

2001 Chemistry Nobel Prize

Continuing Importance of Stereochemistry

Mariappan Periasamy

Ever since the time of Louis Pasteur (1822-1895), stereochemistry played an important role in the advancement of science. If Pasteur's landmark deduction that the formation of optically active organic compounds during the spoilage of wine is due to a biological process, led to his discovery of microbes, his resolution of sodium ammonium tartrate based on the shapes of the crystals led to the idea of requirement of non-superimposable mirror image relationship for an organic compound to be optically active. In the ensuing years, J H van't Hoff (the first Chemistry Nobel Laureate 1901, for his work on osmotic pressure)¹ and J A Le Bel recognised that attachment of four different groups around a tetrahedral carbon atom would lead to non-superimposable mirror images and discovered the tetrahedral geometry of organic compounds in 1874 (*Box 1*). A similar idea helped A Werner (Chemistry Nobel Laureate 1913) to elucidate the geometrical structures of co-ordination compounds (*Box 2*).

Over the years, several scientists who made immense contributions to stereochemistry were honoured with the award of the Nobel Prize – D H R Barton and O Hassel (Nobel Laureates 1969, conformational analysis), J W Conforth and V Prelog (Nobel Laureates 1975, stereochemistry of enzymatic and organic reactions), C J Pederson, D J Cram and J M Lehn (Nobel Laureates 1987, molecular and chiral recognition). The 2001 Nobel Prize was awarded to W S Knowles, R Noyori and K B Sharpless for their pioneering work on the development of catalytic asymmetric reduction and oxidation processes.

Many of the compounds associated with living organisms are chiral, for example DNA, enzymes, antibodies and hormones. Thus, the enantiomers of limonene both formed naturally, smell

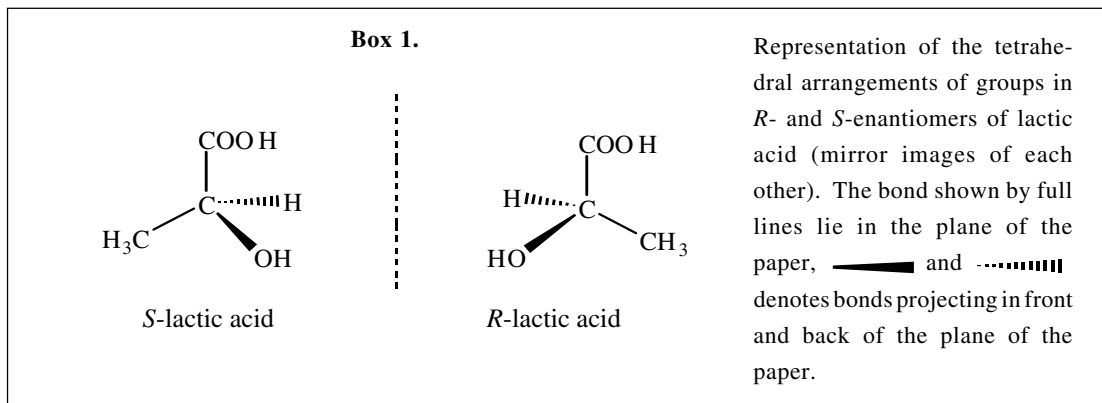


After a postdoctoral stint at Purdue University, USA (with H C Brown), Mariappan Periasamy has been in the faculty, School of Chemistry, University of Hyderabad. His research interests are in the development of organometallics and chiral reagents for applications in synthetic processes. Recently, as a hobby, he has initiated a project on the conversion of 'Farm waste to chemical feedstocks' with an objective of developing sustainable, renewable and environmentally benign energy sources.

Keywords

Stereochemistry, chirality, asymmetric catalysis.

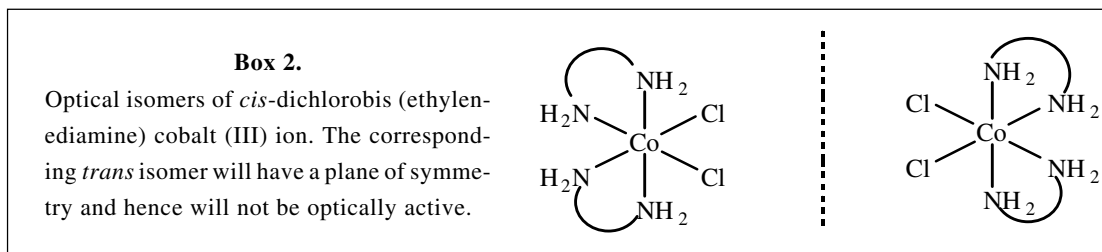




differently (*Box 3*) as our nasal receptors are made up of chiral molecules that interact with these enantiomers differently.

