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Enantioselective catalysis in fine chemicals production

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The application of enantioselective catalysis to the fine chemicals industry has great potential both from economic and ecological points of view, but to date has not been widely implemented on a technical scale. The author hopes that the award of the 2001 Chemistry Nobel Prize in this field will give the necessary impetus to future applications.

Introduction

While there is no generally accepted definition of a fine chemical, in this article the definition schematically depicted in Fig. 1 will be used: 'Building blocks and performance molecules with several functional groups (FG), many possible isomers and an often intricate stereochemistry'. Compared to basic chemicals, fine chemicals are relatively small-scale but high-value products with high purity requirements, traditionally produced *via* multistep non-catalytic syntheses in batch equipment. For pharmaceuticals in particular, the time for development of the production process is often very short since 'time to market' can significantly affect the profitability of a new drug. Owing to a growing emphasis on production cost and waste minimisation, even for high-value life science chemicals, there has been an increase in the application of catalytic methods which has been promoted by the development of corresponding technologies.

While it has long been known that the biological activity of the two enantiomers ('hands', Fig. 2) of a chiral compound can differ considerably, it is only in the last two decades that synthetic chiral pharmaceuticals and vitamins, and agrochemicals, as well as flavours and fragrances have been produced systematically as enantiomerically pure compounds. The main reasons for this are the generally superior performance of the

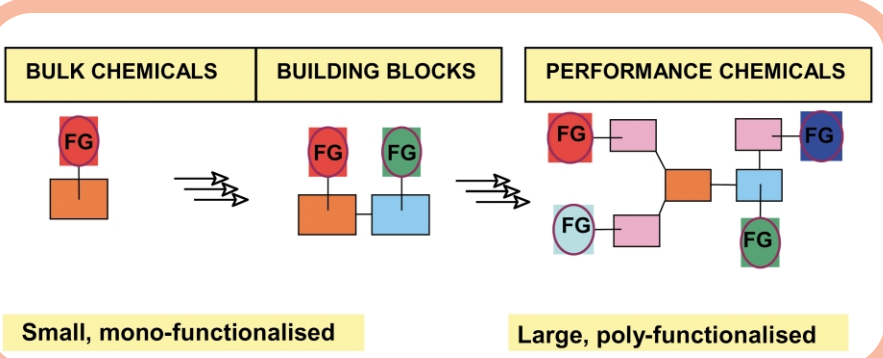

Fig 1. Schematic representation of bulk and fine chemicals.

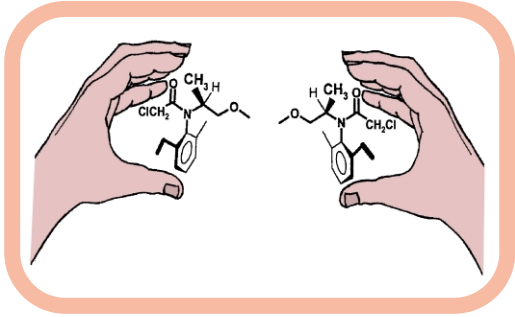

Fig 2. The handedness of the chiral herbicide metolachlor.

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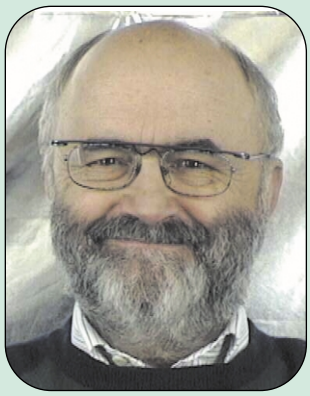

Following a Ph.D. at ETH Zürich, Switzerland and a Post-doctoral fellowships at the University of Chicago, Harvard University, USA and Monsanto Research, Zürich, Switzerland, Dr Blaser held various positions at Ciba-Geigy (subsequently Novartis) in Basel, Switzerland. He was Head of Process Development, Catalysis and Synthesis Services (1978–1986), Head of Catalysis Research, Catalysis and Synthesis Services (1986–1997) and Co-Director of Catalysis and Synthesis Services (1997–1999). Since 1999 he has been an executive director at Solvias AG, founded as a spin-off from the Novartis Group. This new company offers scientific services to customers in the areas of pharmaceuticals, agrochemicals, fine chemicals and nutrition.

