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# Homogeneous Catalysis with Metal Complexes in a Pharmaceuticals' and Vitamins' Company: Why, What for, and Where to Go?

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**Abstract.** Homogeneous catalysis with metal complexes is considered a key methodology to become and remain competitive in the manufacture of biologically active molecules and fine chemicals. Opportunities for such methodology will be discussed. Examples of homogeneous catalytic processes developed at *Roche* are presented, together with a survey of process R&D activities at *Roche* in this field with special emphasis on enantioselective hydrogenation reactions.

## 1. Introduction

Why and for what purpose is a company that is largely a pharmaceuticals' and vitamins' company pursuing homogeneous catalysis with metal complexes, and why particularly with chiral metal complexes? Why work with 'toxic' metals such as palladium, rhodium, ruthenium, osmium, etc.? Why pursue reactions that require expensive high-pressure equipment? And with catalysts and chiral ligands that are not even commercially available! These are some of the questions, which are put to me from time to time. They are, at least in principle, very easy to answer: The potential of homogeneous catalysis with metal complexes, in particular of enantioselective homogeneous catalysis with chiral metal complexes, to provide short, clean, and cost-effective processes is just simply too evident. In other words it is the overwhelming economical and ecological potential of such methodology that makes it so attractive. Thus, homogeneous catalysis with metal complexes – like other catalytic methodologies such as heterogeneous and enzymatic catalysis – is to be considered a key methodology, which is vital to maintain competitiveness and eventually to achieve a competitive advantage in the manufac-

ture of biologically active compounds and fine chemicals.

Historically, interest in catalysis at our company has originated in the areas of vitamin and carotenoid chemistry. In these areas, many heterogeneous catalytic reactions, most prominently hydrogenations, have been utilized. (For more information on the importance of this subject, the reader is referred to the contribution of *Felix Roessler* in this issue, see p. 106.) Homogeneous catalysis with metal complexes at our company also has its roots in vitamin and fine chemicals manufacturing, and it is not surprising that the first applications have been realized in this area. Recently, however, its importance has steadily been growing also for pharmaceuticals.

In this article, the opportunities for homogeneous catalysis with metal complexes will shortly be discussed, and a survey on some of our activities in this area will be presented. From a methodology point of view, our interests focus primarily on homogeneously catalyzed oxidation, carbonylation, and hydrogenation reactions, particularly on enantioselective hydrogenation. It is this last area to which some special attention will be devoted.

## 2. Opportunities for Homogeneous Catalysis with Metal Complexes

Cost of manufacturing is an extremely important and critical issue for products

with long life cycles and for large volume products such as vitamins, carotenoids, and fine chemicals. In the arena of fierce global competition for the lowest cost production of such marketed products, constant efforts to improve the processes, from both a chemical and technical viewpoint, is of decisive importance. In this respect, there is significant opportunity for homogeneous catalysis with metal complexes. Apart from the generation of entirely new synthetic schemes, it is particularly the *replacement of labour- and equipment-intensive resolution processes by enantioselective catalytic processes* and the *reduction of waste* (e.g. elimination of salt freights) where homogeneous catalysis can provide critical contributions.

For pharmaceuticals, cost of goods recently has also become an issue due to the ever increasing complexity of new chemical entities and due to public pressure on drug pricing. Thus, cost-effective manufacturing is also becoming increasingly important. Opportunities for homogeneous catalysis here lie in the realization of *shorter synthetic routes*, e.g. by metal-catalyzed C/C-bond formation, and – since the largest part of new chiral pharmaceuticals is developed in enantiomerically pure form – to provide catalytic processes for *establishing chiral centers and thus to avoid resolution processes*. In the latter respect, enantioselective catalytic transformations such as the reduction of C=C, C=O, and C=N bonds, epoxidation or dihydroxylation of olefins and C/C-bond formation have an enormous potential. An additional important aspect in the development of new pharmaceuticals is the limited time frame available for chemical development. The successful and timely performance of homogeneous catalysis in chemical drug development is strongly dependent on the organizational proximity of both catalysis and pharma process R&D units as well as the efficient use of already established in-house expertise.

