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Opportunities in Asymmetric Synthesis : An Industrial Prospect*

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* Dedicated to my mentor, Prof. Goverdhan Mehta on his 50th birthday.

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1.0 Introduction:

Non-racemic chiral molecules play an important role in the context of biological activity.[1] Consequently, both academic and industrial laboratories have devoted a substantial amount of their research efforts addressing this issue. The interaction of a optically pure material with a receptor may manifest itself as a difference in biological activity. Increased understanding of the pharmacokinetics and mechanism of action of these chemicals in biological systems has led to the development of drugs,[2] agro-chemicals and food additives in optically pure form. According to a recent report,[2c] more than 50% of the commercial drugs available worldwide have stereogenic centers. The racemic drug thalidomide sold as a powerful tranquilizer in the 1960s was prescribed with catastrophic consequences because only the (R) isomer serves as a tranquilizer while the (S) isomer is shown to cause ill effects in fetal development. [3]

It was generally believed that optically pure compounds could only be obtained by biological, enzymatic[4] or resolution methods. In recent years, with the advent of several novel synthetic methods [5] and sophisticated analytical techniques,[6] enantiomerically pure molecules are routinely prepared in laboratory quantities. In fact, some of these methods, such as Sharpless asymmetric epoxidation,[7] binaphthyl strategy,[8] asymmetric hydrogenation process [9] and asymmetric cyclopropanation methodology[10] have reached a level of viability such that industrial applications are feasible.[11]

There are essentially four ways to obtain optically pure organic materials: 1) chiral pool synthesis,[12] 2) resolution of the racemic mixture,[13] 3) catalytic asymmetric synthesis[5u-x] and 4) fermentation technology. Fermentation methods,[14] which are routinely used for the industrial production of natural products such as L-amino acids, vitamins and hormones, will not be discussed here. Furthermore, in order to limit the size of this review, industrially useful enzymatic methods are not discussed here in detail. There are three methods used for the resolution of racemic compounds depending on the nature of the substrate: 1) direct crystallization, 2) resolution *via* diastereomers, and 3) kinetic resolution.[15] Synthesis of optically active materials involves usage of chiral catalysts, or chiral auxiliaries / chiral pool (chiral starting materials such as carbohydrates,[16] amino acids,[17] hydroxy acids and terpenes[18]). Although each of these methods has their own strengths and limitations with regard to chiral molecule synthesis, economic feasibility, time requirements, quantities and structural complexity of the final compound is crucial for the adaptation of an individual method. This review deals with some specific industrial syntheses and also gives an overview of the recent developments in this field.

2.0 Resolution of Racemates:[13]

Resolution of racemates is often the method of choice for the production of optically pure compounds on an industrial scale despite its low-technology image. Molecules that are not convertible to diastereomers or that have more than one racemizable chiral center are not good candidates for this technology.[19] The choice of resolution method depends on the type of solid state racemate on hand. Based on the difference in the nature of packing in the crystal lattice, racemic compounds are divided into three types: 1) racemic conglomerates, 2) true racemic compounds, and 3) pseudoracemates (Fig. 1). In conglomerates, each unit cell in the crystal lattice consists of only one enantiomer whereas in the case of a true racemic compound each unit cell contains an equal

number of enantiomers. In a pseudoracemate the two enantiomers co-exist in a disordered manner in the crystal lattice.[5t, 13]

Fig 1

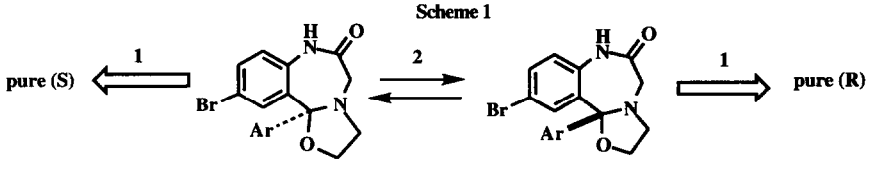
2.1 Direct Crystallization:

Resolution by direct crystallization of a racemate is possible only if the latter is a conglomerate. In this case, essentially two methods are available. In the first of these, the two enantiomers are allowed to crystallize simultaneously in solution and the mother liquor which itself remains racemic. This methodology was used by Merck for resolution of an intermediate in the industrial synthesis of α-methyl-L-dopa. The resolution is carried out by circulating the supersaturated solution of racemate simultaneously through two crystallization chambers that contain seed crystals of the respective enantiomers. [20]

Another practical variation of direct crystallization involves localized crystallization. It involves simultaneous separation of individual enantiomers from a racemic supersaturated solution by addition of two seeds of opposite chirality in two different regions of the same solution. Zaugg reported [21] isolation of (+)-methadone and (-)-methadone from racemic methadone by simultaneous crystallization using this methodology. Among the amino acids, threonine, asparagine, and glutamic acid can be resolved by this technology. In the event that seed crystals are not available, one can also resolve the above three amino acids by addition of crystals of other pure optically active amino acids such as phenylalanine.[22]

The second, called the preferential crystallization method (or resolution by entrainment), crystallization of one of the enantiomers is promoted, while keeping the other in supersaturated state. This process has been used for the commercial production of large quantities of chloroamphenicol.[23]

Scheme 1



1. preferential crystallization 2. Racemization

1,4-Benzodiazepine derivatives were resolved by preferential crystallization. Concomitant *in-situ* racemization resulted in greater than 50% yield (Scheme 1).[24] In an ideal case, this technique can provide 100% optical and chemical yield. This method of crystallization-induced asymmetric transformation is also referred to as a special case of deracemization. For application of this methodology, the target molecule should have a racemizable chiral center. In general, amines, and amino acids are racemized easily in the presence a of carbonyl compound (e.g. benzaldehyde) *via* reversible Schiff base formation. Merck group applied this deracemization methodology to synthesize (S)-3-aminobenzodiazepinone (92% chemical yield, >99.8% ee).[25]

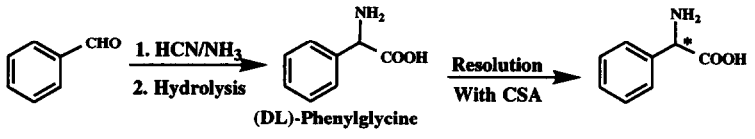
Sometimes a true racemate can be converted into a conglomerate by forming a derivative (e.g., ibuprofen exists as a true racemate, but it's sodium salt exists as a conglomerate). With the present level of knowledge, one can not predict the occurrence of conglomerates from the structure of a molecule.

2.2 Diastereomer Crystallization

This method is used to resolve a true racemate and requires an optically pure resolving agent. Reacting the mixture of enantiomers with an optically active material will produce two diastereomeric adducts with different physical properties. Many times these can be separated by taking advantage of these differences in physical properties, e.g., by crystallization, distillation or chromatographic methods.

The resolving agent used in this technology must fulfill the following conditions: 1) inexpensive, 2) recovered easily without loss of chiral integrity and 3) reacts easily with the substrate to be resolved. Industrial production (1000 tons/year) of D-phenylglycine by the Andeno process[11a] is illustrated in Scheme 2. The maximum once-through yield using diastereomer crystallization is 50%. Easy racemization of the unwanted isomer is necessary for the economic success of this technology.

