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# Heterogeneous catalysis for fine chemicals production

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**Abstract**

The role of catalysis for the production of fine chemicals is reviewed. The following topics are discussed on a general level: Characteristics of the manufacture of fine chemicals, opportunities opened up by catalysis for improving production processes, critical factors for the application of catalysts and the tools that are available to the catalytic chemist to find a suitable catalyst for a specific transformation. A short outlook on future developments is also presented. © 2000 Elsevier Science B.V. All rights reserved.

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## 1. Background

Traditionally, heterogeneous catalysis is associated with the production of petro- and bulk chemicals whereas fine and specialty chemicals are produced predominantly with non-catalytic organic synthesis. While these statements are still basically correct, there is a growing list of examples demonstrating that heterogeneous catalysis is also an opportunity for better production processes for more complex agrochemicals and pharmaceuticals. In the first part of this treatise, the characteristics of fine chemicals manufacture and the potential of catalysis for improving existing and future processes will be described (see Table 1, [1]). In the second part, the (many) difficulties and unsolved problems for routine applications of heterogeneous catalysis together with possible solutions are discussed. Finally, some conclusions and a short outlook are presented.

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## 2. Problems and opportunities for the application of heterogeneous catalysis in fine chemicals manufacture

### 2.1. Characteristics of the manufacture of fine chemicals

The manufacture of fine chemicals and especially of pharmaceuticals and agrochemicals can be characterized as follows (typical numbers are given in parentheses):

- Rather complex molecules (isomers, stereochemistry, several functional groups) with limited thermal stability.
- Production via multistep syntheses (5–10 steps for pharmaceuticals and 3–7 for agrochemicals) with short product lives (often <20 years). Usually classical organic reactions, catalysis as exception.
- Production usually in solution, at ambient pressure and low to medium temperature in relatively small (500 l–10 $m^3$) multipurpose batch equipment.
- Relatively small-scale products (1–1000 t per year for pharmaceuticals, 500–10 000 t per year for agrochemicals).


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Table 1
Important characteristics of fine chemicals manufacture

| Molecules | Synthesis | Requirements for catalysis |
|---|---|---|
| Complex (isomers, stereochemistry, etc.) | Multistep procedures | High chemo-, regio- and stereoselectivities |
| Several functional groups | Classical organic reactions, catalysis as exception | Fit of catalytic step into overall synthesis scheme |
| Limited thermal stability | Batch processes in solution | Good activity at low *T* |
| Moderate to high value | Multipurpose equipment | Simple technology |
| Low volume (1–10 000 t per year) | Short development time | Readily available commercial catalysts |

- High purity requirements (usually >99% and <10 ppm metal residue and ee>98% in pharmaceuticals).
- High value added and therefore tolerant to higher process cost (especially for very effective, small-scale products).
- Short development time for the production process (<few months to 1–2 years) since time to market affects the profitability of the product.
- Typically relatively high *E*-factor [2] with large amounts of unwanted products (solvents, salts, by-products, etc., that must be eventually recycled or discarded).

### 2.2. What can (heterogeneous) catalysis contribute?

Catalysis can contribute on two levels to the clean production of fine chemicals. First, by providing improved production processes, and second, by helping to remove or transform unwanted or even toxic by-products. Here, we will only address how the application of catalytic methods can lead to a better, more environmental friendly and often cheaper production of fine chemicals. One can distinguish the following cases:

Transformations made possible by heterogeneous catalysts:

- Hydrogenation of aromatic systems.
- Metathesis of unfunctionalized olefins.
- Rosenmund reduction of aryl chlorides.
- Selective hydrogenation of C≡C to *cis*-olefins.

Combining several transformations in one step:

- Reductive alkylation of amines with carbonyl compounds (imine not isolated).
- Hydrogenation–acylation of nitroarenes to acylanilines.
- Direct alkylation of amines with alcohols via a dehydrogenation–condensation–hydrogenation sequence.

