Homogeneous catalysts for asymmetric synthesis

Sumit Bhaduri and Hanif Khwaja

The ability to catalytically synthesize only a desired molecule and not its non-superimposable mirror image is a major challenge in chemical research. A few soluble metal complexes have shown great promise towards achieving this end.

The word 'chiral' has its origin in the Greek word for hand. It has been recognized from Louis Pasteur's time (1848) that a large number of molecules have two possible structures which, like a pair of hands, are nonsuperimposable mirror images of each other. The origin and control of this handedness or chirality are important themes of current scientific research[1,2]. The practical implications of manufacturing processes where only one of the mirror images of the target molecule could be selectively obtained are immense. This is because the handedness of a molecule, e.g. a drug or an insecticide, can have remarkable influence on its biological effects. To give one example of tragic consequences it has now been established that foetal abnormalities or the teratogenic effects of the drug thalidomide was associated with its chirality[2].

There are several recent reviews and articles which give up-to-date accounts of advances made in the applications of chiral, metal-based catalysts and reagents[3-5]. The focus and aim of the present article are different. By taking a few representative and aesthically pleasing examples, we attempt to present the developments of chirality-related inorganic and organometallic chemistry in a capsulated form. It is directed towards chemists and scientists whose acquaintance with organometallic chemistry and chirality is marginal. It is for this reason that the evolution of chirality-related research is traced around some of the important developments and basic themes of modern inorganic and organometallic chemistry. We felt in the Indian context it was important to emphasize the technological promise inherent in this area of research. For this reason examples have been chosen from industrially operated processes.

A few terms and concepts

The two structures of a molecule with mirror-image relationship are called *enantiomers*. They have identical physicochemical properties but their *optical activities*, as defined by their interaction with polarized light, are equal in magnitude but opposite in sign.

A mixture containing equal quantities of two enantiomers is optically inactive (magnitude of the interaction is zero) and is called a *racemic* mixture. Molecules with more than one centre that can generate a nonsuperimposable mirror image, i.e. asymmetric centre, can have more than one pair of enantiomers. The term *diastereoisomer* is used to refer to structures where out of two or more asymmetric centres at least one remains unchanged in the two isomers. Chemical transformations where one enantiomer or a diastereoisomer is selectively formed are called *enantiospecific* and *diastereospecific* respectively. The degree of selectivity is expressed by optical yield or *enantiomeric excess* (e.e.) which is the percentage excess of the major enantiomer. A nonchiral molecule that after a specific chemical transformation becomes chiral is called *prochiral*. Finally, soluble metal complexes capable of acting as catalysts are often referred to as *homogeneous catalysts* and when the use of such a catalyst on a prochiral substrate leads to product formation in an enantiospecific manner, the catalyst is termed as an *asymmetric* catalyst.

Tartaric acid and 'BINAP': an axis of symmetry?

It was microscopic inspection of crystals of a tartaric acid salt that led Louis Pasteur to propose the existence of chirality at a molecular level. In fact in the history of chirality-related research, tartaric acid, a naturally occurring, abundantly available chiral compound, appears time and again as an important milestone. In the early seventies, starting from tartaric acid Kagan reported[6] the synthesis of a chiral diphosphine DIOP (Figure 1).

Around the same time Monsanto introduced the synthesis of L-DOPA, a drug used for the treatment of Parkinson's disease, by an asymmetric hydrogenation route developed by Knowles[7] and coworkers (Figure 2).

The authors are in the Alchemie Research Centre, P. O. Box 155, Thane-Belapur Road, Thane 400 601, India

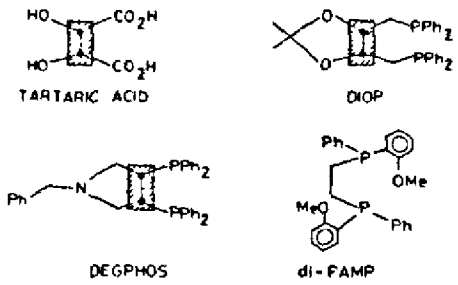

Figure 1. The boxed parts of tartaric acid, DIOP and DEGPHOS show the common chiral fragments. The two chiral carbon atoms are *highlighted as small dark circles. The Monsanto phosphine's (di-*PAMP) chirality is located on the nonplanar phosphorous atoms.