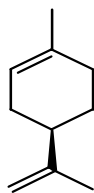
Clearly, biology is very sensitive to chirality and most drugs consist of chiral moieties. Since a drug must match the receptor in the cell, often only one of the enantiomers is of interest. In certain cases, the other enantiomer may be harmful. The story of the effect of the drug thalidomide is a test case (*Box 3*). In the early 1960's, the racemic derivative was prescribed to alleviate morning sickness in pregnant women. Tragically, the drug also caused deformities in the limbs of children born to these women. It seems that one enantiomer of thalidomide was beneficial while the other caused birth defects. Therefore, pharmaceutical companies nowadays have to make sure that both enantiomers of a drug are tested for their biological activity and toxicity before they are marketed. Obviously, there is a strong demand for the pure enantiomer required. It is in this context that the discoveries of the 2001 Chemistry Nobel Laureates have great significance since the catalytic processes discovered by them are useful in the efficient manufacture of chiral compounds. A brief

¹ Sridhar Gadre, Century of Nobel Prizes, *Resonance*, Vol.6, No.12, 2001.

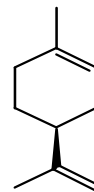


Box 3.

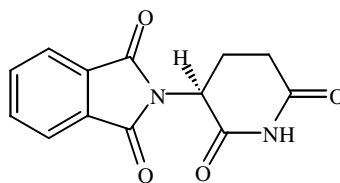
Whereas the *S*-thalidomide alleviates morning sickness in pregnant women, the *R*-thalidomide causes deformities in the limbs of children born to these women.



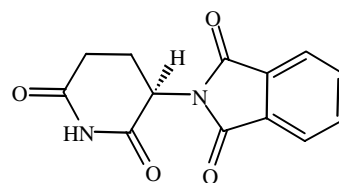
R- (+) - limonene
Smells of oranges



S - (-)-limonene
Smells of lemons



S- thalidomide



R-thalidomide

review of asymmetric synthesis and the contributions of the 2001 Nobel Laureates will be of interest.

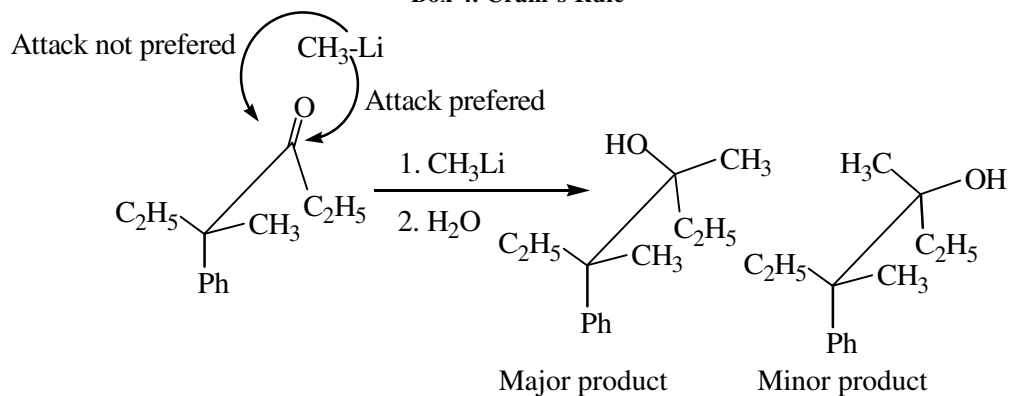
Generally, chemical synthesis of asymmetric compounds results in racemic mixtures, i.e., 1:1 mixture of *R* and *S* enantiomers that are mirror images (*Boxes 1-3*). If the organic substrate already has an asymmetric centre, stereoselectivity may be anticipated as realised in the addition of nucleophiles to carbonyl compounds. The diastereomers are now formed in unequal amounts and the results can be rationalised by Cram's rule² [1] (*Box 4*) (D J Cram, 1987 Chemistry Nobel Laureate).

In the nucleophilic addition reaction to carbonyl compounds of the type shown in *Box 4*, the product contains both the new and old asymmetric centres and it is not easy to retrieve an asymmetric compound containing only the new asymmetric centre from this product. However, in the case of nucleophilic addition to α -keto esters, the product can be readily hydrolysed to obtain the corresponding asymmetric organic product (*Box 5*). The major product that would be formed can be predicted with the aid of Prelog's rule³ [2] (V Prelog, 1975 Chemistry Nobel Laureate).

