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# Part I    Review

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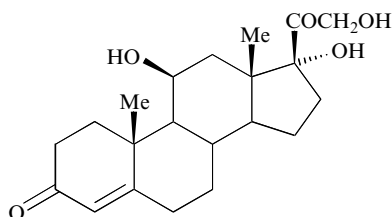
# 1 The Integration of Biotransformations into the Catalyst Portfolio

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The science of biotransformations has been investigated since the days of Pasteur<sup>[1]</sup>. However, progress in the use of enzymes and whole cells in synthetic organic chemistry was relatively slow until the 1950s, when the use of micro-organisms to modify the steroid nucleus was studied in industry and academic laboratories<sup>[2]</sup>. Thus conversions such as the transformation of 17 $\alpha$ -acetoxy-11-deoxycortisol into cortisol (hydrocortisone) (**1**), using the microorganism



(1)

*Curvularia lunata* to introduce the 11 $\beta$ -hydroxy group directly, helped to revive interest in the application of biological catalysis to problems in synthetic organic chemistry. The momentum was continued by Charles Sih, J. Bryan Jones, George Whitesides and others, until, by the mid-1980s, biocatalysis

was being accepted as a powerful method, especially for the production of optically active products<sup>[3]</sup>. At this time the whole field was given another boost by Alexander Klibanov at the MIT who showed emphatically (but not for the first time) that some enzymes (especially lipases) could function in organic solvents, thus broadening the substrate range to include water-insoluble substances<sup>[4]</sup>.

For a while, in the early 1990s, the interest in the use of enzymes in organic synthesis increased at an almost exponential rate and two-volume works were needed even to summarize developments in the field<sup>[5]</sup>. Now, at the turn of the century, it is abundantly clear that the science of biotransformations has a significant role to play in the area of preparative chemistry; however, it is, by no stretch of the imagination, a panacea for the synthetic organic chemist. Nevertheless, biocatalysis is the method of choice for the preparation of some classes of optically active materials. In other cases the employment of man-made catalysts is preferred. In this review, a comparison will be made of the different methods available for the preparation of various classes of chiral compounds<sup>[6]</sup>.

Obviously, in a relatively small work such as this it is not possible to be comprehensive. Preparations of bulk, achiral materials (e.g. simple oxiranes such as ethylene oxide) involving key catalytic processes will not be featured. Only a handful of representative examples of preparations of optically inactive compounds will be given, since the emphasis in the main body of this book, i.e. the experimental section, is on the preparation of chiral compounds. The focus on the preparation of compounds in single enantiomer form reflects the much increased importance of these compounds in the fine chemical industry (e.g. for pharmaceuticals, agrichemicals, fragrances, flavours and the suppliers of intermediates for these products).

The text of this short review article will be broken down into the following sections:

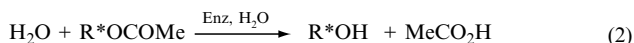
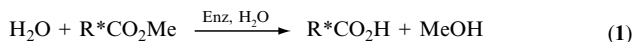
1. Hydrolysis of esters, amides, nitriles and oxiranes
2. Reduction reactions
3. Oxidative transformations
4. Carbon-carbon bond forming reactions.

In each of these areas the relative merits of biocatalysis versus other catalytic methodologies will be assessed. Note that the text is given an asterisk (\*) when mention is made of a catalyst for a reduction or oxidation reaction that is featured in the later experimental section of this book.

## 1.1 HYDROLYSIS OF ESTERS, AMIDES, NITRILES AND OXIRANES

The enantioselective hydrolysis of racemic esters to give optically active acids and/or alcohols (Figure 1.1) is a well established protocol using esterases or lipases. In general, esterases from microorganisms or animal sources (such as

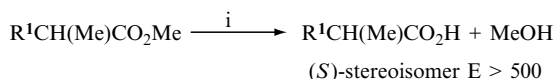
*Pseudomonas putida* esterase or pig liver esterase, (ple) or proteases (e.g. subtilisin) are employed in the reactions described in equation (1), while lipases (e.g. *Candida antarctica* lipase) are more often used for transformations illustrated in



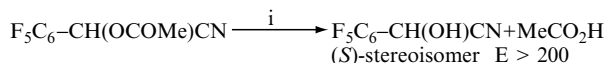
R\* = chiral unit; Enz = esterase or lipase

**Figure 1.1** Generalized scheme illustrating the hydrolysis of esters using enzymes.

equations (2) and (3). Obviously in order to obtain optically active acid and/or alcohol the reaction is not taken to completion but stopped at about the halfway stage. The enantiomer ratio  $E^{[7]}$  indicates the selectivity of the enzyme catalysed reaction. E values > 100 indicate highly enantioselective biotransformations. Typical resolutions are illustrated in Schemes 1<sup>[8]</sup> and 2<sup>[9]</sup>. There have been



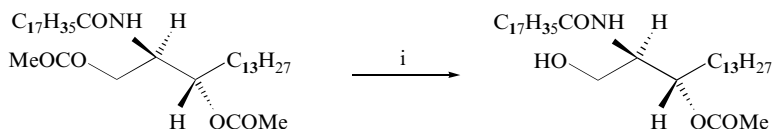
**Scheme 1:** Reagents and conditions: i) *Ps. putida* esterase H<sub>2</sub>O.



**Scheme 2:** Reagents and conditions: i) lipase LIP, H<sub>2</sub>O, buffer pH 5–6.

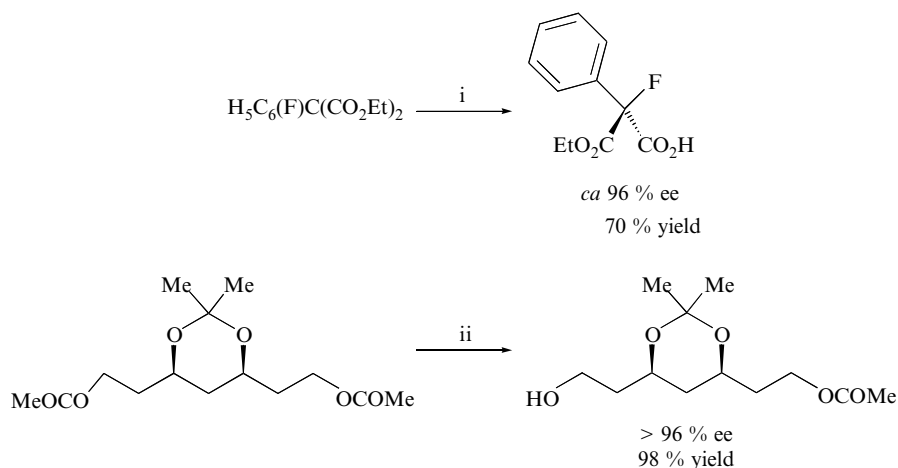
models postulated for many of the popular enzymes (pig liver esterase, *Candida rugosa* lipase) in order better to **predict** the preferred substrate in a racemic mixture<sup>[10]</sup>.

The ability of hydrolases to hydrolyse esters derived from primary alcohols in the presence of esters derived from secondary alcohols has been recognized (Scheme 3)<sup>[11]</sup>.



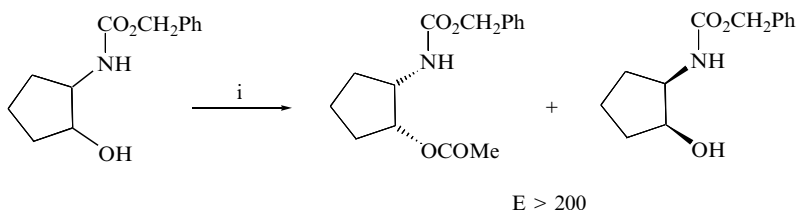
**Scheme 3:** Reagents and conditions: i) *Burkholderia cepacia* lipase, H<sub>2</sub>O, buffer pH 7, decane.

However, the exquisite selectivity of hydrolase enzymes is, perhaps, best illustrated by their ability to produce optically active compounds from prochiral and *meso*-substrates. In both these cases a theoretical yield of 100% for optically pure material is possible (Scheme 4)<sup>[12, 13]</sup>.



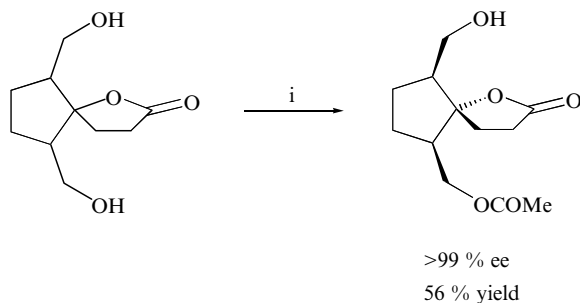
**Scheme 4:** Reagents and conditions i) Porcine pancreatic lipase, H<sub>2</sub>O ii) *Ps. fluorescens* lipase, H<sub>2</sub>O.

No other catalysts compete favourably with the enzymes in this type of work. Similarly lipases are the catalysts of choice for the enantioselective acylation of



**Scheme 5:** Reagents and conditions: i) *Ps. cepacia* lipase, vinyl acetate in *tert*-butyl methyl ether.

a wide a variety of alcohols. This area of research has mushroomed since Klibanov's seminal studies clearly indicating that the procedure is exceedingly simple; a comprehensive review of the methodology is available<sup>[14]</sup>. A typical example of a resolution process involving enantioselective esterification using a lipase is shown in Scheme 5<sup>[15]</sup>. Furthermore, the mono-esterification of *meso*-diols represents an efficient way to generate optically active compounds (Scheme 6)<sup>[16]</sup>.

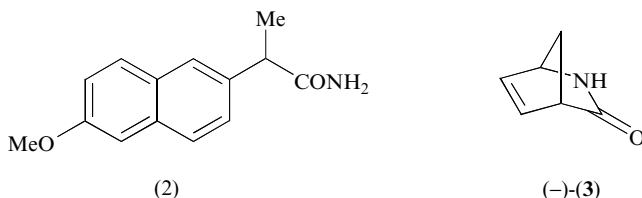


**Scheme 6:** Reagents and conditions: i) *Ps. fluorescens* lipase, vinyl acetate in *n*-octane.

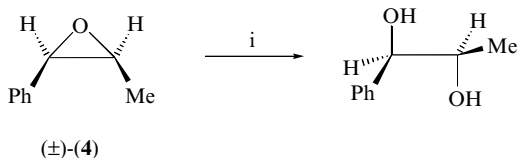
To a much smaller extent non-enzymic processes have also been used to catalyse the stereoselective acylation of alcohols. For example, a simple tripeptide has been used, in conjunction with acetic anhydride, to convert *trans*-2-acetylaminocyclohexanol into the (*R*),(*R*)-ester and recovered (*S*),(*S*)-alcohol<sup>[17]</sup>. In another, related, example a chiral amine, in the presence of molecular sieve and the appropriate acylating agent, has been used as a catalyst in the conversion of cyclohexane-1(*S*), 2(*R*)-diol into 2(*S*)-benzoyloxy-cyclohexan-1(*R*)-ol<sup>[18]</sup>. Such alternative methods have not been extensively explored, though reports by Fu, Miller, Vedejs and co-workers on enantioselective esterifications, for example of 1-phenylethanol and other substrates using *iso*-propyl anhydride and a chiral phosphine catalyst will undoubtedly attract more attention to this area<sup>[19]</sup>.

The chemo-, regio- and stereoselective hydrolysis of amides using enzymes (for example, acylases from hog kidney) has been recognized for many years. In the area of antibacterial chemotherapy, the use of an acylase from *Escherichia coli* to cleave the side-chain amide function of fermented penicillins to provide 6-aminopenicillanic acid *en route* to semi-synthetic penicillins has been taken to a very large scale (16000 tonnes/year). The same strategy is used to prepare optically active amino acids. For instance, an acylase from the mould *Aspergillus oryzae* is used to hydrolyse *N*-acyl DL-methionine to afford the L-amino acid and unreacted *N*-acyl-D-amino acid. The latter compound is separated, chemically racemized and recycled. L-Methionine is produced in this way to the extent of about 150 tonnes/year<sup>[1]</sup>.

The hydrolysis of racemic non-natural amides has led to useful products and intermediates for the fine chemical industry. Thus hydrolysis of the racemic amide (**2**) with an acylase in *Rhodococcus erythropolis* furnished the (*S*)-acid (the anti-inflammatory agent Naproxen) in 42 % yield and > 99 % enantiomeric excess<sup>[20]</sup>. Obtaining the  $\gamma$ -lactam (–)-(**3**) has been the subject of much research and development effort, since the compound is a very versatile synthon for the production of carbocyclic nucleosides. An acylase from *Comamonas acidovorans* has been isolated, cloned and overexpressed. The acylase tolerates a 500 g/litre input of racemic lactam, hydrolyses only the (+)-enantiomer leaving the desired intermediate essentially optically pure ( $E > 400$ )<sup>[21]</sup>.



