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Advanced information on
the Nobel Prize in Chemistry 2001

Catalytic asymmetric synthesis

Three researchers share this years' Nobel Prize in Chemistry; Dr William S. Knowles, who has been working at Monsanto Company, St Louis, USA; Professor Ryoji Noyori, Nagoya University, Chikusa, Nagoya, Japan and Professor K. Barry Sharpless, The Scripps Research Institute, La Jolla, California, USA. The Royal Swedish Academy of Sciences rewards the three chemists for: "their development of catalytic asymmetric synthesis". Knowles and Noyori receive half the Prize for: " their work on chirally catalysed hydrogenation reactions" and Sharpless is rewarded with the other half of the Prize for: "his work on chirally catalyzed oxidation reactions". The discoveries made by the three organic chemists have had a very great impact on academic research and the development of new drugs and materials and are used in many industrial syntheses of drugs and other biologically active compounds. Below is given a background and description of their discoveries.

Chiral molecules

This year's Nobel Prize in Chemistry concerns the development of chiral transition metal catalysts for stereoselective hydrogenations and oxidations - two important classes of synthetic reactions. Through the Laureates' work a myriad of useful chiral compounds have become accessible.
Many of the compounds associated with living organisms are chiral, for example DNA, enzymes, antibodies and hormones. Therefore enantiomers of compounds may have distinctly different biological activity . Thus the enantiomers of limonene, both formed naturally, smell differently - one of the enantiomers (*S*)-limonene smells of lemons, while the mirror image compound (*R*)-limonene smells of oranges (Fig. 1).

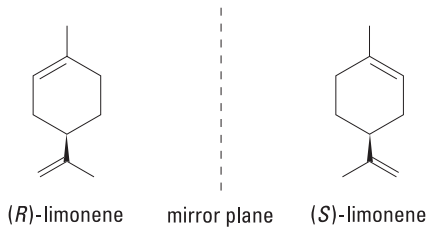

Figure 1: (*R*)-Limonene smells of oranges and (*S*)-limonene smells of lemons.

We distinguish between these enantiomers because our nasal receptors are also made up of chiral molecules that recognise the difference. Insects use chiral chemical messengers (pheromones) as sex attractants and chemists have discovered that one of the enantiomers of the insect pheromone, olean, attracts male fruit flies, while its mirror image operates on the female of the species.
Thus biology is very sensitive to chirality and the activity of drugs also depends on which enantiomer is used. Most drugs consist of chiral molecules. And since a drug must match the receptor in the cell, it is often only one of the enantiomers that is of interest. In certain cases the other enantiomer may be harmful. In the early 1960s, the drug thalidomide was prescribed to alleviate morning sickness in pregnant woman. Tragically, the drug also caused deformities in the limbs of children born by these women. It seems that one enantiomer of thalidomide was beneficial while the other caused the birth defects. This theory is being questioned, partly because the two enantiomers of thalidomide easily can interconvert in the body. 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 to the pure enantiomers.

Catalytic asymmetric syntheses

Industrial companies are concerned about disposing of unwanted compounds and also about the inefficiency and costs involved in the chemical processes. Therefore there is a strong demand for efficient methods for asymmetric syntheses. Thus finding new methods of asymmetric synthesis has in the past 20 or 30 years become a key activity for organic chemists. Ideally, a chiral agent should behave as a catalyst with enzyme-like selectivity. A small amount of material containing the chiral information could generate a large amount of a chiral product. Research has been intensive to develop methods for catalytic asymmetric synthesis i.e. catalytic methods to prepare one of the enantiomers in preference to the other. In a catalytic asymmetric reaction, a chiral catalyst is used to produce large quantities of an optically active compound from a precursor that may be chiral or achiral. In recent years, synthetic chemists have developed numerous catalytic asymmetric syntheses that convert prochiral substrates into chiral products with high enantioselectivity. These developments have had an enormous impact on academic and industral organic syntheses. One single chiral catalyst molecule can direct the stereoselection of millions of chiral product molecules. Such reactions are thus highly productive and economical, and, when applicable, they make the waste resulting from racemate resolution obsolete.
It is researchers in this field who are rewarded with this year's Nobel Prize in Chemistry.

