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A critical outlook and comparison of enantioselective oxidation methodologies of olefins

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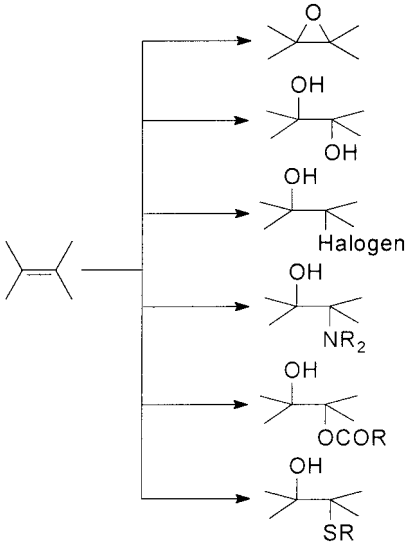
1. Introduction

The importance of asymmetric synthesis as a tool for obtaining enantiomerically pure compounds has grown dramatically in the last two decades not only in synthetic organic chemistry as well as medicinal and agricultural chemistry, but also in the pharmaceutical and agricultural industries. This has been mainly due to the market situation for chiral drugs where the use of racemic compounds, especially for the pharmaceutical industry, has been severely cut by national agencies such as the FDA (Food and Drug Administration) in the USA.

Although several methodologies to obtain enantiomerically pure compounds are available (such as optical resolution of racemates via separation of diastereoisomers, chiral chromatographic separations and biocatalytic or chemical kinetic resolution), asymmetric synthesis appears increasingly to be the future method for the production of pure chiral compounds, and also for industrial use. The aim of this chemistry requires the transformation of a known reaction into an enantioselective process with the use of simple reagents and chiral auxiliaries or, better still, in a catalytic enantioselective process, as normally used by enzymes.

The oxidation of carbon–carbon double bonds into a variety of functionalised compounds is undoubtedly one of the most useful transformations in synthetic organic chemistry.[1] First of all, the olefin substrates can be regarded as probably the most important synthetic organic intermediates because of their inexpensive nature and ready availability, either from the petroleum industry or by simple and well developed synthetic methodologies. In addition the resultant 1,2-oxidised compounds such as epoxides, alcohols and diols, halohydrins or amino derivatives can be further transformed into other classes of compounds with control eventually of the relative stereochemistry of the final compounds (Scheme 1).



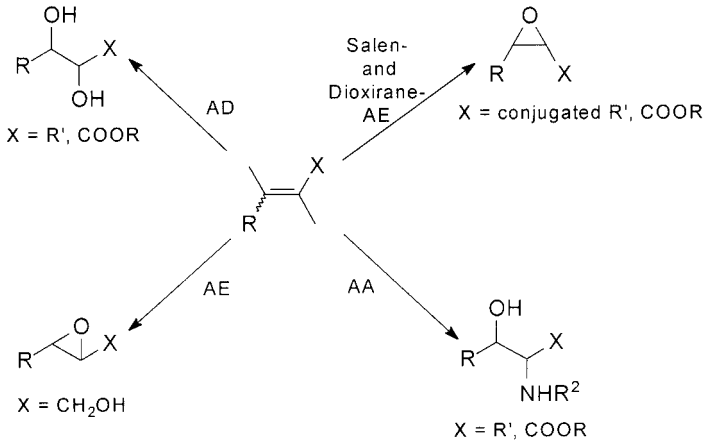
Scheme 1.

As the need for enantioselective processes was increasing in the early 1980s, chemists looked to the known oxidative reactions of olefins and tried to make them enantioselective processes. Although before the 1980s some enantioselective oxidation reactions of olefins had already been developed, the discovery of the Sharpless–Katsuki asymmetric epoxidation (AE) in 1980[2] represents a major breakthrough, not only in the enantioselective oxidation of olefins but in asymmetric synthesis in general.

Other major advances in asymmetric oxidation of olefins followed: the Sharpless asymmetric dihydroxylation (AD) in 1988,[3] the Jacobsen and Katsuki Salen-asymmetric epoxidation (Salen-AE) of unfunctionalised olefins in 1990,[4] and later the Sharpless asymmetric aminohydroxylation (AA) in 1996[5] (Scheme 2). Very recently novel methodologies have enabled the enantioselective epoxidation of unfunctionalised olefins[4f,6] and enones.[7] While these preliminary results appear to be a promising new achievement in this area, they have clearly yet to involve the widespread use of the AE and the AD reactions.

It is worthy of note that oxidation of the carbon–carbon double bond leads to functionalised compounds that can frequently be obtained by different routes. None of the known methods, however, provides for a general asymmetric oxidation protocol. For this reason, a chemist planning a short or lengthy synthesis, i.e. of natural products, frequently has numerous options for the introduction of the correct chirality in a synthon to be elaborated. A complete picture and comparison of the available methodologies, with consideration of their applicability, limits, enantioselectivity, chemical yields and availability of the starting materials, would facilitate a synthetic design.

The number of reviews in journals or books (see Refs. 1–6) concerning the individual methodologies is large as newer and more advanced enantioselective oxidative methods appear in the literature. Critical analysis and comparison of the various asymmetric oxidation methodologies are however not ready available. Consequently, the scope of this report has been directed toward such a critical analysis and comparison between the different methodologies, with particular emphasis on catalysis, chiral ligand and support choice, and transformations of different functional groups. The review is organised to compare all the different aspects



Scheme 2.

of the methodologies in a manner so as to make such a comparative analysis more straightforward and easier for the reader.

After a short description of the older and newer oxidative methodologies (Section 2), a critical comparison of the availability of the starting olefins and of the experimental conditions (Section 3) will be given, followed by a consideration of the importance and complementarity of functional groups obtained directly or by different reactions starting from the chiral functionalised compounds (Section 4). Finally, in order to rationalise the different possibilities when planning a synthesis, Section 5 will directly compare the different methodologies using selected examples from the literature.

It must be noted that, with the aim of obtaining chiral functionalised compounds such as epoxides, alcohols and polyols, aminoalcohols and their derivatives, other methods than the enantioselective oxidation of an olefin, are being increasing discovered and becoming available. Among these methods, mention must be made of to: (a) biocatalytic procedures[8] such as direct epoxidation and dihydroxylation as well as indirect preparation of epoxides, 1,2-diols and halohydrins and (b) chemical kinetic resolution and desymmetrisation of epoxides.[9] The results obtained with these procedures are, for some examples, highly remarkable, but they will be not considered in this report which is dedicated to oxidative enantioselective procedures.

Additionally, other oxidation reactions of olefins, such as double bonds breaking, hydration, hydrohalogenation, or halogenations and other heteroatom addition, will not be considered here, and the reader should refer to earlier reviews[10] where these reactions have been considered.

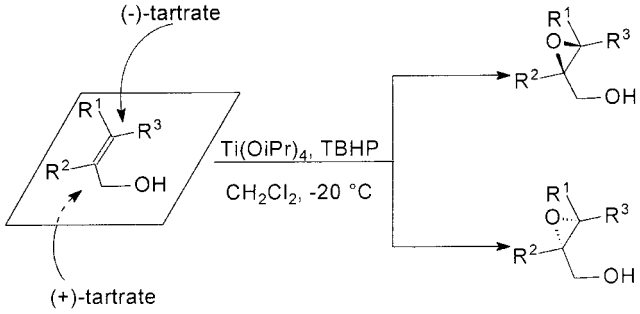
2. Aim, scope and limitations of the most recent enantioselective oxidative methodologies

Although asymmetric processes of olefins oxidation are still a challenging and primary research activity, synthetic organic chemists have at their disposal a series of processes to date, developed in the last 20 years, which have been tested in hundreds of experiments and which could now almost be considered as ordinary synthetic chemistry, in particular the AE of allylic alcohols and the AD of unfunctionalised olefins. Other newer processes such as the Salen-AE or dioxirane oxidation of unfunctionalised olefins as well as the asymmetric aminohydroxylation AA, promise to be as competitive as the other methodologies, although more work is still needed to extend their scope and applicability. The complementarities of these and other recent methodologies are evident and their utilisation will now be illustrated.

2.1. Asymmetric epoxidation (AE) of allylic alcohols

The Sharpless–Katsuki asymmetric epoxidation (AE) of allylic alcohols represents a special example of the scientific progress. The story of its discovery is legendary and came as a thunderclap, since previous attempts were not as promising. The chemical community was struck by the novelty of the growing area of asymmetric synthesis and the AE procedure started to be applied immediately. In spite of later attempts, the original reagent combination still appears today to be quite adequate in providing the best results, and its discovery in 1980,[2a] does represent indeed the start of a new era in asymmetric synthesis.

The asymmetric epoxidation of allylic alcohols and the related kinetic resolution of secondary allylic alcohols have been reviewed[2b–e] also, with a detailed discussion of the mechanism and synthetic utility. For primary achiral allylic alcohols (Scheme 3), a combination of $Ti(OiPr)_4$, a dialkyl tartrate and TBHP is able to distinguish between the two enantiofaces of the substrate, in accord with the



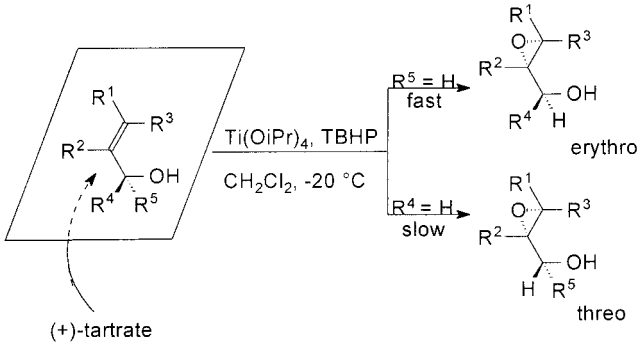
Scheme 3.

empirical rule depicted. The chirality of the tartrate used (typically dimethyl (DMT), diethyl (DET) or diisopropyl (DIPT) tartrates) induces the sense of the oxygen delivery from the top or bottom of the olefin. Normally, there is no exception to the empirical rule depicted in Scheme 3, and it has therefore been frequently used for the assignment of the absolute configuration of the resulting epoxides.

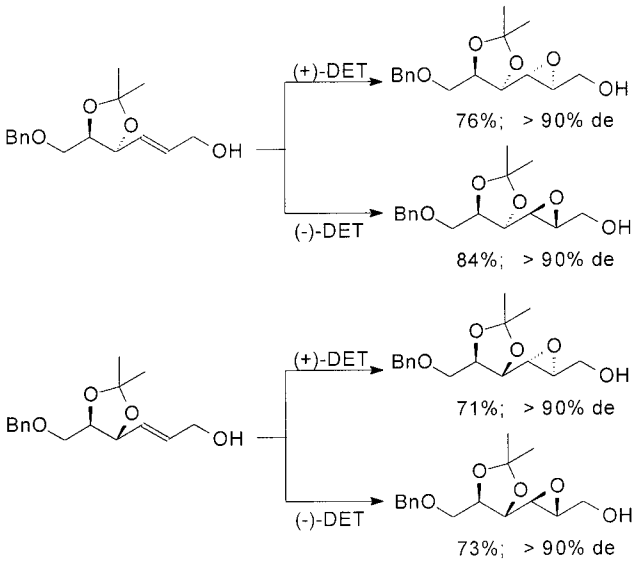
A wide range of allylic alcohols have been shown to be good substrates for the reaction, as demonstrated by the hundreds of applications[2c] reported over 20 years. The reaction usually proceeds with good chemical yields and high enantioselectivity, often >90% ee. The (*E*)-allylic alcohols, with few exceptions, have been shown to be the best substrates for high enantioselectivity, and are easily available by standard methodologies (see the following Section for a more detailed discussion of the availability of the substrates). Although (*Z*)-allylic alcohols have been shown in many cases to be good substrates, the enantioselectivity is significantly influenced by the nature and size of the R^3 substituent. In conclusion, the large number of applications of the AE on a wide variety of primary allylic alcohols can easily allow a correct prediction, in many examples, of the range of enantioselectivity to be expected.

In the presence of a stereogenic centre in the C1 position of the allylic alcohols (Scheme 4), both diastereo- and enantioselectivity must be considered, in order to predict and rationalise the kinetic resolution (KR) of the enantiomeric couple. The first results of the AE/KR were reported in1981.[11] As shown in Scheme 4 the epoxidation of one enantiomer at a much faster rate than the other is dictated by the configuration of the (C-1) R substituent, which hindered the approach of the oxygen from one side of the olefin. The success of the resolution depends on the difference in the epoxidation rates affording the *erythro* isomer only (see Scheme 4). The ratio between the k_{fast}/k_{slow} rate of the two enantiomers has normally been defined as k_{rel}, which bears a mathematical relationship to the enantiomeric excess of the epoxy alcohol and the remaining allylic alcohol. A range of k_{rel} 50–100 is considered to be sufficient to afford products of >90% ee (for a related discussion, see Refs. 2b,d).

The model shown in Scheme 4 clearly accounts for the general stereochemical course of the kinetic resolution, with a high predictability: the slow-reacting enantiomer



Scheme 4.



Scheme 5.

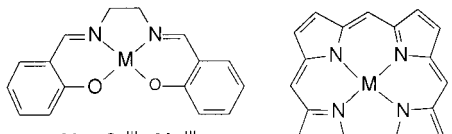
appears as the one with the R^5 substituent at C-1 and interferes with the delivery of the oxygen atom, thus resulting in a preference for obtaining the opposite *erythro* epoxide. Good results, especially with *E* substrates and with olefins without *Z* substituents (R^3=H) are generally expected, although bulky *Z* (R^3) substituents normally give poor selectivity. Many examples have been sufficiently exploited in order to provide a rational explanation for the results of the kinetic resolution.

The clear implication of the size of the substituent in the success of the reaction also highlights that the efficiency of the secondary alcohol epoxidation depends upon the reagent used, in contrast to the epoxidation of the primary allylic alcohols. DIPT is therefore generally used as the chiral auxiliary, with a major preference over DMT or DET.[2c] Additionally a large size of the alkoxy substituents in the Ti species was found to be deleterious for the successful kinetic resolution.[12]

Some particularly interesting results have shown how the chiral catalyst in the AE could overcome the pre-existing chirality in a primary chiral allylic alcohol. The starting chiral isomer can couple with the catalyst (+ or − tartrate) in a *matched* or *mismatched* pair, as shown for one important example in Scheme 5.[2b,c,13] This can be utilised (although with some restrictions) to obtain the desired diastereoisomer with good to excellent diastereomeric excess by simply choosing the appropriate chiral catalyst.

2.2. Asymmetric epoxidation of simple olefins

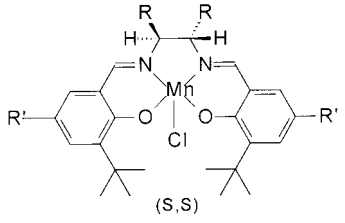
The major limitation of the Sharpless–Katsuki asymmetric epoxidation is the need for the olefins to be functionalised as allylic alcohols, although this condition could be considered, in some cases, as an advantage (see Section 4 for the reactions and applications of epoxyalcohols). The discovery and the limitations of the AE therefore prompted chemists to seek reactions which could lead to unfunctionalised epoxides.



1 2

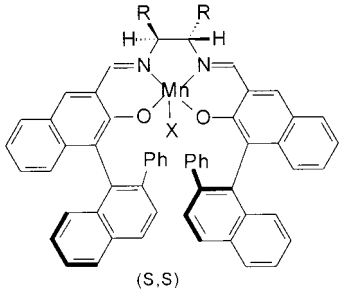
Figure 1.

2.2.1. Jacobsen–Katsuki epoxidation approach (Salen-AE). Ten years after the discovery of the AE of allylic alcohols, the Jacobsen[4a] and Katsuki[4b] groups reported, almost simultaneously, the asymmetric epoxidation of unfunctionalised olefins (Salen-AE), with the use of chiral Mn-salen catalysts. This discovery represents the asymmetric version of the achiral olefin epoxidation catalysed by the salen–metal(III) complexes **1** (Fig. 1), which was described in a fundamental study by Kochi and co-workers.[14] It is important to note the structural correlation between the salen-complexes **1** and the porphyrin–metal complexes **2**, well known as deoxidising reagents in natural and synthetic processes.[4c] Among the different catalysts proposed (see Ref. 4d for a list of the catalysts used) the compounds **3**–**6**, (see Fig. 2) were employed and successively optimised by Jacobsen,[4c] while the catalysts **7**,**8** were developed by Katsuki[4d] in later work. The main differences between the two systems lie in the presence of four different stereocenters (in the Katsuki complexes) and in the replacements (in the Jacobsen complexes) of the stereogenic centres at C-3 and C-3′ with bulky *t*-butyl groups. The epoxidation was best carried out in acetonitrile or dichloromethane, with NaOCl or iodosylbenzene as the oxygen source but other oxidants



(S,S)

3 R, R = -$(CH_2)_4$- R′ = *t*-Bu
4 R, R = Ph R′ = Me
5 R, R = -$(CH_2)_4$- R′ = OSi(*i*Pr)$_3$
6 R, R = Ph R′ = OSi(*i*Pr)$_3$



(S,S)

7 R = 3,5-$Me_2C_6H_3$ X = OAc
8 R = Ph X = PF_6^-

Figure 2.

have also been employed.[4d] In addition the use of an axial ligand on the active oxomanganese species was found to be helpful in optimising of the chemical and optical yields, when amine or isoquinoline *N*-oxides were used.[15] The importance of an axially coordinating N ligand, has been elegantly confirmed by the use of a chiral amine[16a,b] or bipyridine *N*,*N*-dioxide[16c] with an achiral manganese complex, which afforded the optically active epoxides with ees up to 73 and 86%, respectively. The temperature was, in some cases, also found to affect both the enantioselectivity and the chemical yields, these generally increasing by lowering the reaction temperature to −78°C.[17]

The choice of the starting olefins appeared to be crucial to the success of the reaction, and after extensive studies on different substrates, a general picture of the substrate dependence can now be predicted.

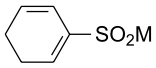
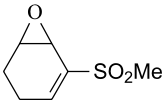
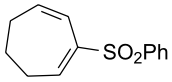
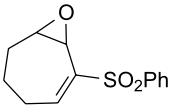
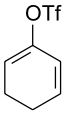
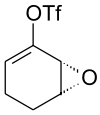
As a general trend, conjugated alkenes are always better substrates than simple unconjugated olefins. The (*Z*)-disubstituted alkenes are the best substrates for the catalysts and the conditions used, with nearly complete enantioselectivity. Simple alkyl-substituted olefins give lower enantioselectivity, although attention must be paid to the conjugation and electronic pattern of the substitutions. Some conjugated (*Z*)-disubstituted olefins exhibit isomerisation during the epoxidation reaction, affording *trans* and *cis* epoxides in different ratios[18,19] and can thus be manipulated advantageously. The analogous *trans* (*E*)-disubstituted olefins are less suitable substrates, with the results varying with the catalysts and the temperature, although the Katsuki catalysts gave a generally superior performance. With respect to the porphyrin-based catalysts, the monosubstituted olefins provide an unusually low selectivity under the normal experimental conditions, with extensive isomerisation of the final epoxide. This problem could be solved, for styrene epoxidation, by the use of mCPBA in dichloromethane at −78°C, with the formation of enantiopure styrene oxide.[20] In contrast to this result, a considerable number of olefins with tri- and tetra-substituted double bonds have been successfully epoxidised,[21] with enantiomeric excesses up to 90%.

Some recent applications have extended the Jacobsen version (catalyst **3**, referred to as Jacobsen's catalyst) of Salen-AE to substrates such as cyclic dienyl sulphones[22a] with moderate to high enantioselectivity (see entries 1 and 2 in Table 1). The same authors also used Jacobsen's catalyst[22c] on a dienyl triflate (see entry 3), which was subsequently elaborated to cyclic and acyclic synthons.

A chromium complex version, utilising the different unsymmetrical salen complexes, was recently tested.[23] The ee reported in the most recent developments[23c] for (*E*)-methylstyrene was found to be superior to the previous attempts on (*E*)-olefins, with some interesting considerations on the proposed mechanism for the metal-oxo side-on approach model for the (*Z*)-olefins.[24]

A novel (NO)ruthenium-salen was recently proposed by Katsuki,[25a] (see Fig. 2) which seems irrespective of the substitution pattern for conjugated olefins (*E* or *Z*), and affords the corresponding epoxides with ees often superior

Table 1. Salen-AE of particular substrates

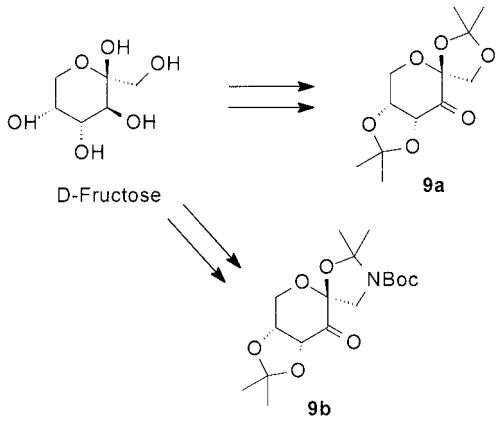
Entry	Diene	Product	Yield (%)	ee (%)	Reference
1			75	>99	22a
2			80	>99	22a
3			65	91	22c

to 80–85%. The reaction is preferably carried out in benzene under light irradiation, with 2,6-dichloropyridine *N*-oxide as the terminal oxidant. A similar catalyst has also been employed[25b] for the aerobic oxidation/KR of sec-alcohols, with promising results.

In conclusion, although with some limitations on the substrate choice and with mechanism of the reaction still being debated,[24] the results obtained with the Jacobsen–Katsuki Salen-AE appear to be of great importance, especially for their use in the preparation of enantiopure epoxides. The major limitation of the Salen-AE, due to the instability of the most common catalysts (e.g. **3**), in prolonged oxidative conditions, has prompted several studies to incorporate the salen ligand into a matrix or support as a means of recycling the chiral catalyst, as will described in Section 3.1.

2.2.2. Recent asymmetric epoxidation by chiral dioxirane derivatives. The major limitation of the Jacobsen–Katsuki Salen-AE due to the lack of broad applicability for the *trans* (*E*)-olefins appears to be circumvented in most recent methodologies employing the generated chiral dioxirane derivatives as the catalytic oxidants.

The most promising catalytic system was developed starting from a report in 1996 by Shi and co-workers,[6,26] with the construction of a D-fructose chiral ketone **9a** (Scheme 6),



Scheme 6.

which demonstrated its ability to act as a powerful catalyst[27] for the dioxirane epoxidation of unfunctionalised *trans*-olefins. The chiral catalyst can be prepared in both enantiomeric forms: from D-fructose in a two-step synthesis and from L-fructose (**ent-9a**), prepared from L-sorbose (five step synthesis). Both catalysts are quite efficient (Table 2) in stoichiometric or catalytic (0.3 equiv.) amounts, with the need for careful pH control[26] due to the catalyst decomposition by Baeyer–Villiger reaction, and with the oxone as the oxidant, although, recently, H_2O_2 has also been used.[28]

A high level (ee>90%) of enantioselectivity for *trans*-olefins was reported (Table 2) and these results were successively extended to different substrates.