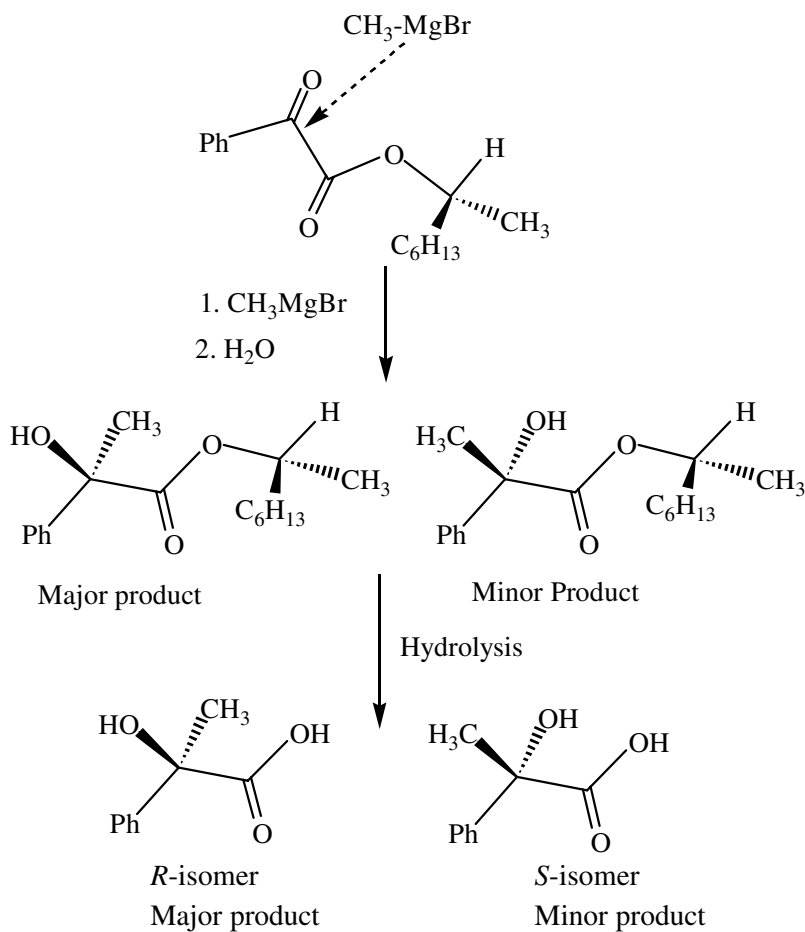
² **Cram's Rule:** Nucleophilic attack on the asymmetric carbonyl compound takes place from the side of the smallest group attached to the asymmetric carbon atom.

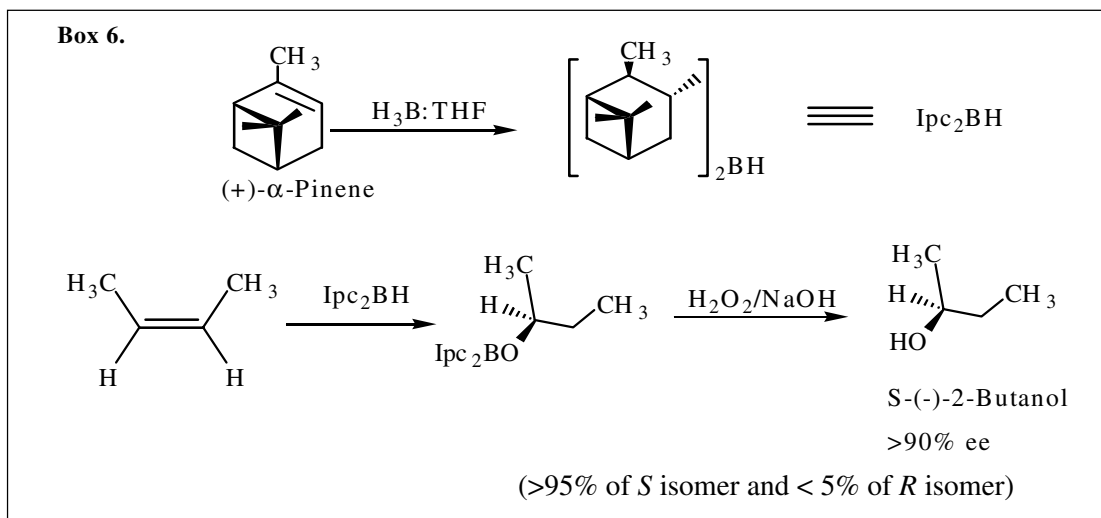
³ **Prelog's Rule:** Nucleophilic attack on the carbonyl group takes place from the side of the medium sized methyl group (backside) in preference attack from the side of the larger octyl group.