Scheme 2



(DL)-Phenylglycine

CSA=(+)-Camphorsulphonic acid

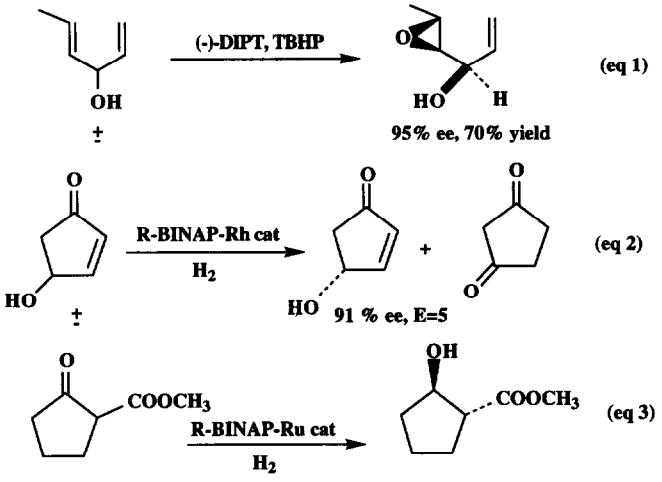
2.3 Kinetic Resolution:[15]

Kinetic resolution is based on the principle that one of the two enantiomers or enantiotopic groups undergoes selective reaction in the presence of an optically active reagent. In an ideal case, one enantiomer (enantiotopic group) is converted to the product while the other remains unchanged, is racemized, or is destroyed. This optically active reagent could be stoichiometric or catalytic; the catalyst may be of chemical, enzymatic, or microbial origin. The increase in enantiomeric excess (ee) of the residual substrate is directly dependent on the difference in reaction rates.

Marckwald and McKenzie reported [26] that when racemic mandelic acid is esterified with a less than equimolar (-)-menthol, (-)-menthyl-(+)-mandelate is formed predominantly leaving behind the unreacted (-)-mandelic acid. One of the oldest biochemical methods involving kinetic resolution is the preparation of optically pure (-)-tartaric acid through fermentation methodology. In this example, the other enantiomer is destroyed during resolution. Many enzymes used in asymmetric synthesis involve kinetic resolution.

The Sharpless asymmetric epoxidation shown in equation 1 is an excellent example of kinetic resolution aided by a chiral catalyst of a chemical nature.[7h] Coordination of the titanium atom of the chiral complex with the hydroxyl group of the compound undergoing epoxidation will result in two intermediate diastereomers. Asymmetric epoxidation of these two diastereomers occurs at different rates and results in kinetic resolution of the racemic secondary alcohol. Noyori's enantioselective rhodium-BINAP-catalyzed isomerisation of the chiral allylic alcohol is another example of this class (eq 2).[8] Recently, Noyori reported asymmetric reduction of an

equilibrating enantiomeric pair of α-substituted-β-ketoesters *via* dynamic kinetic resolution.[27] By use of this methodology the racemic β-ketoester is converted in 100% yield to a single chiral product with well-defined vicinal chiral centers (eq 3). The success of this reaction depends on the fact that racemization of the ketoester is faster than the hydrogenation.



Generally, it is difficult to choose between asymmetric synthesis and kinetic resolution. Among several factors, cost of the raw materials is very important for economic success [28] of either of these chemical processes. There are advantages and limitations in each method. In kinetic resolution, optical purity varies with conversion, and in asymmetric synthesis the optical purity of the product is independent of conversion. Being able to balance optical purity with conversion allows one to generate chiral samples with specific optical purities. These samples can be useful for biological testing. The limitation of this methodology is that the unwanted isomer needs to be recycled *via* racemization. In general, enzymatic kinetic resolution produces only one of the two possible enantiomers. Kinetic resolution involving chemical catalysis would have the advantage of substrate versatility over their enzymatic counterparts, and both enantiomers can be obtained by chemical means. Modest selectivity factors lead to products of high optical purity *via* chemical kinetic resolution.

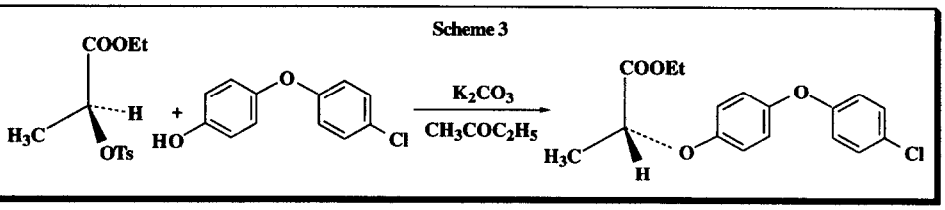
3.0 Chiral Pool Synthesis:[12,16,17,18]

In chiral pool synthesis, all synthetic transformations need to be carried out with a high degree of stereoselectivity. The original chiral molecule is consumed stoichiometrically. Since the stereochemistry of the starting material determines the stereochemistry of the product, the availability of the desired isomers of chiral starting materials can be a limitation to this approach. One can circumvent this problem by using the available antipode as the starting material and, at a later stage in the synthesis, the chiral center can be manipulated, and inverted by appropriate reactions to provide the stereochemistry of the target molecule.

Carbohydrates are very useful sources of chiral starting materials and can be used in the total synthesis of complex target molecules. The chiral pool approach involving carbohydrate precursors would be inefficient to construct a hydrocarbon target with one chiral center and, conversely, one would not use chiral terpenes as starting materials for multi-hetero atom-based chiral targets. Several protection and deprotection steps are unavoidable in carbohydrate chemistry which limits the efficient usage of the carbohydrates in industrial-scale

synthesis. The Hoechst process[29] for the production of an optically active α-phenoxypropionic acid herbicide uses a derivative of lactic acid (Scheme 3).

Scheme 3



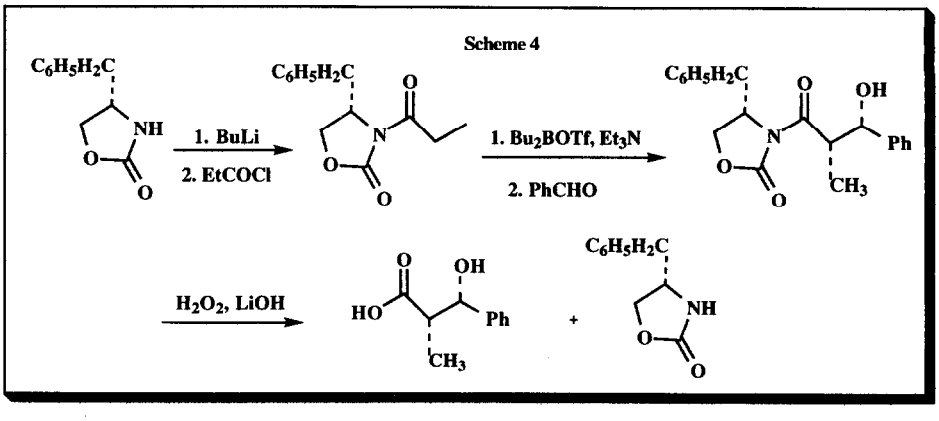
4.0 Asymmetric Synthesis:[5]

Asymmetric synthesis involves the creation of one or more chiral centers from a prochiral starting material under the influence of a chiral substrate. This substrate can be used as a reagent, catalyst or as an auxiliary. Three different approaches: 1) use of chiral auxiliaries, 2) chiral reagents and 3) chiral catalysis are described. Asymmetric synthesis is an alternative to resolution technology for the production of chiral compounds. It is important to distinguish asymmetric synthesis from resolution both on mechanistic grounds and from an operational point of view. Resolution methods can be regarded as physical methods designed to separate previously synthesized enantiomers, whereas asymmetric synthesis consists of formation of one or more chiral centers from prochiral substrates. Enantiomeric excess (ee) is a measure of the efficiency of an asymmetric synthesis.