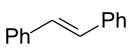
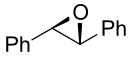
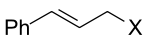
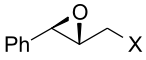
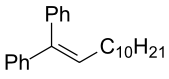
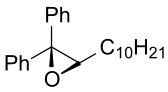
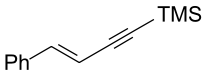
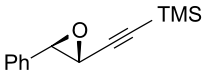
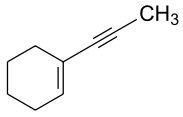
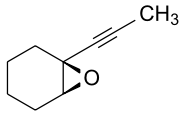
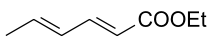
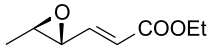
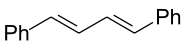
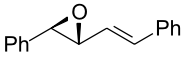
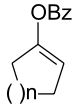
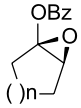
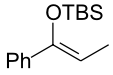
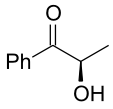
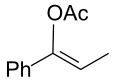
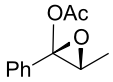
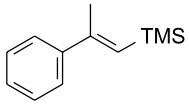
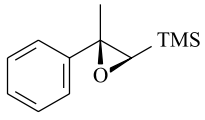
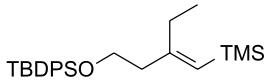
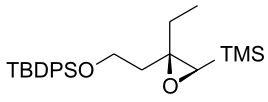
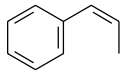
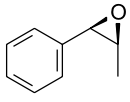
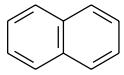
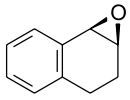
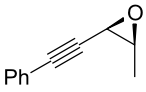
Conjugated dienes[29a] (entries 6 and 7) and enynes[29b,c] (entries 4 and 5), enol ethers and esters[29d] (entries 8–10) and 2,2-disubstituted vinylsilanes[29e] (entries 11, 12), can be regio-, chemo- and enantioselectively epoxidised, giving rise to functionalised epoxides with good to high enantiomeric excess. A recent report[29f] shows, however, that terminal olefins are fair substrates for this procedure with epoxides obtained with ees in the range 71–85%.

While the reaction was initially performed on *trans* substituted olefins, a very recent development by the same group in late 2000,[30] showed highly promising preliminary results on the *cis* substituted olefins (entries 13–15 for selected examples), by the use of the related nitrogen-derived chiral catalyst **9b** (Fig. 2), with excellent ees. The reaction appears, so far, to be limited only to aromatic conjugated olefins, with the use of 15% molar catalyst (to be prepared in several steps).

Although the reaction appears to be of great interest, especially if it could be performed on all classes of olefins, it has been applied only recently by other groups[31] and therefore its broad utilisation should be demonstrated in the near future. Its potential applicability has recently, however, been shown in a spectacular multi-epoxidation with catalyst **9a**, reported by Corey,[32] with the concomitant epoxidation of four and five trisubstituted double bonds with >80% estimated diastereomeric purity.

Other groups have achieved interesting results utilising

Table 2. Chiral dioxirane mediated AE of olefins

Entry	Olefin	Product	Catalyst	Yield (%)	ee (%)
1			**9a**	75	97
2			**9a** X=OH X=Cl X=OTBS	 60 61 74	 84 93 93
3			**9a**	66	93
4			**9a**	59	96
5			**9a**	88	90
6			**9a**	41	96
7			**9a**	77	97
8			**9a** *n*=1 *n*=2 *n*=3 *n*=4	 79 82 87 82	 80 93 91 95
9			**9a**	80	90
10			**9a**	66	91
11			**9a**	74	94
12			**9a**	67	92
13			**9b**	87	91
14			**9b**	88	84
15			**9b**	82	91

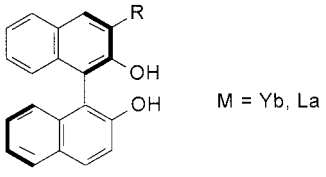
different chiral ketone/oxone systems in order to achieve *trans*-olefin epoxidation, the most successful results being reported by the Denmark,[33] yang[34] and Amstrong[35] groups, with different ketones. The reported chemical and optical yields, however appear to be generally below the results reported by the Shi group.

The mechanism of the proposed asymmetric epoxidation with chiral ketone/oxone systems appears to be of great importance for the design and developments of different catalysts and for predicting the stereochemical outcome. A general overview of the subject with the different proposed mechanisms has recently been published.[6b]

2.2.3. Recent asymmetric epoxidation of enones. The direct asymmetric epoxidation of enones to keto epoxides was extensively explored in the early 1980s with variable results. More recently, some new methodologies have been discovered[7] with the aim of complementing the results obtained in the cases of the AE of allylic alcohols and of the Jacobsen–Katsuki Salen-AE.

The first of these methodologies, the Julia–Colonna AE[36,37] using polyleucine as a catalyst, is still attracting interest for providing further improvements. Among the more recent results, a remarkable diastereoselective epoxidation was performed by the Roberts group on different aryl unsaturated keto and ketoesters,[38a] as well as γ-heterosubstituted α,β-unsaturated ketones.[38b] The same group has very recently reported[38c] the first soluble version of the Julia–Colonna catalyst on a triblock PEG-bound poly-L-leucine which, where employed in the epoxidation of enones, afforded the chiral compounds with excellent ees.

The lanthanide-BINOL-derived catalysts such as **10** and **11** (Fig. 3) have been successfully employed[39] for the catalytic enantioselective preparation of *trans* and *cis* enones with TBHP as oxidant. The results appear to be quite satisfactory and could be improved with the addition of water[39c] or triphenylphosphine oxide.[40]

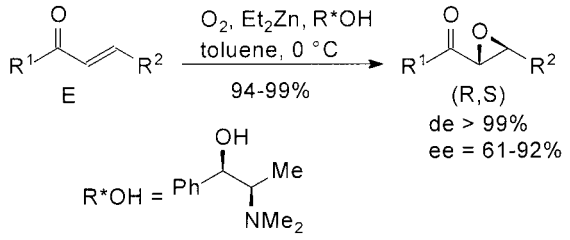


10 R = H
11 R = CH_2OH

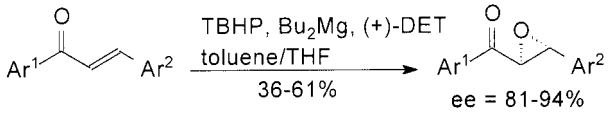
Figure 3.

Chiral α,β-epoxyketones have also been prepared with the use of (*R*,*R*)-*N*-methylpseudoephedrine as a catalyst and with an O_2/Et_2Zn oxidant system[41] with varying ees but superior des (Scheme 7); the reaction is postulated to proceed through a chiral alkoxy(ethylperoxy)zinc complex from the *si*-face of the *s*–*cis* conformation of the (*E*) enones in an oxa-Michael addition fashion.

Li and Mg *t*-butyl peroxides, chirally modified with (+)



Scheme 7.



Scheme 8.

DET, afford diaryl epoxy ketones (Scheme 8) from chalcone derivatives with good enantioselection.[42]

Mild phase transfer-catalysed conditions have also been used successfully with different quaternary chiral ammonium salts, starting with the pioneering work by Wynberg.[43] Recently promising results have been reported with the use of cinchona alkaloids,[44] with superior enantioselectivity as previously reported by Wynberg.

Amongst the most recent methodologies, a novel asymmetric epoxidation of α,β-enones by optically active hydroperoxide (*S*-(−)-(1-phenyl)ethyl hydroperoxide) appeared[45a] as a significant extension of the previously reported Ti(IV)-catalysed asymmetric epoxidation of sulphides and allylic alcohols.[45b] The good enantioselectivity observed was rationalised by a metal coordination between the enone system and the hydroperoxide.

In conclusion, although the improvements in the asymmetric epoxidation of this particular class of olefins are often impressive, some work is still required to achieve a full and broad applicability of these reactions, as well as their utilisation for synthetic purposes.

2.3. Asymmetric dihydroxylation (AD) of olefins

Eight years after the discovery of the Sharpless–Katsuki AE of allylic alcohols, another breakthrough came from the Sharpless group in 1988,[3a] the catalytic asymmetric dihydroxylation (AD) of olefins. Since its discovery, this reaction has been extensively optimised in both alkaloid ligands as well as in the co-oxidant and solvent systems, and has been performed on hundreds of different olefins (functionalised or unfunctionalised). A large part of the olefin can now be dihydroxylated with good to excellent enantioselectivity, by a proper choice of the reagent and reaction conditions.[46] With regard to the actual state of the art, the AD process could probably be considered as the most general oxidation asymmetric reaction of olefins, with virtually no need for particular functionalisation or conjugation of the reacting double bond.

The reaction has been the subject of several reviews on both

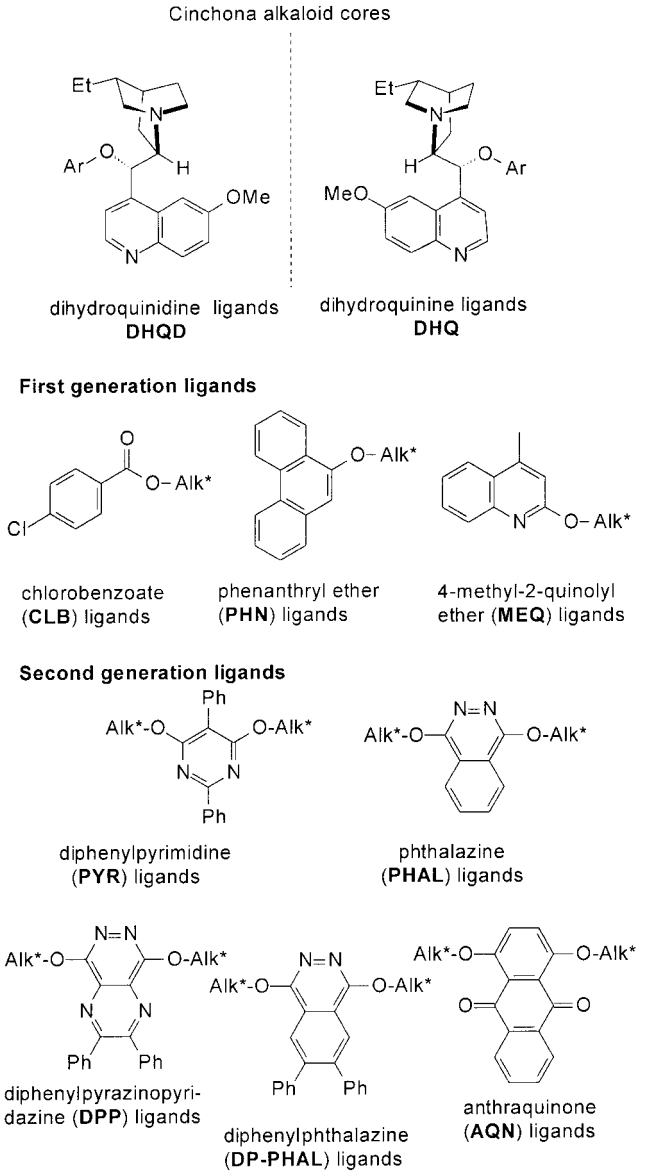


Figure 4.

the mechanistic and synthetic aspects, 3b–e and, therefore, the general aspects of the reaction will be emphasised here and, in the following sections, its most recent applications and a comparison with the other synthetic asymmetric oxidative methodologies.

In an exhaustive study more than 400 alkaloids were tested and a list of the most useful AD ligands can subsequently be drawn (Fig. 4).[47] These long-term studies revealed the cinchona alkaloids to be perfect molecules for the AD, and for the ligand acceleration effect (LAE), and they can exhibit asymmetric induction at a very high level. While modifications of the cinchona core were revealed to be irrelevant, the major improvements were achieved in the modification of the O(9) substituent. As shown in Fig. 4, the presence of at least an aromatic group proved to be decisive for the discovery of the most effective derivatives. The main differences between the first and second generation ligands are in their monomeric or dimeric combination with the core of the alkaloid.

Without doubt, the second generation ligands clearly show a wider scope and application than the earlier ligands. In Table 3, the recommended ligands for each class of olefin are reported, according to Sharpless's suggestions. Among these the PHAL (phthalazine) ligands are the most widely used in the AD owing to their large substrate applicability and are currently employed in the AD-mix formulations (see below). For certain olefins, the more recent AQN,[48] DPP and DP-PHAL ligands[49] are preferred.

Although the catalytic system based on osmium-based potassium ferrocyanide and potassium carbonate oxidation is the most utilised, recent reports have appeared[50] to be particularly promising on the use of different oxidant systems. The use of air under irradiation with visible light,[50a] or of molecular oxygen, as the co-oxidant[50b,c] in the AD of olefins, gave good results, although only preliminary experiments have been carried out. The development of such mild and environmentally friendly reagents would enhance the potency of the AD of prochiral olefins, and its extension to industrial applications.

AD of monosubstituted olefins appeared to be influenced by the substituent (alkyl or aryl), with long and bulky side chains giving the best results, as well as aromatic substituted olefins. Aryl and allyl ethers, highly important as starting materials for chiral synthons, also appear to be good substrates. Independent studies[51a,b] on vinyl furans (Table 4, entry 1), have also shown that such compounds afford in high enantioselectivity and chemical yields chiral furfuryl diols, which may then utilised for the synthesis of natural products.[51c–e]

Table 3. Recommended ligands for the AD of different classes of olefins

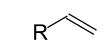
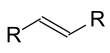
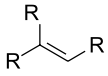
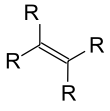
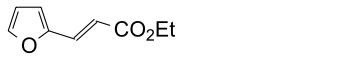
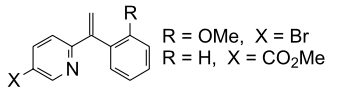
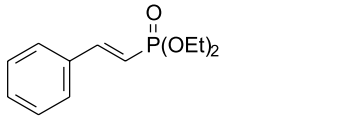
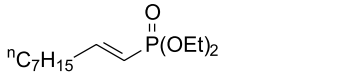
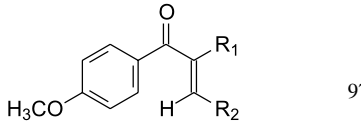
Olefin class						
Preferred ligand	R=aromatic DPP, PHAL R=aliphatic AQN R=branched PYR	R=aromatic DPP, PHAL R=aliphatic AQN R=branched PYR	Acyclic IND Cyclic PYR, DPP, AQN	R=aromatic DPP, PHAL R=aliphatic AQN	PHAL, DPP, AQN	PYR, PHAL
ee range	30–97%	70–97%	20–80%	90–99.8%	90–99%	20–97%

Table 4. AD of particular substrates

Entry	Olefin	ee (%)	Best ligand
1		92	$(DHQD)_2PHAL$
2	 R = OMe, X = Br R = H, X = CO_2Me	>99 98	$(DHQD)_2AQN$ $(DHQD)_2AQN$
3		91	$(DHQ)_2PHAL$
4		84	$(DHQ)_2PHAL$
5		>99	$(DHQ)_2PHAL$
6	 R_1 = H, *c*-hexenylmethyl R_2 = H, CH_3	97–99	$(DHQD)_2PYDZ$

General reaction conditions employing AD-mix for 1 mmol of olefin: 5 l of *tert*-BuOH, 5 ml of H_2O, 1.4 g of AD-mix-α or AD-mix-β; 1 kg of AD-mix contains: $K_3Fe(CN)_6$, 699.6 g; K_2CO_3, 293.9 g; $(DHQD)_2$- or $(DHQ)_2$-PHAL, 5.52 g; $K_2OsO_2(OH)_4$, 1.04 g.

Better results are generally obtained for 1,1 disubstituted olefins, although the aliphatic chains are not suitable for an efficient AD. Very recently, 1-aryl-1-pyridylalkenes (entry 2) have been reported[52] to afford the corresponding 1,2-diols in high chemical and optical yields, depending on the substituent effects and electronic nature of the heterocyclic ring.

1,2-*trans*-(*E*)-Disubstituted olefins appear to be the best substrates for AD with ees normally >90%. The length and nature (aliphatic or aromatic) of the double bond substituent have little or no influence on the enantioselectivity.

Good to excellent results are also obtained for trisubstituted olefins and enol ethers, which are particularly attractive substrates, since they afford α-hydroxyketones.

Electro-deficient olefins provide final chiral diols with excellent ees (>93%) for the amides, and still good for the enones, of sulphur-containing olefins, and, more recently, of *trans*-alkenylphosphonates[53] (entries 3 and 4). Very recent useful results have been obtained in the AD of unprecedented substrates such as differently-substituted thiophenes (entry 5). Where a careful choice of conditions led to good yields of valuable chiral diols.[54]

The major serious limitation of the AD of olefins appears to be the reactions of *cis* disubstituted olefins, including aliphatic, aromatic, cyclic or electron-deficient olefins as well as allylic or homoallylic alcohols.

Sharpless[55a] and Corey[55b] were, however, able to demonstrate that suitable protecting groups of the hydroxyl function (4-substituted phenyl esters) in the allylic alcohol (entry 6) could overcome this limitation. More recently,[55c] the unsubstituted allyl *N*-phenylcarbamate was found to be an excellent substrate for the AD to give the corresponding 1,2-diols.

The asymmetric induction for *cis* (*Z*)-olefins has never exceeded a fair ee of the corresponding *anti* 1,2-diol. Manipulation strategies of the *syn* 1,2-diol (easily obtained on the *trans* olefins) for obtaining the *anti* 1,2-diol have therefore been developed (see Section 4).

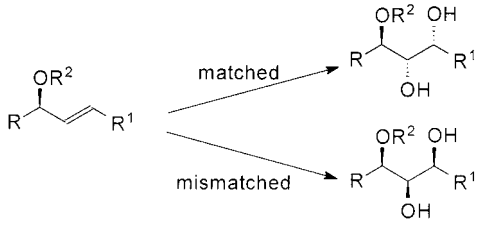
One of the most impressive extensions of the AD process was achieved on polyunsaturated conjugated or unconjugated alicyclic or cyclic polyenes. Generally the control of the regio-, enantio- and diastereoselectivity is excellent, leading to highly functionalised compounds useful as chiral building blocks.[56]

The proper choice of the ligands is crucial for the control of the regio- and diastereoselectivity. The reaction is highly regioselective with *trans* polyenes, both alicyclic and cyclic, while the AD reaction on enynes gave unsatisfactory ees only for the terminal olefin. The regioselectivity of the monodihydroxylation is normally determined by steric and electronic factors. Isolated *trans* di- or trisubstituted double bonds usually react much faster than *cis* or terminal olefins. Electron-rich olefins react better than electron-poor olefins and steric factors are the origin of the observed regioselectivity for the cyclic olefins.

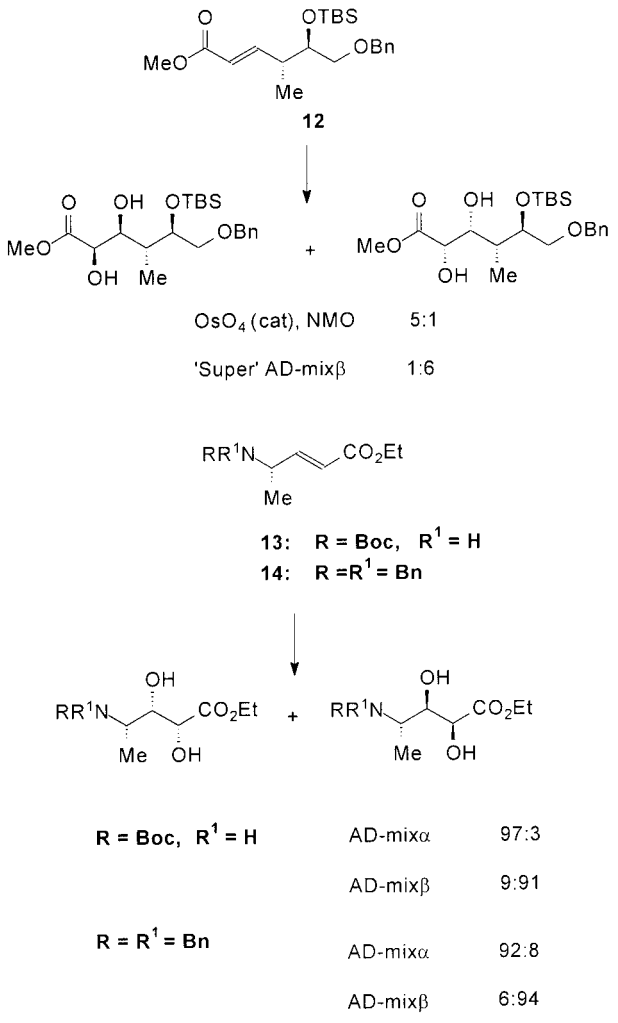
The double diastereoselective asymmetric dihydroxylation of chiral olefins proved to be a valuable tool for the introduction of the 1,2-diol system in many highly-functionalised compounds. The AD was shown to be powerful in several important syntheses: the high level of enantioselectivity was reflected in a high level of diastereoselectivity, in the matched or mismatched pair (Scheme 9), where a chiral proximate centre to the double bond is present. The reaction worked particularly well for di- and trisubstituted olefins, while with monosubstituted olefins, the level of diastereoselectivity was never particularly high.

The influence of allylic or homoallylic alkoxy groups on the diastereoselectivity of the AD has been extensively studied,[57] with interesting observations on the reverse diastereoselectivity[58] with the use of the AD procedure (Scheme 10, compound **12**).

A study by Reetz[59] (Scheme 10, compounds **13** and **14**) has



Scheme 9.



