

the wealth that needs to be conserved amidst the biogeography and biodiversity of the Himalayas.

Finally, a pause for thought. Could the 'symposium' structure have room for change? Perhaps. Suggestions to this effect (from Fellows) is that there could be an 'introductory talk' that preceded each symposium. This would lay the framework for the later 'nuts and bolts' to be presented by respective speakers.

It would, in a nutshell, give a background to the topic of the symposium and explain salient details to an 'across the board' audience. This would in turn facilitate subsequent speakers to immediately go to the results of research, leaving adequate time for discussion. Further, each talk, in its structuring could perhaps begin with a set of conclusions. This would give emphasis and direction to a multidisciplinary audience

leading to discussion and some carry-home thoughts. This, it is hoped would change the content of talks from being too bogged down with data and information that could be gleaned, if required, from appropriate sources.

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Asymmetric catalysis – A novel chemistry to win the Nobel Prize – 2001

The Nobel Prize in Chemistry for the year 2001 has been awarded one half to Karl Barry Sharpless, The Scripps Research Institute La Jolla, California, USA; and the other half has been equally shared by Ryoji Noyori, Nagoya University, Chika, Japan and William S. Knowles, previously at Monsanto Company, St. Louis, Missouri, USA. In fact, this year's award has been equally shared by the chemistry of asymmetric catalytic oxidation reaction and asymmetric catalytic hydrogenation reaction. Both these asymmetric reactions have influenced the world of chemical sciences for the last several decades; however, their impact has only been felt in the practical synthesis of several drugs and drug intermediates, vitamins, materials and other biologically active compounds during the last two decades.

In 1874, J. H. Van't Hoff (Nobel Laureate 1901) and J. A. LeBel independently discovered the tetrahedral arrangement of groups around the central carbon. If all the groups attached to the central carbon are different, the central carbon atom is said to be chiral. The word 'chiral' comes from the Greek word '*Cheir*', which means hand. Our left hand and right hand are like mirror images of each other and are not super-imposable – the minimum criterion for chirality. So are most of the molecules of life. Most of the amino acids, peptides, proteins, enzymes, carbohydrates, nucleic acids like DNA, RNA or any naturally occurring biological catalysts are chiral. For example (*S*)-lactic acid found in milk is chiral (Figure 1).

All the enzymes in the cells are chiral. All the natural receptors in the cell prefer to bind one chiral form of the molecules called enantiomers. Hence, it is essential to produce one enantiomer in pure form. Each enantiomer is often expected to have a totally different effect on cells.

Several drug molecules are chiral. One of their enantiomers may have the desired therapeutic effect, whereas the other may be useless or even harmful. Similarly, several natural products used for various purposes may be chiral. Production of one enantiomer through a resolution would lead to an equal amount of the unwanted enantiomer which needs to be disposed-off or recycled. This process is not ecofriendly, nor it is economical. During the past few decades, research has been going on in developing methods for synthesizing one enantiomer rather than the other. However, the most economical way to prepare one of the enantiomers for industrial production would be through use of a catalyst which would behave like an enzyme, i.e. selectively make one desired enantiomer. Enzymes are small amounts of chiral material which would generate a large amount of

chiral product from an achiral starting material. Scientists across the world have carried out intensive research to develop catalysts which could behave



Sharpless' birthday celebration at his residence.

K. Barry Sharpless was born in Philadelphia in 1941. He got his BA in Dartmouth College (T. A. Spencer) in 1963 and Ph D at Stanford University (E. E. van Tamelen) in 1968. He did his postdoctoral research at Stanford University (J. P. Collman) in 1968 and moved to Harvard University to do further Postdoctoral work with K. A. Bloch. He joined the Chemistry Faculties in 1970 at MIT, Cambridge, USA.

Sharpless moved to Stanford University as full-time Professor in 1970 and continued till 1977. He rejoined the Department of Chemistry at MIT in 1980 and continued as Arthur C. Cope Professor till 1990. From 1990 onwards he joined The Scripps Research Institute, as W. M. Keck Professor, Skaggs Institute for Chemical Biology of TSRI, 1996. He has received various honours and awards.

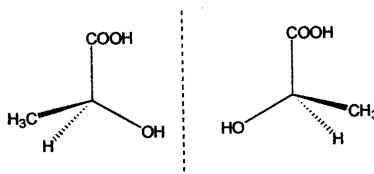


Figure 1. (*S*)-Lactic acid.