Knowles´pioneer work

In the early sixties it was not known whether catalytic asymmetric hydrogenation was feasible. A breakthrough came in 1968 when Knowles at Monsanto Company, St. Louis showed that a chiral transition metal based catalyst could transfer chirality to a non-chiral substrate resulting in chiral product with one of the enantiomers in excess.[1]
Two developments in the mid-sixties offered an attractive approach to making such a catalyst. The first was the discovery by Osborn and Wilkinson of the rhodium complex, $[(PPh_3)_3RhCl]$, as a soluble hydrogenation catalyst for unhindered olefins. Homogeneous catalysts had been reported earlier, but this was the first one that compared in rates with the well-known heterogeneous counterparts.[2]
The other development was the discovery of methods for preparing optically active phosphines by Horner[3] and by Mislow[4]. Knowles' basic strategy was to replace triphenylphosphine in Osborn and Wilkinson's catalyst with the enantiomer of a known chiral phosphine and hydrogenate a prochiral olefine.
Knowles soon verified the validity of this thinking by using the known non-racemic methylpropylphenylphosphine (69% of ee of (-)-methylpropylphenylphosphine) and reducing substituted styrenes (Fig. 2).

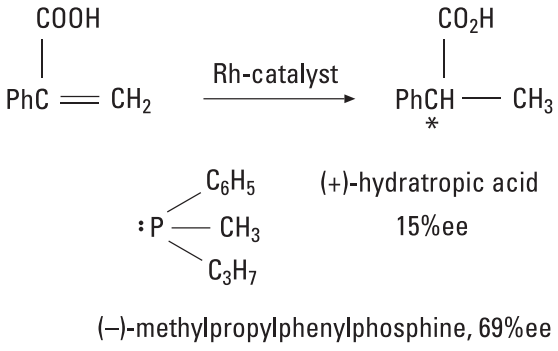

Figure 2: Knowles's catalytic asymmetric hydrogenation of α-phenylacrylic acid using a rhodium catalyst containing (-)-methylpropylphenylphosphine (69% ee) gave (+)-hydratropic acid in 15% ee.

A modest enantiomeric excess (ee) was obtained but it was too small to be of any practictical use. However, the result proved that it was in fact possible to achieve catalytic asymmetric hydrogenation. Other researchers (Horner[5], Kagan[6], Morrison[7] and Bosnich) reached similar results shortly afterwards and they have all contributed to opening the doors to a new, exciting and important field for both academic and industrial research.

The first industrial catalytic asymmetric synthesis

The problem was now to find a proper match between ligand and substrate to achieve synthetically useful efficiencies. As it turned out, good results were obtained only with more functionalized substrates. The best substrate was an enamide precursor of α-amino acids. Knowles's aim was to develop an industrial synthesis of the rare amino acid L-DOPA which had proved useful in the treatment of Parkinson's disease. Knowles and co-workers at Monsanto discovered that a cationic rhodium complex containing DiPAMP , a chelating diphosphine with two chiral phophorus atoms, catalyzes highly enantioselective hydrogenations of enamides such as A (Fig. 3). In the key step of the syntheses of L-DOPA enamide A is hydrogenated in the presence of a catalytic amount of [Rh(*R,R*)-DiPAMP)COD]$^{+}$BF$_4$ affording the protected amino acid B in quantitative yield and in 95% ee. A simple acid-catalyzed hydrolysis step completes the syntheses of L-DOPA[8].

