1 Industrial Catalysts for Regio- or Stereo-Selective Oxidations and Reductions. A Review of Key Technologies and Targets

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CONTENTS

Catalysts for Fine Chemical Synthesis, Vol. 5, Regio- and Stereo-Controlled Oxidations and Reductions
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1.1 INTRODUCTION

In this volume procedures are documented for selective oxidations and reductions that represent the advances in these fields since Volume 1 of this series was published (in 2002). This introduction highlights some examples from the literature that demonstrates the needs of industry and identifies how some of these requirements were met and illustrates a number of the challenging problems that are still to be overcome.

Since the Nobel Prize-winning pioneering work of Knowles and Noyori for reduction reactions (working with phosphine ligands that have phosphorus chirality and axial chirality, respectively) and Sharpless for epoxidations of allylic alcohols a wide range of chiral oxidation and reduction catalysts have been developed. This book gives an insight into some of the practical uses of these protocols along with more detailed experimental procedures for their use. It also seeks to include other examples of selective reactions which could prove useful in industrial applications and presents detailed procedures to implement these.

From an industrial viewpoint there are several drivers that need to be satisfied before a catalyst can be successfully implemented in production plants. Technically there have been various challenges to be met including the synthesis of the requisite ligands, catalyst sensitivity to the environment in which it is applied, reproducibility in product enantiomeric excess (ee) and yield, feasibility in the use of commercial solvents and IP issues around 'freedom to operate'. All these issues have been factors that have influenced commercial exploitation. An example of how one or more of these factors can decide the selection of a catalyst system was described by Hawkins,[1] where Pfizer's selection of the Degussa DEGUPHOS catalyst system over the technically superior DUPHOS system in the synthesis of a Candoxatril intermediate (shown in Figure 1.1) was decided by royalty payments and freedom to operate issues.

Thus, although Rh–MeDUPHOS gave the desired product in excellent yield and 99 % ee it was not chosen to prepare the two metric tons of Candoxatril intermediate required for phase-III clinical trials. Instead MeOBIPHEP was chosen because it was readily available on large scale (up to 10 kg) and Pfizer needed to have the right to use the catalyst in-house. In the large-scale asymmetric hydrogenation 231 kg batches were hydrogenated in a 4000-L reactor and problems related to olefin isomerization were attenuated by switching the solvent from a methanol/water mixture to a THF/water system. The purity specifications were then met by recrystallization.

The reduction of double bonds using chiral phosphine ligands as the precursors for the appropriate catalysts is a widely used strategy in the asymmetric synthesis of

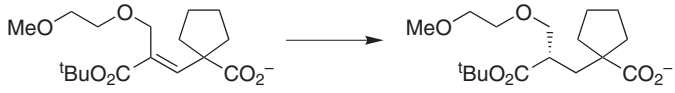


Figure 1.1 Candoxatril intermediate (Pfizer).

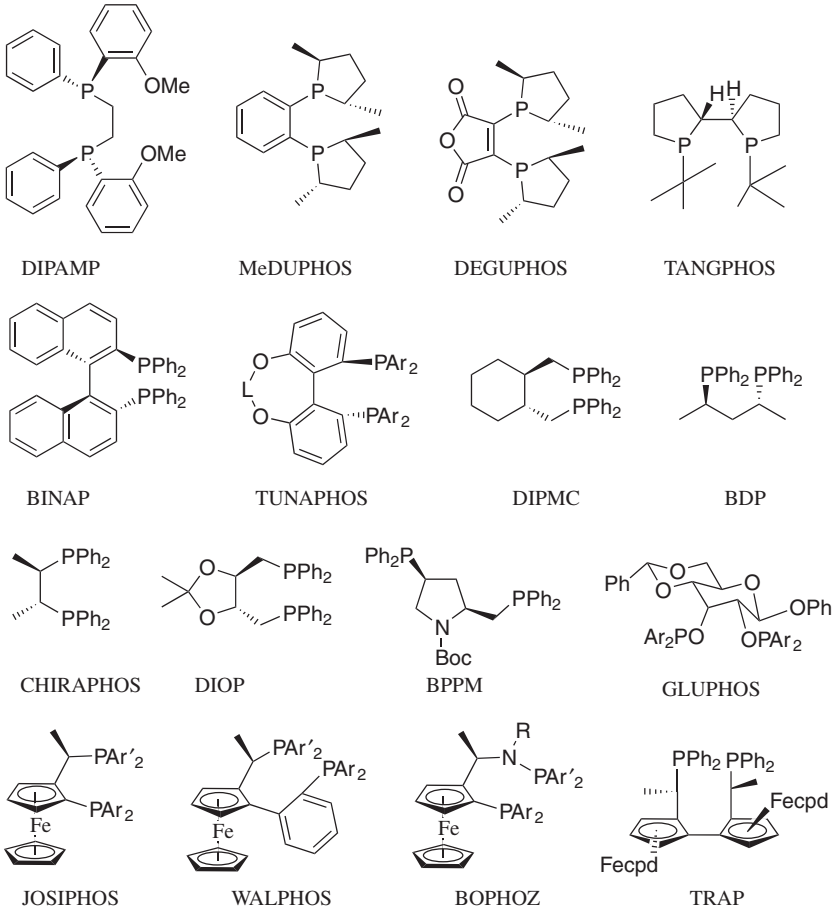


Figure 1.2 Illustrative examples of chiral phosphine ligands.

high value fine chemicals. It is a very powerful tool for introducing chirality into molecules. A large number of different types of chiral phosphines have been investigated for the reduction of a range of unsaturated compounds including alkenes, ketones and imines. Many ligands have been assessed and the structures of some of these that have made a significant impact on industrial processes are shown in Figure 1.2.

1.2 REDUCTION OF CARBON-CARBON DOUBLE BONDS

The chiral phosphines shown in Figure 1.2 represent the typical types of chiral ligands employed to generate those chiral catalysts that have had the most industrial interest in terms of asymmetric reductions. The next section divides these

compounds into groups depending on the substituents on the double bonds that were needed to be reduced and describes some of the challenges that are now being faced by industrial chemists.

The industrial challenges now reside with finding reduction catalyst systems for the emerging drug intermediates for the new classes of pharmaceuticals that are going into clinical application; this introduction intends to give an overview of these pertinent technical issues.

1.2.1 PRIVILEGED STRUCTURES: α-AMINO ACIDS AND ITACONIC ACIDS

The above classes of compounds have the ability to bind to the transition metal of the catalytic species, usually through a carboxylate group, and form the families of chiral reductions that have been the most intensively studied. They also yield products that are key intermediates in a range of active pharmaceutical ingredients (APIs). The catalyst systems for the 'privileged structures' have been well developed and α-amino acids and itaconic acids are routinely synthesized by reduction of unsaturated precursors with high ees and conversions at low catalyst concentrations. Many examples of the reactions shown in Figure 1.3 have been run at industrial scale and a wide range of catalytic systems have been reported that deliver high conversions and greater than 99 % ee.[2]

Perindopril (**A**), an orally active pharmaceutical for the treatment of hypertension, is an important commercial target compound that has a cyclic α-amino acid as an intermediate in its synthetic route. The bicyclic α-amino acid building block is synthesized by reduction of the chiral indoline-2-carboxylic acid (**B**, R=R′=H) shown in Figure 1.4. This chiral cyclic amino acid has so far proven very difficult to synthesize in a highly enantioselective manner using chiral hydrogenation.

Therefore better methods for the chiral reduction of indole-2-carboxylic acid derivatives would provide an elegant synthesis of this intermediate. A study by Kuwano and Kashiwabara[3] of the reduction of indole derivatives into the corresponding indolines found that a range of the more common ligand systems gave almost no enantioselectivity but the TRAP ligand gave the chiral indolines in up to 95 % ee for reduction of the methyl ester (**B**, R=Me, R′=H). Further developments are awaited.

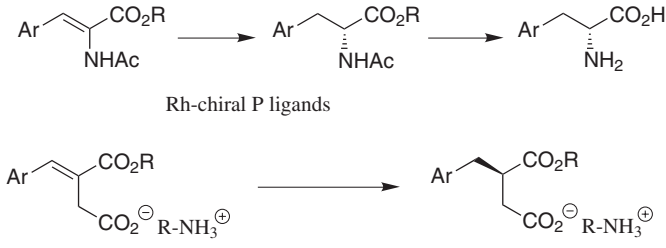
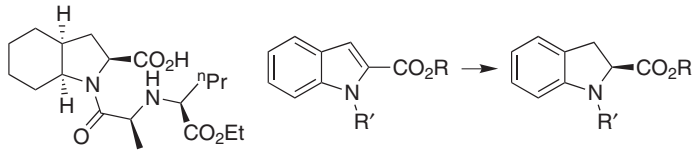


Figure 1.3 Privileged structures for industrial chiral hydrogenation.



(A) (B)

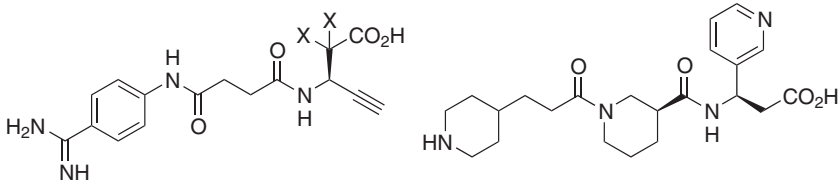
Figure 1.4 Perindopril (**A**) and the key hydrogenation step.

