RIGHT OR LEFT IN CHEMISTRY - ENANTIOSELECTIVE CATALYSIS WITH TRANSITION METAL COMPOUNDS*

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Discussing the phenomenon of chirality in nature, an introduction into the field of enantioselective catalysis with transition metal compounds is given, using as an example the hydrogenation of dehydroamino acids. Future developments of the field are outlined.

Keywords: enantioselective catalysis; transition metal complexes.

INTRODUCTION

A variety of macroscopic chiral structures can be found in nature, e.g. snail shells, flowers, and climbers. Usually, they exhibit a high degree of stereoselectivity. Typically, Fig. 1 shows a right-handed snail shell and Fig. 2 a left-handed hops helix.

The origin of this stereoselectivity is metabolism which uses enantiomerically pure compounds, such as L amino acids, D sugars, and not racemic mixtures. As a consequence, if necessary, living beings should be treated with optically pure chemicals of the correct configuration and racemic mixtures should be avoided. Important examples are additives to human food, suplementation of animal food, drugs, agrochemicals, fragrances etc. This list of applications demonstrates the relevance of optically active compounds for economy. Thus, the synthesis of optically active compounds is a challenging problem for the chemical and pharmaceutical industry[1].

Optically active compounds can be prepared by classical resolution, by transformation of optically active compounds from the chiral pool or by stoichiometric reactions with chiral auxiliaries. However, it is more elegant to use optically active catalysts. An optically active catalyst re-enters each new catalytic cycle with its chiral information. This leads to a multiplication of the chiral information contained in the catalyst. Consequently, with small amounts of optically active catalysts large amounts

Figure 1. A right-handed snail shell.

Figure 2. A left-handed hops helix.

of optically active products can be made. Unrivaled enantioselective catalysts are the enzymes, which have developed during the evolution and which synthesize all the optically active compounds needed in metabolism of man, animals and plants.

At present, chemists use enzymes extensively in water as well as in organic solvents for the synthesis of optically active compounds. However, for molecules, which differ from their natural substrates, usually a drop in reactivity and enantioselectivity is observed. Futhermore, there are many reactions, which cannot be catalyzed by enzymes, and many reaction conditions decompose enzymes. In principle, it should be possible to replace the natural enzymes by artificial chemicals, designed to catalyze specific reactions enantioselectively.

The state-of-the-art of chiral transition metal catalysts in the synthesis of optically active organic compounds is outlined in the present paper, first by giving an overview on the enantioselective hydrogenation of dehydroamino acids. A discussion will follow, in which directions the field of enantioselective catalysis will expand. Then, an example of an old reaction type, the Rh-catalyzed hydrosilylation of a prochiral ketone, will be presented, in which the switch from optically active phosphine ligands to optically active nitrogen ligands has been the main reason for the improved enantioselectivity. Next, a new reaction type, the homo Diels-Alder reaction of norbornadiene

with acetylenes will be discussed, for which recently high enantioselectivities have been achieved. Finally, the stereoselective reduction of folic acid to tetrahydrofolic acid and its conversion to leucovorine will be described to demonstrate how the new methodology can be used in the synthesis of drugs.

ENANTIOSELECTIVE HYDROGENATION OF DEHYDROAMINO ACIDS

The hydrogenation of (Z)-α-N-acetamidocinnamic acid gives N-acetylphenyl-alanine (Fig. 3), which can be hydrolyzed to phenylalanine, an essential and expensive amino acid. The reaction of Fig. 3 is catalyzed by Wilkinson-type Rh-catalysts. Using triphenylphosphine as a ligand, the product is formed as a racemic mixture. Replacement of the achiral triphenylphosphine by an optically active phosphine, renders the catalyst enantioselective and an optically active product should be formed. In 1968, the first optically active phosphines used were so-called Horner-type phosphines, e.g. PMe^{n}PrPh[2] and PMe^{i}PrPh[3]. Optical inductions, however, remained low with these monodentate phosphines.