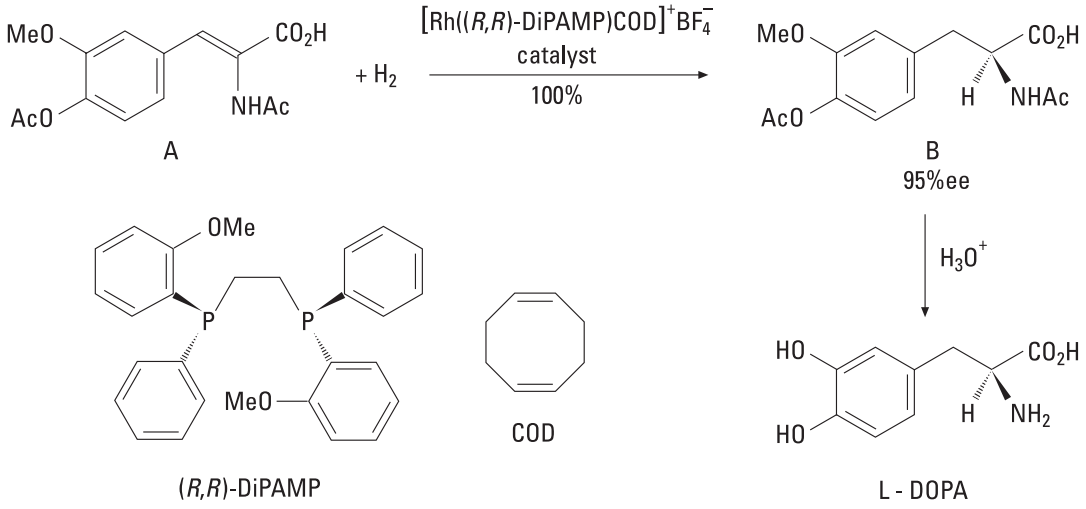

Figure 3: The Monsanto synthesis of L-DOPA using catalytic asymmetric hydrogenation.

The *Monsanto Process* was the first commercialized catalytic asymmetric synthesis employing a chiral transition metal complex and it has been in operation since 1974. 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.

Mechanism of catalytic asymmetric hydrogenation

The reaction mechanism of the phosphine Rh complex-catalyzed hydrogenation has been elucidated by Halpern[9] and the mechanism of hydrogenation of an enamide using a diphosphine yielding a phenylalanine derivative is shown in Figure 4.

