

# A Fervent Advocate of Biocatalysis

## BASF Chemist Klaus Ditrich Receives 2008 Siegfried Medal

**Teamwork** – On Sept. 4, Professor Dr. Klaus Ditrich, who works in BASF's biocatalysis research, received the 2008 Siegfried Medal for Trendsetting Work in Process Chemistry. This renowned prize is awarded every other year by Swiss fine chemicals company Siegfried in cooperation with the Organic Chemistry Institute of the University of Zurich.

Chiral intermediates, marketed by BASF under the Chipros brand, are used by the company's customers as key building blocks in synthesizing active ingredients for crop protection products and pharmaceuticals. Klaus Ditrich was particularly involved in the development of an industrial manufacturing process for optically active amines. The key step in this process utilizes an enzyme-catalyzed reaction that allows the two enantiomers present in the starting material to be separated in a highly efficient manner. Dr. Michael Reubold interviewed the laureate about his research.

*CHEManager Europe: Prof. Ditrich, the award recognizes your research team's work in the development of technically practicable production processes for optically active amines, alcohols and carboxylic acids. When did you start working in this field, and how did you approach this task?*

**K. Ditrich:** I started working in this field in the middle of the 1990s. By education, I am a classic organic chemist, and I was working on asymmetric hydrogenation reactions at the time. I was very skeptical about whether biocatalysis is in fact a suitable process for producing optically active intermediates on an industrial scale and, to be honest, I went to great lengths trying to prove that it is not. In the end, however, I had to acknowledge that biocatalysts are in many cases superior to chemocatalysis with respect to selectivity and efficiency, so I gave up the struggle in a way: Today, I am a fervent advocate of biocatalysis.

*What are the advantages of biocatalysis as compared to conventional processes?*

**K. Ditrich:** There are many aspects I can give you here. Availability is important. Once you have got hold of the microorganism that produces the desired enzyme, you can very easily produce the required catalyst by means of fermentation. Optimizability is another thing. You can fairly easily adapt an enzyme to a given substrate, if necessary, by means of modern methods of genetic engineering. Optimizing a phosphine ligand for a metal-containing catalyst is certainly a more complex task. In most cases, enzyme-catalyzed reactions are highly selective and proceed in moderate reaction conditions so that the resulting straightforward processes and reduced need for cleaning cut the consumption of energy, solvents, etc. A point that I think is essential for technical feasibility is the fact that biocatalysts are often highly tolerant to impurities, which would kill catalysts that contain metals. Oxygen, sulfurous components or water are generally tolerated without complaints, and of course this goes along with the significantly less laborious purification of industrially available starting materials and solvents.

As I said at the outset, I went to great lengths to avoid becoming an



advocate of biocatalysis, but I must say it does have its advantages.

*What were the major obstacles that originally prevented the upscaling of the syntheses created in the lab and blocked the path to industrial practicality?*

**K. Ditrich:** The biocatalytic step is generally the least of the problems, because we use catalysts that have been optimized by nature in the course of about 1.5 billion years – or that our biologists have optimized by biotechnological methods. The desired products are as a rule obtained highly selectively and with very good yields. In many instances, however, isolating the products does pose problems. Most of our customers are pharmaceutical companies who, quite understandably, demand extremely high purity of the intermediates they use to synthesize active ingredients. Customers often will not tolerate more than 0.1% of a by-product, and of course you must prevent any undesirable side-reaction that may occur in preparation.

*How did you solve these problems?*

**K. Ditrich:** Most of these side reactions are the result of impurities that act as catalysts, of long residence times and thermal exposure, and can be avoided only if you apply intelligent process and preparation concepts and ensure optimum plant design. This has been accomplished in BASF's plants producing optically active amines. It is only owing to the special design of the preparation part of the production facility that we can achieve high chemical and optical purities in the manufacture of optically active amines. Our smart engineers have done a wonderful job there.

*So, it really was a team effort.*

**K. Ditrich:** Indeed! I do not consider the award of the Siegfried Medal to be a personal success of mine, but rather as a reward for the work done by the whole Chipros team, which includes many colleagues from research, process development, production facilities and, last but not least, marketing. In my experience, a successful project is always the result of a committed team working together, with everybody working in the same direction. In the case of optically active amines, working in this way, we needed no more than six years from the first steps of working out the process until we put into operation a purpose-built plant that is designed to fit this particular process.

*At which sites do you operate the processes you helped to develop, and what are their output volumes?*

**K. Ditrich:** We currently operate two facilities that produce Chipros in Ludwigshafen, Germany, and one in Geismar, La. (U.S.). While the Ludwigshafen plants are designed to function as multi-product facilities, we use the U.S. production facility exclusively to make an optically active amine that is needed as an intermediate in synthesizing a corn herbicide which BASF markets. The total production



BASF has nearly three decades of experience in biotechnology. The company employs biotechnological processes to manufacture different products, including enzymes, and chiral intermediates, using live cells or enzymatic processes.

capacity of all facilities is around 5,000 mt/y.

*Could you tell us what projects you are dealing with at the moment?*

**K. Ditrich:** My work focuses on the synthesis and production of optically active amines. I am convinced that we have every right to claim that BASF has built an excellent reputation in the pharmaceutical industry as a source for this category of sub-

stances. True to our motto – "We help our customers to be more successful" – we are prepared to support even very early stages in the development of new active ingredients by synthesizing small kilogram batches of optically active intermediates that may be required. At present, we have some very promising amines in our pipeline, which we hope will represent a highly interesting sales potential in the future. Bearing in mind our agreements with customers, I can-

not name any specific molecules, but I can assure you that we are not getting bored.

*Chiral intermediates are examples of white biotechnology, also known as industrial biotechnology, being used successfully. Since when has BASF been looking at biotechnological processes?*

**K. Ditrich:** BASF has been working in white biotechnology since the early

1980s. Our first successes were intermediates obtained by biocatalysis for the synthesis of optically active herbicides, and the fermentation processes for making vitamins (vitamin B2) and amino acids.

*What potential for this key technology of the 21<sup>st</sup> century do you see in other areas?*

**K. Ditrich:** Whether white biotechnology will ever play a significant role in the production of simple bulk chemicals that are currently produced on a petrochemical basis seems doubtful to me. I am, however, firmly convinced that in the future it will play a major role in producing fuels like bioethanol, biobutanol or biogas from renewable resources. At a time when fossil resources are becoming scarcer, it is increasingly important that we use nature's synthesis potential – which in most cases is carbon-neutral to boot – more efficiently, and precisely in this area biocatalysts will be essential.

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The biotech pilot plant is equipped with a large number of pilot-scale reactors complete with process control system for the active further development and optimization of existing processes and the development of new large-scale fermentation processes.