A milestone in the development of enantioselective hydrogenation was the design of the optically active chelate ligand Diop, prepared from tartaric acid in a series of elementary organic transformations, outlined at the bottom of Fig. 3[4,5]. In contrast to the monodentate optically active ligands PMe^{n}PrPh and PMe^{i}PrPh, the bidentate optically active ligand Diop gave optical inductions of 81% ee in the hydrogenation reaction of Fig. 3, both when used in isolated catalysts or when used in *in situ* catalysts. In this context, an isolated catalyst is a Wilkinson-type catalyst, e.g. a stable square planar Rh-complex, whereas an *in situ* catalyst consists of two precursors, the procatalyst (the metal component) and the cocatalyst (the optically active ligand).
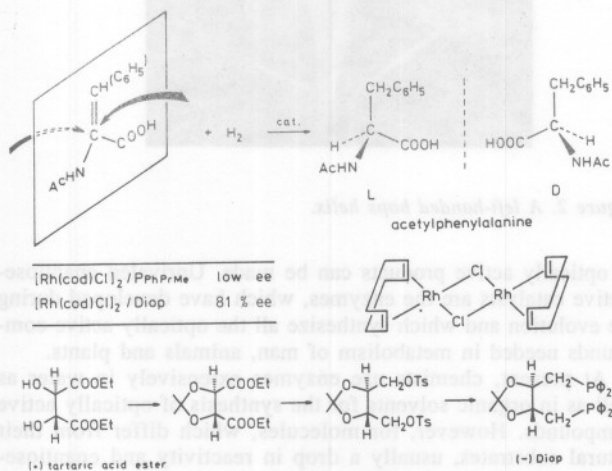

Figure 3. *Hydrogenation of (Z)-α-N-acetamidocinnamic acid and synthesis of Diop.*

The two components of an *in situ* hydrogenation catalyst are [Rh(cod)Cl]$_2$ and Diop, as shown in Fig. 3. These two components are air-stable, commercial products, which in solution combine to give the actual catalyst. The advantage of an *in situ* catalyst is that no catalyst synthesis is required prior to the reaction which has to be carried out.

Meanwhile more than 1000 optically active phosphines have been described in the literature, which have served as ligands in enantioselective transition metal catalysts. These ligands are collected in the Handbook of Enantioselective Catalysis with Transition Metal Compounds. Six well-known examples are shown in Fig. 4. Some of them are synthesized starting from
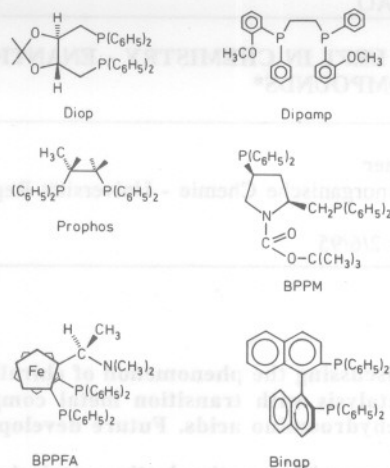

Figure 4. *Six optically active chelate phosphines.*

optically active compounds of the natural pool. Thus, Diop derives from tartaric acid, Prophos from lactic acid and BPPM from hydroxyproline. Others, such as Dipamp, BPPFA and Binap, have been obtained by chemical synthesis and resolution. Dipamp and Binap are applied in the industrial production of L-dopa and (-)-menthol, respectively[1].

In Fig. 5 the formula of the optically active ligand Norphos is given, a contribution from the author's group[7,8].
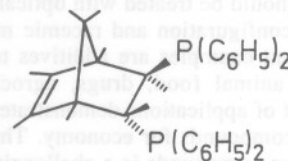

Figure 5. *The optically active ligand Norphos.*

The application of a Norphos-containing Rh-catalyst in the hydrogenation of (Z)-α-N-acetamidocinnamic acid is shown in Fig. 6. A 99:1 ratio in favor of the natural L-isomer of N-acetylphenylalanine is obtained with the experimental procedure given at the bottom of Fig. 6. In this procedure the substrate:catalyst radio is 500:1. In combination with the insert in Fig.6 this demonstrates the elegancy of the approach. A large amount of a substrate is converted into a valuable optically active product, using only small amounts of the two components [Rh(cod)Cl]$_2$ and Norphos of an *in situ* catalyst.

