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Conference Report

Solvias Science Day 2009

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The major goal of the Solvias Science Day is the presentation and discussion of new strategies, concepts, and solutions in the field of synthetic and analytical chemistry by leading experts from universities, the life science industry as well as by Solvias' scientists. The Science Day 2009 took place on November 2, 2009. About 220 colleagues from research, development and production in the life science and fine chemicals industry attended the six sessions with a total of 15 presentations. For the first time, parallel sessions were organized for analytical and synthesis/catalysis topics, respectively. The Science Day was also a suitable setting for honoring the winners of the Solvias Ligand Contest 2009. Looking back, the event was clearly a success: All comments from customers and colleagues showed us that the eighth Solvias Science Day achieved its goals concerning science, information and – yes – also marketing the Solvias services.

The presentations can be grouped into the three categories: 'Synthesis and Catalysis', 'Analysis' and 'Award Lectures'.

Synthesis and Catalysis

Hans-Jürgen Federsel

Dr. ***Hans-Jürgen Federsel*** (AstraZeneca) started off with a plenary lecture entitled 'Where is the Pharmaceutical Industry Heading? Trends, Challenges, and Opportunities from a Process R&D Perspective'. Starting with the big picture in an attempt to describe the present situation of the pharmaceutical industry, he then presented his views on crucial factors capable of potentially discriminating between successful and less successful players with a focus on developing scalable, robust and cost efficient processes for small molecules. He described various concepts which are in operation that define how best to run individual projects, assess their value/risk, and create efficiency on a portfolio level. He came to the conclusion that the whole pharmaceutical branch has now fully embraced the philosophy of being lean, which has left its mark in the form of an intense concentration on continuous improvement (six sigma, kaizen *etc.*). He expressed his belief that combining these concepts in an innovative and forward looking way will eventually take the pharma business out of the present difficult situation and transform it into the flourishing industry it once was.

Prof. ***Helma Wennemers*** (Universität Basel) talked about 'Peptides as Asymmetric Catalysts and Templates for the Generation of Silver Nanoparticles'. She convincingly showed that the large structural and functional diversity of peptides renders them attractive for a variety of applications. Her presentation put the focus on their use as asymmetric catalysts and as templates for the formation of silver nanoparticles. In both cases, high-throughput screening methods were successfully used to identify lead compounds which were then structurally optimized. Using such methods, the peptide H-Pro-Pro-Asp-NH_2 was identified as an effective asymmetric catalyst for aldol reactions. Conformational investigations then allowed the extension of this methodology to asymmetric conjugate addition reactions between aldehydes and nitroolefins with very good catalytic activities and high stereoselectivities. Similarly, peptides were identified that induce the formation of silver nanoparticles in the presence of either light or sodium ascorbate to reduce Ag(I). Structurally diverse peptides were detected in colorimetric on-bead screenings that generate nanoparticles in different sizes in a controlled manner.


Helma Wennemers

In his lecture entitled 'Catalysis for Total Synthesis', Prof. ***Alois Fürstner*** (MPI Mühlheim) gave an up-date on his ongoing programs concerning the total synthesis and evaluation of complex natural products of biological significance. Targets of current interest include the latrunculin family of actin-binding macrolides, the highly cytotoxic polyene iejimalide, various members of the amphidinolide series, the promising matrix metalloproteinase inhibitor berkelic acid, and the potent phosphatase inhibitor spirastellolide. Fürstner's total syntheses are largely catalysis-based, demonstrating the scope of various methodologies developed in his group over the last decade such as ring closing alkene- and alkyne metathesis, iron catalyzed cross coupling reactions or modifications of established Suzuki- and Stille protocols. In addition, Fürstner showed the potential of total synthesis to confirm (or challenge) published structures of complex natural products.


Alois Fürstner

Dr. ***Sebastian Barry*** (Sanofi Pasteur) and Dr. ***Dirk Spielvogel*** (Solvias) gave a joint presentation named 'An Industrial Route to Protoporphyrin IX – From Process Research to Production'. Dr. Barry explained that protoporhyrin IX is a key color component of blood and classically is isolated from bovine or pig blood sources by decomplexation from hemin. He went on to describe its application as a co-factor in the vaccine production using cell culture media and explained that a fully synthetic approach is of interest due to regulatory restrictions relating to TSE contamination. Dr. Spielvogel described the development of a novel fully


Sebastian Barry

synthetic approach to protoporphyrin IX disodium salt ($PPNa_2$). He illustrated how early phase research results and subsequent process development lead to the preparation of commercial quantities of $PPNa_2$. Particular emphasis was given to the development of key intermediates as components of a highly convergent route and to the establishment of an unprecedented macrocyclisation to form the porphyrin core structure without the need of further oxidation.