## 3. Homogeneous Catalytic Oxidation and Isomerization Processes

Examples of homogeneously catalyzed oxidation and isomerization processes are shown in *Scheme 1*. A Cu-catalyzed air oxidation process has been developed for the conversion of 2,3,6-trimethylphenol to 2,3,5-trimethyl-1,4-quinone (*Eqn. 1*) [1], a starting material for the synthesis of  $\alpha$ -tocopherol (vitamin E). Other metal-catalyzed oxidations have been elaborated for conversion of isophorone to ketoisophorone (*Eqn. 2*) [2]. Ketoisophorone

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can be used as a building block for the synthesis of astaxanthin, the red pigment of salmon. A Pd-catalyzed *cis/trans* C=C isomerization [3] is being used in the synthesis of etretinate, the active ingredient of the anti-psoriasis medicine *Tigason*<sup>®</sup> (Eqn. 3).

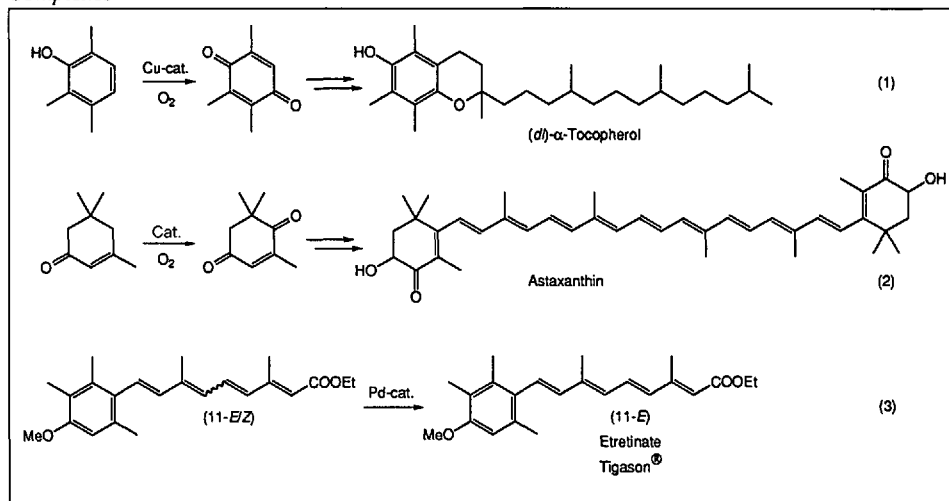
#### 4. Synthesis of Lazabemide: An Ideal Example of Synthesis Shortening by a Carbonylation Process

A Pd-catalyzed amidocarbonylation has been developed and is in use for the production of lazabemide [4], a monamine oxidase B inhibitor, which is currently in a late phase of clinical development as an anti-*Parkinson* medicine (Scheme 2). This example is a particularly striking one for the success of metal-complex catalysis in *synthesis shortening*: the original 8-step research synthesis [4a], which transiently had been shortened to a 4-step synthesis involving a Pd-catalyzed alkylation [4b] of commercially available 2,5-dichloropyridine, eventually was replaced by the one-step amidocarbonylation protocol [4c]. It is worth mentioning that in this process (as well as in the above-mentioned isomerization process) a metal-catalyzed transformation is being carried out in the final step, and consequently traces of the catalyst in the product had to be removed by appropriate work-up and purification procedures.