The synthesis of natural and unnatural optically active amino
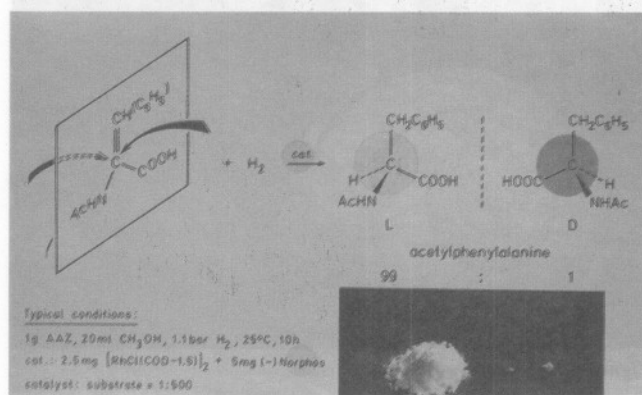

Figure 6. *Hydrogenation of (Z)-α-N-acetamidocinnamic acid with a Norphos-containing Rh-catalyst.*

acids by hydrogenation of the corresponding dehydroamino acids is the show piece of enantioselective catalysis with transition metal compounds[9,10]. There are other reactions, in which enantioselective transition metal catalysts induce extremely high levels of enantioselectivity, including the cyclopropanation reaction, the epoxidation of allylic alcohols, the dihydroxylation of prochiral olefins, and allylic alkylations and isomerizations[9,10]. Numerous examples for these well established reaction types are tabulated in the Handbook of Enantioselective Catalysis with Transition Metal Compounds[6].

EXTENSION OF THE FIELD OF ENANTIOSELECTIVE CATALYSIS

Fig. 7 indicates the future potential of the field of enantioselective catalysis with transition metal complexes.
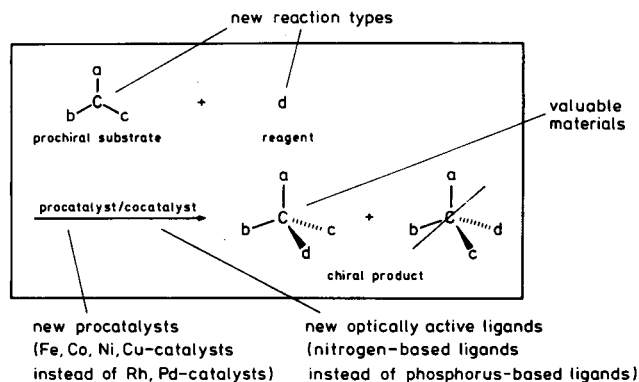

Figure 7. Perspectives for the field of enantioselective catalysis.

Important directions for further developments will be to find new reaction types (new prochiral substrates and reagents) for enantioselective catalysis, which have not been used before. To apply the methodology to the synthesis of valuable materials, such as natural products, drugs, agrochemicals, fragrances etc., will extend the field. The main focus, however, will be on the design of new catalysts (procatalysts and cocatalysts). Substitution of the noble metals rhodium and palladium in these catalysts by cheap 3d metals, such as manganese, iron, cobalt, nickel, copper, is a promising approach. New cocatalysts means design and syntheses of new ligands, in particular the substitution of phosphorus-based ligands (expensive, difficult to synthesize) by nitrogen-based ligands (inexpensive, easy to synthesize). These ideas will be demonstrated with three examples in the following chapters.

ENANTIOSELECTIVE HYDROSILYLATION OF ACETOPHENONE WITH DIPHENYLSILANE

The product of the reduction of a prochiral ketone is a chiral secondary alcohol. Dozens of optically active secondary alcohols play an important role in pharmacy. Acetophenone, the simplest prochiral ketone, is reduced to 1-phenylethanol (Fig. 8). There are many ways to accomplish this reduction, one of them is the hydrosilylation, followed by hydrolysis.

In the hydrosilylation of acetophenone with diphenylsilane first a catalytic addition of a Si-H bond to the C=O bond takes place, giving rise to a silyl ether. Then, the silyl ether
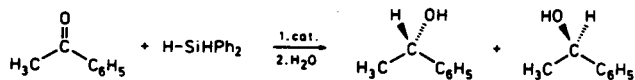

Figure 8. Hydrosilylation of acetophenone with diphenylsilane.

is hydrolyzed at the O-Si bond to 1-phenylethanol (Fig. 8). The first example of this reaction type was described in 1972[11]. Since then many papers appeared in the literature, the catalysts being mainly of the Wilkinson-type[12]. However, the celebrated optically active chelate phosphines, extremely efficient in the hydrogenation of dehydroamino acids, turned out to be inefficient cocatalysts in the hydrosilylation of ketones and only moderate enantioselectivities were obtained.

In 1982 and 1983 we introduced new types of nitrogen ligands as optically active cocatalysts, the pyridine-imines[13,14] and pyridine-thiazolidines[15,16]. Later-on we added pyridine-oxazolines[17,18], a ligand type which has been extensively used and optimized by many other groups[12]. In situ catalysts consisting of [Rh(cod)Cl2]2 and a pyridine-thiazolidine of the Pythia-type give high optical inductions for acetophenone and other alkyl aryl ketones (Fig. 9).

