Chimia 53 (1999) 261–268

ISSN 0009–4293

The Spin-Off of Scientific Services of *Novartis* into a New, Independent Technology Company Offering Services to the Pharmaceutical, Chemical, and Nutrition Industry

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Abstract. Starting on October 1, 1999, the three sections 'Central Analytics', 'Physics', and 'Catalysis Synthesis Services' of the Scientific Services of *Novartis* will operate as an independent company. The new company will have about 180 employees and will offer services to customers in the pharmaceutical, chemical, and nutrition industry as well as to authorities and service firms active in these fields. The focus of activities for the new company is the chemical and physical characterization (analytics), optimization of products and processes, and the development and application of special synthetic methods, in particular by utilizing catalysis. Support is offered *via* single services, comprehensive service packages, or by taking over assignments for entire areas. The combination of a high scientific and technical standard built up on an ISO 9001 quality-management system, including cGMP and GLP, with an attractive working environment will be the basis for an innovative center of chemical and physical expertise.

Outsourcing: A Current Trend and a New Opportunity for Technology Companies

Traditionally, large companies in the field of pharmaceuticals, agrochemicals, and fine chemicals have maintained in-house expertise on a high technical level not only in the discovery and manufacture of high-value products but also in functions supporting these core activities. In many companies, central departments were built up, *e.g.*, for characterizing chemical compounds using highly sophisticated chemical and physical methods, sometimes also for reaction technologies with special requirements such as catalytic hydrogenation or high-pressure reactions. These departments not only provided the necessary services but also developed new state-of-the-art methods. This was possible because specialized scientists were able to focus on the appropriate methods on a long-term basis. In the last few years, the situation has changed gradually and several new trends are now emerging. Especially, the large life-science companies are concentrating their R&D efforts more and more on new discovery technologies such as combinatorial chemistry or genomics. In parallel, the readiness to collaborate with external partners and to outsource activities that only a few years ago were considered critical increases, partly because personnel resources have to be shifted, and partly because of the increased flexibility that can be achieved. As a consequence, there are new opportunities for smaller, technology-oriented companies to maintain the technical expertise and to provide such services on a high level.

Following these trends, it was decided to spin off the three sections 'Central Analytics', 'Physics', and 'Catalysis & Synthesis Services' of the Scientific Services of *Novartis* into an independent technology company. This article describes the idea behind the new company, its structure, its strengths, and the services it can provide to its customers. The name of the new company is currently under evaluation and will be communicated by the end of September 1999.

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Scientific Services of *Novartis* as a New, Independent Technology Company

The new technology company will be independent of *Novartis* and will employ about 180 persons working mainly in the Klybeck and Rosental sites of *Novartis* in Basel. It will be organized in Business Units which are at the same time Centers of Expertise. Although this organization still reflects the individual areas of specialization that have developed over the years as described in the following paragraphs, the new company increasingly will offer comprehensive solutions for broad and complex problems involving several areas of competence. This should be of considerable advantage to many customers because the best methods and techniques will be chosen by experienced experts and, if desired, only one contact person has to be dealt with.

On a more basic level, the spin-off into an independent, technology-oriented company assures that know-how and expertise in the fields of chemical and physical characterization and analysis, the optimization of products and processes, and the development and application of special

synthetic methods, in particular by utilizing catalysis, will be preserved in the Basel area.

Activities and Resources in the Fields of Chemical, Physical, and Biological Analytics, and in Software Development

Both technical progress and today's regulatory and legal environment have led to a significantly increased importance of analytical techniques and of IT applications. The new company has experience and know-how in all of these fields. It will perform analytical services using a wide range of analytical techniques. In the past, these have been developed for specialized applications, and this is reflected in the organization of the different areas of application as described below. However, the combination of various analytical and software tools in the hands of one service provider will be of increasing importance in order to solve multifaceted problems in research, development, quality control, and production. This will be an important strength of the new company because over the last decades a lot of know-how and experience have been accumulated in the various Business Units.

Elemental and Microanalytical Services

The reliable and quick determination of *elements, ions*, and *functional groups* is a necessary prerequisite for successful quality assurance of pharmaceuticals, microelectronic materials, polymers and polymer additives, cosmetics, food and food colors, pigments, and agrochemicals. Nearly all chemical elements, inorganic and organic ions as well as functional groups (*e.g.*, epoxy, aldehyde, multiple bonds, water, *etc.*) starting from percentage amounts down to ultra-trace impurities, belong to the main working areas of the new company. The scientists and technicians are specialized in spectrometric methods, classical microanalysis, microscale wet chemistry, and in electroanalytical methods.