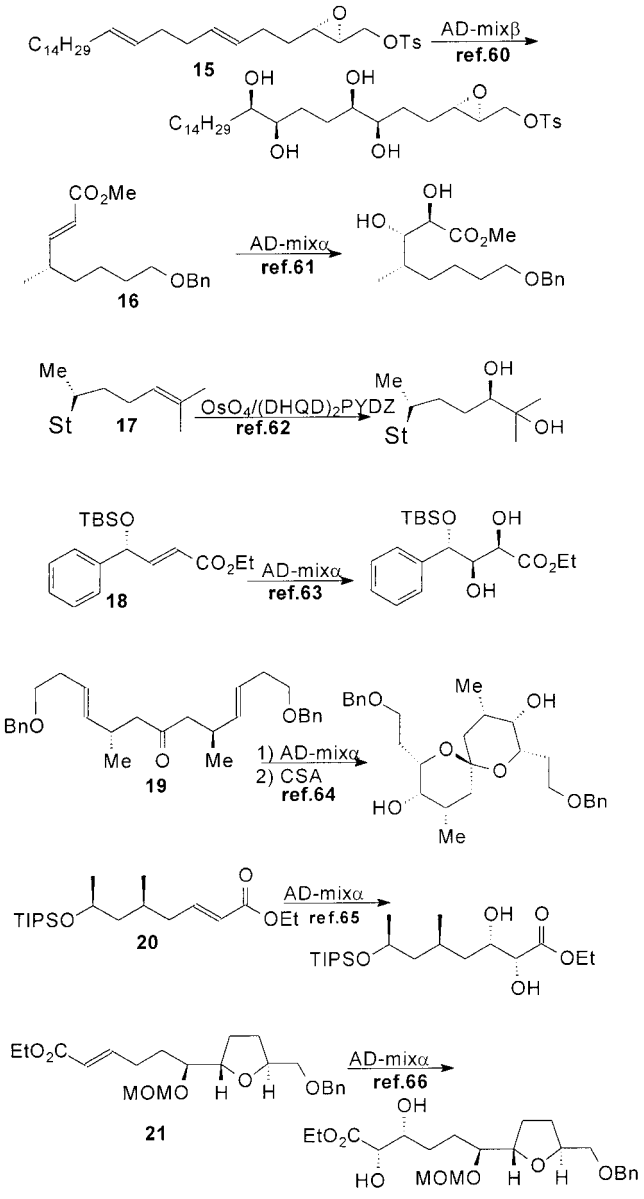
Scheme 10.

shown that the protective group tuning (N-Boc- or Bn-protected α,β-unsaturated esters) leads to optimal diastereoselection in the AD of chiral amino derivatives, with the appropriate choice of the chiral ligand.

The establishment of two hydroxyl stereogenic centres in advanced intermediates for the synthesis of important products appears to be one of the most significant applications of the AD. Some of the more recent investigations are shown in Scheme 11, where the intermediate compounds **15**–**21** are important examples[60–66] of the powerfulness of the AD reaction in order to introduce the appropriate 1,2-diol moiety at an advanced stage for the synthesis of natural products.

Quite unexpectedly, the application of the AD to the kinetic resolution of chiral racemic olefins has often given disappointing results. A remarkable exception to this trend has appeared, with the preparation of the C76 enantiomers (Scheme 12) by AD kinetic resolution:[67] the asymmetric process was able to discriminate between 30 different types of double bonds, where the osmylation occurred preferentially at one of two possible sites.

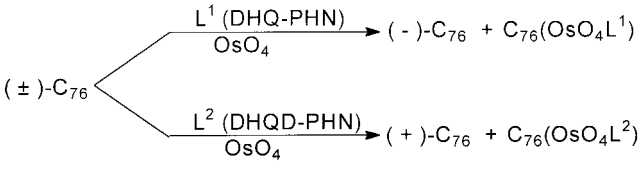
Despite the strenuous efforts by several groups, the



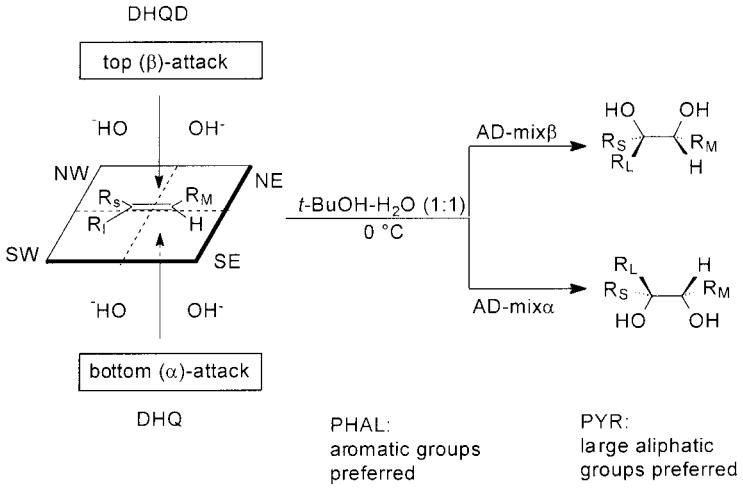
Scheme 11.

mechanism of the stereospecific transfer of the two OH groups on the double bond still retains some uncertainty, and a systematic study of all the possible explanations and mechanistic models is beyond the scope of this review. The most recent studies and models for the explanation of the AD (mainly the concerted 3+2 or stepwise hypothesis) were reviewed[3d] in 1998.

Nevertheless, the reliability of the AD process has led to empirical rules, which are able to predict the face



Scheme 12.



Scheme 13.

selectivity. In Scheme 13, a recent model[3d] for predicting the face selectivity can be found, where the plane of the olefin is divided into four quadrants with the substituents placed according to a simple set of rules. The SW quadrant appears to be of particular importance since it must be occupied by the most sterically demanding substituent, especially aromatic groups. The mnemonic device can be applied for each class of ligand (i.e. PHAL or PYR ligands). Although the predictability of the rules is easily followed, this is not always the case and exceptions have been found, especially with terminal olefins.

2.4. Asymmetric aminohydroxylation (AA) of olefins

Interest in the preparation of the β-aminoalcohol functionality in an optically active form has increased recently, because of the discovery of an increasing number of natural biologically active compounds possessing these subunits in different stereochemical relationships. Since the first report in 1996 by the Sharpless group,[5a,68] the asymmetric aminohydroxylation (AA) of olefins has rapidly became a useful process and its applicability to the synthesis of biologically active compounds has increased of late, promising to become as popular as the other asymmetric oxidative methodologies of olefins.

It must be emphasised that the contemporary addition, in enantioselective fashion, of two different groups to a carbon–carbon double bond, faces a major problem of regioselectivity, in addition to the other stereochemical problems inherent in an enantio- and stereoselective reaction.

The AA is strictly correlated to the parent asymmetric dihydroxylation reaction, since it utilizes the same alkaloid-derived ligands (Fig. 5).

The main variation, with respect to the AD reaction, is represented by the nitrogen source; after the initially utilised chloramine-T trihydrate, yielding the corresponding N-protected (*p*-toluenesulphonyl, Ts) alcohol, several improvements have been made with the use of different nitrogen sources, leading to differently protected amino alcohols (the main difficulty to overcome appears to be the deprotection of nitrogen, which in many examples can be a serious problem). Table 5 summarises the current state of the art in developing different methods for carrying out the AA, although different nitrogen sources are continuously being developed and employed. In two procedures the use of adenine-adenosine bases,[68i] or nitrogen-heterocyclic bases,[68k] with variable results in terms of regioselectivity, can be considered as a useful entry in to different classes of important pharmaceutical products.

Each of the different procedures has been tested on different types of alkenes, and a careful choice of the alkaloid ligands and the nitrogen substituent must be undertaken, in order to optimise regio- and enantioselectivity and chemical yields. The most successful ligands appear to be the $(DHQ)_2PHAL$ or $(DHQ)_2AQN$, where DHQ- and DHQD-derived ligands produce opposite enantiomers as was found for the AD.

Unsaturated compounds such as cinnamates have proved to be the most suitable substrates for a successful reaction (Table 6, entries 1–16), which was also found to be dependent on the substituents on the substrates and on the nitrogen

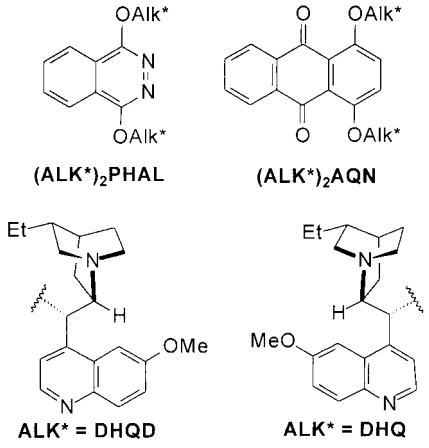


Figure 5.

Table 5. N Sources for the AA of olefins

N source (equiv.)	Solvent	Temperature (°C)	$(DHQ)_2PHAL$ (mol%)	Reference
TsNClNa (3.5)	*t*BuOH/H_2O (1:1)	rt	5	5a
MsNClNa (3)	*n*PrOH/H_2O (1:1)	rt	5	68b
CbzNClNa (3)	*n*PrOH/H_2O (1:1)	rt	5	68c
BocNClNa (3)	*n*PrOH/H_2O (2:1)	0	6	68f,69
TeoCNClNa (3)	*n*PrOH/H_2O (1:1)	rt	5	68g
AcNBrLi (1)	*n*PrOH/H_2O (1:1.5)	4	5	68d
Adenine-NClNa(3)	EtOH/H_2O (1:1)	50	6	68i
Heterocycle-NClNa (3)	EtOH/H_2O (2:1)	rt	5	68k
ClAcNBrLi (1)	*t*BuOH/ H_2O (2:3)	rt	4	68j

sources (compare entries 1–3 and 4–6). A recent application of the AA on *trans*-cinnamates, leads to the short synthesis of *trans*- and *cis*-oxazoline-5-carboxylates[69] as powerful intermediates as synthetic equivalents of α-cations.

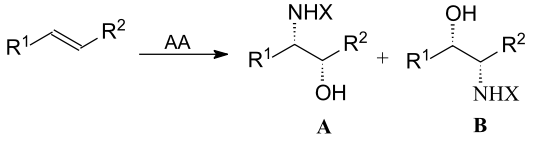
As for the AD, the best substrates are *trans* olefins, which lead to the 1,2-*syn*-aminoalcohols. Terminal olefins of aryl derivatives[70] (entries 7–9) gave variable results also depending on nitrogen sources. In all of these examples the regioselectivity favours the regioisomer A, with the nitrogen on the alkyl or aryl side of the double bond. Very recently, a modified AA procedure (with the use of 1,3-dichloro-5,5-dimethyl hydantoin as the co-oxidant)[71] was applied to several β-substituted styrene derivatives, followed by a base-mediated ring closure to give the corresponding chiral oxazolidin-2-ones. Although the results are still to be improved in terms of regio- and enantioselectivity, the procedure has been successfully applied on a large scale.

The reverse regioselectivity was first achieved with the use of the anthraquinone ligands such as $(DHQ)_2AQN$ and $(DHQD)_2AQN$ instead of the PHAL analogues on *trans* cinnamates[68h] (entry 10) although with a minor ratio (6:4–8:2). The main problem of regioselectivity control in the AA has recently been explored in two different contemporary approaches. In one report,[72] it has been elegantly shown how the reverse regioisomer B can be obtained for non-cinnamyl aryl ester substrates (entries 11–13 in Table 6): a careful choice of the aryl moiety with suitable substituents on the ring (mainly halogens) allows the corresponding β-hydroxy-α-amino acids to be obtained with good regioselectivity and reasonably good ee values. In the second report,[73] the assumed catalyst Ac-*N*-OsO_3-$(DHQD)_2PHAL$, leads to a complex control of the steric, electronic and substrate effects: the combination of all these factors, in the same sense, can greatly enhance the regio control of the reaction, as for entries 14–16 in Table 6.

The AA has also been applied recently to non-standard substrates such as β-substituted vinylphosphonates,[74] silyl enol ethers[75] and different heterocyclic conjugated olefins[75,76] (Scheme 14), with the variable regio- and enantioselectivity mainly influenced by the nitrogen source used.

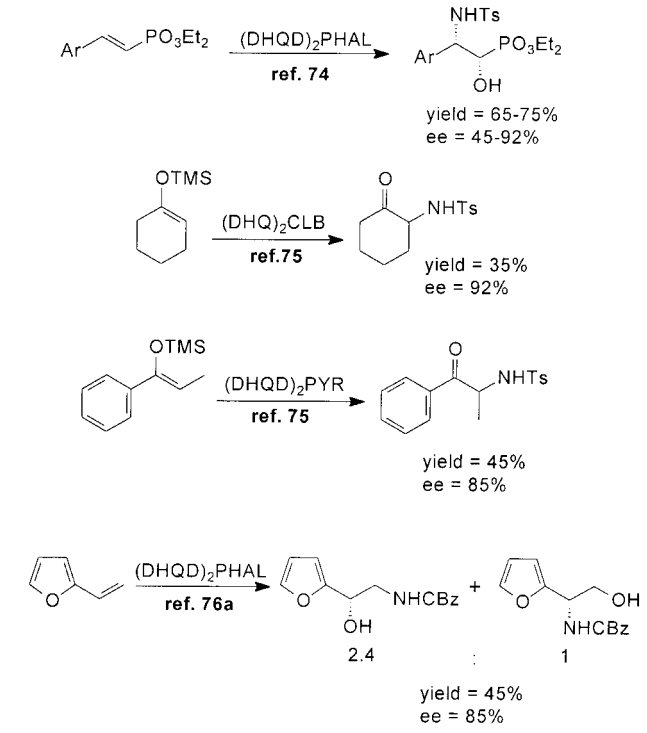
The AA reaction is already a highly valuable method for the introduction of the 1,2 aminoalcohol subunit, although further work still needs to be done to make this reaction

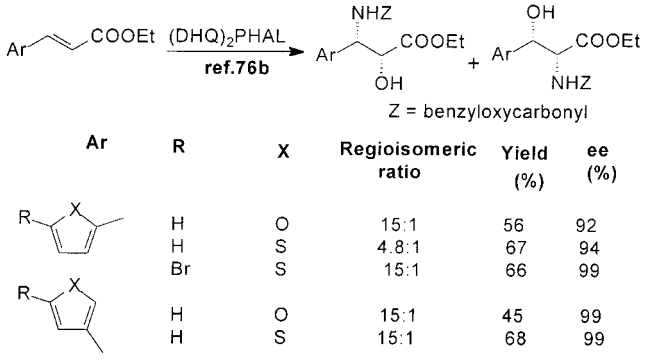
Table 6. Selected examples of AA of olefins



A **B**

Entry	R^1	R^2	X	Ligand	Major product	Yield (%)	ee (%)
1	Ph	COOMe	Ts	$(DHQ)_2PHAL$	**A**	60	82
2	Ph	COO*i*Pr	Ms or CBz	$(DHQ)_2PHAL$	**A**	65	94
3	Ph	COO*i*Pr	Ac	$(DHQ)_2PHAL$	**A**	81	99
4	Me	COO*t*Bu	CBz	$(DHQ)_2PHAL$	**A**	63	89
5	COOMe	COOMe	Ms	$(DHQ)_2PHAL$	**A**	76	95
6	H	COOMe	CBz	$(DHQ)_2PHAL$	**A**	89	84
7	Naphthyl	H	Boc	$(DHQ)_2PHAL$	**A**	70	98
8	Ph	H	CBz	$(DHQ)_2PHAL$	**A** (55:45)	40	93
9	(*p*-Ph)Ph	H	CBz	$(DHQ)_2PHAL$	**A** (91:9)	70	88
10	Ph	COOMe	CBz	$(DHQ)_2AQN$	**B**	58	95
11	*i*Pr	COO*p*BrPh	CBz	$(DHQ)_2AQN$	**B** (7:1)	60	87
12	*i*Pr	COO*p*ClPh	CBz	$(DHQ)_2AQN$	**B** (5:1)	58	89
13	*i*Pr	COO*p*FPh	CBz	$(DHQ)_2AQN$	**B** (3:1)	59	96
14	CH_2-OBz-*p*OMe	COOEt	Ac	$(DHQD)_2PHAL$	**A** (20:1)	79	95
15	CH_2-OTBDPS	COO-2-naphtyl	Ac	$(DHQD)_2PHAL$	**B** (17:1)	63	92
16	CH_2-OTBDPS	CH_2-O-2-naphtoyl	Ac	$(DHQD)_2PHAL$	**B** (20:1)	83	95





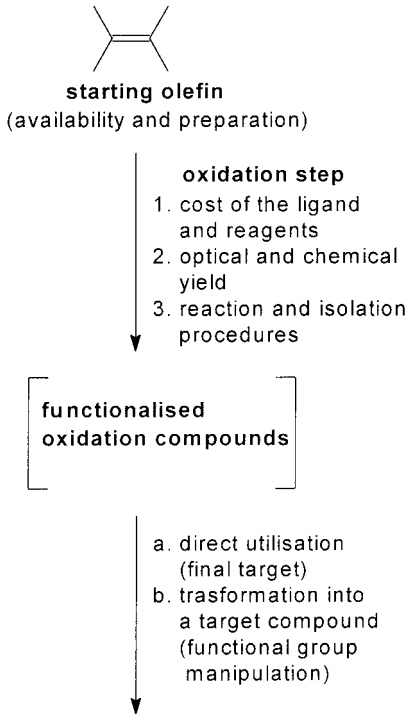
Ar	R	X	Regioisomeric ratio	Yield (%)	ee (%)
R, X	H	O	15:1	56	92
	H	S	4.8:1	67	94
	Br	S	15:1	66	99
R, X	H	O	15:1	45	99
	H	S	15:1	68	99

Scheme 14.

of broader applicability and reliability as for other oxidative procedures and more experiments and results are therefore expected in the near future.

3. Comparison of the most used asymmetric oxidative methodologies

Some of the earliest discovered asymmetric oxidative methodologies of olefins have become very popular in organic synthesis such as the AE of allylic alcohols and the AD. The Salen-AE of unfunctionalised olefins has also been used to prepare optically active epoxides, although not as extensively as the AE of allylic alcohols and the AD. The promising and latest AA of olefins, has been applied very recently to the preparation of 1,2-aminoalcohols, which is a known important functionality present in several natural biologically active compounds. A comparison of the most used methodologies, of their utilisation, restriction and transformation to other functionalised compounds follows in this section. This comparison would be helpful for the



Scheme 15.

proper choice of an oxidation asymmetric methodology as has been summarized in Scheme 15.

3.1. Preparation, availability and cost of the ligands

The discovery of novel ligands for the enantioselective induction has been one of the major achievements in organic synthesis in the last decades. From a practical point of view, the ligands must be successful in the asymmetric induction, but their availability (possibly as natural products or derivatives) or preparation in standard conditions on a large scale is also required; some of the most useful ligands can now be found in chemical catalogues and therefore the cost of a ligand becomes an important factor for their use in organic synthesis. Fortunately many of the oxidative reactions described above can also be performed in a catalytic version, allowing a reduction in the cost of the ligands, which are generally expensive. Another possibility to explore is the use of supported ligand catalysts, which allow a better, cleaner and recyclable use of the catalysts, while the performance of the reaction remains comparatively the same. All these factors are of great importance in the decision whether to use one or another route to the same final chiral molecule especially on a large scale.

The availability of the starting olefins will also be of great importance for the final decision (see discussion in Section 3.3).

In Table 7, a list of all the ligands available in a particular chemical catalogue, with their comparative cost, is shown.

The discovery and optimization of the different ligands already described, makes the tartaric esters some of the more easily available in both enantiomeric forms for the

Table 7. Commercially available ligands with average costs

Entry	Catalyst	Quantity	Cost (US $)[a]
1	$(DHQ)_2AQN$	500 mg	33
2	$(DHQD)_2AQN$	500 mg	33
3	$(DHQ)_2PHAL$	500 mg	31
4	$(DHQD)_2PHAL$	1 g	49
5	$(DHQ)_2PYR$	250 mg	25
6	$(DHQD)_2PYR$	250 mg	25
7	AD-mix-α	10 g	13
8	AD-mix-β	10 g	13
9	D(−)-DET	5 g	14
10	L(+)-DET	25 g	9
11	D(−)-DIPT	10 g	40
12	L(+)-DIPT	25 g	14
13	(*R*,*R*)-Salen	1 g	27
14	(*S*,*S*)-Salen	1 g	26
15	(*R*,*R*)-Co(II)Salen-**ent55**	1 g	35
16	(*S*,*S*)-Co(II)Salen-**55**	1 g	39
17	(*R*,*R*)-Mn(III)Salen-**ent16**	1 g	28
18	(*S*,*S*)-Mn(III)Salen-**16**	1 g	28

[a] From the Aldrich chemical catalogue 2000-2001.

AE of allylic alcohols, although the D(−) enantiomer is more expensive than the L(+) enantiomer (see entries 9–12), but both have reasonably low prices. Additionally the discovery of the AE with the use of the tartaric ligands did not require improvements in the ligand design, since they proved to be the perfect ligand of choice for most of the AE reactions: without particular restrictions due to the ligands used. The limitation, at the beginning, of the use of the tartaric ligands in stoichiometric quantities has now been overcome with their use in catalytic amounts (see the discussion in Section 3.2).

On the contrary, the discovery of, and improvements in ligands used for the AD, and especially for the successive AA, are still continuing, and, since the early attempts with the cinchona alkaloids, many others have been prepared and tested. In Table 7, the costs of the most successful and available ligands are reported, both for the AD and for the AA (entries 1–6). It should be pointed out that the complete set of AD reagents, the *AD mix* formulation, is now commercially available (see entries 7–8). The cost of this complete set appears to be high compared to the prices of the single reagents, and the routine use of this AD-mix reagent must therefore be replaced by that of the standard ligands and conditions. Due to the high cost of the ligands (as well as the toxicity and cost of osmium sources),[77] major interest has been reported in their efficient utilisation on supports and the facile recovery of the catalysts (see the following discussion). The ligands have been now optimised and almost all classes of olefins can be dihydroxylated with good to excellent enantioselectivity by carefully choosing the appropriate ligands. The recommended ligands for each olefin class presented in Table 3, must therefore be compared with their availability and cost as listed in Table 7. This variable use of different ligands, often to be tested in the AD of particular olefins, represents a limitation of the methodology, since there is no general and widespread use of a single ligand for every class of olefins.

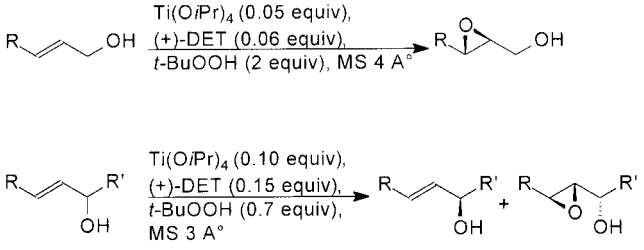
The discovery and optimisation for the Salen-AE ligands required a testing period in order to obtain the most efficient and versatile of the different ligands. The two Jacobsen catalysts **3** and **ent-3** (see Fig. 2) were shown to be the optimum catalysts in terms of availability, cost and broad application to the enantioselective oxidation of many unfunctionalised olefins. They are now commercially available as chiral ligands (Table 7, entries 13–14) and also as their Mn(III) and Co(II) complexes (entries 15–18) for use in different reactions. Alternatively, the synthesis of the required enantiomerically pure salen ligands can be carried out with optically active diamines and substituted salicylaldehydes.[78]

Improved results are also expected in the use of the ligands on both soluble and insoluble supports.[79] There have been many attempts to optimise conditions in the polymer-supported oxidative methodologies. While only little progress has been made for the supported AE of allylic alcohols,[80] more promising results have appeared recently for the AD[81] and related AA[82] processes. Interesting results have also been reported for the Salen-AE,[79d,83] although catalyst decomposition is still the major limitation of this solid-phase application. The developments in the area are continuously growing and appropriate references can be found as cited above.