4.1 Asymmetric Synthesis Using Chiral Auxiliaries:

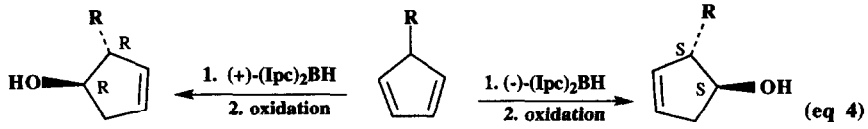
Many chiral auxiliaries have been reported in the literature for asymmetric transformations. The example shown in Scheme 4 is Evans' chiral oxazolidinone auxiliary.[30] This auxiliary is used for controlling the relative and absolute stereochemistry of the aldol reaction. In addition to high levels of asymmetric induction, both acylation and hydrolysis of the chiral auxiliary are facile, high yielding reactions. Introduction and removal of the chiral auxiliary adds two additional steps in the total synthesis of the target molecule and, therefore, is a drawback of the chiral auxiliary approach.

Scheme 4



4.2 Asymmetric Synthesis Using Chiral Reagents:

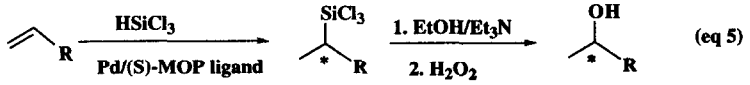
In this methodology, a chiral reagent is treated with the prochiral substrate to deliver the optically enriched product. This approach avoids the attachment of a chiral reagent to the substrate as described in the chiral auxiliary method. Recently, Partridge and co-workers used a chiral borane reagent derived from (-)-α-pinene to prepare prostaglandin intermediates (eq 4).[31e]



(eq 4)

4.3 Asymmetric Synthesis Using Chiral Catalysts:

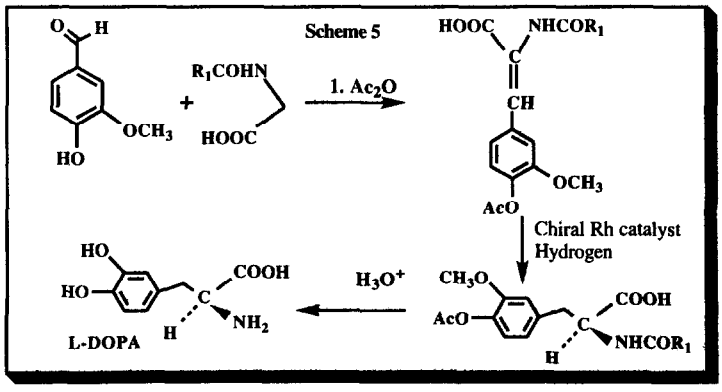
Synthesis of optically pure compounds *via* transition metal mediated chiral catalysis is very useful from an industrial point of view. One can produce large amounts of chiral compounds with the use of very small quantities of a chiral source. The advantage of transition metal catalyzed asymmetric transformations is that there is the possibility of improving the catalysts by modification of the ligands. Recently, olefinic compounds were transformed into the corresponding optically active alcohols (ee 94-97%) by catalytic hydrosilylation-oxidation procedure (eq 5).[32]



(eq 5)

4.31 Asymmetric Hydrogenation (AH):[9]

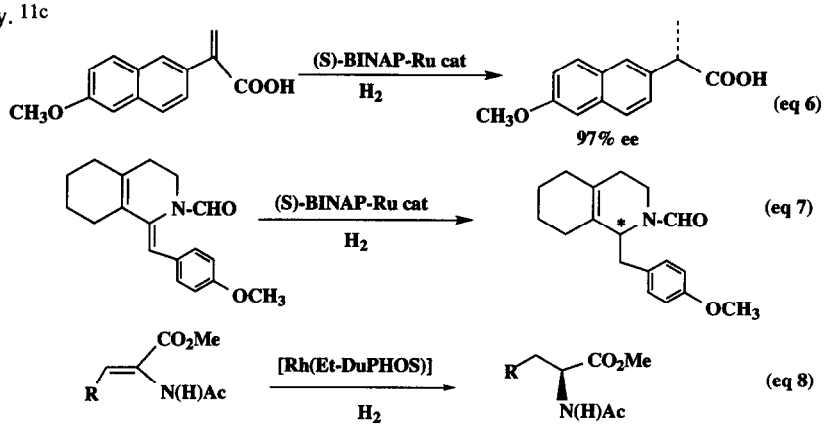
Catalytic asymmetric hydrogenation is a relatively developed process with respect to other asymmetric processes practiced today. There are several milestones which contributed to this state-of-the-art technology. The odyssey began with the discovery of Wilkinson's catalyst.[33] Later on, both Horner[34] and Knowles[35] independently reported the feasibility of asymmetric hydrogen transfer with the aid of optically active Wilkinson-type catalysts. Although they observed low optical yields, the lessons learned as a result of their research laid a solid foundation for the success of Monsanto's asymmetric synthesis of the anti-Parkinson's drug L-DOPA. In 1971 Kagan disclosed[36] an important result with DIOP bi-dentate ligand (first ligand with C_2-symmetry axis)



aimed at improving the stereoselectivity of the asymmetric process by restricting the conformational mobility around the metal atom. In the same year, Morrison reported an interesting neomenthyl diphenylphosphine ligand, which is devoid of any chiral phosphorous atom.[37]

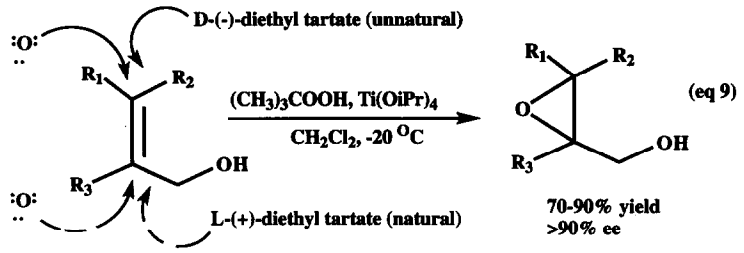
Early lessons learned in asymmetric hydrogenation paved the way to some of the new asymmetric catalytic processes. Many of the successful chiral ligands used for transition metal mediated asymmetric catalysis in general are chelating phosphines possessing a C_2-symmetry axis, the presence of which serves the important function of reducing the number of possible diastereomeric transition states.[38]