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pure enantiomers and—especially for pharmaceuticals—evolving regulation which demands the evaluation of both enantiomers before approval. Today, asymmetric synthesis, enantioselective catalysis, and single isomer drugs are central topics for the life science industries and the economical enantioselective synthesis of chiral chemicals has become a major goal.

Preparative methods for enantiopure molecules

Four general approaches for producing enantiopure (enantiomeric excess or ee >99%) or enantio-enriched compounds have evolved (see Table 1 for a comparison of the different methodologies and an assessment concerning their suitability for industrial applications).

Separation of enantiomers via classical resolution, *i.e.*, crystallisation of diastereomeric adducts, still accounts for the production of more than 50% of enantioenriched drugs. An emerging technology is separation by chiral high-performance liquid chromatography (HPLC) using moving simulated bed technology. While crystallisation of diastereomeric adducts can be applied on any scale, separation *via* HPLC is probably most important in the early phase of product development and is restricted to small-scale (100 kg to tonnes), high-value products. In both cases, large amounts of solvents have to be handled, and of course at least 50% of the material with the wrong absolute configuration has to be either recycled or discarded.

The *chiral pool approach* uses chiral building blocks originating from natural products for the construction of the final molecule. This approach is very often used in the early phases of drug development but, depending on the commercial availability of the starting material, it can also be used for large-scale products. Because natural products very often (but not always!) have high enantiomeric purity, no further enrichment is usually necessary.

Enantioselective syntheses are performed with the help of covalently bound chiral auxiliaries (often from the chiral pool). These are not incorporated in the target molecule but are removed after the stereogenic centres have been established and must be either recycled or discarded.

In many respects the most elegant approach is *enantioselective catalysis*, where prochiral starting materials are transformed to enantiomerically pure products with the help of chiral catalysts. Effective catalysts are either man-made (chemical catalysis) or can be of natural origin (biocatalysis). In this discussion we will focus on the application of chemical catalysts but the use of enzymatic and microbial transformations raises similar opportunities and concerns. An important issue is often the time needed to find and develop an efficient biocatalyst, especially when the starting material is not a very close analogue to the natural substrate. In addition, product isolation can be a serious problem, since reactions are often carried out in a rather dilute aqueous solution. But as several recent publications convincingly show, these hurdles can be overcome.

Table 1 Scope and limitations of major production methods for enriched chiral molecules.

	Chemical catalysis	Biocatalysis	Chiral pool	Crystallisation	HPLC
Enantioselectivity	1–2	1	1	1–2	1–2
Activity and productivity	1–2	2–3	—	—	—
Availability and diversity	1–2	2–3	2	1	1
Substrate specificity	2	3	1	1	2
Work-up and ecology	1–2	2–3	2	2	2
Development time and effort	2	3	1	1–2	1
Application in the lab	2	3	1	1–2	1
Application in development	1-2	2	1	2	2
Small-scale production	1–2	1–2	1	1–2	2
Large-scale production	1	2	2–3	1–2	3

Rating: 1: high scope, 2: medium scope, some problems, 3: low scope, often problematic.

