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Natural products by enantioselective catalysis with transition metal compounds

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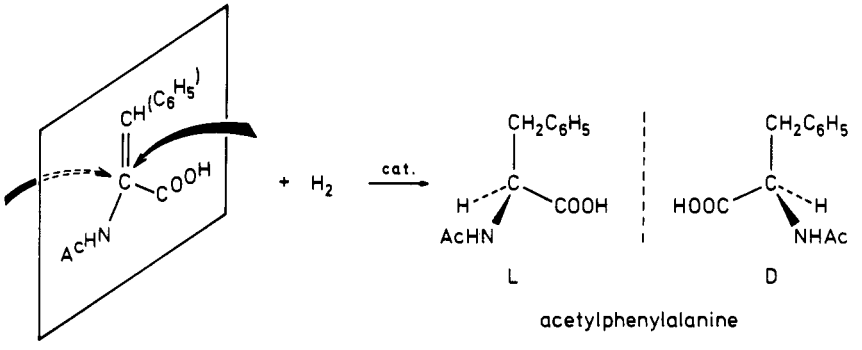
Abstract: The enantioselective synthesis of natural products of the following type (i) amino acid derivatives, (ii) tetrahydrofolic acid, and (iii) 3-hydroxycarotinoides using optically active transition metal catalysts is reported.

In enantioselective catalysis, a prochiral substrate is converted into an optically active product, using an optically active catalyst. As the optically active catalyst re-enters each catalytic cycle anew, a multiplication of the chiral information contained in the catalyst takes place. The best enantioselective catalysts are the enzymes. Chemistry is challenged to provide chemzymes which can be used for processes not applicable to enzymes. In the last decades, an arsenal of enantioselective transition metal catalysts was developed which catalyze a variety of reactions. The use of these catalysts for the enantioselective synthesis of the following types of natural products (i) amino acid derivatives, (ii) tetrahydrofolic acid, and (iii) 3-hydroxycarotinoides is described.

Amino Acid Derivatives

The hydrogenation of dehydroamino acids, such as α-N-acetamidocinnamic acid **1** (Scheme 1), can be carried out with Wilkinson-type catalysts at room temperature in methanol solution. No hydrogen pressure is necessary; a blanket of hydrogen is sufficient to guarantee quantitative hydrogenation within hours. The product of addition of hydrogen accross the C=C bond of the substrate **1** yields the product N-acetylphenylalanine **2** (Scheme 1). Achiral Wilkinson catalysts give racemic mixtures, as frontside and backside attack of the prochiral carbon atom have the same probability. For chiral Wilkinson catalysts,

Scheme 1

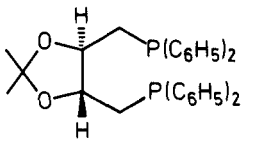


1 2

frontside and backside attack are no longer equivalent. Thus, the two enantiomers of N-acetyl-phenylalanine are formed in ratios different from 50:50.

The first chiral Wilkinson catalysts used were combinations of $[Rh(cod)Cl]_2$, cod = 1,5-cyclooctadiene, as the transition metal component and the optically active Horner-phosphines (+)- and (-)-PPhMe^{i}Pr (1,2). Whereas these catalysts gave only modest enantioselectivities, catalysts derived from the procatalyst $[Rh(cod)Cl]_2$ and the cocatalyst diop **3** (Scheme 2), a chelate phosphine prepared starting from (+)-tartaric acid, attained 81 % ee in the model reaction of Scheme 1 (3).

Scheme 2



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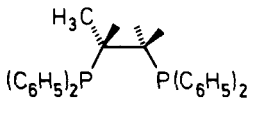

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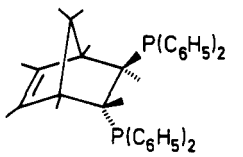

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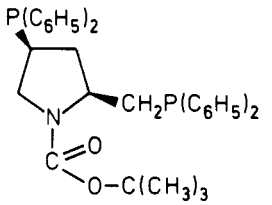

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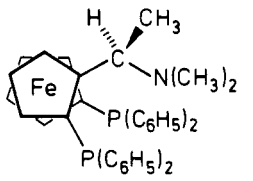