The key steps in L-DOPA synthesis are outlined in Scheme 5. Some important points in this synthesis are delineated here. DIPAMP ligands are expensive to make. Catalyst-to-substrate ratios are as high as 1:20,000. These ligands /catalysts are very robust and the usual poisoning problems are rare. However, low oxygen levels (down to parts per million) during the start of a hydrogenation are crucial for maintaining the catalytic activity. 2,2'-bis(diphenylphosphino)-1,1'-binapthyl (BINAP) ligands are used in asymmetric hydrogenation of various important substrates such as aryl acrylic acids (eq 6),[39] (Z)-N-acylaminoacrylic acids (79-100% ee), and dextromethorphan (eq 7).[40] The cationic Et-DuPHOS-Rh catalyst proved useful for hydrogenation of a variety of unusual α-amino acids (eq 8) under mild reaction conditions (1 atm. hydrogen pressure, 20^0 C).[41] Aspartame synthesis involves another application of asymmetric hydrogenation methodology.[11c]

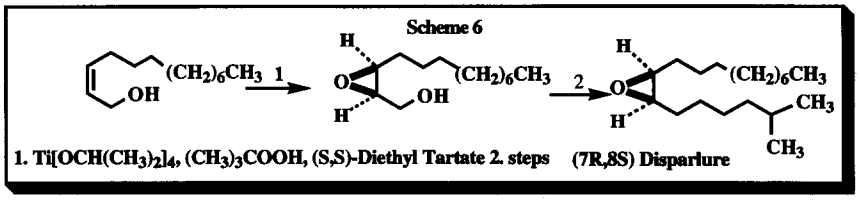


4.32 Asymmetric Epoxidation (AE):[7]

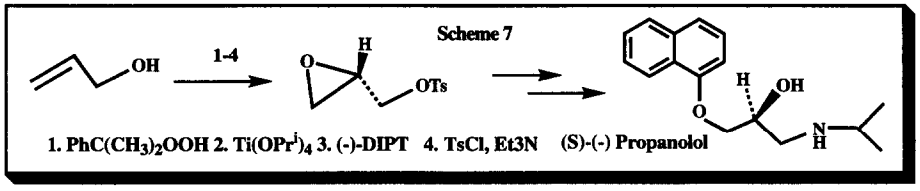
The enantioselective epoxidation method developed in 1980 by Sharpless and coworkers is one of the most important asymmetric transformations known today. This methodology involves the epoxidation of allylic alcohols with t-butyl hydroperoxide and titanium isopropoxide in the presence of optically pure tartate ester (eq 9). This is the first example where the presence of a chelating ligand was observed to facilitate rather than retard metal catalyzed epoxidations. Recently, it was found [42] that the use of molecular sieves greatly improves this process by removing minute amounts of water present in the reaction medium. Water was found to deactivate the catalyst. Catalytic quantities of calcium hydride and silica gel are also known to decrease the reaction times substantially.[43] All these developments led to an improved catalytic version which allows a five-fold increase in substrate concentration relative to the stoichiometric method. Sensitive, water-soluble optically active



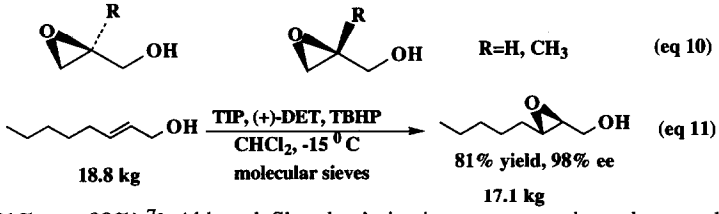
glycidols can be prepared in an efficient manner by *in-situ* derivatization. This epoxidation method appears to be competitive with enzyme catalyzed processes and was applied in the commercial production (in 1981) of the gypsy moth sex attractant, (+)-disparlure (Scheme 6) used for insect control.[7] Recently, an important drug,



chloramphenicol, was prepared *via* Sharpless epoxidation as the key step.[44] Sharpless used asymmetric epoxidation as the crucial step in the preparation of of β-adrenergic blocker, (S)-propanolol (Scheme 7).[45]

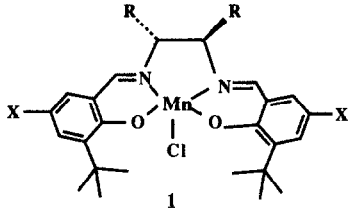


ARCO Chemical Company used this epoxidation method [7a] to produce 10 tons/year of (S)- and (R)-glycidols in 90% ee. Glycidols are useful building blocks for highly functionalized chiral targets (eq 10). [88] Upjohn Chemical Company has made multi-kilogram quantities of C_8- epoxy alcohol in 500 gallon reactors



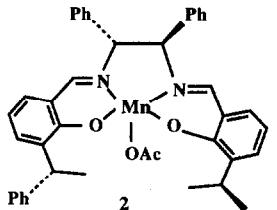
(eq 11) (yield, 81%, ee >98%).[7a] Although Sharpless' titanium tartate catalyst tolerates a high degree of structural variation in prochiral substrates, the method is limited in that it only works with allylic alcohols, so is not applicable to isolated double bonds. Simple olefins do not have a 'handle' (polar functional group) to chelate with metal complexes as in the case of allylic alcohols, so it is more challenging to develop catalysts for asymmetric epoxidation of unfunctionalized olefins.

Jacobsen[46] reported some practical and highly enantiospecific salen catalysts (**1**) for asymmetric epoxidation of unactivated olefinic substrates. These cationic (salen) manganese(III) complexes oxidizes mono-, di- and tri-substituted cis-olefins, using cheap, readily available bleach in an efficient manner providing



1

Jacobsen's catalyst



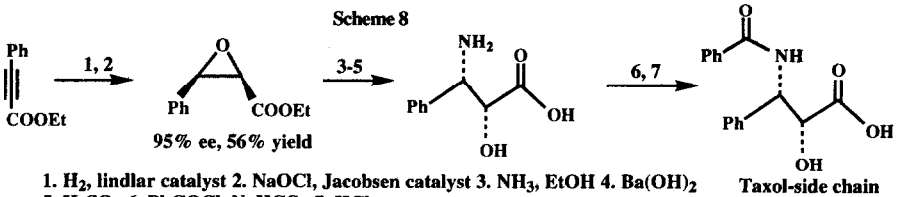
2

Katsuki's catalyst

epoxides with good asymmetric induction. Later on, Katsuki reported similar ligands (e.g.**2**) possess more asymmetric centers, and he claims that these additional chiral centers have strong influence for inducing chirality in the final products.[47] Synthesis of these ligands is more difficult, and the ee's of the epoxides are lower than those obtained *via* the Jacobsen method.

