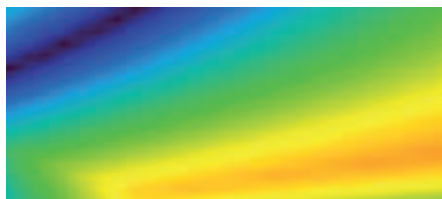


The Solvias Magazine

# prospects

2 | 2009

The fast track to rapid and  
**robust results**



The relevance of solid-state  
**development is  
crystal clear**



Barriers to winning  
**the approval of  
biosimilars in the USA**



10 years of Solvias  
1999-2009

solvias 

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# Dear reader and **valued customer**



**DR. STEPHAN HAITZ** — Head of Marketing and Sales

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We are celebrating our 10th birthday and true to our motto it is „business as usual.“ This very attitude, as scientific service provider with uninterrupted service to our customers, has placed us in the proud position of being able to commemorate this remarkable anniversary.

Back to business as usual, we have compiled a special birthday edition of Prospects. Enjoy reading the 20th issue, which spans some truly hot topics from biosimilars and biobetters of large molecules to CN-coupling technology used for the synthesis of small molecules.

As modern science increasingly leans on computers and robots, we at Solvias are also moving with the times, and you can rest assured that such developments will not fail to show up here as well. But at the end of the day, it is still all about people. The method development platform for analytical development and high throughput screening equipment for solid-state would be meaningless, and the results worthless if not for the highly skilled, trained scientists performing and interpreting them.

Listening to the voice of the customer is undoubtedly one of the most important tasks for a service provider. We keep our ears tuned to their needs and judging by the regular feedback we receive we trust that we are on the right track. Some of our most loyal customers have continued to work with us since we began operations in 1999, and their input and collaboration have contributed significantly to our success.

It's time now to return from "business as usual" to our birthday celebrations. I warmly invite you to share this milestone with us on the occasion of our customer reception at the upcoming CPhI show in Madrid.\* We thank you for your support over the last 10 years and look forward to intensifying our relationship with you over the next decade.

With my best wishes on behalf of Solvias,

A handwritten signature in black ink, appearing to read 'St. Haitz', written in a cursive style.

Dr. Stephan Haitz

\*Wednesday, October 14, at 3.45 pm. We are in hall 3, booth C52.

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# The birth of Solvias – Looking back on 10 years of partnership

Dr. Michael Mutz from Novartis in Basel was one of the first customers of Solvias, although his relationship with Solvias began before 1999. Solvias asked Dr. Michael Mutz to review Solvias' development from a former internal service laboratory to an independent service provider.

*Interview: Dr. Michael Becker*

## ***What were your thoughts when Solvias was formed?***

It wasn't clear to me when Solvias was first formed what direction it would take, what would happen in the future and how the Solvias business model would look. However, the preparations for the spin-off were already in evidence before October 1, 1999. Technologies and procedures were partially divided up and the analytical equipment assigned to different departments so as to ensure that each unit was ready to operate.

## ***What changes immediately became apparent when Solvias was spun off?***

After Solvias was formed, new processes were required, such as commissioning and invoicing. Credit applications had to be made for commissioning, for example. It took quite a while for all this to be set up. And the creation of a marketing organization with business development managers was soon apparent too.

## ***Were there concerns that services may not be as readily available?***

No, not at all. That said, there was some concern as to how, for example, elemental analyses would now be commissioned; these are required for virtually every batch of active pharmaceutical ingredient. This was previously done as an internal laboratory, which became a Solvias laboratory after the company was formed. However, this turned out to work well, even though the analyses were no longer directly performed in-house.

## ***Looking back, what do you think could have been done better when the company was formed?***

Particularly at the start, it would have been expedient to communicate Business Development tasks and interfaces more effectively. Even though the function is undeniably important for maintaining business, it was not clear to me as a scientist to what extent scientific issues could be discussed or not.

## ***Did the formation of Solvias have an impact for you personally on your relationships with former colleagues?***

I personally did not experience any severance of ties and still have very good relationships with former colleagues to this day. I am glad that I can rely on these people. I even cooperate with Solvias colleagues over pure service provision, for example, with regard to sample measurements to assess or install new technologies that are to be acquired by Novartis or Solvias. That way, everybody benefits.

Naturally our cooperation is slightly more formal than before Solvias was formed because a quote has to be made which results in an order, which is then invoiced. But I still value being in direct contact with Solvias scientists with a view to setting up projects as effectively as possible, and coordinating results and opinions.

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## My key expectations are project flexibility, scientific excellence, and high-quality results.

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### ***What do you expect from a service provider in general?***

My key expectations are project flexibility, scientific excellence, and high-quality results. I have to be able to rely on the results of service providers. It is certainly of benefit if the service provider pushes ahead with their own developments, because this may provide fresh insights into one's own work.

### ***What do you think the future holds for the outsourcing market?***

Outsourcing will always be needed so as to be able to cover peak periods. Although cost pressure is ever increasing and we are urged to keep costs down, a certain percentage of our work will always have to be outsourced. Special technologies in particular can be procured more efficiently externally, if such technologies would not be fully utilized in-house.

Dr. Mutz, many thanks for such an informative interview.



**DR. MICHAEL MUTZ** — Senior Fellow, Novartis Pharma AG

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*Michael Mutz is Senior Fellow at Novartis Pharma AG in Basel, Switzerland. He graduated in 1984 from the University of Freiburg with a master's degree in physics and in 1989 from the Free University of Berlin with a PhD in physics of lipid membranes. In 1991, following postdoctoral work at the Ecole Normale Supérieure in Paris, he joined Ciba-Geigy in Basel as Head of Laboratory for Thermochemical Applications. In 1997, he joined the Chemical and Analytical Development department of Novartis Pharma AG, and in 2008 he became Senior Fellow in Pharmaceutical and Analytical Development. He is also a project leader in pharmaceutical development. Michael Mutz is an expert in powder characterization at the European Pharmacopoeia in Strasbourg, France.*

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# Ten years of Solvias – **A reflection**

Dear Reader,

Ten years ago, Solvias was founded out of a small central scientific services unit of Novartis. Based on entrepreneurial spirit and the faith of our employees in the future of the enterprise we felt empowered to take the first step towards independence. Starting out with just a few customers in the Basel region of Switzerland, our customer base today is spread across Europe and in wide parts of the USA.

Over the last 10 years, we have transformed from being a competence center in a large international corporation into a dynamic medium-sized service provider with a profitable business. Thanks to increasing market demand, we were able to flourish and create more than 100 jobs for qualified staff with an additional six training positions for young professionals.

All of this was accomplished primarily thanks to the solidarity of a team pursuing common goals with commitment, perseverance and enthusiasm. We have celebrated successes, learned from setbacks, and through these experiences we have grown closer and stronger as a team. I am convinced that we have the tools and tenacity to face and overcome the challenges of the economic crisis in this, our anniversary year.

Much of our success can be attributed to our systematic development from a specialist for analytical services and technology provider in chemical catalysis to an integrated pharmaceutical service provider for analytical and chemical development. A prime example of this is the new GMP kilo lab, which recently went into operation successfully. This laboratory, supported by the comprehensive analytical services that have always been part of our core competencies, can produce active pharmaceutical ingredients for clinical studies up to phase IIa. With some pride we can say that we have also established ourselves internationally thanks to our scientific excellence in the area of solid-state development.

Any accomplishments we celebrate would not have been possible without the trust of our valued customers. Through partnership and loyalty, your inspiring input and dialog has fostered the growth of our services and been instrumental in Solvias' success. Thank you for being part of this celebration!



Dr. Hansjörg Walther



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**DR. HANSJÖRG WALTHER** — CEO Solvias AG

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# Shorter time to market – **Our contribution for preformulation activities**

Efficient drug development processes are the key to success. In this article, we explore several methods and present our approach for solid-state development.

*Author: Dr. Michael Becker*

One omnipresent trend in pharmaceutical drug development is the tendency to speed up processes. Needless to say, scientific expertise must be at the highest level and risk of failure kept as low as possible, even if processes are accelerated. The final goal is to cut costs, extend patent protection and maintain exclusivity for the drug molecule or its application. But how can processes be rationalized and development times reduced?

polymorphism, and crystallization development represent very good examples where high throughput systems (HTS) are useful. Development times can be cut significantly as the use of multi parallel reactors deliver more results on a certain topic in a shorter time frame.

Bearing this in mind, some thought HTS was the “philosopher’s stone” to solve all drug development issues or in this case,

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**Solvias does handle each and every case uniquely to assure best science for each task we deal with.**

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## **EXPLORING THE METHODS**

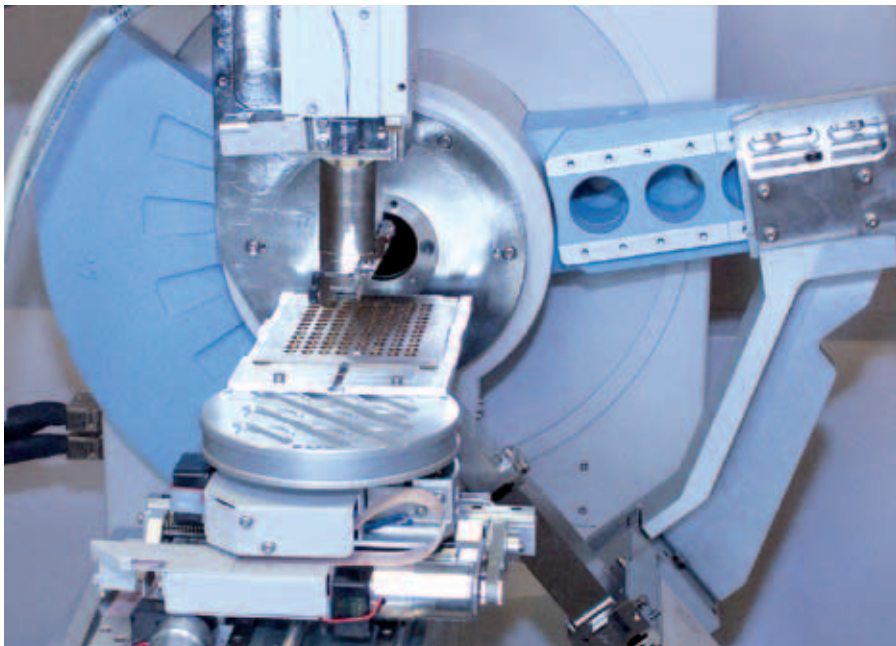
One possibility is to reduce development time by multi parallel project approaches. Different aspects of drug development are performed by individual scientific teams working in parallel, if possible. This method has proved to be successful, but, the efforts required for managing the interfaces also need to be considered.