One of the biggest assets of the various analytical teams is their familiarity with the demands of industry concerning the quality of high-purity materials applying highly sophisticated sample-preparation methods and equipment (*e.g.*, clean rooms) together with specialized know-how in contamination control. Complementary methods for most analytical problems are available allowing highly reliable results and competitive pricing in both sample, and project-oriented analytical work. The available methods and equipment include wavelength- and energy-dispersive X-ray fluorescence, inorganic mass spectrometry (ICP-MS), optical emission with different excitation modes (ICP, DC-arc), atomic absorption (ETAAS, FAAS), ion chromatography (all separation and detection methods), microanalytical combustion automates (for C, H, N, O, S, halogens), microtitrations (*e.g.*, H_2O, pK^*, *etc.*), microgravimetry, polarography, voltammetry, tensammetry, *etc.*

Most of the analytical tasks can be performed on microscale using extremely low amounts of sample, as often required in R&D of expensive chemicals (*e.g.*, proteins) or in identification of samples of unknown composition (forensic problems, customer compliance, *etc.*). All contract work is done under the quality standard specified by the customer. Quality assurance of pharmaceuticals, toxicological and clinical studies, and/or other industrial analyses are routinely performed and documented according to cGMP, GLP, GCP rules, and/or ISO-9001 standard.

Determination of Elemental Impurities in Microelectronics Chemicals by ICP-MS

Problem: The purity requirements of chemicals used in the microelectronic industry are becoming more and more stringent. Critical impurities are:
- Charged species like alkali/alkaline earth and halide ions may cause corrosion and degradation of microelectronic devices
- Heavy metals may increase the resistance and build up potentials on the surface
- The α-emitters thorium and uranium may cause so-called *soft errors* in the storage devices

Approach: A method involving cool plasma ashing followed by ICP-MS has been developed to determine Th and U in the ppt-range achieving limits of quantification of 10 pg/g Th and 5 pg/g U in *polyimide* and *photoresist* samples. The method has been validated by recovery experiments (see below). Further metal impurities are also determined by ICP-MS or by ET-AAS. Halogens and halogenides are determined by XRF, TXRF, IC, and titrimetric methods.

Example: Recovery of Th- and U-spikes from a polyimide sample by ICP-MS.

Element	Test solution (volume: 10 ml)	Sample weight [g]	Spike [pg]	Found [pg]	Recovery [%]
	Blank	–	–	26	–
Th	Sample	2.806	–	29	–
	sample + 10 ppt spike	2.476	100	120	93
	sample + 25 ppt spike	2.522	250	280	100
	Blank		–	<5	–
U	sample	2.806	–	9	–
	sample + 10 ppt spike	2.476	100	110	101
	sample + 25 ppt spike	2.522	250	250	97

From the above results it can be concluded that the Th content of the sample was <10 pg/g (ppt) and the U content was <5 pg/g (ppt). They also clearly demonstrate that it is possible to determine accurately 10–250 pg Th and U added as spikes with this method.

Customer benefit: Less rejects and faulty products due to reliable Th and U analysis.

Literature: B. Gercken, M. Fille, G. Emmenegger, O. Suter, J. Pavel, 'ICP-MS, TXRF and ZGFAAS: Complementary Techniques in Analysis of Trace Element Impurities in Photoresists', Contribution for the *Winter Conference on Plasma Spectrochemistry*, Fort Lauderdale, FL, Jan. 8–13, 1996.

Environmental Analytics

The environmental compartments *soil, air*, and *water* are indispensable for human life. The use of these natural resources is controlled by national laws and international regulations. The Business Unit 'Environmental Analytics' provides methods and procedures to document the compliance with the regulations, but also generates and uses new solutions for the detection of environmental contamination. A team of specialized people offers services and support to customers on the following environmental subjects and industrial processes and developments:
- Air-/waste-air-analysis (continuous monitoring and discontinuous analysis

Determination of Plant-Protection Agents in Ground- and Drinking Water

Problem: The reliable detection and identification of plant-protection agents in trace amounts is a difficult and important problem for environmental analytics (detection limit has to be <0.1 µg/l water). It is complicated by the fact that these agents and interfering compounds are present in very variable concentrations. Until now, the normal procedure was the off-line concentration of a one-liter water sample followed by the quantitative analysis by GC, LC, or GC-MS (most often used). Disadvantages: Large sample, time-consuming concentration process and difficulties with very polar/ thermolabile compounds

Approach: Develop a new on-line LC-MS method.

Example: The off-line concentration is replaced by an on-line concentration of a small sample volume on a pre-column (*RP-18* material). In a second step, the retained plant-protection agents are transferred onto an analytical column using a suitable solvent, separated and analyzed over an LC/MS-interface. Comparison with a reference standard allows unambiguous identification and quantification. The high cost for the instrumentation is more than compensated by a much faster analysis (especially for duplicate determinations) and the wider scope of LC over GC.

Customer benefit: No regulatory problems, safe drinking water.

of pollutants in air, waste-air, and combustion gases)
- Working hygiene (personal and room monitoring for dust and organic substances; MAK-values)
- Ecotoxicology (aquatic and terrestrial toxicity tests with algae, daphnia, fish, and earthworm, bacterial toxicity tests)
- Biological degradability
- Analysis of drinking water (microbiological and chemical analysis)
- Analysis of water for pharmaceutical purposes according to USP or Ph. Eur.
- Notification of industrial chemicals
- Chemical analysis of ground-, surface-, and waste-water
- Soil-analysis
- Analysis of waste material

Bioanalytics

The Business Unit 'Bioanalytics' operates as a center of expertise for analytical methods based on molecular-biology techniques. Its mission is to support the life-science community by providing a comprehensive package of services in the fields of DNA-sequencing, applications of the PCR technology and supporting molecular-biology techniques. Specific consulting and continuous support are important aspects in order to meet the specific needs of every customer in an optimal way.