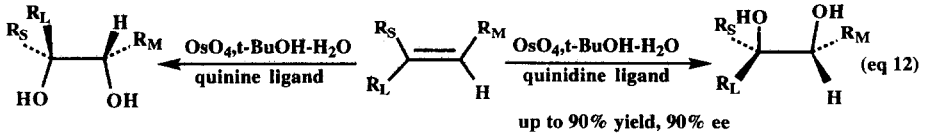
The origin of high enantioselectivity for these chiral salen complexes is interpreted in terms of the side-on approach of the active oxomanganese intermediate to the substrate. Jacobsen observed that the presence of sterically demanding t-butyl groups are necessary to achieve high asymmetric induction. External additives such as pyridine-N-oxide are shown to increase the chemical and optical yields of the epoxides. Low turnover numbers and limited substrate applicability (high ee's only with cis-olefins) are limitations of this methodology. Using this technology, Deng and Jacobsen reported a practical four-step synthesis of Taxol-side chain starting with commercially available ethyl phenylpropiolate in 25% overall yield as shown in Scheme 8.[48]

Scheme 8



4.33 Asymmetric Dihydroxylation (AD):[49]

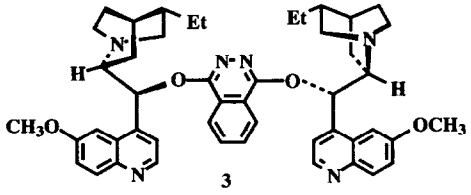
Vicinal addition of hydroxy groups to the C-C double bond can occur in either *syn* or *anti* fashion.[50-52] Generally, the AD method involves generation of two new chiral centers from prochiral olefins. Asymmetric dihydroxylation was reported [53] by Sharpless et al. in 1980 (eq 12), and since then continuous



up to 90% yield, 90% ee

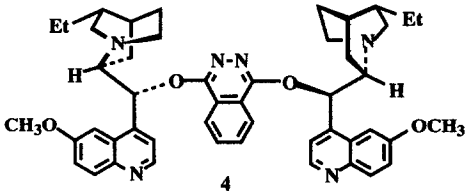
attempts have been made to upgrade this process by optimizing the reaction conditions. In a recent report, Sharpless group introduced phthalazine derived cinchona ligands $(DHQD)_2$-PHAL (**3**) and $(DHQ)_2$-PHAL (**4**) and also observed that osmate ester hydrolysis was accelerated in presence of organic sulfonamides.[54d] The catalyst recipe was prepared from a mixture of one of the cinchona ligands, potassium osmate, potassium ferricyanide, and potassium carbonate as a powder mix. This 'ready-mix' is also available from Aldrich as AD-mix α or β.

Some of the historical events leading to the discovery of catalytic AD deserves a comment. Based on Criegee's observation[55] that nucleophilic ligands such as pyridine accelerate osmium tetraoxide mediated dihydroxylations, Sharpless reasoned that an analogous chiral ligand might be a useful candidate for AD. Griffith and co-workers observed that tertiary alkyl bridgehead amines, such as quinuclidine, form complexes with osmium tetraoxide which are more stable than corresponding pyridine complex.[56] It was also well established from the work of Wynberg[57] that quinine (**5**) or quinidine (**6**) are efficient catalysts for asymmetric



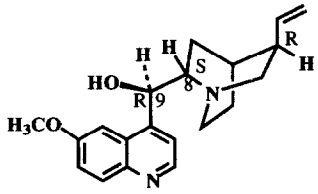
3

$(DHQD)_2$-PHAL (ligand used in AD-mix-β)

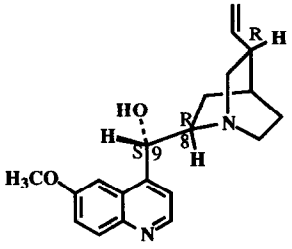


4

$(DHQ)_2$-PHAL (ligand used in AD-mix-α)



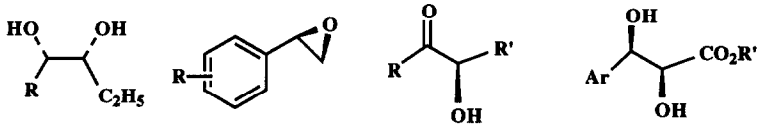
5 (-)-Qunine



6 (+)-Quinidine

phase transfer reactions and asymmetric Michael additions.[58] In the initial stages osmium tetraoxide was used in stoichiometric amounts. Later on, to address the problems associated with cost and toxicity of osmium, N-methyl morphiline N-oxide was used as reoxidant.[54c] Use of a catalytic amount of osmium tetroxide with hindered alkenes gave poor optical yields. Ingenious mechanistic probing of this reaction[54a] revealed that two catalytic cycles operate simultaneously, and the cycle responsible for the production of the unwanted enantiomer was suppressed by maintaining low concentration of olefin during the reaction. Alternatively, the undesired cycle can be precluded by use of a one-electron oxidant, potassium hexacyanoferrate(III), as the re-oxidant resulting in a superior AD process.[54e] Recently it was shown that the chiral cinchona alkaloid can be immobilized on a polystyrene-based polymer and was used for AD.[59,60] The chiral ligand and osmium tetraoxide are recycled without isolation, and the diols obtained are separated by simple filtration or centrifugation of the reaction mixture. Unlike AE, AD is insensitive to water and oxygen and can be performed

Scheme 9



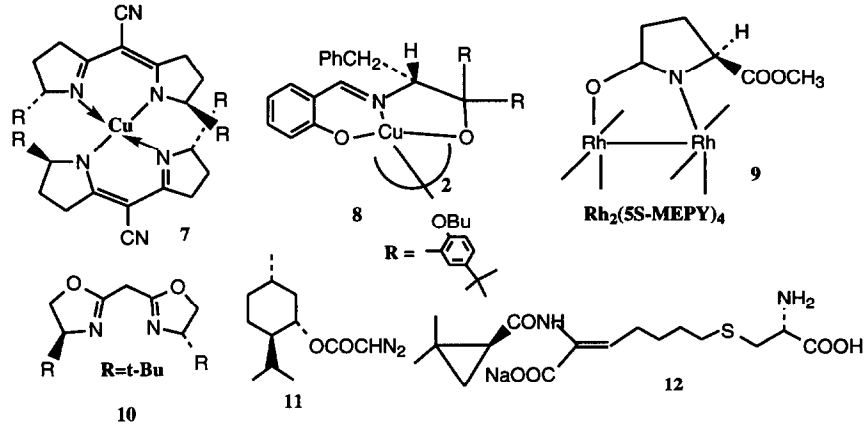
Chiral Intermediates from Sharpless ADH Chemistry

without special conditions. Sepracor chemists has developed a broad range of technologies to manufacture chiral epoxides and chiral dilos *via* Sharpless ADH at the 4000 L scale (Scheme 9).[61] These diols can be used as precursors to epoxide-like building blocks.[62-64]

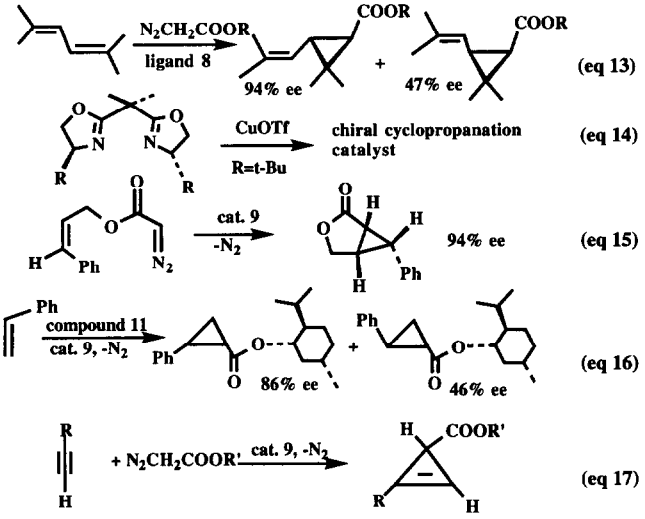
4.34 Asymmetric Cyclopropanation (ACP):[65]

