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Fifth Solvias Science Day

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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 fifth Science Day took place on June 23, 2006 under the motto 'New Strategies, Technologies, and Concepts in Research and Development' and encompassed the areas of synthesis, catalysis and pharmaceutical technology. About 200 colleagues from research, development and production in the life science and fine chemicals industry attended the four sessions with ten presentations. This occasion was also a suitable setting for honoring the winners of the Solvias Ligand Contest 2006. Looking back, the event was clearly a success: All comments from customers and colleagues showed us that the fifth 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: 'Synthetic and Catalytic Methodologies and Pharmaceutical Technology', 'Industrial Research and Development' and 'Award Lectures'.

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Synthetic and Catalytic Methodologies and Pharmaceutical Technology

Prof. *Stephen L. Buchwald* (MIT) gave on overview on 'Transition Metal-Catalyzed Carbon-Carbon and Carbon- Nitrogen Bond-Forming Processes: Progress, Applications and Mechanistic Studies'. In his lecture he described his recent results in the field of cross-coupling methodology which has become part of the everyday repertoire of synthetic organic chemists. First, Buchwald described studies on structure–reactivity relationships of ligands and also explained how his best ligands get their names. He went on to describe the latest progress in the catalyst development as well as applications to the preparation of heterocycles. Finally, he made a comparison between the use of catalysts derived from Pd and from Cu and showed that these methods are complementary.

Prof. *Eric N. Jacobsen* (Harvard University) spoke on 'Asymmetric Catalysis by Chiral Hydrogen-Bond Donors'. He started his lecture with a description of the role of hydrogen bonding which in addition to its crucial role as a structural determinant, plays an important functional role in catalysis. H-bonding is one of the principal mechanisms by which enzymes promote a wide range of chemical processes, and organic chemists have begun to appreciate the tremendous potential offered by hydrogen bonding as a mechanism for electrophile activation in small-molecule, synthetic catalyst systems. In particular, chiral hydrogen bond donors have emerged recently as a broadly applicable class of catalysts for enantioselective synthesis. He then provided an analysis of the structural and mechanistic features that contribute to high enantioselectivity in hydrogen bond-mediated catalytic processes and illustrated this with examples of his work with chiral urea- and thiourea-based catalysts for several asymmetric transformations such as the Strecker and Pictet-Spengler reactions or the addition of nitroalkanes to imines.

Prof. *Benjamin List* (MPI, Mülheim) gave a lecture entitled 'Developing New Organocatalytic Reactions' where he described recent developments in organocatalysis. He is of the opinion that low-molecular weight molecules without a metal as part of the catalytic principle can be as efficient and selective as metal catalysts. List described some important discoveries made in his laboratories including several new amine- and amino acid (especially proline)-catalyzed asymmetric reactions such as intermolecular aldol, Mannich, Michael, α-amination and aldehyde α-alkylation reactions. More recently the List group has shown that α,β-unsaturated carbonyl compounds and imines can be reduced *via* an organocatalytic asymmetric transfer hydrogenation where the chiral counter anion of a strong Brønsted acid controls the stereochemistry.

Prof. *Hans Leuenberger* (Universität Basel) entitled his lecture 'Pharmaceutical Formulation and Process Technology: From Art to Science'. He first gave a short introduction on bioavailability, defined as the extent of drug absorbed and the speed of achieving the optimal drug concentration in the systemic circulation. He then went on to discuss actual research trends in the area of pharmaceutical powder technology and the impact of the FDA's PAT (Process Analytical Technology) Initiative on this research field. The PAT initiative requires a rigorous, science-based approach

concerning the design of the dosage form, *i.e.* the formulation and the pharmaceutical manufacturing processes. Since pharmaceutical formulations are complex systems which are difficult to model and analyze, special tools such as the percolation theory, concept of fractal dimensions, dielectric spectroscopy are necessary and typical results with these novel tools obtained in Leuenberger's group were presented.

Industrial Research and Development

The next four presentations described either collaboration projects with industrial partners or results of Solvias research projects.

Dr. *Michelangelo Scalone* (Roche Basel) talked on 'Asymmetric Hydrogenation Syntheses of Dextromethorphan: An Overview'. Dextromethorphan is a morphinane analogue widely used in cough relieving and analgesic preparations. In its current synthesis the so-called 'S-octabase' intermediate is obtained by classical optical resolution and the undesired enantiomer has to be racemized and recycled in a labor-intensive step. In a first part, Scalone described the approaches taken in the last two decades by various research groups in academia and industry for the asymmetric synthesis of S-octabase or a derivative thereof. In the second part, the most recent results concerning the asymmetric hydrogenation of hexabase salts in the presence of iridium, rhodium and ruthenium catalysts partly obtained in collaboration with Solvias were discussed in detail. A technically feasible process was developed based on the Rh–MeObiphep catalyzed hydrogenation of the sulfuric acid salt of S-octabase.

