2001 Nobel Prize in Chemistry

TIMELY RECOGNITION FOR RHODIUM, RUTHENIUM AND OSMIUM-CATALYSED CHIRAL REACTIONS

William S. Knowles, a retired chemist from Monsanto Company, U.S.A., and Professor Ryoji Noyori, Nagoya University, Japan, shared one half of the 2001 Nobel Prize for Chemistry for their work on chiral-catalysed hydrogenation reactions. Professor K. Barry Sharpless, Scripps Research Institute, U.S.A., received the other half of the prize for his work on chiral-catalysed oxidation reactions.

In nature, molecules, such as hormones, DNA, antibodies and enzymes, display the property of chirality. Such molecules have the same chemical formula but different spatial orientations, making a significant difference to their biological properties; for example, (*R*)-limonene smells of oranges, (*S*)-limonene smells of lemons. Chiral molecules in our nasal receptors can recognise these differences. Biochemical reactions are sensitive to chirality and the activity of a drug depends on the nature of the enantiomer. Many drugs are chiral, and it is essential that a drug is matched to the receptor in the cell to which it is directed. Mismatch will reduce the potency of the drug and could be extremely harmful. (*S*)-(+)-Ibuprofen is an example of a drug where only the (*S*) isomer is efficacious for anti-inflammatory use (1).

Enantioselective syntheses involve two major approaches: resolution or asymmetric synthesis. In resolution the mixture of chiral compounds is separated by physical means whereas in chiral syntheses the novel concept is that a very small amount of catalyst can drive chemical selectivity towards the desired isomer. As an active catalyst can produce millions of molecules of optically pure compound, the waste associated with racemate resolution can be minimised.

Knowles' Rh Catalysed Chiral Hydrogenation

In the 1960s G. Wilkinson with J. A. Osborn (2) synthesised the hydrogenation catalyst $RhCl(Ph_3P)_3$. At the same time L. Horner and K. M. Mislow synthesised optically active phosphines. Knowles combined these two discoveries. Using a Rh complex of (-)-methylpropylphenylphosphine he was able to hydrogenate α-phenylacrylic acid to (+)-hydratropic acid in 15% ee. These results, along with reports by Horner, H. B. Kagan, J. D. Morrison and B. Bosnich, prompted him to investigate the proper match between ligand, metal and substrate to enhance selectivity. After much systematic work Knowles and colleagues at Monsanto were able to make the rare amino acid, L-DOPA, in 100% yield with 95% ee, using [Rh((*R*,*R*)-DiPAMP)COD]BF_4 (Figure 1). Monsanto commercialised the process in 1974. It is recognised as the first industrial process using catalytic asymmetric synthesis. In the catalytic chiral hydrogenation cycle, Rh(I) becomes Rh(III) by oxidative addition of two H atoms. These H atoms are later transferred to the double bond in the substrate, and the catalyst is regenerated.

Noyori's Rh and Ru Catalysed Hydrogenations

Ryoji Noyori has worked in the area of chiral catalysis from the mid-1960s and has sought throughout his career to understand chiral hydrogenation. The co-discovery of the ligand BINAP (3) and its applications in chiral synthesis was of great help. Other powerful ligands are now available, but BINAP is still one of the most versatile in chiral synthesis. Noyori's enantiopure isomerisation reaction of allylic amines to (*R*)-(-)-diethyl-(*E*)-citronellalenamine in the presence of [Rh-(-)-BINAP(COD)]ClO_4 resulted in commercialisation of a multi-ton L-menthol process (Figure 2).

Noyori also used Rh-BINAP catalysts for the chiral hydrogenation of several α-(acylamino)-acrylic acids or esters, and his work on BINAP-Ru(II) complexes is used for the enantioselective hydrogenation of α,β- and β,γ-unsaturated carboxylic acids. The anti-inflammatory drug (*S*)-(+)-naproxen (Figure 3) is synthesised in very high ee and yield using [$Ru(OAc)_2$((*S*)-(BINAP)].

