Applications of Catalytic Organic Reactions in Fine Chemicals and Pharmaceuticals

by Mukund K. Gurjar, Srinivas Hotha, A.M.S. Murugaiah

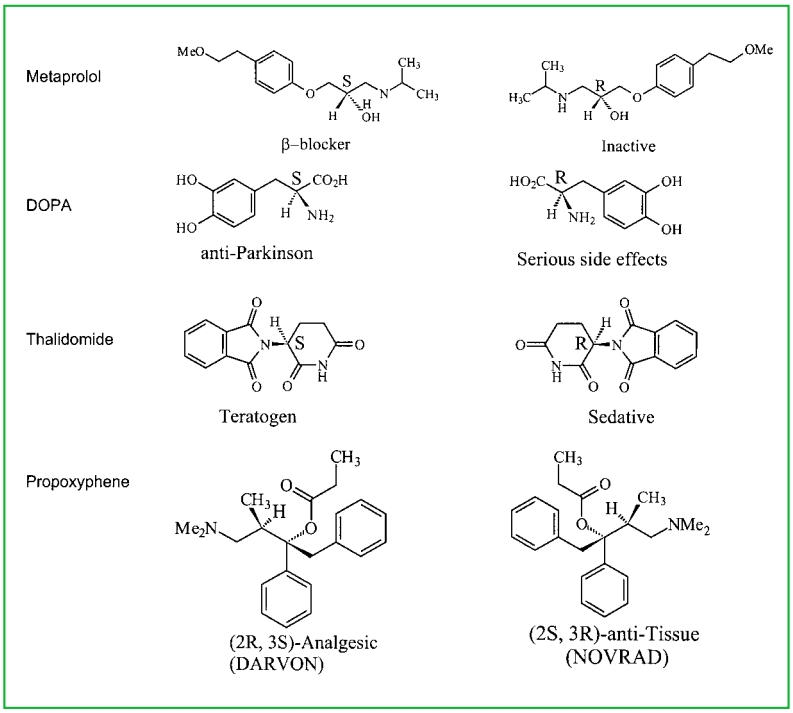
Introduction of new regime of drug substances in consumer market has become increasingly difficult since the introduction of new regulations by Food and Drug Administration, USA. The number of single enantiomer drugs is steadily increasing because of better safety and efficacy of single enantiomer over its racemate. The dose related efficacy of a single enantiomer is an additional advantage. Approval for racemic mixture is almost impossible unless it is proven beyond doubt that the racemate displays no undesirable side effects and is safe for human consumption.

Although enantiomers are chemically indistinguishable, the chiral nature of the biological milieu including plasma protein binding sites, enzymes and receptors recognizes them as discrete species leading to pharmacological differences. Examples in Scheme 1 clearly demonstrate this chiral recognition [1,2].

The combinatorial chemistry has revolutionized the drug discovery through diversity based protocols, high-throughput synthesis, screening and selection in the search for effective therapeutic agents [3]. This has led to the dramatic increase of chiral drugs discovered in the recent past. Among the top ten block buster drugs in 1995, only one was marketed as a racemate (Table 1). Nonetheless, out of 44 new chemical entities introduced in the market in 1998, 32 were single enantiomers, 11 were achiral and one was racemate [4]. Further, the sales of chiral drugs are growing rapidly with 11% per annum (Tables 2, 3) [5]. These developments in addition to the perpetual increase in racemic switches have usurped the academicians and industrial chemists in the past decade to develop catalytic asymmetric processes to the chiral building blocks (Scheme1) that would cater the exigency in the fine chemical, pharmaceutical, agrochemical and life sciences markets. The enantioselective technologies which utilise chemo- and bio-catalysts for asymmetric induction can be successfully transferred to the industrial applications provided they are:

i) efficient by route selection;
ii) economically viable;
iii) environmentally benign.

Catalyst efficiency is also the crucial factor in terms of catalyst selectivity (*ee*), catalyst productivity (turn over number), catalyst activity (turn over factor) and availability and cost. Since asymmetric catalysis is a multi-faceted and boundless field and also the current topic of discussion theme in several symposia and mono-



Scheme 1

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Table 1 - Top Ten Drugs Marketed Worldwide in 1995

Name	*Rank*
Ranitidine	1
Omeprazole	2
Amoxicillin	3
Ethinylestradiol	4
Nifedipine	5
Enalapril	6
Diclofenac	7
Diltiazem	8
Fluoxetine*	9
Simvastatin	10

**Marketed as racemate*

Table 2 - Sales of Chiral Drugs in 1998

Name	*US $ in billions*
Antibiotics	23.25
Cardiovascular	21.14
Harmones	11.58
CNS	7.80
Cancer	7.60
Anti-viral	6.22
Respiratory	4.25
Gastrointestinal	1.42

Table 3 - Enantiomers comprise more than half of drugs approved world wide

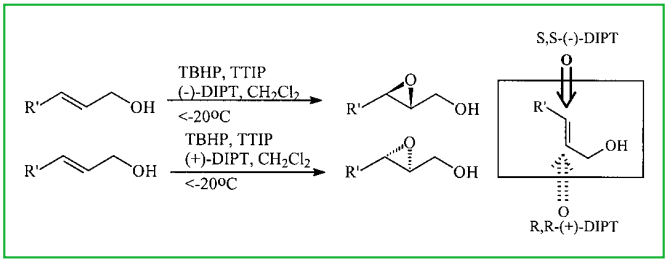
	1994	*1996*	*1998*
Single enantiomer	26	29	32
Racemic	7	6	11
Achiral	14	16	1

graphs including up-to-date accounts [6], the author in the ensuing section will provide an insider's view based on his own intuition and experience in this area and regrets for not covering whole catalytic asymmetric synthesis. Accordingly, the review has been divided into the following parts:

- asymmetric oxidation;
- asymmetric hydroboration;
- asymmetric isomerisation;
- asymmetric hydrocyanation;
- asymmetric aldol.