In 1966 Nozaki reported for the first time a catalytic ACP of olefins by the action of a diazo ester in the presence of chiral Schiff base complexes.[66a,b] Aratani and his co-workers [65a] reported cyclopropanation of various olefins and conjugated dienes by dimeric chiral complexes as catalysts (eq 13). This methodology was extended to the synthesis of the reversible enzyme inhibitor cilastatin (**12**). Chrysanthemic acid was prepared through chiral copper carbenoid chemistry. Although significant advances in cyclopropanation methodology using chiral catalysts have been made, a total control of the stereoselectivities is still out of reach in most cases. Thermodynamically less stable *cis* isomers can not be obtained by this technology. The role of the ligand is important in controlling the approach of the olefin to the carbene center. Therefore the steric environment around the chiral ligand is very critical in obtaining high enantioselectivities. Besides steric effects, the presence of large lipophilic groups both in the diazoester and in the catalyst dramatically improve yields for these carbene insertion reactions. It was shown that the cyclopropane yield from *trans* -4-octene increases from 7% with methyl diazoacetate and rhodium acetate up to 80% with *n*-butyl diazoacetate and rhodium pivalate.[67]

Since the first report, several advances have been made in the design of various catalysts both for inter- and intramolecular synthesis of cyclopropane derivatives. Some of them include Pfaltz's C_2-symmetric semicorrins (**7**)[10a] chiral salicylaldimines (**8**),[65] and dirhodium(II) carboxamides (**9**).[10b] Several groups reported that these corrin ligands are effectively used for ACP of various olefins delivering a high *trans /cis* ratio with good enantioselectivity. Masamune's group reported catalytic ACP with copper complexes of C_2-

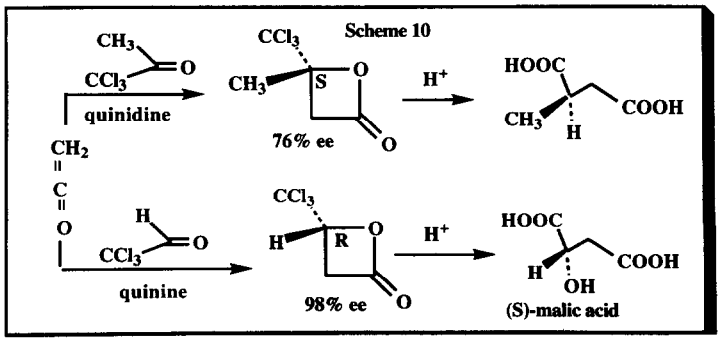


symmetric bis(4,5-dihydrooxazolyl)methane (**10**).[68] These ligands are obtained directly from diethyl malonate and the corresponding β-amino alcohols. Very high enantioselectivities are observed with these cyclopropanating reagents (*trans*, 90% ee; *cis*, 77% ee). Use of the chiral cyclopropanating reagent (-)-menthyl diazoacetate (**11**) increases the diastereomeric ratio and improves ee [*trans* (98% ee): *cis* (96% ee) = 86:14]. Evans and his colleagues [69] have shown that the chiral cyclopropanation catalyst (eq 14) derived from the bisoxazoline and copper triflate is a single-stranded helical polymer with three fold symmetry. This catalyst is stable in the solid state and can be used for enantioselective cyclopropanations giving optical yields up to 98% and excellent *cis/trans* ratios (4 : 96 for styrene). Chiral dimeric rhodium(II) compounds are effective catalysts for inter- and intramolecular cyclopropanation reactions.[66c-e] Double asymmetric synthesis involving chiral rhodium(II) carboxamides and L-menthyl diazoacetate (**11**) is applicable to various cyclopropanations as shown in eq 15 and 16. Dimeric chiral rhodium catalysts are very useful for cyclopropenation of the alkynes where the copper catalysts give ring opening products (eq 17). [66f]



4.35 Asymmetric Cycloadditions:[70]

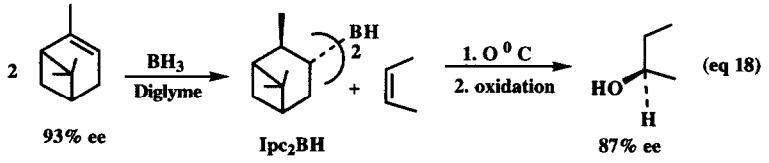
Cycloadditions are among the most widely-used reactions for the construction of structurally diverse molecules in organic synthesis. Wynberg reported 2+ 2 cycloaddition reactions to prepare multi-kilogram quantities of useful chiral building blocks such as malic and citramalic acids (practiced by Lonza chemical company). The synthetic steps involve cycloaddition of ketene to chloral by use of a catalytic quantities of



quinidine or quinine, giving the oxetanones in 98% optical yield and 89% chemical yield (Scheme 10).[58b] Known hydrolysis converts these lactones to the optically pure acid derivatives. Various chiral catalysts were reported in the past for effecting asymmetric cycloaddition reactions. The use of oxazaborolidines in asymmetric cycloadditions was reviewed recently.[71]

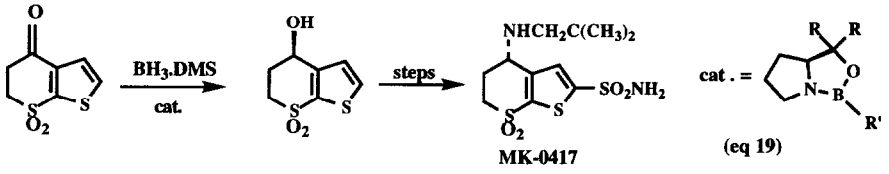
4.36 Asymmetric Hydroboration: [31, 72-78]

In 1961, Brown and Zwifel reported[72] the first asymmetric hydroboration reaction (eq 18). Optically enriched 2-butanol (87%) was produced by hydroboration-oxidation of *cis*-2-butene by diisopinocamphenylborane (Ipc_2BH), prepared from commercially available (+)- or (-)-α-pinene (ee 93%). Later on, it was discovered that by equilibrating the Ipc_2BH with a 15% excess of α-pinene at O ^{0}C, the major enantiomer crystallized with an optical purity >99%. Several terpene-derived hydroborating agents have been cited in the literature. These are very useful for several types of stoichiometric asymmetric reactions.[31]



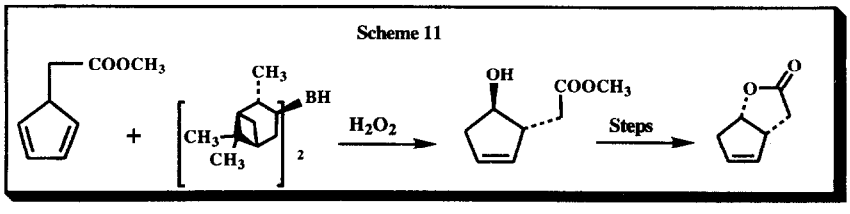
The reagent-controlled asymmetric hydroboration methods for functionalization of prochiral alkenes have several limitations from an industrial point of view. These limitations are: 1) large scale synthesis of chiral boranes is expensive and poses handling problems on an industrial-scale, 2) limited substrate applicability. [Z-alkenes give good diastereoselectivity; E-alkenes are not good substrates] 3) regeneration and recycling of chiral borane is not easy and 4) isolation of the two equivalents of the by-product formed during the oxidation step adds a substantial cost to the over-all process.