A wide range of ketones has also been hydrogenated with the aid of [RuX(arene)BINAP]X or [RuX_2(BINAP)] (X = halogen) complexes. The antibacterial agent levofloxacin is produced industrially this way. Ru(II) BINAP complexes are also used in

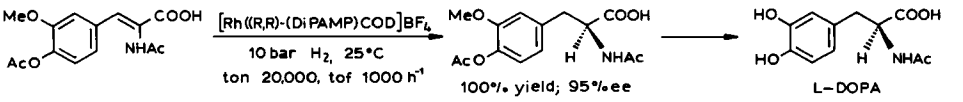
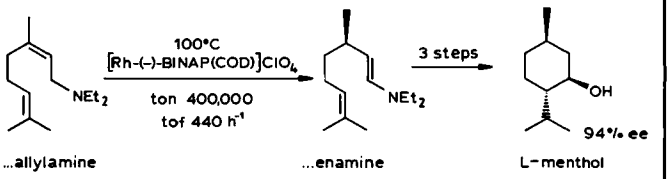


Fig. 1 Industrial production of L-DOPA developed by Knowles using [Rh((R,R)-DiPAMP)COD]BF4

Fig. 2 [Rh-(-)-BINAP(COD)]ClO4 is the catalyst used in the manufacture of L-menthol.*

**Catalyst data from: H. U Blaser, F. Spindler and M. Studer, Appl. Catal. A: Gen., 2001, 221, (1–2), 119*



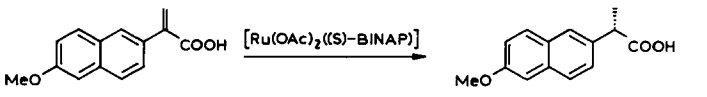
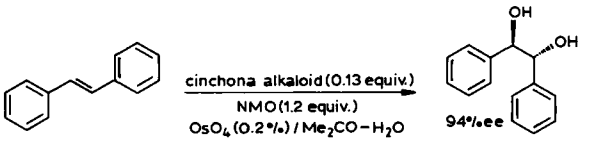


Fig. 3 (S)-(+)-Naproxen is produced using Noyori's catalyst [Ru(OAc)2((S)-BINAP)]

Fig. 4 Catalyst OsO_4 as used in Sharpless' chiral dihydroxylation



production of chiral propanediol, and for an enantiopure azetidinone for carbapenem synthesis.

In recent years, Noyori has demonstrated asymmetric hydrogen transfer reactions in simple ketones, such as acetophenone. Adding ethylenediamine in the presence of KOH in isopropanol enhances the activity of the Ru catalysts. The synthetically challenging substrates α,β-unsaturated ketones have been reduced with high ees and yields. The modified Ru BINAP complex, $RuCl_2$-(xylylbinap)(diamine) transforms enone to chiral allyl alcohol with high turnover number. Noyori's work has been used in the pharmaceutical, agrochemical, flavours and fine chemical industries.

Sharpless' Oxidation Chemistry

In the 1980s, Sharpless centred his work on the chiral oxidation of allylic alcohols to epoxides, useful synthons for various organic compounds. Transformation utilises Ti(IV) tetraisopropoxide, *tert*-butylhydroperoxide, and enantiomerically pure dialkyltartrate. Choice of the appropriate tartrate ligand permits oxygen addition either to the top or bottom face of the olefin. Production methods for (R)- and (*S*)-glycidol and methylglycidol have resulted. Glycidol is used to produce β-blockers. The Sharpless epoxidation is also used industrially to produce the pheromone (7*R*,8*S*)-disparlure.

Sharpless also introduced 'ligand accelerated catalysis' where catalytic amounts of OsO_4 and cinchona alkaloid were used with a stoichiometric amount of co-oxidant, *N*-methylmorpholine *N*-oxide, to give asymmetric dihydroxylation (Figure 4).

The platinum metals catalysts used in these reactions have contributed to their success and efficacy, and have formed an essential part of this most prestigious award to Knowles, Noyori and Sharpless (4). Organometallic chemistry now sits firmly in the main-stream of modern chemistry.

References

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4 http://www.nobel.se

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