Surprisingly, in the hydrosilylation of prochiral ketones nitrogen-based ligands, accessible in one-step condensation reactions, proved to be superior to optically active phosphines, a finding, which gave rise to a renaissance of nitrogen-based ligands in enantioselective catalysis[19].
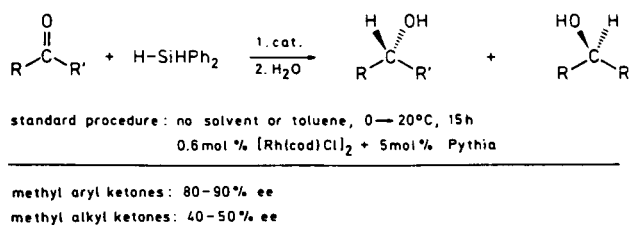

Figure 9. Hydrosilylation of prochiral ketones with diphenylsilane: standard procedures, results, pyridine-thiazolidine ligands.

ENANTIOSELECTIVE HOMO DIELS-ALDER REACTIONS

Using catalysts derived from the 3d metal cobalt, norbornadiene reacts with phenylacetylene according to a homo Diels-Alder reaction (Fig. 10). The acetylene adds to the two unsaturated front carbon atoms of norbornadiene, forming a five-membered cyclopentene ring. At the backside of the molecule, a three-membered cyclopropane ring completes the polycyclic skeleton, called the deltacyclene skeleton. 4-Phenyldeltacyclene (Fig. 10) is a chiral molecule, consisting of a pair of enantiomers. The molecule contains six asymmetric carbon atoms. However, only the two mirror image isomers are possible, as a consequence of the two different attachments of the monosubstituted acetylene to the norbornadiene framework.

The reaction in Fig. 10 is catalyzed by an *in situ* catalyst, consisting of the procatalyst Co(acac)3 and the cocatalyst
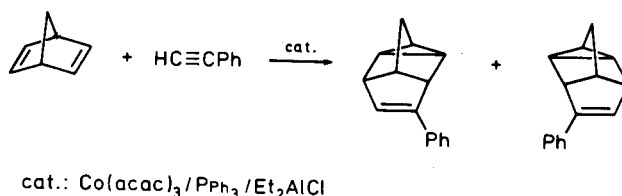

cat.: Co(acac)3/PPh3/Et2AlCl

Figure 10. Homo Diels-Alder reaction of norbornadiene and phenylacetylene.

triphenyphosphine. Diethylaluminum-chloride serves as a reducing agent. Thus, a reduced cobalt species stabilized by triphenylphosphine is the actual catalyst.

Replacing the achiral triphenylphosphine by an optically active phosphine renders the homo Diels-Alder reaction of norbornadiene with phenylacetylene enantioselective (Fig. 11).
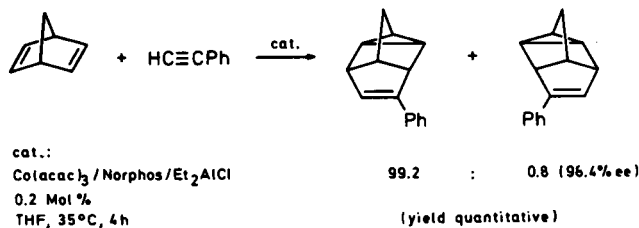

cat.:
Co(acac)₃ / Norphos / Et₂AlCl   99.2   :   0.8 (96.4% ee)
0.2 Mol %
THF, 35°C, 4h   (yield quantitative)

Figure 11. Enantioselective synthesis of 4-phenyldeltacyclene.

A spectacular stereocontrol is achieved with the chelate phosphine Norphos (Fig. 5). 4-Phenyldeltacyclene is obtained in an enantiomer ratio of 99.2:0.8 and a quantitative chemical yield after 4 hours in thf solution at 35 °C with catalyst quantities as little as 0.2 mol%[20-22].

The deltacyclene formation can be extended from phenylacetylene to other monosubstituted acetylenes. Thus, hexyne-1 gives 4-n-butyldeltacyclene in a 99:1 enantiomer ratio and a quantitative chemical yield using the same *in situ* catalyst Co(acac)₃/Norphos/Et₂AlCl[21]. The enantiomer analysis of the deltacyclene derivatives, which are hydrocarbons, is achieved by gas chromatography with perpentylated β-cyclodextrin columns[20,21]. The high stereoselectivity in the homo Diels-Alder reactions can be explained with the model used to predict the correct product configuration in the hydrogenation of dehydroamino acids[22].