The DNA-sequencing services cover all types of applications including EST-sequencing, sequence confirmation, large-scale sequencing projects, food analysis (*i.e.*, species identification) and diagnostics (*i.e.*, heterozygote detection). A particular strength is based on the combination of the broad expertise represented by the team members and a particular hardware and software setup to form a fully automated ultrahigh-throughput sequencing factory. Processes automated by robotic equipment and software solutions are used at every stage of the analysis (template preparation, enzymatic reactions, gel loading, and data analysis). This setup is based on an integrated instrument setup and leads to a strict control of the data flow throughout the entire process, resulting in a very high sample throughput in an extremely reliable fashion. A continuous commitment to keep up with the latest development of new techniques and instruments led to being the first European service lab to introduce the *ABI PRISM 3700* ultrahigh-throughput *96-CE* sequencer. After the integration of this instrument, the annual sequencing capacity exceeds 250000 samples.

Services offered based on applications of the PCR technology include method optimization and validation of new assays for the characterization of animals, plants, and microorganisms, routine analysis for sequence detection (*e.g.*, genotyping), as well as preparative amplifications (*e.g.*, production of hybridization probes). Using a real-time fluorogenic 5'- nuclease assay ('TaqMan') on an *ABI PRISM 7700* sequence detector, very efficient and reliable services for genotyping of transgenic animals, allelic discrimination (detection of polymorphisms), quantification of the expression of genes, and quantitative detection of genetically modified organisms ('GMOs'), as well as of different bacteria and viruses are provided. Services supporting molecular-biology processes include design of primers and probes, transformation, template preparation, subcloning, site-directed mutagenesis, the construction of targeting vectors for homologous recombination, and support in data analysis and bioinformatics.

Separation and Quantification of Product Mixtures

The qualitative and quantitative analysis of mixtures of organic substances in different matrices is often a very demanding task. Services offered are in the areas of method development, method validation, and quality control using chromatographic (HPLC, TLC, GC, *etc.*), electrophoretic (CE, gel electrophoresis, FFE), and spectroscopic techniques (IR, UV, FL, MALDI-TOF, MS). Hyphenated techniques such as GC-MS, HPLC-MS, TLC-AMD, GC-IR *etc.* are available as well. Chemical analyses are carried out according to the required quality standards such as GLP, ISO-9001 or GMP. There exists a large experience in sample-preparation techniques for a broad class of products in the fields of life science, agro business, and fine chemicals.

Typical examples of the services offered are
- method development and quality control work for development laboratories, quality-control units, pilot and chemical production
- analytical support in the fields of isolation, identification, and characterization of byproducts and degradation products
- analytical support for cleaning validation
- stability tests and determination of dissolution rates according to USP
- determination of impurities in active substances or formulations
- quantitative analysis of residual solvents using head-space techniques
- analytical trouble shooting *etc.*

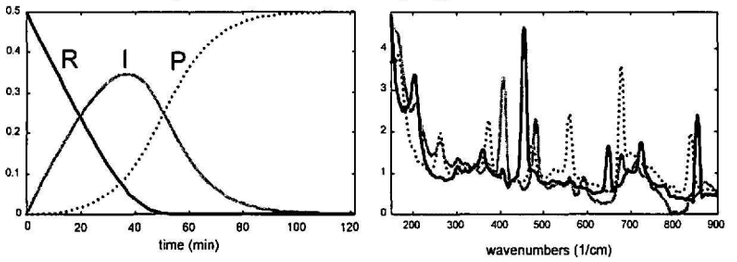
Online Technology

Online analytics is a very efficient way to get real-time information about processes used in the chemical industry (*e.g.*, chemical reactions, crystallizations, distillations, *etc.*). It allows the direct determination of important decision points (op-

On-line Reaction Monitoring of a Catalytic Hydrogenation

Problem: It is usually very difficult to have information on the composition of the reaction mixture during high-pressure and/or heterogeneous catalytic reactions.

Approach: Use IR-ATR and *Raman* probes to monitor the progress of the reaction *in situ*.