William Knowles, presently at 84, earned a Bachelor's degree in chemistry at Harvard in 1939 and a Ph D in steroid chemistry at Columbia University in 1942. He accepted a position at Monsanto, in St. Louis, immediately after graduating from Columbia. In 1951, he studied the total synthesis of steroids while on a company-sponsored postdoctoral fellowship in the laboratory of Harvard chemistry professor and Nobel Laureate Robert B. Woodward. The postdoc represented 'a turning point in my career', Knowles says, because it gave him an appreciation for a type of synthesis that was much more complex than the industrial process development projects he had been involved in up to that point.

At Monsanto, Knowles had specialized in exploratory process development on organic chemicals and intermediates, including fine chemicals and plasticizers, but after the postdoc with Woodward, he began a programme on the total synthesis of steroids. In the late 1960s, Knowles headed a three-man team that set out to develop a catalyst that could be used to synthesize individual enantiomers of chiral compounds directly.

His group's Nobel Prize-winning project on asymmetric catalysis is 'an excellent example of how a modest and inexpensive exploratory effort in industry can produce significant results'.

like enzymes in their reactivity and selectivity. In an asymmetric catalytic reaction, a chiral catalyst is needed to produce a large quantity of an optically active compound from a precursor that may be chiral or achiral. One single chiral catalyst molecule can direct the

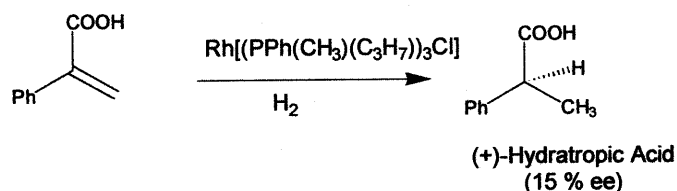


Figure 2. Knowles' catalytic asymmetric hydrogenation.

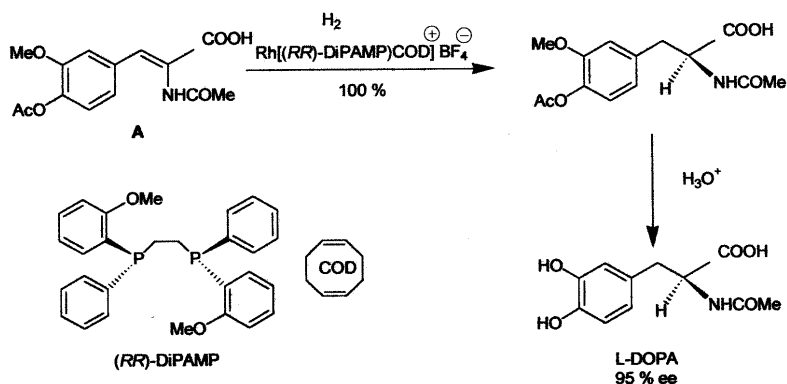


Figure 3. Catalytic asymmetric synthesis of L-DOPA: A Monsanto process.

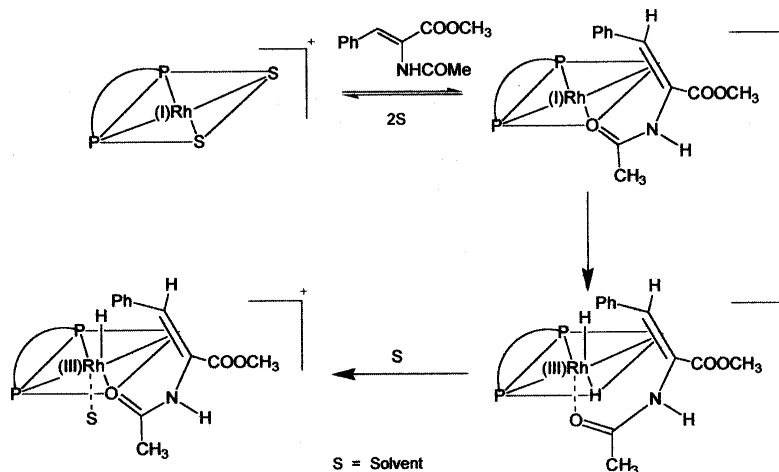


Figure 4. Mechanism of Rh-diphosphine-catalysed hydrogenation of an enamide.

stereoselectivity of millions of chiral product molecules. Such reactions are highly productive and economical. It is this type of research that has been awarded this year's Nobel Prize in Chemistry.

