

## F. Hoffmann-La Roche Ltd.

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# Catalysis in the Industrial Production of Pharmaceuticals and Fine Chemicals

Felix Roessler\*

**Abstract.** The history of catalysis at *Roche* and its present relevance for the company is described. The main focus is on catalytic hydrogenation, which serves as an example to show the historic background of catalysis at *Roche* and to demonstrate the importance of a transdisciplinary approach used in industry – in particular in the *Roche* group – for the design and development of catalytic processes. The article concludes with the statement that catalysis will maintain or even strengthen its position in fine chemicals production.

## 1. Introduction

The use of catalysis at *Roche* goes back to the 1930ies when the company developed syntheses for vitamins, and introduced ascorbic acid (1933), B1 (1936), B2 (1937), E (1938), K (1940), niacin (1942), panthenol (1944), B6 (1945), folic acid (1946), and A (1946) on the market. In 1939 *Roche* was already number one for the vitamins B1, C, and E. Catalysis gained importance when *Roche* further developed the syntheses for these products, which were based on mainly catalytic transformations. This development is closely linked with persons such as *Tadeusz Reichstein*, *Alexander Todd*, *Franz Bergel*, just to mention a few of them, and later by *Otto Isler* and the chemists in his group. Today, *Roche's* actual processes for the production of fine chemicals and, to a lesser degree also pharmaceuticals, are all based on reactions that are catalyzed by homogeneous or heterogeneous catalysts. Catalysts are used for economic and ecologic reasons or because reasonable alternatives do not exist. Thus, essentially all reaction steps in *Roche's* production of vitamins

such as tocopherol or ascorbic acid, that are produced on a large scale are catalyzed by homogeneous and heterogeneous catalysts. The most frequently used catalysts for the industrial production of fine chemicals and pharmaceuticals are acids or bases (both homogeneous and heterogeneous, *Brønsted* and *Lewis* type), transition metals, phase-transfer catalysts, and hydrogenation catalysts. In a typical synthesis pathway for the production of a fine chemical a very large portion (up to 50%) of all reaction steps are catalyzed by homogeneous or heterogeneous acids and bases and another 10–20% are catalytic hydrogenations. Homogeneous noble-metal catalysts (chiral and achiral types) are gaining importance and are on the way of being used also in production (for information on this area see the contribution of *R. Schmid* in this issue, p. 110).

## 2. Development of Catalytic Processes from an Industrial Point of View

The function of catalysis in industry is to contribute to the development of economic, ecologic, and safe processes. Unlike catalysis in academia, which normally deals with basic research and looks deeply into one singular aspect of catalysis in an isolated manner, applied catalysis in industry is part of a larger framework of disciplines that are needed to achieve such ideal processes. *Roche*, like other multina-

tional companies, therefore, holds centers of expertise in heterogeneous (particularly hydrogenation, dehydrogenation, solid acid/base catalysis, metal oxides) and homogeneous catalysis (particularly metal complexes, chiral catalysis) that support and closely interact internationally with research, development, and production. The development of a catalytic process from the laboratory to production scale does favorably not take place in clearly separated institutions, but rather in individual process-oriented teams of people from disciplines such as organic chemistry, catalysis, surface science, physical chemistry, and reaction engineering (*cf. Fig. 1*). Multiple interactions between the various actors is required on all levels of the development of a new process; the willingness of people to diversity and mobility is essential, and transdisciplinarity united in the same person is the ideal case.

Several tools are used to support research and development on all stages. On one hand all the established analytical methods are used to help interpreting the results of the experiments. On the other hand, with the ample availability of computers, the dimensions of theory and experiment have been supplemented by computing, modelling, and simulation in order to limit the number of experiments needed to achieve an optimum of the catalytic overall process. Simulation and modelling, are particularly useful on the reaction, reactor, and scale-up level.