The potential of enantioselective catalysis

Over the years, three types of enantioselective catalysts have proven to be synthetically useful. The most versatile ones are *homogeneous metal complexes* with chiral, usually bidentate, ligands with a chiral backbone carrying two coordinating heteroatoms. For noble metals, especially Rh, Pd, Ru, Ir and Os, these are tertiary P or N atoms; for the metals such as Ti, B, Zn, Co, Mn or Cu, ligands with coordinating O or N atoms are preferred. This methodology has just received its due recognition in the 2001 Nobel Prize to W. S. Knowles and R. Noyori for enantioselective hydrogenation and to K. B. Sharpless for enantioselective oxidation catalysis (Fig. 3).[1] Also useful for synthetic application are *heterogeneous metallic catalysts*, modified with chiral auxiliaries, and finally there is a current revival of the use of chiral soluble *organic bases or acids*. Less easy to apply are chiral polymeric and gel-type materials, phase-transfer catalysts or immobilized complexes.

As shown in Table 2, very considerable efforts both in academia and in industry have led to a wide variety of catalytic transformations with ee′s often reaching >99% .[2] However, many of the very selective catalysts have been developed for reactions with selected model substrates but not (yet) tested on ‘real world’

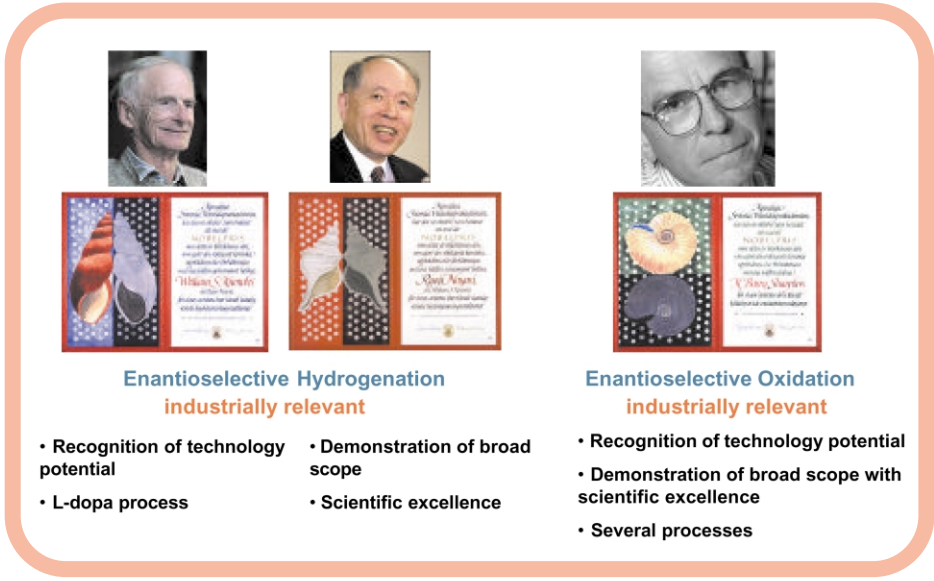

Fig 3. Enantioselective catalysis. The Chemistry Nobel Prize 2001.

Table 2 State of the art and assessment of important enantioselective catalytic transformations.[3]

Transformation	ee[a]	potential[b]/synthetic scope/ton, tof[c]
Hydrogenation of properly functionalized C=C, C=O and C=N groups	90–99	high/broad/good to high
Epoxidation of C=C, kinetic resolution of epoxides	80–99	medium/medium/low to medium
Dihydroxylation of C=C	85–95	medium/medium/low to medium
Hydroformylation, hydrosilylation and hydroboration of C=C	85–95	low/narrow/very low to medium
Michael addition and (hetero) Diels–Alder reactions	85–95	low/narrow/very low to medium
Addition to RCHO (aldol, cyanohydrin)	90–95	low to medium/broad/very low
Cross coupling, allylic substitution, cyclopropanation	90–99	low/narrow/low to medium

[a] For 'suitable' substrate and optimal catalyst. [b] Potential for industrial application. [c] Ton, turnover number, tof, turnover frequency.

molecules. In addition, for many catalysts little information is available on catalyst activity, productivity or functional group tolerance making the assessment of their industrial potential difficult.