Box 4. Cram's Rule



Box 5. Prelog's Rule

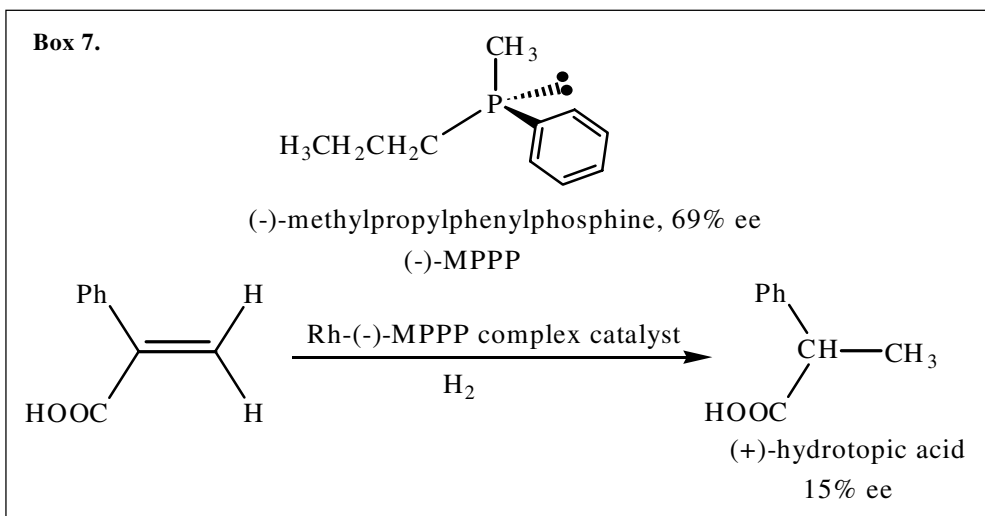




In the above-mentioned asymmetric syntheses, the asymmetric centres are created because of the presence of asymmetric carbon atoms in the starting organic substrates. H C Brown (1979 Chemistry Nobel Laureate) discovered a new type of asymmetric synthesis through hydroboration-oxidation of prochiral olefinic substrates in which the asymmetric induction is due to the asymmetric borane reagent, Ipc_2BH (Box 6) [3]. In this way, the corresponding alcohols containing asymmetric centre were obtained in very high levels of selectivity (high enantiomeric excess, e.e.)

The hydroboration-oxidation was the first non-enzymatic transformation in which very high levels of enantioselectivities were realised. A drawback is that the valuable borane reagent cannot be recycled as the isopinocampheyl group is also oxidised in this transformation.

Although several such stoichiometric asymmetric reagents have been developed over the years, there have been sustained efforts towards the development of asymmetric synthetic methods that would require only catalytic amounts of chiral moieties. The first breakthrough in this field came in 1968 through the work of the 2001 Nobel Laureate, Knowles who showed that a chiral