Application: Hydrogenation of 2-chloro-1-nitrobenzene to form 2-chloroaniline (see also box on 'Hydrogenation of Multifunctional Nitroarenes'). The formation and disappearance of the unwanted hydroxylamine can be clearly seen in the *Raman* spectra measured *in situ*. The raw data is decomposed into the concentration profiles and spectra of the three species (R: reactant, I: intermediate, P: product). The decomposition is achieved using a hard modeling approach. The simplest kinetic model capable of representing the data can be summarized in the equation:

R + catalyst → R–catalyst → I + catalyst → I–catalyst → P + catalyst

Hydrogen can not be seen using this kind of spectroscopy and does therefore not enter the equation. Also, the catalyst and the adsorbates (R–catalyst and I–catalyst) cannot be seen directly, but they must be included in the model to produce the correct shapes of the species R, I, and P. The graph shows the result of the decomposition of the raw data: the calculated concentration profiles (left) and the calculated *Raman* spectra of the pure components (right). In the next step, these results can be used to optimize the yield of the reaction or to minimize byproducts using computer modeling.

Customer benefit: Safer process, mechanistic insight and possibility of higher product quality.

Literature: H. Danigel, N. Graber, M. Länzinger, M. Studer, H. Thies, A. Zilian, Chemical Processing Technology International, Special Achema Issue **1997**, 99.

Atomic Force Microscopy and Spectroscopy: Microscopic Surface Characterization at the Molecular Level

Problem: For a state-of-the-art surface characterization, a spatial resolution down to molecular dimensions under *in situ* or sample-relevant conditions is required.

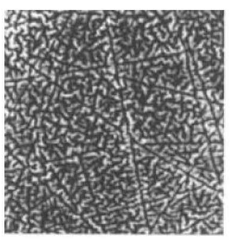
Approach: Use of atomic force microscopy (AFM). Nowadays, AFM offers the required resolution combined with speed, reliability, and versatility. Furthermore, AFM complements nearly ideally the well-established light and electron microscopes.

Examples: The following three examples give an impression of the broad applicability of AFM in modern research and development.

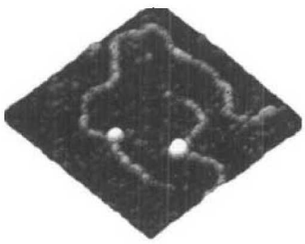
1) Surface analysis of coated soft-polymer contact lenses. Their high water content causes considerable swelling of the coating under physiological conditions. Atomic force microscopy gives access to the real surface morphology, roughness and coating properties like homogeneity, elasticity, and thickness under physiological conditions.

2) Very-high-resolution analysis of individual molecules or molecular complexes. The image below shows the interplay of two λ-DNA fragments with restriction enzymes on a molecular level.

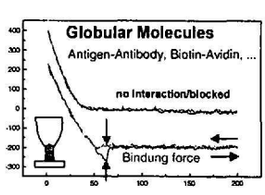
3) Measurement of binding force between molecules. The extreme sensitivity of atomic force spectroscopy and the possibility to operate under physiological conditions allows the measurement of molecular binding forces, elasticity, and even reaction rates at the level of molecular individuals such as in this antibody-antigen (Ab-Ag) experiment.



1) Contact Lens
(Image Size: 30 mm)



2) DNA fragments with enzymes
(Image Size: 250 nm)



3) Atomic force spectroscopy
(Ab-Ag binding force: 70 pN)

Customer benefit: More effective optimization of the lens-production process, mechanistic and structural insight down to a molecular level under relevant conditions .

Literature: J. Fritz, D. Anselmetti, J.J. Jarchow, X. Fernandez-Busquets, *J. Structural Biology* **1997**, *119*, 165; J. Fritz, A. Katopodis, F. Kolbinger, D. Anselmetti, *Proc. Natl. Acad. Sci.* **1998**, *95*, 12283.

timal yield, end of reaction, appearance of a byproduct) and is therefore of great importance for process control. Furthermore, investigations of reaction mechanisms and optimizations can become much easier because high-quality data is obtained. Especially where taking samples is difficult, complicated, or dangerous, online analytical methods are an invaluable tool for the chemist in production, development, and research.

Several spectroscopic methods are suited for online analytics. UV-VIS, NIR and, recently, also IR and *Raman* (see example) are the ones that are used most often. The first fiber UV-VIS process photometers were installed at *Ciba-Geigy* about 15 years ago. Today, about 200 UV-VIS and 40 NIR installations work reliably in process control. Successful applications include distillations, checking of raw materials, storage-tank control, crystallizations, granulation, drying, bromination, standardization and endpoint of hydrogenations and other reactions. Often- payback times of one year or less were obtained.

A broad experience allows to assess new online projects very efficiently and to install custom-designed online methods including all aspects- like fiberoptic probes, instruments, chemometrics, and interface to the process-control system. Every project has three clearly defined milestones: *1*) Develop a concept with the customer, 2) carry out a feasibility study in which the validity of the initial concept is checked on lab-scale, *3*) installation of the optimized solution in the process (sometimes rented equipment is used first). All these steps are taken in close collaboration with the customer .

Physical Chemistry

Experts with broad industrial experience work in the general area of physical chemistry. In the fully equipped labs, one can find just about any current physical-chemical method, including specialties such as atomic force microscopy in aqueous systems, scanning electron microscopy with electron-dispersive X-ray analysis, analytical ultracentrifugation, coupled thermal/spectroscopic methods, ellipsometry, and radiometry.