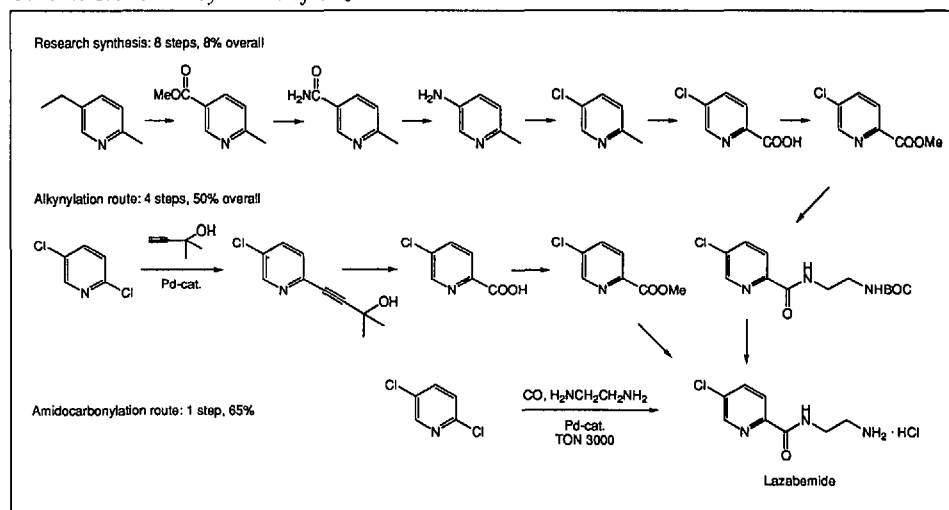
#### 5. Enantioselective Hydrogenation Processes as Replacements of Traditional Resolution Procedures

Pantothenic acid is being manufactured from (*R*)-pantolactone and  $\beta$ -alanine (Scheme 3). Most processes for (*R*)-pantolactone are based on resolution procedures, the resolution being carried out at the stage of the open-chain hydroxy-acid equivalent and the undesired stereoisomer being recycled by racemization. On the basis of precedent with the Rh(BPPM)Cl catalyst [5] an enantioselective hydrogenation process for the conversion of keto-pantolactone (obtained from racemic pantolactone by a gas-phase dehydrogenation [6]) to (*R*)-pantolactone was developed in our laboratories [7]. Catalyst tailoring and reaction optimization led to a highly efficient process with a Rh(*m*-TolPOPPM)-TFA catalyst; it afforded total turnover numbers (TON = moles of product/moles of catalyst) of 100 000 to 200 000, average turnover frequencies (TOF = moles of product/moles of catalyst and unit of time)

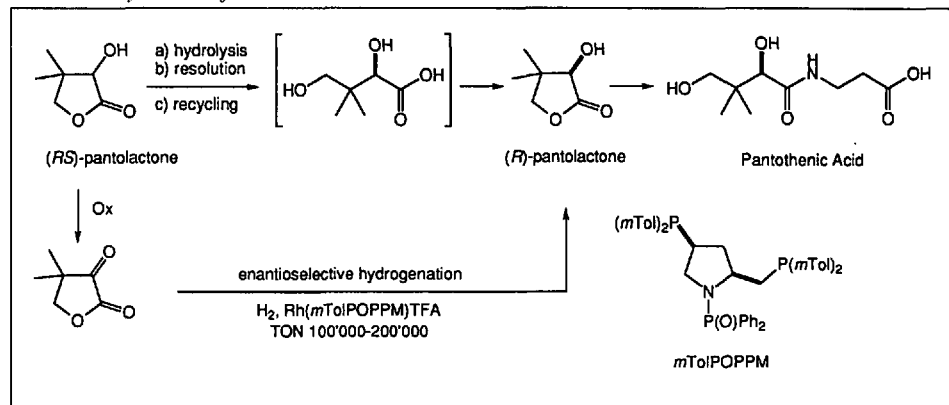
Scheme 1. Oxidation and Isomerization Processes Involving Homogeneous Catalysis with Metal Complexes



Scheme 2. A Short Synthesis of Lazabemide



Scheme 3. Synthesis of Pantothenic Acid



in the order of  $10 \text{ s}^{-1}$  and an enantioselectivity of 91% ee. Isolation by distillation and enantiomer enrichment by crystallization produced (*R*)-pantolactone of >99.9% ee. The almost racemic material from the mother liquor is recycled back into the oxidation step. This hydrogenation was successfully scaled-up and run in the pilot plant on a 200 kg batch scale. The process, therefore, fulfils all technical re-

quirements for plant implementation. It is important to note that in this, as well as in many other applications where enantiomer enrichment is possible, catalyst productivity and activity are more important to us than very high initial enantioselectivity.