Another method of reducing development times is to automate time-consuming work and use high throughput devices, such as are in use 24/7. Salt,

particularly, with pre-formulation. However, it turned out that although HTS does deliver a massive amount of data, if the HTS approach is not rational and the experiments not set up by savvy scientists, even hundreds or thousands of experiments will not provide the right answers to your question.

## **THE SOLVIAS APPROACH**

This is why Solvias’ HTS philosophy is based on a fundamental understanding of the specific drug substance prior to



< PanAnalytical X'Pert PRO-MPD

screening. High throughput screening is used for salt/co-crystal, polymorphism, and crystallization development projects and additionally support projects for specific hydrate screening, stabilization of amorphous compounds or enhancement of enantiomeric excess.

Solvias implemented its first HTS capabilities in 2000, and since then we have gained experience using this technology for over 600 customer projects.

To support our customers even better we introduced a new lab automation platform which is capable of performing any kind of experiment for the purposes described above. Amongst others, the platform will support:

- Evaporation experiments
- Temperature cycling experiments
- Slurry experiments at different temperatures
- Filtration experiments for various solvents and temperatures
- Solvent screenings with direct HPLC coupling

The leads of such screening experiments will be analyzed by two independent technologies to assure that salt/co-crystal

formation or formation of new polymorphic forms has occurred. Over and above our Raman microscopic investigations we now also offer X-ray powder diffraction (XRPD) on each sample generated within a screening project. New detector technologies and software tools to evaluate the single XRPD spectra will further diminish the evaluation time and customer reporting. Since July 1, 2009, a new PanAnalytical device has been installed in our laboratories, now ready for use.

Fortunately, or unfortunately, reality shows that not every drug candidate may benefit from high throughput techniques as every project is unique. Solvias does handle each and every case uniquely to assure best science for each task we deal with. Our combination of experience, rational design, scientific excellence and up-to-date technology, including high throughput devices, may not be the "philosopher's stone" but we might be quite close.

Solvias' Solid-State Department has over 20 years of industrial experience in the field of drug development. Out of several projects, more than 50 customer patents were filed to support and secure intellectual property for our clients.



**DR. MICHAEL BECKER** — Product Manager  
Solid State Development

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# The relevance of solid-state development is crystal clear

A better knowledge of solid-state properties offers a host of advantages for drug development. We had the opportunity to speak with Dr. Luc Quéré, Head of solid-state chemistry at UCB in Braine-L'Alleud, Belgium.

*Interview: Silke Oeschger*

## ***What relevance does solid-state chemistry have at UCB?***

The importance of solid-state chemistry has increased significantly over the last five years. In the course of later development steps and through troubleshooting we learned, as a number of companies have, that solid-state chemistry is of the utmost importance. In response to what we learned, we decided to set up a specific team which could deal with such issues and hopefully anticipate them. This department has been up and running for three years now. Moving from empiricism to a more in-depth exploration of the physical principles upon which we conduct the drug development is our main mission.

## ***Which questions are answered with solid-state development?***

There is actually a wide variety of questions which are investigated every day, from a new polymorph search to a scuff mark examination on a tablet. At UCB, we support process chemistry, formulation and manufacturing, as well as IP (intellectual property) and RA (regulatory affairs) departments. Solid-state issues cross the boundaries that we draw in our organizations.

## ***Which is the most crucial step regarding solid-state investigations during product development?***

The main effort occurs before phase I. Nowadays, we place the most emphasis on doing things earlier in the drug development process. Before a substance reaches the human clinical phases, we need a reasonable, developable form. For this, we have a kind of check list of important criteria to meet. After proof of concept (POC), we conduct even more extensive screening.

## ***Is this mainly considered from an intellectual property point of view?***

At the stage after POC, yes. The closer we are to product launch, the more we invest in ensuring that we do not miss anything and plug some potential loopholes in the fence. It is about protecting, but also about being proactive in creating new materials. We are developing new IP through new ideas. Anyway, at the end of the day, those efforts are made in order to bring benefit to the patient.

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**The closer we are to product launch, the more we invest in ensuring that we do not miss anything and plug some potential loopholes in the fence.**

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## ***Do you have a general procedure in place for such investigations?***

It is not easy to define a general procedure that fits for all candidates. For sure, we usually start by exploring the polymorphism landscape or by screening alternative options like salts or co-crystals. Our lab looks like a crystal farm. And based on the harvested results, we decide how to proceed on a case-by-case basis.

***How does knowledge of solid-state properties benefit process chemistry?***

It is vital to know what is happening in the vessel. For example, physical purity of your powder might influence the outcome of a filtering or drying step. Checking for any physical transformation is also crucial. A solvate, for instance, which forms at a certain point of the crystallization could be very undesirable if, for example, it blocks the whole stirring system. Many small or large problems can be linked to unwanted crystallization products. The aim is to have a process which ensures that the right solid form of the drug is robustly obtained.

***What role does solid-state development play for life cycle management?***

As I said earlier, a stronger solid-state knowledge enables us to extract the best value we have at hand and improve the product for our patients. In specific cases, for example, providing a patch instead of a tablet may encourage patient compliance. Then, the active pharmaceutical ingredient would be in a completely different environment and the guidelines we used for developing a tablet may not apply any more. Or, we could think of changing the composition (salt/co-crystal) or the crystal shape for whatever good reason. It reminds me of the famous

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**... a stronger solid-state knowledge enables us to extract the best value we have at hand and improve the product for our patients.**

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***Solid-state development is often seen as a mediator between chemistry and pharmacy. Would you agree with this statement?***

Yes, in my opinion, process chemistry, pharmacy and solid-state development form an important trinity, but all of them speak quite different languages. As solid-state development supports both chemical development and the formulation department, I suppose we sometimes assume the role of mediator. What is clear to me is the specificity of those three approaches. Each demands unique expertise with – for instance – a big emphasis on physical sciences for solid-state chemistry.

example of Ajinomoto, which gained advantage over Nutra-sweet by producing crystalline aspartame with spherical particles. Aspartame, be it from Ajinomoto or Nutrasweet, is of the same form but Ajinomoto produced spherical crystalline material which brings a definitive advantage from a manufacturing perspective.

Again, those examples demonstrate that new solid-state investigations are necessary at various stages of development as well as postlaunch sometimes.

***When you are working with external service providers, what are the main success factors?***

First of all, I need to feel that the external service provider acts as a colleague. This means he or she shows initiative in finding the best solution and is as motivated as I am. The scientific excellence of the project leader is also a top priority for me. In the end, there must be a very solid report that does not need to be repeated or extended in any way to answer the primary question.

***Are there any trends or technologies that will influence solid-state development in the future? What improvements do you expect?***

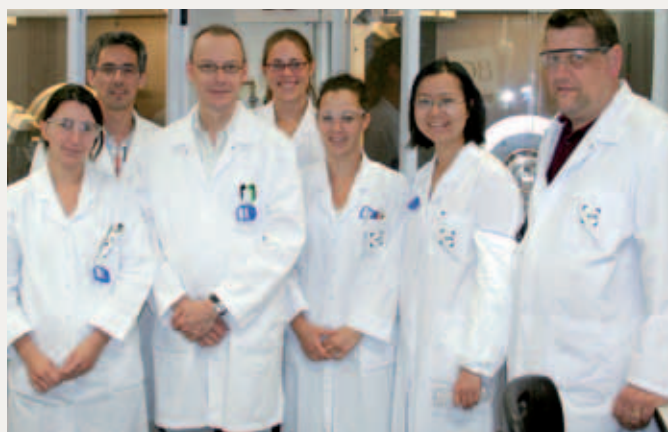
In my opinion, the old well-developed (sometimes forgotten) techniques like microscopy or IR in combination with elaborated spectroscopic means like Raman, X-ray diffraction or solid state NMR lead to a high level of analytical characterization. I would just stress the growing importance of solid-state nuclear magnetic resonance (NMR) to studying pharmaceutical solids. This non-invasive and non-destructive analysis brings immense benefits to the study of solid phases, being amorphous or crystalline. Be it applied for drug product or drug substance, the approach is highly quantitative and allows us to access more subtle information like drug excipient interactions or the exact role of residual solvent molecules, for example. If the sensitivity could also be improved, this technique could really become the "gold standard".

Thank you for your time, and for answering our questions.