1.2.2 β-AMINO ACIDS

β-Amino acids are key building blocks for several industrial API targets as they form part of the structure of several new potentially commercially important compounds. Although the chiral hydrogenation route has not been investigated as thoroughly as for α-amino acids there is a significant number of published catalyst systems that yield these types of chiral building blocks[4]. β-Amino acids possess several biologically interesting properties including a remarkable stability of their derived amides towards peptidases: when used in the construction of peptidomimetics they confer the ability to fold into distinct secondary structures (similar to α-peptides) such as helices, turns, sheets and tubular structures. Such properties make them powerful tools for medicinal chemistry[5]. β-Homophenylalanine has been a widely reported as an example from this family of compounds. Other structures that use members of this family as their components are exemplified by the 'fiban' compounds (shown in Figure 1.5) which display various β-amino acid residues, including a cyclic constrained structure that forms an important sub-group of the β-amino acids family[6].

The enantioselective synthesis of the β-amino acid ester shown in Figure 1.6 has recently been reported by Kubryk and Hansen[7] (Merck) where good ees were obtained by asymmetric hydrogenation. Using an *in-situ* reaction with diBoc-anhydride to protect the amine group a crystalline product was obtained that was recrystallized to the required 99 % + ee purity very easily.

A recent example from Pfizer reported by Hoge[8] involves the synthesis of the β-amino acid shown in Figure 1.7. Initially the BINAPINE ligand gave the higher diastereomeric excess but only 85 % conversion while the TRICHICKENFOOT ligand was giving incomplete conversion. By running the reaction with the first ligand system until the reaction stalled and then adding a second catalyst based on



X = H SC 54701, X,X = O Xemilofiban Elarofiban

Figure 1.5 Exemplification of β-amino acids as API building blocks.

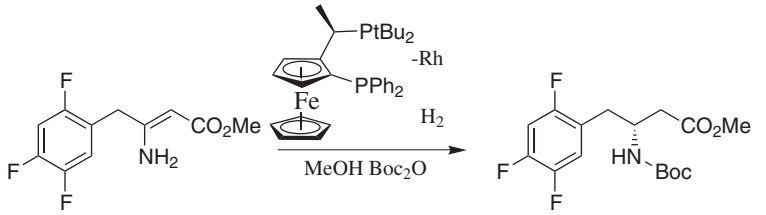


Figure 1.6 Merck β-amino acid synthesis.

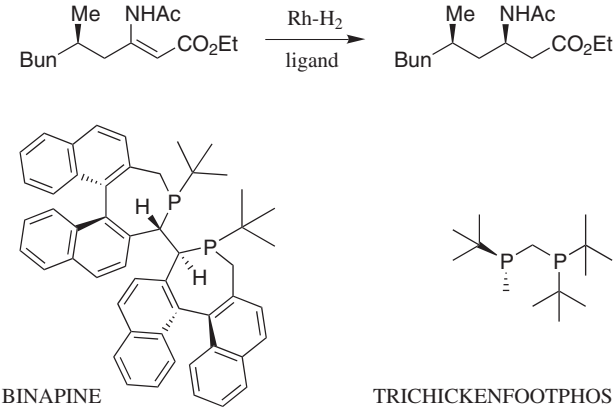


Figure 1.7 Pfizer β-amino acid synthesis.

the other ligand optimum performance was obtained. However, on further optimization by adjusting the solvent mixture and using careful control of water content Pfizer's own TRICHICKENFOOT ligand gave suitable performance and circumvented unwanted IP issues.

1.2.3 α-ALKYL SUBSTITUTED ACIDS

Another important acid derived from the corresponding unsaturated acid family is the α-alkyl substituted acid (**C**). This compound is used in the synthesis of Aliskiren (the active ingredient of Tekturna®) which Novartis has recently been granted FDA approval as the first-in-class renin inhibitor for control of blood pressure. It is estimated that large volumes of this intermediate will be required in the future but the best ee reported so far for production of this intermediate is 95 % as shown in Figure 1.8.[9]

A study by Hoen *et al.*[10] in collaboration with scientists from DSM indicates that the MONOPHOS derivative (**D**) together with added triphenylphosphine improves both the rate of reaction and enantioselectivity and may offer an improved

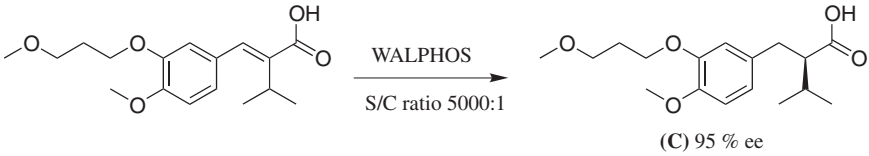


Figure 1.8 Novartis Aliskiren intermediate hydrogenation.

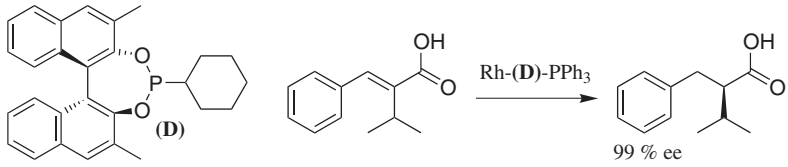


Figure 1.9 DSM MONOPHOS hydrogenation ligand system.

system for this important target as can be seen from the analogous reaction reported by these authors and shown in Figure 1.9.

The drug candidate OPC-51803 is the first nonpeptide vasopressin V_2-receptor-selective agonist that is in phase II clinical trials and the best chiral reduction to the intermediate acid (**E**) was with ruthenium acetate-[(*S*)-H8-BINAP] that gave a 77 % ee[11] (Figure 1.10). An improved catalyst system will be needed for large scale production.

Tipranavir is a unique, nonpeptidic protease inhibitor currently in phase III clinical trials for HIV treatment. In this compound a phenolic hydroxyl group behaves as a pseudo carboxylic acid group and the chiral hydrogenation step shown in Figure 1.11 gives reasonable enantioselectivity. Benincori *et al.*[12] have investigated the diastereoselective reduction of the tipranavir intermediate (**F**) using ullaPHOS, a more electron rich variant of DUPHOS, and have found this catalyst system increases the rates of hydrogenation and gives reasonable diastereomeric excesses (de's). Further optimization of this transformation is awaited.

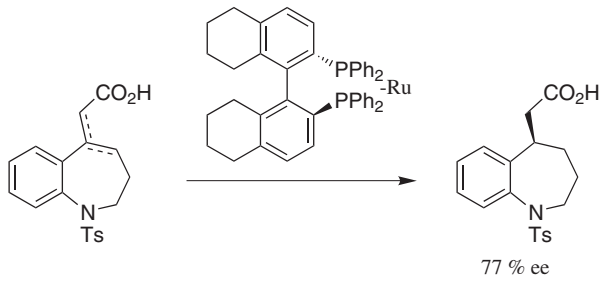


Figure 1.10 OPC-51803 intermediate.

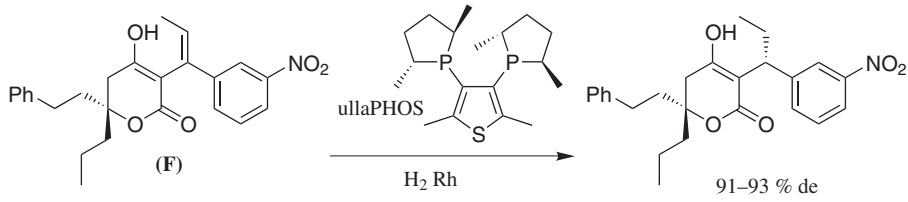


Figure 1.11 Tipranavir intermediate synthesis.

1.2.4 α-ALKOXY SUBSTITUTED ACIDS

Another important family of emerging pharmaceutical substances is the 'glitazar' portfolio of pharmaceuticals. These are peroxime proliferator activated receptor (PPAR) agonists that have attracted significant attention due to their potential usefulness in the treatment of type 2 diabetes and dislepedimia. Several compounds of this class are now in various stages of development and many contain a chiral α-alkoxy carboxylic acid motif (Figure 1.12) that has often been introduced by techniques other than asymmetric hydrogenation.[13]

However, with relevance to this review, Houpis *et al.*[14] screened over 250 ligands and catalysts from the Lilly catalyst libraries (containing representatives from most commercial ligand families) under their standard conditions to synthesize the key intermediate for Naveglitazar synthesis. They obtained the best results (92 % ee) employing WALPHOS as exemplified in Figure 1.13.

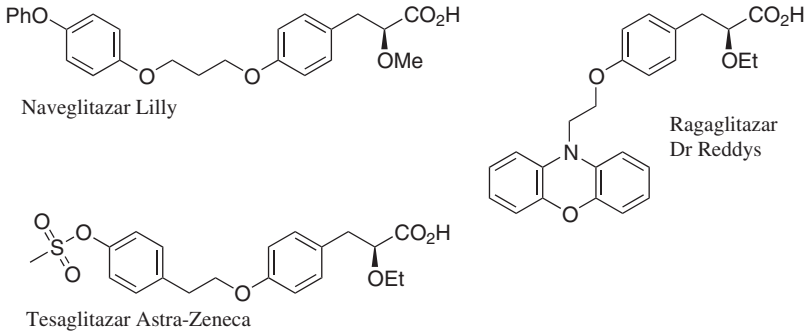


Figure 1.12 Glitazar API structures.