TETRAHYDROFOLIC ACID

Folic acid (Fig. 12, top) is a vitamin, which in the body is reduced enzymatically to tetrahydrofolic acid. In this reaction, the two imino groups of the pteridine system are hydrogenated and a new stereogenic center is formed in 6-position. Enzymatic reduction exclusively gives the natural 6S-configuration. In metabolism, tetrahydrofolic acid is a carrier of C1 fragments. These C1 fragments, bound to N5 of the pteridine system, are used in the synthesis of the DNA bases and other physiological methylations.

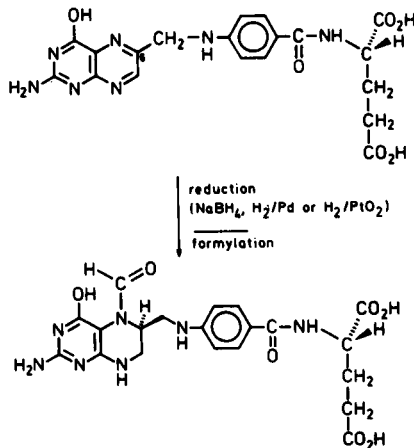In the treatment of cancers, in particular osteosarcomas, high

Figure 12. Reduction of folic acid to tetrahydrofolic acid and formylation to leucovorine.

doses of methotrexate are used to inhibit the enzyme dihydrofolate reductase. A stop of the DNA synthesis is the result, which damages especially fast growing tissues, such as cancers. To maintain a minimum of metabolism, the patients are treated with leucovorine as a rescue agent. Leucovorine is the Ca salt of the 5-formyl derivative of tetrahydrofolic acid (Fig.12, bottom), the formyl group of which functions as the C1 fragment needed in metabolism. In combination with 5-fluorouracil, leucovorine is also used in the treatment of colorectal cancers. Another application of leucovorine is in megaloblastic anaemia.

In the pharmaceutical industry, leucovorine is synthesized by catalytic hydrogenation of folic acid with Pt and Pd catalysts, respectively, and by a subsequent formylation at N5 (Fig. 12). In this procedure, tetrahydrofolic acid is formed as a 1:1 mixture of the isomers 6S,S and 6R,S. Thus, there is no optical induction of the S-configuration of natural glutamic acid, present in the molecule, in the formation of the new stereogenic center at C6 of the pteridine system. This 1:1 mixture of 6S,S/6R,S-leucovorine is used world-wide, although it is known that the unnatural 6R,S-isomer is only slowly metabolized and enriches in the central nervous system, leading to intoxications on the long run. As the separation of the two diastereoisomers 6S,S and 6R,S of leucovorine is extremely difficult, it is a challenging task to synthesize 6S,S-leucovorine by stereoselective hydrogenation of folic acid. With immobilized Rh-catalysts containing optically active phosphines we managed to achieve high enrichments of the natural 6S,S-isomers of tetrahydrofolic acid and leucovorine[23,24].

The salts of folic acid and tetrahydrofolic acid are soluble in water and insoluble in organic solvents. Tetrahydrofolic acid is a biomolecule sensitive to air, acids and bases. In the literature, there are no reports on the stereoselective hydrogenation of folic acid to tetrahydrofolic acid using homogeneous Wilkinson-type catalysts. We succeeded to solve this problem by immobilizing the rhodium/phosphine catalysts[23,24]. We dissolve the procatalyst [Rh(cod)Cl]₂ and the optically active phosphine in CH₂Cl₂ and add silica. The catalyst precipitates on the surface of the silica and a heterogeneous system is obtained, which is insoluble in the buffered aqueous medium used for the hydrogenation of folic acid. The hydrogenation takes place in an autoclave at 80°C during 20 hours at 50 bar H₂ pressure. After formylation with methyl formate, the analysis of the stereoisomers of leucovorine is accomplished by HPLC using a protein column (SiO₂ covered with bovine serum albumine). The product ratio 6S,S:6R,S is strongly dependent on the optically active ligand and on the type of silica used. The best results (up to 94:6) in favor of the natural 6S,S-isomer were obtained with the proline-derived optically active phosphine ligand BPPM (Fig. 4) and with a silica of extremely homogeneous particle size.

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