3.2. Catalysis in the enantioselective oxidation

The need for catalytic processes in organic reactions has become even more important than in previous work, given the higher cost of the new complex reagents, as well as the associated environmental problems, especially with the use of toxic and polluting reagents on a large scale. The catalytic version of an asymmetric oxidation of olefins therefore appears to be particularly desirable and efforts have been made in all the processes to make these reactions truly catalytic. While the first AE procedure in 1980 was performed in a stoichiometric quantity, the other more recent oxidative processes (the AD, Salen-AE and the last AA, as well as the oxone-catalysed oxidation) were all designed and realised in a catalytic version, in order to make them immediately of high appeal for large-scale reactions.

Since its discovery, the stoichiometric version of the AE of allylic alcohols has often encountered some difficulties, especially in the isolation/purification of unstable and/or water-soluble epoxyalcohols, probably due to the mild acidity of the $Ti(OiPr)_4$ and to the tedious aqueous work-up. In 1986, it was first reported[84] that the addition of molecular sieves was able to reduce the use of the Ti–tartrate complex to only 5–10%, for the complete achievement of the epoxidation reaction. The most recommended catalytic procedure[85] utilised is reported in Scheme 16. The



Scheme 16.

Table 8. Estimate cost for asymmetric oxidation of 1 mmol of olefin

Procedure	Cost (US $)
AE (asymmetric epoxidation)	0.4
AD (asymmetric dihydroxylation)	1.9
AA (asymmetric aminohydroxylation)	5.7
Salen-AE (salen asymmetric epoxidation)	1.6

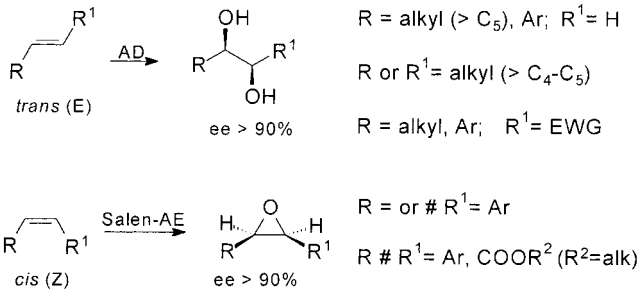
amount of the Ti–tartrate complex cannot be <5%, while the amount of tartrate to be used must be carefully controlled, since a large excess will decrease the reaction rate, and contrarily, minor amounts will result in a lower enantioselectivity. This procedure has the following advantages: (a) the total cost of the reaction, already reasonable, can be significantly cut; (b) the procedure has been applied to the preparation of unstable water-soluble compounds, with advantages in separation and purification procedures; and (c) the substrate concentration can be substantially higher (0.5–1.0 M) than the corresponding stoichiometric version (0.1–0.3 M).

The other asymmetric oxidative procedures were developed in a catalytic version, thus allowing a more economical use of the often expensive ligands and regents.

In Table 8 a comparison is presented of the estimated costs of the most utilised catalytic oxidation procedures, on the basis of the catalogue prices for the ligands, the oxidant, the solvent and all the other reagents required for a standard '1 mmol olefin' oxidation reaction. The total estimated cost does not, however, consider the availability of the starting olefins, which is not the same for every process and often requires a synthetic preparation. The estimated costs reported must therefore also be evaluated with other considerations such as substrate, time-consuming reactions, number of steps etc.

3.3. Availability and restrictions in the utilisation of the starting olefins

The commercial availability of simple olefins, being inexpensive products from the petroleum industry, is particularly widespread today: for the AD (and the more recent AA) and the Salen-AE, of simple olefins the choice of the starting material is therefore particularly broad. Care must be taken, however, with the purity of di-, tri- or tetrasubstituted olefins where the *E*/*Z* ratio is not always acceptable and must be checked before use. From a typical catalogue, hundreds of terminal olefins, as well as substituted olefins, may be found. More complex olefins can also be easily prepared by a large variety of standard reactions developed for their stereospecifc preparation.[1]

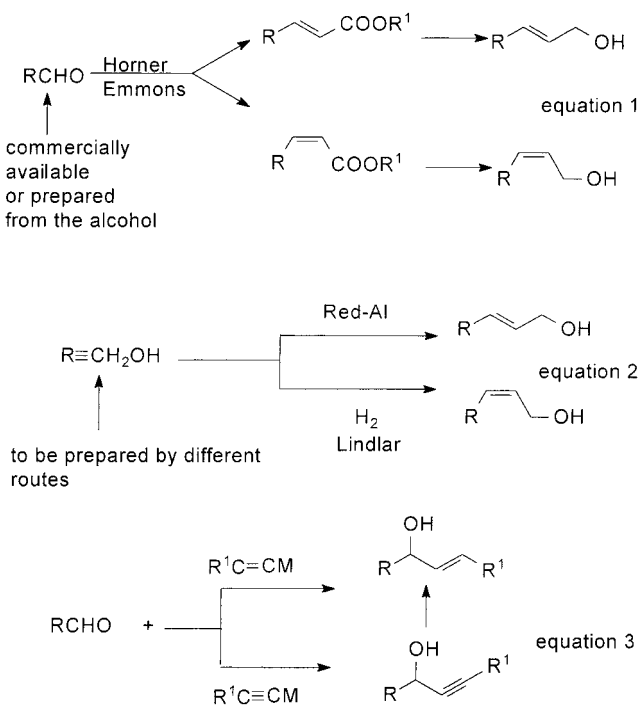


Scheme 17.

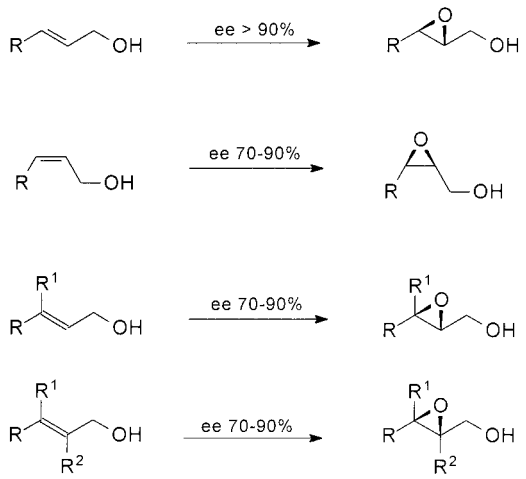
In Scheme 17, the most important types of olefins which can be oxidised by the AD or the Salen-AE are listed, together with the expected final product. The scheme highlights that the AD appears to be particularly favourable in the dihydroxylation of *trans* (*E*)-olefins, while, for the Salen-AE, *trans* (*E*)-substrates do not appear to be as good as the *cis* (*Z*)-substrates (also electron-deficient olefins), and that, for best performance, the olefin must be part of a conjugated system.

The availability of simple allylic alcohols as suitable substrates for the AE is more limited and, so far, no more than 100 of these alcohols are available from commercial sources, although several suitable precursor aldehydes may be purchased. Care must also be taken here with the stereochemical purity of *E*/*Z* allylic alcohols as well as the optical purity of allylic alcohols, which are eventually used for the AE/KR. Due to the increasing use of allylic alcohols as starting materials for the AE, many routes have been developed to various classes of these compounds (Scheme 18), the most used sequence for their preparation being:

(1) the Horner–Emmons reaction of dialkyl carboalkoxymethylene phosphonates with aldehydes to produce *trans*[86a] or *cis*[86b] α,β-unsaturated esters which, in turn, can be reduced to alcohols, (Eq. (1)) and
(2) the use of propargylic alcohols, prepared by different



Scheme 18.



Scheme 19.

routes, as precursors of both *cis*[87a] or *trans*[87b] allylic alcohols, by stereoselective reduction of the triple bond (Eq. (2)).

The preparation of the substrate for the AE/KR (the 1-substituted allylic alcohols) has frequently been achieved by simple addition of the appropriate alkenyl or alkynyl organometallic reagent to the carbonyl compound, followed by manipulation of the chiral allylic alcohol (Eq. (3)).

Some restrictions on the starting allylic alcohols must also be considered and, in Scheme 19), a range of different substrates are listed with an indication of their ability to act as a good substrate for the standard AE.

3.4. Experimental conditions

The simplicity and reproducibility of the reaction conditions have always been carefully considered by organic chemists. The main reaction conditions for the AE, the AD[88] and the Salen-AE are comparable with respect to reaction time, temperature (−20°C to rt), and concentration. The need for pure organic solvent in the AE is less stringent for the AD, the Salen-AE and the AA, where aqueous conditions can be used. No doubt, the mild oxidant for the Salen-AE (PhIO or NaOCl) appears to be superior for safety and toxicity reasons to the TBHP (AE) or to the more toxic OsO_4 (AD and AA). The quenching and work up for the AE is more tedious, although the catalytic version makes tartrate elimination easier; generally, the separation of the various components can easily be handled in a normal laboratory apparatus for all the procedures, but the Salen-AE still appears to be superior for a large-scale reaction.

The chemoselectivity represents a major advantage of the reactions. Some care must be taken, when using the AE, in the location of particular functional groups which can limit the epoxidation or lead to epoxy ring opening.[89] Noteworthy is the chemoselectivity of the AD process, and also with sulphur-containing compounds,[90] where the catalytic AD displays an interesting chemoselectivity with respect to other stoichiometric oxidative processes.

4. Manipulation and transformation of the chiral compounds obtained by asymmetric oxidative methodologies: complementary stereochemical aspects

The great success of the most popular asymmetric oxidation of olefins is due not only to the possibility of directly obtaining important chiral products (i.e. epoxides or diols), but also to the manipulation and transformation of the initially obtained compounds into a large variety of related functional groups. A flood of methods for such a transformation has therefore appeared and these are still in progress with the major emphasis being on the chemo-, regio- and stereocontrol of the transformation. Comparing the chiral products obtained by the AE, AD and the Salen-AE, the potential for transformation of these compounds seems to be linked to the possible sites of attack by the reagents. Fig. 6 summarises the possible and studied sites of transformation of the chiral starting compounds.

Exhaustive lists of transformations of epoxyalcohols (see Refs. 2b–d), 1,2-diols (see Refs. 3b–d) and simple epoxides Ref. 4c) have also been recently reviewed, and therefore in this section a summary of the most important transformations will only be reported where the appropriate references can readily be found in the previously cited reviews. A major emphasis will be given to some of the most recent methodologies (in the last 3–4 years). The aim of this section is to provide a clear perspective on the different possibilities of obtaining the same class of compounds, with special attention being paid to the stereochemical aspects of the final products. A more detailed insight into the competition of the different routes to the same compounds will be given in Section 5, where some selected examples will be reported and compared.

4.1. Transformation and utilisation of 1-epoxyalcohols

The epoxyalcohol possesses three reactive sites for its transformation (Fig. 6), namely in the carbon proximate to the hydroxyl group (C-1), and in the two carbons of the oxirane ring (C-2 and C-3), regio- and stereocontrolled reactions being essential to completely explore the potential utility of the compound. The main transformations can be catalogued as follows:[91] (a) direct substitution and/or transformation of the hydroxyl group at C-1; (b) rearrangement

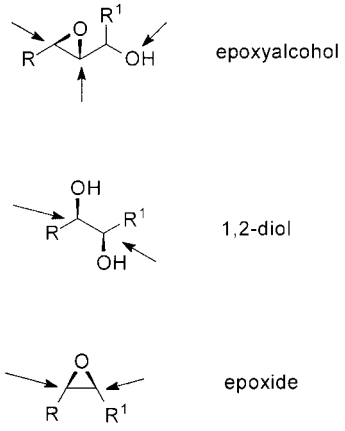


Figure 6.

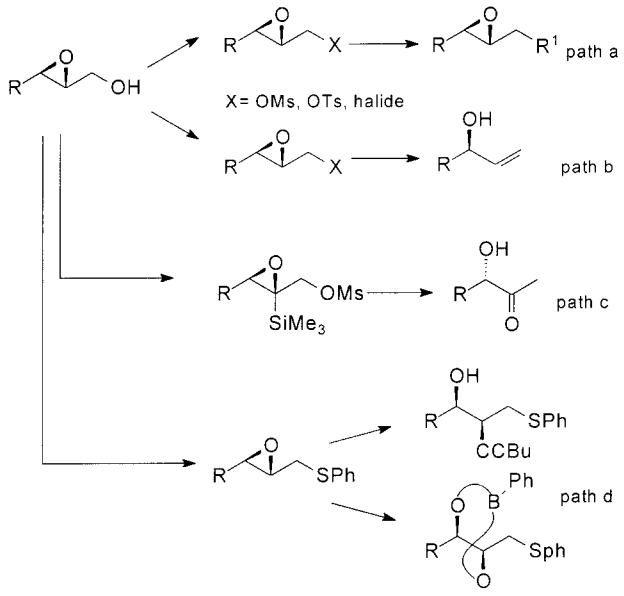
of 2,3-epoxy alcohols into 1,2-epoxyalcohols (Payne rearrangement) and subsequent regioselective substitution at C-l; and (c) oxirane ring opening at C-2 or C-3. From a synthetic point of view, the large range of possibilities for the three active sites, which could eventually lead to three stereogenic consecutive centres, makes the epoxyalcohols the most versatile compounds obtained by the oxidative olefin methodologies. Some limitations could occur in the flexibility of the stereochemical products, since the starting chiral epoxy alcohols are normally obtained by the AE of *E*-olefins.

4.1.1. Reactions at C-1 and subsequent transformations. For 2,3-epoxyalcohols, the free primary hydroxyl group can be utilised for a series of transformations. The most straightforward transformation is the activation of the primary hydroxyl group as shown in Scheme 20, and involves:

(1) transformation of the primary hydroxyl group into a leaving group and its displacement by a variety of nucleophiles leading to different non-symmetrically-disubstituted chiral epoxides. The reaction sequence is an alternative methodology to other direct epoxidations of olefins: the success of this approach is strictly related to the starting allylic alcohol availability and to the relative stereochemistry of the desired epoxides (path a) and
(2) activation of the primary hydroxyl group (normally as a halide) followed by rearrangement or transformation into allylic alcohols or secondary alcohols (path b) as an alternative to the direct preparation by reduction of carbonyl compounds or asymmetric addition to aldehydes. In recent work, particular epoxy mesylates (path c) were transformed into the corresponding α-alkoxyketones by a variety of sodium alkoxides.[92] An interesting complementary reaction (path d), affording 2,3-*syn*-diol phenylboronic esters sulfides[93a] or alkynyl hydroxy sulfides,[93b] has appeared via a double inversion of configuration at C-2, through a probable episulfonium ion, with high chemical and stereospecific control. In a recent report,[93c] by the same authors, the intramolecular substitution reaction of 1-silyloxy-2,3-epoxyalcohols, effects the C-2 opening of the oxirane, leading to a final cyclic allenylsilane, with the results variable in terms of regioselectivity and chemical yields.

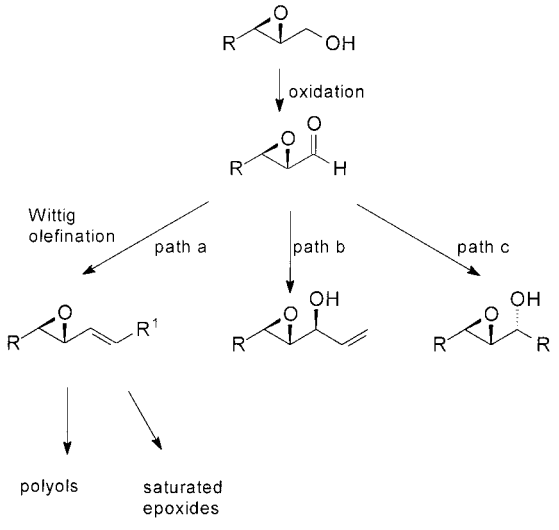
The primary hydroxyl group can also be oxidised to the corresponding carbonyl compounds, without apparent epimerisation, with standard methodologies, which have been particularly studied for such sensitive compounds.[2c] The corresponding, aldehydes (Scheme 21) can be further transformed into a series of useful chiral compounds as follows:

(1) a Wittig type olefination (path a) can lead to a variety of vinyl epoxides which can undergo a series of other useful transformations towards the synthesis of saturated epoxides, allylic or homoallylic alcohols and then to the final skipped 1,3-polyols and
(2) the addition reaction (path b) to the carbonyl group, (although the high sensitivity of the epoxyaldehydes did not allow extensive use of this important functionality) could lead to the introduction of a further asymmetric centre with fair to good results. More recently (path c) particular epoxyaldehydes have been treated with the anion of *t*-butyl acetate to afford the corresponding γ,δ,-epoxy-β-hydroxy esters with high *anti* diastereoselectivity.[94a] The use of particular experimental conditions (e.g. chelating agents) has very recently[94b] allowed the induction of a good level of *anti* selectivity in the addition of different Grignard reagents to standard epoxyaldehydes.

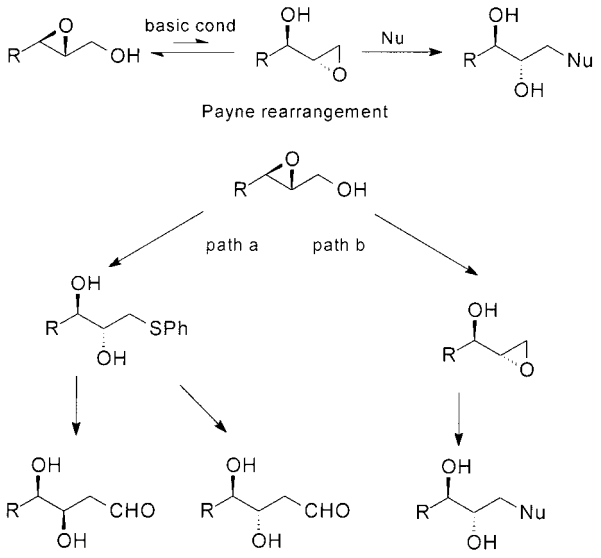


Scheme 20.

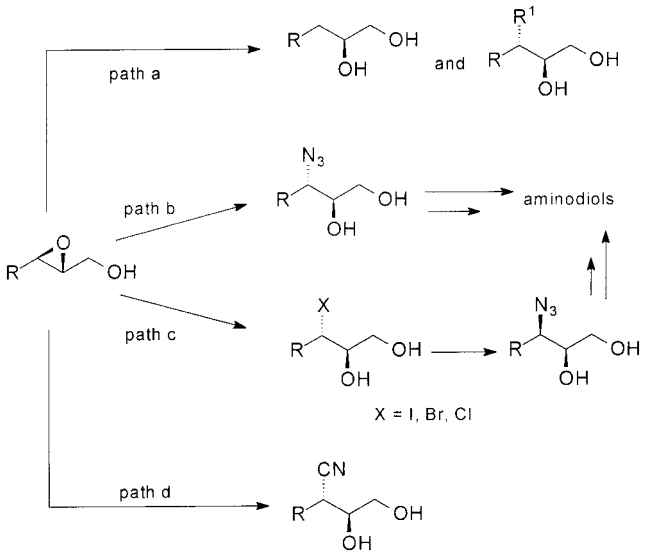
4.1.2. Regioselective substitution at C-1 by Payne rearrangement sequence. The well-known Payne rearrangement of 2,3-epoxyalcohols (Scheme 22) has become an alternative to the C-1 substitution of the epoxyalcohols, since it was possible to shift the equilibrium by introducing a proper nucleophile on the rearranged 1,2-epoxyalcohol. The sequence, which was originally developed by the Sharpless group,[13,95] leads preferentially to the 1,2-*anti*-diols with different nucleophiles (path a),



Scheme 21.



Scheme 22.



Scheme 23.

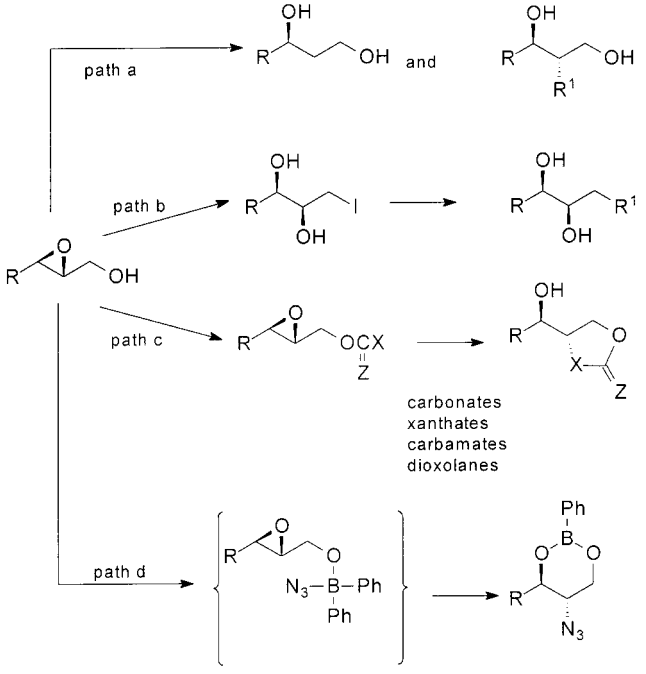
although an alternative pathway with inversion at the C-2 position has been developed, with the isolation of the intermediate 1,2-epoxyalcohols (path b).

4.1.3. Oxirane ring opening at C-2 or C-3 of epoxyalcohols and derivatives and subsequent transformations. The regio- and stereocontrol of chiral primary and secondary 2,3-epoxyalcohols has been extensively explored in recent years and a large variety of C-2 or C-3 substitutions of the oxirane ring can now be performed with high stereochemical control. Apart from eventual steric hindrance, the C-3 substitution by nucleophiles for 2,3-epoxyalcohols often appears to be more favourable for electronic effects (the presence of the C-1 hydroxyl group). The possible formation of a chelate between the hydroxyl group and the oxirane oxygen was found, after the preliminary account by Sharpless,[96] to be the most effective in enhancing the C-3 selectivity. In Scheme 23 the most useful sequences in order to obtain synthetically useful compounds are reported.

Stereodefined 1,2-diols (path a) have also been obtained very recently by several different reducing agents.[97] In addition, the corresponding 3-substituted alkyl 1,2-diols have been regio- and stereoselectively obtained with different organometallic reagents; in more recent work, the sequence affords α-silylaldehydes[98] as the final compounds. Especially important are the nitrogen nucleophilic substitutions (path b) leading to the very important *anti*-3-amino-l,2-diol moiety present in many natural products. Halogen nucleophiles can also regioselectively open the oxirane ring,[99] affording the corresponding 3-halohydrins (path c), which may be eventually transformed to the *syn*-3-amino-l,2-diols. More recently, a new procedure was developed[100] (path d), improving the previous results,[96] to selectively introduce the CN function at the C-3.

The C-2 nucleophilic substitution (Scheme 24) can now be effected with good regio- and stereocontrol. In this way, stereodefined 1,3- and 2-alkyl-1,3-diols can be obtained, while, via a stereocontrolled inter- and intramolecular opening sequence (path a), the 1-iodo-2,3-*syn*-diols can also be obtained, and eventually coupled with carbon nucleophiles to yield unsymmetrical *syn*-1,2-diols (path b).