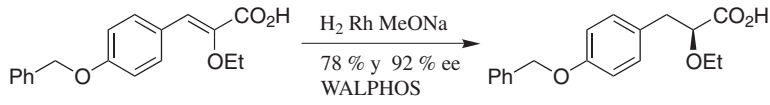


Figure 1.13 Lilly Azar intermediate formed by chiral hydrogenation.

1.2.5 UNSATURATED NITRILES

The asymmetric reduction of unsaturated nitriles to introduce chirality is a very useful process for the synthesis of many pharmaceutical intermediates. An important application of this strategy involves the further reduction of the nitrile group to yield chiral amines. The amine moiety is an important functional group which features in many APIs. As the nitrile group tends to bind 'end on' to rhodium, the high selectivities obtained from acids are not reproduced and the earlier work in this arena tended to concentrate on nitriles which had other functional groups in the molecule. This is exemplified by the synthesis of the Pregabalin intermediate made by hydrogenation of an unsaturated nitrile as shown in Figure 1.14. Hoge *et al.*[15] demonstrated that the three hindered quadrant phosphine TRICHICKENFOOTPHOS catalyst system gave results that were superior to those reported for Rh-MeDUPHOS, in respect to enantioselectivity (98 % ee vs 95 % ee at 100-g scale) using two times more concentrated reaction solutions and a catalyst loading of 27 000:1 substrate to catalyst ratio. These factors could have a profound impact on the cost of goods for producing a pharmaceutical intermediate on a scale required for the industry.

A more challenging example of an unsaturated nitrile reduction that lacks the carboxylate functional group is the asymmetric reduction of the nitrile[16] shown in Figure 1.15. The product was required in the synthesis of chiral

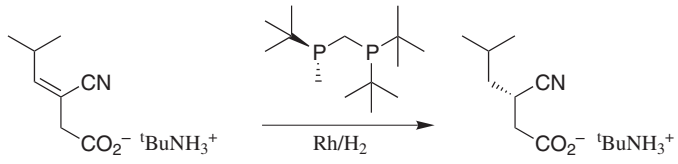


Figure 1.14 Pfizer Pregabalin intermediate synthesis.

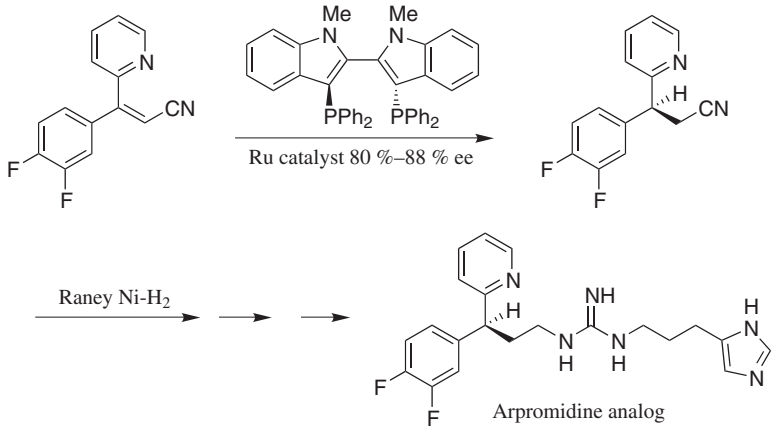


Figure 1.15 Asymmetric unsaturated nitrile reduction.

3,3-diarylpropylamine (**G**) which is an intermediate for the synthesis of the Arpromidines. These compounds are the most potent histamine H_2 receptor agonists known and are promising positive inotropic vasodilators for the treatment of severe congestive heart failure. Note the use of a ruthenium-based catalyst rather than the more usual rhodium catalysts.

The bis-indole diphosphine delivers the best ee and as the heterocyclic units are also electron rich aromatics this also gives the added advantage of the highest activity of the catalyst system. This overcomes one drawback often encountered, that high hydrogen pressures are frequently needed for ruthenium-based catalysts.

1.2.6 ALKENES AND ALLYL ALCOHOLS

Alkenes with no heteroatom functional groups and also allyl alcohols have attracted considerable attention as starting materials for chiral hydrogenation. These are particularly difficult substrates for reduction because a polar group adjacent to the alkene bond is required for the more conventional rhodium-catalyzed highly enantioselective reductions. The most successful class of catalysts for the title substrates has been iridium-based catalysts with substituted oxazoline-phosphine ligands. These relatively air- and moisture-tolerant cationic iridium complexes are efficient catalysts for the asymmetric hydrogenation of olefins; the field has recently been reviewed by Kallstrom *et al.*[17]

Several variations of these catalyst systems have been investigated and the asymmetric reduction of methylstilbene (Figure 1.16) has been the usual test reaction for new catalysts.

High ees have been obtained for several different catalytic systems for an extended range of substrates.

Lightfoot *et al.*[18] have developed one of these iridium-based systems for the stereocontrolled synthesis of lilial by asymmetric reduction of an allyl alcohol and subsequent oxidation of the alcohol, as shown in Figure 1.17.

Good methods for the chiral reduction of tetrasubstituted and terminal alkenes have yet to be fully developed.

1.2.7 α,β-UNSATURATED ALDEHYDE REDUCTION

Asymmetric reduction of α,β-unsaturated aldehydes with transition metal catalysts has not yet proven ready for widespread industrial application. One area, namely the chiral reduction of enals to yield chiral alcohols using bakers' yeast has been

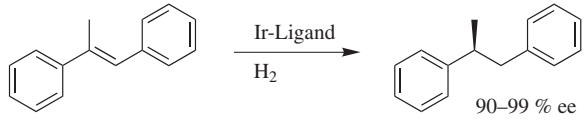


Figure 1.16 Trisubstituted alkene reduction.

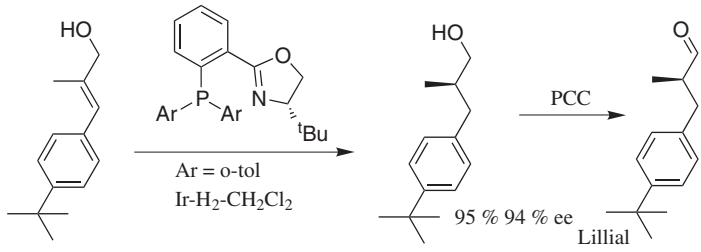


Figure 1.17 Lilial synthesis via iridium catalytic reduction.

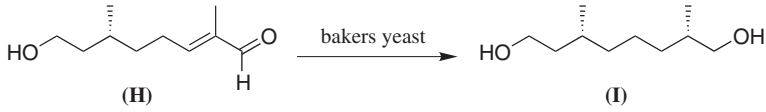


Figure 1.18 Bakers' yeast reduction of unsaturated aldehydes.

known for over 30 years and has attracted considerable attention because, when applied to terpene chemicals, the products can be utilized as chiral building blocks for many pheromones and fragrance chemicals. This is exemplified by the reactions shown in Figure 1.18 where (+)-citronellol was oxidized with selenium dioxide to give the unsaturated aldehyde (**H**), this was reduced by bakers' yeast on a relatively small scale to give the chiral diol (**I**) in high de which is a useful building block for many natural product syntheses.[19]

A recent interesting development in the reduction of carbon-carbon double bonds is the organocatalytic hydride transfer reductions of α,β-unsaturated aldehydes, whereby a Hantzsch ester acts as a good NADH mimic in the hydride-transfer to an iminium ion, formed when the α,β-unsaturated aldehyde reacts with the amine of the organocatalyst. These systems are being developed into metal-free biomimetic transfer hydrogenations. Ouellet and co-workers[20] use salts of chiral amines as organocatalysts, with impressive results as exemplified in Figure 1.19.

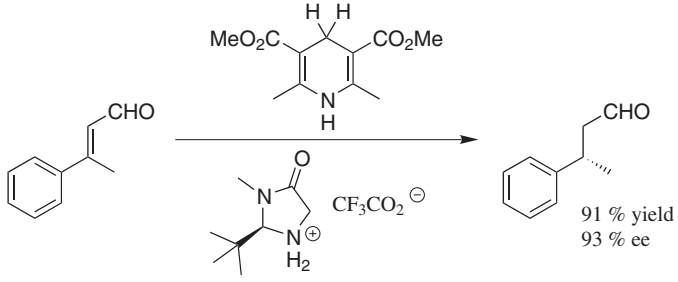


Figure 1.19 Organocatalytic reduction of an unsaturated aldehyde.

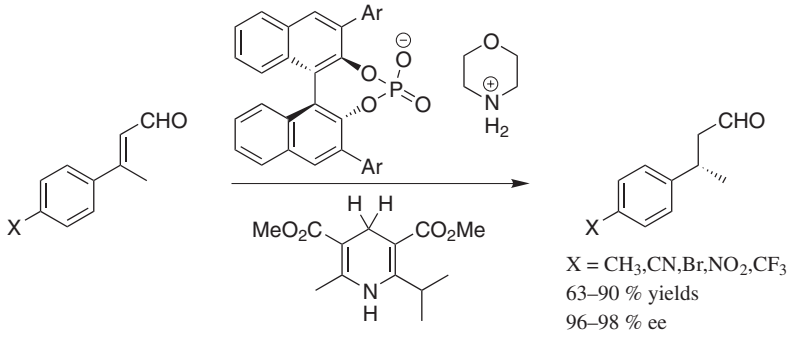


Figure 1.20 Chiral Bronsted acid induced reductions.