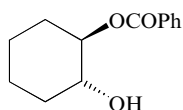
The enzyme-catalysed hydrolysis of epoxides has been reviewed<sup>[22]</sup>. Much of the early work featured liver microsomal epoxide hydrolases but the very nature and origin of these biocatalysts meant that they would always be limited to the small scale. In recent years the use of epoxide-hydrolase enzymes within organisms has become popular, with the fungus *Beauveria sulfurescens* being featured regularly. For instance, incubation of styrene oxide with this organism provides (*R*)-1-phenylethanediol (45 % yield; 83 % ee) and recovered (*R*)-styrene oxide (34 % yield; 98 % ee)<sup>[23]</sup>. A particularly interesting example, shown in Scheme 7, is the stereoconvergent ring-opening of the racemic epoxide (**4**) which gives (*R*), (*R*)-1-phenylpropane-1, 2-diol in 85 % yield and 98 % ee (one enantiomer of the epoxide suffers attack by water adjacent to the phenyl group, the other enantiomer is attacked by water at the carbon atom bearing the methyl group)<sup>[24]</sup>.



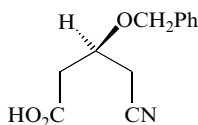
**Scheme 7:** Reagents and conditions i) *B. sulfurescens*, H<sub>2</sub>O.

A major drawback in this area is that a portfolio of epoxide hydrolases is not available<sup>[25]</sup> and chemists remain reluctant to embark on processes which

involve the use of whole cells (such as *B. sulfurescens*). Not surprisingly, therefore, the use of a non-enzymic method for the kinetic resolution of terminal epoxides and the stereoselective opening of *meso*-epoxides, involving salen-cobalt complexes, has aroused interest. For example, use of the organometallic catalyst in the presence of benzoic acid and cyclohexene epoxide afforded the hydroxyester (**5**) (98 % yield; 77 % ee)<sup>[26]</sup>.



(5)



(6)

The same disadvantage (lack of commercially available enzymes, and the consequent necessity for the employment of whole cells) dogs the otherwise extremely useful biotransformation involving the hydrolysis of nitriles to the corresponding amides (under the influence of a nitrile hydratase) or acids (by a nitrilase). The conversion takes place under very mild conditions of temperature and pH and some useful transformations have been recorded; for example the cyanocarboxylic acid (**6**) (a precursor of the lactone moiety of mevinic acids) is available from the corresponding prochiral dinitrile in good yield (60–70 %) and high enantiomeric excess (88–99 % ee), on a multigram scale, over a period of 24 hours using *Rhodococcus* sp. SP361 or *Brevibacterium* sp. R312<sup>[27]</sup>.

In summary, the formation of optically active compounds through hydrolysis reactions is dominated by biocatalysis mainly due to the availability and ease of use of a wide variety of esterases, lipases and (to a lesser extent) acylases. Epoxide ring-opening (and related reactions) is likely to be dominated by salen-metal catalysts while enzyme-catalysed nitrile hydrolysis seems destined to remain under-exploited until nitrilases or nitrile hydratases become commercially available.

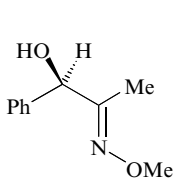
## 1.2 REDUCTION REACTIONS

The balance between biocatalytic and other, organometallic-based, methodology is heavily biased in favour of the latter section when considering reduction reactions of importance in synthetic organic chemistry. Two areas will be described to illustrate the point, namely the reduction of carbonyl groups and the reduction of alkenes, not least since these points of focus complement experimental work featured later in the book.

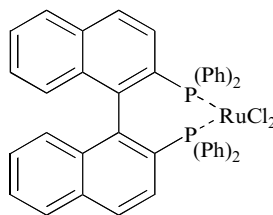


## 1.2.1 REDUCTION OF CARBONYL COMPOUNDS

It is well known that bakers' yeast is capable of reducing a wide range of ketones to optically active secondary alcohols. A recent example involves the preparation of the (*R*)-alcohol (**7**) (97% ee) (a key intermediate to (–)-norephedrine) from the corresponding ketone in 79% yield<sup>[28]</sup>. Other less well-known organisms are capable of performing similar tasks; for instance, reduction of 5-oxohexanoic acid with *Yamadazyma farinosa* furnishes (*R*)-5-hydroxyhexanoic acid in 98% yield and 97% ee<sup>[29]</sup>.



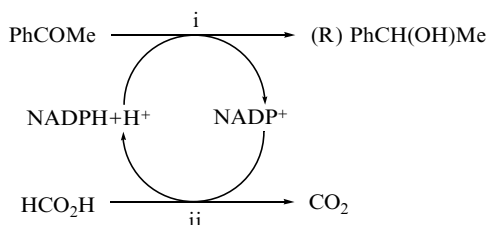
(7)



(8)

However, the use of the whole cells of the microorganisms can lead to some difficulties. For instance, an aqueous solvent system is generally employed<sup>[30]</sup>, certainly when the cells need to be in an active state and often when the cells are 'resting'<sup>[31]</sup>. The solubility of the substrate in the aqueous system can be problematic, as can the related transport of the starting material in to, and out from, the cytosol. At the end of the reaction, harvesting and disposal of the mycelial mass may be disconcerting, especially when considering large scale work. If a biocatalyst other than a readily available organism (such as bakers' yeast) is necessary then access to sterile equipment including fermenters is required, often considered a drawback for a person working in a conventional chemical laboratory. Thus, despite the various methods for improvement of particular protocols (including the immobilization of whole cell biocatalysts in alginate beads\*)<sup>[32]</sup>, whole-cell reduction reactions of carbonyl compounds remain, almost exclusively, in the small scale research arena.

It is possible to use isolated, partially purified enzymes (dehydrogenases) for the reduction of ketones to optically active secondary alcohols. However, a different set of complications arises. The new C–H bond is formed by delivery of the hydrogen atom from an enzyme cofactor, nicotinamide adenine dinucleotide (phosphate) NAD(P) in its reduced form. The cofactor is too expensive to be used in a stoichiometric quantity and must be recycled *in situ*. Recycling methods are relatively simple, using a sacrificial alcohol, or a second enzyme (formate dehydrogenase is popular) but the real and apparent complexity of the ensuing process (Scheme 8)<sup>[33]</sup> provides too much of a disincentive to investigation by non-experts.



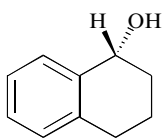
**Scheme 8:** Reagents and conditions i) dehydrogenase from *Lactobacillus* sp. ii) NADPH-dependent formate dehydrogenase.

Thus the methods of choice for the reduction of simple carbonyl compounds reside in the use of hydrogen and organometallic reagents\*. Originally, reduction reactions using organorhodium complexes gained popularity. Thus hydrogenation of acetophenone in the presence of rhodium (*S,S*)-2,4-bis(diphenylphosphinyl)pentane [(*S,S*)-BDPP or Skewphos] gave (*S*)-1-phenylethanol<sup>[34]</sup>.

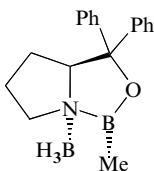
However, the employment of chiral ruthenium diphosphine–diamine mixed-ligand complexes has displaced much of the original experimentation to become the methodology of choice<sup>[35]</sup>. Such catalyst systems are prepared (sometimes *in situ*) by mixing a complex of BiNAP–RuCl<sub>2</sub> (**8**) with a chiral amine such as 1,2-diphenylethylenediamine (DPEN). In the presence of a base as co-catalyst such systems can achieve the reduction of a wide variety of alkyl arylketones under 1–10 atmospheres of hydrogen, affording the corresponding secondary alcohols in high enantiomeric excess<sup>[36]</sup>. A similar hydrogenation of tetralone using an iridium complex gave the (*R*)-alcohol (**9**) in 88 % yield and 95 % ee<sup>[37]</sup>.

As an alternative to the use of hydrogen gas, asymmetric ruthenium-catalysed hydrogen transfer reactions have been explored with significant success\*<sup>[38]</sup>.

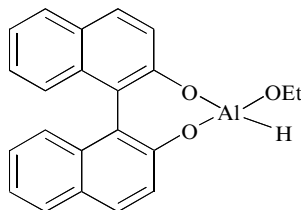
The reduction of dialkylketones and alkylaryl ketones is also conveniently accomplished using chiral oxazaborolidines, a methodology which emerged from relative obscurity in the late 1980s. The type of borane complex (based on (*S*)-diphenyl prolinol)<sup>[39]</sup> responsible for the reductions is depicted below (**10**). Reduction of acetophenone with this complex gives (*R*)-1-phenylethanol in 90–95 % yield (95–99 % ee)\*<sup>[40]</sup>. Whilst previously used modified hydrides such as BiNAL–H (**11**), which were used in stoichiometric quantities, are generally unsatisfactory for the reduction of dialkylketones, oxazaborolidines



(9)



(10)

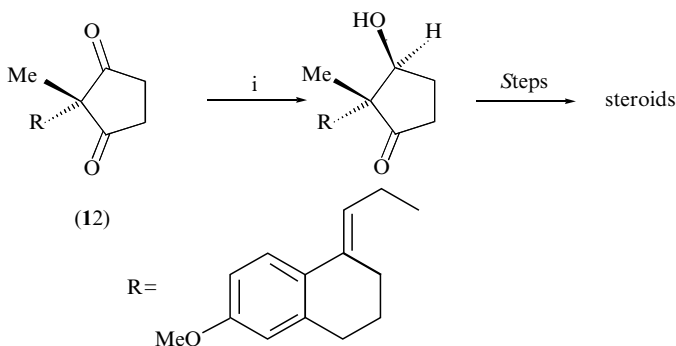


(11)

can be employed often with the production of secondary alcohols with high ee. For example *iso*-propylmethyl ketone and *tert*-butylmethyl ketone are good substrates giving secondary alcohols with  $> 91\%$  ee<sup>[41]</sup>. Alternatively oxazaphosphinamides\* and hydroxysulfoximines\* have been used to control the stereochemistry of the reduction of simple ketones by borane.

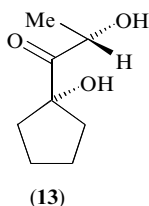
Brook has effectively modified a procedure (introduced by Hosomi) which employs a trialkoxysilane as the stoichiometric reducing agent which, in the presence of amino acid anions reduces aryl alkyl ketones or diaryl ketones to the corresponding (*S*)-secondary alcohols, albeit in modest ee (generally 25–40 %)\*.

Much the same situation pertains to the asymmetric reduction of diketones and ketoesters. Thus, some years ago, a yeast reduction of the diketone (**12**) formed a key step in the preparation of important steroids (Scheme 9). Work in



**Scheme 9:** Reagents and conditions: i) *Saccharomyces* sp., H<sub>2</sub>O.

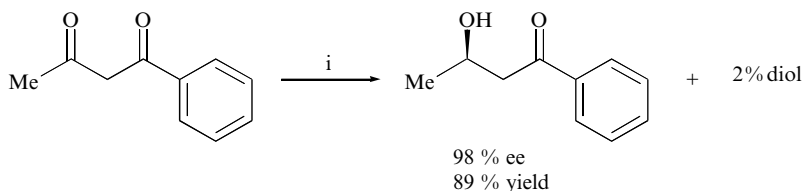
this area has continued, with closely related 2,2-disubstituted cyclopentane-1,3-diones<sup>[42]</sup> and other diketones. Indeed the diol (**13**) has been manufactured on a large scale by reduction of the corresponding hydroxydione using bakers' yeast<sup>[43]</sup>. The same microorganism is used in the reduction of a classical substrate, ethyl-3-oxobutanoate (aka ethyl acetoacetate), to give (*S*)-hydroxyester in a process optimised by Seebach\*<sup>[44]</sup>. (Interestingly it has recently been shown that anaerobically grown bakers' yeast yields the corresponding (*R*)-alcohols with impressive optical purity [96–98 % ee].)<sup>[45]</sup>



However, as for simpler carbonyl systems, organometallic catalysts offer a powerful alternative to biotransformations. By way of comparison methyl-3-oxobutanoate is reduced to the (*R*)-3-hydroxyester (> 99 % ee) quantitatively using (*R*)-BiNAP–RuCl<sub>2</sub> under 100 atmospheres of hydrogen<sup>[46]</sup>. A variation of this reaction using immobilized catalyst yields the chiral alcohol (92 % ee) at roughly the same rate<sup>[47]</sup>, while Genêt's modification of the original procedure, preparing the catalyst *in situ* and employing a hydrogen pressure of one atmosphere, allows the reaction to be performed without special apparatus\*. Note that other ligands have been employed for the ruthenium catalysed reduction of β-ketoesters. For example, a new diphosphine (BisP\*), (+)-ephedrine and other amino alcohols (for asymmetric transfer hydrogenation of arylketones and β-ketoesters\*) are described later, in the relevant experimental section.