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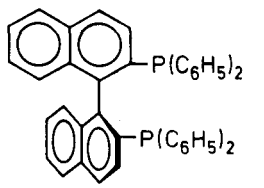

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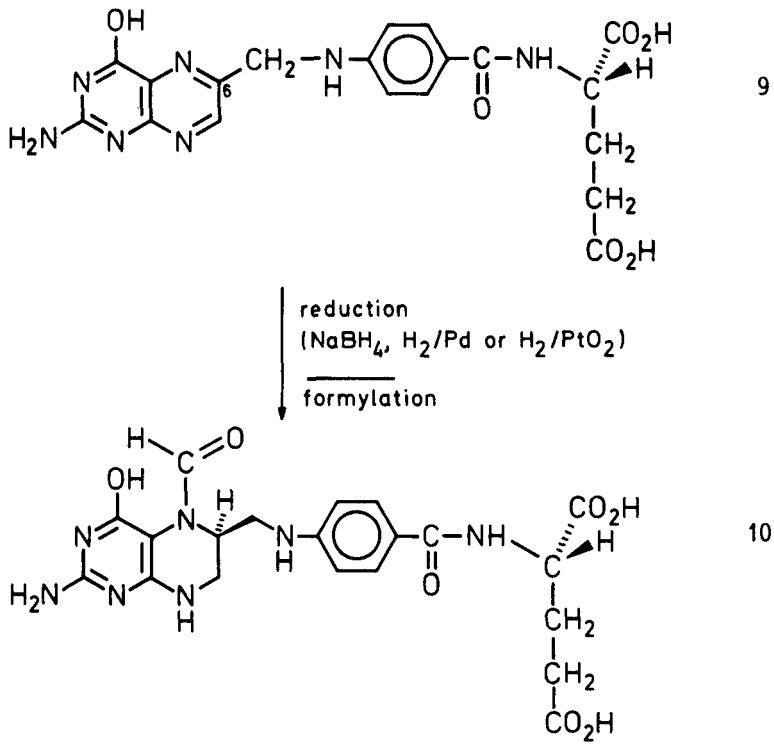
In the last two decades a variety of optically active chelate phosphines for the enantioselective hydrogenation of dehydroamino acid derivatives have been reported. They are quantitatively accumulated in the "Handbook of Enantioselective Catalysis with Transition Metal Compounds" (4). A selection of successful optically active phosphines is given in Scheme 2. With Rh or Ru complexes of these ligands, the conversion of dehydroamino acids into amino acids in enantioselectivities close to 100 % is state of the art.

Tetrahydrofolic Acid

Folic acid **9** is a vitamin which is reduced enzymatically to tetrahydrofolic acid in the body. In this reduction, the two imino groups of the pteridine system take up four reduction equivalents and a new stereogenic center is formed in 6-position of the pteridine ring. Enzymatic reduction exclusively leads to 6S-configuration. In metabolism, tetrahydrofolic acid is a carrier for C1 fragments, which are bound to N5 of the pteridine ring. These C1 fragments are used in the methylation of functional groups and in the synthesis of the DNA bases.

In the treatment of cancers, such as osteosarcomas, high doses of methotrexate are used, which inhibit the enzyme dihydrofolate reductase. This results in a breakdown of the DNA synthesis, hurting especially fast growing tissues like cancers. To guarantee a minimum of metabolism, the patients have to be treated with leucovorine as a rescue agent. Leucovorine is the Ca salt of the 5-formyl derivative **10** of tetrahydrofolic acid, the formyl group of which functions as the C1 fragment essential in metabolism. Leucovorine is also used in the treatment of colorectal cancers.

Scheme 3



In the pharmaceutical industry, leucovorine is synthesized by a hydrogenation of folic acid with Pt and Pd catalysts, respectively, followed by a formylation at N5 (Scheme 3). In this procedure, tetrahydrofolic acid is formed as a 1:1 mixture of the isomers 6S,S and 6R,S. Thus, the S-configuration of glutamic acid does not induce an optical induction in the formation of the new stereogenic center at C6 of the pteridine ring. It is with this 1:1 mixture 6S,S/6R,S that even today medical doctors work, although it is known that the unnatural 6R,S isomer is only slowly metabolized. It enriches in the central nervous system and leads to intoxications on the long run. The separation of the two diastereoisomers 6S,S and 6R,S is extremely difficult. To synthesize 6S,S-leucovorine by stereoselective hydrogenation of folic acid, at present, is an unsolved problem. With immobilized Rh catalysts containing optically active phosphines we succeeded to get high enrichments of the natural 6S,S-isomers of tetrahydrofolic acid and leucovorine (5).