Asymmetric catalytic hydrogenation reaction

In the mid-sixties, the first catalytic hydrogenation of unhindered olefins

was reported by Osborn *et al.*¹ using rhodium complex $[(\text{Ph}_3\text{P})\text{RhCl}]$ – a soluble hydrogenation catalyst. In 1968, Knowles² at Monsanto showed that the chiral transition metal-based catalyst could transfer chirality to a non-chiral substrate, resulting in a chiral product. Knowles used (–)-methyl propyl phenyl phosphine of 69% ee as the chiral ligand for Rh- to catalyse the asymmetric catalytic hydrogenation of α -phenyl acrylic acid to give hydratropic acid in 15% ee (Figure 2).



Ryoji Noyori was born in Kobe, Japan on 3 September 1938. He got his Bachelor's degree from Kyoto University in 1961. He got his Master's degree in 1963 and Ph D in 1967 from the same university. He did postdoctoral work at Harvard University (E. J. Corey) during 1969–1970. He has more than 400 publications to his credit and has received many awards and honours.

Although the % ee was hardly of any practical use, the result provided the clue that catalytic asymmetric hydrogenation is possible. This result aroused interest of several researchers in catalytic asymmetric hydrogenation of prochiral substrates to chiral products using various chiral phosphine ligands. Prominent among them were Horner³, Kagan⁴, Morrison⁵ and Bosnich, whose work led to clearer understanding of catalytic asymmetric hydrogenation reaction. During the seventies and eighties, there was considerable interest in academia and industries looking for practical application of this novel reaction.

Knowles himself developed the first industrial application of catalytic asymmetric hydrogenation reaction at Monsanto while trying to find a practical synthesis of a rare amino acid L-DOPA, which had proved to be useful in the treatment of Parkinson's disease (Figure 3). Knowles⁶ and co-workers discovered that a cationic rhodium complex containing (*R,R*)-Di-PAMP, a chelating diphosphine with two chiral

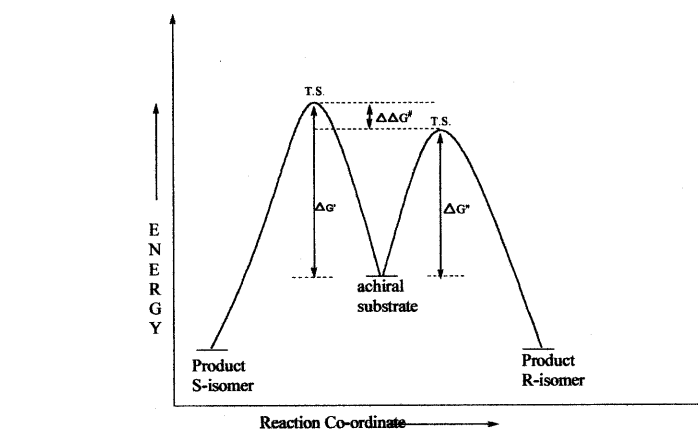


Figure 5. Reaction coordinates for asymmetric synthesis from prochiral substrate.

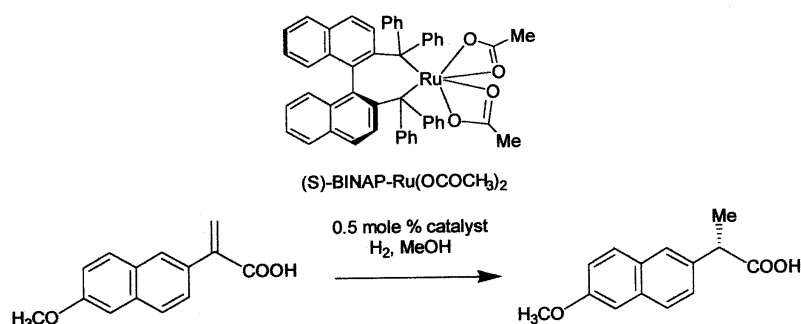


Figure 6. Catalytic asymmetric synthesis of chiral (*S*)-naproxen using Noyori's catalyst.