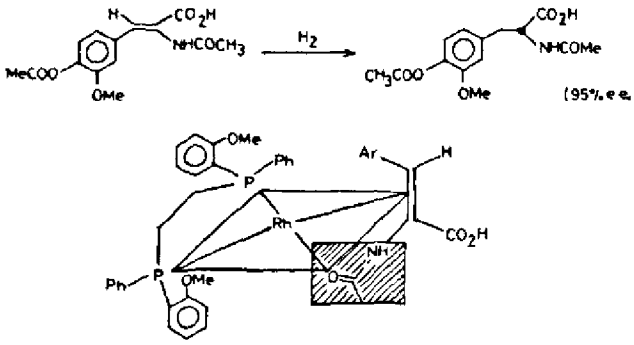

Figure 2. Top: Synthesis of the precursor of L-DOPA (3,4-dihydroxyphenyl alanine) by asymmetric hydrogenation. The chiral carbon atom in the product is shown as a small dark circle. Bottom: A diastereomeric intermediate. The boxed part shows the interaction between the side arm of the substrate with the metal atom. The two phosphorus, oxygen and the mid-point of the olefinic double bond form an approximate square-plane with the rhodium atom situated at the centre. 'Ar' refers to the aromatic group of the substrate.

Both these discoveries took place in the background where Wilkinson had already shown that phosphine complexes of noble metals, such as rhodium and ruthenium, are capable of acting as efficient homogeneous hydrogenation catalysts for olefins[8]. Spurred by these notable achievements a tremendous effort has since then gone into the syntheses of a variety of chiral phosphines. Nagel *et al*[9]. used the tartaric acid backbone again to synthesize phosphine ligands such as 'Degphos' (Figure 1), the rhodium complex of which is a highly efficient catalyst for the asymmetric hydrogenations of prochiral substrates of the type shown in Figure 2.

One limitation of the early asymmetric catalysts based on ligands such as DIOP or di-PAMP is the fact that the range of substrates for which high enantioselectivities could be obtained is narrow. Also, by and large, for the catalytic hydrogenation of ketones, these complexes are ineffective.

These limitations have recently been overcome to a large extent by Noyori and co-workers, who have used ruthenium complexes of the ligand 'Binap' as catalysts (Figure 3). This truly is a versatile catalytic system, and a variety of unsaturated substrates could be hydrogenated with very high enantioselectivities[3,10]. 'Binap' has also been used with rhodium to give an asymmetric isomerization catalyst—a discovery which is the basis of Takasago Process for the manufacture of (−)menthol.

The phosphines DIOP and 'Degphos' underline the importance of tartaric acid as the chiral backbone for ligands in asymmetric hydrogenation reactions. Tartaric acid esters also find fascinating applications as ligands in asymmetric epoxidation reactions—or 'Sharpless oxidation' as it is commonly known after the name of its discoverer[11]. Tartarate–titanium complexes catalyse the enantioselective transfer of an oxygen atom from an organic hydroperoxide on to the double bond of allylic alcohols (Figure 4). The active catalyst, a dimer, retains the same structure both in the solid state and in solution[12]. Arco's commercial process for the manufacture of one enantiomer of glycidol is based on this discovery. Optically pure glycidol is used for the manufacture of propranolol—a drug for heart disease and hypertension.

A few generalizations could be made on the basis of the examples discussed so far. First, the chiral ligands have one important characteristic in common. The ligands themselves, or their metal complexes, possess C_2-axes of symmetry. In other words, rotation of these molecules at 180° along a suitable axis (C_2 axis)

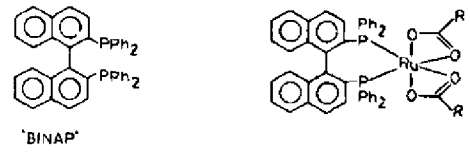

Figure 3. The ligand 'BINAP' and a 'BINAP' containing ruthenium catalyst. Due to steric reasons the ligand is *nonplanar* and therefore chiral. In the catalyst four oxygen and two phosphorus atoms occupy the vertices of an octahedron with the ruthenium atom at the centre. 'R' is an alkyl group.