Existing industrial processes (production, pilot, bench-scale)

Despite this dramatic progress in the scientific domain with literally hundreds of catalytic transformations of very high enantioselectivity and the recognition of the importance of enantioselective catalysis, a recent survey has revealed that relatively few enantioselective catalytic reactions are used on an industrial scale today as summarized in Table 3.[4]

An analysis of the processes listed in Table 3 shows that hydrogenation of C=C and C=O is by far the predominant transformation applied for industrial processes, followed by epoxidation and dihydroxylation reactions. On the one hand, this is due to the broad scope of catalytic hydrogenation and on the other hand it could be attributed to the early success of Knowles with the l-dopa process, because for many years most academic and industrial research was focused on this transformation. The success with epoxidation and dihydroxylation can essentially be attributed to the efforts of Sharpless, T. Katsuki and E. N. Jacobsen. If one analyzes the structures of the starting materials, it is quite obvious that many of these compounds are often complex and multifunctional, *i.e.*, the successful catalytic systems are not only enantioselective but tolerate many functional groups.

Hurdles on the way to an industrial process

But the large scale application of enantioselective catalysts does present some very special challenges.[3] Some of these problems arise from the special situation for manufacturing chiral products, as described above, while others are due to the nature of the (enantioselective) catalytic process. Whether a synthetic route containing an enantioselective catalytic step can be considered for a particular product is usually determined by the answer to two questions:

- *Can the costs for the overall manufacturing process compete with alternative routes?*
- *Can the catalytic step be developed in the given time and cost frame?*

The choice of a development strategy that promises the best answer in the shortest time is the first decision at the start of every process development. This strategy will depend on a number of considerations, such as the goal of the development, the know-how of the investigators, the time-frame, the available manpower and equipment, and so on. In process development, there is usually a hierarchy of goals (or criteria) to be met. It is simply not possible to reach all the requirements for a technically useful process in one step. The catalyst selectivity (combined, of course, with an acceptable activity) is the first criterion—just as in academic research. But when a reasonable selectivity has been obtained, other criteria will become important: catalyst activity, productivity and stability, catalyst separation (and maybe recycling). Then, questions such as the effect of substrate quality and, last but not least, the cost and availability of the chiral catalyst and other materials have to be addressed. The final process is a compromise since—quite often—it is not possible to fulfil all of these requirements. It is useful to divide the development of a manufacturing process into different phases; however, it is rarely possible to proceed in a linear fashion and very often one has to go back to an earlier phase in order to answer additional questions before it is possible to go on.

In our experience, the following critical factors determine the technical feasibility of an enantioselective process step, but it has to be stressed that even if all these criteria are met there is no guarantee that it is actually used!

Catalyst performance

The *enantioselectivity* expressed as enantiomeric excess (ee, %) of a catalyst should be >99% for pharmaceuticals if no purification is possible. This case is quite rare and ee's >90% are often acceptable. *Chemoselectivity* (or functional group tolerance) will be very important when multifunctional substrates are involved. The *catalyst productivity*, given as turnover number (ton: mol product/mol catalyst) or as substrate/catalyst ratio (s/c), determines catalyst costs. For hydrogenation reactions ton's ought to be >1000 for high value products and >50,000 for large-scale or less expensive products (catalyst re-use increases the productivity). The *catalyst activity* given as average turnover frequency (tof = mol product/mol catalyst/reaction time, h^{-1}), affects the production capacity. For hydrogenations, tof's ought to be >500 h^{-1} for small and >10,000 h^{-1} for large scale products. Owing to lower catalyst costs and often higher added values, lower ton and tof values are acceptable for enantioselective oxidation and C–C bond forming reactions.

Availability and cost of the catalyst

Chiral ligands and many metal precursors are expensive and/or not easily available.