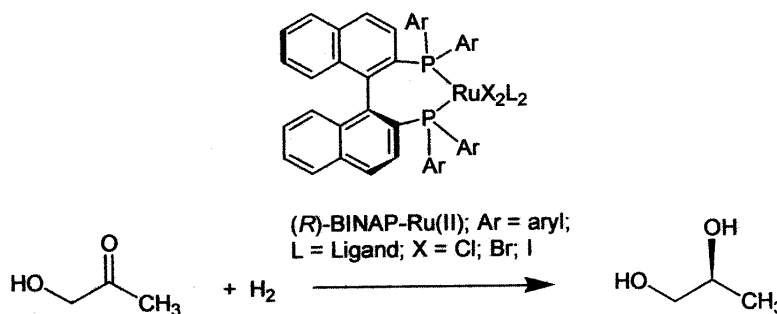


Figure 7. Catalytic asymmetric reduction of acetol to 1,2-propane-diol; currently for industrial synthesis of levofloxacin.

phosphorus atoms catalyses highly enantioselective hydrogenations of amides **A** (Figure 3) to furnish L-DOPA. This process to produce L-DOPA is in operation since 1974. The spectacular success of L-DOPA synthesis has significantly contributed to the explosive growth in the research aimed at the development and practical application of catalytic asymmetric synthesis, in the years to follow.

Mechanism of catalytic asymmetric hydrogenation

The reaction mechanism of the phosphine Rh complex-catalysed hydrogenation has been elucidated by Halpern⁷. Hydrogenation of an enamide using a Rh-diphosphine complex yielding a phenylalanine derivative is shown in Figure 4.

Initially the solvent molecules, *S*, which are present in the $[\text{Rh}[(\text{Ph}_3\text{P})_2\text{S}_2]]$ complex are displaced by the olefinic substrate to form a chelate-Rh complex in which the olefinic bond and the carbonyl oxygen interact with the Rh(I) centre. Hydrogen is oxidatively added to the metal to form a Rh(III) dihydride intermediate. The two hydrogen atoms on the metal are successively transferred to the carbons of the coordinated olefinic bond by way of a five-membered chelate alkyl-Rh(III) intermediate. The secondary binding of the carbonyl oxygen of the amide moiety results in a ring system that stabilizes the reactive intermediate. Kinetic data suggest that, at room temperature, the oxidative addition of H_2 is rate-limiting for the overall reaction. When an appropriate chiral phosphine ligand and proper reaction conditions are chosen, high enantioselectivity is achieved. If a diphosphine ligand of C_2 symmetry is used, two diastereoisomers of the enamide coordination complex can be produced, because the olefin interacts with either the *re* face or the *si* face. This interaction leads to enantiomeric phenylalanine products via diastereoisomeric Rh(III) complexes.

The understanding of the mechanism of asymmetric reaction led to the belief that the difference between racemic reaction and enantioselective reaction lies in differentiating the two transition states, leading to the production of '*R*' and '*S*' isomers. In a racemic reaction, both the transition states are of equal energy and therefore, both *R* and *S* isomers are produced in equal amounts to yield a racemic product.

In other words, $\Delta G' = \Delta G''$. In an enantioselective reaction, the catalyst facilitates one of the transition states to be at lower energy than the others as shown in Figure 5, a reminiscence of an enzyme-catalysed biological reaction. The catalyst interacts with a chiral substrate in which transition state leading to '*R*' product has been lowered by ΔG^\ddagger from $\Delta G'$, whereas transition state for the formation of '*S*' product may remain unaffected or may increase or decrease. In an enantioselective reaction the value of $\Delta\Delta G^\ddagger$ plays a crucial role in determining the selectivity of the reaction. The value of $\Delta\Delta G^\ddagger$ between 2.5 and 3.0 kcal/mol may result in 98–100% ee, depending upon the reaction. This understanding

was exploited by Noyori to develop another catalytic asymmetric hydrogenation catalyst – the leader of this

development is the other Nobel Laureate of this year in Chemistry, Ryoji Noyori.

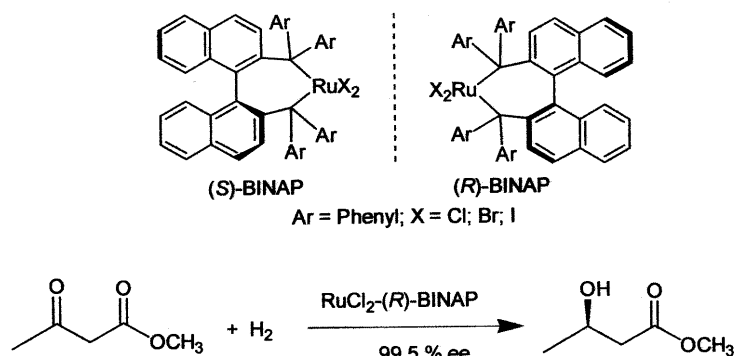


Figure 8. Catalytic asymmetric reduction of β -ketoester to β -hydroxyester.