Dirk Spielvogel

Dr. ***Benoît Pugin*** (Solvias) talked about 'Chiral Ligands with Secondary Phosphine Oxides (SPOs): A New, Highly Promising Tool for Asymmetric Catalysis'. He explained that chiral phosphines are the most frequently used ligands in asymmetric catalysis with a number of industrial applications. In contrast, chiral secondary phosphine oxides are very little explored giving only moderately active and selective catalysts. Since SPOs can have different coordination modes, binding to a metal *via* either P or O atom, novel properties should be expected. In a collaboration with Prof. Pfaltz (Universität Basel) and sponsored by the CTI, several families of novel mixed phosphine–SPO ligands were designed and prepared. In contrast to published results, these mixed ligands exhibited very interesting catalytic properties for the Rh and Ru catalyzed hydrogenation of various substrate classes.

Benoît Pugin

Prof. ***Donald Hilvert*** (ETH Zürich) gave his lecture the provocative title 'Whatever Happened to Catalytic Antibodies?' Catalytic antibodies, introduced two decades ago, were widely advertised as a general means of creating entirely new enzymatic activities tailored to specific transformations. Today, there is a general sense that catalytic antibody technology has failed to fulfill its original promise. Prof. Hilvert explained that while it is relatively easy to generate moderately active catalysts for a variety of reactions, the production of truly efficient enzyme mimics with high rates has proven exceptionally difficult. He then went on to describe the use of sophisticated computational methods for enzyme design, allied with directed evolution, which may ultimately be the more powerful way forward. He presented examples where the combination of programmable design with the powerful selective forces of biology made it possible to create macromolecules with novel catalytic activities which have no counterparts in Nature.

Donald Hilvert

Analysis

Prof. ***Melvin R. Euerby*** (Hichrom Ltd.) talked about 'Practical and Smarter Ways of Increasing Resolution in HPLC'. Applying the resolution equation, he showed how separation can be affected by changing the efficiency (N), the selectivity (α) or the retention factor (k). He presented a clever scouting approach focusing on the selectivity term of the equation, which provided useful insights into different stationary phase chemistries. Then he showed how the choice of sub-two, supra-two and supra-three micron porous particles or of superficially porous (fused core) particles at high flow rates and pressure can lead to an increase of the efficiency term. Finally, the use of temperature to increase efficiency and alter chromatographic selectivity was also discussed. Conclusion of his talk was that reliable semi-automated column and solvent switching technologies combined with elevated temperature is a powerful approach to optimize the chromatographic selectivity term.

Melvin R. Euerby

Prof. ***Patrik Petersson*** (AstraZeneca): 'Implementation of U(H)PLC within a Global Pharmaceutical Company: A New Way of Working.' Prof. Petersson described in his presentation the evaluation and subsequent implementation of U(H)PLC to increase productivity and efficiency within global Pharmaceutical Analytical R&D, a project involving six sites and 203 LC users in Sweden, UK and US. The rational for investing in U(H)PLC was presented and it was shown how a structured four-stage plan was used to perform the evaluation and subsequent implementation of this technique throughout the entire company. Furthermore he explained that in order to really make a difference, it is not enough to just provide equipment, adequate training and support, it is also necessary to change the way of working.

Patrik Petersson

Dr. ***Mansoor Saeed*** (Syngenta) entitled his talk 'An Industrial Perspective on the Identification of Metabolites Using State of the Art Accurate Mass Spectrometry'. He described how high accuracy mass spectrometry (sub-ppm accuracy, and resolution in excess of 60,000 Da) using the principle of mass defects may be used to identify pesticide metabolites, *i.e.* the xenobiotics that arise though degradation pathways found in plant, animal or environments such as soil. The methods are even effective in the absence of the traditionally used radiolabels. Experiments that were unheard of outside of academia just a few years ago such as multiple mass defect filters and isotope pattern filtering were shown to be more than up to the task. "This is the first time in my career I felt on a par with NMR" said Dr. Saeed.

Mansoor Saeed

Dr. ***Justice Tettey*** (UNODC) talked about 'Making Laboratories Fit-for-purpose: The UNODC Forensic Work Programme'. He spoke about the dynamics and complexities of drugs and how organized crime presents major challenges to the International community. The Laboratory and Scientific Section of the United Nations Office on Drugs and crime (UNODC) contributes to the worldwide availability and use of quality scientific and forensic services by providing national drug testing laboratories in Member States with quality assurance support, chemical refer-

Justice Tettey

ence standards, manuals and guidelines, and expert advice. The presentation highlighted UNODC's activities in the forensic and laboratory sector with emphasis on the resources available to assist laboratories to work at internationally accepted standards.

Dr. ***Daniel Spencer*** (Ludger Ltd.) entitled his lecture 'Glycoprofiling of biopharmaceuticals by HPLC and MS'. Dr. Spencer started this session by outlining the structural complexity of glycans, heterogeneous branched polysaccharides built-up from several monosaccharides. During the protein biosynthesis glycans may become attached to several specific sites along the peptide backbone. Glycans cannot be ignored since they affect both the safety and efficacy of therapeutic antibodies, EPO and other biologics. Consequently, several analytical methods are required in order to characterize fully glyco-proteins. The methods described in depth by Dr. Spencer included several modes of liquid chromatography, MALDI-TOF mass spectrometry and enzyme digestion and sequencing strategies.