Depending on our customers' requirements, both single physico-chemical parameters for quality control are determined, and complete packages for release analytics of raw materials, intermediates, and final products are offered. Furthermore, binding studies, optimizations, stability studies, and kinetic investigations are carried out. The large range of methods and vast know-how make it possible to tackle problems efficiently and to help speed up research and development in an effective way. The various specialists have a lot of experience in solving problems fast, which helps to avoid costly interruptions. In addition, consulting and contract research are also offered.

An example of important strengths are studies of polymorphism (see also example below). More than 50% of the current pharma- and agro-active substances can exist in at least two different crystal modifications. These modifications or polymorphs have different pharmaceutical (*e.g.*, bioavailability) and physical (*e.g.*, stability, density, processability) properties. It is, therefore, extremely important to know the thermodynamic and kinetic stabilities of all forms as a function of temperature and other environmental var-

Protein Binding Studies

Problem: How tight is the binding of an active substance to the target protein? What is the binding mode (*e.g.*, 1:1 binding, 2:1 binding with or without cooperativity, *etc.*). This information is typically needed to understand the mode of action of a drug molecule and combined with molecular modelling, it helps to improve a lead structure.

Approach: While various methods are available for binding studies, titration calorimetry offers the unique possibility to measure all thermodynamic parameters, *i.e.*, $\Delta G°$, $\Delta H°$, $\Delta S°$, and the binding stoichiometry in a single experiment. In the experiment, the heat release (or uptake) is observed upon stepwise addition of one binding partner to the other. From the shape of the curve of heat evolution *vs.* added binding partner, association constants K and binding enthalpies $\Delta H°$ can be calculated.

Example: In oncology research, a protein was to be inhibited through the binding of a small drug molecule. From earlier experiments it was clear that the drug binds to the protein but there was poor understanding on how tight the binding was and how many drug molecules per protein were bound. The figure below shows a titration-calorimetry experiment in which the protein was present in the measurement cell of the calorimeter and a solution of the drug molecule was added step by step through a syringe. Various binding models were fitted to the integrated heats (bottom panel in the figure) but only a model with two drug molecules binding to the protein gave a satisfactory fit. The two binding steps are actually resolved in the bottom-panel data as the curve first drops, then passes a minimum and eventually rises again. In addition, the data suggest only low or no cooperativity of the binding, *i.e.*, after binding of one drug molecule, the binding of a second drug molecule is neither strongly favored nor disfavored.

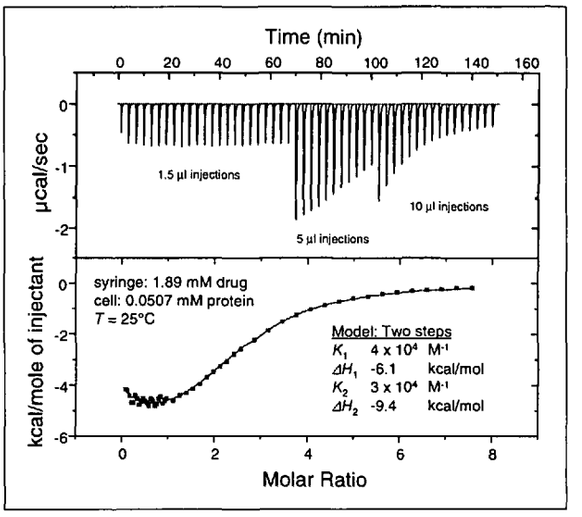


Fig. *Titration calorimetry of a protein with a drug molecule.* Top panel: raw data. Bottom panel: Integrals of the individual peaks in the top panel as a function of the molar drug-to-protein ratio.

Customer benefit: Faster lead optimization, information about mechanistic details (mode and strength of target-substance/protein binding)

iables in order to avoid undesired changes during the production process or during the product lifetime. Moreover, it has been demonstrated several times that a sound polymorphic characterization is a powerful means to extend the lifetime of one's own patent or, under favorable conditions, to get patent protection on generic drugs.

Some other examples of strong points are surface characterization, protein characterization, optimization of crystallization, distillation, and drying conditions, as well as formulation stabilities.

Certified Reference Compounds

In order to determine the purity of a pharmaceutical according to a validated analytical method, certified reference standards are needed. However, byproducts are commonly neither on stock nor commercially available as well-characterized references. Another problem is that the expiration date of standards has to be tracked. The following services are offered:

- Isolation, purification, and characterization of (by)products with a broad range of analytical tools to the defined standards of the customer.
- Synthesis on the mg to kg scale and characterization as above if the required compound cannot be isolated in an easy way.
- Keeping a stock of customer compounds or byproducts and deliver them in the required amount at the right time.

Special Software Development

In production, development, and research, it is extremely important to have access to the right information at the right time and at the right place. Custom-built software can help to run research, production, and analytical equipment in a more efficient way. An important application is to map existing processes on new software solutions. This allows to manage complicated customer environments (*e.g.*, instruments, research databases, LIMS). More robust processes very often are an additional benefit of this strategy. Important areas for the special software are:

- Automation and information processing in quality control/analytics of production processes and in pharma-release analytics
- Control of and integration of automated systems in research and development.