Another example for replacing a resolution by an enantioselective hydrogenation was developed for the so-called (*S*)-phthaloyl acid, an intermediate for the

synthesis of our angiotensin converting enzyme inhibitor cilazapril [8], the active ingredient of *Inhibace*<sup>®</sup> (Scheme 4). The hydrogenation substrate, an  $\alpha,\beta$ -unsaturated acid of a new type containing an  $\alpha$ -hydrazino substituent, was simply prepared by the isomerization and hydrolysis of a  $\beta,\gamma$ -unsaturated ester intermediate from the current plant synthesis. Enantioselective hydrogenation of this substrate was achieved with very high productivity (TON 20 000–40 000) and enantioselectivity (95–99% ee) with a Ru(*p*-TolMeOBIPHEP)(OAc)<sub>2</sub> catalyst [9]. The process again was developed to a practical scale, ready

for piloting and implementation into the current plant process.

Still another example is concerned with the synthesis of the chiral so-called (*S*)-sulfoacid, a building block of various developmental renin inhibitors (Scheme 5) [10]. The highly enantioselective enzymatic ester resolution approach [11] shown in Scheme 5 proved eventually inferior in terms of costs to the enantioselective hydrogenation route [12]. Decisive for the cost advantage of the hydrogenation route proved the very inexpensive synthesis of the unsaturated acid through a *Baylis-Hillman* reaction. Cost of starting materials for

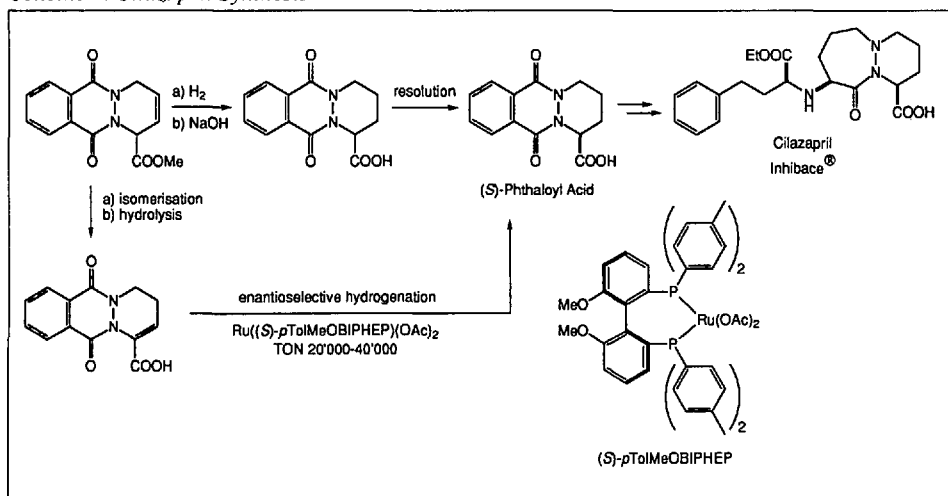
an asymmetric process is an aspect that must be always taken into consideration.