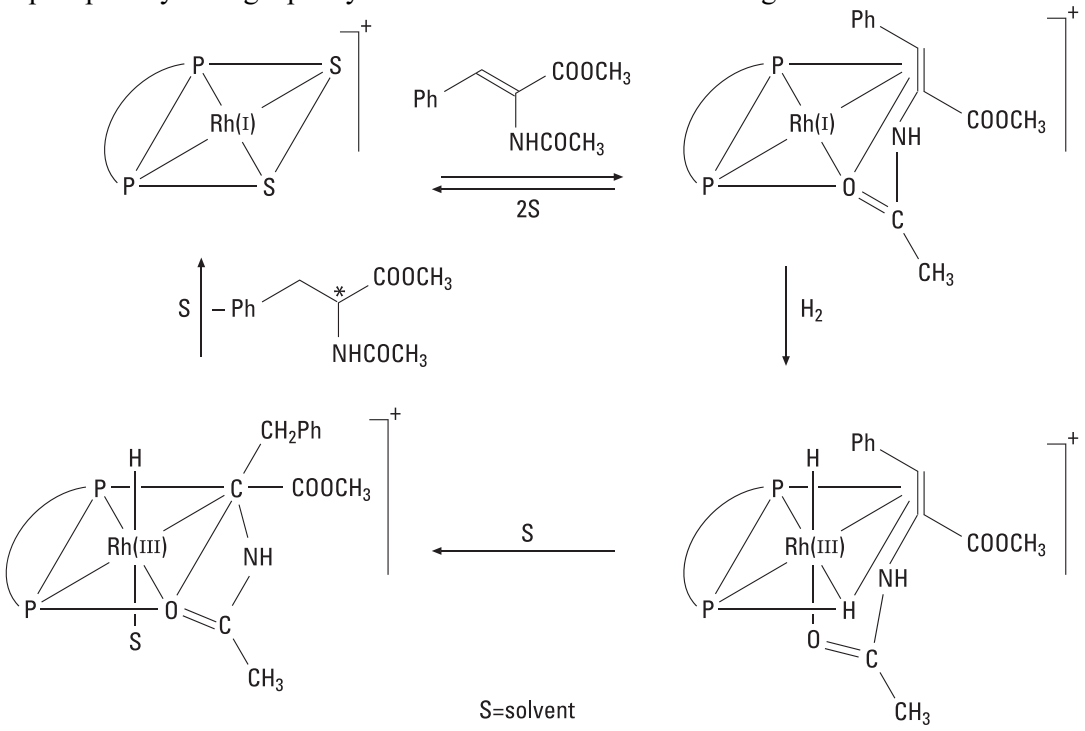

Figure 4: Mechanism of Rh-diphosphine-catalyzed hydrogenation of an enamide.

First, solvent molecules, S, in the catalyst precursor 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) center. 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.
In order to develop improved asymmetric catalysts the energy difference between the diasteroisomeric activated complexes has to be increased to yield larger ee. This is important for industrial applications. The leader of this development is another of this year's Laureates in Chemistry, Ryoji Noyori.

Noyori's general hydrogenation catalysts

An early example of molecular asymmetric catalysis using homogeneous transition metal complexes - enantioselective cyclopropanation of olefins - was reported in 1966 by Noyori, together with H. Nozaki. However, the stereoselectivity was low.
In 1980, Noyori, together with Takaya, discovered an atropisomeric chiral diphosphine, BINAP. Rh(I) complexes of the enantiomers of BINAP are remarkably effective in various kinds of

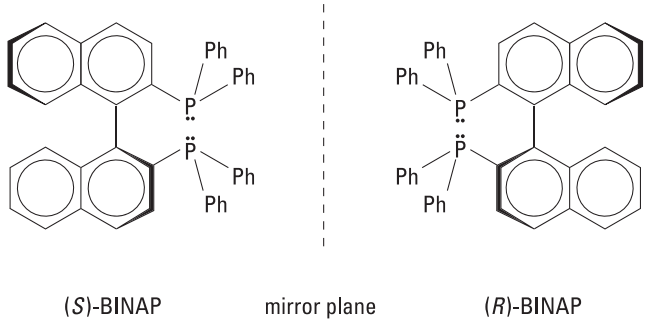

Figure 5: The two enantiomers of the versatile diphosphine ligand BINAP is shown.

asymmetric catalysis.[10] This includes enantioselective hydrogenation of α-(acylamino)acrylic acids or esters, giving amino 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 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 acids.[11] An example is shown in Figure 6.

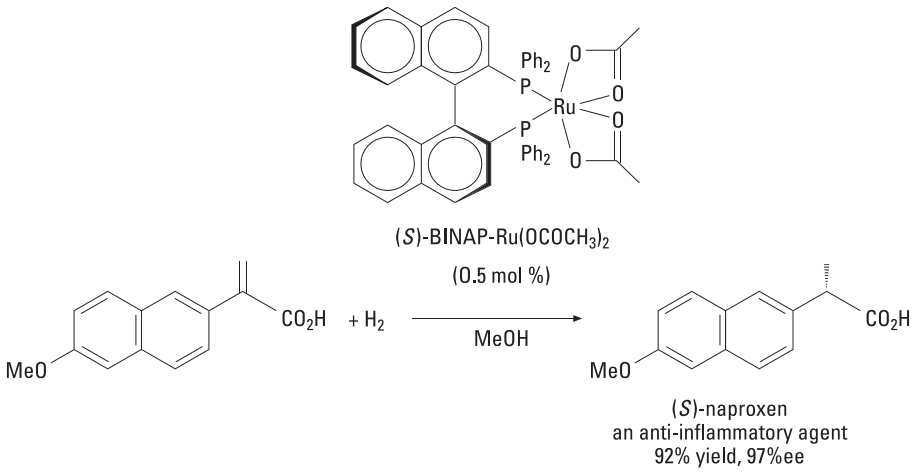

Figure 6: The anti-inflammatory agent (*S*)-naproxen is produced in high yield and high enantiomeric excess using Noyori's catalyst.