A pool of reusable components forms the basis of a modular, network-adapted software package. This software satisfies the demanding validation requirements in an environment regulated under GMP, GLP, or ISO standards. The end-user is involved in the software-development process from the very beginning of the project that is always carried out in close collaboration with the customer. In addition, software design and implementation by the IT professionals is supported by experts in the area of concern such as analytical chemistry *etc.*

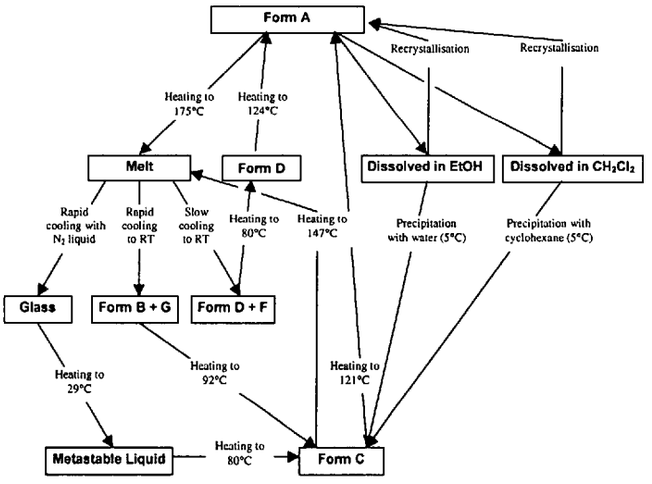
Activities and Resources in the field of Catalysis & Synthesis Services

There are certain types of reactions that pose great problems to the chemists in research and development laboratories, either because special equipment or expertise is needed, or because toxic reagents or otherwise hazardous conditions are involved. In this domain, the four Catalysis & Synthesis Services Business Units offer their services with a team of highly specialized scientists and techni-

Solid-State Characterization of Organic Compounds (Polymorphs, Solvates, Hydrates, Amorphous Forms, Inclusion Compounds)

Problem: Organic molecules often crystallize in various solid forms. These polymorphs have different physical properties, such as melting point, solubility or stability. The physicochemical properties can affect the formulation characteristics, the shelf-life of the final drug product, and even the therapeutic effect (bioavailability). Therefore, it is important to identify and control the polymorphic form throughout all the stages in the development of a product: from research, to development, to final production. Furthermore, it is necessary to know the thermodynamic stability and the phase relationship of all crystal modifications. The use of subsidiary patents on desirable polymorphic forms has produced an added incentive to study polymorphism.

Approach: Identify and characterize the various solid forms in clearly defined steps



Example: For lufenuron (a benzoylphenyl urea derivative), which is marketed as a racemate, a series of new polymorphic forms were found and characterized. Small changes of the experimental conditions influence the crystallization of different polymorphs. Form A is the thermodynamically stable modification. Considerable stability was also found for the metastable form C. When form C is kept at room temperature, no transformation takes place over months. In slurries, form C transforms into form A within a short period of time. The modifications B, D, F, and G were not found to be stable enough to be readily prepared in larger quantities. The situation is even more complex for the single enantiomers. Here, the most important modification is form E.

Customer benefit: Possible patent protections, reproducible product formulation, less problems during product storage.

Literature: M. Szelagiewicz, C. Marcolli, S. Cianferani, A.P. Hard, A. Vit, A. Burkhard, M. von Raumer, U. Ch. Hofmeier, A. Zilian, E. Francotte, R. Schenker, *J. Thermal Analysis*, **1999**, in press.

cians with long and successful careers in catalysis. One reason for the very low turnover of our personnel (as opposed to the high turnover frequency of our catalysts) is the fact that catalysis is still a very empirical science and that experience is an important success factor.

Preparative Services

A preparative service can only be successful, if a desired reaction can be carried out with an acceptable yield on a very short term. Since there is usually no time to develop an appropriate method, high effectiveness in selecting the right catalyst and reaction conditions is a prerequisite. For this task, the service team relies not only on the published literature but also on experience that has been collected and documented over the last 50 years (>40000 reactions). At the moment, about 2000 reactions are carried out every year and the 'hit rate' is 80–90%, *i.e.*, the desired transformation is achieved with >50% yield in the first or second attempt.

The following preparative services are offered on a mg to kg scale:

- *Chemo-, regio-, stereo-, enantioselective hydrogenations* using both heterogeneous and homogeneous catalysis. This is still the dominant field of activity, supported by an internal database that documents hydrogenations with more than 31 500 different substrates.
- *Catalytic dehydrogenation* in the liquid phase, very often using hydrogen acceptors in order to facilitate the reaction.
- *Catalytic carbonylation and hydroformylation reactions* are versatile transformations gaining growing interest especially for the synthesis of carboxylic-acid derivatives and aldehydes. Our internal database documents already over 1000 reactions with carbon monoxide.
- Reactions under *high pressure and with hazardous gases* such as of HF, SF_4, or F_2 are carried out. Over 10000 reactions are documented in the high-pressure documentation. Recently, the necessary equipment was installed for performing operations in supercritical media, *e.g.*, CO_2.