Replacing toxic or problematic reagents (and reactants):

- Alkylation of amines or aromatics with alcohols instead of alkyl halides (reduction of salt production).
- Use of $H_2$ instead of metals, metal hydrides or sulfides.
- Use of $H_2O_2$ or $O_2$ instead of metal oxides or peracids.
- Solid acids and bases to replace soluble ones.

### 2.3. Critical factors for the application of heterogeneous catalysts

An impressively large number of highly selective catalytic transformations is recorded in the literature that in principle can be applied to the synthesis of fine chemicals. However, quite many prerequisites must be fulfilled in order to render a catalytic process technically viable and to really profit from the opportunities described above. In our experience, there are a few key problems when applying heterogeneous catalysis to the manufacture of fine chemicals that have no generally applicable solution, some of these points are further described below:

- Insufficient catalyst performance (selectivity, activity, productivity, stability) of catalysts developed in academic research.
- Substrate specificity of highly selective catalysts leading to lack of predictability and making synthesis planning very difficult.
- Lack of time (and money) to find a suitable, commercially available catalyst.
- High demands on the purity of starting materials and control of reaction conditions.

#### 2.3.1. Catalyst performance

The *selectivity* of a catalyst (chemo-, regio-, stereo- and enantioselectivities) plays a dominant role for the synthesis of fine chemicals. Due to often high cost of starting materials and intermediates as well as of separation steps, selectivities >95% are usually required to make a catalytic method attractive. The catalyst *productivity*, given as turnover number (ton) or as substrate/catalyst ratio (s/c), determines catalyst costs, the catalyst *activity* (turnover frequency, tof ($h^{-1}$)), affects the production capacity. For ton and tof, it is more difficult to give general numbers because both catalyst prices and the value added by the catalytic transformation play an important role.

#### 2.3.2. Substrate specificity

Catalytic methods are often more substrate specific than stoichiometric ones, i.e., even small changes of the structure of the starting material can strongly affect the catalyst performance of a given catalyst. This is especially true for highly optimized stereo- and enantioselective catalysts thereby leading to a low predictability for new substrates. This fact renders synthesis planning difficult for the synthetic chemist who by definition must be a generalist and often does not know the scope and limitations of catalytic methodologies. In our experience, catalytic methods are usually abandoned if they do not succeed almost at first try, because development time and costs for fine chemicals are limited.

#### 2.3.3. Commercial availability of catalysts

This a major problem for products where relatively small amounts of a heterogeneous catalyst are needed — usually not enough to make it worthwhile for a catalyst manufacturer to develop the tailor-made catalyst that might be required for good performance. Heterogeneous catalysts cannot be characterized on a molecular level and it is well known that even small variations in the preparation procedure or impurities can alter significantly the structural and chemical properties of a heterogeneous catalyst. Therefore, reproducible catalyst performance requires reproducible catalyst preparation methods and this needs special expertise.

#### 2.3.4. Practical problems

Most catalytic processes are sensitive to the presence of impurities that can act as poisons or can modify the selectivity of a catalyst. This is due to the fact that the catalyst is present in very small concentration and that the active centers are very reactive towards all kinds of species and reagents. The quality of the starting material as well as of the reagents (solvent, gasses, etc.) is therefore absolutely crucial.

Catalyst separation from the reaction mixture is a problem that has to be addressed for every catalytic system. Solid catalysts can be usually separated from the reaction mixture by simple filtration. This makes the work and isolation of the desired product easier and is also the most obvious advantage of a heterogeneous catalyst. However, leaching of the active species such as noble metals can contaminate products and require an expensive purification.

### 2.4. The toolbox of heterogeneous catalysis

In the following section, the tools are sketched that are available for developing heterogeneous catalysts in order to make a desired transformation technically feasible. For this endeavor, the example of metallic catalysts that are by far the most widely applied catalysts in the manufacture of fine chemical will be used.