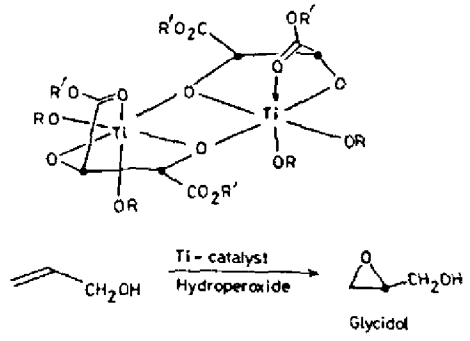

Figure 4. Top: The proposed structure for the active epoxidation catalyst. R and R' are alkyl groups. Bottom: Synthesis of glycidol through asymmetric epoxidation. The chiral carbon atom is shown as a small dark circle.

generates structures that are identical with original ones. It is believed that the presence of this element of symmetry minimizes the number of possible diastereomeric reactive intermediates and transition states which, in turn, leads to high enantioselectivity. Secondly, in all substrates the presence of side arms capable of interacting with the metal atoms is necessary for high enantioselectivity. Though less stringent, this requirement is comparable to the 'lock and key' relationship between substrates and enzymes in biological systems. Finally, structures of the metal complexes, shown in Figures 1–4, and a few of their derivatives have been unequivocally established in the solid state by single-crystal X-ray diffraction studies. Sophisticated and imaginative spectroscopic (mainly NMR) and kinetic studies have also been carried out on a few of these catalytic systems to unravel intricate mechanistic details.

Chiral 'sandwich' and 'half-sandwich' molecules

Sandwich complexes discovered in the early fifties constitute a landmark development in the history of organometallic chemistry of the transition metals[13]. The picturesque name describes structures of this class of complexes graphically—a metal atom sandwiched between two planar aromatic molecules or ions. Similarly 'half-sandwich' means that only one side of the metal ion is covered with an aromatic ring. In the early fifties Wilkinson *et al.*[14] predicted the correct structure of ferrocene (Figure 5) largely on the basis of theoretical arguments. Functionalization of ferrocene to give chiral phosphines has been reported by Hayashi *et al.* These ligands not only look esoteric, they are also capable of imparting high enantiospecificities in certain reactions where other phosphines are less effective[15].

It is often possible to carry out chemical transformations on selected regions of an enantiomer in a diastereospecific manner by conventional organic reagents. By knocking off the original enantiomeric fragment at the end of the reaction sequence one is left with a desired enantiomerically pure compound. In this technique the starting enantiomer is called a chiral auxiliary, since it provides the chiral environment necessary for the enantiospecific synthesis. Two 'half-sandwich' chiral complexes of chromium and iron have been put to ingenious use as chiral auxiliaries by Davies[5] and co-workers (Figure 6). The iron complex which, unlike a lot of other organometallic complexes, is easily synthesized *and* very stable, has been used in elegant syntheses of optically pure captopril, actinonin, β-lactam, etc.—all important drugs or drug intermediates.

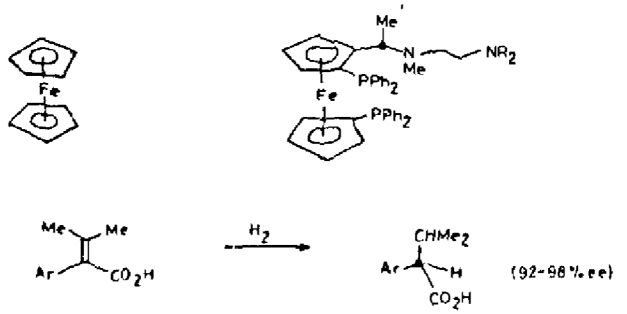

Figure 5. Top: Ferrocene (left) and ferrocene-derived chiral phosphine. The chiral carbon atom in the side-arm is shown as a small dark circle. Bottom: Asymmetric hydrogenation of a substrate with the ferrocene-based phosphine complex of rhodium. Other asymmetric catalysts do not work as well.

Polynuclear metal complexes

All the organometallic complexes discussed so far contain single metal atoms. Particularly interesting and intensely investigated class of complexes with two metal atoms are the ones where the short distances between the metal atoms could be explained only by involving multiple metal–metal bonds. The theoretical basis of multiple metal–metal bonds was first presented in the early sixties by Cotton[16]. In Figure 7, two *chiral* molecules with multiple metal–metal bonds are shown.