Contract Synthesis

Optimal integration of a catalytic step into a multi-step synthesis is often a difficult task because it requires a profound knowledge of the scope and limitations of a large spectrum of catalytic reactions. If done properly, however, catalysis can offer significant advantages concerning the efficiency and thereby the economical and ecological quality of a synthesis. A team of organic chemists together with various catalysis specialists offers support and services on different levels:

- Advice and information for chemists involved in synthesis planning concerning the feasibility of a synthetic route as well as of a particular catalytic step
- Synthesis design: proposal and assessment of possible routes for a given target molecule
- Demonstration of chemical feasibility of proposed routes on a laboratory scale
- Optimization of a selected route and preparation of up to kg amounts of the target compound.

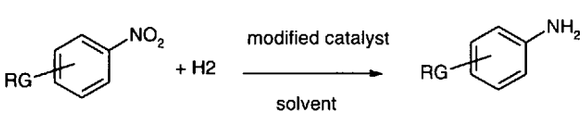
Process Development and Trouble Shooting

The development of a technically viable catalytic process (as opposed to simply producing a few grams of a compound) is a very interactive task and requires a high degree of cooperation and teamwork between the catalysis specialist and the development chemist. Usually, a laboratory procedure for the catalytic step (choice of the catalyst, solvent, optimization of reaction conditions *etc.*) is developed first. The goal is to show the chemical feasibility of the catalytic transformation and a first estimate of the production costs. Next, aspects such as adaptation to the operations preceding and following the catalytic step (purity of substrate, solvents), handling, reuse, and separation of the catalyst, and optimization of the catalyst in collaboration with the catalyst manufacturer *etc.* are investigated in close contact with the development and/or the production chemists.

For multi-purpose reactors, the results obtained on small scale are usually sufficient for a direct transfer to the plant scale. A classical pilot study (10–1000 kg scale) is carried out if either the process integration or logistics need special attention, or larger amounts of a product are needed for toxicological or clinical studies and for registration purposes. Once the catalytic process is introduced in the production plant, the catalysis group can support the production crew with trouble shooting, *e.g.*, when problems with the performance of the catalyst occur. In addition, catalysis

Hydrogenation of Multifunctional Nitroarenes

Problems: *Chemoselectivity, i.e.*, reduction of other reducible groups (RG) present. *Hydroxylamine intermediates* that form during the reduction of the nitro group and which affect the product quality and safety of the process.



RG: Reducible Group

-C≡N, -C≡CH, -CH=NOH
-CH=CH_2, other C=C bonds
-Cl, -Br, -I,

Approach: Modification of commercially available hydrogenation catalysts with promoters such as metals or organic modifiers.
Results: New (and patented) selective catalyst systems and modifiers:

- Pt/C catalyst modified with phosphoric-acid derivatives as process modifier; suitable in apolar solvents for the chemoselective hydrogenation of nitroarenes with RGs as depicted in the scheme.
- Pt-Pb/$CaCO_3$ catalyst; suitable in polar solvents for the chemoselective hydrogenation of nitroarenes with RGs as depicted above.
- Pt/C or *Raney*-nickel catalysts modified by formamidine acetate, especially for selective hydrogenation of halogenated nitroarenes
- Vanadium promoters that strongly suppress the accumulation of the undesired hydroxylamine intermediates.

Customer benefit: Safer and more economical processes, less waste and better product quality.

Literature: U. Siegrist, P. Baumeister, H.U. Blaser, M. Studer, *Chem. Ind. (Dekker)* **1998**, *75*, 207; P. Baumeister, H.U. Blaser, M. Studer, *Catal. Lett.* **1997**, *49*, 219.

specialists act as consultants for process improvements.

Catalysis Research

The goal of the research projects is to make selected catalytic technologies accessible to the synthetic chemists in discovery research, chemical development and, ultimately, to allow the application of catalysis in chemical production. For this purpose, method-oriented research and development projects are carried out. The former serve to establish a specific method in the service laboratories, whereas the latter aim to establish a new state of the art. If possible, the results are protected by patents. In order to ensure contacts with the scientific frontier, there are collaborations with several academic laboratories both in Switzerland and abroad. In addition, contacts with colleagues in catalyst groups of other companies are maintained.

The following topics are currently investigated:

- *Long term research projects:* 'Homogeneously catalyzed C–C-bond-forming reactions', 'Design and synthesis of chiral ligands', 'Oxidation', 'Modification of commercial heterogeneous catalysts'.
- *Shorter term development projects:* 'Hydrogenation with chiral metal complexes', 'Separation methods for soluble metal-complex catalysts', 'Automatization of catalytic reactions'.