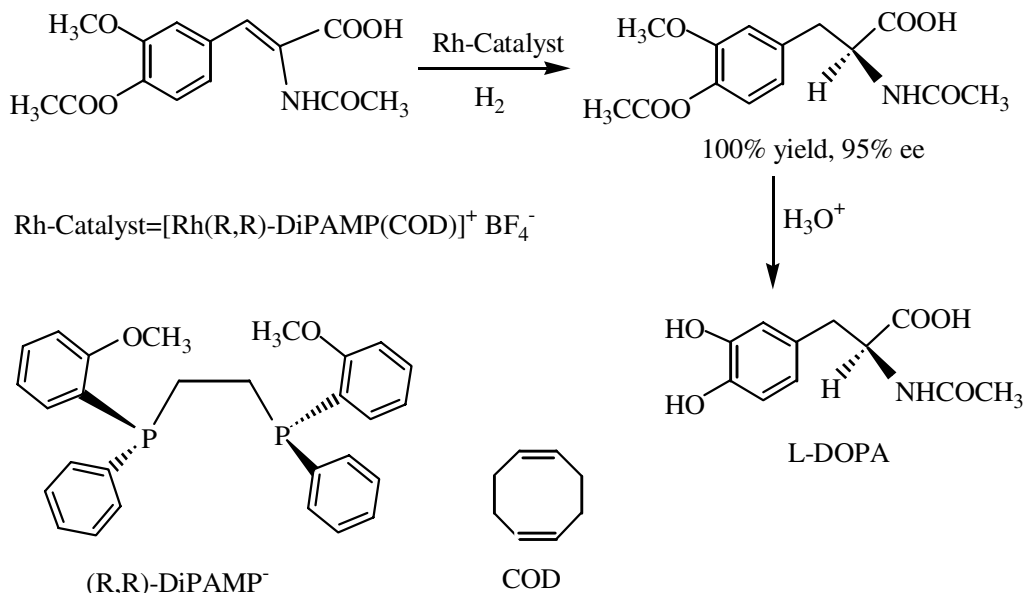


transition metal based catalyst could transfer chirality to a non-chiral substrate in asymmetric hydrogenation, resulting in chiral product with one of the enantiomers in excess [4]. The discovery of the Wilkinson catalyst $(\text{Ph}_3\text{P})_3\text{RhCl}$ in the 1960's (G Wilkinson, 1973, Chemistry Nobel Laureate) as a homogeneous hydrogenation catalyst helped Knowles in making chiral Rh catalysts using optically active phosphines. Knowles demonstrated that the rhodium catalyst prepared using (-)-methylpropylphenylphosphine (69% ee) gave a modest asymmetric induction (15% ee) in the hydrogenation of α -phenylacrylic acid (*Box 7*) [4].

The spectacular success of this L-DOPA synthesis has significantly contributed to the explosive growth of research aimed at the development and application of other catalytic asymmetric reactions in ensuing years.

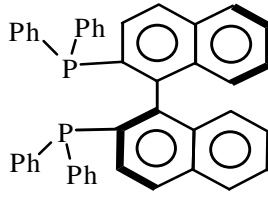
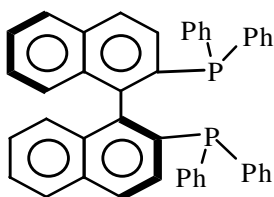
Soon Knowles' group at the Monsanto Co, USA came up with a process using the cationic rhodium complex containing the bidentate phosphine ligand, DiPAMP, for the manufacture of L-DOPA, which had proved useful in the treatment of Parkinson's disease (*Box 8*). Thus, the spectacular success of this L-DOPA synthesis has significantly contributed to the explosive growth of research aimed at the development and application of other catalytic asymmetric reactions in ensuing years.

In 1980, the other 2001 Chemistry Nobel Laureate, Noyori discovered the atropisomeric C2 chiral diphosphine BINAP

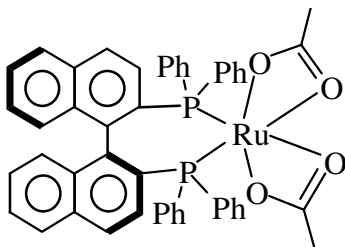
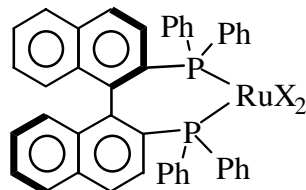
Box 8. Knowles' Monsanto Process for the Manufacture of L-DOPA.

(Box 9) [5]. The corresponding Rh(I) and Ru(II) complexes are remarkably effective in several asymmetric reactions [5].

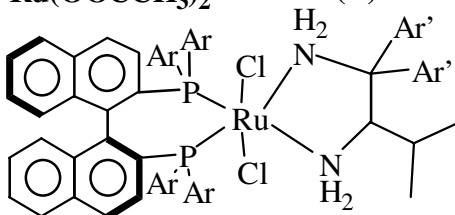
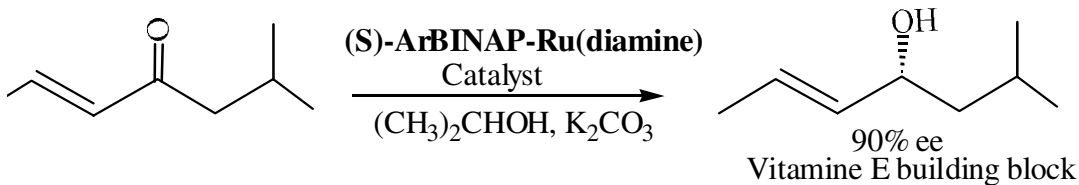
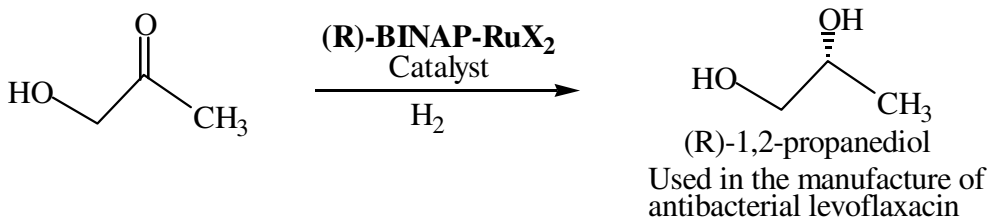
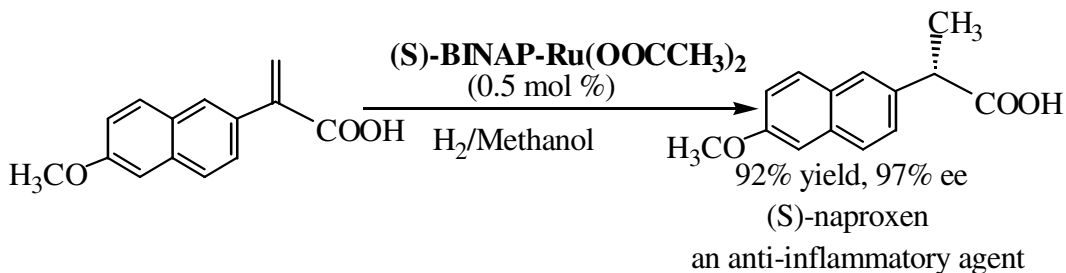
Whereas the Rh(I)-BINAP complexes are useful in reactions like asymmetric hydrogenation of α -(acylamino)acrylic acids or esters and in the enantioselective isomerisation of allylic amines to enamines, the BINAP-Ru(II) catalysts have enormous scope in several transformations, like hydrogenation of α -arylacrylic acids, asymmetric hydrogenation of functionalised ketones and in selective transfer hydrogenation of carbonyl compounds in the presence of CC double bonds (Box 10).