Asymmetric Oxidation

Oxidation reaction is a powerful tool in organic synthesis to generate functional groups useful for further transformation. Asymmetric oxidation of olefins, specially, epoxidation and dihydroxylation lead to two contiguous chiral centers that can regio- and stereo-selectively be manipulated to provide versatile synthetic intermediates.



Scheme 2

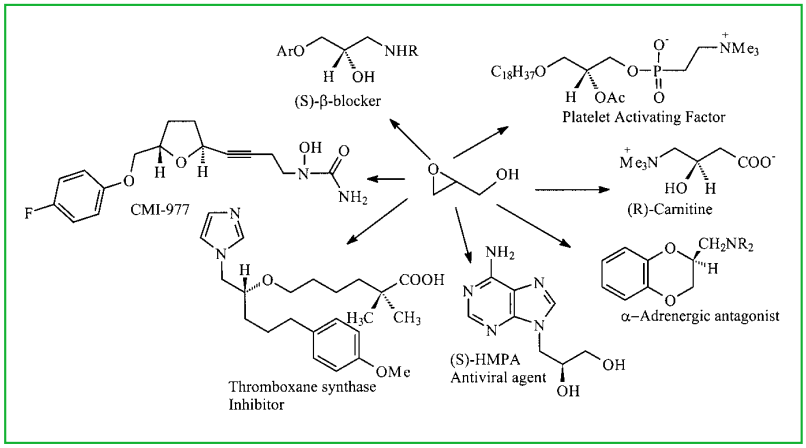
Asymmetric Epoxidation of Allyl Alcohols

The discovery of asymmetric epoxidation of allyl alcohols by Sharpless [7] in early 1980s constitutes one of the landmark achievements in asymmetric catalysis. The original stoichiometric reaction involving the titatium tetraisopropoxide-dialkyltartarate complex as catalyst and alkyl hydroperoxide as oxodonor was later fine-tuned to catalytic version by the addition of molecular sieves (4Å or 5Å) to eliminate traces of water (Scheme 2).

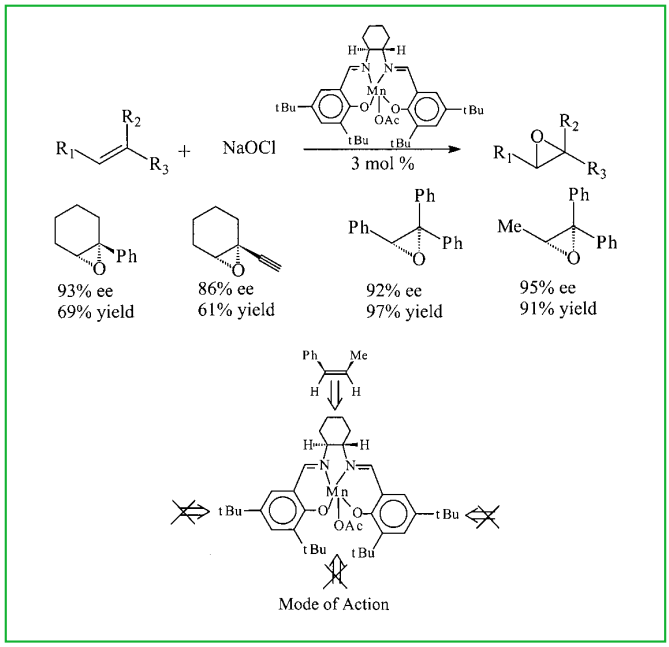
The factors like: (i) oxidation of wide spectrum of substrates with different substituent patterns including meso compounds; (ii) inexpensive reagents; (iii) compatibility of various functional groups; (iv) excellent *ee*'s; (v) feasibility of either enantiomeric product and (vi) predictability of product configuration by mnemonic device made this reaction one of the most sought by synthetic and industrial chemists. Asymmetric epoxidation of allylic alcohols at the industrial scale in multi kilogram quantities was truly outstanding, providing optically pure isomers of glycidol. Glycidol and its derivatives are valuable C3-chirons [8] to realize several enantiopure pharmaceutical intermediates and drugs esp. enantiomeric β-blockers [8] and phospholipids [8], including our own commercially viable process to CMI-977[9], a lead clinical candidate for chronic asthma (Scheme 3).

Asymmetric Epoxidation of Unfunctionalized Olefins

The shortcoming of Sharpless method is its substrate specificity for allyl alcohols. This was remedied in later years through the development of catalysts effective for enatioselective oxo transfer to unfunctionalised olefins.