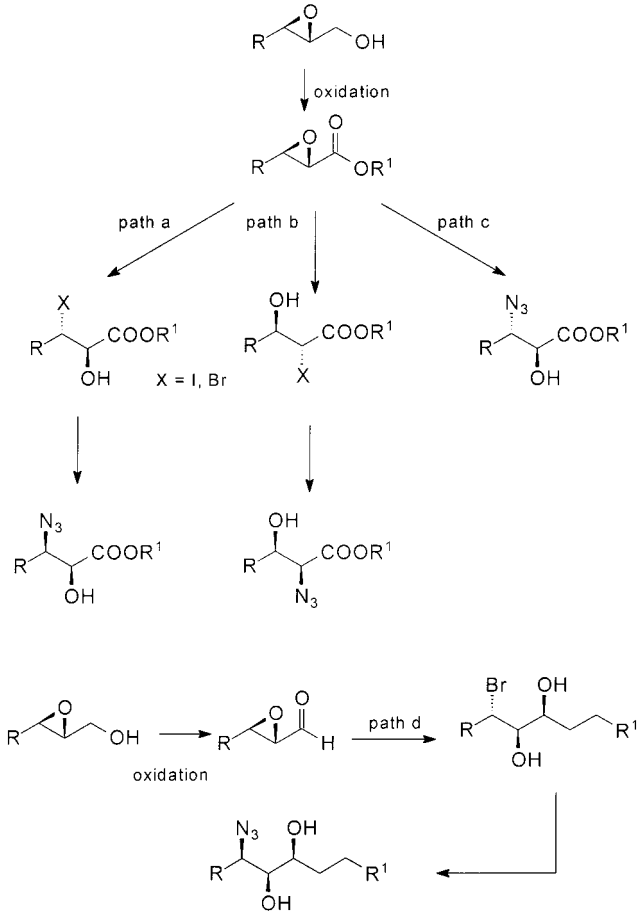
The most useful approach to the C-2 substitution can been achieved via intramolecular nucleophilic opening, by anchoring the nucleophile to the primary hydroxyl group. In this way, useful compounds such as carbamates, xanthates and carbonates can be prepared (path c), as precursors of *anti*-2-amino-, sulfide- or hydroxy-substituted diols. Recently, a highly regioselective azide opening to the C-2 position was effected (path d, Scheme 24),[101] leading to the *anti*-2-azido-1,3-diols, with good applicability to several substrates.



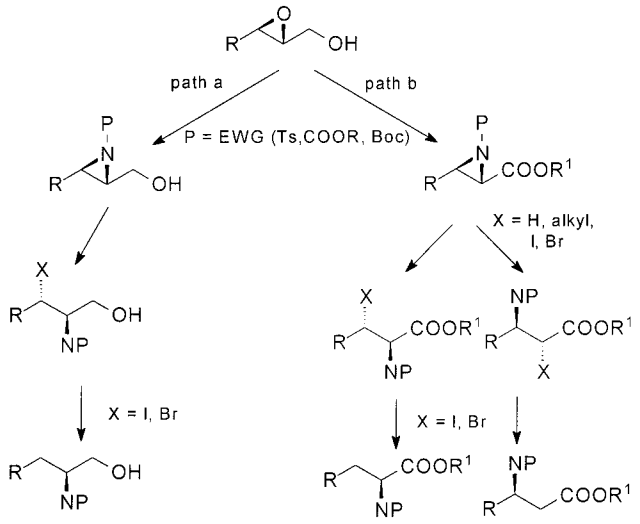
Scheme 24.

The regioselective opening by nucleophiles has also been extensively performed on different 2,3-epoxyalcohol derivatives. The easily obtained epoxy esters, can therefore be opened (Scheme 25) at the C-2 (path b) or C-3 position (path a and path c) by some nucleophiles, leading to the important classes of hydroxy acids, halo hydroxy acids, or hydroxy amino acids, with defined stereochemistry. More recently, epoxy aldehydes have been opened by halogens and then reacted with organometallic reagents (path d) affording, in a highly stereochemical fashion, 3-bromo-1,2-*syn*-diols, useful synthons for further transformations.[102] Along with these transformation, very recent findings[103] allow the regioselective C-2 or C-3 opening of epoxyacids with halogens (NaBr and NaI) and azide (NaN_3), but in water: careful pH control is needed in order to obtain the best overall yields, together with the use of *water-tolerant* Lewis acids,[103b] responsible for the C-3 regioselectivity.

The transformation of 2,3-epoxyalcohols to the corresponding 2,3-aziridino alcohols[104] or esters,[105] has opened the way to useful transformations of these interesting synthons (Scheme 26). Following the behaviour of the corresponding epoxy alcohols or esters, the aziridino alcohols have been opened at the C-3 position (path a) by hydrides and cuprates[105] and, more recently, via H_2[106] or metal halides.[99b,107a] On the other hand, aziridino esters (path b) initially opened with alkyl and heteroatom nucleophiles at C-3[106] can now be regioselectively opened at C-2 or C-3 by metal halides.[99b,107b] In conclusion, the manipulation of the chiral epoxy alcohols obtained by AE (mainly on *E*-allylic alcohols) has led to the preparation of a series of particularly attractive compounds with different functionality and defined stereochemistry.



Scheme 25.



Scheme 26.

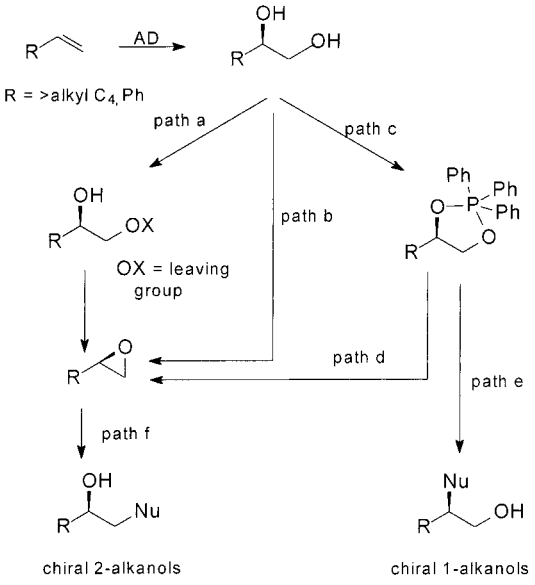
4.2. Transformation and utilisation of 1,2-diols

The 1,2-diol subunits are often the final product of a synthetic sequence, especially in the field of carbohydrates or polyols, the syntheses of which have taken on the major advantages from the AD methodology. From a strategic point of view, the 1,2-diol system can be introduced in the latest steps of the synthesis, because of the high reagent stereocontrol shown by the AD (examples of this powerful application will be reported in Section 5). This makes the AD an incomparable methodology to obtain syn-l,2-dios, over other possible methodologies and transformations.

If the *syn*-1,2-diol is not the final functionality required, manipulation of the starting chiral compound can be performed and, for this reason, the chemical transformation and manipulation of diols prepared by the AD have been the subject of several studies.

Several applications of the manipulation and transformation of 1,2-diols have been the subject of exhaustive reviews[3c,f] and, therefore, a general summary will be presented here, with the major emphasis on the final products with the proper stereochemistry and the more recently introduced methodologies.

4.2.1. Differentiation and transformation of terminal 1,2-diols. The strategy for the transformation of the 1,2-diol system requires the selective manipulation of one of the two OH groups.[3c] This clearly occurs, more easily in the presence of either a primary and secondary hydroxyl group or a secondary and tertiary hydroxyl group. As shown in Scheme 27, the easy functionalisation of the primary hydroxyl group with a good leaving group can be utilised for the preparation of chiral 1,2-epoxides (path a), a strategy which has also been utilised for the preparation of disubstituted epoxides (see below). Care must be taken,



Scheme 27.

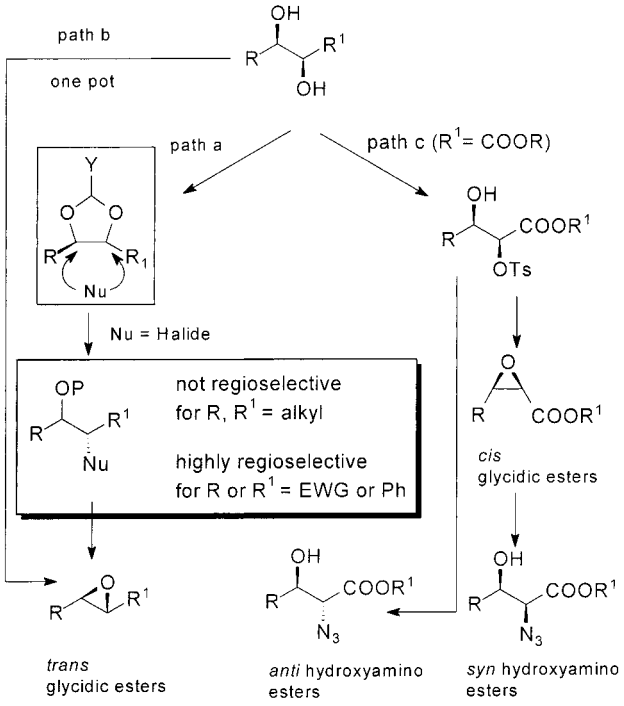
however, since a possible partial racemisation can occur. A 'one-pot' procedure for conversion of diols directly to epoxides (path b) has been also proposed, with the formation of a cyclic orthoester intermediate, its opening and subsequent base-mediated cyclisation to the epoxide ring in one reaction vessel.

The use of the intermediate halohydrins or acetoxy bromides (with AcBr and subsequent alkaline treatment), affords the chiral 1,2 epoxides by cyclodehydration of the diols (path d) via 1,3,2λ^5-dioxaphospholanes (path c), although racemisation can occur. It is noteworthy that the same intermediate derivatives can be functionalised to the secondary carbon, leading to chiral 1-alkanols (path e).

The preparation of these 1,2-epoxides can be followed by nucleophilic opening of the epoxy ring (path f), which ultimately leads to chiral 2-alkanols, if organometallic reagents are used. The overall sequence (which can be conveniently performed in a two-step procedure)[108] represents the transformation of an olefin into a variety of enantiomerically pure carbinols.

4.2.2. Differentiation and transformation of unsymmetrically substituted 1,2-diols. If the final desired compound is an epoxide, the selective manipulation of the two substituted hydroxyl groups is not relevant.[3c] This occurs for the formation of epoxides through an intermediate halohydrin or acetoxy bromide, which arise from a cyclic intermediate (Scheme 28, path a), prepared as an unstable or stable 1,3-dioxolan-2-ylium cation. Given some limitation in the direct enantioselective epoxidation of olefins with an *E* geometry (see Salen-AE utilisation), the overall sequence from the starting olefins, which can be performed in one pot (path b), represents a straightforward way to obtain important chiral compunds (i.e. *trans* glycidic esters), by two stereocenters inversions.

Similarly, *cis* glycidic esters can be obtained[3c] by mono activation of the diol, via the tosyl or *p*-nitrobenzene-

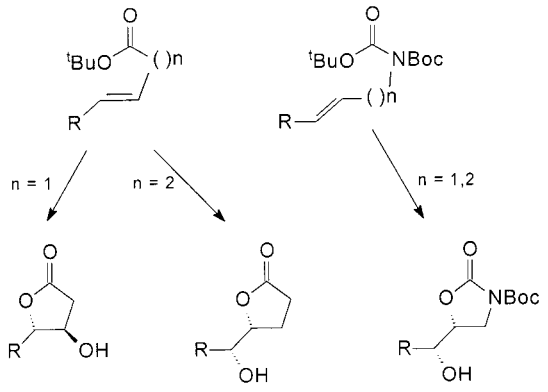


Scheme 28.

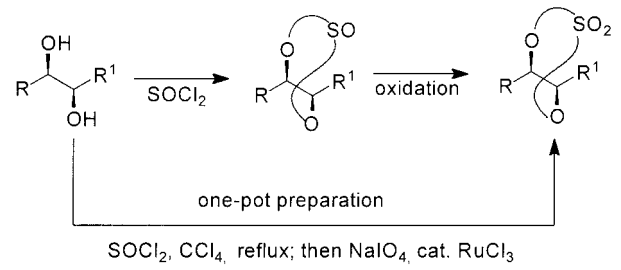
sulphonyl derivative, with one stereocenter inversion (path c). The epoxides obtained can be manipulated by regioselective opening and substitution to give other important compounds such as aminoalcohols.

If a specific halohydrin is required, the regioselective manipulation of the diols becomes decisive, but this can be performed only for a well-defined electronic differentiation of the two carbons of the 1,2-diols, i.e. when aromatic groups are present or when EWG, such as carboxylic derivatives, are proximate to one of the two hydroxyl groups (path a).

An elegant differentiation of the hydroxyl groups can be performed[3c] by intramolecular cyclisation directed by an appropriate proximal reacting group. By this approach (Scheme 29), γ-lactones and carbamates have been prepared, leading to important intermediates for the synthesis of natural products, further demonstrated in a short synthesis of (+)-laurediol.[109]



Scheme 29.



Scheme 30.

4.2.3. Differentiation and transformation of substituted 1,2-diols via cyclic sulfites and sulfates. One of the most useful transformation of the 1,2-diol moiety leads to cyclic sulfites and sulfates, which can be considered as epoxide equivalents[110] and are even more reactive. Different preparations have been studied and developed: most of them required the initial preparation of the sulfites (less utilised due to the liability at the sulfur centre and to the minor reactivity), eventually followed by the oxidation to cyclic sulfates (normally more utilised) by a variety of oxidising reagents and conditions, also depending on the acid-sensitive groups present in the molecule (Scheme 30).

The cyclic sulfur derivatives obtained can be conveniently opened, as oxiranes, by nucleophilic reagents (Scheme 31) to a sulfate monoester which now possesses an *anti* relationship between the OH and the incoming nucleophile (path a); this monosulfate ester can be subjected to a further more difficult second displacement (path b), with a final double inversion of configuration with respect to the starting 1,2-diol. Care must, however, be taken in the final hydrolysis of the sulfate monoester, since acidic conditions are normally used.

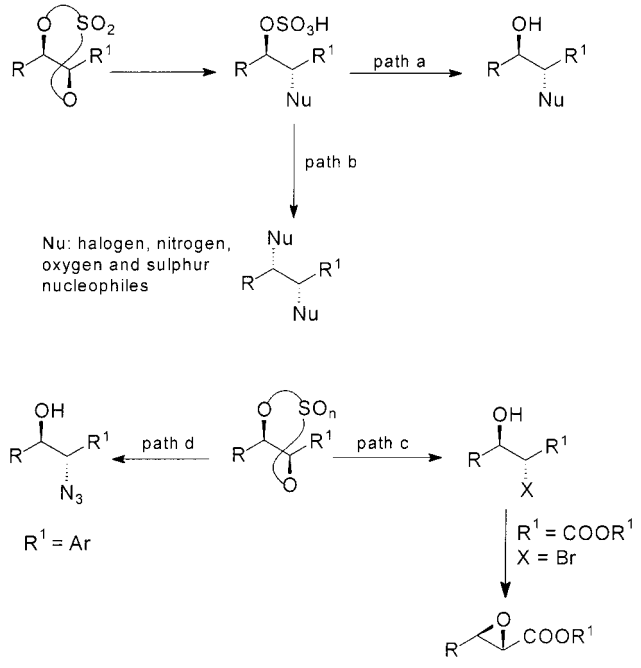
It should be noted that the regioselective opening of the cyclic sulfites and sulfates depends strictly on the unsymmetrical substitution pattern of the 1,2-diols. Many examples of the reaction have therefore been performed on symmetrically disubstituted diol derivatives, or by intramolecular nucleophilic cyclisation; the presence of a proximate electron-effecting group to one of the two carbons can help in a regioselective opening of the cyclic derivative. A recent example of a regioselective azide opening of sulfite derivative (path d), demonstrates the applicability and the limit of this transformation.[111] A new general three-step procedure[112] (path c) allows the preparation of a large variety of glycidic esters starting from the chiral dihydroxy esters, via cyclic sulfate and Br-opening followed by cyclisation to the epoxide.

To overcome this limitation, an irreversible Payne rearrangement (as described in Scheme 32, path a) has been elegantly proposed[113] for the preparation of *anti*-1,2-diols, which was utilised for the synthesis of polyhydroxylated,[113a] as well as for *cis* epoxides-containing, natural compounds.[113b] Another two related rearrangement reactions of cyclic thionocarbamates and iminocarbamates have been successively proposed by the same authors (path b), yielding *syn* β-hydroxythiol[114] and *syn*-β-hydroxy-α-amino[115a] or α-hydroxy-β-amino compounds,[115b] with variable yields and regioselectivity which were better with an aromatic substituent) still to be improved after considering the final deprotection step of the cyclic products.

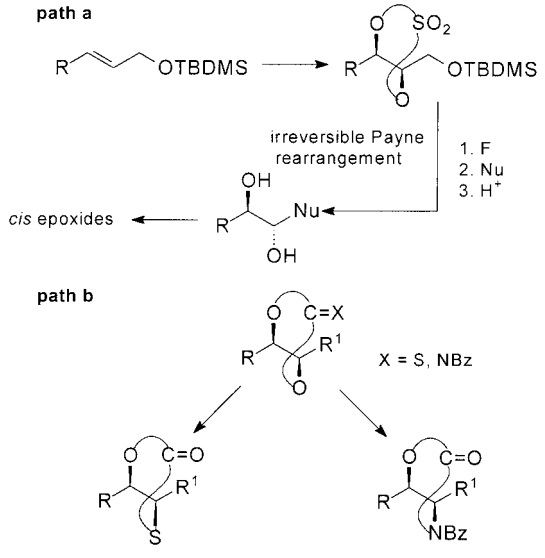
The exhaustive work in the transformation and manipulation of the enantiomericallly pure 1,2-diols obtained by the AD, makes it now possible to obtain almost all varieties of proximate functional groups.

4.3. Transformation and utilisation of simple epoxides obtained by the Salen-AE

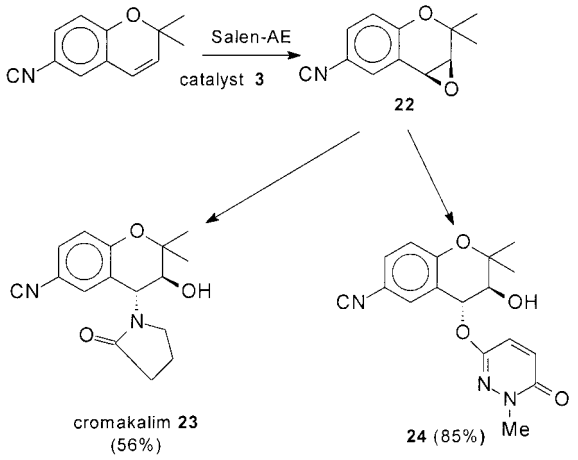
Without doubt the chiral epoxyalcohols and the 1,2-diols, described above, have demonstrated their usefulness by the number of transformations to which they have been subjected. The possible transformations of the enantio-



Scheme 31.



Scheme 32.



Scheme 33.

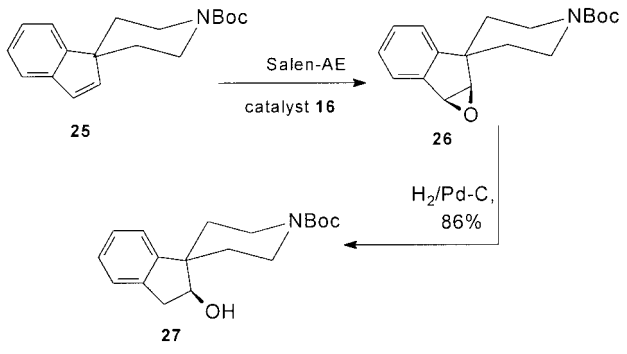
merically pure epoxides obtained by the Jacobsen–Katsuki Salen-AE protocol or by the most recent Shi procedure with chiral dioxirane derivatives have been less studied but some general considerations can be discussed.

The simple epoxides obtained directly by an enantioselective reaction, also possess two reactive sites for the opening and the manipulation of the oxirane ring (Fig. 6). In spite of these two possible reactive sites, the reactivity of the oxirane ring, if not normally located in the proximity of functional groups, appears to be more limited for regioselective reactions. So far the Salen-AE has therefore successfully been applied to the preparation of particular epoxides, with minor emphasis on the subsequent transformation.

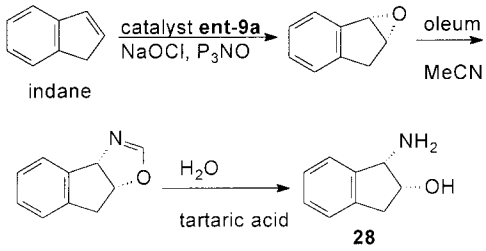
In some particular but important examples, however, a regio- and stereoselective transformation of the epoxide has been performed on other functional groups.

The remarkably high enantioselectivc epoxidation, performed via the Jacobsen catalyst, on a dimethyl chromene derivative to compound **22** (Scheme 33) was followed by regioselective opening with nitrogen and oxygen nucleophiles, leading to the efficient synthesis[116] of the antihypertensive agent cromakalim **23** and the related compound **24**.

A more recent report has described the preparation of a key



Scheme 34.



Scheme 35.

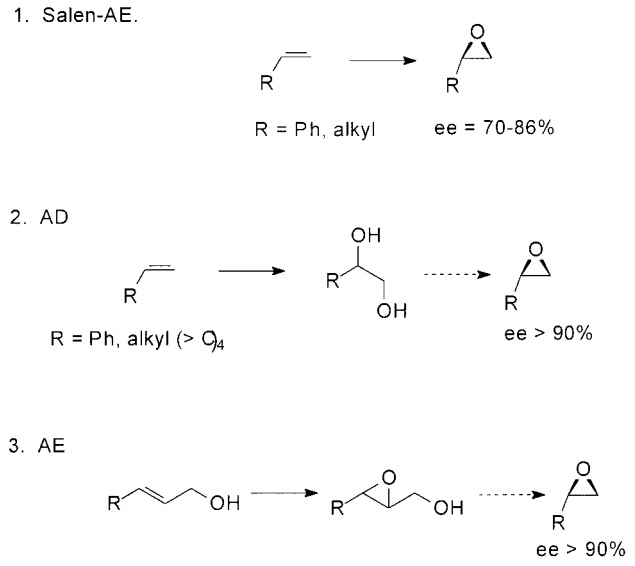
chiral compound **27** (Scheme 34) for the synthesis of a tachykinin receptor antagonist.[117] The indene analogue **25**, subjected to the Salen-AE with the Jacobsen catalyst **3**, afforded the epoxide **26** (ees up to 93%) which was then regioselectively reduced to the alcohol **27** with 86% yield.