## 3. Catalytic Hydrogenation and Dehydrogenation

### 3.1. History of Catalytic Hydrogenation and Its Present Importance for *Roche*

Catalytic hydrogenation and dehydrogenation have a long tradition in the area of fine chemicals production at *Roche*. No other reduction method has proved to be as versatile and industrially as important as catalytic hydrogenation. Catalytic hydrogenation as an important tool in the synthesis of fine chemicals at *Roche* was used already in the early 1940ies, when a laboratory for carrying out reactions under elevated pressure was built up in Basel. It was in the 1960ies, when *Herbert Lindlar* introduced his famous '*Lindlar* catalyst' for the selective transformation of alkynes to alkenes. This invention was a decisive factor in the development of economic

\*Correspondence: Dr. F. Roessler  
Hochdruckzentrum Kaiseraugst  
F. Hoffmann-La Roche AG  
CH-4070 Basel

processes for the production of vitamins such as A and E and carotenoids. It is not exaggerated saying that Lindlar's catalyst represented a strategic key method for the production of these products. The so-called HLR (hydrogenation laboratory Roche) was also of strategic importance in the development of production processes for vitamin C, where Roche developed a highly selective process for the transformation of glucose to sorbitol, the first step in Reichstein's vitamin C synthesis. When Roche acquired the Givaudan group in 1963, the tool of catalytic hydrogenation proved of equal importance also in the flavours business, as was the case also when Roche was active in agrochemistry (Maag group), not to mention all the pharmaceuticals whose synthetic pathways rely on selective catalytic hydrogenations.

The hydrogenation laboratories of Roche have in recent times further developed to a center for heterogeneous catalysis and reactions in multiphase systems. Thanks to a favorable cost/benefit ratio of the HLR's developments, ca. 60 Mio. CHF were invested within the last 25 years for new HLR buildings, infrastructure, and equipment. In the same time the number of HLR employees has increased by a factor of three. In 1989 the hydrogenation laboratory moved to its new site in Kaiseraugst. Although operated by the vitamin and fine chemicals division of Roche, the HLR carries out R+D for the whole Roche group (i.e. also pharmaceuticals and flavors/fragrances) on the basis of R+D contracts. Thanks to the new communication tools, Roche R+D groups from all over the world make regular use of the HLR's expertise in heterogeneous catalysis.

In addition to contract R+D, the HLR makes also some efforts in areas of rather basic research. Among other topics the influence of supercritical fluids on heterogeneous catalysis is presently investigated and a number of slurry-batch hydrogenations are further developed to continuous processes.

Today an average of 10–20% of all reaction steps in the synthesis of vitamins (e.g. even 30% in the Roche Vitamin E synthesis), pharmaceuticals and fine chemicals that are carried out on a production scale at Roche are catalytic hydrogenations. Many of these reactions are very selective with almost quantitative yield. As the metals are recovered from the spent catalysts, and organic by-products can be burnt after separation, essentially no non-combustible waste is produced. The economy of hydrogenation processes is normally favorable compared with other reduction methods such as hydrides or met-

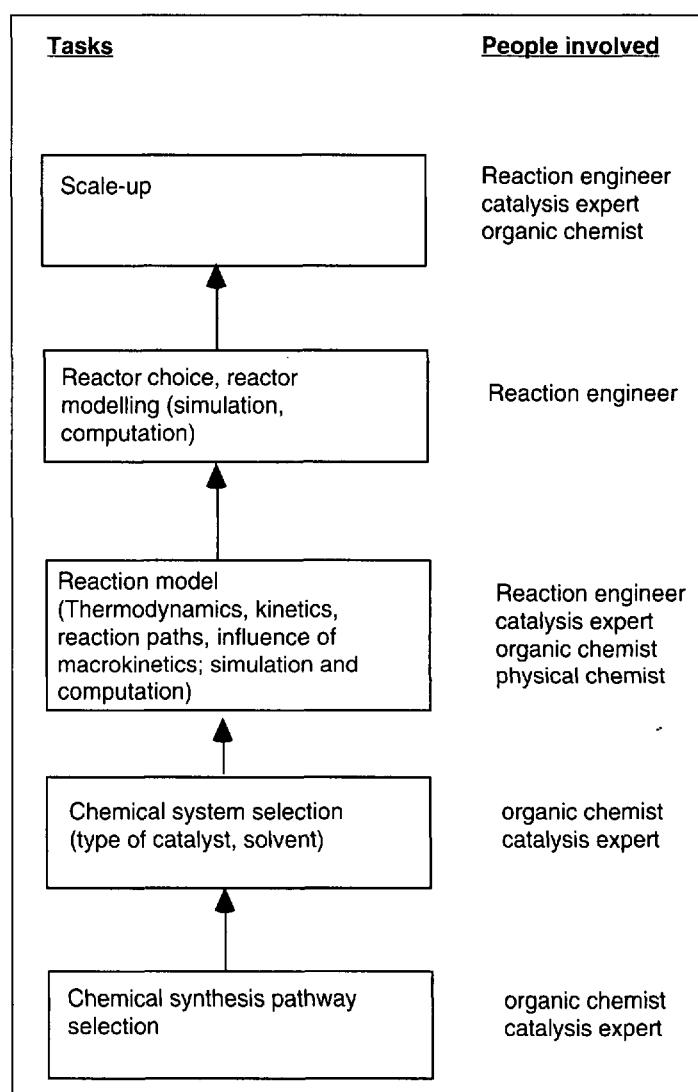


Fig. 1. Stages in the development of catalytic processes

als, as the most frequently used noble metals can be recovered from the spent catalysts almost quantitatively.