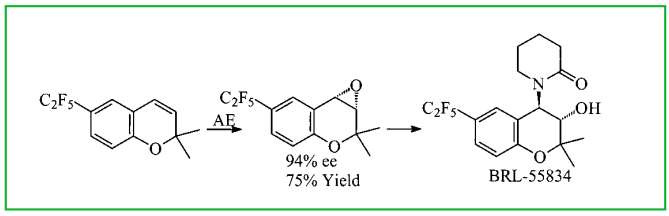


Scheme 3

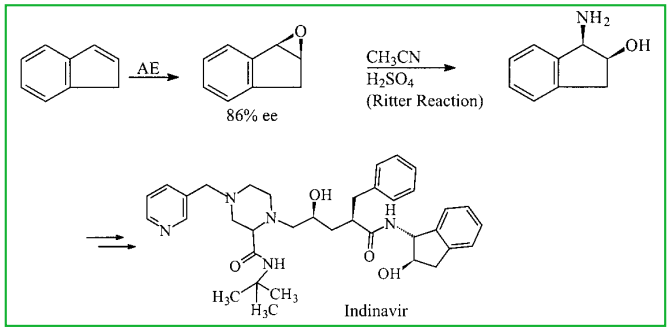


Scheme 4

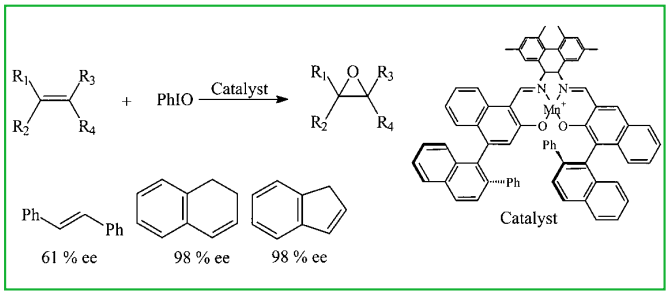
The pioneering efforts of Jacobsen *et al.* [10] paved the introduction of chiral Mn^{III}(salen) catalysts for epoxidation of prochiral olefins along with an oxidant (NaOCl, *t*-BuOOH, mCPBA, amine *N*-oxides, ozone, oxone, oxygen, H_2O_2 and $NaIO_4$). *Cis*- and trisubstituted olefins are excellent substrates while diminished face selectivity was observed for *trans*- and terminal olefins (Scheme 4). This reaction seems to be solvent-sensitive, which was observed during the epoxidation of chromane derivatives [11a]. The reaction proceeded sluggishly with poor *ee* in CH_2Cl_2 with oxone as an oxidant but with good *ee* and higher rate of conversion in CH_3CN. Recently, Song *et al.* have disclosed a practical recycling (Scheme 4) procedure for Jacobsen's catalyst by immobilization in stable ionic liquid, [bmim][PF_6] [11b]. Important industrial applications include asymmetric synthesis of potassium channel activator BRL



Scheme 5a



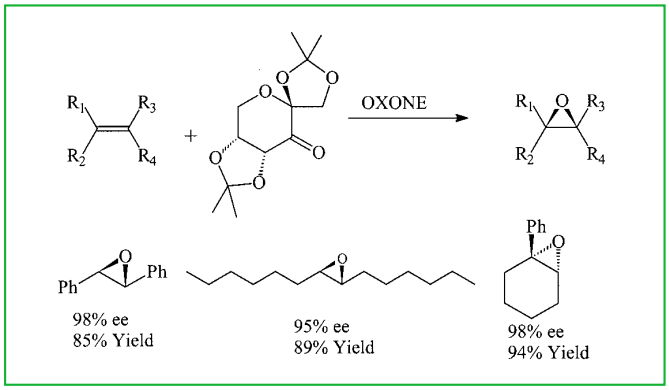
Scheme 5b



Scheme 6

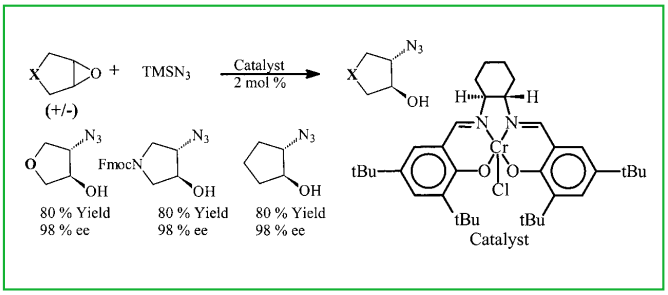
55834 [12] (Scheme 5a) and Indinavir [13], a HIV protease inhibitor (Scheme 5b).
The success of Jacobsen's epoxidation prompted Katsuki [14] and co-workers to introduce Mn-based more versatile catalyst (Scheme 6) through "steric and electronic modulation" of metal environment.

Asymmetric Epoxidation using Chiral Dioxirane
Another recent and interesting development is the advent of fructose-derived ketone as AE catalyst in the presence of oxone. The ketone catalyst [15a] and oxone produce the chiral dioxirane as an intermediate whose consequent exposure to olefin substrate induces epoxidation through enantioface discrimination. This reaction is particularly suited for the epoxidation of *trans*-olefins, hitherto inaccessible by previous methods. Excellent *ee*'s for *trans*-disubstituted, tri-substituted olefins and enol ethers or ester, high functional group tolerance, availability of inexpensive either enantiomer of the catalyst, and simple work-up are attractive features for commercial exploitation in future [15b] (Scheme 7).

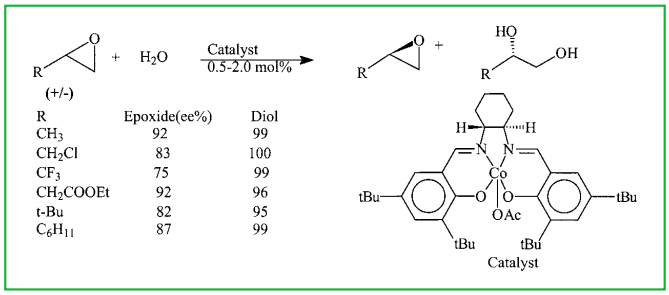


Scheme 7

Asymmetric Epoxide Opening
In the aftermath of applicability of multidentate C_2-symmetric salen ligand grafted to Mn to effect asymmetric epoxidation of unfunctionalised olefins (see section above), Jacobsen could later develop a different protocol for asymmetric epoxide ring opening by replacement of cataphoric Mn with cobalt and chromium. Racemic epoxides are relatively easy to prepare. The inherent strain in the three membered epoxide ring could be exploited by coordination of the epoxide ring oxygen to a chiral Lewis acid, facilitating the subsequent nucleophilic ring opening in the chiral environment. Jacobsen and co-workers have demonstrated the practical kinetic resolution/enatioselective ring



Scheme 8



Scheme 10

opening of terminal/meso epoxides with three principal nucleophiles, $TMSN_3$, H_2O and phenol.