A remarkable example of the application of the Jacobsen catalyst for Salen-AE and successive selective manipulation is represented by the Merck approach to the *cis* 1*S*,2*R*-aminoindanol **28**, which constitutes a key intermediate for the synthesis[118] of the potent HIV protease inhibitor, crixivan.[119] Scheme 35 summarises the developed sequence as reported,[120] where the inexpensive starting indene can be epoxidised on a 600 kg scale; subsequent treatment with oleum and CH_3CN afforded in a regioselective and stereoselective fashion the *cis* oxazoline, probably through a Ritter-type mechanism. The final production of the hydrolysed compound **28** represents one of the most important examples of the practical application on an industrial scale of a developed oxidative asymmetric methodology for olefins.

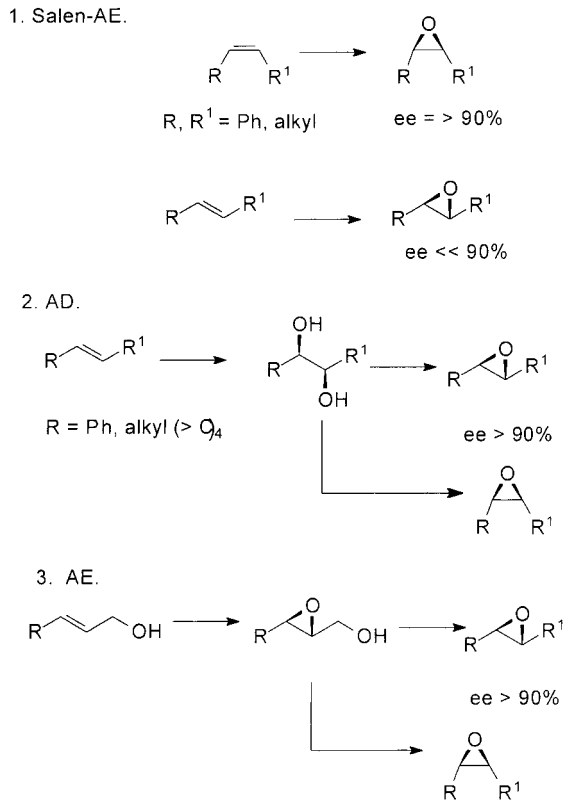
5. How to make the right choice: a comparison of selected examples of different routes to the same target

A survey of the most reliable asymmetric oxidative procedures of olefins establishes that all the described procedures give access to a wide variety of oxidative products with reasonable to good chemical yields and, in general, high enantioselectivity (ee>90%). Since many of the primary oxidative products can be transformed into functionalised compounds by selective manipulation (Section 4), an organic synthetic chemist, when planning a synthesis of target chiral compounds, could be faced with alternative routes to the final products. As described below, alternative routes have been developed to different classes of functionalised compounds, where the advantages and the disadvantages are comparable.

Apart from the direct end products such as epoxides or 1,2-diols, very important considerations must be made in order to transform the products, directly obtained in the oxidative procedure, into the final compounds, by a series of transformations which must be chemo-, regio- and stereoselective and high yielding. Hydroxyesters, aminoalcohols and aminoesters etc, which could in principle be obtained in different ways, can therefore offer an interesting case study as proof of the general improvements made in the field of asymmetric synthesis.



Scheme 36.



Scheme 37.

5.1. Chiral epoxides

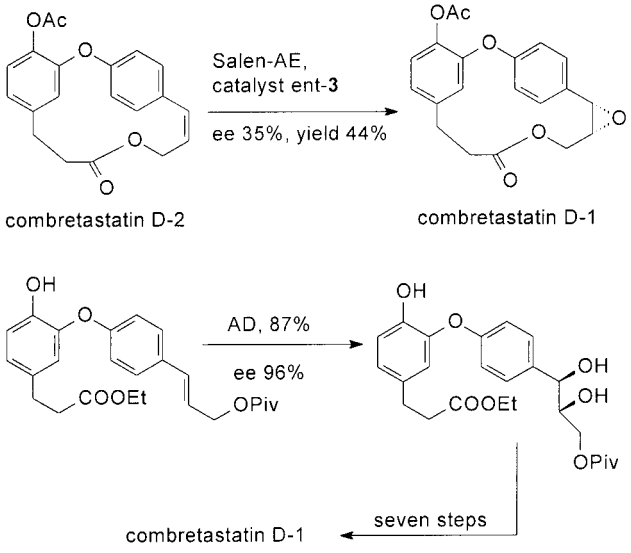
Chiral epoxides have been regarded as versatile products for their easy stereospecific ring opening reactions to form functionalised compounds (chiral building blocks). Although the epoxides are involved in the metabolism of many aliphatic and aromatic compounds in plants and living organisms, examples of epoxides as end products are rare. The most important chiral epoxides encountered are as sex attractants of Lepidopteran pests,[121] in leukotrienes[122] and as self-defensive substances against blast disease.[123]

A chiral 1,2-epoxide can be obtained by three different methods as illustrated in Scheme 36. While the most direct Salen-AE of monosubstituted olefins does not generally afford terminal epoxides with high ee, the AD route normally does proceed with high ee, although it requires a two-step sequence. In addition the AE of allylic alcohols can be followed by easy manipulation to yield terminal epoxides.

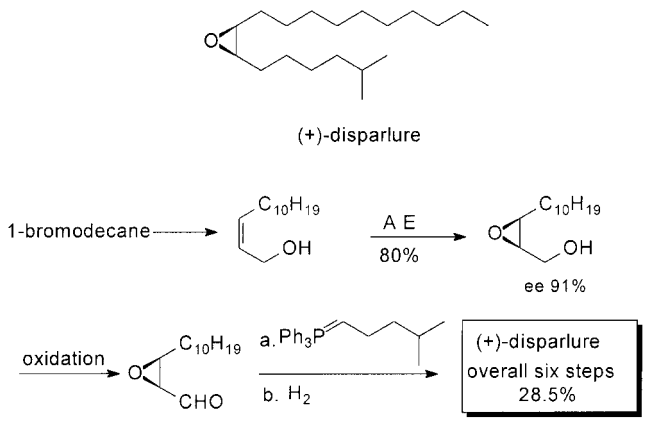
Chiral disubstituted epoxides appear to be more easily prepared (Scheme 37) and the three main possibilities are outlined. Interestingly, the Salen-AE and the AD appear complementary (*cis* or *trans* epoxides, respectively), although with the known limitation for the Salen-AE (the double bond must be conjugated), or a longer reaction sequence for the AD-mediated preparation of *trans* or *cis* (see Section 3).

The AE of allylic alcohols offers an alternative to *trans* or *cis* disubstituted epoxides starting from (*Z*) allylic alcohols. In this longer sequence, the choice of the starting epoxy alcohol, and of the second chain introduced is crucial for a competitive comparison with the other two approaches.

The different choices for the synthesis of epoxides must be carefully examined when planning a synthesis, because an apparently shorter route does not always prove to be practical. An interesting example can be examined in the synthesis of (+)-combretastatin D-l, a 15-membered macrocyclic lactone isolated from a South African tree and found to show PS cell line activity (*p*-388).[124] The structure shown in Scheme 38 possesses two chiral centers on an oxirane ring conjugated to an aromatic ring. The target compound appeared easily obtainable by the Jacobsen-catalysed Salen-AE of the corresponding natural analogue combretastatin D-2. This direct approach, however, when initially attempted,[125] afforded the desired epoxide in a modest 35% ee, although the *cis* double bond and the conjugation with an aromatic ring were found, in many cases, to be



Scheme 38.



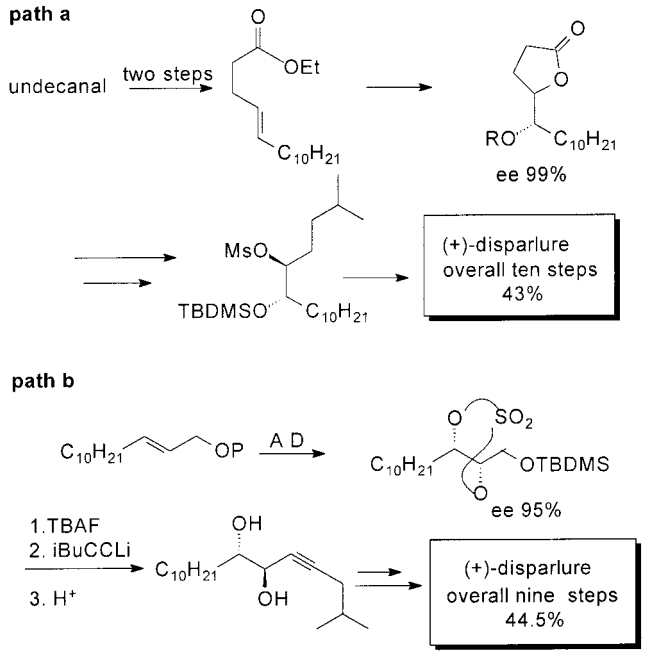
Scheme 39.

suitable for a high enantioselective epoxidation. Much better results, in terms of enantioselectivity (ee 96%), were obtained by the use of the AD methodology on the described olefin (Scheme 38), despite the subsequent tedious elaboration to the final compound.[126]

The same AD-based strategy for the installation of the epoxide moiety has very recently been successfully applied to the synthesis of cryptophycin 52,[127] and the eicosanoid, (11*R*,12*S*)-oxidoarachinonic acid.[128]

5.1.1. (+)-Disparlure and related natural epoxides. One of the most important epoxides found in nature is the sex attractant pheromone of the female gypsy moth (*Lymantria dispar* L)[129] (Scheme 39) which has become and still is a popular target of several asymmetric syntheses. Many of the approaches are based on the asymmetric epoxidation of an appropriate olefin, with the use of the AE of allylic alcohols[130] and of the AD[113b,131] of simple olefins.

It must be emphasised that the AE approach has been utilised for the industrial preparation[132] of the final compound with a short sequence (as illustrated in Scheme 39) based on the first report by Sharpless group.[130a]



Scheme 40.

Other unsaturated epoxides have recently been prepared by the AE approaches[133] but the number of steps and the overall yield do not appear to be competitive.

The AD methodology requires the selective manipulation of the obtained 1,2-diol (Scheme 40), which was achieved in two different ways by the Sharpless group (path a)[131] and by Ko et al. (path b).[113b] An alternative diol manipulation has recently been applied for the synthesis of related unsaturated epoxides.[134]

By comparison of the different routes, it appears that the first approach via the AE of the appropriate allylic alcohol, is still the most straightforward process to the title compound. The apparently more direct route by the AD approach suffers from the need to manipulate the *syn*-l,2-diol to yield the desired *cis* epoxide. On the other hand the direct Salen-AE or the oxone-based AE of an appropriate olefin have not yet been reported.

5.2. Chiral alcohols, diols and polyols

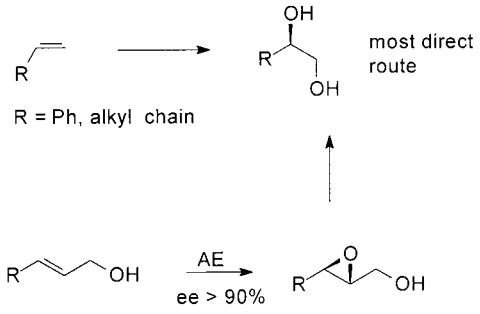
The 1,2-diol and polyol subunits, due to their presence in the structure of several biologically important compounds (natural or synthetic), have been the subject of intensive research activity for their preparation in optically active form.[135]

In principle, these subunits can be prepared (directly or via transformation) by the known asymmetric methodologies.

Sometimes the 1,2- or 1,3-diols are the final target compounds, but often the subunit is part of a large molecule, where the introduction of the stereochemically appropriate diol system can also be achieved at a certain step of the synthetic sequence (diastereoselective reaction) instead of at the beginning of the sequence (enantioselective reaction). As already stated in Section 3, the AD has revealed its enormous utility in the preparation of such 1,2-diol frameworks with a preference for (*E*) olefins to yield *syn*-(*threo*) diols.

The most simple terminal 1,2-diol can be prepared directly from a monosubstituted olefin via the AD methodology (Scheme 41). This represents a very powerful strategy, which, apparently, surpasses the other known approaches. The aliphatic chain length of a terminal olefin can, however, influence the AD enantioselectivity and good ees can be obtained more easily for alkenes with at least a C-5 or bulky chain.

This is illustrated in Scheme 42 for the preparation of the compound **29** (a chiral synthon for the synthesis of complex natural products)[135] where the more straightforward sequence (path a via AD) afforded the desired diol in ee of 65%.[136] On the other hand, by using the AE strategy (path b) the final diol could be obtained in ee>98%, although with a longer sequence which involves a developed[137] high-yielding regio- and chemoselective ring



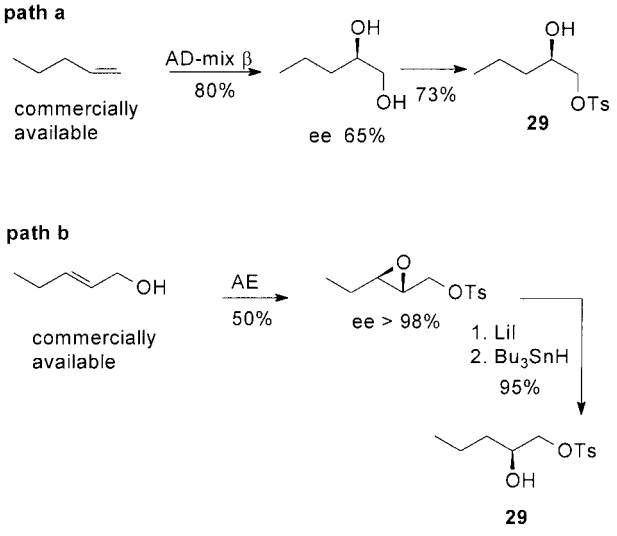
Scheme 41.

opening-reduction sequence with LiI/Amberlyst 15 and radical reduction.

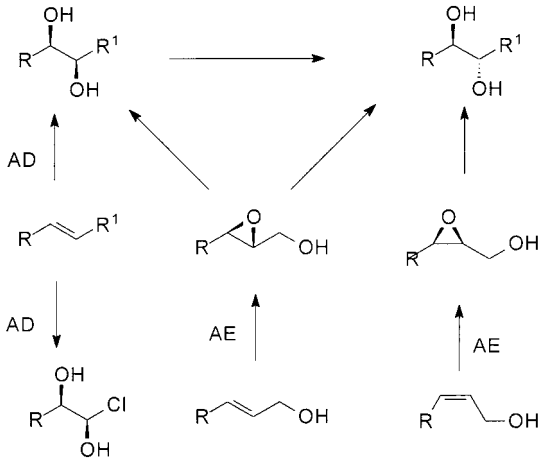
The disubstituted 1,2-diol system presents an additional problem of the relative stereochemistry (*syn* or *anti*) of the two hydroxyl groups and, in this case, the most direct way to prepare the 1,2-diol utilises (Scheme 43) the AD strategy. The longer sequence via the AE strategy may sometimes represent an alternative route, depending on the availability of the starting olefin. In this second approach the second substituent is introduced subsequent to the rearrangement reaction.

A direct efficient synthesis of the *anti* diols is not yet available and therefore the choice is between the AE and the AD strategy and relies on the Payne rearrangements (reversible or irreversible, respectively). In these two different approaches, the second R substituent is introduced in the final steps and the proper choice may be strongly influenced by the availability of the starting olefins as well as the enantioselectivity observed in the two asymmetric procedures.

Among the hundreds of complex molecule which have been prepared utilising the AE or the AD methodologies for the introduction of the proper diol chirality, of particular note is the most recent case of the Annonaceous acetogenins. In past years, there has been an explosion of activity in the



Scheme 42.



Scheme 43.

isolation (about 300 compounds), structure elucidation and synthesis of this class of compounds,[138] because of their remarkable activity as cytotoxic, antitumour, antimalarial, immunosuppressive, pesticidal and antifeedant agents. They are structurally characterised by the presence of one to three tetrahydrofuran rings at the centre of two hydrocarbon chains with one chain possessing a final butenolide moiety (Fig. 7). The stereocontrolled construction of the THF units, with both *anti* or *syn* ring junctions, still represents the major challenge in the total synthesis of this class of substance.

The required 1,2-diol subunits needed to construct the THF rings, can be prepared in different ways, but the AD has revealed its strategic importance in this field.[139]

Interestingly, the AE of allylic alcohols has been often used as a complement to the AD and, in several approaches, the AE and the AD were successfully utilised for the introduction of the correct chirality in the core centres of these interesting compounds.[140]

This simultaneous utilisation of the AE and AD[141] can be considered a further confirmation of the confidence that synthetic organic chemists have in these standard methodologies.

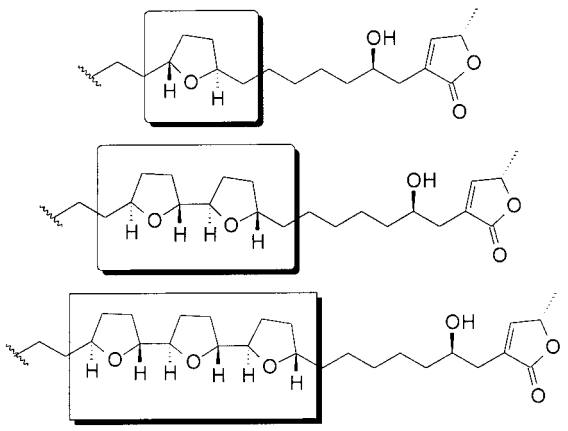
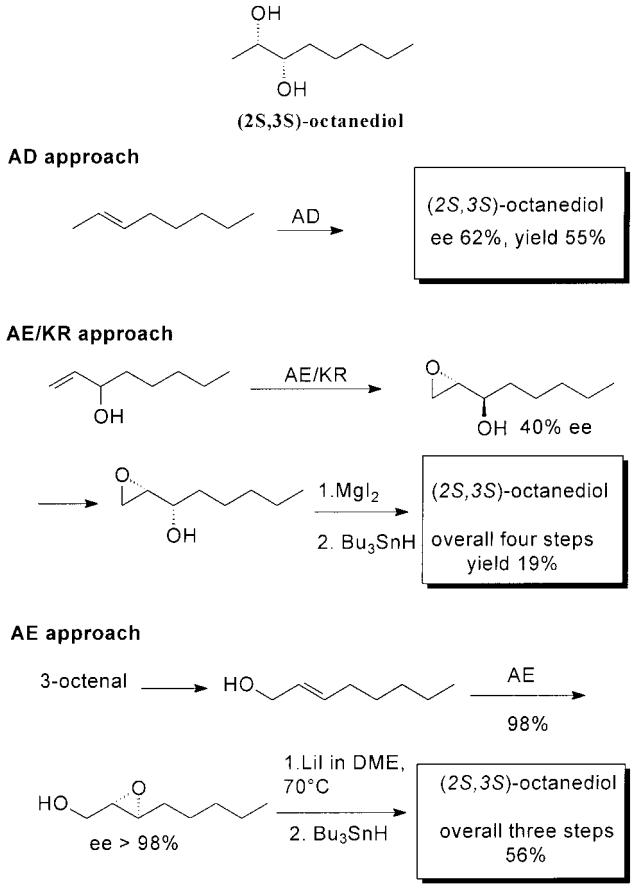


Figure 7.

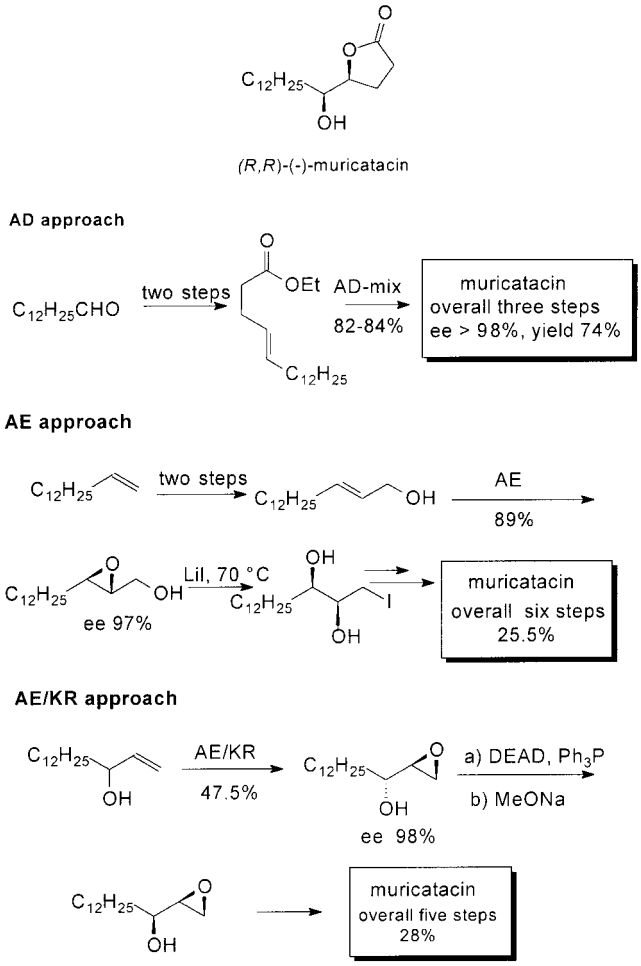


Scheme 44.

5.2.1. (2*S*,3*S*)-Octanediol. (2*S*,3*S*)-Octanediol, a well known pheromone of the grape bore *Xylotrechus pyrrhoderus*,[142] can be considered an interesting example of the apparently more simple and direct route. Application of the AD on the commercially available oct-2-ene, (Scheme 44) would be expected to directly afford the 2,3-diol, with the superior optical purity normally observed for the AD of (*E*)-disubstituted olefins, but the attempts only yielded the desired compound in a 55% yield (together with a significant amount of α-hydroxy ketone) and with an ee of 62%.[143]

Although the synthesis was more lengthy, much better results, in terms of enantioselectivity, were obtained via the AE/KR of a secondary allylic alcohol,[144] but the fair overall yield mirrored the resolution step. The use of the AE on primary allylic alcohols proved to be quite useful, coupled with the developed[145] ring-opening rearrangement of allylic alcohols with LiI to the 2,3-*syn*-diols, followed by in situ reduction. In this way, optically pure (2*S*,2*S*)-octanediol could be obtained,[146] starting from the commercially available 3-octenal, in a three-step high-yielding route.

5.2.2. (*R*,*R*)-Muricatacin. Another example of a *syn* (*threo*) diol as a natural compound is that of (*R*,*R*)- or (*S*,*S*)-muricatacin,[147] a simple acetogenin derivative (Scheme 45) isolated from the seeds of *Annona muricata* in both enantiomeric forms, the synthesis of which has attracted the attention of many groups. Among the different approaches to its synthesis, the use of the AE[146,148] and



Scheme 45.