Mayer and List[21] used achiral amines and chiral phosphoric acids to form the counter ion and these also induce asymmetry in the process of hydrogen transfer as shown in Figure 1.20.

Adolfsson[22] published an overview of these types of reactions and these systems are also reported to be active for imine reduction (see Section 1.3).

1.3 KETONE AND IMINE REDUCTION

An important field of investigation for new industrial catalysts is the development of improved catalysts for the reduction of ketones and imines to obtain the corresponding chiral secondary alcohols and amines. These are used as key components in many active pharmaceutical intermediates. These heteroatom double bonds can be reduced by conventional hydrogenation with hydrogen gas or by transfer hydrogenation methods that use alcohols or formate as a hydrogen donor. Other significant catalytic reductions used in industry involve the use of chiral borohydride reagents and biocatalytic reductions. These different systems will be discussed in turn.

1.3.1 CATALYTIC HYDROGENATION OF KETONES AND IMINES

A good example of conventional gaseous hydrogenation methodology is the very efficient imine reduction shown in Figure 1.21 using iridium XYLIPHOS catalyst.

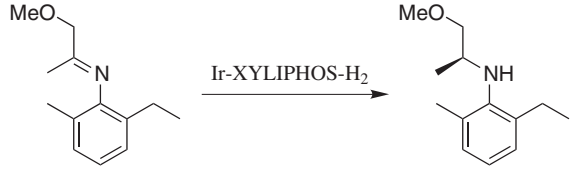


Figure 1.21 Syngenta imine reduction for Dual Magnum™ intermediate.

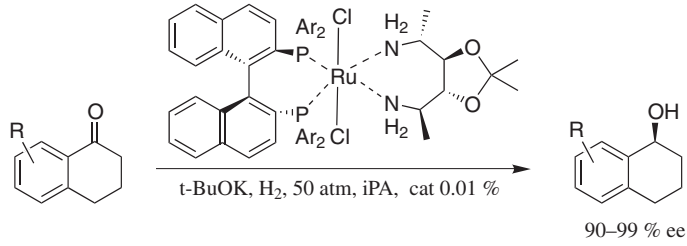


Figure 1.22 Noyori tetralone reduction.

This was developed for Syngenta and was a landmark product for enantioselective industrial catalytic synthesis. The full story behind this remarkable piece of work has been reported by Blaser.[23] Catalyst turnover numbers of 2 000 000 and turnover frequency values of around 600 000 h^{-1} allow highly efficient production of this important intermediate maize crop herbicide (Dual Magnum™).[23]

Catalysts for ketone hydrogenation continue to be developed but one of the best systems is still the BINAP-DPEN catalyst first reported by Ohkuma *et al*. in 1995.[24] In this system ruthenium is combined with both a chiral diphosphine and a chiral diamine, forming an octahedral complex which gives a high degree of enantioselectivity. This stereoselectivity is considered to be a result of the synergistic effect of the chiral diphosphine and diamine ligands.

More recent developments illustrating the importance of this type of system have been (a) the use of a chiral 1,4-diamine ligand to give a catalyst system that gave high ees for the hydrogenation of tetralones[25] (Figure 1.22) and (b) the use of 2-pyridylmethylamine for the reduction of highly hindered ketones such as t-butylmethylketone[26] (Figure 1.23).

Another recent example of the application of these catalyst systems is the efficient synthesis of the chiral alcohol (**J**) in a route to L-869,298, a potent PDE4 inhibitor, by O'Shea *et al*.[27] at Merck Frost, as shown in Figure 1.24.

During an investigation of transfer hydrogenations with complexes prepared *in situ* from $RuCl_2(PPh_3)_3$ and chiral phosphine-oxazoline ligand (**K**), Naud *et al*.[28] developed a catalyst for which activity (turnover frequency and turnover number) increased significantly when the reaction was carried out under hydrogen pressure whilst the ees only dropped marginally. This catalytic system is effective for the

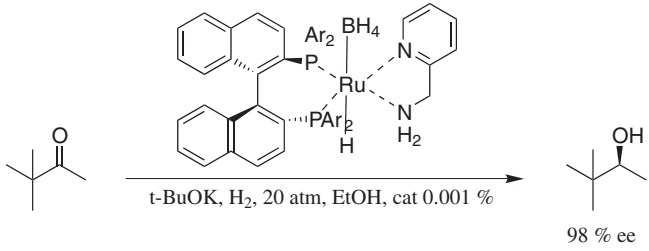


Figure 1.23 Noyori t-butylmethylketone reduction.

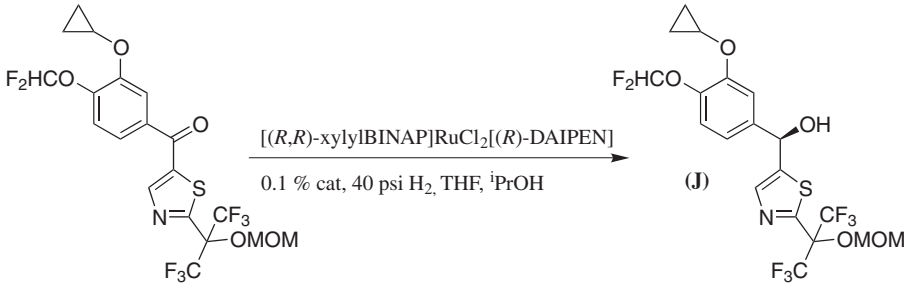


Figure 1.24 L-869,298 intermediate synthesis.

hydrogenation of various aryl ketones with ees up to 99 % and substrate to catalyst ratios of 10 000 – 50 000:1 whilst using high substrate concentrations. This observation makes this protocol attractive for scale-up and a pilot process has already been developed for the hydrogenation of 3,5-bistrifluoromethylacetophenone to produce the Aprepitant intermediate as shown in Figure 1.25.

Tellers *et al.*[29] from Merck optimized this catalyst system for the reduction of an α-substituted ketone that was needed as an intermediate for a drug development candidate. They obtained the best result (93 % ee) with ligand (**L**) in a method using 90 psi hydrogen pressure that was suitable for use at large scale (Figure 1.26).

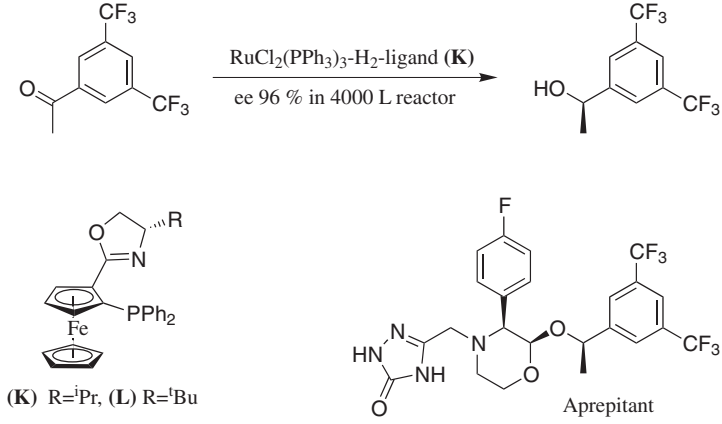


Figure 1.25 Oxazoline ligands for ketone hydrogenation.

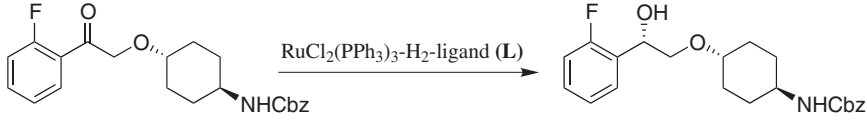


Figure 1.26 Merck process for ketone reduction.

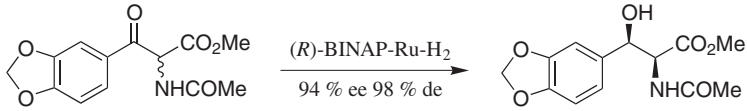


Figure 1.27 *Anti*-selective DKR of an amino keto ester derivative.

The synthesis of β-hydoxy-α-amino acids is important since these compounds are incorporated into the backbone of a wide range of antibiotics and cyclopeptides such as vancomycins. These highly functional compounds are also subject to dynamic kinetic resolution (DKR) processes, as the stereocenter already present in the substrate epimerizes under the reaction conditions and hence total conversions into single enantiomers are possible. These transformations can be *syn*-selective[30] for N-protected derivatives as shown in Figure 1.27 when using a ruthenium-BINAP catalyzed system and *anti*-selective[31] when the β-keto-α-amino acid hydrochloride salts are reduced by the iridium-MeOBIPHEP catalyst as shown in Figure 1.28. One drawback is that both these reductions use 100 atm hydrogen pressure.

1.3.2 ASYMMETRIC TRANSFER HYDROGENATION (ATH) CATALYSTS

A wide range of metals and ligand combinations have been demonstrated to effect the ATH reaction and in this book we concentrate on the systems that have demonstrated high activities and ees that would be the requirement of an industrial application. The initial breakthrough in this area came in 1995 with the report from Ohkuma *et al.*[32] on the use of chiral monotosylated diamine complexes for asymmetric transfer hydrogenation.