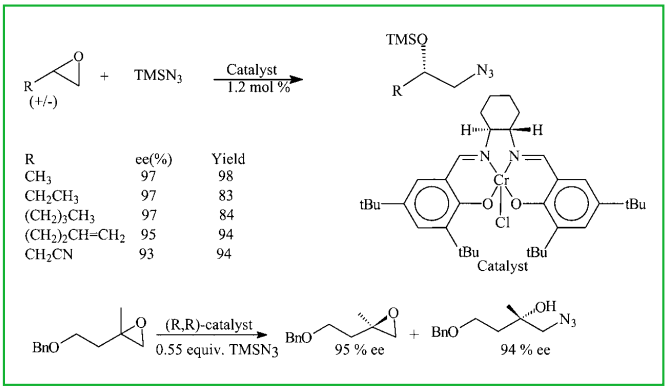
$TMSN_3$ in the presence of chiral Cr(salen) catalyst promotes the enantioselective ring opening of mesoepoxides with high degree of chiral induction (Scheme 8) [16]. The application of Cr(salen) catalysed asymmetric ring opening [16] with $TMSN_3$ was demonstrated to prepare range of chiral building blocks useful for the synthesis of bioactive substances such as balanol [17], prostaglandins [18] and carbanucleosides [19].

Kinetic resolution of racemic epoxides was effected with Cr(salen)complexes to provide valuable 1-amino-2-alkanol precursors with excellent chiral discrimination (K_{rel}=44 to 230) and chemical yield [20a].

Another feature [20b] is the resolution of even difficult substrates like 2,2-disubstitued epoxides (Scheme 9).

The most outstanding modification [21a] was the hydrolytic kinetic resolution (HKR) of racemic epoxide in the presence of Co(salen)OAc catalyst and water. This approach leads to the formation of mixture of unreacted epoxide and the ring opened diol both obtainable in more than 90% *ee*. Scheme 10 invites attention about the versatility of HKR reaction. The HKR of racemic epichlorohydrin and propylene oxide has been effected on a multi-hundred kilogram scale. The distinct advantages of HKR are:

i) many functional groups are relatively stable toward HKR reaction;
ii) low cost process for enantiopure terminal epoxides [21,b,c,d] and diols, which otherwise require multistep synthesis from chiral pool or via costly high-volume biocatalytic processes;
iii) separation and purification of epoxide diol through fractional distillation taking advantage of volatality-bias;
iv) inexpensive starting materials and catalysts, producing either enantiomer of epoxide or diol;



Scheme 9

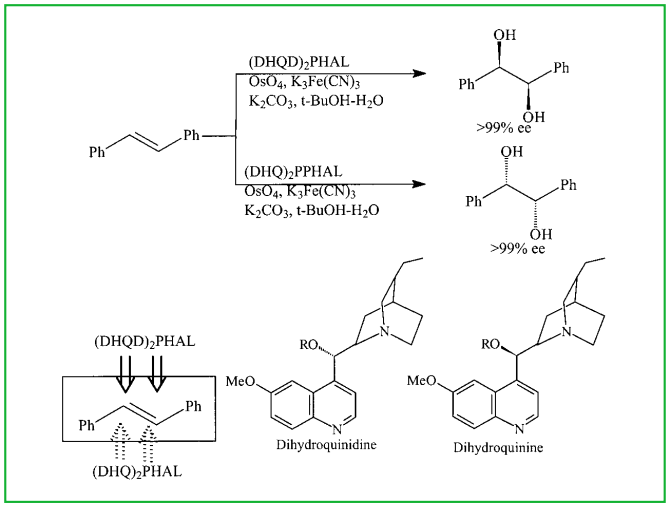
v) high-volume efficiency;
vi) recovery and reuse of the catalyst via catalyst immobilization.

Phenol promoted opening [22] of terminal epoxides with Co(salen) catalyst which leaves mono-protected 1,2-diol is yet another attractive technology. The reaction was shown efficient with broad spectrum of phenols (*ortho*-, *meta*- and *para*-substitution, electron-withdrawing or electron-donating groups). This made inroads to enatiopure aryl glycidyl ethers, important intermediates for β-blockers (Scheme 10).