Table 3 Statistics for the various types of industrial processes.[4]

Transformation	Production >5 r/y	Production <5 t/y	Pilot >50 kg	Pilot <50 kg	Bench scale
Hydrogenation of enamides	1	1	2	6	4
Hydrogenation of C=C–COOR and C=C–CH–OH	2	0	3	4	6
Hydrogenation of other C=C systems	1	0	1	1	2
Hydrogenation of α and β functionalized ketones	2	3	3	2	4
Hydrogenation/reduction of other keto groups	0	0	2	2	4
Hydrogenation of C=N	1	0	1	0	0
Dihydroxylation of C=C	0	1	0	0	4
Epoxidation of C=C, oxidation of sulfide	2	2	1	0	2
Isomerization, epoxide opening, addition reactions	2	4	2	0	1
Total	11	11	15	15	27

Typical costs for chiral diphosphines are $100–$500 per gram for laboratory quantities and $2000–>$100,000 per kilogram on a larger scale. Chiral ligands such as salen or amino alcohols used for early transition metals are usually much cheaper. At this time, only selected chiral ligands are available commercially.

Development time

The development time can be a hurdle, especially when the optimal catalyst has yet to be developed or no commercial catalyst is available for a particular substrate (substrate specificity) and/or when not much is known on the desired catalytic transformation (technological maturity). When developing a process for a new chemical entity (NCE) in the pharmaceutical or agrochemical industry, time restraints can be severe. In these cases it is more important to find a competitive process on time than an optimal process too late. So-called second generation processes, *e.g.*, for chiral switches, for generic pharmaceuticals or the manufacture of other fine chemicals have different requirements; here the time factor is usually not so important but a high performance process is necessary.

The players in industrial enantioselective catalysis

Industrial interest in the application of enantioselective catalysts started in earnest in the mid-sixties when the first publications of successful enantioselective transformations using homogeneous metal complexes were published. Within a surprisingly short period, production processes for two small scale products were developed and implemented by Monsanto (l-dopa) and Sumitomo (cilostatine). For quite some time it was not really clear whether these applications where mere curiosities or whether this would be the beginning of a new area of producing chiral compounds. One reason for this state of affairs was that both companies were very reluctant to disclose information on the new technology. Very soon some other chemical and pharmaceutical companies entered the field with an appreciable research effort. Examples are Roche, Ciba-Geigy (S-metolachlor), Takasago (menthol), Enichem or VEB-Isis (l-dopa). Some of these companies worked in collaboration with academic laboratories, other relied on strong in-house research efforts. In the meantime, a new type of player has entered the field—that is, smaller companies more or less exclusively dedicated to the development and application of enantioselective processes to manufacture chiral intermediates and products. Many of these enterprises were either start-ups such as ChiroTech, ChiRex or Oxford Asymmetry, concentrating on a few promising technologies or spin-offs from a large corporation such as our own company, Solvias (a spin-off from Ciba-Geigy/Novartis) or NSC Technologies (a spin-off from Monsanto), usually with a broader technology base. Interestingly, many of these small companies have been bought by larger custom manufacturing companies who wanted to complement their technology portfolio. For instance, ChiroTech is now part of Dow, ChiRex belongs to Rhodia and NSC Technologies is part of Great Lakes.

Conclusions and outlook

In my personal opinion, enantioselective catalysis has not yet attained its appropriate position in the production of fine chemicals. By appropriate, I mean in accord with its potential for economical as well as ecologically superior production processes. Even allowing for the time taken for a new technology to be adopted by the notoriously conservative production managers (conservative for good reasons!) – there are additional hurdles responsible for this unsatisfactory situation. Some of the described issues are technical, others might be more psychological.

As the short description of the industrial players shows, much is happening in this exciting field of chemical technology. I am convinced that the Nobel Prizes for Knowles, Noyori and Sharpless will give more visibility to enantioselective catalysis and will give new impetus to its application to fine chemicals production.

Acknowledgements

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Notes and references

1 For details see Nobel Lectures, *Angew. Chem., Int. Ed.*, 2002, **41**, 998–2022.

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