From an industrial standpoint the most useful catalysts are those based on transition metal complexes that are neutral and stable 18-electron catalyst precursor complexes that have the following structural elements: (a) an η^6/η^5-aryl complexing group; (b) a metal from Rh, Ir and Ru at the correct oxidation level to give a neutral complex; (c) a chiral bifunctional ligand modifier with an amine group; and (d) an anionic leaving group as shown in Figure 1.29. The most common hydrogen donors are isopropanol which forms an equilibrium mixture with the substrate [therefore these reactions are usually run at high dilutions (typically 0.5 M)] and the 5:2 formic acid–triethylamine azeotrope which makes an irreversible system due to carbon dioxide elimination. This formic acid mixture is incompatible with amino alcohol ligands and is only useful for application with the diamine monosulfonate ligands.

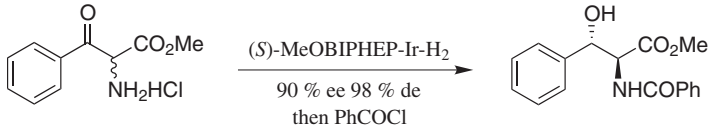


Figure 1.28 *Syn*-selective DKR of an amino keto ester compound.

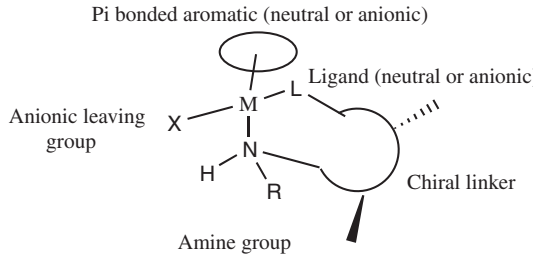


Figure 1.29 General structure for ATH catalysts.

The aromatic complex can be a neutral η^6-benzene derivative or an anionic η^5-cyclopentadienyl ring. Substituents on these aromatic rings can greatly influence the effectiveness of these catalysts. For example, with benzene derivatives the unsubstituted benzene rings give lower ees and the use of hexamethylbenzene results in lower catalytic activities whilst the cumenyl or mesityl rings give optimum catalyst systems. The two types of chiral bifunctional linkers that have been most practical are anionic ones based on monosulfonated diamines and amino alcohols.

Figure 1.30 exemplifies two types of systems that have attracted the most attention for this reaction, namely the Ru(II) complexes (**M**) (originally reported by Ohkuma *et al.*[32]) with monotosyldiphenylethylamine which can reduce arylalkyl ketones with high ees using both 2-propanol or triethylamine-formic acid. Alternatively, the Rh(III) complexes of the type (**N**) have been commercialized as the CATHy^{TM} system by Blacker and Mellor[33] (from Avecia now NPIL) using the anionic pentamethylcyclopentadienyl group as the aromatic ligating system. Several case studies describing the scale-up for several processes have been described.[34]

The mechanism of this reaction was fully elucidated by Noyori *et al.*[35] who showed that the relatively stable 18-electron precatalyst complex eliminates HX to give the 16-electron active catalyst complex that then reacts with the hydrogen donor (2-propanol or formic acid) to give the dihydrogen metal complex (and eliminates acetone or carbon dioxide from the hydrogen donor). Transfer of two hydrogens to the substrate in a six-membered ring transition state regenerates the active catalyst (Figure 1.31).

A detailed review of the mechanisms of the hydrogenation of polar double bonds by ruthenium hydride species have been published by Clapham *et al.*[36] The article examines the properties of over 100 catalyst systems for transfer and

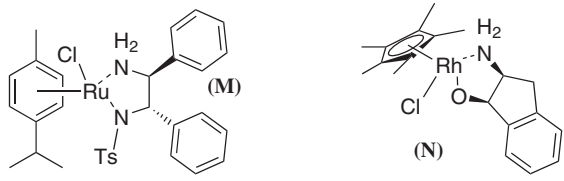


Figure 1.30 Catalytic ATH systems reported for industrial application.

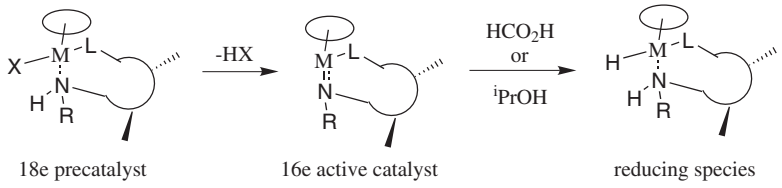


Figure 1.31 Transfer hydrogenation active catalyst species.

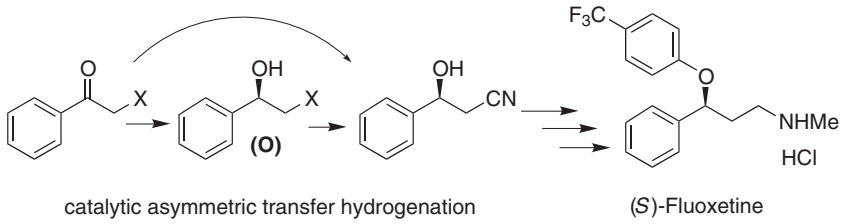


Figure 1.32 Chiral Fluoxetine synthesis using ATH.

gaseous hydrogenation methods to give insights into the critical features of this transformation.

The family of substituted acetophenones shown in Figure 1.32 have been studied in detail as these ketone substrates, on being reduced by ATH, allow the synthesis of the family of chiral phenylalkanols **(O)** (where X = Br, Cl, CN, CO_2R and CONHR) which are used as intermediates in the synthesis of (*S*)-Fluoxetine and related compounds.[37,38]

The above mentioned catalysts also have the advantage of being robust and they can be attached to scaffolds that allow them to be recycled.[38]

Another field where ATH catalysts have made an industrial impact is in the area of chiral amine synthesis by stereocontrolled reduction of imines. First demonstrated by Uematsu *et al.*,[39] the reduction of cyclic imines to yield chiral amines has proved to be a highly versatile and successful strategy for the synthesis of chiral tetrahydroisoquinolines and related compounds. This is exemplified in Figure 1.33 which shows the synthesis of the natural product Salsolidine in 95 % ee by the reduction of the precursor cyclic imine. Several other similar types of imines were

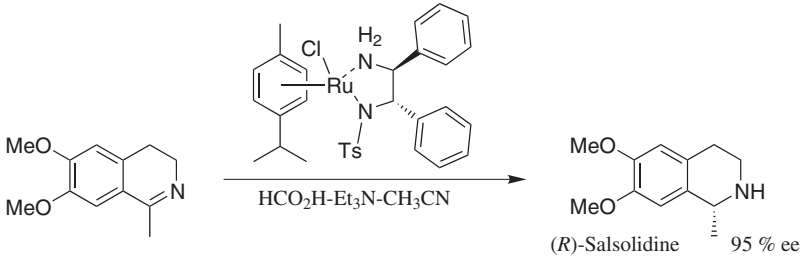


Figure 1.33 ATH chiral imine reduction.

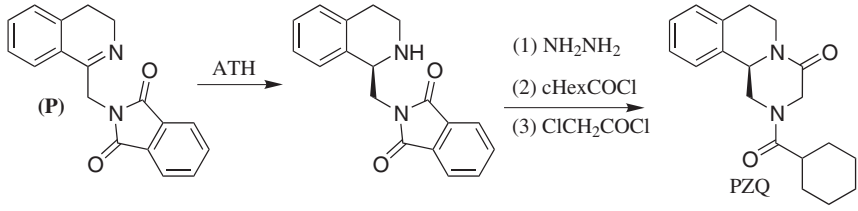


Figure 1.34 ATH as chiral step in PZQ synthesis.

also reduced using these types of catalysts to give cyclic chiral amines that are important structural units in many biologically active pharmaceuticals and alkaloid natural products. These imine reductions require the formic acid–triethylamine reducing hydrogen donor and also an organic cosolvent (acetonitrile, dichloromethane or DMF) to ensure that the reaction is fast enough to be useful, and hence the popular combination of ruthenium(II) with amino alcohol ligands is incompatible with formic acid and therefore not suitable for imine reduction.

Roszkowski *et al.*[40] have described a method for the enantioselective preparation of Praziquantel (PZQ) a pharmaceutical for the treatment of schistosomiasis and soil-transmitted helminthiasis. Starting with the imine (**P**) (readily available from phenylethyl amine, phthalyl anhydride and glycine) an asymmetric transfer hydrogenation yielded the chiral intermediate in 62 % ee, and the crude product was easily crystallized to the required high ee and converted into the Praziquantel as shown in Figure 1.34.

Williams *et al.*[41] extended the reaction to produce a range of chiral cyclic amines by reacting an aryl metal species with Boc-lactams to yield Boc-aminoketones which could then be deprotected, cyclized and reduced in a one-pot reaction. However, whilst salsolidine could be made in high ee from this one pot method, the cyclic amines shown in Figure 1.35 could be produced in good yield but these were nearly always produced in racemic form.

For the synthesis of simple amines, including valuable resolving agents such as the (1-naphthyl)ethylamines, ATH can be useful but an N-linked phosphorus-based electron withdrawing group was found to be a necessary addition to the substrate. Blacker and Martin[34] demonstrated that the reduction may be run at very low levels of catalyst when triethylammonium formate was fed into the reactor and nitrogen gas passed into the system as shown in Figure 1.36.