Reduction of diketones such as pentane-2,4-dione using (*R*)-BiNAP–RuCl<sub>2</sub> under hydrogen (75–100 atm) gives the corresponding diol, in this case (*R*),(*R*)-2,4-pentanediol with an excellent diastereomer ratio (98 %) and optical purity (>99 %)<sup>[48]</sup>.

When the dione has different terminal groups the Ru–BiNAP reduction can be selective towards one carbonyl group (Scheme 10)<sup>[49]</sup>.

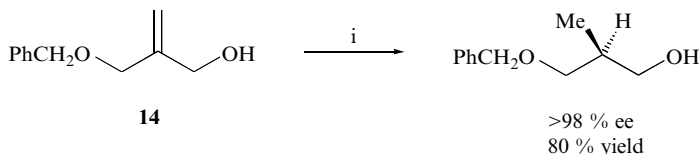


**Scheme 10:** Reagents and conditions: i) H<sub>2</sub> (48 atm) [(*R*-BiNAP)RuCl(μ-Cl)<sub>3</sub>][NH<sub>2</sub> (C<sub>2</sub>H<sub>5</sub>)<sub>2</sub>], MeOH, 50 °C.

## 1.2.2 REDUCTION OF ALKENES

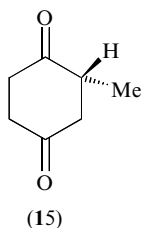
Very few enzyme-catalysed reactions involving the reduction of alkenes have achieved any degree of recognition in synthetic organic chemistry. Indeed the only transformation of note involves the reduction of α, β-unsaturated aldehydes and ketones. For example, bakers' yeast reduction of (*Z*)-2-bromo-3-phenylprop-2-enal yields (*S*)-2-bromo-3-phenylpropanol in practically quantitative yield (99 % ee) when a resin is employed to control substrate concentration<sup>[50]</sup>. Similarly (*Z*)-3-bromo-4-phenylbut-3-en-2-one yields 2(*S*), 3(*S*)-3-bromo-4-phenylbutan-2-ol (80 % yield, >95 % ee)<sup>[51]</sup>. Carbon-carbon double bond reductases can be isolated; one such enzyme from bakers' yeast catalyses the reduction of enones of the type Ar–CH = C(CH<sub>3</sub>)–COCH<sub>3</sub> to the corresponding (*S*)-ketones in almost quantitative yields and very high enantiomeric excesses<sup>[52]</sup>.

One facet of the whole cell work that draws attention is the sometimes profitable operation of a cascade of reactions in the multi-enzyme portfolio of the microorganism. For instance (Scheme 11), the allylic alcohol (**14**) is reduced to the corresponding saturated compound in high yield and optical purity (though in a slow reaction) via the intermediacy of the corresponding enal and (*S*)-2-benzyloxymethylpropanal<sup>[53]</sup>.

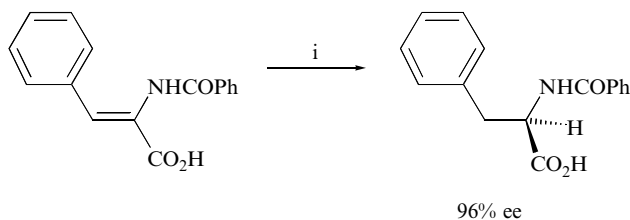


**Scheme 11:** Reagents and conditions: i) Bakers' yeast, 30 °C, 14 days.

Historically the biotransformations of cyclic enones have been important, not least Leuenberger's transformation of the appropriate cyclohexenedione into the saturated ketone (**15**), a precursor for tocopherol<sup>[54]</sup>. Similarly 2-methylcyclohex-2-enone is reduced by the microorganism *Yamadazyma farinosa* (also known as *Pichia farinosa*) to give a mixture of saturated alcohols and ketone; pyridinium chlorochromate oxidation of this mixture afforded 3(*R*)-methylcyclohexanone (95 % ee) in 67 % yield<sup>[55]</sup>.

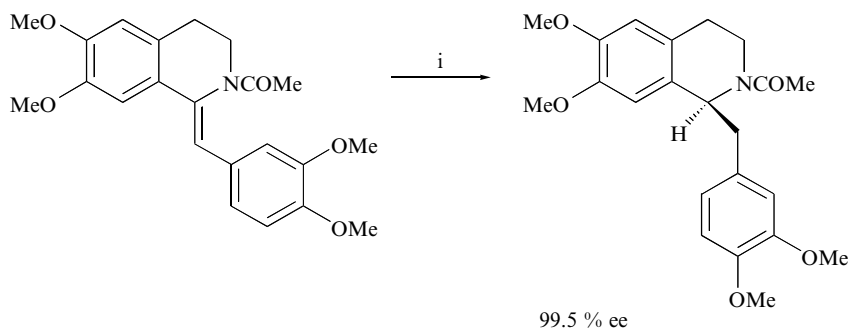


In the area of organometallic chemistry enantioselective hydrogenation of prochiral functionalised alkenes using chiral phosphine complexes of rhodium or ruthenium as catalysts has been extensively researched and, widely reported; the early work has been reviewed<sup>[56]</sup>. The first systems investigated involved organorhodium species particularly for the reduction of dehydroamino acid derivatives (Scheme 12)<sup>[57]</sup> but the emphasis shifted, some twenty years ago, to organoruthenium complexes, for example, the ruthenium–BiNAP system of Noyori<sup>[58]</sup>. The latter catalyst was found to be capable of catalysing the reduction of a wider range of substrates: for example, promoting the reduction of geraniol to (*R*)-citronellol (99 % ee) under hydrogen (100 atm) using methanol as the solvent and in the synthesis of benzomorphans and morphinans<sup>[59]</sup>.

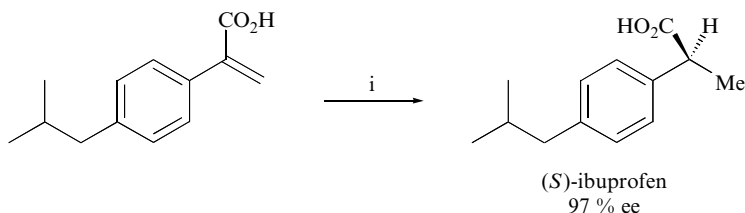


**Scheme 12:** Reagents and conditions: i) [(BINAP)Rh(MeOH)<sub>2</sub>]<sup>+</sup>[ClO<sub>4</sub>]<sup>-</sup> cat., 1 atm H<sub>2</sub>, MeOH.

The broad range of alkenes undergoing asymmetric hydrogenation using ruthenium-based systems as catalysts has attracted the attention of chemists engaged in the synthesis of chiral biologically active natural products (Scheme 13)<sup>[60]</sup> and other pharmaceuticals (Scheme 14)<sup>[61]</sup>.  $\alpha$ ,  $\beta$ -Unsaturated phosphoric acids and esters have also proved to be suitable substrates for Ru(II)-catalysed asymmetric hydrogenation\*<sup>[62]</sup>.



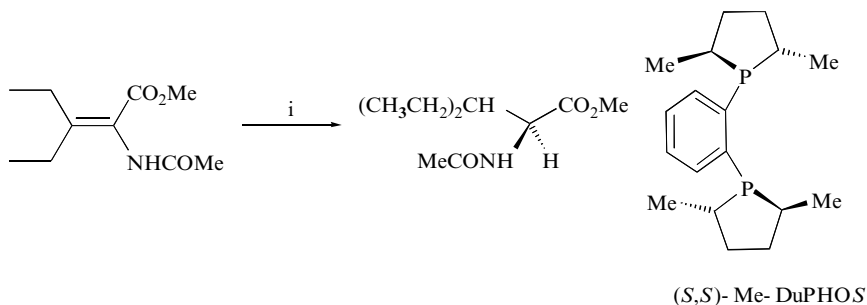
**Scheme 13:** Reagents and conditions: i) Ru-BiNAP (1 mol%), H<sub>2</sub> (4 atm) methylene chloride in MeOH.



**Scheme 14:** Reagents and conditions: i) Ru(*S*)-tetrahydroBiNAP (0.5 mol%), H<sub>2</sub> (100 atm), MeOH, 8 h.

Since these early days different ligands for rhodium complexes have been invented that more efficiently catalyse asymmetric reduction of a range of

dehydroamino acids. One of the more popular ligands for general usage has been Burk's DuPHOS (Scheme 13)\*<sup>[63]</sup>.

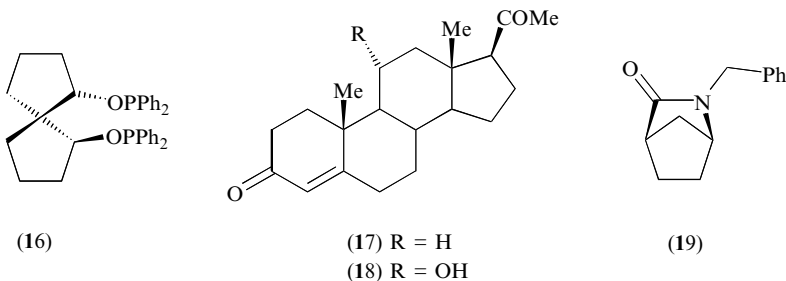


**Scheme 15:** Reagents and conditions: i) Rh–DuPHOS (0.2 mol%), H<sub>2</sub> (6 atm), benzene.

This strategy also gives access to a variety of non-natural  $\alpha$ -amino acids. Furthermore, rhodium–DuPHOS complexes catalyse the asymmetric reduction of enol esters of the type  $\text{PhCH}=\text{CH}-\text{C}(\text{OCOCH}_3)=\text{CH}_2$  to give (*R*)-2-acetoxy-4-phenylbut-3-ene (94 % ee)<sup>[64]</sup>.

The use of chiral rhodium complexes fashioned from ferrocene derivatives has gained in popularity significantly in recent years\*<sup>[65]</sup>.

The portfolio of bisphosphine ligands for rhodium-catalysed asymmetric hydrogenation of dehydroamino acids is now becoming complemented by a set of bisphosphinite ligands\*, typified by Chan's spirOP (**16**)<sup>[66]</sup> and carbohydrate-based systems invented by Selke and RajanBabu<sup>[67]</sup>. The attraction of the use of the bisphosphinites lies in the simplicity of the preparation of the ligands (by reacting optically active diols with chlorophosphines in the presence of base)<sup>[68]</sup>. A remarkably selective one-pot procedure for sequential alkene and carbonyl reduction using chiral rhodium and ruthenium catalysts allows the preparation of amino alcohols with up to 95 % ee\*<sup>[69]</sup>.



### 1.3 OXIDATIVE TRANSFORMATIONS

In this important area of synthetic chemistry honours are more equally shared between biocatalysis and other forms of catalysts, the latter being made up, almost invariably, of man-made organometallic species. Thus biotransformations are the preferred pathway for the hydroxylation of aliphatic, alicyclic, aromatic and heterocyclic compounds, particularly at positions remote from pre-existing functionality<sup>[70]</sup>. In contrast organometallic species are the catalysts of choice to convert alkenes into epoxides and diols. Both natural and non-natural catalysts are adept at the conversion of some sulfides into the corresponding sulfoxides and in performing stereoselective Baeyer–Villiger oxidations. Some of the details are provided hereunder.

The ability of microorganisms to convert alicyclic compounds into related alcohols by regio- and stereo-controlled hydroxylation at positions distant from regio- and stereo-directing functional groups was used extensively in the modification of steroids<sup>[71]</sup>. In a classical example the hydroxylation of progesterone (**17**) with *Rhizopus* sp. or *Aspergillus* sp. furnished the oxidized product (**18**), forming a key step in a highly efficient pathway to the anti-inflammatory steroids such as Betnovate<sup>[72]</sup>. Other complex alicyclic natural products and closely related compounds (e.g. taxanes)<sup>[73]</sup> have been selectively hydroxylated using some of the more easily handled organisms such as *Mucor* sp., *Absidia* sp. and *Cunninghamella* sp.

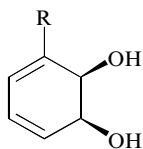
The selective monohydroxylation of heterocyclic compounds such as piperidine derivatives<sup>[74]</sup> and the  $\gamma$ -lactam (**19**)<sup>[75]</sup> have been studied. It is also been shown that hydroxylation of phenylcyclohexane can be effected using cytochrome P450 and the regioselectivity of hydroxylation can be altered by site-directed mutagenesis of the enzyme<sup>[76]</sup>.

While undoubtedly powerful methodology, the major problem concerning enzyme-catalysed hydroxylation of alicyclic and saturated heterocyclic compounds is the unpredictability of the site of hydroxylation. Not surprisingly a start has been made to control the regioselectivity of microbial hydroxylation by using an easily-introduced and easily-removed directing group which, if such a suitable auxiliary could be found, would very conveniently promote hydroxylation at a set distance from the temporary appendage<sup>[77]</sup>.