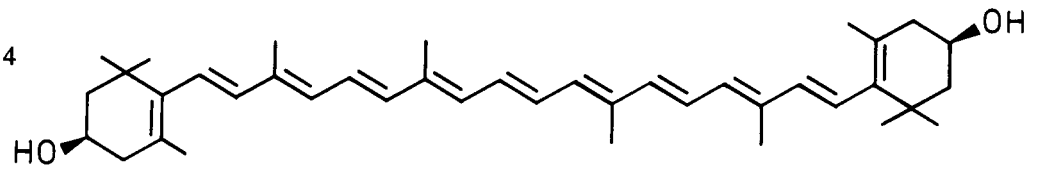
Folic acid and tetrahydrofolic acid are only soluble in the form of their salts in water; they are insoluble in the usual organic solvents. The hydrogenation product tetrahydrofolic acid is a biomolecule sensitive to air, acids and bases. Up to now, a hydrogenation of folic acid to tetrahydrofolic acid using enantioselective transition metal catalysts was not possible. We found a solution to this problem by an immobilization of the Rh/phosphine catalysts. We dissolve the procatalyst $[Rh(cod)Cl]_2$ and the optically active phosphine in methylenechloride and add silica. On evaporation of the solvent, a heterogeneous catalyst is obtained, the Rh/phosphine load of which is insoluble in the buffered aqueous medium used for the hydrogenation of folic acid. The hydrogenation is carried out in an autoclave with 50 bar H_2 pressure at 80 °C during 20 hours. After formylation with methyl formate, the analysis of the stereoisomers of leucovorine is achieved by HPLC using a SiO_2 column, covered with bovine serum albumine. The product ratios 6S,S : 6R,S are strongly dependent on the optically active ligand and on the

type of silica used. The best results (above 90:10) were obtained with the proline derived optically active ligand BPPM **7** (Scheme 2) and with a silica of extremely homogeneous particle size.

3-Hydroxycarotinoides

Natural 3-hydroxycarotinoides are optically active. Zeaxanthin **11** of 3R,3R'-configuration (Scheme 4) is the dominating component of the yellow color of corn.

Scheme 4



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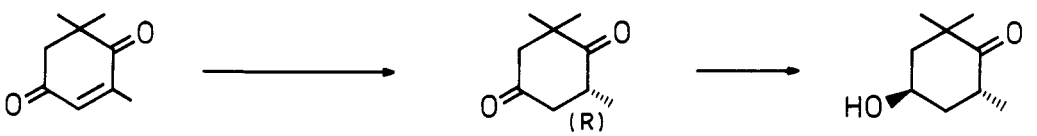
A starting material for the synthesis of zeaxanthin is 4R,6R-4-hydroxy-2,2,6-trimethylcyclohexanone **14**, which can be obtained by fermentative reduction of 4-oxoisophorone (2,2,6-trimethylcyclohex-2-en-1,4-dione) **12** with yeast to give 6R-2,2,6-trimethylcyclohexan-1,4-dione **13**. **13** can be converted into the key intermediate **14** by a diastereoselective reduction (Scheme 5).

Scheme 5



12 **13** **14**

Alternatively, intermediate **13** can be obtained in the enantioselective hydrogenation of 4-oxoisophorone **12** with Ru catalysts containing the optically active phosphine binap **8** (Scheme 2) (6). As catalysts the complexes $[(C_6H_6)RuCl(binap)]Cl$ and $Ru(binap)(OAc)_2$ are used. The substrate:catalyst ratio is 2000:1. The reaction is carried out with 50 bar H_2 pressure in thf solution at 80 °C for 15 hours. **R-13** is obtained in 85 % chemical yield and 50 % ee. Two recrystallizations from petroleum ether/methylenechloride 4:1 reduce the yield to 25 % but increase the optical purity to > 98 % ee.

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