A major impact in the treatment of HIV involves anti-retroviral therapy with APIs that belong to a class known as the 'avir' family of highly active pharmaceuticals. A number of these 'avirs' contain the 1-phenyl-2,4-diamino-butan-3-ol fragment (**Q**).

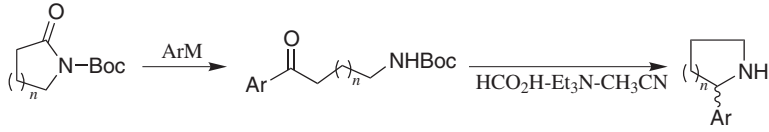


Figure 1.35 Cyclic amine synthesis by transfer hydrogenation.

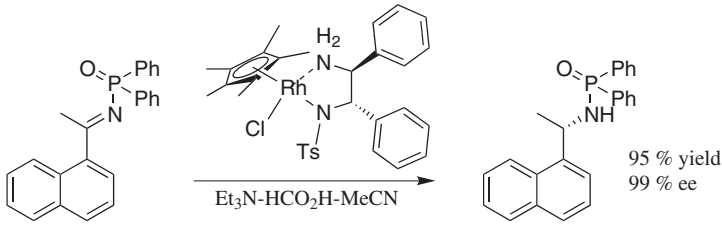


Figure 1.36 ATH of phenylphosphinylimine.

A very good route to these entities is from the protected amino epoxides derived from L-phenylalanine shown in Figure 1.37. Economic methods for this conversion have been developed, involving the treatment of the N-protected amino acid with isobutyl chloroformate, then diazomethane and finally hydrochloric acid in industrial continuous reactors that have been designed for this purpose.[42] The (2*S*,3*S*)-chloroalcohol has been synthesized in good yield using sodium borohydride reduction or by ATH using the ruthenium TsDPEN catalyst.[43] Recently Pennington and Hodgson[44] have described diastereoselective reduction to give the (2*R*,3*S*)-chloroalcohol in 94 % de using MeBOPHOS coordinated to ruthenium catalyst, with 99 % conversion in 20 hours being achieved using a 0.2 % catalyst loading at 10 atm hydrogen pressure. These results are summarized in Figure 1.37. The chloroalcohols

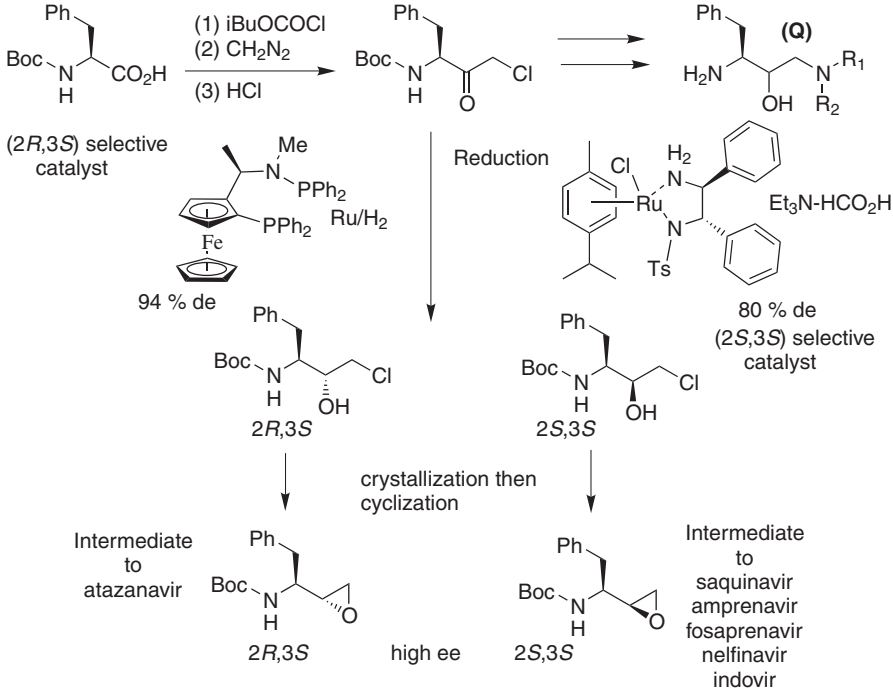


Figure 1.37 Avir intermediate synthesis by ketone hydrogenation.

can be easily crystallized to enhance the ees to the levels needed for pharmaceutical application before conversion into the desired epoxides.

1.3.3 MODIFIED BORANE REAGENTS

One popular method that has been applied to industrial processes for the enantioselective reduction of prochiral ketones, leading to the corresponding optically active secondary alcohols, is based on the use of chiral 1,3,2-oxazaborolidines. The original catalyst and reagent system [diphenyl prolinol/methane boronic acid (**R**)] is known as the Corey–Bakshi–Shibata (CBS)[45] reagent. Numerous examples describing the application of this method are known, as exemplified by the synthesis of the chiral ferrocene bis-alcohol needed for ligand synthesis described by Schwink and Knochel[46] (Figure 1.38). Although very good enantio- and diastereoselectivities were achieved, high catalyst loadings were required.

Such high catalyst loadings have resulted in polymer supported systems being developed. These higher molecular weight species still give good selectivity but allow the catalyst to be recycled.[47]

The use of CBS-type catalysts has been extended to the reduction of oximes into chiral amines. Chu *et al.*[48] have described the BINOL-proline-borate complex shown in Figure 1.39 that can reduce acetophenone oxime into chiral 1-phenylethylamine with 98 % ee, but the ee drops when the borate complex is used catalytically.

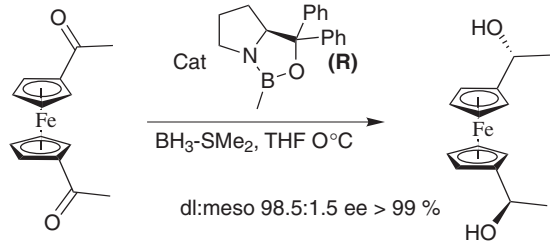


Figure 1.38 CBS catalyzed double ketone reduction.

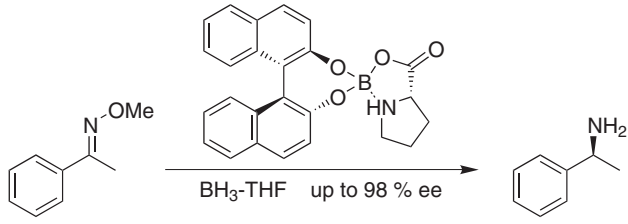


Figure 1.39 Chiral amine synthesis using modified boranes.

1.3.4 BIOCATALYSTS (ALCOHOL DEHYDROGENASES AND KETOREDUCTASES)

The biocatalytic reduction of prochiral ketones, using either whole cell systems or isolated enzymes, shows great potential in terms of mild reaction conditions and good selectivities.[49,50] These attractive properties have resulted in this class of biocatalysts being intensively studied and many potential applications have been identified. Biocatalytic reductions can be accomplished using whole cell systems but these biotransformations can be hampered by low productivity and complicated by the presence of multiple ketoreductases, which can lower the selectivity. The requisite enzymes are commercially available with high activity and the necessary employment of cofactors is no longer an obstacle as they can be efficiently regenerated *in situ* by glucose dehydrogenase (NADPH) and formate dehydrogenase (NADH).[51] Formate dehydrogenase irreversibly oxidizes formate to carbon dioxide process at a rate of about $8000\,h^{-1}$. Both substrate and product are relatively inert with the carbon dioxide being removed as a gaseous by-product; this method has been demonstrated to work on industrial scale for the production of tert-leucine.[52]

Pollard *et al.*[53] from Merck required both enantiomers of 3,5-bistrifluoromethylphenyl ethanol since the (*R*)-enantiomer can be incorporated into Merck's orally active NK1 receptor antagonist for the treatment of chemotherapy induced emesis, while the (*S*)-enantiomer is used as a chiral synthon for a number of antagonists which the same company currently have under clinical evaluation. Using proteins from a library of commercially available alcohol dehydrogenases both enantiomers were obtained with ees of 99 % (Figure 1.40).

The versatility of these reduction systems are demonstrated by the next few examples, chosen to show that a wide range of functional groups are tolerated by these biocatalysts and how the biotransformations can be applied to synthesize intermediates in API production. Zhu *et al.*[54] from Biocatalytics have developed a library of new recombinant ketoreductases (via genome mining) and have reported their properties, including enantioselectivities and rate of reductions, for a range of β-ketoesters. Stewart *et al.* have reported the reduction of α-chloro-β-ketoesters in good yields and high ees and used these transformations in the elegant syntheses of (−)-bestatin[55] and taxol side chains[56] as shown in Figure 1.41.

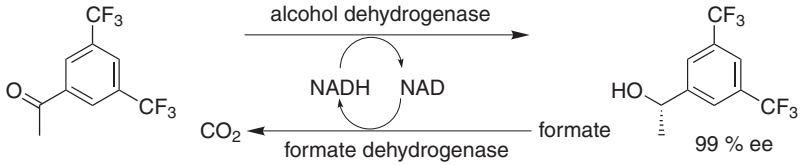


Figure 1.40 (*S*)-3,5-Bis(trifluoromethyl)phenyl ethanol synthesis via bioreduction.