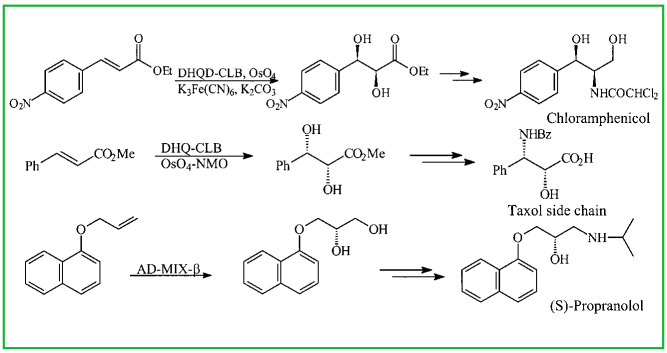
Catalytic Asymmetric Dihydroxylation

Asymmetric dihydroxylation developed by Sharpless [23] and co-workers is yet another hallmark in asymmetric oxidation. The following four prominent discoveries were the cause of key success:

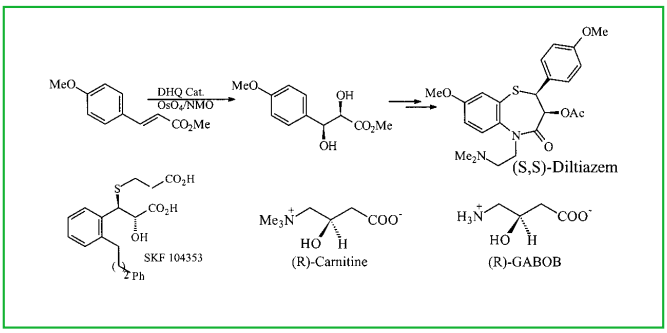
i) the ligand accelerated catalysis by cinchona alkaloids (LAC) to channel all product formation by chiral pathway;
ii) potassium ferricyanide as co-oxidant in basic biphase which suppressed non-enantioselective secondary cycle;
iii) "$MeSO_2NH_2$ effect" accelerated hydrolysis of osmium glycolate complex and allowed to perform the reaction at 0° C boosting enatioselectivity;
iv) third generation ligands, bis-cinchona alkaloids with aromatic appendage esp. Phthalazine bis-dihydroquinidine $(DHQD)_2PHAL$ and its dihydroquinine analogue $(DHQ)_2PHAL$ which enhanced enantioselectivity through enzyme-mimic binding cleft (Scheme 11).



Scheme 11

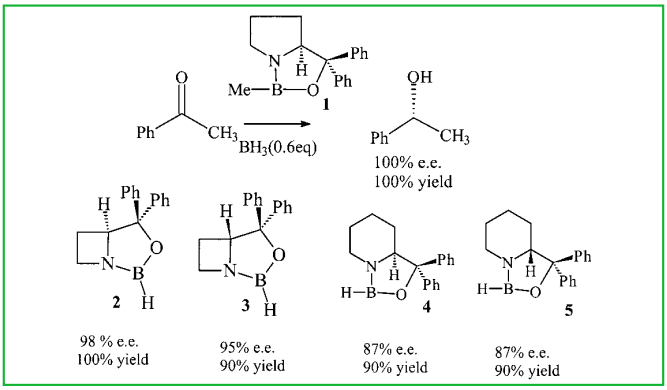


Scheme 12a



Scheme 12b

The incentive factors reactivity of OsO_4 with all olefins and only olefins, broad substrate scope including difficult tetra-substituted, electron deficient and sulfur containing olefins, higher catalytic turn over, chemical yield and optical purity, predictability of stereochemical outcome and selective functionalization of diols have bound synthetic chemists in magic spell to consider AD as most-reliable reaction and subsequent applications for synthesis of bioactive compounds, chiral building blocks and auxiliaries. Notable industrial applications include asymmetric route to broad-spectrum antibiotic chloramphenicol [24], taxol side chain *S*-propranolol [23], a well known β-blocker (Scheme 12a), the leukotriene antagonist SKF-10435323, diltiazem [25] and *R*-(-)-carnitine [23] and GABOB [23] (Scheme 12b). The recent discovery by Beller group opens the gateway for green technology version of AD with the use of molecular oxygen as reoxidant and incorporation of both oxygen atoms in atom-economical fashion. Industrial scale perspective and no by-product formation are salient features [26].



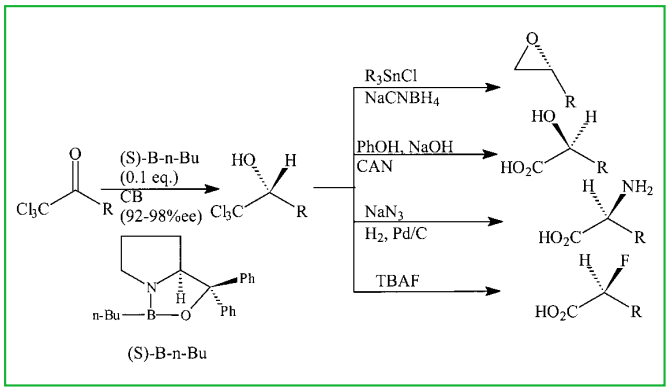
Scheme 13

Asymmetric Hydroboration

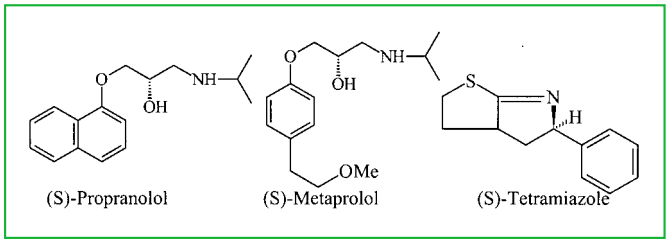
The enatioselective reduction of prochiral ketones has been the subject of serious investigation over four decades since the discovery of borane reduction by Brown [27]. These methodologies which use chirally-modified borohydrides in stoichiometric quantity proved incompetent, because of poor enatioselectivity, high cost, marginal practicability, and no mechanistic rationale. Itsuno [28] and co-workers for the first time demonstrated the utility of chiral oxazaborolidine prepared *in situ* from borane and β-amino alcohols. The limitation of Itsuno's approach was the use of stoicheometric amount of chiral oxazaborolidine. However, the unprecedented modification came from Corey's group [29] who demonstrated the catalytic enantioselective reduction of prochiral ketones with proline-derived oxazaborolidine as catalyst and BH_3 as reductant (Scheme 13). The enormous success of proline-derived oxazaborolidine catalyst (**1**) inspired many research groups and us [29] (catalysts **2-5**) to prepare several fused oxazaborolidines with ample structural rigidity and steric demand, to understand the relationship between catalyst structure and enantioselectivity. The catalysts (**2-5**) were equally effective in enantioselective reduction with various oxazaborolidine catalysts [29].