This reaction, unlike Rh(I)-catalyzed 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 the 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. Various functionalities can act as directing groups.[12]

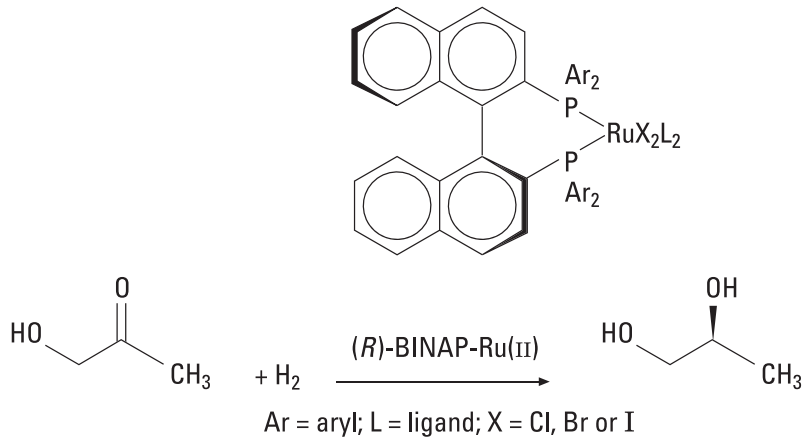

Figure 7: The (*R*)-BINAP-Ru-(II)-catalyzed hydrogenation of acetol to (*R*)-1,2-propanediol is currently used for the industrial synthesis of antibacterial levofloxacin.

The hydrogenation method is effective for converting β-keto carboxylic esters into β-hydroxy esters in high (up to 100%) enatiomeric purity. 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 homogeneous and heterogeneous catalyses using molecular hydrogen 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-selective.[13]
Efficient asymmetric hydrogenation of α,β-unsaturated ketones has been an enduring problem in organic chemistry. In the example in Figure 8 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 100 000. This chemoselectivity is remarkable in view of the large catalytic activity of diamine-free BINAP-Ru complexes for hydrogenation of CC double bonds in allylic alcohols.

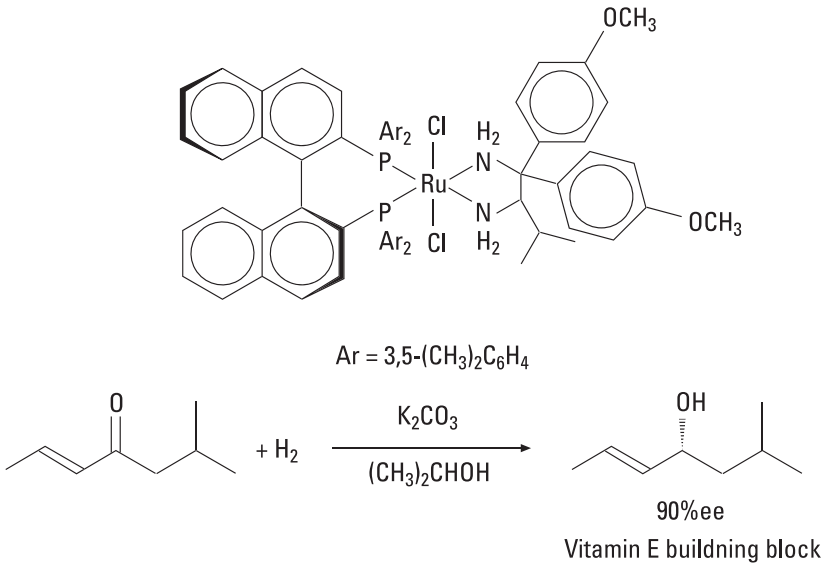

Figure 8: A simple enone is transformed by enantioselective hydrogenation into a chiral allylic alcohol using a novel Noyori catalyst.

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.

Sharpless's chirally catalyzed oxidations

Parallell to the progress in catalytic asymmetric hydrogenations Barry Sharpless has developed chiral catalysts for very important 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) tetraisopropoxide, *tert*-butyl hydroperoxide, and an enantiomerically pure dialkyl tartrate, the Sharpless reaction accomplishes the epoxidation of allylic alcohols with excellent stereoselectivity. This powerful 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 9 (i.e. OH group in lower right hand corner).