### 3.2. Hydrogenation Processes at Roche

Roche hydrogenation processes that run on a production scale are carried out with catalyst/substrate ratios of less than 1/1000 to even 1/1. For high catalyst loadings the catalyst is of course repeatedly used in many cycles. As in many cases the substrates to be hydrogenated are costly or are multifunctional molecules, the requirements in terms of chemo-, regio-, and stereoselectivity are normally high; i.e. the hydrogenations are frequently carried out under mild conditions and often solvents are used even for liquid substrates. Pressures of 1–40 bar are the normal case. Most processes are carried out batchwise using powder catalysts in stirred tank or ventury type loop reactors. Reactor sizes are up to 10–20 m<sup>3</sup>.

### 3.3. Catalysts Used at Roche

Catalysts most frequently used at Roche are based on palladium on various

supports, followed by nickel catalysts (mostly Raney type), but also platinum, rhodium, and ruthenium catalysts are used in production. A large variety of hydrogenation catalysts is supplied by a number of catalyst manufacturers. Most catalyst manufacturers are active in the noble-metal business; thus the supply and the recycling of the catalysts is guaranteed by the same company. Metal catalysts that are used on an industrial scale are normally supported catalysts for economic, selectivity, and stability reasons. The catalysts used vary in the chemical composition of the support, the metal content, the metal location on the support, the porosity, the metal area, the metal-crystallite size; etc.

For all processes the ideal catalyst has to be found, i.e. the catalyst which has high activity, selectivity, lifetime, stability, filterability, and favorable economics. In order to achieve this goal, a close collaboration between catalyst manufacturer and catalyst user is often practised when it comes to the development of a proper catalyst for a certain individual process.

### 3.4. How Roche Develops a Catalytic Hydrogenation Process

As many aspects of heterogeneous catalytic hydrogenations are not fully understood or cannot easily be quantified, a purely rational approach in the planning and optimization of a selective transformation is not possible. The methods which are used for the prediction and planning of an appropriate catalytic system for a specific transformation, therefore, reach from theoretical considerations, literature and patent retrieval, empirical correlations, experience, intuition to even trial and error. Nevertheless, a successful approach in the planning of experiments starts with exploratory experiments. To carry out these experiments, a unique system allowing a rapid catalyst/solvent screening at conditions between 1 and 300 bar pressure and room temperature to 300° on a very small scale (1–20 ml liquid volume) has been developed by the HLR. Then, in a second step a specific strategy to improve the selectivity of the desired reaction can be

developed. These experiments are favorably carried out in the kinetic region to find out reaction pathways and causes for undesired side reactions. Here again the experiments are carried out in laboratory reactors that are specially suited (*i.e.* sampling devices for taking very small samples during reactions under pressure, exact temperature control, stirrers that guarantee high gas/liquid and liquid/solid interface if desired, catalyst addition devices, *etc.*) to perform the experiments needed for a safe scale-up.

As catalytic hydrogenation in the liquid phase is a three-phase process, all the aspects of such processes must be investigated, *i.e.* it must be clearly differentiated between physical (transport aspects) and chemical aspects (adsorption, reaction, desorption) of the process. Both, chemistry and physics are integral parts of the heterogeneous process and, therefore, determining factors for rate and selectivity. The *Table* gives an idea of the many parameters that have to be investigated for

their influence on selectivity and rate of catalytic hydrogenations.

From a dimensional point of view of a catalytic process, the chemical reaction on the surface (Å scale) is studied first, if such an approach is feasible. The next step is the integration over the catalyst (µm to mm scale), which takes diffusion phenomena into consideration. Then follows the integration over the reactor (meter scale). Finally the process is integrated over the plant (*Fig. 2*).