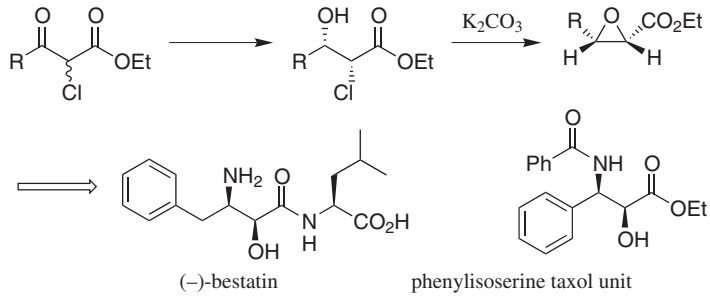


Figure 1.41 α-Chloro-β-ketoester using engineered *Escherichia coli* cells.

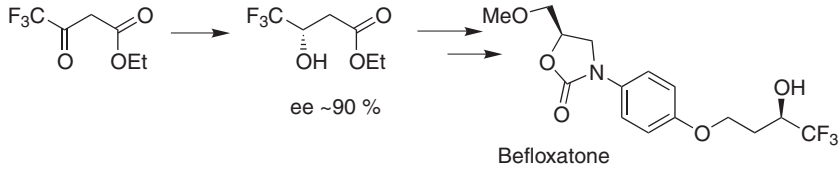


Figure 1.42 Befloxatone fluorinated side chain synthesis.

The reduction of ethyl trifluoroacetoacetate by bacterial alcohol dehydrogenases has been reported by Zhang *et al.*[57] and the product used as an intermediate in the synthesis of Befloxatone as shown in Figure 1.42.

The 'statin' family of pharmaceuticals require a chiral side chain, representing a target that has attracted a great deal of activity focused on preparing various potential intermediates. A number of reports have been published on the reduction of chloroacetoacetate esters for conversion into this target molecule. A method suitable for large-scale production has been published that operates at $36.6\,g\,L^{-1}$ and 95.2 % yield with 99 % ee.[58] This reaction is shown in Figure 1.43.

An elegant approach to address the same need was the double reduction of the diketoester shown in Figure 1.44 reported by Holt *et al.*[59] from Avecia (now NPIL). The chiral triol was produced in a whole cell reduction process and was then selectively protected at the primary alcohol by enzymatic acylation using Novozyme 435 (CAL-B). Finally the key intermediate was produced by protecting the two secondary alcohols as they cleanly reacted with dimethoxypropane to give a crystalline product (>99 % ee, >99 % de, 96 % purity) which was subsequently used for Lipitor production (Figure 1.44).

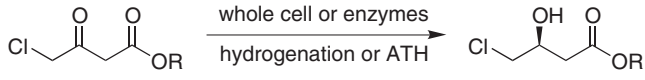


Figure 1.43 Reduction of ethyl chloroacetoacetate.

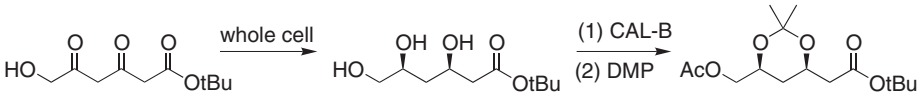


Figure 1.44 Double ketone reduction in a whole cell process.

1.4 OXIDATION

1.4.1 SHARPLESS CHIRAL EPOXIDATION OF ALLYL ALCOHOLS

The original titanium catalyst invented by Sharpless and Katsuki has been used for the epoxidation of an immense number of allylic alcohols to yield high value industrial synthons very effectively, as shown in Figure 1.45.[60]

This transformation has been applied to several chiral production processes, the first being the synthesis of a pheromone (Disparlure) intermediate[61] (**S**) albeit with low turnover numbers and only 91 % ee. Another industrial product is the epoxide of allyl alcohol as developed by PPG-Sipsy,[62] to give a process where catalyst loading was decreased by molecular sieve addition and the safety factors involving peroxide contamination were overcome. These examples are shown in Figure 1.46.

1.4.2 DIOXIRANE CATALYZED EPOXIDATION

Chiral ketone-catalyzed asymmetric epoxidation has received intensive interest since the first reported by Curci *et al.* in 1984.[63] The reaction is performed with oxone™ (potassium peroxomonosulfate) as the primary oxidant which generates the chiral dioxirane catalytic species in situ, which in turn, transfers the oxygen

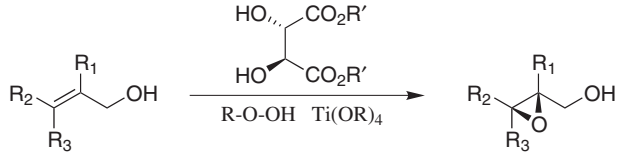


Figure 1.45 The Katsuki–Sharpless epoxidation reaction.

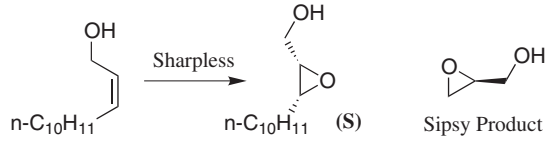


Figure 1.46 Industrial products manufactured using Sharpless epoxidation.

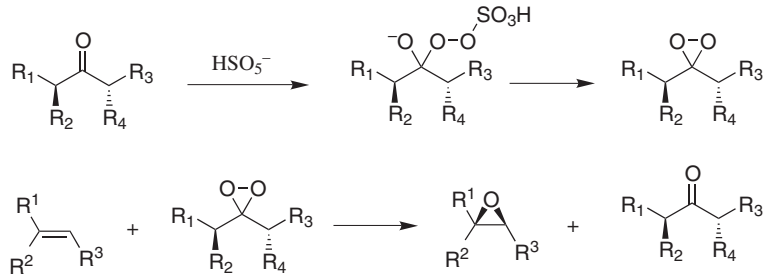


Figure 1.47 The dioxirane catalyzed alkene epoxidation.

atom to the alkene (Figure 1.47). Shi[64] has published an in-depth review of this oxidation method inter alia describing the wide range of substrates that have been successfully epoxidized with these systems.

Discovering highly enantioselective chiral ketone catalysts has proven to be challenging, due to a number of undesired processes that can compete with the catalytic cycle of the epoxidation, including Baeyer–Villiger oxidation of the catalytic ketone into inactive esters. The complication of side reactions has meant fairly high levels of the ketone catalyst are often required. The development of an efficient ketone catalyst thus requires delicately balancing the sterics and electronics of the chiral control elements around the carbonyl group. On the other hand the ketone-catalyzed epoxidation has several positive features including a broad substrate scope. For example, the fructose-derived ketone (**T**) is a highly general and enantioselective catalyst for the epoxidation of *trans* and trisubstituted olefins whilst the ketone (**U**) gives high enantioselectivity for a number of *cis*-olefins and useful levels of enantioselectivity for some terminal olefins (Figure 1.48).

Other advantages include a mechanism that allows one to rationalize and predict the stereochemical outcome for various olefin systems with a reasonable level of confidence utilising a postulated spiro transition state model. The epoxidation conditions are mild and environmentally friendly with an easy workup whereby, in some cases, the epoxide can be obtained by simple extraction of the reaction mixture with hexane, leaving the ketone catalyst in the aqueous phase.

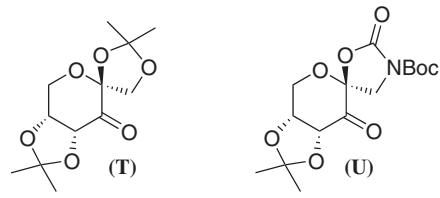


Figure 1.48 Shi epoxidation catalysts.

1.4.3 AMINES AND IMINIUM SALTS

The epoxidation of olefins catalyzed by iminium salts and amines (or ammonium salts) is emerging as a new technique for the functionalization of simple alkenes. These catalysts have relatively simple structures and hence are easily produced at scale; they offer potential as green oxidation catalysts. These organic salts are effective oxygen transfer reagents towards electron-rich unfunctionalized olefins. For the iminium salt systems oxone™ oxidizes an iminium salt to the oxaziridinium intermediate,[65] which then transfers oxygen to the olefin and as oxone™ reacts readily with iminium ions to regenerate the oxaziridinium species catalytically, efficient oxidation is possible.

Goncalves *et al.*[66] have compared the amine (**V**) and the iminium salt (**W**) for the enantioselective epoxidation of some prochiral olefins in acetonitrile/water and found that the yields and ees are nearly the same for the epoxidation of a selection of olefins. The amines of type (**X**) are less well developed. Armstrong[67] has summarized the developments in this field and suggested mechanisms based on hydrogen bonded species, one of which is shown in Figure 1.49. Typical yield and ee data for the epoxidation of 1-phenylcyclohexene for these catalysts are also shown in Figure 1.49.

