahedron* **1990**, *46*, 3155-3166.
68. Hildbrand, S.; Troxler, T.; Scheffold, R. *Helv. Chim. Acta* **1994**, *77*, 1236-1240.
69. Essig, S.; Scheffold, R. *Chimia* **1991**, *45*, 30-32.
70. Zhang, Z.; Scheffold, R. *Helv. Chim. Acta* **1993**, *76*, 2602-2615. See also: Hayashi, M.; Ono, K.; Hoshimi, H.; Oguni, N. *Tetrahedron* **1996**, *52*, 7817-7832.
71. Troxler, T.; Scheffold, R. *Helv. Chim. Acta* **1994**, *77*, 1193-1201.
72. DattaGupta, A.; Singh, V. K. *Tetrahedron Lett.* **1996**, *37*, 2633-2636, and references cited therein. Zondervan, C.; Feringa, B. L. *Tetrahedron: Asymmetry* **1996**, *7*, 1895-1898.
73. Li, G.; Chang, H.-T.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 451-454.
74. Jacobsen, E. N. Asymmetric Catalytic Epoxidation of Unfunctionalised Olefins. In *Catalytic Asymmetric Synthesis*; Ojima, I. Ed.; VCH: New York. 1993, pp. 159-202; Jacobsen, E. N. Transition Metal-catalyzed Oxidations: Asymmetric Epoxidation. In *Comprehensive Organometallic Chemistry II*; Abel, E. W.; Stone, F. G. A.; Wilkinson, G., Eds.; Pergamon: New York. 1995, Vol. 12, pp. 1097-1135; Katsuki, T. *Chem. Coord. Rev.* **1995**, *140*, 189-214.

(*Received* 18 *September* 1996)