## 6. On the Enantioselective Hydrogenation of Nonconventional Substrates and on the Usefulness of Ligands and Catalyst Libraries

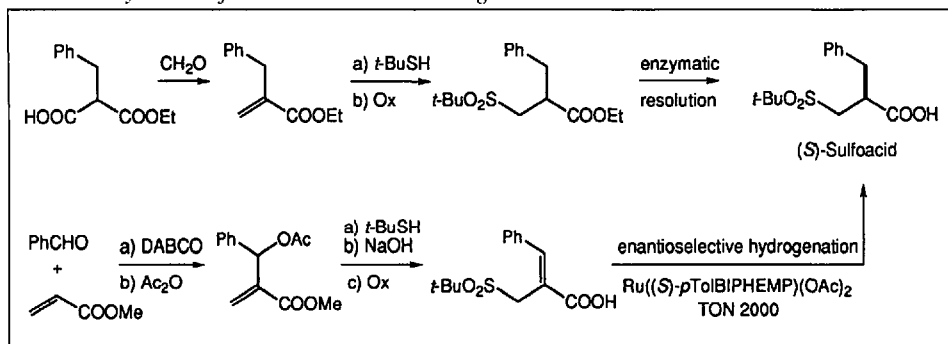
In the application of enantioselective hydrogenation, the catalysis process research chemist not only faces the task of developing economical processes for substrates of precisely defined structure (with no or only very little room to vary the substrate structure), but he often has to develop processes for substrates that do not belong to the standard structural classes known to be amenable to enantioselective hydrogenation. In such a situation, the only way to proceed quickly is to conduct a screening of catalysts from an existing library of metal complexes and chiral ligands. Preferably, *in situ* methods for the preparation of the metal complexes from a common precursor and chiral ligands can be applied [13]. An example of such a development is shown in Scheme 6. It relates to the enantioselective hydrogenation of an  $\alpha$ -pyrone unit to an optically active dihydropyrone. The dihydropyrone is an intermediate in the synthesis of tetrahydrolipstatin [14], the active ingredient of our developmental anti-obesity medicine *Xenical*<sup>®</sup>. It is noteworthy that the pyrone substrate has no possibility for chelate mode binding of the double bond with a transition-metal catalyst. Rh-catalysts led to nonselective mono- and dihydrogenation. Standard Ru-BINAP or Ru-BIPHEMP catalysts were of very low activity but showed moderate enantioselectivity. From a screening of over 50 chiral Ru catalysts, the bicationic Ru complex derived from the sterically encumbered 3,5-di-*t*-BuMeOBIPHEP ligand showed excellent regio- and enantioselectivity (> 97% dihydropyrone, up to 96% ee) [15]. Although the currently achieved TON of 1000 is still somewhat low, this example nicely demonstrates that solutions may be achievable also for nonconventional substrate types. It indicates also that the width of substrate types accessible for enantioselective hydrogenation may be much larger than previously thought.

Other examples have been elaborated in our laboratories where the usefulness of catalysts and ligand libraries became evident, too. The maintenance of such libraries is a very important aspect of our work. Currently a collection of over 250 ligands and derived metal complexes are available at *Roche*. Particular emphasis has been