**DR. LUC QUÉRÉ** — Head of solid-state chemistry at UCB

*After earning a PhD in physical chemistry from FUNDP Namur University, Belgium, Luc Quéré did his postdoc at the Max-Planck Institute in Munich. His academic interests were focused on drug design. In 1998, he joined UCB, first as a team leader in physicochemical drug profiling and is now currently Head of the New Chemical Entity Characterization department where solid-state development is performed. He is author or co-author of about 25 scientific publications or patent applications.*



*From left to right: Gaëlle Simon, Luc Quéré, Luc Aerts, Sabrina Graffeo, Sarah Le Meur, Qionqzhi Wu, Yves Mary*

**ABOUT UCB**

*Headquartered in Brussels, Belgium, UCB is a biopharmaceutical company dedicated to the research, development and commercialization of innovative medicines with a focus on the fields of central nervous system (CNS) and immunology disorders. UCB is driven by a passionate desire to liberate families living with severe diseases so that they can enjoy normal, everyday lives. Employing almost 10,000 people in over 40 countries, UCB achieved revenue of € 1.6 billion in the first half of 2009.*

[www.ucb.com](http://www.ucb.com)

# The fast track to rapid and **robust results**

A well-thought-through strategy guarantees fast and efficient method developments ensuring methods that are reliable and robust.

*Author: Dr. Barbara Channer*

## STRATEGIC APPROACH – A SHORTCUT TO METHOD DEVELOPMENT

Traditional methods for HPLC (High Pressure Liquid Chromatography) separations were often developed in an unsystematic and time-consuming manner that does not address all the factors which are essential to establishing a robust method. Failing to do so may subsequently lead to deterioration in the performance of an analytical method.

## TAKING THE CHROMATOGRAPHIC METHOD DEVELOPMENT TO THE NEXT LEVEL

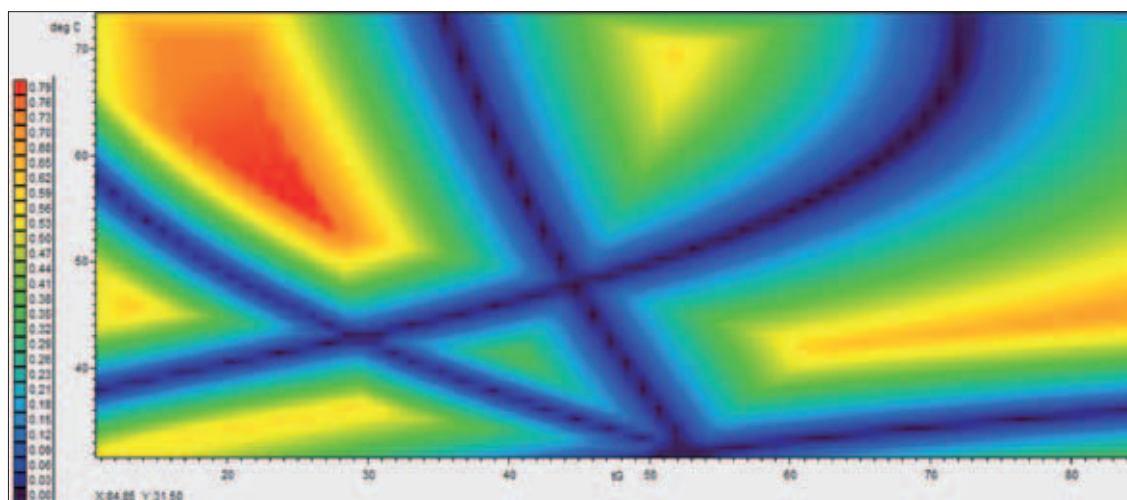
Accelerated approaches which provide robust methods, supported by scientifically sound design space, are today achieved by using a combination of state-of-the-art practices and experience. In the past, accelerated approaches were often limited by the instrumentation which was only capable of delivering

up to 450 bar pressure. With the implementation of ultra performance liquid chromatography (UPLC) in 2004 by Waters, with pressures going up to 1,000 bar, a huge step forward was achieved in overcoming this limitation. Today there are several commercially available instruments with pressures reaching up to 1,200 bar, making faster sample throughput possible. Combining this technology with a column selection approach (using different stationary phases) shortens development times and enables the evaluation of various parameters in less time than the classic development strategy.

A typical development design, based on our experience with the below outlined system, would contain a set of up to six short columns containing sub-3 micron particles. The mobile phase is optimized with up to 12 aqueous and 2 organic eluents in a single run. Key parameters for modeling might include temperature and pH.

COLUMN	MOBILE PHASE A	MOBILE PHASE B	GRADIENT	TEMPERATURE
C 1	phosphate-buffer pH 7.0	methanol	tG 1	20°C
C 2				
C 3	phosphate-buffer pH 5.0	acetonitrile	3 x tG 1	40°C
C 4				
C 5				
C 6	phosphate-buffer pH 2.7			

^ Possible combination of the five scouting parameters



^ Resolution map for the gradient time/temperature model

Prior to the actual experiments the following parameters will be set, based on the aim of the development project:

- Assess the physico/chemical properties of the analytes
- The number of short sub-3 micron LC columns for fast chromatography
- Selection of stationary phases based upon selectivity differences and security of supply of columns
- Selection of mobile phases, e.g. different pHs based upon pKa, log P, and theoretical stability of the analytes
- Selection of gradient times
- Selection of temperatures for the experiments

Experiments will then be conducted according to the parameters set, and the results analyzed using retention modeling software. In accordance with the target of the individual development project (e.g. run time, resolution, robustness), the optimal conditions, delivered by the software, will be verified in a separate experiment. If required, the method could later be scaled up to longer LC columns and validated according to ICH (International Conference on Harmonization) guidelines.

### PREPARED FOR THE FUTURE

Solvias' technology platform for method development has proven to be fast and therefore cost-effective in customer drug development projects. Not only for de novo method development projects but also as a support for stability investigation. If new stability data are available, that information can easily be incorporated to expand the model reliably for stability indication purposes.

Furthermore, the analytical group at Solvias has established technologies to perform development and validation projects for any kind of new chemical or biological entity supplemented by comprehensive stability investigation (accelerated, ICH conform). Release testing of drug substance/drug product, following ICH guidelines in accordance with cGMP (current Good Manufacturing Practice) quality standards of customer-specific or pharmacopeia methods rounds out our portfolio of analytical investigations within drug development.



DR. BARBARA CHANNER — Product Manager  
Analytical Services

# Ten years catalysis at Solvias: from R&D to industrial processes

Combining innovative synthesis with sophisticated catalytic methods is one of the strengths of Solvias. Hans-Ulrich Blaser, Chief Technology Officer, describes in the following article how this technology has developed during Solvias' first decade.

*Author: Dr. Hans-Ulrich Blaser*

## CATALYSIS IN THE FINE CHEMICALS INDUSTRY – WHAT IT'S ALL ABOUT

Fine chemicals are still predominantly produced using stoichiometric organic methods. This is in strong contrast to the production of bulk chemicals which relies heavily on catalysis. The difference can be explained on the one hand by the higher complexity of fine chemicals which makes catalysis more demanding and on the other hand by the fact that process chemists are usually more familiar with sophisticated organic synthesis. Nevertheless, the application of selected catalytic methods has increased in recent years in part because both production costs and waste minimization are of growing importance, even for high-value pharmaceuticals, and also due to the new catalytic methods developed in academic laboratories which are now slowly finding their way into industrial laboratories.

At Ciba-Geigy, we found that only very few catalytic methods are actually applied on a regular basis. The most important ones being heterogeneous hydrogenation, coupling catalysis and homogeneous enantioselective hydrogenation with the successful methods sharing the following properties: They have a broad scope to make important structural moieties; the catalysts are easy to apply and commercially available and, not least, process chemists „believe“ in the potential of the technology (success breeds success). In all three areas, we could build on a substantial basis of important R&D results as well as significant production processes.

## HETEROGENEOUS HYDROGENATION – REVIVAL OF AN OLD TECHNOLOGY

Heterogeneous hydrogenation is the most widely applied catalytic reaction in the fine chemicals industry. Indeed, over 34,000 different substrates have been hydrogenated since the start of the hydrogenation laboratory in the former Geigy in the 1930s. This technology got a new boost when it was discovered that modification

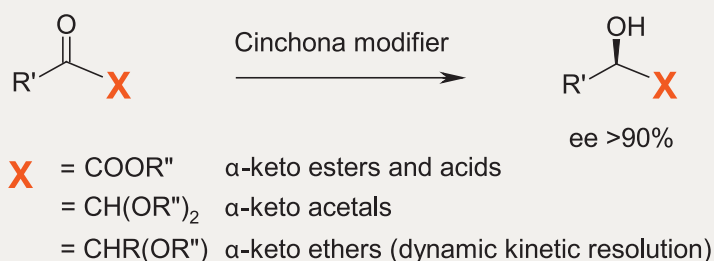


**DR. HANS-ULRICH BLASER** — Chief Technology Officer

*After obtaining a PhD degree from the ETH Zurich and several postdoctoral positions at the University of Chicago, Harvard University and Monsanto (Zurich), Blaser joined the Central Research Laboratories of Ciba-Geigy in 1976 and has been involved in building up the catalysis department ever since, first as research chemist and later in various executive functions. At Solvias he has been Chief Technology Officer since its start.*

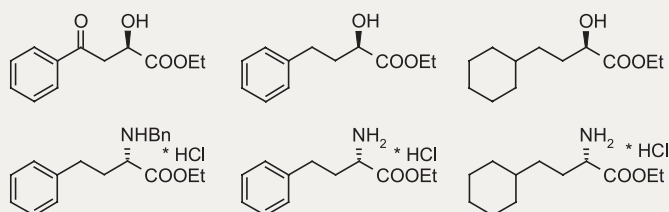
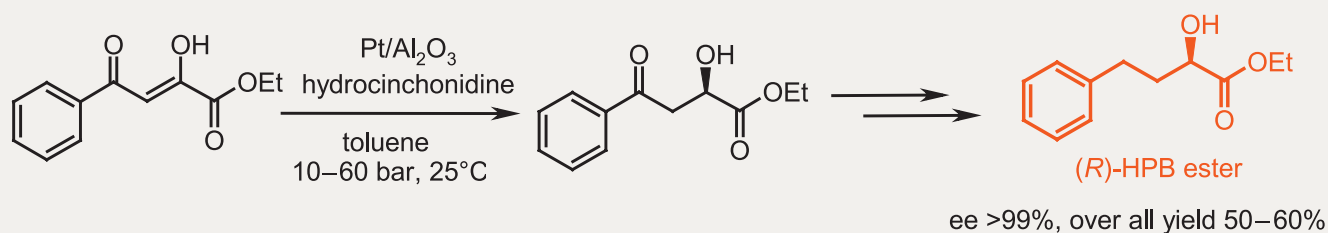
of the classical catalysts could significantly improve their selectivity and indeed, we concentrated our research efforts on this approach. We had considerable success for the enantioselective hydrogenation of activated ketones and the chemoselective reduction of nitroarenes with other reducible substituents.