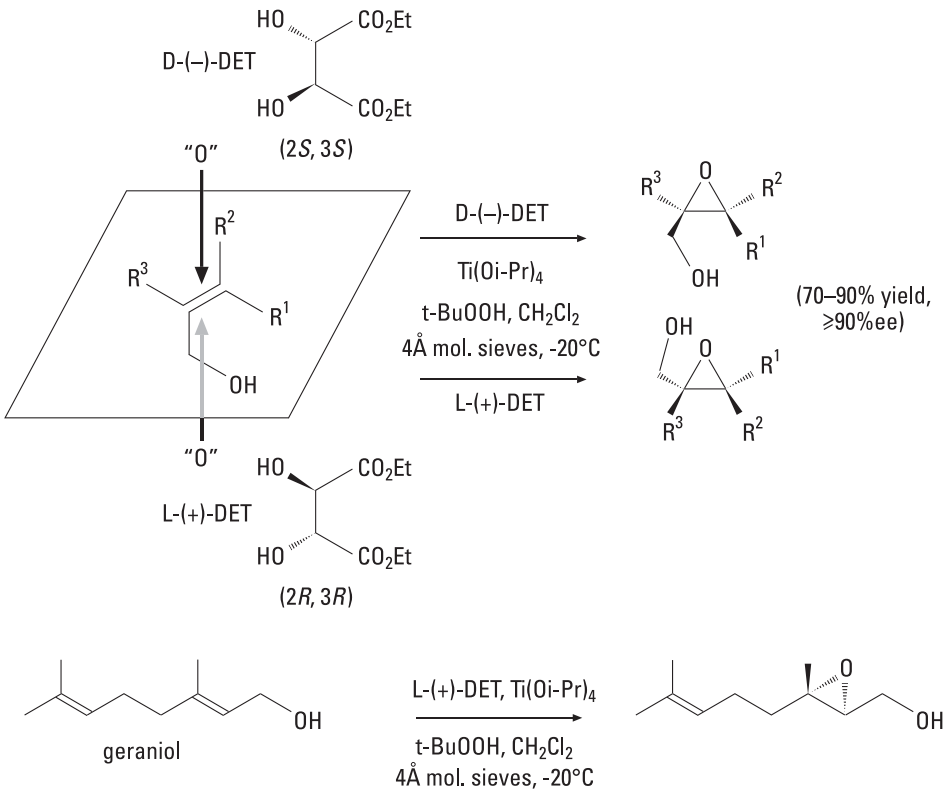

Figure 9: The predictive stereoselectivity of the Sharpless epoxidation is shown together with an example of its regioselectivity.

The L-(+)-tartrate ligand (L-(+)-DET), on the other hand, allows the bottom face of the olefin to be epoxidised. When achiral allylic alcohols are employed, the Sharpless reaction exhibits exceptional enantiofacial selectivity (ca. 100:1) and provides convenient access to synthetically versatile epoxy alcohols.
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 epoxidised with exceptional stereoselectivity. Interest in the Sharpless epoxidation as a tool for industrial organic synthesis increased substantially after Sharpless *et al*. 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 mixture.[14] Using this practical and reproducible catalytic variant, an industrial process for ton-scale productions of (*S*)- and (*R*)-glycidol and (*S*)- and (*R*)-methylglycidol has been developed. These low molecular weight epoxy alcohols are versatile building blocks for the synthesis of a number of chiral molecules. As an example glycidol is used in the pharmaceutical industry to produce β-blockers, used as heart medicines.
Another successful industrial application of the Sharpless epoxidation, is the synthesis of (7*R*,8*S*)-disparlure, the pheromone of the gypsy moth.

The *cis* dihydroxylation of olefins first reported early last century is another most useful oxidation reaction. It converts an olefin to a vicinal diol present in many natural products and unnatural molecules. The original dihydroxylation reaction used stoichiometric

amounts of osmium tetroxide (OsO_4), which is expensive, volatile and toxic, with the result that even small-scale reactions were inconvenient. However, the dihydroxylation shows specificity for double bonds and has no particular substrate requirements, which were advantages. Over the years, the original dihydroxylation procedure has been modified to operate catalytically, more rapidly, and in better yield.