András Guttman

Prof. ***András Guttman*** (University of Debrecen and Barnett Institute) spoke about 'The Challenge of Glycan Analysis of Biopharmaceuticals by Differential Electromigration Techniques: Sample Preparation and Regulatory Issues'. First of all he pointed out that glycosylation is often incorrectly referred to as a post-translational modification whereas in fact it is co-translational modification commencing whilst the peptide chain is growing. However the main emphasis of the talk was the analytical information that can be obtained by labeling released glycans with an APTS-derived fluorophore followed by separation using high resolution capillary electrophoresis often giving superior performance to liquid chromatography. In addition it was shown how the specific affinity associated with lectins may also be used to probe analytical features.

Dirk Chelius

Dr. ***Dirk Chelius*** (Trion Pharma) discussed 'LC/MS Methods for the Characterization of Trifunctional Bispecific Antibodies'. Whilst there are many analytical scientists currently working on monoclonal antibodies, Dr. Chelius has the privilege of working on a very special class. Typical antibodies are composed of four chains of amino acids, two identical heavy chains with a mass of approx. 50 kDa each and two identical light chains of approx. 25 kDa each. Trion Pharma however are developing a novel type which are not composed of identical pairs. The desired therapeutic consists of a heavy and light chain of 'mouse' type and a heavy and light chain of 'rat' type, in addition to the usual glycan features. Mass spectrometry in conjunction with liquid chromatography, provides an elegant and comprehensive solution to the verification of the desired structure and to the assignment of structures to impurities including information concerning the distribution of different glycoforms.

Solvias Ligand Contest Award Lecture

The Solvias Ligand Contest invites researchers to submit accounts describing new or improved applications of Solvias ligands. The jury awarded the first prize jointly to Prof. ***F. Dean Toste*** (UC Berkeley, USA) and to Dr. ***Nicolai Cramer*** (ETH Zürich) in recognition of their significant contributions in the area of asymmetric catalysis and the application of Solvias ligands.

Nicolai Cramer

Dr. Cramer was honored for his work on rhodium-catalyzed C–C and C–H activation with the following laudation: "In recognition of the development of unprecedented Rh/MeO-biphep and Rh/Josiphos catalyzed rearrangements of cyclobutanols leading to chiral indanols and cyclohexenones with quaternary stereogenic centers. This is one of the first synthetically useful C–C activation reactions and the multifunctional products offer many possibilities for further transformations."

Professor Toste was honored for his contribution on gold catalyzed rearrangement reactions with the following laudation: "In recognition of the development of highly enantioselective Au/MeO-BIPHEP catalyzed rearrangements leading to chiral cyclobutanones and benzopyrans with quaternary stereogenic centers. Examples of high enantioselectivity in Au-catalyzed reactions are still rare and this represents significant progress in this respect. Both reactions reported offer opportunities for application in complex molecule synthesis."

Dr. Cramer presented his results under the title 'Construction of Quaternary Stereocenters through Catalytic Enantioselective C–H- and C–C-Bond Activations'. He convinced the audience that reactions involving the activation of C–H and C–C bonds by transition metal complexes can have considerable synthetic potential even though up to now, most of these reactions still suffer from harsh conditions and modest selectivities. For this reason he started to investigate small rings as starting materials since in this case C–C cleavage releases ring strain. Indeed he was able to present very impressive results for the rearrangement of tertiary cyclobutanol derivatives catalyzed by Rh-MeO-biphep or Rh–Josiphos complexes to give structurally complex indanols and cyclohexenones with quaternary stereogenic centers with very good enantioselectivities. Mechanistic studies showed that depending on substitution pattern and conditions different reaction pathways are accessible, enabling access to diverse functionalized products.

F. Dean Toste

Prof. Toste entitled his award lecture 'Reactivity Driven Discovery of Gold(I)-Catalyzed Reaction for Organic Synthesis'. He described his approach to use mechanistic hypotheses as basis for the discovery of gold-catalyzed transformations such as cycloisomerization, rearrangement, cycloaddition and addition reactions. In this respect the electronic structure of gold render the metal unique among the electrophilic late transition metals, since it is able stabilize cationic intermediates in the course of Au(I)-catalyzed reactions. He then went on to illustrate the success of his mechanistic approach with the award winning work on the Au/MeO-BIPHEP catalyzed rearrangements leading to chiral cyclobutanones and benzopyrans with quaternary stereogenic centers with high enantioselectivies.

Conclusion

From the many comments both during and after the symposium we can conclude that also the eighth Solvias Science Day was an unqualified success and we have every intention to continue the series. Indeed, the next Solvias Science Day is planned to take place on October 25, 2010.

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