While our early research in the area of the enantioselective ketone hydrogenation was focused on fundamental and mechanistic aspects of the cinchona-modified platinum catalysts, work at Solvias was dedicated to broadening the substrate scope and to synthetic applications. We showed that besides the  $\alpha$ -keto esters,  $\alpha$ -keto acetals and ethers can also be reduced with high enantioselectivities, giving access to  $\alpha$ -hydroxy acetals and ethers which are valuable chiral building blocks.

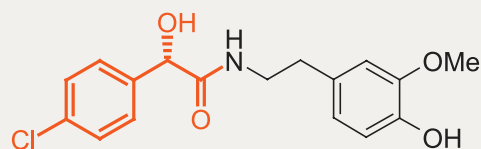


< Extended scope of the cinchona-modified Pt catalysts

The optimized catalyst system was applied on a technical scale to an improved total synthesis of (R)-HPB ester, key intermediate for the so-called PRIL family of ACE inhibitors as well as related chiral building blocks and for the chiral part of an experimental fungicide.



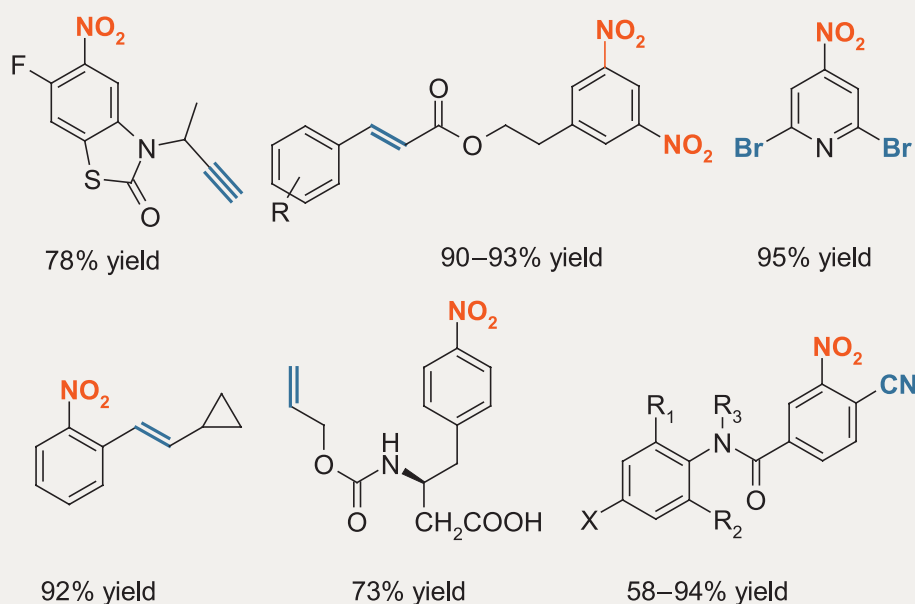
Chiral building blocks, preparative scale  
 ee >99%, chemical purity >98%



Experimental fungicide

^ Technical applications of cinchona-  
 modified Pt catalysts

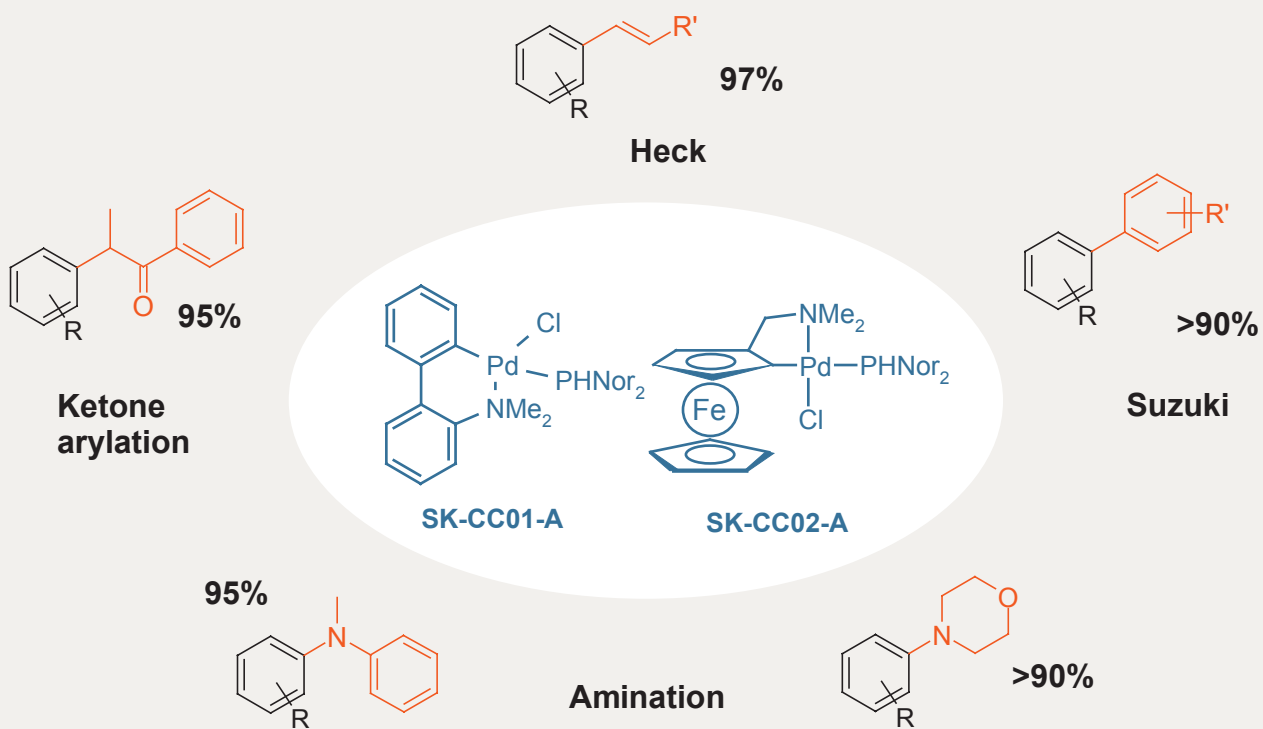
The two modified Pt catalyst systems developed in the mid nineties for the effective catalytic chemoselective hydrogenation of nitroarenes with a wide variety of reducible functional groups were applied to an array of customer problems. Especially the 5% Pt/C catalyst modified with  $\text{H}_3\text{PO}_2$  and promoted with vanadium compounds proved to be very effective. The new methodology is now used on a technical scale to produce highly pure aniline derivatives as intermediates for agrochemicals, pharmaceuticals and electronic materials.



< Selected examples for the chemoselective hydrogenation of functionalized nitroarenes using a Pt/C-H<sub>3</sub>PO<sub>2</sub>-V catalyst (reducible functions in blue)

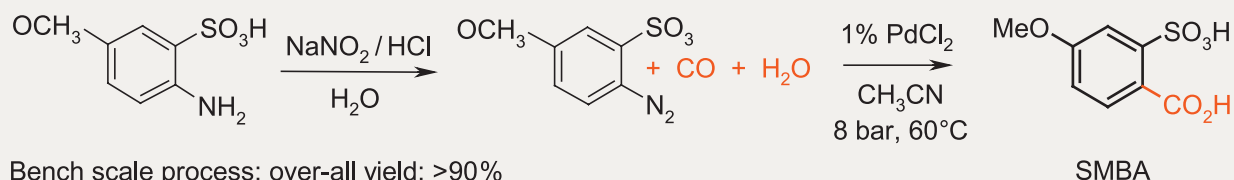
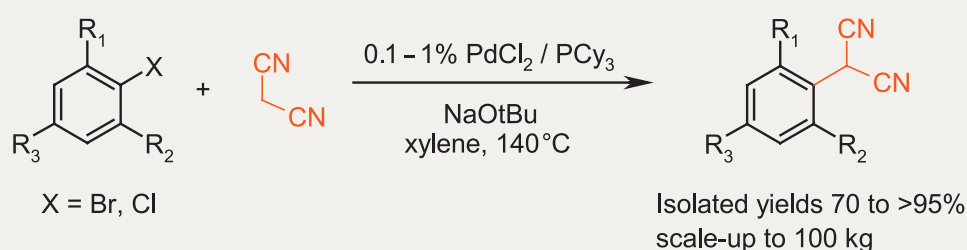
### COUPLING CATALYSIS – THE MOST ELEGANT APPROACH TO SUBSTITUTED AROMATICS

The Pd-catalyzed C-C and C-N coupling reactions are among the most important industrial methods to produce substituted aromatic moieties. As a matter of fact, we developed a number of production processes for Ciba-Geigy. At Solvias, we concentrated our efforts on the development of easy-to-handle single component SK-CC catalysts able to activate the cheap aryl chlorides for Buchwald-Hartwig aminations, Heck and Suzuki reactions, and ketone arylations. In September 2008, we completed our catalyst portfolio by in-licensing the cataCXium catalysts from Evonik. In collaboration with the academic groups of Beller and Hartwig it was shown that Pd-Josiphos complexes are very active catalysts for the carboxylation and amination of aryl chlorides with turnover numbers up to 100,000.