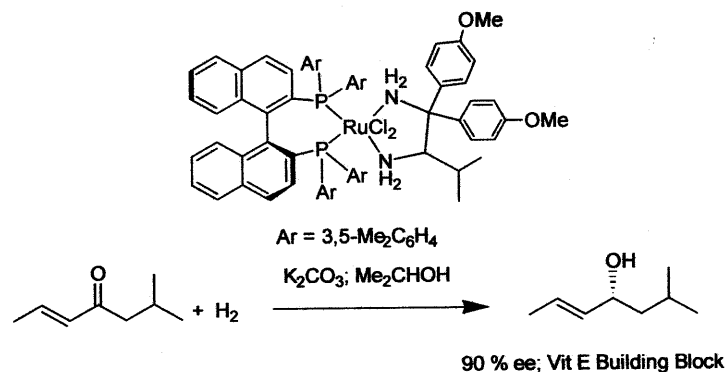


Figure 9. Catalytic asymmetric reduction of α,β -unsaturated ketone to allylic alcohol.

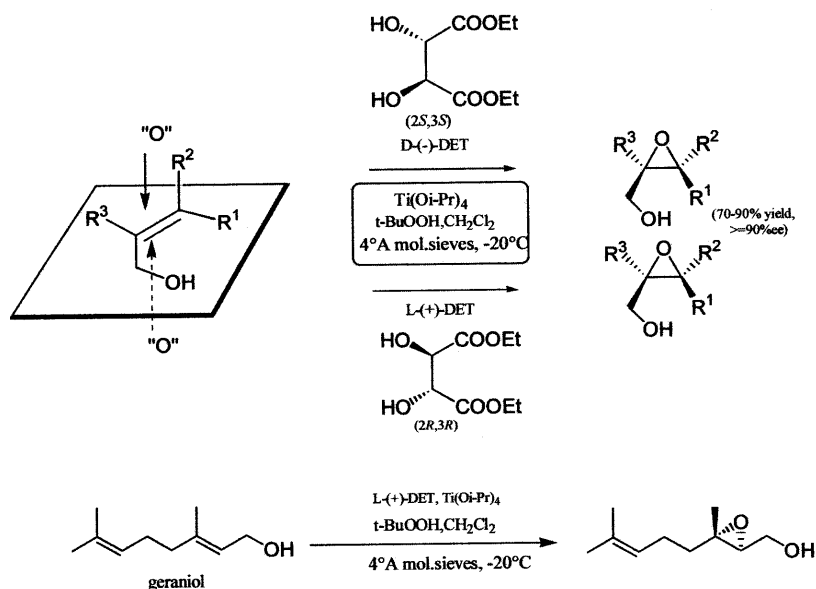


Figure 10. Predictive stereoselectivity of the Sharpless epoxidation together with an example of regioselectivity.

Noyori's hydrogenation catalyst

In 1980, Noyori developed a new atropisomeric chiral diphosphine ligand 'BINAP'. Rh(I) complex of chiral BINAP was found to be remarkably effective in asymmetric catalysis⁸. This includes enantioselective hydrogenation of α -(acylamino)acrylic acids or esters, giving acid derivatives and also includes enantioselective isomerization of allylic amines to enamines. The chiral efficiency of BINAP chemistry originates from unique dissymmetric templates created by a transition metal atom or ions and the C_2 symmetric chiral diphosphine.

Noyori's discovery of the BINAP-Ru(II) complex catalysts was a major advance in stereoselective organic synthesis. The scope of the application of these catalysts is far-reaching. These chiral Ru complexes serve as catalyst precursors for the highly enantioselective hydrogenation of a range of α,β and β,γ -unsaturated carboxylic acids⁹. An example is shown in Figure 6. This reaction, unlike Rh(I)-catalysed olefin hydrogenation, proceeds via a metal monohydride mechanism. The enantioselectivity is much higher than when utilizing the Rh catalyst and the sense of asymmetric induction is opposite. In the presence of the halogen-containing complexes $[RuX(arene)(binap)]X$ or $RuX_2(binap)$ ($X = Cl, Br, I$), a wide range of functionalized ketones can be hydrogenated in a highly enantioselective and predictable manner (Figure 7). Various functionalities can act as directing groups¹⁰.