The tungsten and the rhenium complexes contain metal–metal triple and quadruple bonds respectively. The chirality of both these complexes are ligand-derived and in both the cases the ligands bridge the

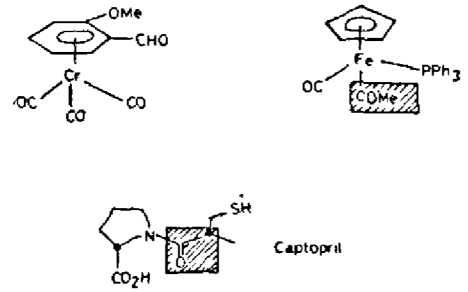

Figure 6. Top: Chromium and iron 'half-sandwich' complexes used as chiral auxiliaries. Bottom: The antihypertensive drug captopril with two chiral centres (dark circles). The boxed parts show the molecular fragment from the auxiliary where chirality is introduced and retained in the target molecule.

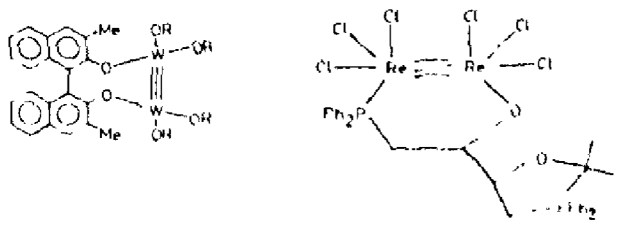

Figure 7. Chiral complexes with triple and quadruple bonds between two metal atoms

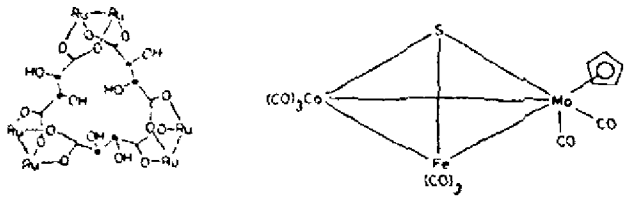

Figure 8. Left: The six-ruthenium-atom-containing cluster with three tartarato groups. The CO groups are not shown for clarity. Right: The chiral tetrahedral cluster used for hydrosilylation of prochiral olefins.

metal atoms. In the tungsten compound the two metal, four carbon and two oxygen atoms form a *nonplanar* eight-member ring[17]. In the rhenium complex a structurally rearranged 'DIOP' binds to the metal atoms through phosphorus and oxygen atoms rather than two phosphorus atoms[18]. (Compare Figures 1 and 7.)

Molecules with more than two metal atoms are often referred to as metal clusters. A nonplanar arrangement of four different atoms in a cluster core makes the cluster chiral. These molecules have a core of three or more metal atoms surrounded by ligands such as carbon monoxide. Such a cluster (Figure 8) designed by Vahrenkamp[19] was tested as an asymmetric catalyst for the hydrosilylation of a prochiral olefin. Unfortunately the rate of racemization of the complex was faster than the rate at which it catalysed this particular reaction. Had this not been the case, and had high optical induction been achieved, it would have been a strong evidence for the maintenance of intact cluster-core during the reaction. The other six-metal-atom cluster shown in Figure 8 reemphasizes the prevalence of tartaric acid as a versatile chiral ligand[20]. A 24-member ring, an organometallic macrocycle, is formed by three tartarato groups and six metal atoms.

Conclusions

In the last twenty years major advances have been made in asymmetric catalysis and synthesis. This has been possible through painstaking search for the correct combination of metals and ligands for a specific catalytic or synthetic reaction. It is expected that in future more effort will be directed towards the development of catalysts for a wider range of reactions, and for each reaction a wider range of substrates than is currently available. The lead in this area of research has so far been taken mainly by organic chemists. This is not surprising since, to borrow a management phrase, they are the 'natural customers' of this versatile tool—metal-based asymmetric synthesis and catalysis. However, as we have tried to point out in this article, syntheses and investigations of the physicochemical properties of a variety of chiral metal complexes also present challenging and attractive research opportunities to inorganic chemists.

Acknowledgement. We thank ICI India Limited for financial assistance.

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