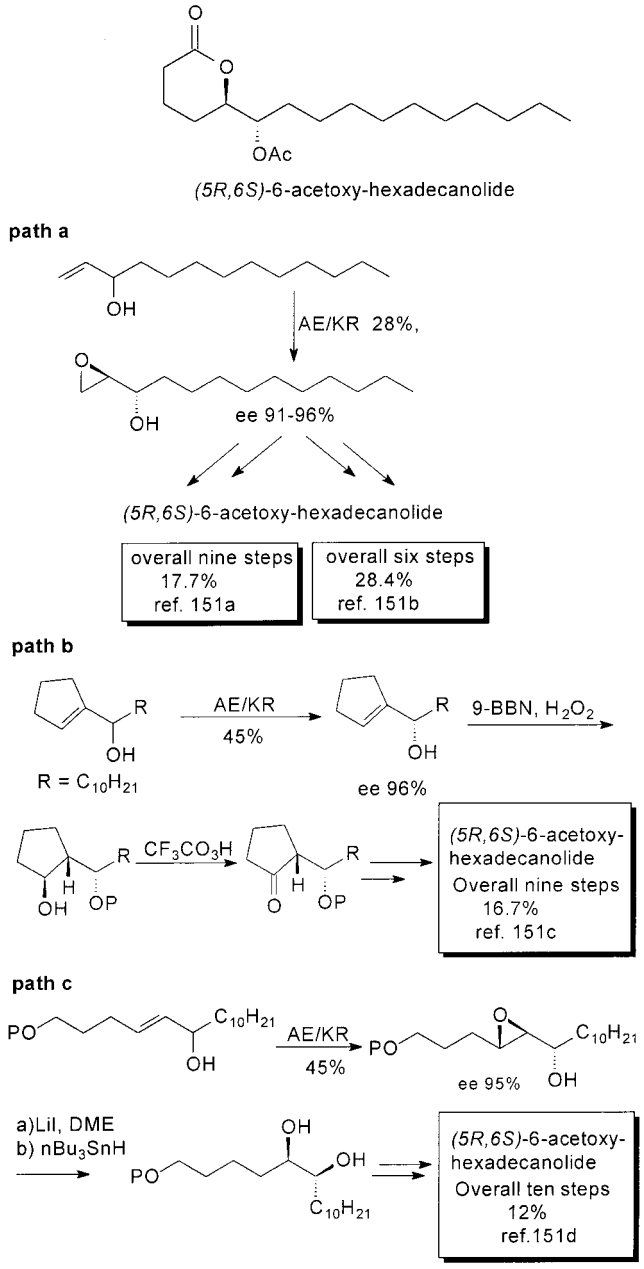
AD[149] for the introduction of the 1,2-diol unit has received much attention since the discovery of this natural product. Some of the different routes are compared in Scheme 45. The AD approach by the Sharpless group,[149a] as a general approach to γ-lactones, immediately appears to be as the most straightforward route to this compound. A more recent, similar approach by AD[149b] does not favourably compete with the route.

Some of the other most competitive approaches (Scheme 45) utilising the AE of allylic alcohols[146] or the AE/KR,[148a] do not exceed a 25–28% overall yield in five steps.

In contrast to the preparation of 2,3,-octanediol, the synthesis of the acetogenin precursor, muricatacin, possessing the 1,2-diol *syn* configuration, clearly establishes the superior advantage of the AD methodology.

5.2.3. (5*R*,6*S*)-5-Acetoxy-hexadecanolide. A popular synthetic target possessing an 1,2-diol unit with a relative *anti* (*erythro*) configuration is represented by (5*R*,6*S*)-5-acetoxy-hexadecanolide (Scheme 46), a mosquito oviposition attractant pheromone isolated from the apical droplet of eggs of the mosquito, *Culex pipiens fatigans*.[150]

In comparison with the syntheses discussed in Sections 5.2.1 and 5.2.2, the direct asymmetric introduction of the

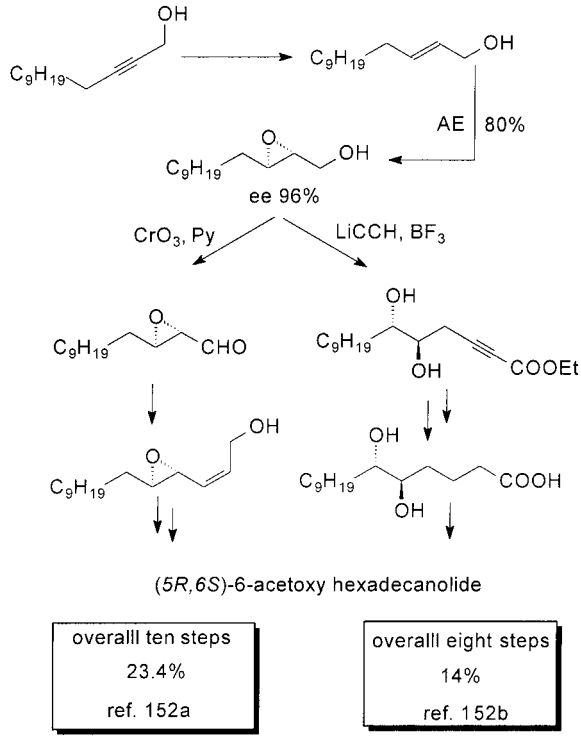


Scheme 46.

syn-1,2-diol subunit cannot be straightforward, and therefore a longer sequence is required, although the molecule appears simple. Some of the more direct approaches to the synthesis of the target compound require the AE/KR[151] or the AE[152] of allylic alcohols and, more recently,[149b] the AD of the appropriate olefin.

As shown in Scheme 46, the AE/KR was performed on different racemic allylic alcohols (to be prepared) with excellent enantioselectivity for all reactions.[151] The number of steps (six to ten) and the final overall yields were, however, not completely satisfactory, due to the key step of the racemic resolution.

The AE on the appropriate allylic alcohol[152] (Scheme 47) does not appear to significantly improve the process with respect to the AE/KR approaches.

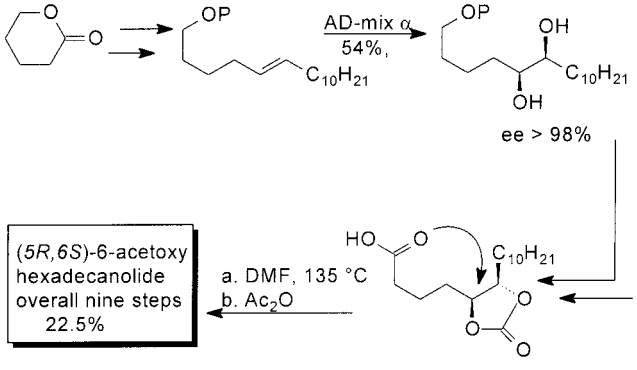


Scheme 47.

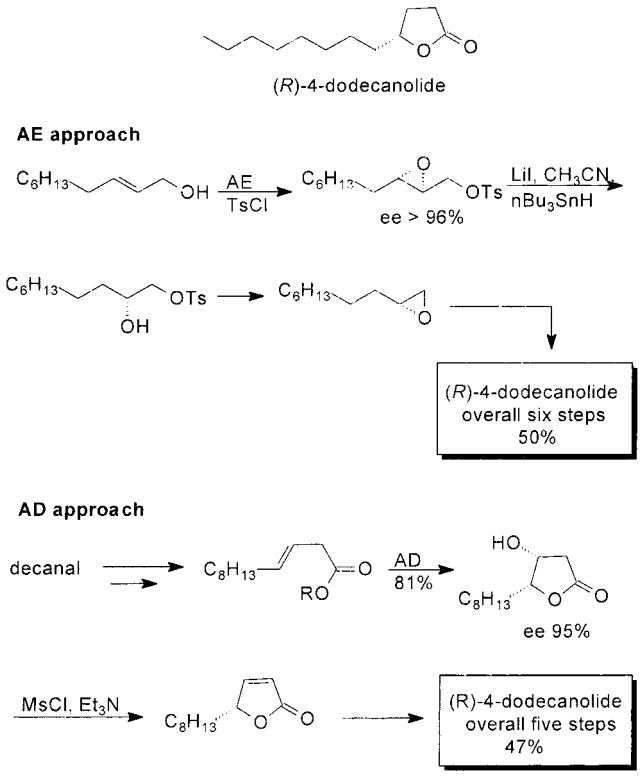
A more recent AD approach,[149b] coupled with an interesting lactonisation which allows the inversion of the configuration to the desired *anti* diol (Scheme 48) only slightly improved the overall yield to the target compound with a comparable number of steps (nine) with respect to the AE approaches.

In conclusion, this case study reveals that when direct methodology for obtaining the 1,2-diol subunit is not available, both the AE and the AD gave similar and comparable results and therefore the choice of the shortest route to the same target is largely influenced by the general strategy followed in the synthesis, and less so by the asymmetric methodology applied.

5.2.4. (4*R*)-Dodecanolide. The sacrifice of a chiral centre may be necessary for the synthesis of a particular compound, since the introduction of the proper chirality may use asymmetric methodologies with the introduction of more chiral centres than required. This was the case for



Scheme 48.



Scheme 49.

(4*R*)-dodecanolide, a defensive secretion of rove beetles.[153] The stereostructure (Scheme 49) reveals the presence of one chiral centre of a γ-lactone, but the AE and the AD approaches can be conveniently utilised, on comparable routes.

As shown in Scheme 49, the AE approach[146] utilises the opening[137] of the known epoxy tosylate, prepared in one pot from commercial decen-2-ol in 89% yield. Regioselective LiI opening was followed by radical elimination of the iodine (which could be eventually performed in one step via DIBAL),[154] and then by standard conversion to the final dodecanolide.

The more recent AD approach,[155] as part of a more general route to butenolides and γ-lactones, employs a highly enantioselective AD on an unsaturated ester, followed by the elimination of hydroxyl group and reduction of the double bond, finally leading to the target compound in 49% overall yield and five steps starting from decanal.

In the present example, where both the AE and the AD approaches gave similar results, it must be emphasised that the target compound appears not to be clearly related to structures obtained by the two asymmetric methodologies, thus implying a profound modification of the starting epoxy alcohol and 1,2-diol.

5.3. Chiral β-aminoalcohols

The β-amino alcohol subunits, since their discovery in many biologically active compounds especially as α-amino. β-hydroxy or α-hydroxy, β-amino acids,[156] have

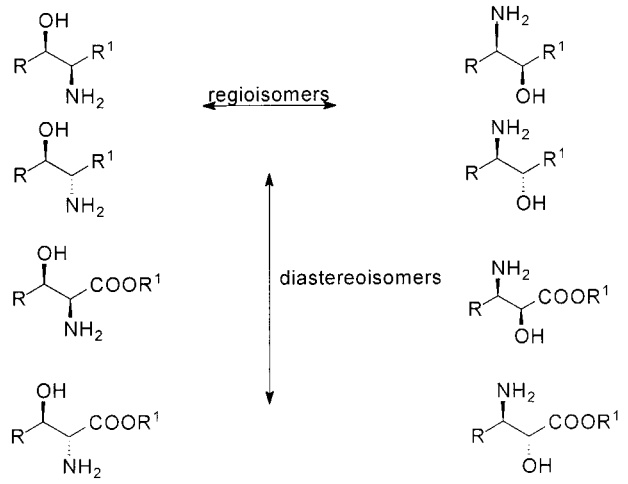
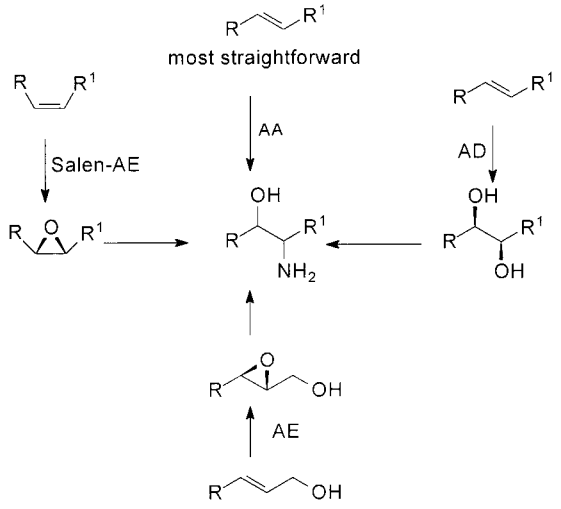


Figure 8.

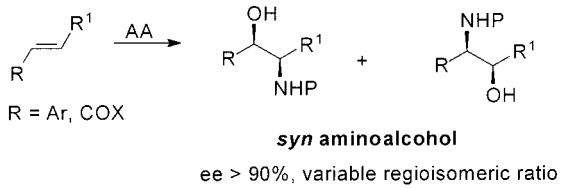
attracted the attention of synthetic chemists and several approaches to the synthesis of these units have now been developed[157]

The appropriate relative and absolute stereochemistry, which may be present in many substrates (Fig. 8), requires total stereocontrol for obtaining such subunits in optically active form. This can be performed from a suitable olefin with the asymmetric methodologies reviewed in this article, with eventual manipulation and transformation of the oxidative products as has been summarised in Scheme 50.

The recently developed AA of olefins[5] is the most straightforward route to obtain the chiral β-aminoalcohol moiety (Scheme 51): there are, however, still some limitations in the use of this methodology, especially in the regioselectivity of the reaction as well as in the starting olefin, where the substrate of choice is often limited to *trans*-conjugated disubstituted olefins. Care must be taken in the deprotection of the nitrogen group, where the choice of the P group can influence the enantioselectivity of the reaction. Good results can be obtained, in some cases, as illustrated by some examples of recent applications to amino



Scheme 50.



Scheme 51.

cyclitols,[158] amino acids of the vancomycin skeleton[159] and 2,3-diaminobutanoic acids,[160] where *syn*(*threo*) aminodiols are easily obtained in high ee and reasonable chemical yields.

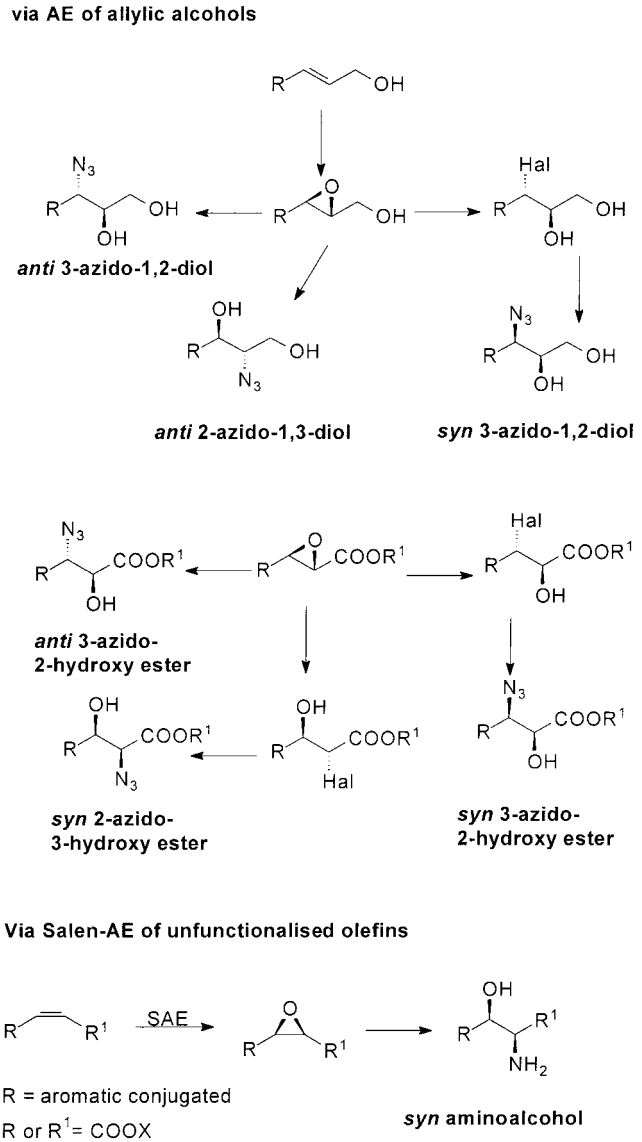
The Salen-AE (Scheme 52) followed by nitrogen opening of the epoxide, also appears to be suitable for this purpose. In this methodology, however, the limitations in the olefinic substrate (*cis* conjugated olefins) and in the regioselective opening of the epoxide with nitrogen nucleophiles still confine the approach to a small number of substrates. In this example, as for the AA, the *syn* (*threo*) β-aminoalcohol subunits are obtained.

The older AE of allylic alcohols has been widely utilised for the introduction of the β-aminoalcohol moiety (Scheme 52). In spite of the number of steps required for the transformation of the starting chiral epoxyalcohols to the final aminoalcohols, this approach frequently gives access to a large variety of possible regio- and diastereoisomers, with more flexibility than the direct AA and Salen-AE. The introduction of the nitrogen substituents (i.e. azido), if carried out on different 2,3-epoxyalcohols, normally gives rise to *anti* 3-azido-l,2-diols,[161] with high levels of regio-and stereoselectivity or, in a few cases to *anti* 2-azido-l,3-diols.[101,162] On the contrary, the regioselective opening with metal halides[163] and subsequent replacement of the halogen by azide could give access to *syn* 3-azido-1,2-diols.

Starting from the corresponding 2,3-epoxy esters, regioselective opening directly affords the *anti* 3-azido-2-hydroxy esters,[162] while regioselective opening with halides, followed by stereoselective replacement by azide, affords the *syn* 3-azido-2-hydroxy esters[163] and the *syn* 2-azido-3-hydroxy esters[164] with virtually all types of R substituents. Very recently, the C-3 BF_3–OEt_2 catalysed regioselective opening of non-aromatic glycidic esters or amides, has been reported[165] to afford the corresponding 2-oxazolines in mild conditions and good yields, which can be hydrolysed into the β-amino, α-hydroxy esters or amides.

The appropriate choice of the starting substrate, as well as the reaction conditions, can be therefore quite helpful for a correct strategy to achieve the synthetic goal, utilising the 2,3-epoxyalcohols as chiral synthons.

The AD approach also requires several steps to yield hydroxy amino subunits. The obtained *syn* 2,3-diol ester can firstly be transformed (Scheme 53) to the cyclic sulfate and then conveniently opened by N_3 with high regioselectivity for aromatic R groups and lower for alkyl R moiety to afford, finally,[3c,110] the *anti* 2-amino-3-hydroxy

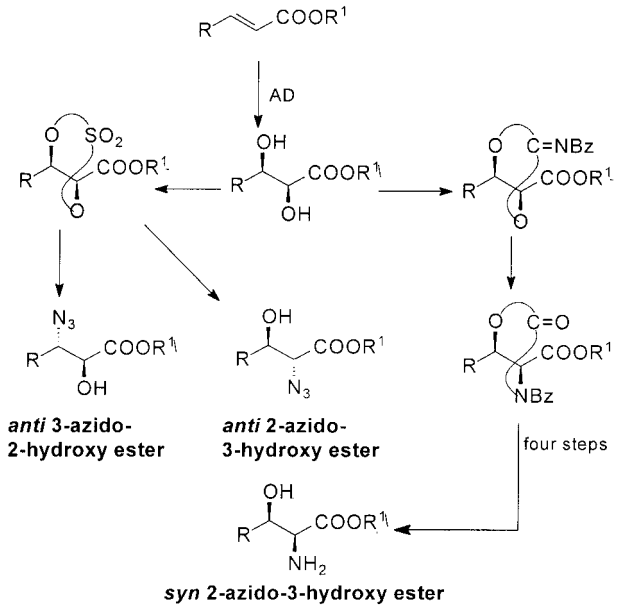


Scheme 52.

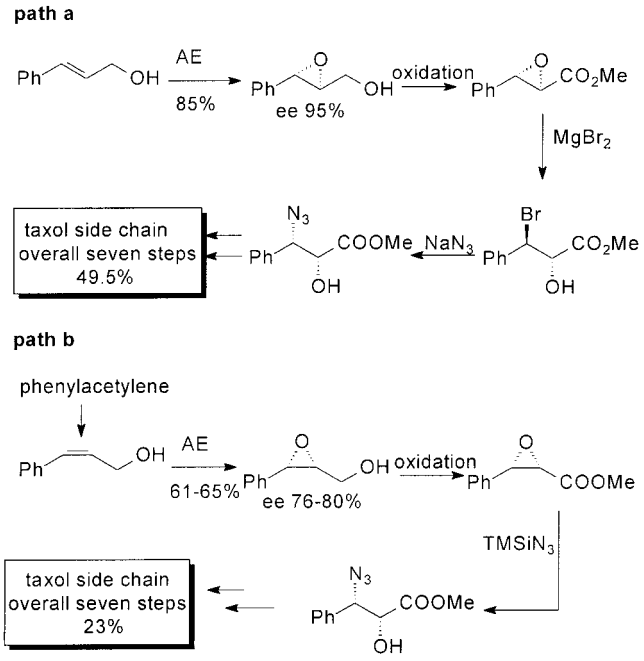
ester or the *anti* 3-amino-2-hydroxy ester: the corresponding *syn* 2-amino-3-hydroxy ester can be produced by a more recent procedure[114] using an internal process which allows the conversion of the starting *syn* diol to the final *syn* amino hydroxy ester, although the regioselectivity of the rearrangement is strongly dependent on the substituents.

As clearly demonstrated the β-aminoalcohol unit represents a unique case of complementarity and competition of the most common asymmetric oxidative methodologies, and their applications in many significant examples of biologically active compounds will be illustrated below.

5.3.1. Taxol side chain. Since the discovery of the essential importance of the C-13 side chain of the taxol family for the antitumour activity,[166] the synthesis of the (2*R*,3*S*)-3-phenylisoserine (Fig. 9) has become of great interest not only for academic research but also for industrial-scale production.[167] All of the asymmetric oxidative methodologies of olefins described in this review have been



Scheme 53.



Scheme 54.

employed for the synthesis of this important target, thus demonstrating an interesting and useful example of the development of and progress in the asymmetric synthesis.

The application of the AE approach[163b,168] (Scheme 54, path a) on the (*E*) cinnamyl alcohol was followed by standard oxidation to the epoxy ester: the elaboration to the final *syn* aminoalcohol was performed via a highly regioselective opening[163b] of the epoxy ring with $MgBr_2$, subsequent halide replacement by azide and final reduction and protection of the benzoyl amine. Although the overall yield is acceptable (49.5%), the number of steps (seven) from commercially available (*E*) cinnamyl alcohol is high. A similar route[169] via AE of the (*Z*) cinnamyl alcohol (Scheme 54, path b), suffered from a predictably low (76–80%) ee.

Almost the same results, in terms of chemical and optical yields were obtained using the approach via Salen-AE, with the Jacobsen catalyst, on the *cis* ethyl cinnamate[170] and subsequent elaboration to the final product (Scheme 55).