^ Scope of the SK-CC catalysts for the preparation of substituted aryl building blocks

Several industrial processes using Pd catalysts were developed for our customers, among them the synthesis of 2,4,6-trialkylaryl malononitriles, key intermediates for oxopyrazoline herbicides and 2-sulfo-4-methoxybenzoic acid (SMBA), starting from the very cheap 2-amino-4-methoxy-sulfonic acid.

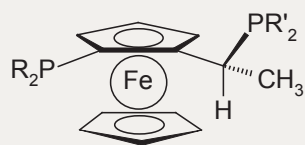
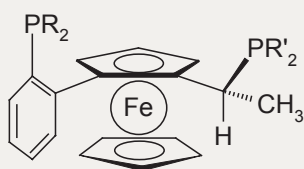
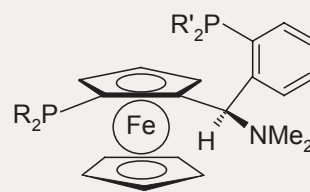
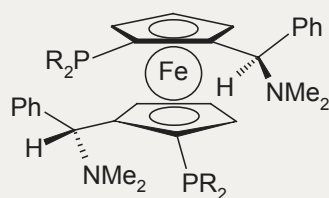
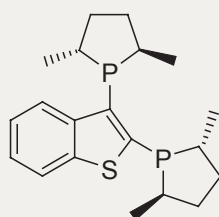
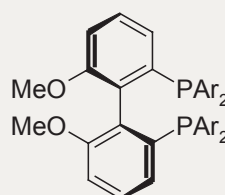
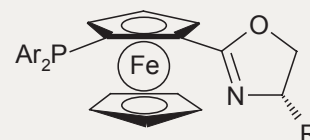


### HOMOGENEOUS ENANTIOSELECTIVE HYDROGENATION – ON ROUTE TO A MATURE PRODUCTION TECHNOLOGY

^ Industrial processes using Pd-coupling catalysts

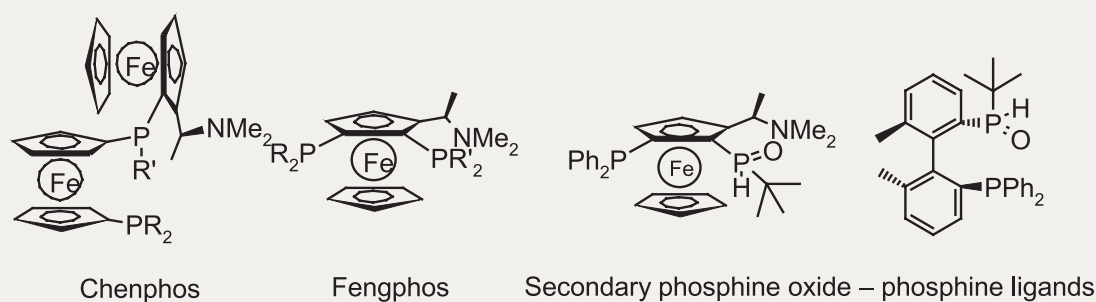
When Nobel Prize Winner Jeremy Knowles published his results for producing L-dopa via homogeneous enantioselective hydrogenation in 1977, it was not clear whether this technology could really be applied on a general basis. This doubt was laid to rest when we succeeded in finding a catalyst for the production of (S)-metolachlor. This process is currently the largest enantioselective catalytic process and Ir-Josiphos is the most active and productive catalyst developed to date. This achievement has motivated us to continue to develop new chiral ligands, efficient screening methods and to apply our know-how to solve „real-world“ problems for our customers.

While there are now literally thousands of chiral ligands known in the literature only very few have ever been made on a larger scale and even fewer are available commercially in technical volumes. In recent years, Solvias has arguably developed the most comprehensive portfolio of chiral phosphine families which are available for screening (Solvias Ligand Kit) as well as for production purposes on a scale up to 100 kg. In addition, in September 2008, we obtained an exclusive license for the catASium ligands from Evonik.

**Josiphos****Walphos****Taniaphos****Mandyphos****Butiphane****MeO-Biphep****Naud Catalyst**

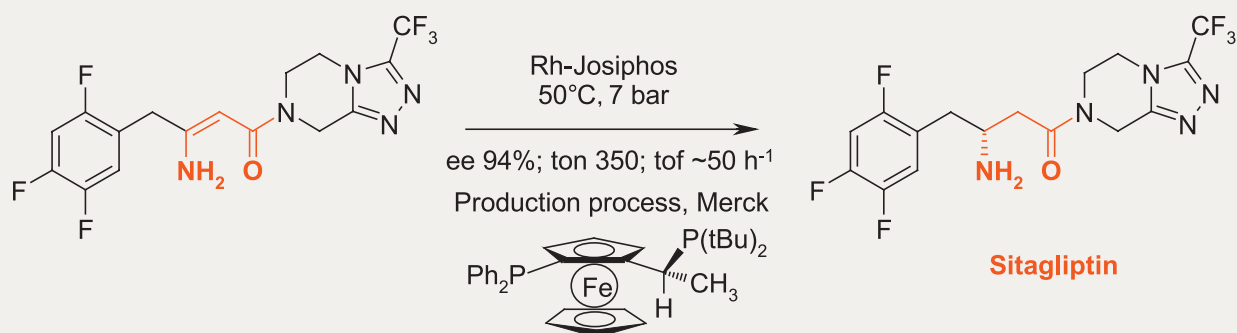
Furthermore, we have a number of experimental ligands such as Chenphos and Fengphos under development which are regularly included in the HT screening for customer problems but which up to now have only scaled to multigrams. Another exciting development is our finding that ligands containing secondary phosphine oxide and phosphine groups have very interesting catalytic properties. This is a new class of modular and readily accessible ligands with an as yet unknown industrial potential.

^ *The Solvias Ligand Kit*



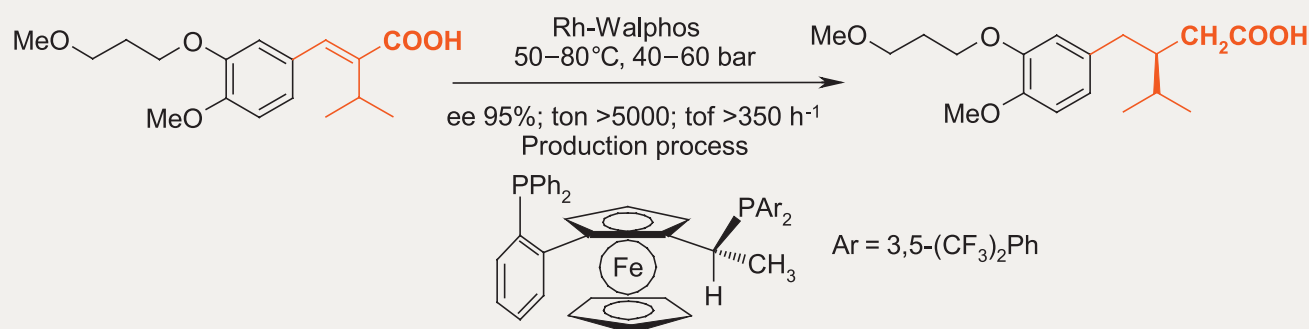
Among the many customer projects where Solvias catalysts have been successful we can present two cases where efficient production processes with rather difficult substrates have been implemented on a multiton scale. The first example is the Rh-Josiphos-catalyzed hydrogenation of an unprotected dehydro  $\beta$ -amino acid which is the key step of a new synthesis for Sitagliptin, a DPP-IV inhibitor for the treatment of type 2 diabetes, now being marketed by Merck. This discovery required the screening of dozens of ligands and additives carried out in a collaborative effort both at Merck as well as at Solvias.

^ Structures of experimental ligands



^ Rh-Josiphos-catalyzed process for Sitagliptin

The second example is the Rh-Walphos-catalyzed hydrogenation of a sterically hindered  $\alpha,\beta$ -unsaturated acid, a precursor of synthon A in the total synthesis originally developed by Solvias for the renin inhibitor Aliskiren of Speedel/Novartis. The Rh-Walphos catalyst is easy to handle and achieves high turnover numbers and high ee values.



^ Rh-Walphos-catalyzed process for an Aliskiren building block

### SOME FINAL COMMENTS

This short account shows that catalysis is indeed a valuable technology to not only produce simple bulk chemicals but that it is also applicable to the synthesis of complex, multifunctional molecules for the life science industry. I am convinced that the three methodologies described above will be able to successfully compete against other synthetic methods. On the other hand, it is also clear that it will require continuous efforts to remain competitive in this rapidly developing area of synthetic methodology.

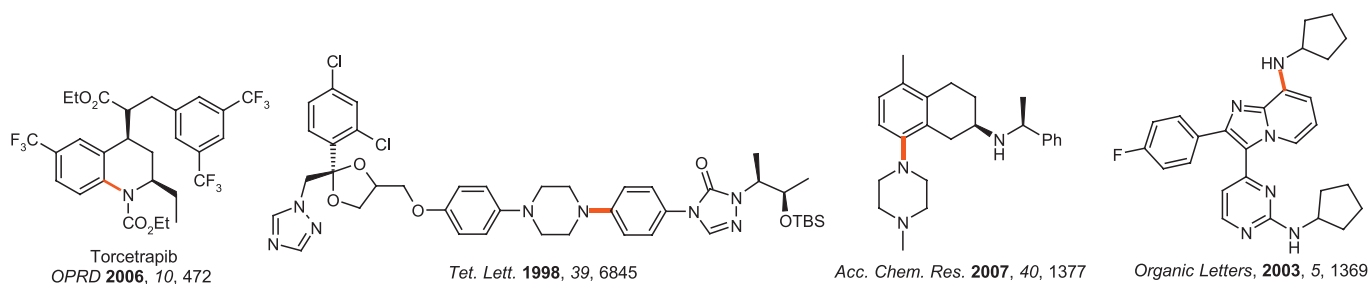
# CN coupling makes its mark as a preferred method for synthesizing arylamine APIs

Solvias responds to the hot CN coupling market with the introduction of a high throughput screening (HTS) protocol that provides best leads in terms of chemistry and cost.