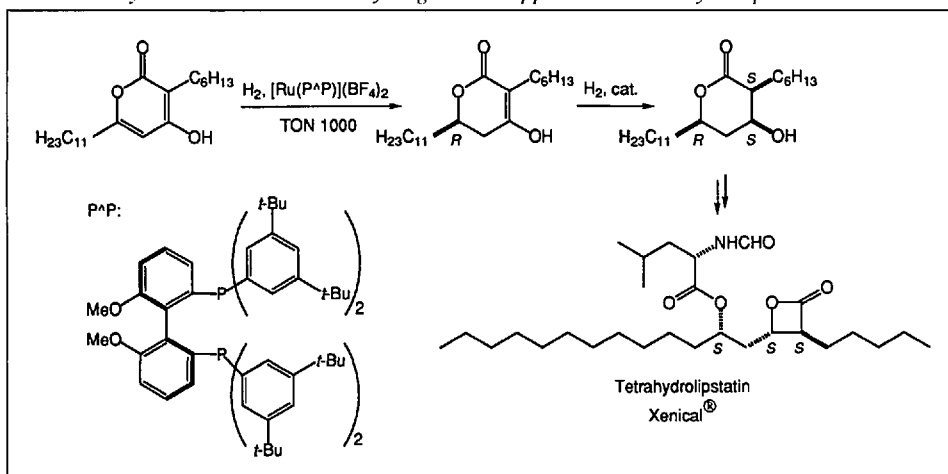
Scheme 4. *Cilazapril* Synthesis



Scheme 5. Synthesis of a Renin Inhibitor Building Block



Scheme 6. Pyrone Enantioselective Hydrogenation Approach to Tetrahydrolipstatin



given in the last years to establish ligand diversity within certain classes of diphosphine ligands, *e.g.* within the class of atropisomeric biphenyldiphosphines [16].

## 7. On the Requirement of High-Pressure Equipment

Discussions on the technical application of homogeneous catalysis, particularly on the application of enantioselective hydrogenation, often focus on the need of pressure equipment. Fortunately, such reactions often can be carried out at rather high concentrations. Thus, *e.g.*, in the pantolactone or the cilazapril examples, concentrations of 25 and 50%, respectively, have been achieved. Space/time yields consequently can be very high. Nonetheless, substantial autoclave volumes have to be built for larger-scale applications. While this is not an issue in the case of products with long life cycles, it can be more of a problem in case of pharmaceuticals with relatively small volumes and limited life cycles. For such cases, an obvious solution is to make available multi-purpose autoclave systems at a site particularly suited to such a task. An attractive variant is to build up such equipment in a way allowing continuous mode operations and thus reducing total reactor volume requirements, *e.g.* as a cascade autoclave system. Recently, such a system has been established on a laboratory scale [17]. In an actual application a 180 bar pressure continuous mode process has been demonstrated with this equipment.

## 8. Concluding Remarks and Outlook

What path will homogeneous catalysis with metal complexes take in our industrial environment? The ever increasing importance of metal-complex-catalyzed C/C-bond formation processes has already been mentioned. Particularly, *Heck*-type alkenylations, alkynylations, cross-couplings, and carbonylation reactions of various types (amido-, alkoxy-, hydroxycarbonylation, hydroformylation, and hydrocarboxylations) will gain in importance. Many of these processes will involve catalysis with Pd complexes. Fundamental research in metal-complex-catalyzed C/C-bond formation is an area actively pursued in academia and industry. It will lead to many new significant discoveries and applications.

Another very important area is enantioselective homogeneous catalysis for the production of enantiomerically pure inter-

mediates and products. As mentioned above, enantioselective hydrogenation of C=C, C=O, and C=N bonds is considered an area of particular significance. Hydrogen is not only the least expensive reductant, but hydrogenations are very frequently applicable in the synthesis of biologically active compounds. This is possibly because syntheses often start with building blocks of higher oxidation state, such as carbonyl-group-containing compounds. It is also important to note that enzymatic processes, while being very efficient and simple for hydrolytic kinetic resolutions of racemates, are more demanding to execute for double bond reductions due to the necessary requirement of co-factors, and they are particularly limited in scope in the area of C=C bond reduction. Therefore, enantioselective hydrogenation will become evermore important for such reductions.

The doors for the industrial application of enantioselective catalysis with metal complexes have been opened by the spectacular discoveries in the last two decades. Since fundamental research in this field is highly dynamic, many new discoveries can be expected in future. The further development of complex catalysts will be a focal point of such research. Capitalization on such progress by industry will and should inevitably follow.

I like to thank all colleagues who were originators and investigators of and/or contributors to the presented examples of homogeneous catalytic processes developed at *Roche*. Their names are quoted in the list of references. Special thanks go to *Emil A. Broger* who was leading the development of most of the enantioselective hydrogenation processes presented here.

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