#### 2.4.1. Design parameters for heterogeneous catalytic systems [3]

Of the many parameters of a heterogeneous metallic catalyst that affect its catalytic performance, the following are the most important ones: type of metal (most often used are Pd, Pt, Ni, Cu, Rh, Ru, bimetallic catalysts are also a possibility); type of catalyst (supported, powder, skeletal); metal loading of supported catalysts; type of support (active carbon, alumina, silica). Important parameters for the active metal are the surface area, the dispersion (typically only 10–60% of the metal atoms are exposed), the size of the crystallites (typically in the range 20–200 Å), the location in the pores of the support and oxidation state (reduced or unreduced). Important support parameters are the particle size (for slurry catalysts typically 1–100 μm), the surface area (typically in the range of 100–1500 $m^2/g$), the pore structure (pore volume, pore size distribution) and acid–base properties.

Many types of heterogeneous catalysts are now available on a commercial basis and several catalyst producers offer customized catalysts where some of the above parameters have been adjusted to a specific transformation. In our experience, such an adjustment can only be carried out in a close collaboration with a catalyst producer specialized in catalyst applications for the fine chemical industry.

#### *2.4.2. Catalyst modifiers and promoters*

In the cases where a commercially available catalyst lacks a desired property or selectivity, the addition of a modifier is an interesting option. Both organic molecules (e.g. amines, chiral modifiers such as cinchona alkaloids or tartaric acid) or inorganic salts/metals are known for this purpose. The modifier can either be added to the catalysts before it is introduced into the reaction (often done with inorganic compounds) or added directly to the reaction mixture as process modifier. Factors that may be influenced are catalyst selectivity, activity, reduction of intermediate/side product formation and catalyst recovery.

In our experience, this option is a very promising one for the solution of difficult selectivity problems, but requires a lot of expertise by the development chemist that is usually available only in specialized catalysis groups.

#### *2.4.3. Reaction conditions*

The catalyst performance can be optimized by choosing a suitable reaction system and the proper reaction conditions. Important parameters are the solvent, the temperature, in case of hydrogenation the hydrogen pressure, the concentration of the substrate and the catalyst, and process modifiers. Very often, the choice of the solvent is the most important of these parameters. The optimal solvent can improve catalyst performance. Furthermore, the separation of the catalyst, and if necessary, of the undesired enantiomer or racemate can be facilitated by the proper solvent system (see below). Last but not the least, the solvent also has to fit into the sequence of reactions.

#### *2.4.4. Reaction control (endpoint)*

Monitoring the progress of a catalytic reaction can be difficult, especially if the catalyst is air-sensitive or the reaction carried out in an autoclave. Nevertheless, in the laboratory it is usually possible to find a suitable solution. This is by no means the case under the conditions of large-scale production. There, one has to very often rely on relatively inaccurate measurements or defined reaction times. On-line monitoring of substrate and/or product concentrations could be of great help, especially for reaction where a precise end point control is crucial for high yield and/or selectivity. Here, ATR- and other in-line probes can sometimes be very useful for on-line spectroscopy.

## 3. Conclusions and outlook

In the preceding sections, it was shown that how catalysis can help to optimize existing processes or to open up new syntheses. Illustrative examples performed in the laboratories of Ciba-Geigy/Novartis/Solvias [1] can be found in a recent review [1]. Despite the problems detailed in Section 2, we are convinced that the application of catalytic methods for the production of fine chemicals will increase in the coming years. It is clear, however, that due to the rather conservative nature of most people involved in applying chemical technology, one should not expect a radical change. Some new developments already being described in the literature might help to accelerate the rate of application. In addition to the more traditional approaches, the following new trends are now discernible that should help to address some of the most pressing problems:

- Automated high through-put screening of catalysts and reaction conditions will decrease the time required to find a suitable catalytic system for any desired transformation.
- More readily accessible catalyst families (homogeneous, heterogeneous, enzymes) with tunable properties and well-defined scope and limitations will help to make the design and planning of synthetic routes more reliable.
- In situ process control and improved (micro) analytical techniques will lead to higher yields and less side products.
- Specialized (small) companies offering catalyst and process development will make up-to-date catalyst

[1] Formerly part of the Scientific Services of Novartis. Since 1 October 1999, Solvias is an independent service company in the areas of chemical, physical and biological analytics and synthesis and catalysis (www.solvias.com).

know-how and expertise accessible to research and development departments in the fine chemicals industry.

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