The hydrogenation method is effective for converting β -keto carboxylic esters into β -hydroxy esters in high (up to 100%) enantiomeric purity (Figure 8). This entirely chemical approach is far superior to any biological versions, including bakers' yeast reduction, where efficiency is often variable.

Thus Noyori's newly invented BINAP-Ru(II) complexes exhibit an extremely high chiral recognition ability in the hydrogenation of a variety of functionalized olefins and ketones. Both product enantiomers can be synthesized efficiently and with equal ease by choosing the proper enantiomers of the catalysts. This transition metal catalysis is clean, simple and economical to operate and hence is capable of conducting a reaction on any scale from < 100 mg

to > 100 kg, with a very high (up to 50%) substrate concentration in organic solvents. In addition to industrial production of compounds such as (*R*)-1,2-propanediol (10 tons/year) and a chiral azetidinone for carbapenem synthesis (120 tons/year), this hydrogenation method is utilized in academic and industrial research laboratories to develop pharmaceuticals, agrochemicals, flavours and fragrances.

Most existing homogenous and heterogeneous catalysts use molecular hydrogen to saturate carbon-carbon multiple bonds, preferentially over a carbonyl moiety. Thus $RuCl_2[P(C_6H_5)_3]_3$ normally shows feeble catalytic activity in the hydrogenation of simple ketones such as

acetophenone. However, Noyori recently reported a remarkable enhancement in the reactivity of the Ru(II) catalyst by the addition of ethylene diamine and KOH in 2-propanol. The addition of very small amounts of these basic agents entirely reverses the chemoselectivity from olefin-selective to carbonyl-selective¹¹. Efficient asymmetric hydrogenation of α,β -unsaturated ketones has been an enduring problem in organic chemistry. In the example in Figure 9, the combined use of chiral $RuCl_2(xylylbinap)(diamine)$ and the weak base K_2CO_3 transforms a simple enone by enantioselective hydrogenation into a chiral allylic alcohol. The substrate/catalyst ratio approaches 100000. This chemoselectivity is re-

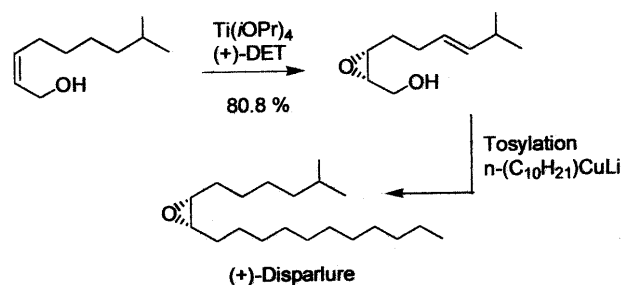


Figure 11. Synthesis of (+)-disparlure by Sharpless asymmetric epoxidation.

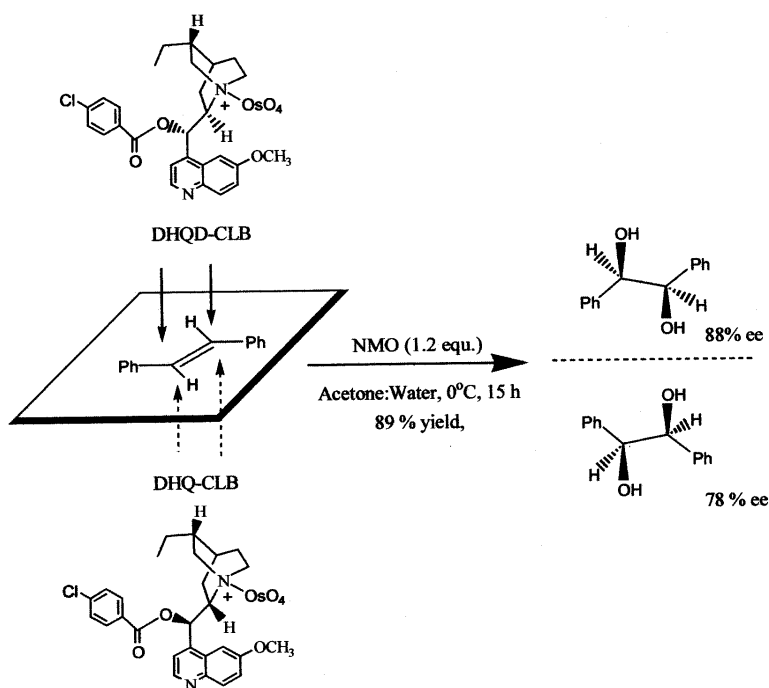


Figure 12. Catalytic asymmetric dihydroxylation developed by Sharpless.

markable in view of the large catalytic activity of diamine-free BINAP–Ru complexes for hydrogenation of C=C double bonds in allylic alcohols.