1.4.4 PHASE TRANSFER CATALYSTS

The epoxidation of enones using chiral phase transfer catalysis (PTC) is an emerging technology that does not use transition metal catalysts. Lygo and To[68] described the use of anthracenylmethyl derivatives of a cinchona alkaloid that are capable of catalyzing the epoxidation of enones with remarkable levels of asymmetric control and a one pot method for oxidation of the allyl alcohol directly into

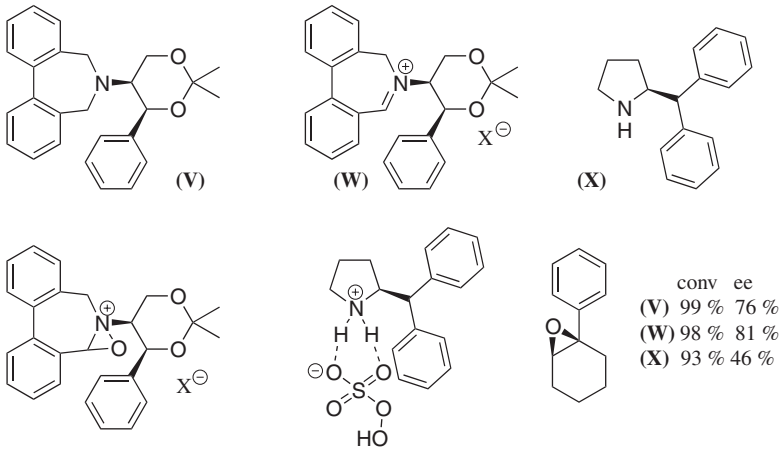


Figure 1.49 Amines and iminium salt epoxidation catalysts.

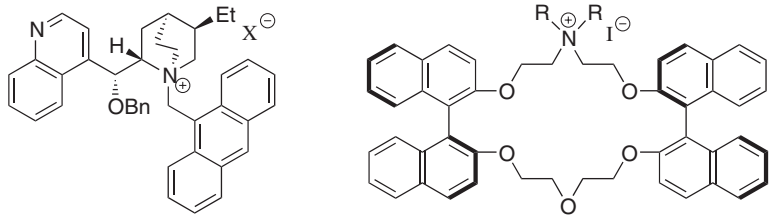


Figure 1.50 Phase transfer catalysts for enone epoxidation.

the epoxide was described. Ye *et al.*[69] developed an enantioselective epoxidation with similar catalytic chiral quaternary ammonium salts using trichloroisocyanuric acid as the oxidant giving good yields of epoxy ketones from chalcones with enantioselectivities up to 96 %.

Hori *et al.*[70] have recently reported aza crown ether chiral quaternary ammonium salts for the epoxidation of (*E*)-chalcone with alkaline hydrogen peroxide as the terminal oxidant. The oxidation proceeded in high yield and good enantioselectivity; the success of the reaction depended on the length of the carbon chain on the nitrogen atom. These PTC catalysts are shown in Figure 1.50.

1.4.5 THE JULIÁ–COLONNA METHOD (POLYLEUCINE OXIDATION)

The oxidation of electron-deficient chalcone-type compounds with hydrogen peroxide and poly-amino acid catalysts is known as the Juliá–Colonna protocol. Optically active epoxides with high ees are obtained from facile processes that use small amounts of catalyst and simple reagents. Gerlach and Geller[71] have reported the process development studies that allow the reaction to be run on pilot plant scale. The resulting epoxides can be converted into a wide range of interesting products,[72] including a Diltiazem intermediate as shown in Figure 1.51.[73]

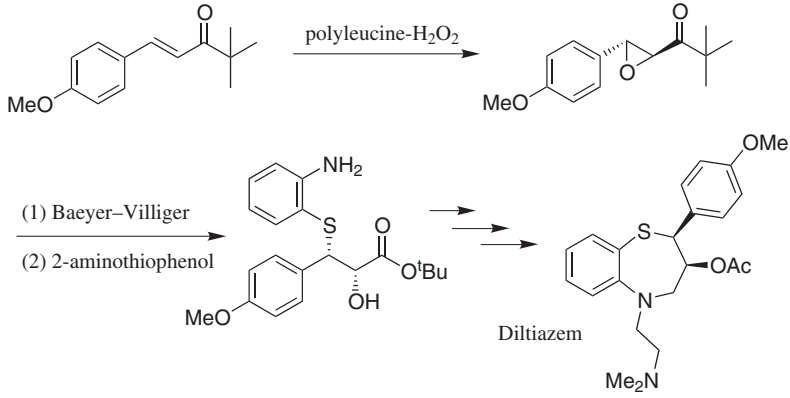


Figure 1.51 Diltiazem synthesis using polyleucine epoxidation.

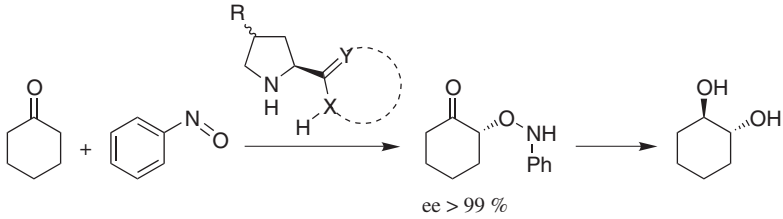


Figure 1.52 Organocatalyst α-hydroxylation of ketones.

1.4.6 ORGANOCATALYTIC α-HYDROXYLATION OF KETONES

A newer method of oxidation that is attracting considerable attention is the reaction of ketones with nitrosobenzene and proline-based organocatalysts (Figure 1.52). Effective hydroxylation of the ketone is achieved in exceptionally high ee.[74–76]

1.4.7 BAEYER–VILLIGER OXIDATION

The Baeyer–Villiger oxidation of ketones represents a powerful synthetic method that breaks carbon-carbon bonds in an oxygen insertion process to deliver lactones. A recent comprehensive review by ten Brink *et al*.[77] describes the different methods used for this reaction and highlights the technical and environmental advantages of the transformation. Symmetrical ketones can be converted into chiral lactones that are frequently used synthons for many target molecules in modern pharmaceuticals. A review by Mihovilovic *et al*.[78] discusses enantioselective Baeyer–Villiger oxidations by chemical and biotransformation approaches, including scope and limitations, the improvement of optical purity and implications upon scale-up.

Figure 1.53 shows the Fluka (kilogram-scale) asymmetric microbial Baeyer–Villiger oxidation of racemic bicyclo[3.2.0]hept-2-en-6-one (**X**) using a 50 L bioreactor as described in a publication by Wohlgemuth *et al*.[79]

High productivity was obtained by a combination of several (bio)chemical engineering techniques including resin-based *in situ* substrate feeding/product removal methodology, a glycerol feed control and an improved oxygenation regime.

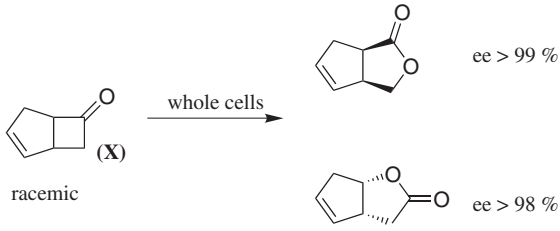


Figure 1.53 Baeyer–Villiger biotransformation of ketones.

Both regioisomeric lactones were obtained in nearly enantiopure form (ee $> 98\,\%$) and good yield.

1.4.8 CHIRAL SULFOXIDES

The development of the single enantiomer 'azole' within the family of compounds used for gastrointestinal treatments is exemplified by Astra-Zeneca's Esomeprazole (a potent gastric acid secretion inhibitor) (Figure 1.54). This development gave the impetus for the search for industrial chiral sulfoxidation catalysts.

The development of a large scale manufacturing route to Esomeprazole is described by Federsel and Larsson[80] using the titanium catalyst originally described by Kagan and Luukas.[81] Employment of a tartaric acid derived chiral auxiliary, with the addition of a base such as diisopropylethylamine to the reaction mixture, resulted in a full-scale catalytic process capable of delivering multi-ton quantities of product with optical yields well above 90 %, a figure which could be raised to 99.5 % ee by recrystallization from methyl isobutyl ketone.

The Kagan protocol for asymmetric oxidation of sulfides to sulfoxides has been used for other plant scale processes the structures of which are shown in Figure 1.55. These include the intermediate for Sulindac, a nonsteroidal anti-inflammatory drug for which some other biological effects have been attributed to single enantiomers and a neurokinin antagonist candidate intermediate where the scale-up required the use of cumyl peroxide and careful control of oxidant addition to keep the temperature sufficiently low to achieve very high ees when run on pilot scale process.[82] The Astra-Zeneca candidate drug ZD3638, an atypical antipsychotic agent for the treatment of schizophrenia, was formed from the corresponding

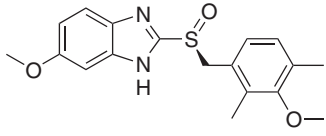


Figure 1.54 Esomeprazole.

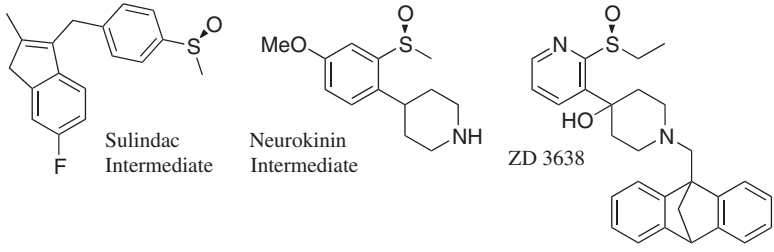


Figure 1.55 Industrial scale chiral sulfoxides from titanium catalyzed asymmetric oxidations.

sulfide with a moderate enantiomeric excess of only 60 % ee when using the standard conditions but addition of Hunig's base improved the results and avoided the formation of the corresponding sulfone by-product.[83] This is one of the rarer examples whereby a side-chain longer than a methyl group has been enantioselectively oxidized.

These reactions may give very high enantioselectivities, particularly for structures such as ArS(O)Me and this approach has been used on a multi-kilogram scale in industry.

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