The hydroxylation of aromatic compounds using microorganisms is more predictable and a number of processes have been adapted to large scale, for example the preparation of 6-hydroxynicotinic acid<sup>[78]</sup> and (*R*)-2-(4-hydroxyphenoxy)propanoic acid<sup>[79]</sup>, important intermediates to pesticides and herbicides respectively.

The biotransformation that has caught the imagination of many synthetic organic chemists involves the conversion of benzene and simple derivatives (toluene, chlorobenzene, etc.) into cyclohexadienediols (**20**) using a recombinant microorganism *E. coli* JM109. The one step oxidation, via reduction of the





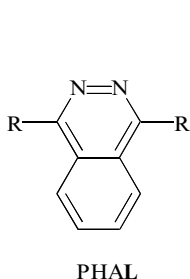
R = H, Me, Cl

(20)

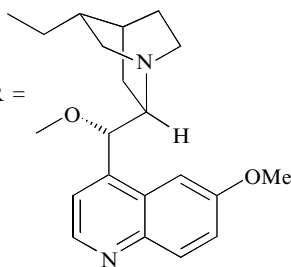
corresponding dioxetane, is impossible to emulate using any other simple process. Cyclohexa-3,5-diene-1,2-diol produced in this way was used as a starting material in the polymer industry. The dienediol products from toluene and chlorobenzene are even more interesting being essentially optically pure and, for this reason, they have been used to prepare optically active morphinans, carbohydrate analogues, pancratistatin and *cis*-chrysanthemic acid, generally by selective transformations involving the two alkene bonds<sup>[80]</sup>.

However, for the dihydroxylation of alkenes the microbiological method is not so effective and the biocatalytic methodology pales into insignificance compared with the powerful chemical technique introduced by Sharpless.

Also fifteen years of painstaking work and the gradual improvement of the system, the Sharpless team announced that asymmetric dihydroxylation (AD) of nearly every type of alkene can be accomplished using osmium tetroxide, a co-oxidant such as potassium ferricyanide, the crucial chiral ligand based on a dihydroquinidine (DHQD) (**21**) or dihydroquinine (DHQ) (**22**) and methanesulfonamide to increase the rate of hydrolysis of intermediate osmate esters<sup>\*[81]</sup>.

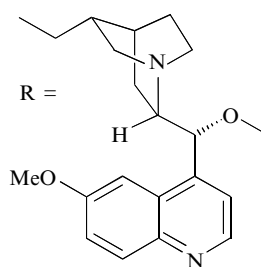


(21) R =



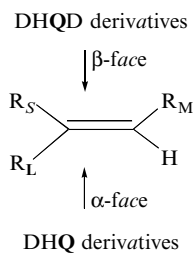
(21) DHQD

(22) R =



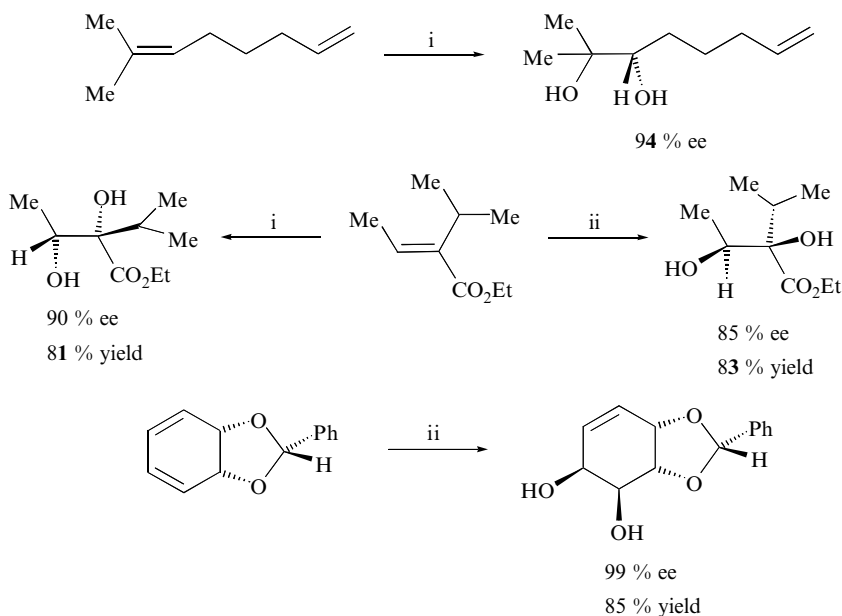
(22) DHQ

A wide range of alkenes undergo the Sharpless AD reaction and the stereochemistry of the product diols can be predicted with a high degree of certainty, in most cases, through a simple mnemonic device (Figure 1.2). Thus the DHQD derivatives supplied with the oxidant have become known as AD-mix  $\beta$  while the DHQ derivatives (with oxidant) comprise AD-mix  $\alpha$ <sup>[81]</sup>. Chosen from the



**Figure 1.2** Predictive model for dihydroxylation of alkenes.

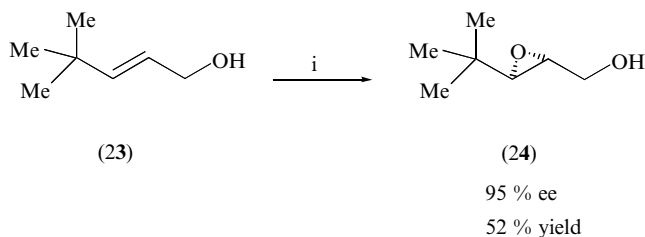
very many reports in the literature<sup>[82]</sup> three examples are given in Scheme 16<sup>[83]</sup>. A modification of the dihydroxylation reaction allows for the aminohydroxylation of alkenes and this reaction is also assuming an important role in organic synthesis\*<sup>[84]</sup>.



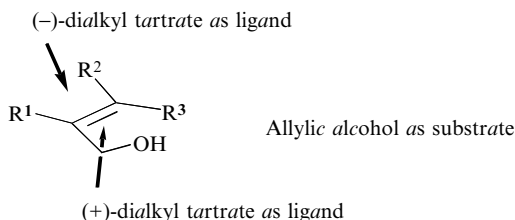
**Scheme 16:** Reagents and conditions: i) AD-mix  $\alpha$ ,  $\text{K}_3\text{Fe}(\text{CN})_6$ ,  $\text{MeSO}_2\text{NH}_2$ , *t*-BuOH,  $\text{H}_2\text{O}$  ii) AD-mix  $\beta$ ,  $\text{K}_3\text{Fe}(\text{CN})_6$ ,  $\text{MeSO}_2\text{NH}_2$ , *t*-BuOH,  $\text{H}_2\text{O}$ .

The asymmetric dihydroxylation protocol was the second massive contribution by Professor Barry Sharpless to synthetic organic chemistry. The first procedure, introduced with Katsuki, involves the catalytic asymmetric epoxidation of allylic alcohols. A typical example is shown in Scheme 17, wherein (*E*)-allylic alcohol (**23**) is epoxidized with *tert*-butylhydroperoxide, in the presence of titanium tetra-isopropoxide and optically active diethyl tartrate to give the

epoxyalcohol (**24**)<sup>[85]</sup>. (Note, however, that the isomeric (*Z*)-alkene undergoes asymmetric epoxidation much less efficiently.) Such reactions are rendered catalytic by the addition of 4Å molecular sieves to adsorb adventitious water which otherwise attacks the key component, the titanium tartrate complex. The sense of asymmetric epoxidation of *E*-allylic primary alcohols is highly predictable\*. The preferred products of the Katsuki–Sharpless oxidation are shown in Figure 1.3. (*Z*)-Allylic alcohols undergo less predictable oxidation, as mentioned above.

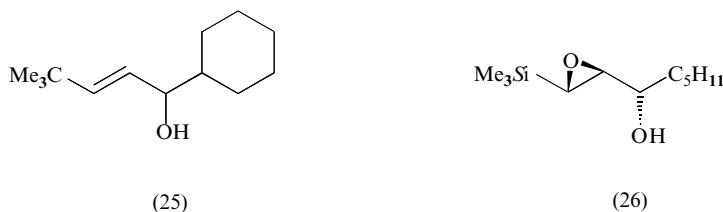


**Scheme 17:** Reagents and conditions: i)  $\text{Ti}(\text{O}-i\text{-Pr})_4$  (+)-diethyl tartrate, *t*-butylhydroperoxide,  $-20^\circ\text{C}$ .



**Figure 1.3** Oxidation of allylic alcohol using  $\text{Ti}(\text{O}-i\text{-Pr})_4$ , TBHP and tartrate ligand.

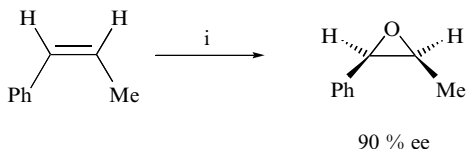
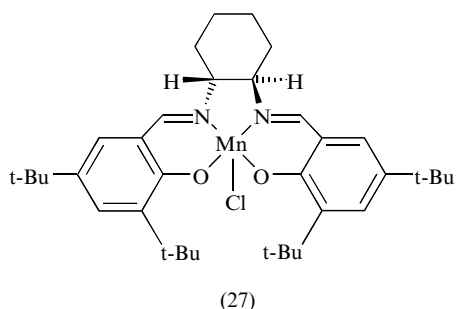
Secondary allylic alcohols also undergo asymmetric epoxidation; in many cases, when the alcohol unit is attached to a stereogenic centre, kinetic resolution of the enantiomers takes place. This is particularly apparent for compounds of type (**25**), where the two enantiomers are epoxidized at rates which are different by two orders of magnitude<sup>[86]</sup>.



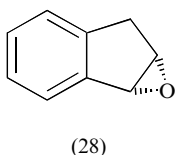
Similarly, racemic 1-trimethylsilyloct-(1*E*)-en-3-ol is epoxidized with  $\text{Ti}(\text{O} - i\text{-Pr})_4$ , *t*-butylhydroperoxide and (+)-di-*isopropyl* tartrate at  $-20^\circ\text{C}$  to give the epoxide (**26**) (> 99% ee, 42%) and recovered (*R*)-unsaturated alcohol<sup>[87]</sup>. In general, when using (+)-tartrates, the (*S*)-enantiomer of the allylic alcohol will react faster.

The requirement for the presence of an adjacent alcohol group can be regarded as quite a severe limitation to the substrate range undergoing asymmetric epoxidation using the Katsuki–Sharpless method. To overcome this limitation new chiral metal complexes have been discovered which catalyse the epoxidation of nonfunctionalized alkenes. The work of Katsuki and Jacobsen in this area has been extremely important. Their development of chiral manganese (III)–salen complexes for asymmetric epoxidation of unfunctionalized olefins\* has been reviewed<sup>[88]</sup>.

A typical manganese–salen complex (**27**)<sup>[89]</sup> is capable of catalysing the asymmetric epoxidation of (*Z*)-alkenes (Scheme 18) using sodium hypochlorite ( $\text{NaOCl}$ ) as the principle oxidant. Cyclic alkenes and  $\alpha$ ,  $\beta$ -unsaturated esters\* are also excellent starting materials; for example indene may be transformed into the corresponding epoxide (**28**) with good enantiomeric excess<sup>[90]</sup>. The epoxidation of such alkenes can be improved by the addition of ammonium acetate to the catalyst system<sup>[91]</sup>.

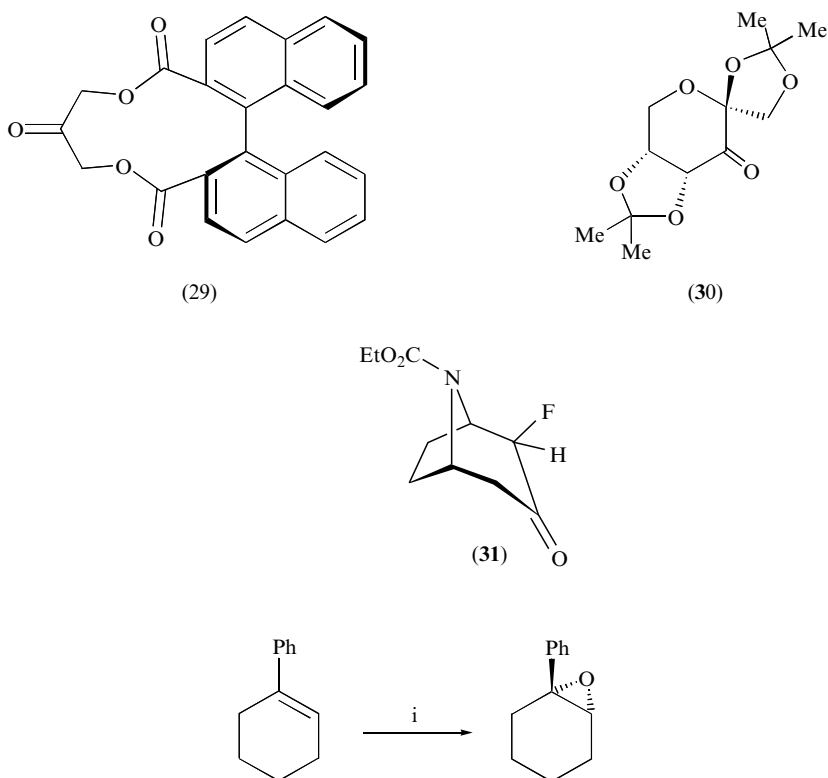


**Scheme 18:** Reagents and conditions: i)  $\text{NaOCl}$ , complex **27**.



The asymmetric epoxidation of *E*-alkenes and terminal alkenes proved to be more difficult, though a recent finding, describing the use of a modified salen complex to epoxidize (*E*)- $\beta$ -methylstyrene to form the corresponding epoxide in 83 % ee, represents another important step forward. Alternatively, chiral ( $D_2$ -symmetric) porphyrins have been used, in conjunction with ruthenium\* or iron, for efficient asymmetric oxidation of *trans*- and terminal alkenes<sup>[92]</sup>.