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. A useful stoichiometric co-oxidant is *N*-methylmorpholine *N*-oxide (NMO).

The first attempt at non-enzymatic asymmetric dihydroxylation utilized a chiral, enantiomerically pure pyridine to determine if this induced asymmetry in the diol. A modest ee was obtained. However, the cinchona alkaloid ligands proved to have more balanced properties and gave more pronounced "ligand accelerated catalysis". This concept was introduced by Sharpless in the same paper where he reported the first *catalytic* asymmetric dihydroxylation. The seemingly trivial marriage of the Sharpless cinchona alkaloid stoichiometric dihydroxylation process (now optimized with the ligand in Figure 10) with the practical qualities of NMO resulted in good yields and moderate to good enatiomeric excesses.[15] An example is shown in Figure 10.

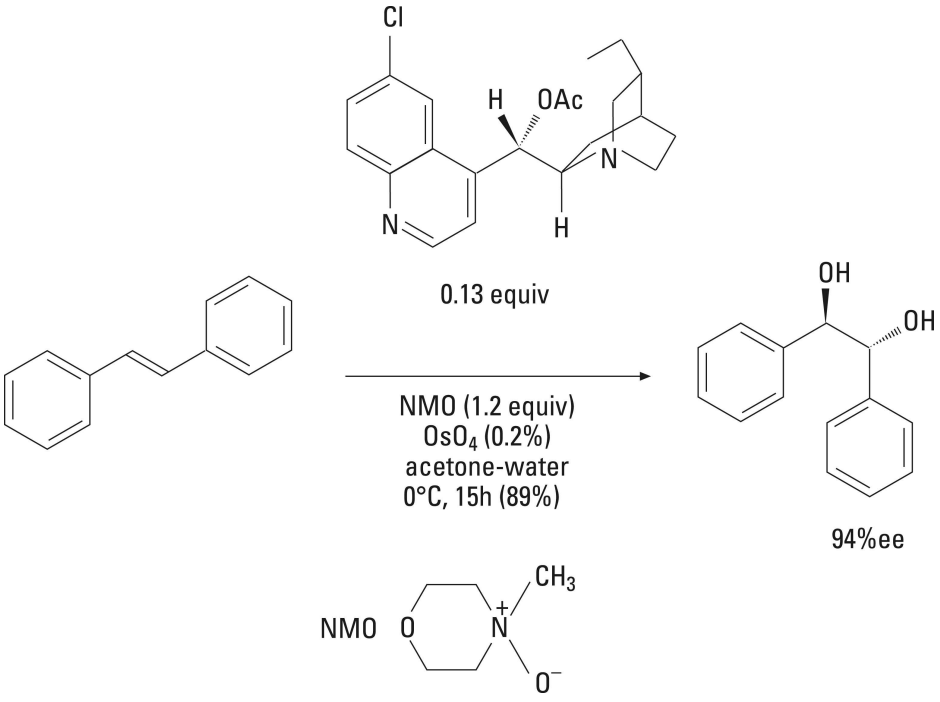

Figure 10: Catalytic asymmetric dihydroxylation developed by Sharpless.

Since Sharpless's discovery of the chirally catalyzed dihydroxylations, there has been considerable progress with respect to the understanding of the reaction mechanism. Better ligands have been designed and procedures have been improved making Sharpless's catalytic asymmetric dihydroxylation an extremely useful reaction.

Consequences and applications

Some of the applications of the Laureates' pioneering work have already been discussed. It is especially important to emphasise the great significance their discoveries and improvements have for industry. Industrial syntheses of new drugs are 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 catalytic asymmetric syntheses that have been inspired by the Laureates' discoveries. Their developments have provided academic research with many important tools, thereby contributing to more rapid advances of 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.

Per Ahlberg,
Professor of Organic Chemistry, Göteborg University,
member of the Nobel Committee for Chemistry

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