Authors: Dr. Garrett Hoge\*, Dr. Ulrike Nettekoven, Patrick Furer

## CN COUPLING IN THE PHARMACEUTICAL INDUSTRY

The utilization of CN coupling, or the synthetically useful catalytic formation of carbon-nitrogen bonds from aryl halides and amine substrates, holds great promise for the production of pharmaceutically active compounds. Because of the development of new ligands and conditions that promote these transformations in a highly generalized fashion, these types of transformations have experienced a recent boom in interest and application. Figure 1 shows examples of pharmaceutically active compounds that were developed and scaled up with CN coupling as the lynchpin step in the synthesis. This industrial interest is understandable given that many drugs contain an arylamine functionality. In fact, approximately 25% of new chemical entities (NCEs) approved by the FDA between January 2008 and June 2009, have an arylamine functional group.<sup>1</sup> In addition, the inherent synthetic advantage of using only small amounts of a catalyst to promote a reaction coupled with the harnessing of a powerful transformation that cannot be accomplished directly via classical methods, presents a convincing argument for the industrial use of this technology.



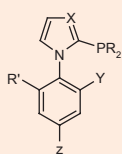
^ Figure 1: Industrial examples of CN coupling<sup>1</sup>

<sup>1</sup>Emboldened red-colored bonds indicate where CN coupling occurred.

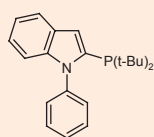
## HIGH THROUGHPUT SCREENING FOR RAPID RESULTS

Based on this evidence, it is not so surprising that Solvias has seen an increased request rate for CN coupling projects. In order to handle these customer requests in the most efficient and state-of-the-art fashion possible, Solvias has developed a high throughput screening (HTS) strategy for finding the best ligand and reaction conditions for any screened CN coupling transformation. Key benefits for the customers are peace of mind that a wide scope of ligands and conditions are tested for the enablement of their transformation, fast identification of leads that promote faster time of a process to manufacturing, and a low cost due to efficiency gains in the utilization of standardized protocols.

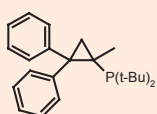
### MONOPHOSPHINES



- 1: X=N, R=Cy, R',Y,Z=Me  
(cataCXium PlCy, Solvias)  
2: X=C, R=Cy, R',Y,Z=H  
(cataCXium PCy, Solvias)  
3: X=H, R=tBu, R'=MeO, Y,Z=H  
(cataCXium POMetB, Solvias)



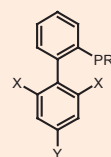
- 4: (cataCXium PlntB)



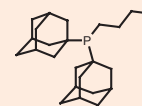
- 5: (c-bridp, Takasago)



- 6: R=Cy (generic)  
7: R=Ph (generic)  
8: R=o-anisyl (generic)  
9: R=MOD (generic)  
10: R=tBu.HBF<sub>4</sub> (generic)

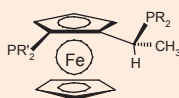


- 11: R=Cy, X=H, Y=H  
(Johnphos, Shasun)  
12: R=Cy, X=OiPr, Y=H  
(Sphos, Shasun)  
13: R=Cy, X=OMe, Y=H  
(XPhos, Shasun)  
14: R=Cy, X=iPr, Y=iPr  
(Ruphos, Shasun)

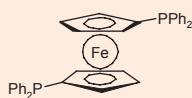


- 15: (cataCXium A, Solvias)

### DIPHOSPHINES



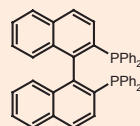
- 16: R=tBu, R'=Cy  
(Josiphos, Solvias)  
17: R=Cy, R=Cy  
(Josiphos, Solvias)



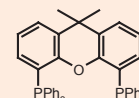
- 18: (dppf, generic)



- 19: (dppp, generic)

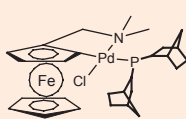


- 20: (binap, generic)

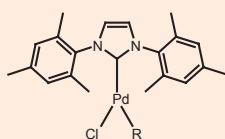


- 21: (xantphos, generic)

### PALLADIUM COMPLEXES



- 22: (CC02, Solvias)



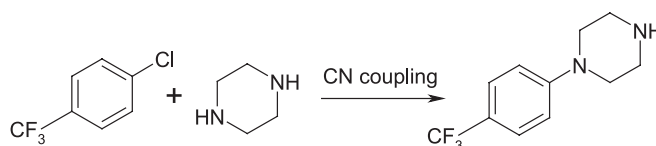
- 23: R=allyl  
(CX22, Umicore)  
24: R=benzallyl  
(CX31, Umicore)

^ Figure 2: Solvias standard CN coupling HTS plate:  
24 ligand design

### THE CN COUPLING STRATEGY

A key parameter of the Solvias CN coupling screening strategy is neutral screening of all available ligands by Solvias including: 3rd-party ligands (ligands owned by companies other than Solvias), IP-free ligands (ligands whose composition of matter is not covered under patent), and Solvias CX coupling ligands. Figure 2 shows the standard design ligands that Solvias utilizes for its 24-ligand standard design plate for CN coupling.<sup>2</sup> The ligands in Figure 2 represent monophosphines, diphosphines, and preformed palladium complexes. This design allows for these

24 ligands from all available ligand classes to be tested with four parameters each to equal  $24 \times 4 = 96$  total reactions to be performed in our 96-well HTS reactor. Parameters, of course, are chosen based on typical choices of metal precursor, base, and solvent. Parameters such as ratio of starting materials, substrate: catalyst, base equivalents, and concentration can also be varied. We feel that this standard design best positions Solvias to quickly find the leads necessary for our customers' drug development projects.



^ Figure 3: CN coupling of an arylchloride with piperazine

### AN EXAMPLE

Figure 3 depicts a transformation that has been carried out at 100 g scale using a Buchwald ligand.<sup>3</sup> This example shows the utility of CN coupling using Buchwald ligands at suitable scale to demonstrate scalability of a process. Although most would agree that this is an excellent example of industrially useful CN coupling chemistry, many of those involved in the development of pharmaceuticals are interested in finding the best lead in terms of chemistry and cost. For instance, a generic ligand will most definitely have a cost advantage over a patent-protected one. For this reason, it is in the best interest of the process chemist to screen widely in order to find the best lead for development. This is an effort that lends well to a high throughput screening strategy. To demonstrate the CN coupling HTS approach, the transformation in Figure 3 was screened against the Solvias standard CN coupling plate to determine how many other potential development leads existed for this transformation. The following 4 parameters were used for this study:

Parameter 1: Pd(OAc)<sub>2</sub>, Toluene, NaOtBu

Parameter 2: Pd<sub>2</sub>(dba)<sub>3</sub>, DME, K<sub>3</sub>PO<sub>4</sub>

Parameter 3: Pd(OAc)<sub>2</sub>, Toluene, K<sub>3</sub>PO<sub>4</sub>

Parameter 4: Pd<sub>2</sub>(dba)<sub>3</sub>, DME, NaOtBu

Conversion was judged versus an internal standard because of starting material volatility. Overall, % conversion was determined along with by-product formation (including the double addition by-product). Conditions were: 1 eq. ArCl, 1.5 eq. Piperazine, 2 eq. Base, 0.25 eq. Trimethoxybenzene (internal standard), 80 C, 100:1 S/C, 16 hours.

As a result, 11 ligand leads were found which provided a significant conversion that would be suitable for further development (Table). From this hit list, we derived the following conclusions:

- Buchwald ligands are excellent ligands for this transformation. Six of the eleven hits were found using Buchwald ligands (entries 3–8).
- There are four other ligand classes that provide a number of hits that were suitable for further development (entries 1, 2, 9 and 10). Of these leads, three (entries 1, 2, and 9) were from the Solvias ligand systems cataCXium P series (ligands 1 and 3)

and the Hartwig system based on Josiphos (ligand 16). Entry 10 was a lead generated from Umicore (ligand 24).

- Only a small amount of double addition was observed for any of the leads in Figure 2 (< 0.5%).
- Generic ligands did not compete well with patented ligands. Tri-*t*-butylphosphine, ligand 10, provided the best lead among the generics (47% conversion) which was significantly lower than any of the best leads with patented ligands.

ENTRY	1	2	3	4	5	6	7	8	9	10
LIGAND	1	3	12	12	12	13	13	14	16	24
PARAMETER <sup>i</sup>	1	2	2	1	4	2	3	2	2	2 <sup>ii</sup>
CONV. (%)	72	70	74	66	57	67	56	69	57	63

<sup>^</sup> Table: Best results of the CN coupling 96-reaction HTS plate

<sup>i</sup> Parameter numbers 1–4 with their associated conditions can be found in the text.

<sup>ii</sup> 24 is an ML complex. Only solvent and base from conditions 2 were applied.



DR. GARRETT HOGE — Product Manager Catalysis

### A CLEAR ADVANTAGE OF THE HTS SCREENING APPROACH

Four alternative catalyst systems other than Buchwald ligands were found for the CN coupling in Figure 3. These results demonstrate the advantages of utilizing an HTS screening approach to discover enabling ligands and conditions for CN coupling transformations.