The epoxidation of nonfunctionalized alkenes may also be effected by chiral dioxiranes\*. These species, formed *in situ* using the appropriate ketone and potassium caroate (Oxone), can be formed from C-2 symmetric chiral ketones (29)<sup>[93]</sup>, functionalized carbohydrates (30)<sup>[94]</sup> or alkaloid derivatives (31)<sup>[95]</sup>. One example from the laboratories of Shi and co-workers is given in Scheme 19.

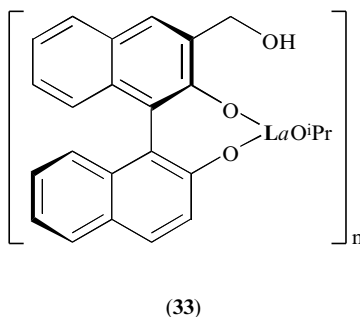
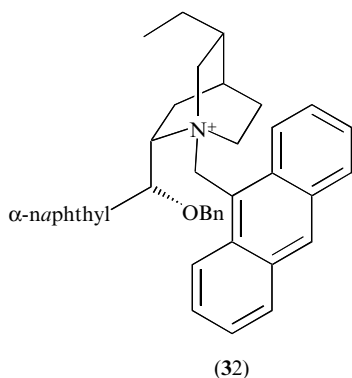


**Scheme 19:** Reagents and conditions: i) Oxone,  $\text{NaHCO}_3$ ,  $\text{CH}_3\text{CN}$ , ketone (30) (30 mole %),  $-10^\circ\text{C}$ .

Historically, the asymmetric synthesis of epoxides derived from electron-poor alkenes, for example  $\alpha$ ,  $\beta$ -unsaturated ketones, has not received as much attention as the equivalent reaction for electron-rich alkenes (*vide supra*). However, a recent flurry of research activity in this area has uncovered several

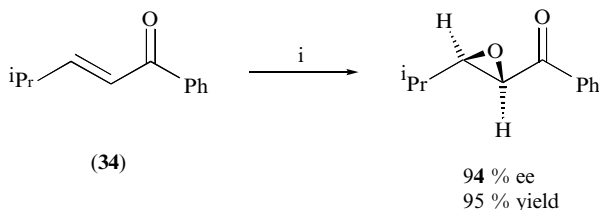
new methods. For example, Enders has shown that oxygen in the presence of diethylzinc and *N*-methyl ephedrine converts enones into epoxides in excellent yields and very good enantiomeric excesses\* (up to 92%)<sup>[96]</sup>. Alternatively, Jackson *et al.* have reported the employment of *tert*-butyl hydroperoxide as the oxidant together with catalytic amounts of dibutyl magnesium and diethyl tartrate. Chalcones are oxidized to the corresponding epoxides under these conditions in yields varying between 40–60% and good to excellent enantiomeric excess<sup>[97]</sup>.

For a similar series of chalcone derivatives the use of aqueous sodium hypochlorite in a two phase system (with toluene as the organic solvent) and the quinine derivative (**32**) as a chiral phase-transfer catalyst, produces epoxides with very good enantiomeric excesses and yields<sup>[98]</sup>.



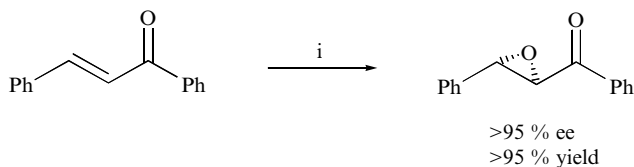
However, the two methods of choice for the oxidations of  $\alpha$ ,  $\beta$ -unsaturated ketones are based on lanthanoid–BINOL complexes\* or a biomimetic process based on the use of polyamino acids as catalysts for the oxidation\*<sup>[99]</sup>.

In the first of these techniques the lanthanoid complex (**33**) (5–8 mol%) is used as the organometallic activator in cumene hydroperoxide or *tert*-butyl hydrogen peroxide-mediated oxidation of chalcone (epoxide yield 99%; 99% ee)\* or the ketone (**34**) (Scheme 20)<sup>[100]</sup>.



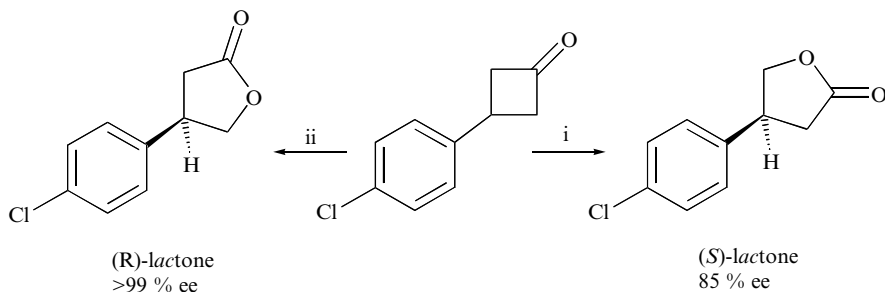
**Scheme 20:** Reagents and conditions: i) cumene hydrogen peroxide, 4Å molecular sieve, THF, complex (**33**).

The biomimetic protocol was invented by Juliá and Colonna, and involves the use of polyamino acids (such as poly-(*L*)-leucine) as the catalysts for peroxide oxidation of chalcones, styryl alkyl ketones and conjugated alkenones. The substrate range is broad, especially when using immobilized catalysts and an organic solvent containing the substrate, urea–hydrogen peroxide and an organic base (Scheme 22)<sup>[101]</sup>.



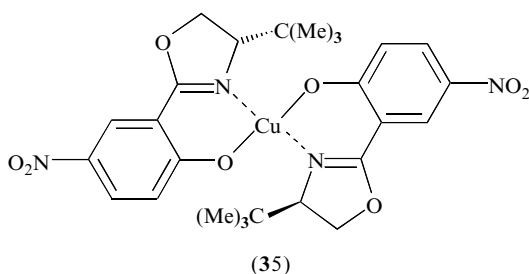
**Scheme 22:** Reagents and conditions: i) poly-L-leucine, urea–hydrogen peroxide, THF, diazabicycloundecene.

Neither biocatalysts nor non-natural catalysts have yet been found that provide a robust method of choice for stereocontrolled conversion of a ketone to an ester (or lactone) via a Baeyer–Villiger reaction. Thus whole cell biocatalysts can be used for very elegant transformations (Scheme 23)<sup>[102]</sup> but the microorganisms (such as *Acinetobacter* sp.) need to be grown and harvested before use (an anathema to most organic chemists, particularly for organisms which are potentially pathogenic) and the use of the relevant isolated enzymes (Baeyer–Villiger monooxygenases) is plagued with the problem of cofactor (NADH or NADPH) recycling and, often, progressive poisoning of the catalytic action of the enzyme by the product as it is formed<sup>[103]</sup>. The cloning of useful Baeyer–Villiger monooxygenases into bakers' yeast may give, in time, more widely-available, easily-used microorganisms<sup>[104]</sup>.



**Scheme 23:** Reactions and conditions: i) *Acinetobacter calcoaceticus*, H<sub>2</sub>O ii) *Cunninghamella echinulata*, H<sub>2</sub>O.

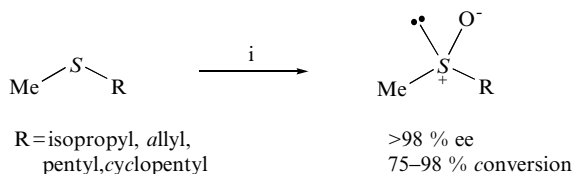
3-Phenylcyclobutanone has been a substrate for a copper-catalysed Baeyer–Villiger oxidation. Thus the complex (**35**), (*ca* 1 mole%) in conjunction with



pivaldehyde in benzene under an atmosphere of oxygen gives a high yield of the (*S*)- $\gamma$ -lactone but in only 44% ee<sup>[105]</sup>. Similarly stereoselective oxidation of 3-hydroxymethylcyclobutanone has been accomplished with dialkyl tartrate/titanium complexes and *tert*-butyl hydroperoxide (conditions similar to those used in Sharpless asymmetric epoxidations). However, yields are modest and the enantiomeric excess of the (*R*)-lactone was just 75%<sup>[106]</sup>.

In contrast to the situation with the Baeyer–Villiger oxidation, synthetic chemists have a choice of both enzymatic or non-enzymatic methods for the oxidation of sulfides to optically active sulfoxides with good to excellent yields and enantiomeric excesses.

Thus a number of enzymes have been shown to be able to control the oxidation of sulfides to optically active sulfoxides; most extensive investigations have concentrated on mono-oxygenases (e.g. from *Acinetobacter* sp., *Pseudomonas putida*) and haloperoxidases<sup>[107]</sup> (from *Caldariomyces fumago* and *Corallina officinalis*). A comparison of the methodologies<sup>[108]</sup> led to the conclusion that the haloperoxidase method was more convenient since the catalysts are more readily available (from enzyme suppliers), the oxidant ( $\text{H}_2\text{O}_2$ ) is cheap and no cofactor recycling is necessary with the haloperoxidases. Typical examples of haloperoxidase-catalysed reactions are described in Scheme 24.

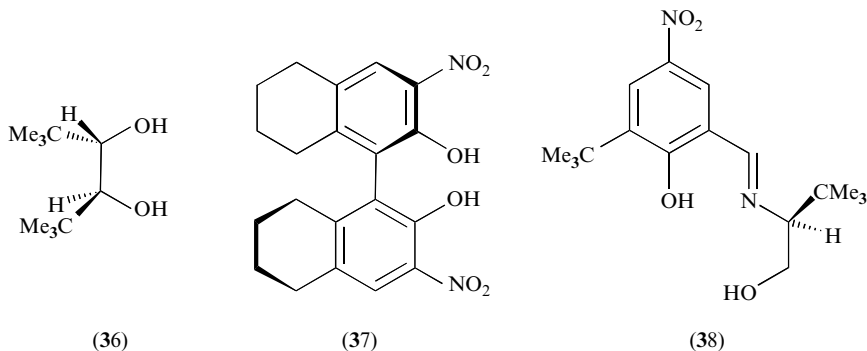


**Scheme 24:** Reactions and conditions: i) Chloroperoxidase from *Caldariomyces fumago*,  $\text{H}_2\text{O}_2$ , halide ion,  $\text{H}_2\text{O}$ .

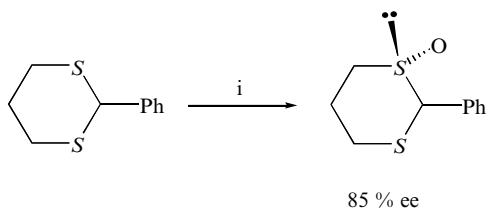
Of several procedures for the stereoselective oxidation of sulfides using organometallic complexes\*, two adaptations of Kagan's original process have gained prominence. In the first method the diol (**36**) is reacted with  $\text{Ti}(\text{O}^i\text{Pr})_4$  to form the catalyst. With cumyl hydroperoxide as the stoichiometric oxidant, methyl *para*-tolyl sulfide was converted into the optically active sulfoxide in 42% yield (98% ee)<sup>[109]</sup>.



In the second noteworthy adaptation of the Kagan method, Reetz and co-workers utilized the dinitrooctahydronaphthol (**37**). Oxidation of methyl *para*-tolylsulfide under similar conditions to those in the above paragraph furnished the optically active sulfoxide (86 % ee)<sup>[110]</sup>.