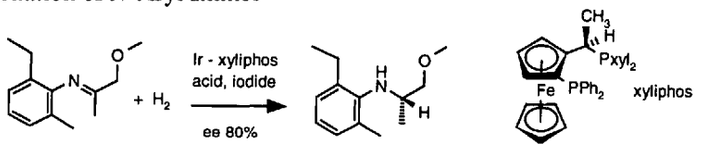
Development of Technical Catalytic Systems for the Manufacture of Key Intermediates

Problems: Especially in the field of agrochemicals, the pressure on the costs as well as on the ecological impact of chemical production steadily increases. As a consequence, it is of growing importance to have the best synthetic technology available, if possible with good patent protection. While there is no doubt that catalytic reactions open up new, potentially cheaper synthetic routes, many catalysts are not yet ready for technical application.

Approach: Method-oriented research and development projects concentrating on potentially useful catalytic transformations in order to improve the insufficient catalyst performance to a technically useful level.

Results: Here, this will be illustrated with two examples that both got rewarded with the *Sandmeyer* Prize of the *New Swiss Chemical Society*: A new catalyst and process for a enantioselective imine hydrogenation (*Sandmeyer* Price 1999) and a process for an alkylation of an aromatic ring (*Sandmeyer* Price 1996).

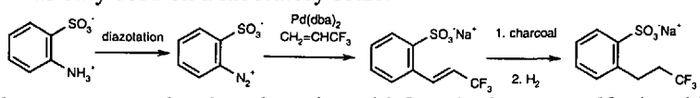
1. The Development of a New Ir-diphosphine Catalyst for the Enantioselective Hydrogenation of *N*-Aryl Imines



(*S*)-NAA is the key intermediate for (*S*)-metolachlor the active ingredient of the herbicide *Dual Magnum*®, the enantiomerically enriched form of the herbicide *Dual*®. It was introduced on the market in 1997 after a development effort of more than ten years. The key step was the enantioselective hydrogenation of the MEA imine with a new Ir-xyliphos catalyst. The catalyst performance is extraordinary with turnover numbers >>1'000'000 and initial turnover frequencies of >180'000/h. This catalyst system sets a new standards for the commercial application of enantioselective catalysts (see also the account on page 275 in this issue of *Chimia*)

2. Alkylation of an Aromatic Ring: Combination of a Homogeneous and Heterogeneous Pd-Catalyzed Reaction

Sodium 2-(3,3,3,-trifluoropropyl)benzenesulfonate is a key intermediate for the sulfonyl urea herbicide *Prosulfuron*. Because all attempts failed to find a classical synthetic method such as a *Friedel-Crafts* alkylation, a process-development team had to find a technically feasible production process based on a methodology that until now was only used on a laboratory scale.



In the end, a process was developed starting with 2-aminobenzenesulfonic acid and ending with sodium 2-(3,3,3-trifluoropropyl)benzenesulfonate without isolation of the diazonium or olefin intermediates, producing only 2 kg wastes/kg product over the three consecutive synthetic steps. Moreover, the yield over these three steps is 93%, *i.e.*, an average of 98% per step.

Literature: F. Spindler, B. Pugin, H.P. Jalett, H.P. Buser, U. Pittelkow, H.U. Blaser, *Chem. Ind. (Dekker)* **1996**, *68*, 153; P. Baumeister, W. Meyer, K. Oertle, G. Seifert, U. Siegrist, H. Steiner, *Stud. Surf. Sci. Catal.* **1997**, *108*, 37.

Equipment, Catalyst and Ligand Collection of the Catalytic Laboratories

Catalytic reactions are often carried out in special equipment. Since many reactions involve a dissolved organic substrate, a (solid) catalyst and a gaseous reactant, all reactors are designed for an efficient gas-liquid mixing. Besides glass reactors for low-pressure reactions, most frequently used are magnetically stirred high-pressure autoclaves (50 ml to 16 l with max. 300 bar and 350°, various materials available; 50 l autoclave with max. 70 bar and 250°). Most operations can also be carried out under cGMP. Fixed-bed reactors allow the study of continuous reactions in the gas phase and under trickle-bed conditions. A heat-flow calorimeter (up to 150 bar) allows investigations concerning the exothermicity and the heat flow of catalytic reactions. A glove box, vacuum lines, and sophisticated safety equipment (*e.g.*, special containment boxes and special areas for storing and handling explosives) are also available.

Just as the catalytic equipment is special, most heterogeneous catalysts and chiral ligands are not commercially available. Over the years, a sizable collection of heterogeneous hydrogenation catalysts (*ca.* 500 samples), of zeolites, clays, and similar contacts (*ca.* 700 samples), and of organometallic catalyst precursors and ligands (>200 samples) was built up. Most of these catalysts are also available to customers.

We thank *C. Abt, D. Anselmetti, P. Baumeister, H. Ehrhardt, B. Gercken, M. Güggi, P. Herold, R. Hilfiker, U. Hofmeier, A. Hörmann, M. Jakobi, P. Loew, M. Looser, J. Pavel, U. Siegrist, H. Steiner, M. Szelagiewicz, F. Thommen, U. Weber,* and *A. Zilian* for their contributions and valuable discussions.

Received: May 4, 1999