Apart from asymmetric catalysis, this carbonyl-selective hydrogenation provides a real advance in organic synthesis. A wide range of ketones and aldehydes possessing carbon–carbon multiple bonds are hydrogenated preferentially at the carbonyl group, leading to unsaturated alcohols. Both conjugated and unconjugated enones and enals may be used.

Catalytic asymmetric oxidation reactions (Sharpless oxidation catalysts)

Parallel to the progress in catalytic asymmetric hydrogenations, Sharpless has developed chiral catalysts for asymmetric oxidation reactions. The epoxidation reaction discovered in 1980 by Sharpless and Kazuki is a very fine example of a strategy of using a reagent to achieve stereochemical control. Using titanium(IV) tetrakisopropoxide, *tert*-butyl hydroperoxide, and an enantiomerically pure dialkyl tartrate, the Sharpless reaction accomplishes the epoxidation of allylic alcohols with excellent stereoselectivity¹². The stereochemical outcome of this reaction is very 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 allylic alcohol is depicted as in Figure 10 (i.e. OH group in lower right hand corner).

The L-(+)-tartrate ligand (L-(+)-DET), on the other hand, allows the bottom face of the olefin to be epoxidized. When achiral allylic alcohols are employed, the Sharpless reaction exhibits exceptional enantiofacial selectivity (ca. 100 : 1) and provides convenient access to synthetically versatile epoxy alcohols¹³.

The emergence of the powerful Sharpless asymmetric epoxidation in the 1980s has stimulated major advances in both academic and industrial organic synthesis. Through the action of an enantiomerically pure titanium–tartrate complex, a myriad of achiral and chiral allylic alcohols can be epoxidized with exceptional stereoselectivity. Interest in the Sharpless epoxidation as a tool for

industrial organic synthesis increased substantially after Sharpless and co-workers had discovered that the asymmetric epoxidation process can be conducted with catalytic amounts of the enantiomerically pure titanium–tartrate complex, simply by adding molecular sieves to the epoxidation reaction mixture¹⁴. Using this practical and reproducible catalytic variant, an industrial process for ton-scale production of (*S*)- and (*R*)-glycidol and (*S*)- and (*R*)-methylglycidol has been developed. These low molecular weight epoxy alcohols are versatile building blocks for pharmaceutical industry to produce β -blockers. Another successful industrial application of the Sharpless epoxidation is the synthesis of (7*R*,8*S*)-disparlure, the pheromone of the gypsy moth (Figure 11)¹⁵.

Catalytic asymmetric dihydroxylation of alkenes

Another most significant contribution in catalytic asymmetric oxidation reaction is the *cis*-dihydroxylation of olefins. It converts an olefin to a vicinal diol, present in many natural and unnatural molecules. The original dihydroxylation reaction used stoichiometric amounts of osmium tetroxide (OsO₄), which is ex-

pensive, volatile and toxic, with the result that even small-scale reactions were inconvenient. However, the dihydroxylation proceeded without any particular substrate requirements, unlike asymmetric epoxidation of allylic alcohols¹⁵. Over the years, the original dihydroxylation procedure has been modified to operate catalytically, more rapidly, and in better yield¹⁶.

Methods for the conversion of olefins to diols with only catalytic amounts of osmium tetroxide and a stoichiometric co-oxidant have been known almost as long as the reaction itself. Criegee first observed that the addition of amines, such as pyridine to the dihydroxylation reaction increases its rate. Presumably this is due to the formation of an electron-rich coordination complex with the osmium atom.

The reaction can be carried out in the presence of stoichiometric amount of co-oxidant *N*-methylmorpholine *N*-oxide. This idea of *ligand accelerated catalysis* was exploited by Sharpless by using appropriate cinchona alkaloid ligands with catalytic amount of OsO₄ and stoichiometric amount of *N*-methylmorpholine *N*-oxide to produce diol in very good yield and good enantiomeric excess, as shown in Figure 12 (ref. 16). This reaction underwent numerous modifications in the last decade,