In addition, a recent report details a very efficient nonenzymatic method for the asymmetric oxidation of sulfides; this employs an organo-vanadium species featuring the imine (**38**) (Scheme 25)<sup>[111]</sup>. A second, complementary strategy for the preparation of optically active sulfoxides involves the enantioselective oxidation of racemic sulfoxides.\*



**Scheme 25:** Reagents and conditions: i) VO(acac)<sub>2</sub>, compound (**38**), H<sub>2</sub>O<sub>2</sub>, H<sub>2</sub>O, CH<sub>2</sub>Cl<sub>2</sub>.

## 1.4 CARBON–CARBON BOND-FORMING REACTIONS

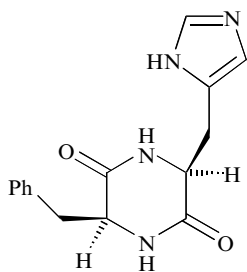
In the arena of carbon–carbon bond-forming reactions, obviously a central feature in synthetic organic chemistry, the number of nonbiocatalytic methods in regular use far outweighs the small portfolio of biotransformations that can be considered to be available for general employment.

Indeed the only conversion where biocatalysis should be seriously considered is the transformation of aldehydes into optically active cyanohydrins<sup>[112]</sup>. For example, the conversion of aryl aldehydes into the appropriate (*R*)-cyanohydrins using almond meal may be accomplished in quantitative yield and gives products

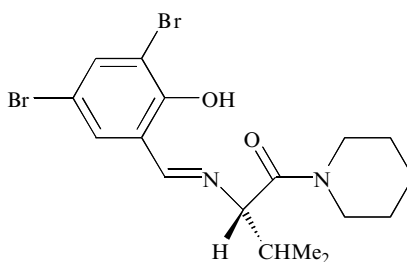
of high optical purity<sup>[113]</sup>. The method is much less successful for the vast majority of ketones.

(*S*)-Cyanohydrins are formed from a wide range of alkyl and aryl aldehydes (and also some methyl ketones) often in good yield and high enantiomeric excess using the enzyme (hydroxynitrile lyase) from *Hevea brasiliensis*<sup>[114]</sup>. The same range of substrates and the same cyanohydrins ((*S*)-configuration) are formed on catalysis of the addition of HCN using the hydroxynitrile lyase from *Manihot esculenta*. This enzyme has been cloned and over-expressed in *E. coli*<sup>[115]</sup>.

A biomimetic method using a cyclic dipeptide (**39**) is available. In the presence of HCN in toluene containing 2 mole% of (**39**), benzaldehyde is converted into the (*R*)-cyanohydrin in 97% yield (97% ee)<sup>[116]</sup>.



(39)

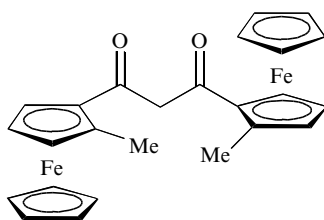


(40)

Complexation of an amino acid derivative with a transition metal to provide a cyanation catalyst has been the subject of investigation for some years. It has been shown that the complex formed on reaction of titanium(IV) ethoxide with the imine (**40**) produces a catalyst which adds the elements of HCN to a variety of aldehydes to furnish the (*R*)-cyanohydrins with high enantioselectivity<sup>[117]</sup>. Other imines of this general type provide the enantiomeric cyanohydrins from the same range of substrates<sup>[117]</sup>.

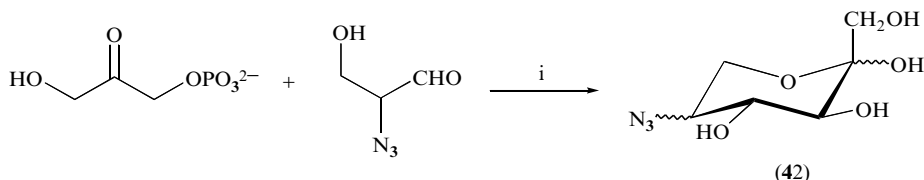
The addition of trimethylsilyl (TMS) cyanide to aldehydes produces TMS-protected cyanohydrins. In a recent investigation a titanium salen-type catalyst has been employed to catalyse trimethylsilylcyanide addition to benzaldehyde at ambient temperature<sup>[118]</sup>. Several other protocols have been published which also lead to optically active products. One of the more successful has been described by Abiko *et al.* employing a yttrium complex derived from the chiral 1,3-diketone (**41**)<sup>[119]</sup> as the catalyst, while Shibasaki has used BINOL, modified so as to incorporate Lewis base units adjacent to the phenol moieties, as the chiral complexing agent<sup>[120]</sup>.

The aldol reaction is of fundamental importance in organic chemistry and has been used as a key reaction in the synthesis of many complex natural products. There are biocatalysts for this reaction (aldolases) and one (rabbit muscle



(41)

aldolase, RAMA) has been quite widely used for the preparation of carbohydrates and closely related compounds. For example, the azidotetraol (42) (a precursor of novel cyclic imine sugars active as  $\alpha$ -fucosidase inhibitors) has been prepared by coupling dihydroxyacetone monophosphate and 2-azido-3-hydroxypropanal using RAMA as the catalyst, followed by dephosphorylation (Scheme 40)<sup>[121]</sup>.

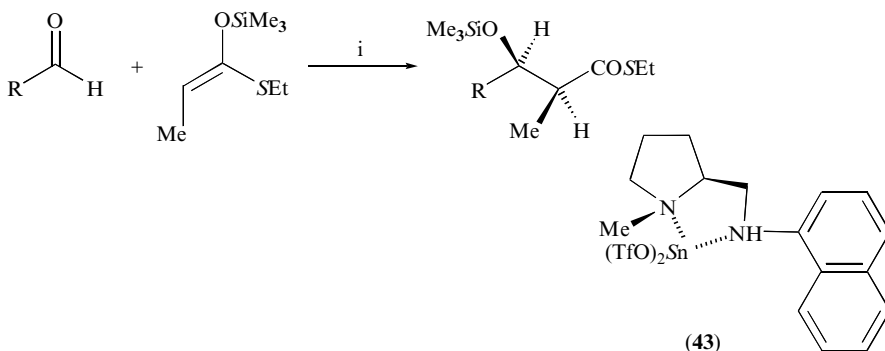


**Scheme 40:** Reagents and conditions: i) RAMA, H<sub>2</sub>O then dephosphorylation using acid phosphatase.

Other aldolases, from microorganisms, have been cloned and overexpressed. For instance, L-threonine aldolase from *Escherichia coli* and D-threonine aldolase from *Xanthomonas oryzae* have been obtained and used to prepare  $\beta$ -hydroxy- $\alpha$ -amino acid derivatives<sup>[122]</sup>.

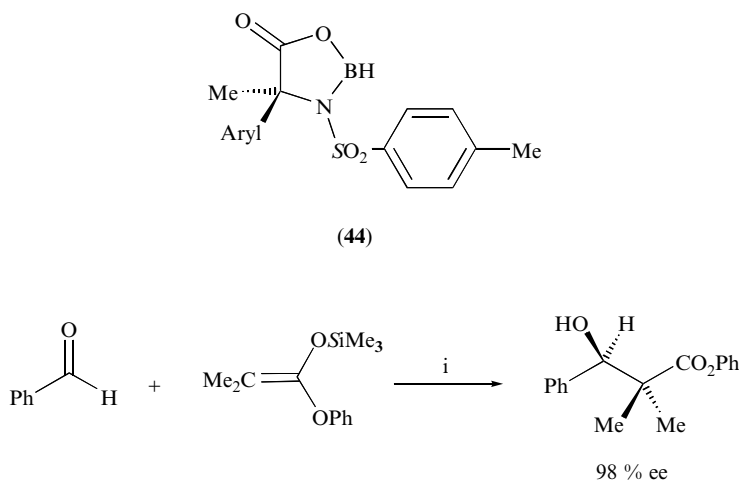
On moving away from carbohydrate chemistry one finds that non-natural catalysts are the materials of choice for the promotion of the classical aldol reaction and more recently-discovered variants. A wide range of methods are available and a small selection of these is described below.

One of the most widely studied aldol-type reactions is the Mukaiyama coupling of enol silanes of various types to aldehydes, catalysed by Lewis acids (notably organotin, organoboron, organotitanium and organocopper species). A typical example of the stereocontrolled coupling of an aromatic or aliphatic aldehyde and a silylthioetene acetal is described in Scheme 41. The products are generally obtained in 70–80% yield with a good to excellent diastereomeric excess of the *syn* isomer in 90–100% ee on using 10–30 mol% of the catalyst (43)<sup>[123]</sup>.



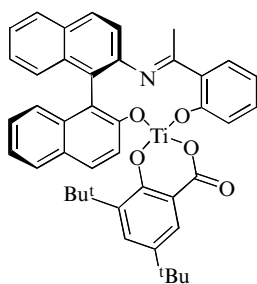
**Scheme 41:** Reagents and conditions: i)  $C_2H_5CN$ ,  $-78^\circ C$ , 10–30 mol% complex **(43)**.

Of the catalysts that are based on boron, the Masamune oxazaborolidines (**44**) are typical, being able to promote aldol reactions of the type described in Scheme 42<sup>[124]</sup>.

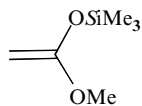


**Scheme 42:** Reagents and conditions: i) 20 mol% catalyst **(44)**.

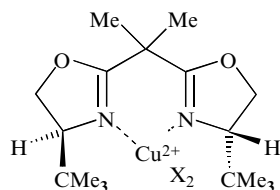
From the organotitanium family of catalysts  $BINOL-TiCl_2$  and  $BINOL-Ti(iPrO)_2$  catalysts have been complemented by related catalysts of type **(45)** introduced by Carreira<sup>[125]</sup>. The simple enol silane **(46)** adds to a variety of aldehydes in high yields and excellent enantiomeric excesses, using as little as 0.5 mol% of the catalyst **(45)**. The reacting aldehydes can bear some other functional groups, such as *tert*-butyldimethyl silyl ether moieties.



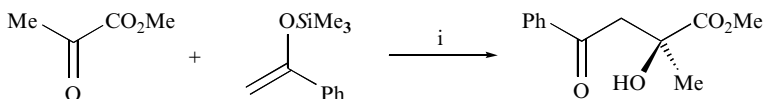
(45)



(46)

(47):  $X = CF_3SO_3^-$ (48):  $X = [SbF_6]^-$ 

The utilization of copper complexes (**47**) based on bisoxazolines allows various silyl enol ethers to be added to aldehydes and ketones which possess an adjacent heteroatom: e.g. pyruvate esters. An example is shown is Scheme 43<sup>[126]</sup>.  $C_2$ -Symmetric Cu(II) complexes have also been used as chiral Lewis acids for the catalysis of enantioselective Michael additions of silylketene acetals to alkylidene malonates<sup>[127]</sup>.



**Scheme 43:** Reagents and conditions: i)  $CH_2Cl_2$ ,  $-78^\circ C$ , 10 mol% catalyst (**47**).

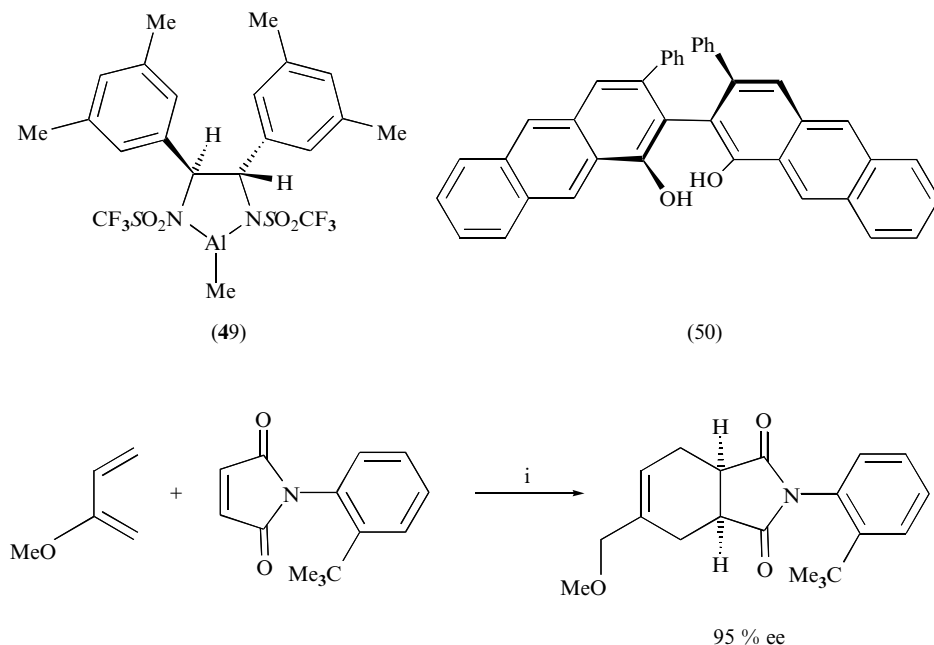
Direct asymmetric aldol reactions, that is between aldehydes and unmodified ketones has been accomplished using a lanthanum trilitium tri(binaphthoxide) complex<sup>[128]</sup>.