Aspects that have to be considered and studied in the sequence given in *Fig. 2* are physicochemical properties of the reaction mixture (heat capacity, diffusion coefficients, viscosities, thermal conductivity, *etc.*), chemical reaction data (micro- and macrokinetics, reaction orders, reaction enthalpy, activation energy, catalyst effectiveness), catalyst properties (activity, selectivity, life time, location of the active component, physical strength, porosity, *etc.*), reactor (type, diameter, mixing, heating/cooling efficiency, *etc.*) and

Table. Influence of Variables on Chemistry and Physics of the Hydrogenation

Parameters/tools	Influence on homogeneous chemical processes	Influence on surface chemistry (adsorption, desorption, surface reaction)	Influence on physics (mass and heat transport)
Metal	+ <sup>1)</sup>	+	-
Chemical composition of the support	+ <sup>2)</sup>	+	-
Catalyst particle size	-	-	+
Morphology of catalyst particle	-	-	+
Porosity of catalyst, location of the active centers	+ <sup>3)</sup>	-	+
Size of active centers, metal particle size of supported metal catalysts	-	+	-
Catalyst preparation method	+ <sup>4)</sup>	+	+ <sup>5)</sup>
Solvent	+	+	+
Acidity of reaction medium	+	+	-
Modifiers	+ <sup>6)</sup>	+	-
Temperature	+	+	+
Hydrogen pressure	-	+	+
Substrate concentration	+	+	+
Ratio of catalyst to substrate	+ <sup>7)</sup>	-	+ <sup>8)</sup>
Agitation/mixing	-	-	+ <sup>8)</sup>

<sup>1)</sup> Dissolved metal; <sup>2)</sup> if support is dissolved; <sup>3)</sup> concentration in pores is different from concentration in bulk solution; <sup>4)</sup> by residual impurities on the catalyst (*e.g.* acids, bases); <sup>5)</sup> *via* porosity, metal location; <sup>6)</sup> if dissolved modifier causes side reactions; <sup>7)</sup> hydrogenation is speeded up compared with homogeneous side reaction; <sup>8)</sup> if transition from kinetic to transport-controlled regime.

control factors (temperature of liquid feed, backmixing, dispersion, catalyst wetting, residence-time distribution, etc.). All these aspects demonstrate the importance of the aforementioned interdisciplinary approach in order to succeed with the best possible catalytic process.

### 3.5. A Recent Example

The recently developed process for the production of the new *Roche* HIV-protease inhibitor Saquinavir (Ro 31-8959) demonstrates nicely, that using the described integrated approach high selectivities can even be achieved in complex catalytic hydrogenations. The production of the key intermediate 'isomer B' in the multistep synthesis of Saquinavir requires the chemo- and diastereoselective hydrogenation of tetrahydroamide **1**; in addition, racemization of the optically pure **1** has to be prevented (see *Scheme*). The process has been developed to such a degree, that large amounts of the intermediate 'isomer B' can be made with up to 94% selectivity at very competitive transformation costs.

## 4. Outlook

Catalysis will certainly maintain its importance in the industrial production of fine chemicals and pharmaceuticals. There are mainly two directions, into which applied catalysis might move and thereby even strengthen its position in fine chemicals production.

One direction is the industrial application of new catalysts such as homogeneous metal complexes which are well established on the laboratory scale. These catalysts are essentially new synthetic tools that enable the organic chemist to develop new and often more straightforward synthesis pathways. There are various possibilities how these catalysts can be improved in terms of applicability for industrial processes as *e.g.* by improving their recuperability or separability by making them water-soluble or by immobilization by various techniques.

The other direction is the improvement of running plant processes. Many catalytic processes carried out on a production scale have been developed ten or twenty years ago. Some of them are essentially scale-ups of preparative laboratory procedures without taking into account all the aforementioned important aspects of catalysis and reaction engineering. These processes are no longer state of the art from today's view and, therefore, have strong potential for improvement.