The AD was consecutively used in three different approaches[171] on *trans*-methylcinnamate (Scheme 56) with varying results in terms of enantioselectivity (good in path a[171c] but, after recrystallisation, better in path b[171a] and in path c[171b]). The different elaboration yielded the common intermediate azidoalcohol, which was then transformed into the final product. The total numbers of steps were comparable while the overall chemical yields reflect different yields in common transformations (i.e. from the azidoalcohol). It must be noted that, while path b[171a] gave the higher overall yields in less steps, path c[171c] was performed on a scale (2 mol) which makes the route suitable for large-scale production. A comparison of the AD approaches with the previously described AE and Salen-AE approaches does not make it possible to highlight any significantly superiority of one route over another.

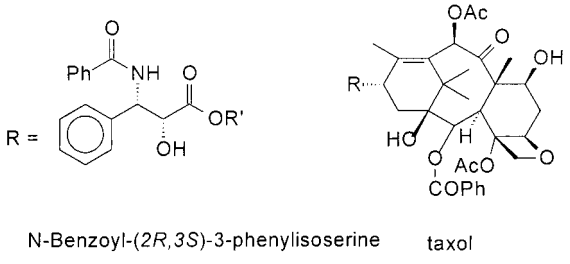
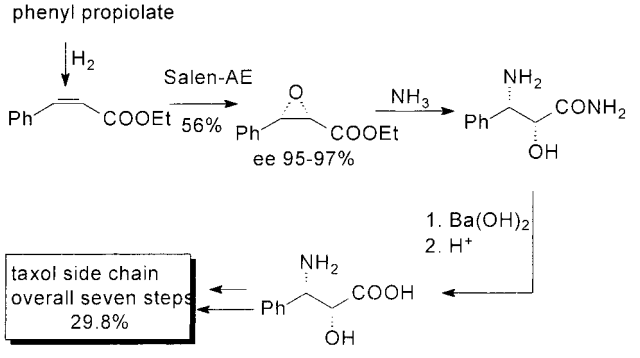
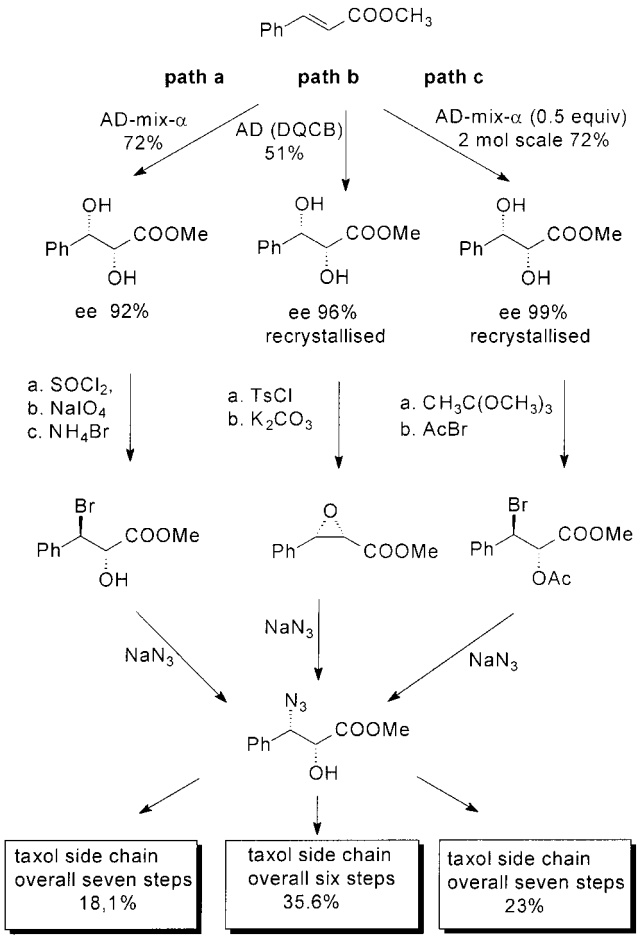


Figure 9.

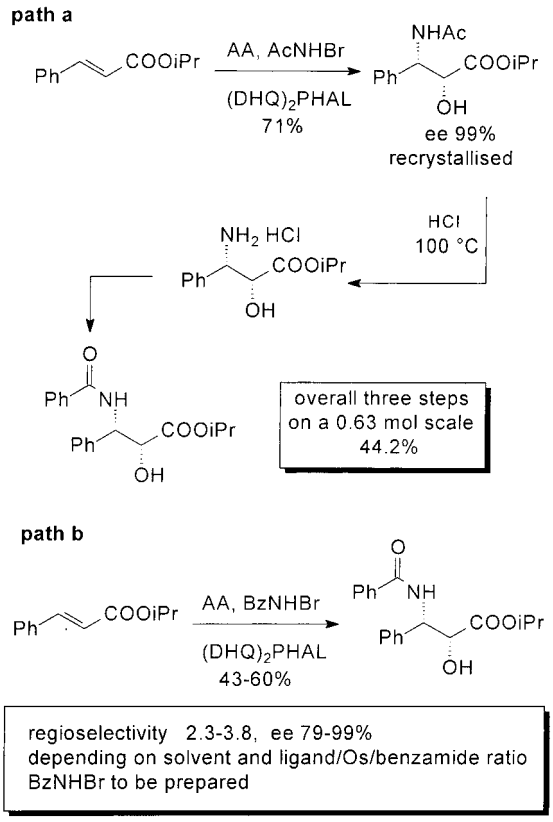
On the contrary, the application of the most recent AA (Scheme 57) to the *trans*-isopropyl cinnamate (prepared from the commercially available cinnamic acid) proved to be superior to all the preceding procedures. Two similar successive approaches[68a,d] by the Sharpless group, led to an outstanding three-step procedure (path a) on a large scale (0.63 mol),[172] with the final compound in 44% yield from cinnamate and ee>99% (although after recrystallisation of the oxidation product). In addition a recent modified procedure[173] using *N*-bromobenzamide (to be



Scheme 55.



Scheme 56.



Scheme 57.

prepared) as the nitrogen source (path b), directly afforded the protected palitaxel side chain, in a 46% one-step synthesis, although the regio- and enantioselectivity were markedly dependent on different parameters such as solvent, ligand ratio etc.

This described case study clearly demonstrates that, for particularly favourable substrates like cinnamates or their derivatives, the recently developed AA appears to be the most advantageous for the introduction, with acceptable regioselectivity, of the β-amino, α-alcohol function, with shorter procedure and high yields.

5.3.2. (2*R*,3*S*)-3-Hydroxyleucine. 3-Hydroxyleucine has attracted considerable interest as a constituent in naturally occurring peptide antibiotics in both 2*S*,3*S* and 2*S*,3*R* diastereomeric forms.[174] More recently, the 2*R*,3*S* isomer has also been isolated in the (+)-lactacystin, a metabolite which exhibits significant neurotrophic activity (Fig. 10). The synthesis of these optically active constituents has therefore attracted much attention.[175]

Attention is focused here on the 2*R*,3*S* diastereoisomer,[176] which can be prepared by different asymmetric oxidative methodologies.

The older application of the AE/KR resolution of the racemic allylic alcohol (Scheme 58),[177] although the number or steps (seven) and the overall yield (22.4%) and ee (93%) were acceptable, suffered from an extensive reaction time for the AE/KR (several days).

Two other approaches[174b,178] started with the AE of (*E*)-4-methyl-2-penten-1-ol (Scheme 59) to its known epoxy-alcohol (ee 95%): one route (path a)[174b] employed the isocyanate-induced epoxide opening with saponification and epimerisation of the free acid to afford the final compound in nine steps, and 22.4% yield. The other route (path b)[178] employed the regioselective halide opening of the epoxy ester, followed by the nucleophilic displacement of the iodine to effect both nitrogen insertion and inversion of the configuration, to afford the final compound in eight steps and, curiously, with the same 22.4% overall yield reported for all the AE or AE/KR approaches.

The more recently reported AD and AA approaches reveal the possibility of drastically reducing the number of steps to obtain the desired aminohydroxy ester.

The AD route (Scheme 60) toward the total synthesis of

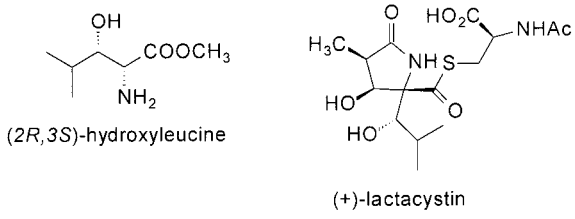
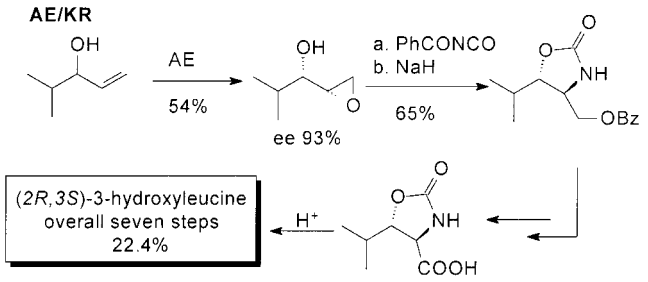


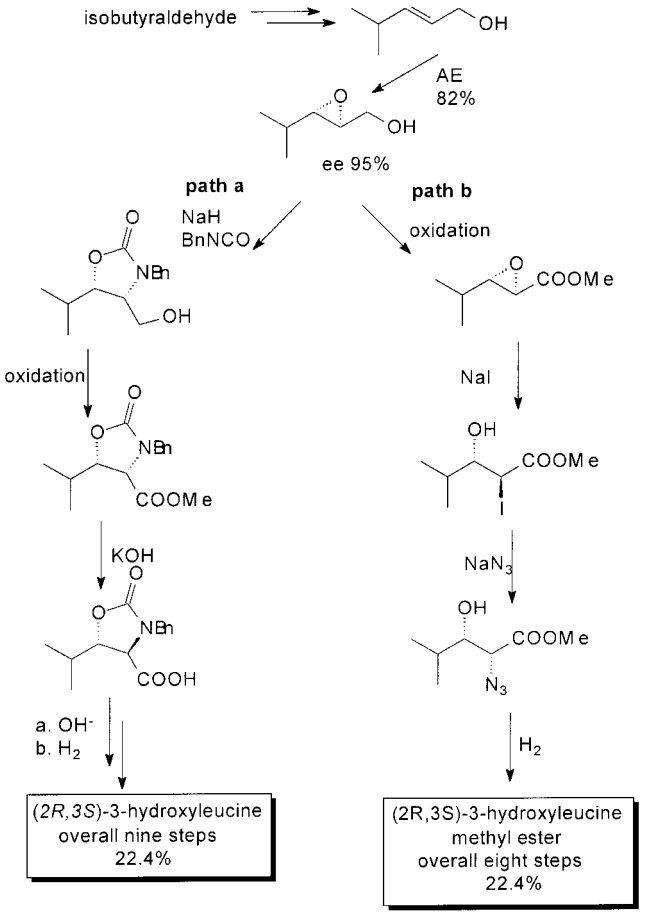
Figure 10.



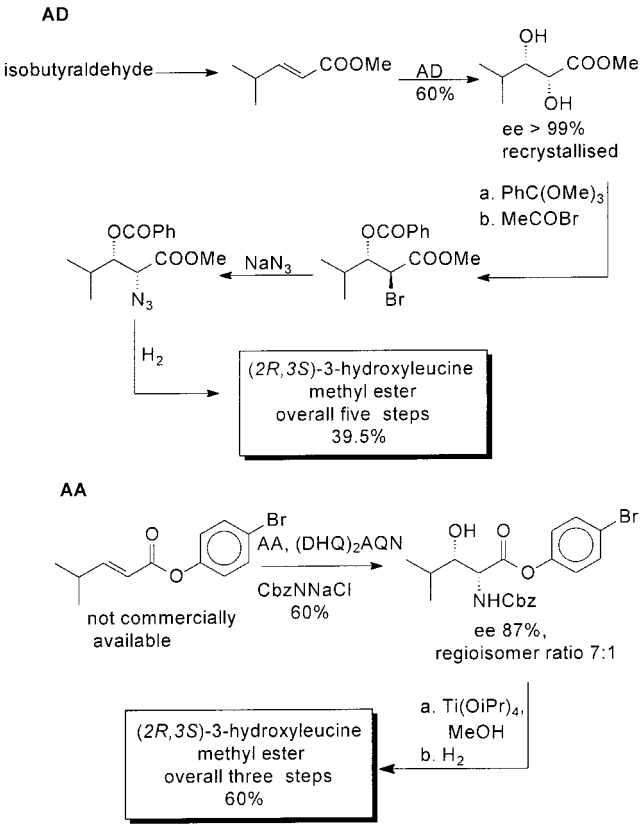
Scheme 58.

(+)-lactacystin[179] requires a careful double inversion of configuration of the C-2 on the *syn* diol ester obtained with the AD. In spite of the low enantioselectivity (70% ee of the AD process) in the key reaction step (improved by crystallisation: 60% yield and ee 99%), the overall five-step process, with a 39.5% yield, represents a major advancement over the previously reported oxidative approaches.

An even more improved method is the AA route[180] to the synthesis of the 3-hydroxyleucine towards the total synthesis of lactacystin. The starting unsaturated ester, not commercially available and to be prepared (Scheme 60), was shown to afford the aminoalcohol with a good degree of enantio- (ee 87%) and regioselectivity (7:1 ratio of the two regioisomers), as noted for other related unsaturated



Scheme 59.



Scheme 60.

olefins. The subsequent straightforward two-step sequence afforded the desired 3-hydroxyleucine in 60% overall yield and only three steps.

The overall processes described here demonstrate just how important suitable substrates (e.g. cinnamates and, generally, conjugated olefins for the AD and the AA process) are to improve results in the oxidative methodologies.

5.3.3. Cyclohexylnorstatin. The isopropyl ester of cyclohexylnorstatin (*2R,3S-3*-amino-4-cyclohexyl-2-hydroxy-

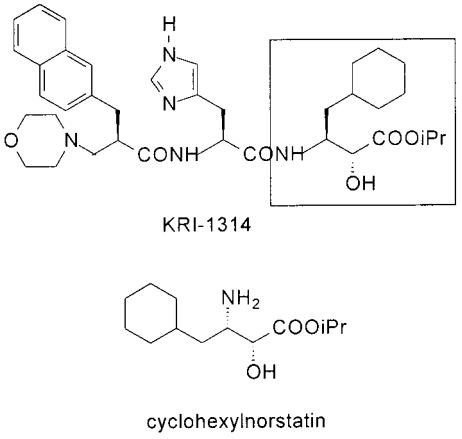
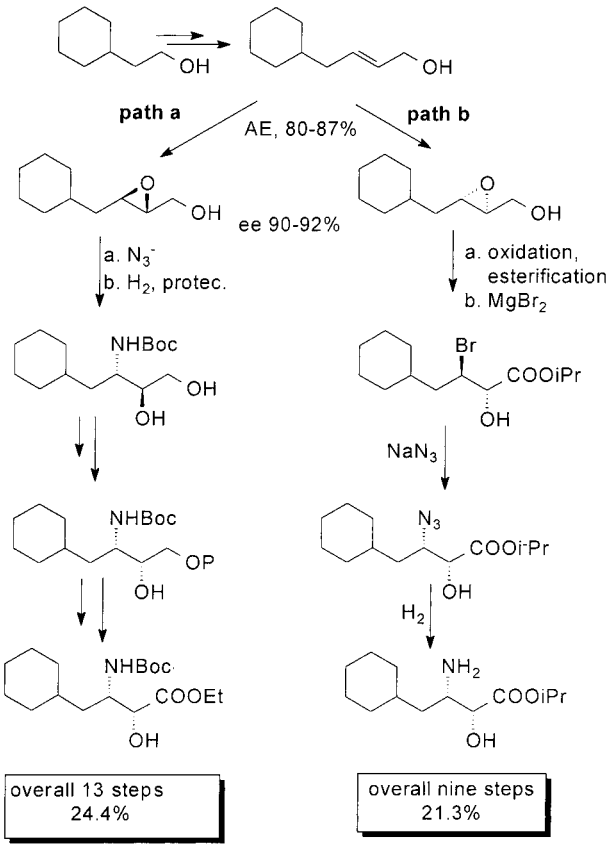


Figure 11.



Scheme 61.

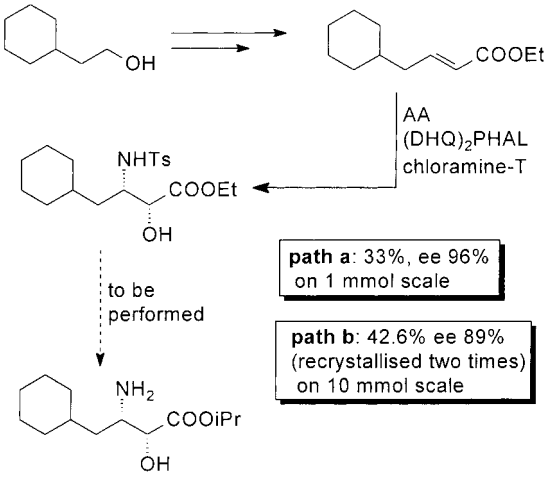
butyrate) constitutes the C-terminal moiety of a potent renin inhibitor, the tripeptide KRI- 1314 (Fig. 11),[181] and this subunit has also been found in other bioactive small peptides.[182]

This subunit has been the object of several synthetic approaches,[183] some of which have utilised the asymmetric oxidation of olefins as a key reaction step.

The two older approaches,[163b,184] based on the AE of allylic alcohols (Scheme 61), started from the same allylic alcohol (obtained from the commercially available cyclohexanol in three steps with 86–70% overall yield).

In the first approach (path b)[163b] the introduction of the nitrogen with the correct relative configuration was achieved via the known developed regioselective opening of epoxy esters with halide and the subsequent nucleophilic displacement by azide. The final target compound was obtained in nine steps overall and 21.3% yield.

The other approach (path a),[184] employs a more lengthy strategy (ten steps overall and 24.4% yield), where the initial introduction of the nitrogen is followed by the required inversion of configuration of the hydroxyl carbon centre. The final product, however, is the corresponding ethyl butyrate instead of the isopropyl ester and possesses the N-Boc-protected function and its final deprotection and transformation to a known derivative was given without experimental details and yield.



Scheme 62.

For cyclohexylnorstatin, the more recent AA would also be expected to reduce the number of steps for its synthesis. Two identical approaches have been reported, employing the AA as the key asymmetric step for the preparation of a cyclohexylnorstatin derivative. As described in Scheme 62, however, the results appear, to some extent to be in sharp contrast.

In the early report (path a),[183] the AA on the unsaturated ester prepared in two steps from 2-cyctohexylethanol was claimed to afford the (2*R*,3*S*)-*N*-(*p*-toluensulphonyl)-3-amino-4-cyclohexyl-2-hydroxybutyrate as a *colourless oil*, with a 60% yield and ee 96% after chromatographic purification.

The more recent report (path b),[185] with the goal of preparing the correlated Abbott amino-diol, reported the AA on the same ester with the same reagents to afford the same (2*R*,3*S*)-*N*-(*p*-toluenesulphonyl)-3-amino-4-cyclohexyl-2-hydroxybutyrate, but with 65% yield and ee 89% after two crystallisations as a *white solid* and mp 112–116°C).

The two reports gave no regioisomeric ratio (which could be responsible for the fair yields observed for the two syntheses) and apparently the asymmetric induction observed was quite different.

The only remarkable differences between the two experiments concerned the molar scale of the AA (1:10 ratio between path a and path b) and the use of $K_2OsO_2(OH)_4$ for path b, OsO_4 for path a. Finally, although the spectroscopic data were similar, the physical properties of the final products were remarkably different.

In this example, therefore, although the use of the AA methodology is apparently highly superior to the AE approach, the published data do not allow an immediate answer to the crucial questions about the asymmetric induction and the regioselectivity observed with the above substrate, which could be very useful to better rationalise and expand the scope of the AA.[186]

6. Conclusions

The olefinic functional group is ubiquitously distributed in organic molecules, because of its easy introduction by different routes. The methodologies to enantioselectively introduce heteroatoms on a double bond have therefore been explored and developed in depth from the early 1980s, when the need for chiral molecules became urgent in academic and industrial use. Today synthetic organic chemists have several possibilities for the asymmetric induction on an achiral molecule and this may be often carried out in an oxidative process on double bonds. The developed methodologies allow the introduction of one oxygen to both sides of the double bond (AE to chiral epoxides), two oxygens on both sides of the double bond (AD to 1,2-diols) and oxygen and nitrogen on both sides of a double bond (AA to 1,2-aminoalcohols). The broad spectrum of possibilities offered by the developed methodologies therefore covers all types of different substrates. In addition, the manipulation of the introduced functional groups has reached a high level of sophistication in terms of stereo-, regio- and chemoselectivity. This allows broadening of the scope of the asymmetric methodologies in order to prepare optically active compounds, which are apparently far from the precursors obtained by the asymmetric oxidation. The level of manipulation of the various functional groups can allow the same final compounds to be obtained by different routes and starting from different precursors. The newly introduced methodologies allow shorter synthetic sequences and higher yields in many instances, with respect to the originally developed methodologies (see AA for the direct introduction of nitrogen and oxygen). Careful analysis of all the methodologies is still requited, however, in planning a synthesis that implies an asymmetric reaction for the introduction of the correct absolute configuration.

In the future, other asymmetric oxidative methodologies will be focussed on the regioselective introduction of other different heteroatoms (halogen, sulfur, phosphorus), which should permit avoiding the procedure for the indirect introduction of such functionalities. On the other hand, even better results are expected in the improvement of the applicability of the Salen-AE and the other recent oxidative methodologies of unfunctionalised olefins or enones, or in the AD of poor substrates like (*Z*) olefins, or again in a larger substrate applicability and better regioselectivity in the AA reaction.

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Biographical sketch

Carlo Bonini was born in Roma in 1948. He graduated in the University 'La Sapienza' in Roma in 1972. Then he spent eight years as doctoral fellow in the same University, working on the isolation, structural elucidation and modification of natural products, associated to the CNR. Center of Natural Product Chemistry. Then he became a Research Associate in 1980 in Roma. In 1982 he was awarded of a CNR. fellowship and he spent one year at Stanford University in the Professor Carl Djerassi's group. In 1987 he moved as Associate Professor to the University of Basilicata (Potenza), where he became Professor of Organic Chemistry in 1994 and where he is now. His research interest is focused on the enantioselective synthesis of natural products (via original chemical or biocatalytic routes) as well as on the reactivity of three membered heterocycles such as epoxides and aziridines.

Giuliana Righi was born in Latina in 1957. She graduated in Chemistry at the University 'La Sapienza' in Rome in 1981. Since 1984 she has been a researcher at the CNR Centre for the Study of Natural Products Chemistry in Rome. At first, she worked on the isolation and structural elucidation of glucosidic iridoids, natural products extracted from plants and, more recently, on the study of new methodologies toward the synthesis of biologically active compounds. In particular, her attention is focused on the regio- and stereoselective opening of three membered heterocyclic rings and subsequent elaborations.