### CONCLUSION

The industrial process chemist is always looking for the best leads for development, and it is clear that by screening a wide array of conditions and ligands multiple hits can be found from which the chemist can choose. The ability to screen large numbers of reactions is simplified with high throughput screening techniques and workflow. HTS often offers the luxury of having good options and alternatives in process development and allows the best process to be implemented in terms of chemistry and overall cost. HTS for CN coupling provides these advantages and enables the development of superior synthetic routes for arylamine APIs.

<sup>1</sup> Based on Solvias' internal product manager research utilizing the FDA Orange Book and integrity databases.

<sup>2</sup> Solvias also offers a 32 ligand HTS design for CN coupling that allows 3 parameters to be tested (32 x 3 = 96). The project leader at Solvias can choose between the two designs based on the need to screen more ligands (32-ligand design) or more parameters (24-ligand design).

<sup>3</sup> Presented by Professor Buchwald at Professor Pfaltz' 60th birthday symposium at the University of Basel in Basel, Switzerland 2009.

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# Barriers to winning the approval of biosimilars in the USA

The political debate surrounding generic biologics in the USA rages on. How can the best balance be struck between rewarding innovation and using competition to drive down the cost of health care, whilst at the same time protecting public safety? Opinions differ. Many factors are hotly debated but one stands out above all the others, namely data exclusivity. The lobbyists are hard at work. Billions of dollars are at stake.

*Author: Dr. Frank Moffatt*



**DR. FRANK MOFFAT** — Product Manager  
Biopharmaceutical Analysis

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Biologics are produced from genetically engineered cells. Considerable effort is needed to engineer a product of consistent quality in order to support claims of safety and efficacy. This applies equally to new innovator products and to biosimilars. Solvias has been heavily involved in a substantial proportion of the cGMP analytical chemistry manufacturing and controls (CMC) support for a leading biosimilar producer. From the analytical perspective, the key task has been the demonstration of comparability between the innovator biologic and the generic version. In our experience the data must be scientifically rigorous and of the highest quality. After all, regulators are risk averse and the world would not be deprived of a new treatment if a generic medicine is not approved.

## THE EUROPEAN EXPERIENCE

In Europe, a pathway is in place to approve what are referred to as biosimilars. There are not so many examples because most of the products on the market are still protected by patents. The biosimilars approved so far include: human growth hormone (rHGH, Omnitrope® Sandoz, Valtropin® BioPartners), epoetin α (EPO, Binocrit® Sandoz, Epoetin α Hexal® Hexal Biotech Forschungs, Abseamed® Medice Arzneimittel Pütter etc.), and granulocyte-colony stimulating factor (g-CSF, Filgrastim® Ratiopharm, Sandoz & Teva). Each protein-active ingredient is used in several products with different applicants. Our experience in Europe is that companies are willing to compete in the face the

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## From the analytical perspective, the key task has been the demonstration of comparability between the innovator biologic and the generic version.

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regulatory uncertainties and the commercial risks despite price reductions are only of the order of 10–40%. A much smaller figure than the 80–90% price reductions that often occur when generic versions of a small molecule drug appear.

### THE USA SITUATION

The modern era of small molecule generic drugs in the USA came into being on September 24, 1984, with the Hatch Waxman Drug Price Competition and Patent Term Restoration Amendment to the Federal Food, Drug, and Cosmetic (FD&C) Act. The amended act created abbreviated applications (ANDAs). Data exclusivity was granted for five years following the approval for marketing of an innovator drug. The system runs independently of any patents. An application to market a generic drug requires only analytical and limited bioequivalence data. There is reliance upon the fact of approval of the innovator drug and not upon the data itself. The original application is not reexamined.

The complication in the US arises because of the distinction between drugs and biologics. Drugs are approved under the FD&C Act. Hatch Waxman added two pathways 505(j) and 505(b)(2) for abbreviated applications. The 505(b)(2) relies upon investigation(s) not conducted by the applicant with no right of use or reference from the innovator. The 505(j) uses data establishing bioequivalence and showing the generic product is

identical to a previously approved reference listed drug. Most, but not all, protein-based biologics were approved under the Public Health Services (PHS) Act with no pathway for abbreviated applications. A few proteins have been approved under the FD&C Act, largely as an accident of history but this was enough to pave the way for the approval of the human growth hormone Omintrope®. Sandoz, however, had to use the courts to force the FDA to make a decision. Since most protein-based medicines were approved under the PHS Act, the FDA refuses to approve the so-called follow-on biologics in the absence of legislation that provides the necessary authority.

### COMPETITION VERSUS INNOVATION – WHAT LEGISLATION CAN WE EXPECT?

So far there are two competing bills, the “Access to Life-Saving Medicine Act” (Waxman, H.R. 1038) and the “Pathway for Biosimilars Act” (Eshoo, H.R. 1548). The latter proposes 12 years of data exclusivity whereas the former would only allow 5 years.

An Amgen spokesperson stated a position typical of innovator companies: “Without a fair and sustainable cycle of investment and returns in innovative R&D, biotech discovery will be stifled.” Support for this position comes from an academic study by Grabowski, Long and Mortimer of Duke University (Working Paper, no. 2008–10) who concluded that “limiting the data exclusivity period to less than 12–16 years results in failure of the



representative portfolio of biologics to break even within an extended period, under reasonable assumptions.”

Tom Moore, President of the generics company Hospira, begs to differ, citing Professor Kotlikoff’s conclusion that “long periods of marketing exclusivity lead to less innovation over time – not more.” In a report of March 2009 (“Potential unintended consequences of follow-on biologics”), Deloitte stated that limited exclusivity could trigger the need to maximize sales as early as possible to cover as many indications as possible as soon as possible, and that might skew development towards blockbusters.

The commissioner of the US Federal Trade Commission (FTC), Pamela Jones Harbour, supports “... the development of an abbreviated approval pathway for follow-on biologics, balanced by... recognition of consumer safety and incentives to innovate” and states that “the 12–14 year regulatory exclusivity period is too long to promote innovation.” In June 2009, Nancy-Ann DeParle, Director of the White House Office of Health Reform, described seven years of data exclusivity as a generous compromise, saying “Lengthy periods of exclusivity will harm patients by diminishing innovation and unnecessarily delaying access to affordable drugs.” The administration of President Obama is determined to reduce the costs of health care. Legislation is on the way. During the preparation of this article, on July 14, 2009, the Senate Committee on Health, Education, Labor and Pensions (HELP) examined biosimilars and concluded that

“a minimum of 12 years of data exclusivity establishes a fair and reasonable period to ensure continued biomedical innovation and provide the benefits of expanded competition” and at this time the Eshoo bill seems to be gaining more support than the Waxman Bill. The outcome remains uncertain as the debate swings back and forth.

### **MEETING THE CHALLENGE OF DEMONSTRATING COMPOSITIONAL SIMILARITY**

Reference to “generic biologics” raises some hackles because different versions of biologics are likely to be analytically distinguishable, and therefore can at best only be “similar.” This has a consequence. Safety testing will almost always require clinical studies and a post-authorization pharmacovigilance program. Biosimilars for the most part are not substitutable with the innovator product in the way that small molecule drugs are. This is yet another controversial area to be resolved.

Monoclonal antibodies (MAbs) are the largest class of biologics, based upon the number of products in development, but they are somewhat more complicated than the biosimilars approved to date; with patent expiries looming this will change.

Whilst the production of the protein amino acid sequence part of a MAb is merely a matter of correctly encoding and expressing the DNA sequence within whatever cellular expression system

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**Whether it is called a biosimilar or a follow-on biologic, the day will arrive when legislation all over the world will be harmonized such that these drugs are available for widespread use.**

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is chosen, the protein needs to be correctly folded and further modified by the addition of glycans. The heterogeneous composition of glycans is the outcome of cellular metabolic processes via different cellular compartments and families of enzymes. Furthermore, proteins are subject to aging processes leading to the phenomenon referred to as microheterogeneity. Proteins are relatively unstable. Finally, when a product is isolated from a living system it will contain trace quantities of product- and process-related impurities along with specific risks of contamination with adventitious agents including viruses and microorganisms. The International Committee on Harmonization (ICH) guideline Q6b gives an overview of the parameters that should be considered for characterization and specification setting as well as applicable analytical techniques. Consequently, it is said of biologics “the process is the product.” Because processes may not readily be copied, it is argued the products may not be copied. Hence, the widespread preference for a term such as “biosimilar” rather than “generic” or “biogeneric.”

What’s in a name? Whether it is called a biosimilar or a follow-on biologic, the day will arrive when legislation all over the world will be harmonized such that these drugs are available for widespread use. Qualified providers will then need to be equipped to handle the demand that is bound to follow. Of all the chemical parameters of a protein that can be measured, the composition of the glycans often pose the greatest challenge in delivering consistent quality because variants can trigger different clinical outcomes. Therefore, it is essential that a biopharmaceutical provider has the necessary experience of using a broad range of techniques including separation science, biochemistry and mass spectrometry within a robust cGMP environment. All of these competencies and more are now well established at Solvias.

**INFORMATION** — Commonly used terms

**Monoclonal antibodies (MAbs)**

*MAbs have a molecular weight of 150 kDa and comprise two heavy (ca. 50 kDa) and two light (ca. 25 kDa) peptide chains linked together by disulphide bridges. The peptide chains have primary, secondary, tertiary and quaternary structures, and further chemical or enzymatic post-translational modifications. A modification that may be particularly important for safety and efficacy is glycosylation that produces heterogeneous-branched N-linked glycans that are attached to certain asparagine residues.*

**Biosimilars (EMA) and follow-on biologics or follow-on protein products (FDA)**

*Biosimilars or follow-on biologics are terms used to describe officially approved new versions of innovator biopharmaceutical products following the expiry of patents or data/marketing exclusivity.*

## News



### GMP KILO LABORATORY

#### Swissmedic grants Solvias approval to manufacture APIs for clinical trials

Solvias complements its services with a new GMP kilo laboratory. The initial custom manufacturing campaign for an active pharmaceutical ingredient (API) has already started.