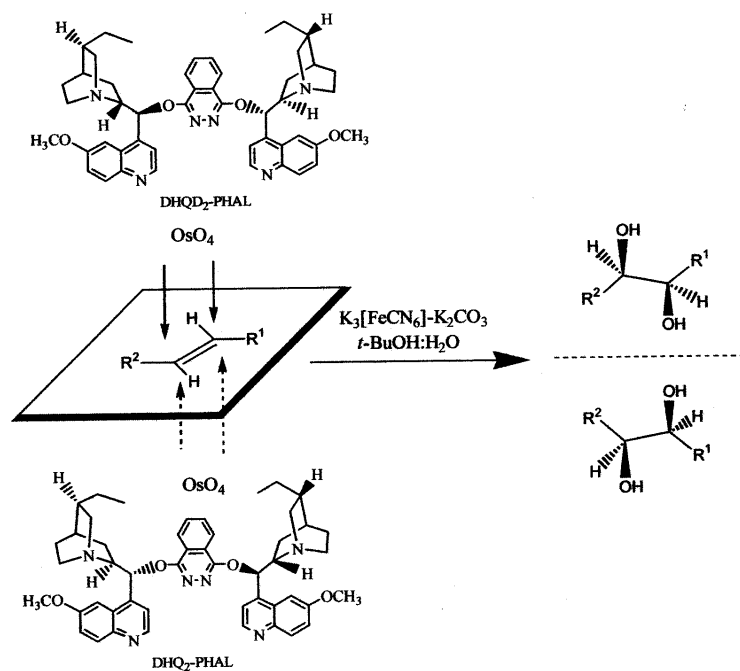


Figure 13. Catalytic asymmetric dihydroxylation of unfunctionalized alkenes.

to develop a very good catalytic asymmetric oxidation of unfunctionalized alkenes to diol. Using $K_3Fe(CN)_6 - K_2CO_3$ as source of oxygen-transferring agent in *t*-BuOH-H₂O system at 0–5°C, most of the olefins undergo dihydroxylation with high selectivity¹⁷. Generally used chiral ligands are DHQD₂-PHAL or DHQ₂-PHAL and potassium osmate as the catalyst. Several of these ligands were developed based on the understanding of the mechanism of asymmetric dihydroxylation reaction.

Consequences and applications

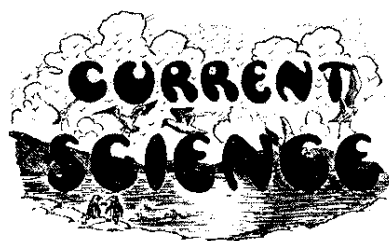
Some of the applications of the Nobel Laureates' pioneering work have already been discussed. It is especially important to emphasize the great significance that their discoveries and improvements have for industry. Industrial synthesis of new drugs is of major importance, but we may also mention the production of agro-chemicals, including pheromones, flavours, fragrances and sweetening agents. This year's Nobel Prize in Chemistry shows that the step from basic research to industrial application can sometimes be a short one.

All around the world many research groups are busy developing other cata-

lytic asymmetric syntheses that have been inspired by the Nobel Laureates' discoveries. Their developments have provided academic research with many important tools, thereby contributing to more rapid advances in research – not only in chemistry but also in materials science, biology and medicine. Their work gives access to new molecules needed to investigate hitherto unexplained and undiscovered phenomena in the molecular world.

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Indian museums

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Central Museum, Nagpur

Most provinces in India have their museums but it is regrettable how very few of these museums have developed a provincial aspect, which should be the

foremost thought in their system of development.

Recently there has been a tendency to develop archaeology only in these museums to the detriment of other branches and sections. Archaeological museums are certainly the easiest to curate whilst biological ones are the most difficult. As archaeologists or numismatists are frequently in charge of such institutions, it is natural that natural history and other sections will suffer, although the latter are more popular with the general public...

Nowadays most colleges teach biology but even an elementary display of zoological types are non-existent in most provincial museums. I once met a post-graduate student in zoology, who said his thesis had been on the moths of Lahore, yet this same student when

shown a Uranid moth, pronounced it to be a butterfly!!

The complaint in most museums is lack of funds and mismanagement by those at the head through want of proper technical knowledge on the subject of museums. Sometimes a few persons who perhaps are uninterested and have never visited a museum are appointed to select a curator and of course the man with the highest degree amongst the applicants is selected, although he may be quite unsuited for the post. The result is that valuable collections already accumulated are lost or rejected before he gets initiated or learns his work.

Then again a person cannot be an expert in all the branches of a museum and it becomes necessary to have assistants for certain sections; this prevents