Box 9.

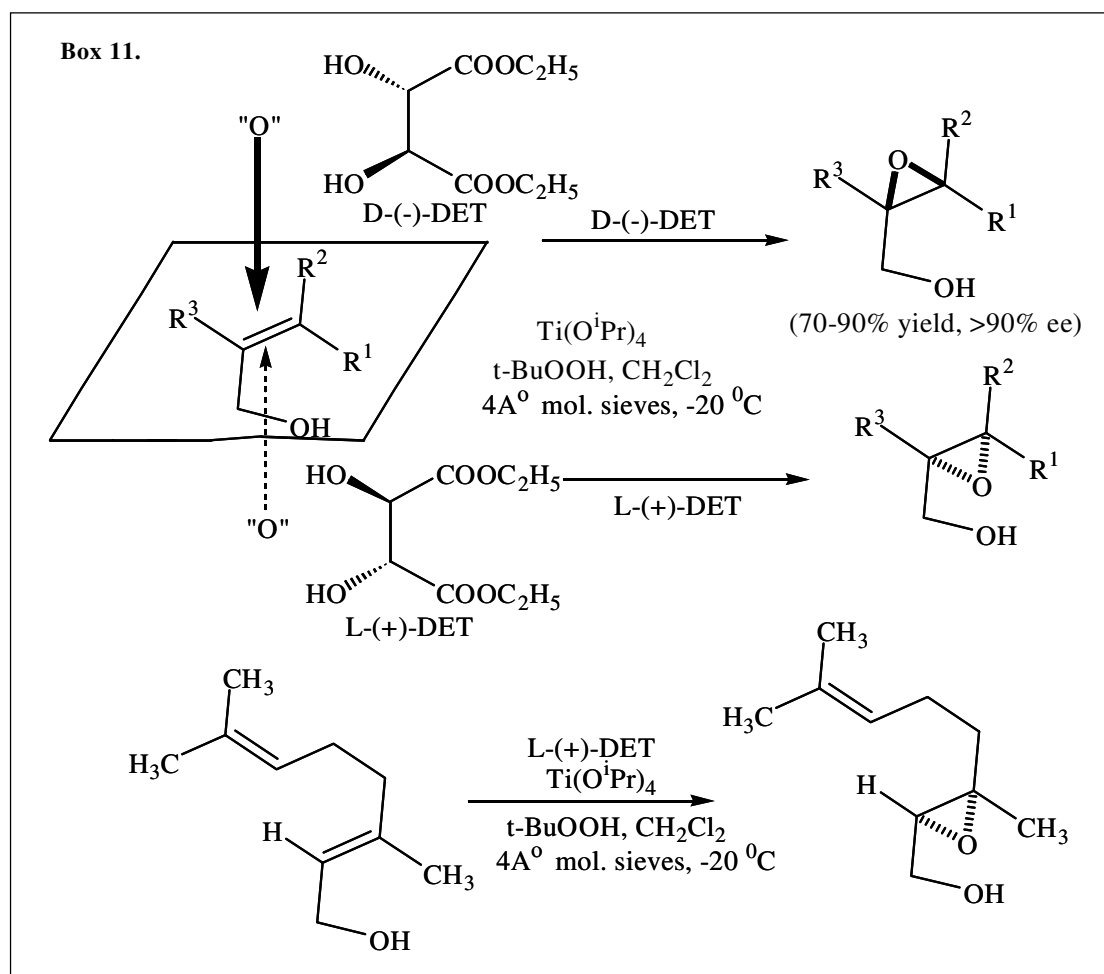
Box 10.