Enantiomerically pure MK-0417 has been prepared[73] from thiophene derivative which involves oxazaborolidiene-catalyzed borane reduction methodology[71b] which was initially developed by Itsuno[74] and Corey.[75]

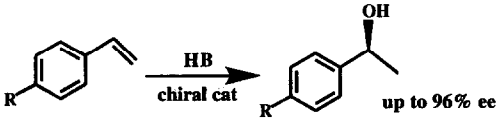


Chinoin pharmaceutical company has employed hydroboration reaction to prepare the Corey lactone, which is a very useful intermediate for prostaglandin synthesis. In this sequence, the hydroboration reaction must be carried out at a very low temperature, because the cyclopentadiene intermediate undergoes isomerisation even at room temperature (Scheme 11).[31e,11c] This reagent-controlled, stoichiometric reaction is used only when the cost of the final product is very high.

Scheme 11



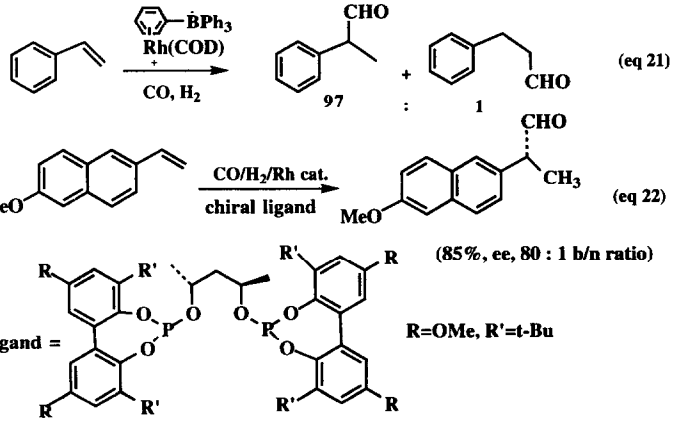
In 1985 Mannig and Noth reported hydroboration of alkenes catalyzed by Wilkinson's catalyst using catecholborane.[76] This mechanistically distinct catalytic process opened up new avenues for chemo-, regio-, stereo-, and enantioselective hydroboration methodology. Optically active 1-arylethanols were obtained (eq 20) by hydroboration (HB) of styrene derivatives with catecholborane catalyzed by chiral rhodium complexes.[78c] The by-product catechol can be removed by simple extraction with aqueous base. The more conventional, non catalytic methods for asymmetric hydroboration of prochiral olefins are based on reagent-controlled diastereoselectivity and have limited applicability in large scale synthesis because stoichiometric quantities of the chiral reagents are used. Although these rhodium catalyzed enantioselective hydroborations are very useful, they have not been used in any large-scale industrial applications.

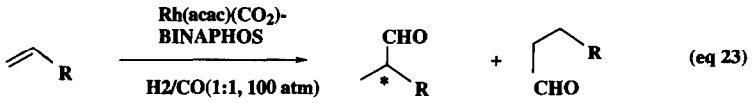


(eq 20)

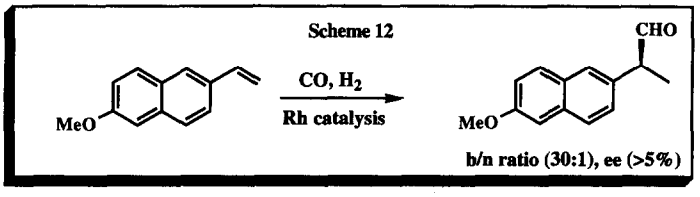
4.37 Asymmetric Hydroformylation (AHF):[79]

The hydroformylation reaction (oxo process), first reported by Roelen[80] in 1938, is an industrially important process for the production of aldehydes from olefins, carbon monoxide, and hydrogen. Various group-VIII metals catalyze this reaction, and typical solvents used for this reaction are benzene and toluene. The main emphasis in industrial oxo processes is the production of the linear isomer whereas AHF produces the branched isomer. Several rhodium complexes have recently been shown to be a good catalyst for hydroformylation; [81] and styrene can be hydroformylated to give the branched aldehyde with 97% selectivity (eq 21). The first AHF was reported in 1972.[82] This reaction has not been studied as intensively as some other processes (e.g. AH). Union Carbide group reported the synthesis of 2-(6-methodxy-2-naphthyl)-propionaldehyde, which is a precursor to (S)-naproxen *via* hydroformylation reaction (eq 22).[83] Enantioselective hydroformylation of olefins was reported recently (ee 95%) by using phosphinephosphite Rh(I) complexes (eq 23).[84]





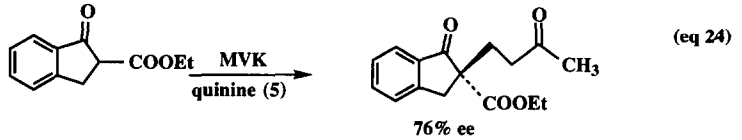
Brown [85] studied the hydroformylation of 2-ethenyl-6 methoxynaphthalene to generate 2-(6-methoxy-2-naphthyl) propionaldehyde. The rhodium and sugar-based ligand catalysts gave high b/n (branched/normal) ratios but with low enantioselectivity (Scheme 12).

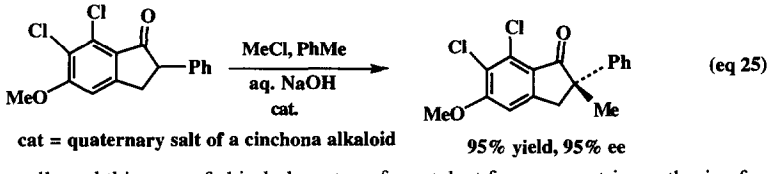


Polymer-bound ligands were synthesized and used in combination with platinum and rhodium catalysts.[86-87] The optical yields are comparable to those obtained by homogeneous counterparts, and the catalysts were reused without loss of activity.

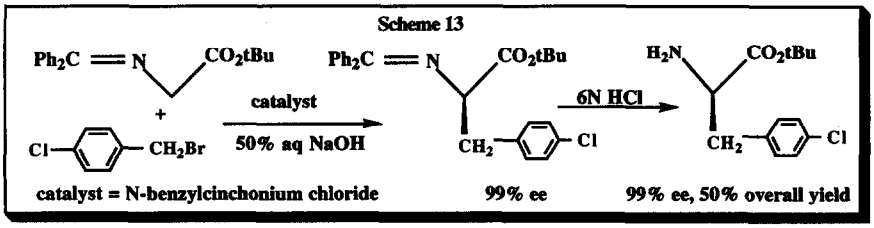
4.38 Asymmetric Phase Transfer Catalysis:

Asymmetric phase transfer reactions generally use cinchona-based alkaloids. Bredig and Fiske reported in 1912[89] the first use of quinine (**5**) for optically active cyanohydrin formation (ee 20%) from benzaldehyde and hydrogen cyanide. Since 1975, Wynberg's group[90] has used these alkaloids extensively for various synthetic transformations such as Michael addition and 2+2 cycloaddition and found that catalytic quantities of quinine (**5**) or quinidine (**6**) are sufficient to provide high levels of asymmetric induction.[57-58] Michael addition of indanone with methylvinylketone in presence of quinine as catalyst gave the addition product in 76% ee (eq 24). Later on, Cram and Soga obtained this adduct with increased optical yield by using a chiral crown ether.[91] Based on Wynberg's methodology, Merck developed the industrial synthesis of indacrinone (eq 25).[92] They also used *cinchona* alkaloid for studying Michael addition reactions.