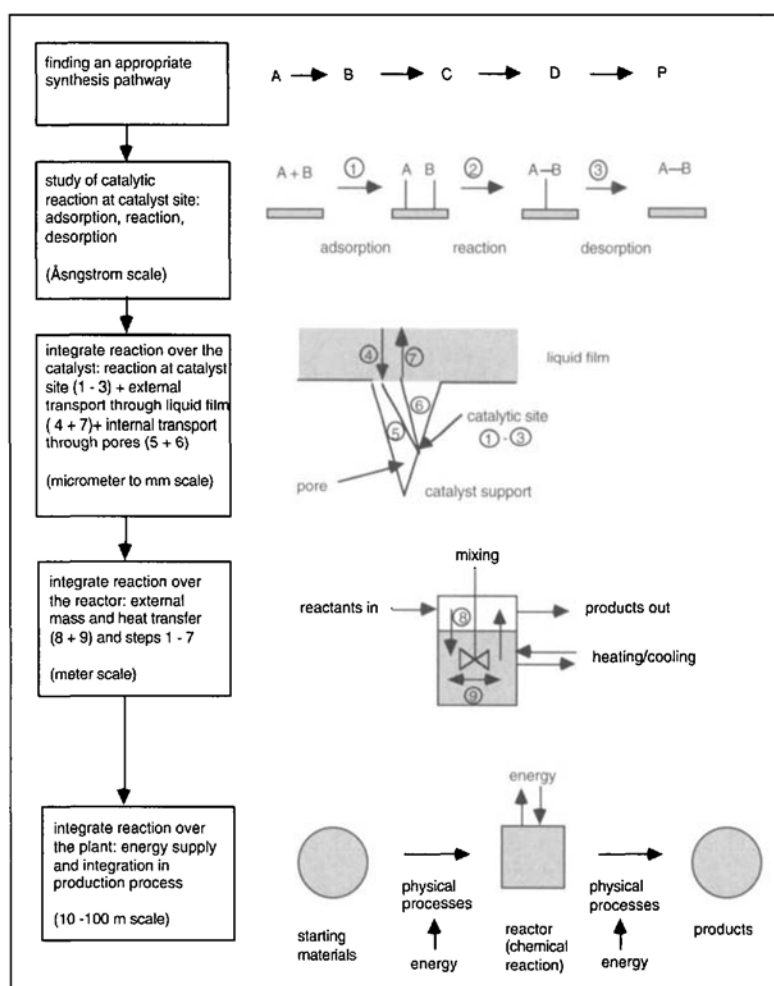
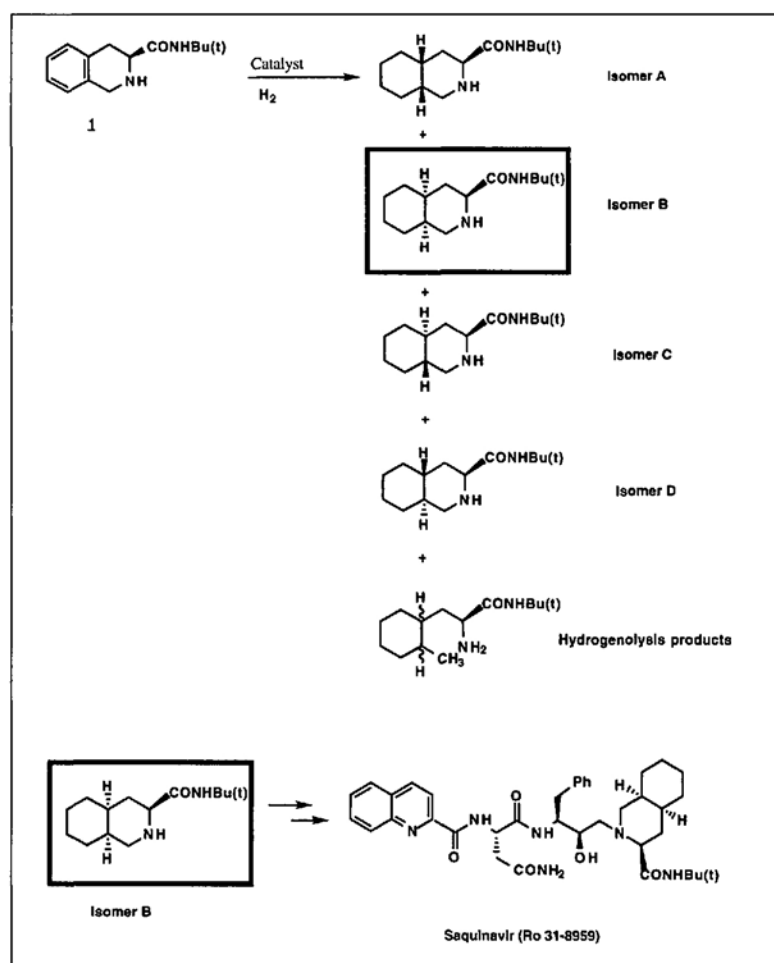


Fig. 2. Stages in the development of a three-phase heterogeneous catalytic process



Scheme. Synthesis of Roche Protease Inhibitor Saquinavir (hydrogenation step)