The mechanistic generality has expanded the ever increasing scope of substrates, including aryl ketones, α,β-enones, α,β-ynones and dialkyl ketones of diverse complexity. The competitive hydroboration of olefins in the case of α,β-enones can be suppressed by replacing BH_3 with catechol borane .

The distinct advantages like catalytic use of ligand, cheap reagents, substrate generality, high chemical and optical yield and mechanistic rationale were the strong drives behind successful industrial applications for chiral medicinals, catalytic ligands and complex natural products. Enantiopure trichloromethyl carbinols [31], easily available



Scheme 14

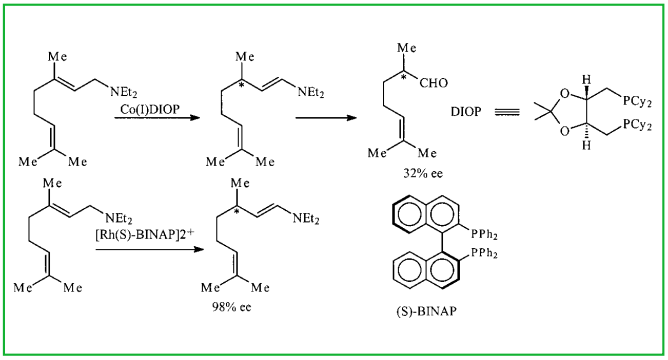


Scheme 15

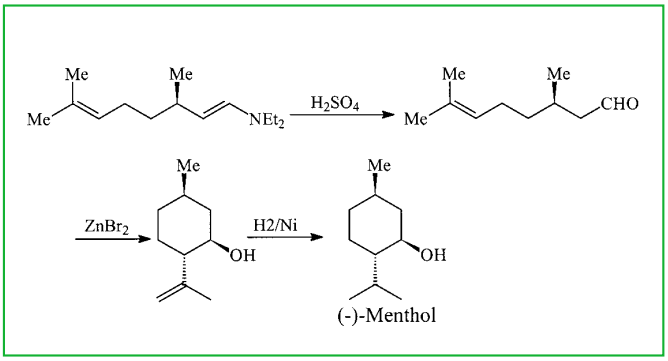
through asymmetric reduction of corresponding ketones are readily converted into several chiral intermediates (Scheme 14).
Corey's reduction of α-haloacetophenone [29] has enabled several β-agonists used in the treatment of asthama and bronchitis for racemic switch overs because of the enhanced efficacy of single eneantiomers [(R)-form=eutomer]. Our own efforts [30] led to the asymmetric process development routes to (S)-propranolol, (S)-metaprolol and (S)-tetramizole (Scheme 15).
Other applications of Corey's chirotechnology include [29] the enantioselective processes to (S)-carbinoxamine (histamine antagonist), cetrizine hydrochloride (antihistamine known for nonsedating properties and potency), fluoxetine hydrochloride (anti-depressant) and PAF antagonist factors.

Asymmetric Isomerisation

Isomerisation of C=C bond is a thermodynamically favoured process. Transition metal catalysed isomerisation of allyl alcohol and amine substrates to provide carbonyl compounds has been thoroughly studied till date [31]. The first asymmetric isomerisation was performed [31] on *N,N*-diethylnerylamine with $Co(acac)_2$, (+)-DIOP and DIBAL-H to afford citronellanamine in moderate chemical and optical yields (Scheme 16). Extensive exper-

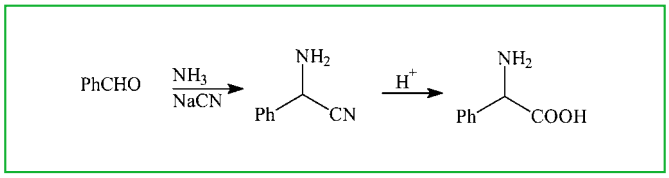


Scheme 16

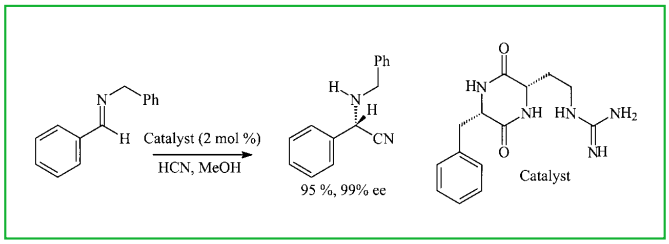


Scheme 17

imentation on catalyst engineering led to the serendipitous discovery of cationic rhodium-BINAP complex $[Rh\{(R- \text{ or } S-)\text{-BINAP}\}_2]^+ClO4^-$ as ideal candidates to offer excellent enantioselectivity, chemoselectivity and catalyst efficiency. This led to the development and commercialization by Takasago of industrial scale [32] (Scheme 17) process for