**(S)-BINAP-Ru(OOCCH₃)₂**

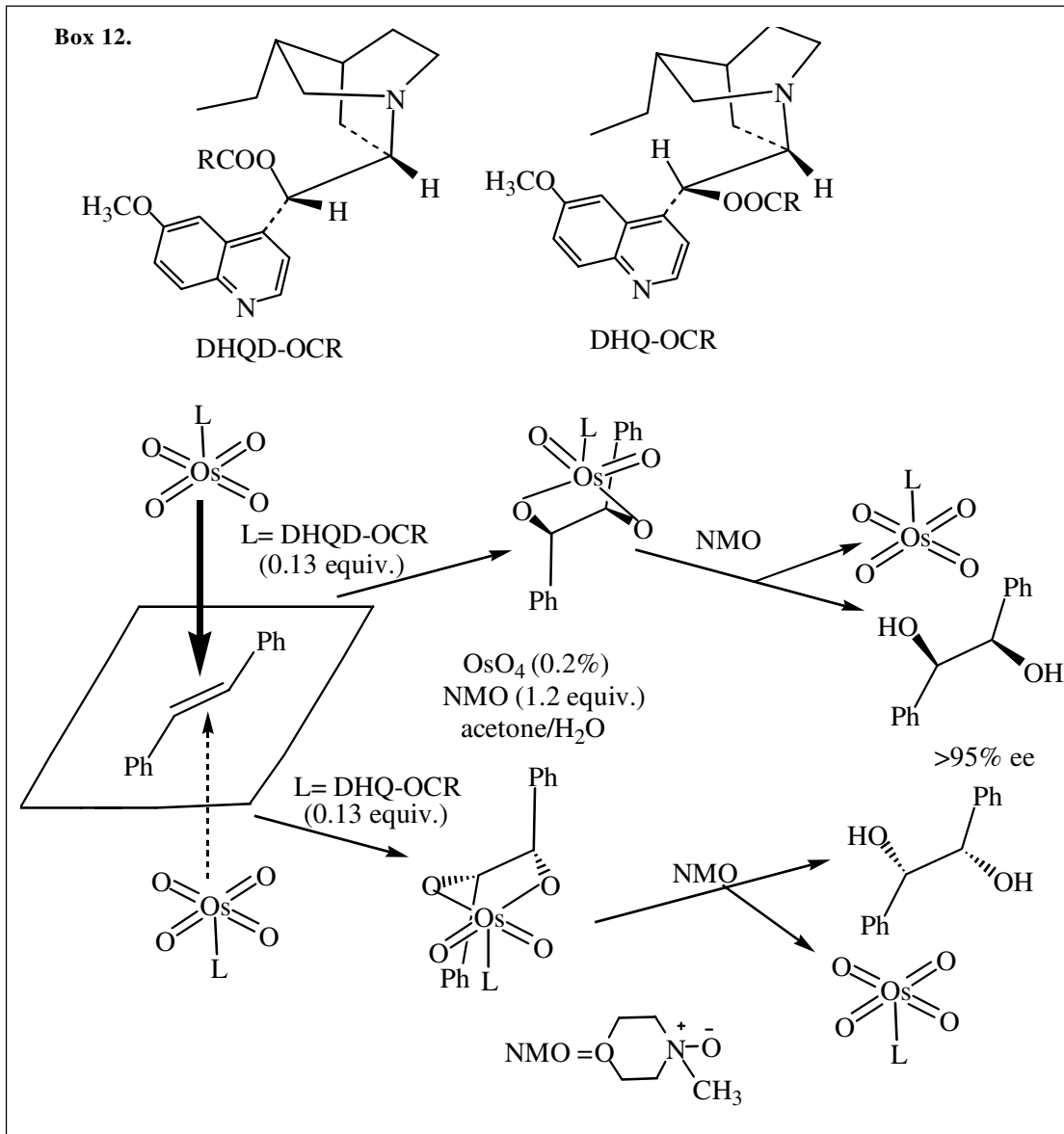
X=Cl, Br, I

(R)-BINAP-RuX₂Ar=3,5-(CH₃)₂C₆H₃, Ar'=p-CH₃O-C₆H₄**(S)-ArBINAP-Ru(diamine)**

Powerful tools for achieving catalytic asymmetric oxidation of olefinic groups were discovered by the other 2001 Chemistry Nobel Laureate, Sharpless [6, 7]. In 1980, Sharpless group discovered the catalytic asymmetric epoxidation of allylic alcohols using titanium tetraisopropoxide, tert-butyl hydroperoxide and an enantiomerically pure dialkyl tartrate (*Box 11*) [6]. This powerful reaction is highly predictable. When the *D*(-)-tartrate ligand (*D*(-)-DET) is used in epoxidation, the oxygen atom is delivered to the top face of the olefin when the allyl alcohol is depicted as shown in *Box 11*. The epoxy alcohols produced in this way are versatile synthetic intermediates. For example, (*S*)- and (*R*)-glycidol and (*S*)- and (*R*)-methylglycidol have been



Box 12.



produced in ton-scale in industry for the manufacture of β -blockers used in the treatment of heart diseases.

Catalytic asymmetric dihydroxylation of olefins is another major transformation discovered by the Sharpless group [7]. They discovered that the cinchona alkaloid derivatives give pronounced 'ligand accelerated catalysis' (i.e. the OsO_4 reacts faster

with olefins upon co-ordination with quinidine or quinine derivatives), producing asymmetric diols from olefins using catalytic amounts of OsO_4 and the chiral ligand and stoichiometric quantities of *N*-methylmorpholine oxide or $\text{K}_3\text{Fe}(\text{CN})_4$ (Box 12). In recent years, new ligands and improved procedures appeared, making the Sharpless's catalytic asymmetric dihydroxylation an extremely useful reaction [7].

In addition to being useful in the manufacture of compounds of medical importance, the discoveries of the 2001 Chemistry Nobel Laureates are also useful in the production of agrochemicals including pheromones, flavours, fragrances and sweetening agents. Moreover, their work gives access to new molecules, thereby contributing to more rapid advances of research – not only in chemistry but also in material science, biology and medicine.