One of the key features of such stereocontrolled aldol reactions is the predictability of the absolute stereochemistry of the enantiomers (or diastereomers) that will be formed as the major products. The preferred intermediate for an archetypal aldol reaction, proceeding by way of a metal enolate, can be tracked using the Zimmerman–Traxler transition state and the results from the different variations of the aldol reaction can be interpreted from similar reasoning, and hence predictions made for analogous reactions<sup>[129]</sup>.

The second well-known and much-used carbon–carbon bond forming reaction is a [4 + 2]-cycloaddition, the Diels–Alder reaction. Very many chiral Lewis acid catalysts have been used to promote this reaction and a *pot-pourri* of organo-aluminium, -boron and -copper catalysts are described, in brief, below.

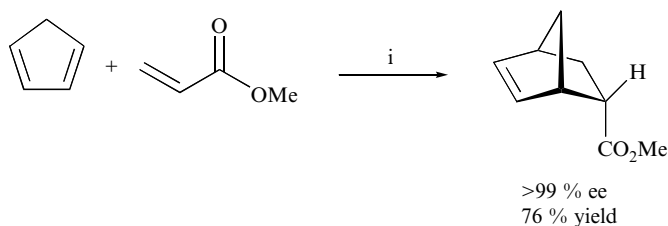
The first organoaluminium complex that catalysed a Diels–Alder reaction was formed from menthol and ethylaluminium dichloride. This finding was complemented by work of Corey who showed that the aluminium–diamine complex (**49**) was effective for controlling the stereochemistry of Diels–Alder reactions involving cyclopentadiene and acryloyl and crotonyl amides (e.g.

$\text{CH}_3\text{CH}=\text{CHCONR}_2$ ). Later investigations showed the catalysts were also effective stereocontrolling systems for the coupling of a maleimide to an acyclic diene (Scheme 44)<sup>[130]</sup>.



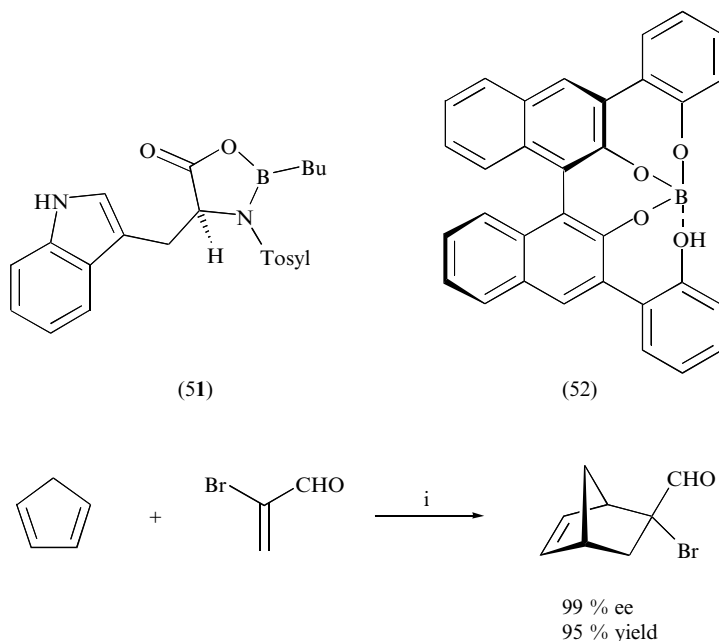
**Scheme 44:** Reagents and conditions: i)  $\text{CH}_2\text{Cl}_2$ ,  $-78^\circ\text{C}$ , 10–20 mol% catalyst (49).

The biaryl compound (50) forms a complex with diethylaluminium chloride to provide a catalyst able to promote enantioselective reaction between cyclopentadiene and methacrolein or acrylates (Scheme 45). The addition of di-*tert* butyl 2,2-dimethylmalonate to the reaction mixture was found to enhance the enantiomeric excess of the product<sup>[131]</sup>.



**Scheme 45:** Reagents and conditions: i)  $(\text{Me}_3\text{CO}_2\text{C})_2\text{CMe}_2$  50 mol%,  $\text{Et}_2\text{AlCl}$  and compound (51) 10 mol% each,  $\text{CH}_2\text{Cl}_2$ ,  $-78^\circ\text{C}$  to  $-40^\circ\text{C}$ .

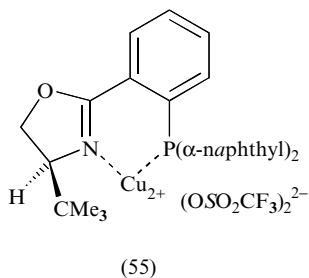
Acyloxyboron complexes and oxazaborolidines have been shown to catalyse Diels–Alder reactions featuring aldehydes as one component: for example, the complex (**51**) allows the coupling of cyclopentadiene and  $\alpha$ -bromoacrolein in high yield to give a product of high optical purity (Scheme 46)<sup>[132]</sup>. The immobilized catalyst system of this genre, recently introduced by Itsuno, is



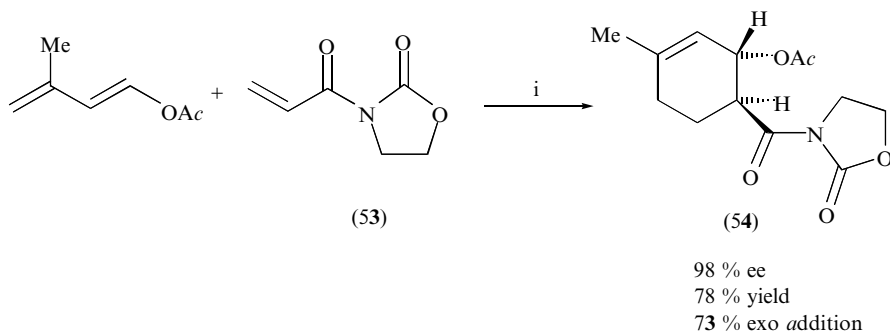
**Scheme 46:** Reagents and conditions: i)  $\text{CH}_2\text{Cl}_2$ ,  $-78^\circ\text{C}$ , 5–10 mol% catalyst (**51**).

also worthy of note<sup>[133]</sup>. In a further development Brønsted acid-assisted chiral Lewis acids such as compound (**52**) were shown to promote stereocontrolled reactions of dienes with a range of  $\alpha, \beta$ -unsaturated aldehydes<sup>[134]</sup>.

Copper(II)-bis(oxazoline) complexes (**48**) are robust, valuable catalysts for a wide variety of stereoselective Diels–Alder reactions. In a key step *en route* to

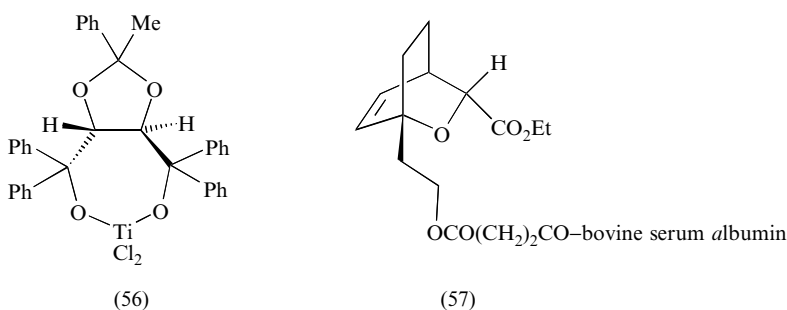


optically active cannabinoids, Evans and co-workers showed that an acyclic dienol ester combined with the amide (**53**) to give the cyclohexane derivative (**54**) (Scheme 47)<sup>[135]</sup>.



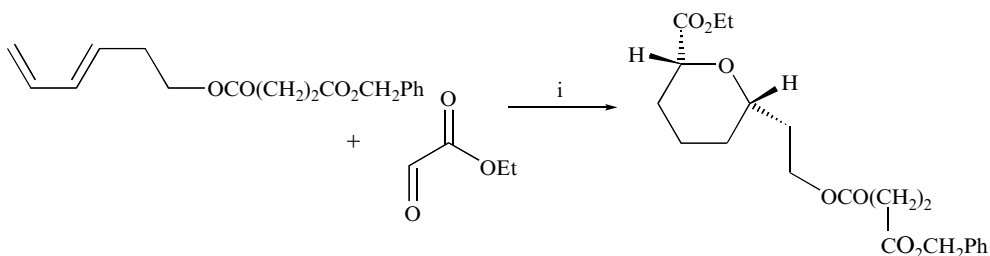
**Scheme 47:** Reagents and conditions: i) Compound (**48**) (2 mol%),  $\text{CH}_2\text{Cl}_2$ ,  $-20^\circ\text{C}$ .

The phosphino-oxazoline copper(II) complex (**55**) has also been found to be an effective catalyst<sup>[136]</sup> as have some titanium complexes, such as the extensively researched titanium–TADDOL system (**56**)<sup>[137]</sup>. A modified Ti(IV)–TADDOL compound is the catalyst of choice to promote Diels–Alder cycloaddition reactions between cyclopentadiene and alk-2-enyl phenylsulfonylmethyl ketones<sup>[138]</sup>.



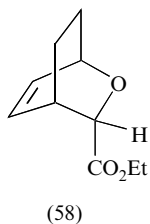
The library of natural catalysts has very little to offer for the catalysis of Diels–Alder (and the reverse) reactions (Diels–Alderases)<sup>[139]</sup>. For this reason one of the intriguing areas of biomimicry, namely the formation and use of antibodies exhibiting catalytic activity, has focused on  $[4 + 2]$  reactions to try to furnish proteins possessing useful catalytic properties. Thus in early studies a polyclonal catalytic antibody raised to hapten (**57**)<sup>[140]</sup> showed a modest rate enhancement for the reaction depicted in Scheme 48.



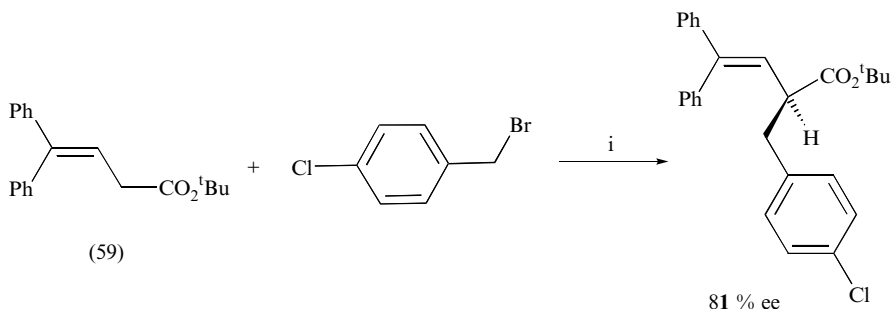


**Scheme 48:** Reagents and conditions: i) polyclonal antibody raised against hapten (57).

The same, understandable bias towards the preferred use of ‘man-made’ catalysts, rather than biocatalysts, continues in the area of hetero-Diels–Alder reactions<sup>[141]</sup>. For example, in the presence of 5 mol% of copper complexes of the type (47), cyclohexadiene and ethyl glyoxylate produce the oxabicyclooctene (58) (66 % yield, 97 % ee)<sup>[142]</sup>.



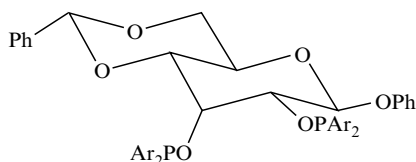
Asymmetric alkylation of enolates can be effected using chiral phase transfer reagents. In an example from O’Donnell’s group, the ester (59) is alkylated in a two-phase solvent system containing an N-benzylcinchoninium salt (Scheme 49)<sup>[143]</sup>. Again, there is no competing methodology in the armoury of biocatalysis.



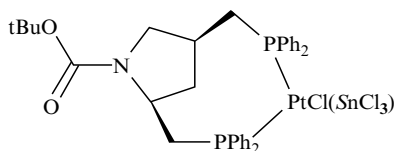
**Scheme 49:** Reagents and conditions: i) 50 % NaOH, toluene and  $\text{CH}_2\text{Cl}_2$ , 5 °C N-benzylcinchoninium salt.

The promotion of carbon–carbon bond forming reactions involving alkenes is, once again, almost entirely within the domain of non-natural catalysts. One example each from five important areas are described below. It should be noted that this area is one of intense current interest and new catalysts and novel methodologies are appearing monthly; thus the following selection gives the reader only a glimpse of the important ground-breaking work in this area.