The newly designed and approved facility complements the existing kilo laboratory with rapid and cost-effective manufacturing of materials for use in phase I/IIa clinical studies. The plant is equipped with state-of-the-art 30 L to 100 L multi-purpose reactors capable of running reactions from  $-85$  to  $+160^{\circ}\text{C}$  and comprises a separate finishing area.

The chemical development group will be supported by the Solvias analytical unit, which has an outstanding track record in providing analysis of pharmaceutical products under GMP since 2000. Essential pre-formulation work will be executed in conjunction with Solvias' renowned solid-state department. With the new GMP kilo laboratory, Solvias is now well positioned to offer its customers an integrated API development program for early drug development.

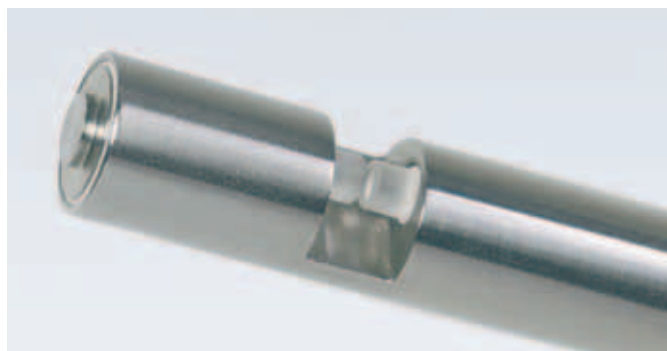
"We are not just another API supplier on the market. Our GMP facility enables our customers to accelerate time to market by relying on a partner with an unbeatable track record in chemical and analytical development and vast experience, now in the position to efficiently supply initial quantities of an API for clinical studies. Our overall manufacturing capabilities are accompanied by a strong technology base in the area of homogeneous catalysis and the ability to handle hazardous and high-pressure chemistry," says Michael Quirnbach, Product Manager for Chemical Development.



### REFLECTOR REMOTE

Fiberoptic reflection-immersion probes with remote control.

REFLECTOR REMOTE probes combine Solvias' proven technology with a high level of usability. Using the integrated remote control feature, it is possible to begin taking measurements regardless of the location of the computer or spectrometer. REFLECTOR REMOTE probes are distinguished by their remarkable signal-to-noise ratio.



### ZAFIRO BIOFIT

Fiberoptic transmission-immersion probes.

ZAFIRO BIOFIT probes are the first choice for inline analytical applications in food and biopharmaceutical production. They are remarkable for their robust design and superior materials for all wetted parts. Their CIP/SIP-compliant design fulfils the most demanding requirements for reliable application in sterile production environments. The Sapphire optic core is standard, with an optical path length of 1, 2, 5 or 10 mm. ZAFIRO BIOFIT probes can also be customized to meet your individual needs.



## SOLVIAS COMPLETES A MAJOR MANUFACTURING CAMPAIGN FOR ROLIC TECHNOLOGIES LTD.

Solvias delivered more than 200 kg of a key component, meeting Rolic's very high quality expectations for application in their photo alignment technology.

Commencing with initial process research and development, Solvias moved the campaign swiftly along achieving the efficient scale-up and production of a key component to more than 200 kg.

Dr. Andreas Schuster, Head of Photoalignment Technologies at Rolic acknowledged this achievement, saying: "We were impressed with Solvias' commitment in rapidly supplying us with our material in high quality and meeting all our ambitious timelines. As a result we will continue our collaboration and are looking forward to another success story of the recently started new campaign."

"We are extremely glad to provide world-class small-scale manufacturing service to Rolic Technologies. With our exceptional infrastructure and highly skilled employees, we were able to rapidly advance the project for Rolic Technologies," said Michael Quirnbach, Product Manager Synthesis at Solvias.

The chemical development and scale-up was performed in Solvias' state-of-the-art kilo-lab facilities in Basel. Equipped with multi-purpose plants, including reactors ranging from 10L to 100 L scale, able to run cryogenic, high-temperature and pressure reactions, this facility is ideally suited to rapidly supply material for the pharmaceutical, agrochemical and specialty chemicals industries.

### About Rolic

Rolic Technologies Ltd., a subsidiary of Rolic AG (Zug), is a privately owned company located in Allschwil near Basel (Switzerland). The company provides advanced products and supports technology leadership for its partners/customers throughout the world in the field of optical and electro-optical applications.

## 8TH SOLVIAS SCIENCE DAY 2009 – WITH NEW TOPICS

For the first time, we will be offering parallel sessions.

The focus will be on **chemical development and catalysis, and on analytical aspects** of research and development processes – both framed by specialized lectures and case studies.

**Location:** Congress Center Basel (Switzerland)

**Date:** November 2, 2009.

The program will feature world-leaders in the life science industry and academia, who will present new trends, technologies and solutions.

### For detailed information and registration

[www.solvias.com/scienceday](http://www.solvias.com/scienceday)



**DR. DIRK CHELIUS** — Head of Protein Characterization at TRION Pharma, Munich, Germany

*LC/MC methods for the characterization of trifunctional bispecific antibodies (triomab®)*



**PROF. MEL R. EUERBY** — Head of R&D and Training at Hichrom Ltd. and Visiting Professor at Strathclyde University, Glasgow, United Kingdom

*Practical and smarter ways of increasing resolution in HPLC*



**DR. HANS-JÜRGEN FEDERSEL** —

Director of Science, AstraZeneca, Södertälje, Sweden

*Where is the pharmaceutical industry heading? – Trends, challenges, and opportunities from process R&D perspective*



**DR. SEBASTIAN BARRY** — Raw Materials Project Manager at Sanofi Pasteur, Marcy-L'Etoile, France

*An industrial route to protoporphyrin IX – from process research to production*



**PROF. ALOIS FÜRSTNER** — Adjunct Professor and Director at the Max-Planck-Institut für Kohlenforschung (coal research) in Mülheim an der Ruhr, Germany

*Catalysis for total synthesis*



**DR. DIRK SPIELVOGEL** — Head of Chemical Development and Catalysis at Solvias, Basel, Switzerland

*An industrial route to protoporphyrin IX – from process research to production*



**PROF. ANDRÁS GUTTMAN** — Head of the Horváth Laboratory of Bioseparation Sciences at University of Debrecen, Hungary, and also Professor at the Barnett Institute in Boston, MA, United States

*The challenges of glycan analysis of biopharmaceuticals: Sample preparation and regulatory issues*



**PROF. DONALD HILVERT** — Professor at the Laboratory of Organic Chemistry at the ETH Zurich, Switzerland

*What happened to catalytic antibodies*



**DR. JUSTICE TETTEY** — Head of the Laboratory and Scientific Section at the United Nations Office on Drugs and Crime (UNODC), Vienna, Austria

*Making drug testing laboratories fit for purpose – The UN quality assurance program*



**PROF. PATRIK PETERSSON** — Associate Professor at Uppsala University, Sweden, and Associate Principal Scientist within AstraZeneca, Lund, Sweden

*Implementation of U(H)PLC within a global pharmaceutical company – A new way of working*



**PROF. HELMA WENNERMERS** — Associate Professor at the Department of Chemistry at the University of Basel, Switzerland

*Peptides as asymmetric catalysts and templates for the generation of silver nanoparticles*



**DR. BENOÎT PUGIN** — Leading Scientist at Solvias, Basel, Switzerland

*Secondary phosphine oxide ligands: A promising tool for asymmetric catalysis*



**DR. MANSOOR SAEED** — Research Leader at Syngenta Ltd., Jealott's Hill, Bracknell, United Kingdom

*An industrial perspective of the identification of metabolites using state-of-the-art mass spectroscopy*



**DR. DANIEL SPENCER** — Principal Scientist and Head of Analytical Services at Ludger, Oxfordshire, United Kingdom

*Glycoprofiling of biopharmaceuticals by HPLC and MS*

## Events

### CPHI WORLDWIDE

*October 13–15, 2009*

*Madrid, Spain*

*Booth 3C52*

#### Find out more about

- Polymorphie, Salt and Crystallizations
- Chemical Development and GMP Manufacturing
- Catalysis
- Analytical Development

This year's CPhI is going to be a particularly special one for Solvias since we are celebrating our 10th anniversary as an independent company after the formation of Solvias on October 1, 1999. We would be delighted to share this milestone event with you at our buffet party on October 14, at 1 pm, offering freshly sliced Jamón Serrano, traditional tapas and refreshing drinks.

### AAPS ANNUAL MEETING

*November 8–12, 2009*

*Los Angeles, CA, USA*

#### Find out more about

- Polymorphism, Salts and Crystallization
- Analytical Development

### INFORMEX 2010

*February 16–19, 2010*

*San Francisco, CA, United States*

*Booth 1712*

#### Find out more about

- Analytical Development
- Catalysis
- Chemical Development and GMP Manufacturing
- Polymorphism, Salts and Crystallization

#### SOLVIAS – YOUR RELIABLE PARTNER IN THE PHARMACEUTICAL INDUSTRY

If you are looking for increased capacity or profound know-how for your development or manufacturing activities, our experience and proven track record gives you confidence that your projects will be expertly performed and delivered on time.

With our services, products and technologies in the field of analytical, chemical and biopharmaceutical development, we provide integrated solutions to enhance the value chain of our customers.

- Analytical Services
- Biopharmaceutical Analysis
- Polymorphism, Salts, and Crystallization
- Chemical Development and GMP Manufacturing
- Catalysis
- Process Analytical Technology (PAT)
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