Scheme 18

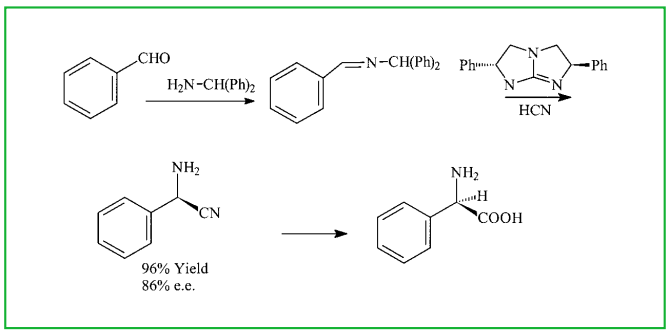


Scheme 19

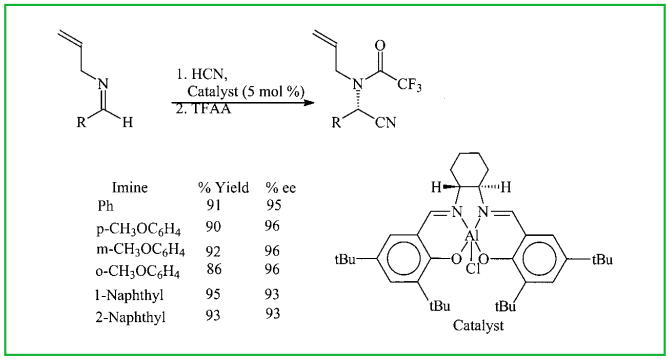
(-)-menthol, which accounts for 2300 tons per annum, the most-impressive achievement to date in the arena of asymmetric synthesis.

Asymmetric hydrocyanation

Strecker reaction is a classical route to α-amino acids [33] (Scheme 18). Asymmetric hydrocyanation of imines, a Strecker-type synthesis is now gaining special reverence since it provides rapid access to a library of valuable chiral building blocks, esp. α-amino-esters, acids (both natural and unnatural), aldehydes, alcohols and diamines [6d]. Two types of catalysts, peptide-derived compounds with a basic moiety and chirally-grafted organometallics have been shown to be efficient for this transformation. The first practical asymmetric hydrocyanation was kicked off by Lipton [34] in the presence of a cyclic peptide (Scheme 19) as catalyst.



Scheme 20



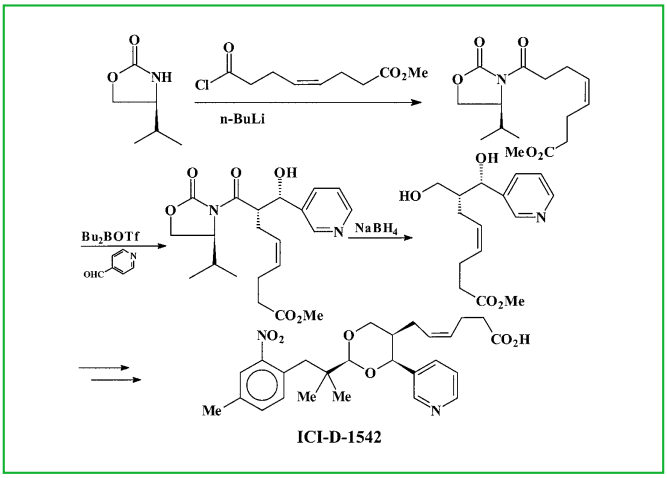
Imine	% Yield	% ee
Ph	91	95
p-$CH_3OC_6H_4$	90	96
m-$CH_3OC_6H_4$	92	96
o-$CH_3OC_6H_4$	86	96
1-Naphthyl	95	93
2-Naphthyl	93	93

Scheme 21

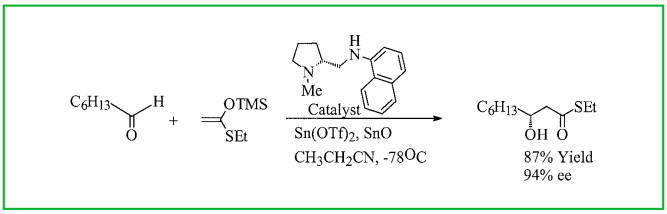
Corey *et al.* has recently reported a similar conversion with cyclic quanidine catalyst [35a] (Scheme 20) with good yield and exceptional enantioface discrimination.
The illustrative works of Jacobsen, and Hoveyda have elaborated the generality of this transformation. Jacobsen has successfully employed both peptide-born and chiral Al(salen) complexes (Scheme 21) with high enantiomeric excess and chemical yield, expanding the substrate scope and practicality [35b]. Jacobsen also developed resin-bound peptide catalysts which work in equal efficiency as simple catalysts. Hoveyda *et al.* have described recently a Ti- catalysed regio- and enantio-selective strecker reaction of α,β-unsaturated imine substrates in good yield and enantiocontrol in the presence of the optimised ligand, identified through combinatorial synthesis and screening of parellel ligand libraries with a stock of sixty [35b]. Application of bifunctional Lewis acid-base catalysts by Shibasaki *et al.* is another recent advancement in this area [35c].