Hydrocyanation of alkenes (and alkynes) is an efficient route to nitriles *en route* to many types of fine chemicals. Initial studies of the hydrocyanation of vinylarenes such as styrene involved the use of a nickel–DIOP system, but ee's were disappointing at *ca* 10%. More success was achieved with carbohydrate derived phosphinite-nickel catalysts. For example the glucose-based bisphosphinite (**60**), on complexation with the metal, promoted the hydrocyanation of 4-methyl styrene to afford (*S*)-2-*para*-tolylpropanonitrile in 70% ee<sup>[144]</sup>. The same ligand promoted the asymmetric hydrocyanation of 2-methoxy-6-vinyl naphthalene to give an important intermediate to the nonsteroidal anti-inflammatory (NSAI) agent naproxen in *ca* 90% ee, using Ni(COD)<sub>2</sub> as the source of the metal. Also recently discovered has been a practical synthetic route to  $\alpha$ -amino acids using titanium-catalysed enantioselective addition of cyanide to imines<sup>[145]</sup>.



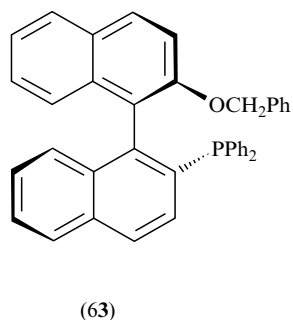
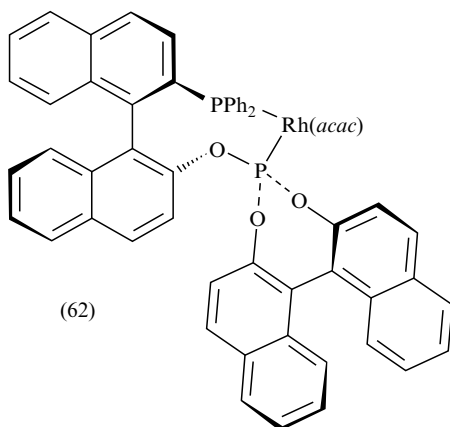
(60) Ar = 3,5-bis-trifluorophenyl



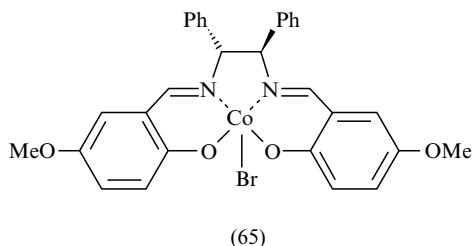
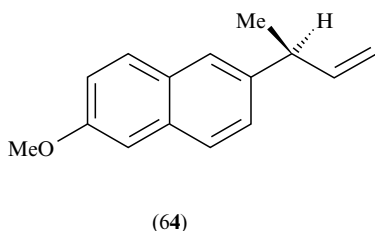
(61)

Rhodium (I) complexes of chiral phosphines have been the archetypical catalysts for the hydrocarbonylation of 1-alkenes, with platinum complexes such as (**61**) making an impact also in the early 1990s<sup>[146]</sup>. More recently, rhodium(I)-chiral bisphosphites and phosphine–phosphinites have been investigated. Quite remarkable results have been obtained with Rh(I)–BINAPHOS (**62**), with excellent ee's being obtained for aldehydes derived for a wide variety of substrates<sup>[147]</sup>. For example, hydroformylation of styrene gave a high yield of (*R*)-2-phenylpropanal (94% ee). The same catalyst system promoted the conversion of *Z*-but-2-ene into (*S*)-2-methylbutanal (82% ee).

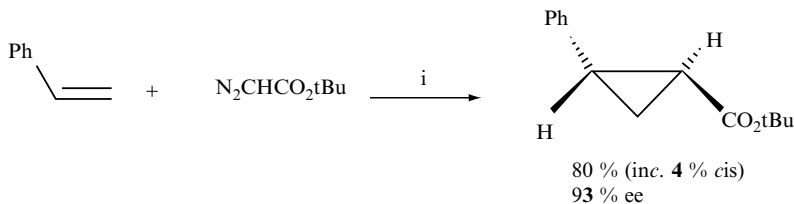
The related field involving the hydrocarboxylation of alkenes is also under investigation<sup>[148]</sup>, not least because of its potential importance in the synthesis of NSAI drugs. An indirect way to the latter compounds involves the hydrovinylation of alkenes. For example catalysis of the reaction of ethylene with 2-methoxy-6-vinylnaphthalene at  $-70^{\circ}\text{C}$  using (allylNiBr)<sub>2</sub> and binaphthyl (**63**)



furnished the naproxen precursor (**64**) in 97% yield and 80% ee<sup>[149]</sup>. While nickel complexes have been most widely used for this type of process, palladium with a menthol-derived phosphinite has been used to convert ethene and styrene into (*S*)-3-phenylbut-1-ene in 66% yield and 86% ee<sup>[150]</sup>.



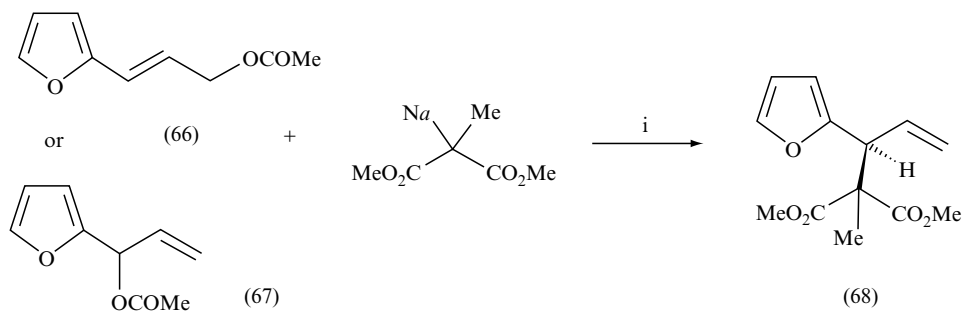
Cyclopropanation reactions can be promoted using copper or rhodium catalysts or indeed systems based on other metals. As early as 1965 Nozaki showed that chiral copper complexes could promote asymmetric addition of a carbenoid species (derived from a diazoester) to an alkene. This pioneering study was embroidered by Aratani and co-workers who showed a highly enantioselective process could be obtained by modifying the chiral copper



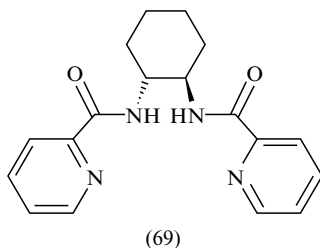
**Scheme 50:** Reagents and conditions: (i) Catalyst (**65**), room temperature, CH<sub>2</sub>Cl<sub>2</sub>, 24 h.

complex<sup>[151]</sup>. Subsequently many excellent metal-catalysed methods have been developed for asymmetric cyclopropanation<sup>[152]</sup>, most being trans-selective for the addition of diazo-ester to an alkene such as styrene: one example is shown in Scheme 50<sup>[153]</sup>. Only a few catalysts (for example a ruthenium–salen system) have been found that promote asymmetric cyclopropanation to give *cis*-products<sup>[154]</sup>. The range of asymmetric reactions of diazoesters has been extended to additions to imines to furnish aziridine derivatives<sup>[155]</sup>.

Finally allylic substitution reactions involving, for example, replacement of an acetate unit with a malonate residue (or other nucleophiles) has been researched extensively by Trost and co-workers<sup>[156]</sup>. This group originally used  $\text{Pd}(\text{PPh}_3)_4$  in the presence of a chiral phosphine to induce asymmetry but has shown more recently, *inter alia*, that the isomers (66) and (67) are both converted into the diester (68) in good yield and >95 % ee using the dipyridine ligand (69) in a molybdenum-based catalyst (Scheme 51). The extensive range of chiral catalysts that have been used to effect enantioselective C–C and C–heteroatom bond formation is such allyl displacement reactions has been reviewed<sup>[157]</sup>.



**Scheme 51:** Reagents and conditions: (i) 10 %  $(\text{MeCN}_3\text{Mo}(\text{CO})_3)$  ligand (69).



## 1.5 CONCLUSIONS

It is clear that in the following areas of synthetic chemistry the use of isolated enzymes or whole cell organisms should be considered (sometimes alongside

other forms of catalysis) when one is faced with the transformation of the novel substrate.

- Enantioselective hydrolysis reactions, especially esters, amides and nitriles.
- Stereocontrolled oxidation of aromatic compounds (hydroxylation or dihydroxylation) and hydroxylation of some alicyclic compounds, especially at positions remote from pre-existing functionality.
- Stereocontrolled oxidation of sulfides to sulfoxides.
- Formation of optically active cyanohydrins.

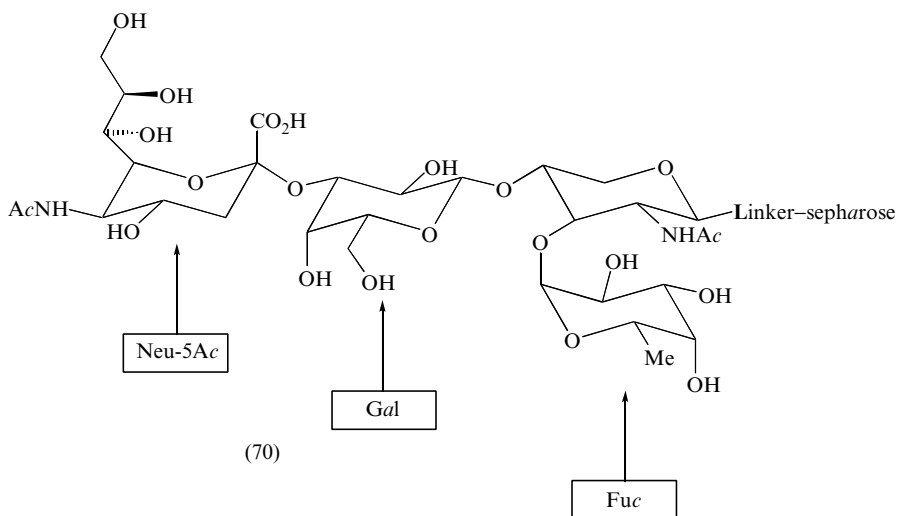
Biomimetic reactions should also be considered for the preparation of optically active cyanohydrins (using a cyclic dipeptide as catalyst) and also for the epoxidation of  $\alpha$ ,  $\beta$ -unsaturated ketones (using polyleucine or congener as a catalyst).

In most other areas, especially in the field of carbon-carbon bond formation reactions, non-natural catalysts reign supreme.

However, while it is clear that biocatalysts may only provide viable and reliable methods in about 5–10 % of all transformations of interest to synthetic organic chemists, it is also clear that in some cases the biotransformation will provide the **key step** in the best method in going from a cheap substrate to a high value, optically active fine chemical. Thus ignoring biotransformations altogether means one may occasionally overlook the best pathway to a target structure.

In addition there is at least one area where enzyme-catalysed reactions have established themselves as the first line of attack for solving synthetic problems; that area involves the transformations of carbohydrates. Indeed, biocatalysed transformations of saccharides is becoming increasingly popular and roughly 10 % of the recent literature (Year 2000) on biotransformations involves the preparation and modification of carbohydrates. Early literature on chemoenzymatic approaches for the synthesis of saccharides and mimetics has been reviewed by a pioneer in the field, C.-H. Wong<sup>[158]</sup>. For one of the most popular areas, enzyme-catalysed glycosylation reactions, a useful survey is also available, penned by the same senior author<sup>[159]</sup>.

One advantage of using enzyme-catalysed reactions in this field is that exquisite regio- and stereo-selectivity can be obtained, without recourse to long-winded protection/deprotection strategies. Furthermore, it is perfectly feasible to use different enzymes sequentially, quickly to produce complex polysaccharides. In the example shown in Scheme 50; N-acetylglucosamine is appended by a linker to a Sepharose bead: thereafter galactosyltransferase (with UDP-galactose), sialyltransferase (with CMP-neuraminic acid 5-acetate) and fucosyltransferase (with GDP-fucose) were used sequentially to prepare sialyl Lewis tetrasaccharide (**70**) attached to the solid support; an impressive overall yield of 57% was recorded<sup>[160]</sup>.



The sharp rise in the number of enzymes capable of promoting coupling reactions involving carbohydrate moieties mirrors the increased activity and interest in this field. Obviously this will provide an important niche area where enzyme-catalysed reactions will probably remain the methodology of choice at least for the foreseeable future.

So, in the final analysis, biocatalysis should not be considered in a separate sector available only to the specialist bioorganic chemist. It is one method, in the portfolio of catalytic techniques, that is available to all chemists for the solution of present and future problems in organic synthesis. To erect a 'Chinese wall' between the natural and non-natural catalysts is totally illogical and prevents some creative thinking, particularly in the area of coupled natural/non-natural catalysts<sup>[161]</sup> and biomimetic systems<sup>[162]</sup>.

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7.  $E = \ln[(1 - c)(1 - ee_s)] / \ln[(1 - c)(1 + ee_s)]$  where  $c$  = conversion ( $100\% = 1.0$ );  $ee_s$  = enantiomeric excess of substrate ( $100\% = 1.0$ ).
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