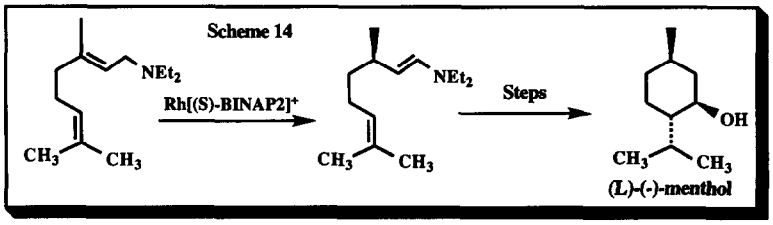


O'Donnell used this type of chiral phase transfer catalyst for asymmetric synthesis of α-amino acid derivatives.[93] This method involves asymmetric alkylation of Schiff bases in the presence of chiral catalysts with electrophiles (ee 64%). Simple recrystallization increases the optical yields up to 99%. Hydrolysis of the alkylated products gives the optically pure amino acids (Scheme 13).



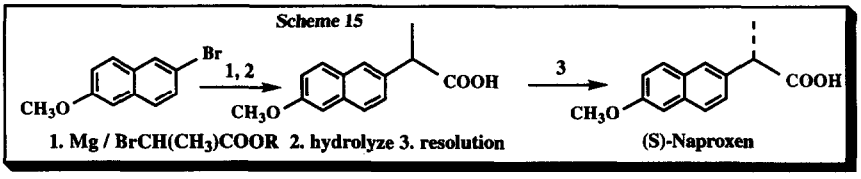
5.0 Miscellaneous Synthesis:

An important industrial application of BINAP ligands is the asymmetric isomerization of allylic amines to optically active enamines.[94] This methodology was used to the large scale production of (-)-menthol (Scheme 14). This is a unique example of very large scale chemical production that utilizes a catalytic asymmetric

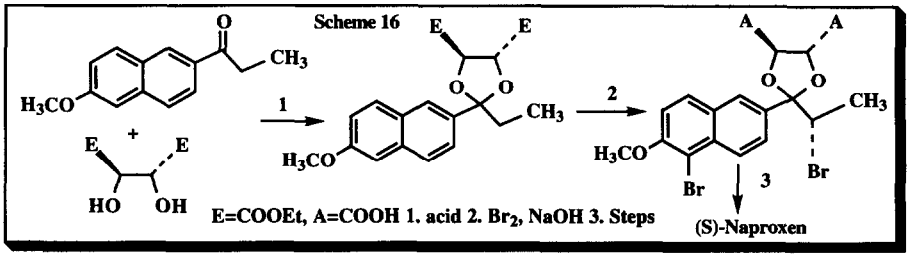


reaction (9-ton scale, >96% ee, 1500 ton/year of chemicals are produced using this process). The catalytic reaction is carried out in a batch process. The catalytic rate and turnover number have been greatly improved by elaborate as well as ingenious process improvements. Functionalized allylic compounds such as allylic amines and alcohols have been shown to be good substrates for BINAP-based catalysts.

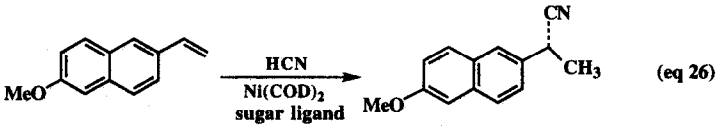
(S)-Naproxen[95] is one of the best-selling prescription drugs for the treatment of arthritis, with annual sales around 1 billion dollars. Currently practiced commercial synthetic approaches for this useful drug by



Syntex and Zambon are shown in Schemes 15 and 16. Syntex's process depends on a Grignard reaction and a resolution as the key steps.[96] Zambon's multi-step synthesis involves a ketal rearrangement as the key step.[97]



Du Pont workers RajanBabu and Casalnuovo reported [98] synthesis of optically pure (S)-(-)-6-methoxy-2-naphthalene-2-propionitrile, a precursor to naproxen. This methodology involves asymmetric Markovnikov addition of HCN to vinyl naphthalenes with the aid of nickel catalysts (eq 26).

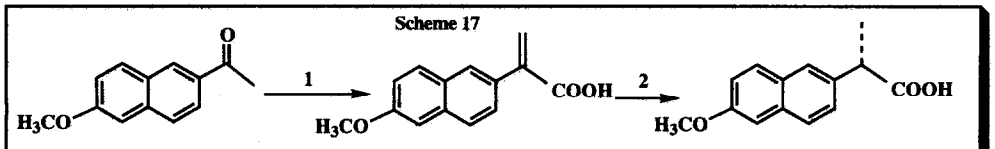


(eq 26)

99% ee (after crystallization)

Monsanto's naproxen approach starts with 6-methoxy-2-acetyl naphthalene as the starting material, and enantioselective asymmetric hydrogenation of 2-(6'-methoxy-2'-naphthyl) acrylic acid is the key step in generating the required chiral center (Scheme 17). Electrochemical addition of carbon dioxide (90%) followed by dehydration gives the acrylic acid intermediate in this methodology. [11g]

Scheme 17



1. electrolysis, CO_2 (b) H^+ 2. Noyori's catalyst, H_2

6.0 Conclusions:

There is no single "best" method for preparation of optically active molecules. Among several factors, structural complexity of the target and the availability of raw materials are crucial for economically feasible synthesis of a particular target.

Increased understanding of the pharmacological aspects of these chiral materials in living systems combined with global competition will continue to provide the driving force for the production of optically active molecules. [99] Although this review put more emphasis on resolution methods and asymmetric catalysis, it is not my intention to undermine the use of enzymatic and biological methods to produce enantiomerically pure compounds. Due to time and space constraints, it is not possible to cover all the important asymmetric transformations (e.g. asymmetric organozinc reactions catalyzed by chiral amino alchols, asymmetric reactions with chiral lewis acid catalysts, reactions involving chiral bases etc.) reported in the literature. [5, 100]

7.0 Acknowledgements: I would like to thank CCTC-TIC staff for their help in getting some of the articles mentioned in this review. Useful suggestions from Dr. G. Williams, Dr. K. Davenport, Dr. B. Keys, Dr. A. Bhattcharya, Dr. T. V. RajanBabu, Prof. H. Brunner, Prof. H. Kagan, Prof. B. Sharpless, and Prof. E. Jacobsen are greatly appreciated.

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