Inspired by the achievements of the 2001 Chemistry Nobel Laureates in catalytic asymmetric reduction and oxidation processes, there have been enormous efforts by scientists on the development of catalytic asymmetric CC bond forming processes that further widen scope of catalytic asymmetric syntheses. Also, in recent years there have been remarkable advancements on efforts towards amplification of chirality in asymmetric catalysis (i.e., obtaining higher ee of the product using a ligand with lower ee) and asymmetric autocatalysis (i.e., a chiral compound catalysing its formation). These developments are relevant to the origin of homochirality, which is prevalent in Nature but continues to remain a mystery. Hence, the field of stereochemistry continues to be one of the challenging and rewarding areas of research.

Suggested Reading

- [1] D J Cram and F A A Elhafez, *J. Am. Chem. Soc.*, Vol.74, p.5828, 1952.
D J Cram and J D Knight, *J. Am. Chem. Soc.*, Vol.74, p.5835, 1952.
[2] V Prelog, *Helv. Chim. Acta.*, Vol.36, p. 308, 1953.
[3] H C Brown, N R Ayyangar and G Zweifel, *J. Am. Chem. Soc.*, Vol. 86, p.397, 1964.

- [4] W S Knowles and M J Sabacky, *Chem. Commun.*, p.1445, 1968.
W S Knowles, *Acc. Chem. Res.*, Vol.16, p.106, 1983.
[5] A Miyashita and others, *J. Am. Chem. Soc.*, Vol.102, p.7932, 1980.
T Ohta, H Takaya and R Noyori, *Inorg. Chem.*, Vol. 27, p.566, 1988.
M Kitamura and others, *J. Am. Chem. Soc.*, Vol.110, p.629, 1988.
T Ohkuma and others, *J. Am. Chem. Soc.*, Vol.117, p. 2675, 1995.
[6] T Katsuki and K B Sharpless, *J. Am. Chem. Soc.*, Vol.102, p. 5974, 1980.
[7] E N Jacobsen and others, *J. Am. Chem. Soc.*, Vol.110, p. 1968, 1988.
H C Kolb, M S Van Nieuwenhze and K B Sharpless, *Chem. Rev.*, Vol.94, p.2483, 1994.
[8] M B Smith and J March, *Advanced Organic Chemistry*, 5th edition, Wiley Interscience, NY, 2001.
[9] F A Carey and R J Sundberg, *Advanced Organic Chemistry*, 3rd edition, Plenum Press, NY, 1990.
[10] E L Eliel and S H Wilen, *Stereochemistry of Organic Compounds*, John Wiley and Sons, Inc., NY, 1994.

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