Asymmetric C-C bond formation (aldol reaction)

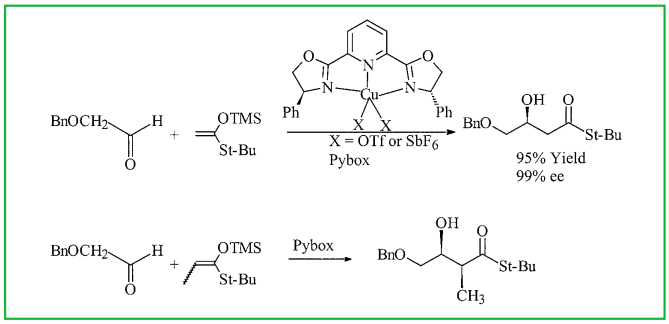
Aldol reaction, addition of an enolate donor to a carbonyl acceptor is one of the fundamental reactions for C-C bond formation. The control of the relative and absolute configuration of created stereogenic centers by biochemical catalyst like aldolases and catalytic antibodies and chemical catalysts, has been systematically investigated in the recent years [36]. The chemical mode of aldol reaction can be realized through either activation of the acceptor (Mukaiyama aldol), activation of donor and activation of both donor and acceptor (Direct aldol).
The stoichiometric asymmetric aldol condensation using chiral imide enolate derived from chiral oxazolidinone



Scheme 22



Scheme 23

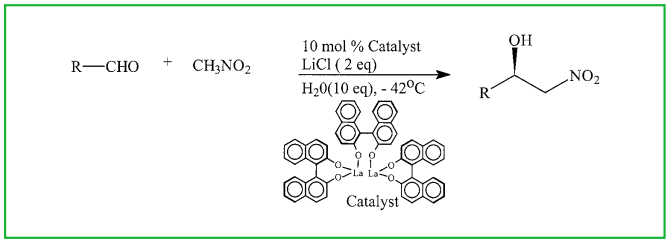


Scheme 24

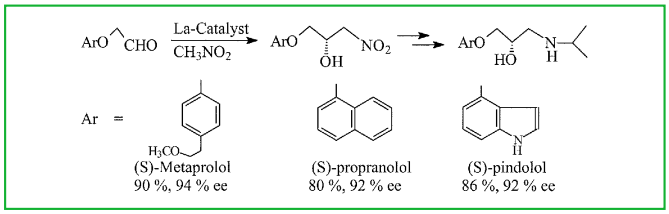
which was prepared from amino acids such as *L*-valine or *L*-phenylglycine was developed by Evans group. The synthesis of thromboxane antagonist ICI-D-1542 [37] becomes an elite example for application of aldol reaction in industrial scale even with stoichiometric chiral auxiliaries (Scheme 22).
In Mukaiyama aldol, the chiral catalyst, normally Lewis acid coordinates to the aldehyde, creating an asymmetric environment which follows the addition of enolate (silyl enol ether) in enantio selective fashion. The first asymmetric aldol was performed with tin(II) complexes of proline-derived diamines, between aldehyde and silyl ketene acetals with excellent enantioselelctivity in the presence of a cofactor like dibutyltin acetate. The simple diastereoselective control will depend on the co-ordinating ability of silyl ketene acetals. Thus non-coordinating substitutents like alkyl and *t*-butylsilyloxy are converted to syn-products while coordinating substituents like α-benzyloxy group into anti-products (Scheme 23). A broad range of substrates undergo aldol with high enantioselectivity and chemical yield.
Bis(oxazolinyl)copper(II) complexes have been shown to be the efficient chiral catalysts by Evans group [38]. The prerequisite is the aldehydes with α-substitution capable of chelation (Scheme 24).

Asymmetric Henry Reaction

Although Henry reaction is a century old reaction for C-C bond formation to provide valuable nitroalcohols, its utility in modern organic synthesis was sparse because of ab-



Scheme 25



Scheme 26

sence of asymmetric version. In 1992, Shibasaki *et al.* reported the first practical enantioselective Henry reaction (Scheme 25) [39a] with chiral heterobimetallic lanthonoid complexes as catalysts. Subtlities in ionic radii of central lanthanoid atom leads to dramatic changes in *ee*.
Applications include pragmatic asymmetric approaches to enantiomerically enriched β-blockers, (S)-metaprolol, (S)-propranolol and (S)-pindolol (Scheme 26) [39b].

Epilogue

Asymmetric catalysis has now emerged as a matured field with its own well-developed concepts and methods, like non-linear effects, autocatalysis, asymmetric amplification [40], dynamic and parellel kinetic resolution [41] etc. Exciting discoveries have been made over the design and development of asymmetric processes over the two decades. But only a few technologies have seen large-scale production so far because the availability of catalysts affording high *ee*, turn over number and turn over factor were relatively sparse. This trend will reverse in the future since many chiral catalysts, recently developed, meets these requirements offering *ee*>98% and TON>50000.
Chemo and biochemo catalysis do complement each other, each having its own advantages and pitfalls. Advances in genetic engineering, immobilization and stabilisation technologies have enabled the introduction of stable enzymes that meet the specific needs required for chemical manufacturing such as solvent stability and the ability to function at different temperature and pH ranges. The arrival of combinatorial biosynthesis is a shot in the arm. The new concept Biopharmaceuticals [42], the products of recombinant proteins is steadily shaping up.
In future, combinatorial chemistry holds the key to change the way of research in the discovery [43, 44] and optimization of robust catalysts which can be dramatically accelerated by coupling automated library synthesis with high-throughput screening methods and sophisticated high capacity informatics systems. Hetereogenisation of homogeneous catalysts via immobilization either by anchoring on a solid support or by use of a two phase system including the recent ionic-liquid technology will find widespread use to facilitate the catalyst filtration. The synergism between academics and industries will continue unabated with the former to discover new reactions and cutting-edge technologies and the latter to transform them to practical processes. The practitioners should also care for environment by developing atom-economical, less-hazardous, emission and waste-avoiding processes. One solution to address this is to use supercritical fluids since it benefits as non-toxicity, nonflammability and elimination of solvent residues and waste. Few enantioselective green technologies with supercritical CO_2 have already sprung up with the advantage. At the last, so the mother nature plays the drama of homochirality [45] for her safety, she will blossom the activity of chirochemists to produce chirocompounds for her discrimination, safety and pleasure.

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