Dr. *Dirk Spielvogel* (Solvias AG) entitled his lecture 'Process Development of Catalytic Asymmetric Ring Opening Reactions for the Production of Highly-functionalized, Chiral Scaffolds'. He described the ring opening reaction of *meso* oxa-olefinbicycles by chiral transition metal catalysts whereby two adjacent chiral centers are formed *via* a desymmetrization reaction. A rhodium Josiphos combination has been found to be a highly productive catalytic system leading to a *trans* arrangement of the heteroelement and the nucleophile in the resulting tetrahydronaphthalenes ('Lautens technology', named for the work of the first winner of the Solvias Ligand Contest). The presentation focused on the chemical development work for two selected product families of chiral building blocks for pharmaceutical research. Topics presented included catalyst preparation, process optimization, work-up procedures and ultimately the scale-up to the multi kg scale as well as the further derivatization of the ring-opened products.

Dr. *Benoît Pugin* (Solvias AG) gave a lecture entitled 'Two for One: Twinphos, a Successful Concept for New Chiral Tetra-Phosphine Ligands'. In his introduction he stressed that chiral diphosphines are the ligands of choice for asymmetric catalytic hydrogenation of C=C double bonds, ketones and imines. Most of the actual commercial Solvias diphosphine ligands contain a ferrocene backbone, a prominent example being the Solvias Josiphos ligands. Since these ligands make use of only one cyclopentadienyl (cp) ring of the ferrocene, the idea was tested to use both cp rings of the ferrocene. This indeed worked and several types of formally tetradentate ligands were prepared which are called 'Twinphos' and which will soon become commercially available. Pugin showed, that although these ligands offer a large number of different binding modes, they surprisingly give excellent for the hydrogenation of a number of model substrates.

Dr. *Anita Schnyder* (Solvias AG) lectured on 'The Use of Automated High Throughput Technology in Homogeneous Hydrogenation'. She pointed out that in many respects the asymmetric homogeneous hydrogenation reaction of C=C double bonds, ketones or imines can be considered to be a mature technology. However, finding the optimal catalyst (metal/ligand combination) and reaction conditions fulfilling high specifications for a given target is quite difficult given the large number of ligands, metal precursor, additives etc available today. From this follows that automated screening of catalysts and reaction conditions is key to meet the tough development timelines associated with early drug development. In her presentation she described solutions to the above issues and displayed first results for different hydrogenation reactions using the automated Symyx High Throughput Tool recently acquired by Solvias. Her conclusion was that combining experience, intuition and a "reasonable degree" of serendipity through HTS leads not only to an acceleration of the development process but also to the discovery of unexpected new catalysts.

Solvias Ligand Contest Award Lectures

The Solvias Ligand Contest invites researchers to submit accounts describing new or improved applications for Solvias ligands. For the year 2006, the jury has awarded the first prize *ex aequo* to two winners in recognition of their significant contributions in the area of chiral catalysis utilizing Solvias' proprietary chiral ligands:

- To Prof. *Ken Tanaka* (Tokyo University of Agriculture and Technology) in recognition of "the development of a novel Rh-Walphos catalyzed carbocyclization methodology leading to 3,4-disubstituted cyclohexanone derivatives with very high enantioselectivity. The reaction has a significant synthetic potential since the resulting products have useful functionality allowing further structural elaboration".
- To Prof. *Michael J. Krische* (University of Texas at Austin) in recognition of "the development of an unprecedented Rh-Walphos catalyzed reductive coupling reaction leading to chiral tertiary alcohols. The reaction is rare example of a hydrogen-mediated, Rh-catalyzed C-C coupling reaction and the products are multifunctional, providing many possibilities for further transformation".

Award Ceremony (M.J. Krische, H.U. Blaser, K. Tanaka)

Prof. Ken Tanaka entitled his award lecture 'Cationic Rhodium(I) Complexes-Catalyzed Highly Enantioselective Cycloaddition Reactions'. He stated that transition-metal-catalyzed cycloaddition reactions are one of the most valuable tools for the rapid construction of cyclic frameworks. Even though Rh-catalyzed reactions are widely used for the construction of carbocyles and heterocycles, only a few examples have been reported for cycloadditions through cyclic acylmetal intermediates. Tanake then described his recent work on the [4+2] carbocyclization of 4-alkynals with electron deficient alkenes catalyzed by cationic rhodium(I) complexes leading to cyclohexenones through five-membered acylrhodium intermediates. The use of the Solvias Walphos as a ligand dramatically enhanced the catalytic efficiency and excellent regio- and enantioselectivities were realized. In a second part of his lecture he described highly chemo-, regio-, and enantioselective [2+2+2] cycloaddition reactions catalyzed by Rh-BINAP and Rh-Solphos complexes.

In his award lecture, Michael J. Krische talked on 'Hydrogen-Mediated C–C Bond Formation: Catalytic Couplings Beyond Alkene Hydroformylation'. In his introduction he stated that alkene hydroformylation is the largest volume application of homogeneous metal catalysis and that this reaction can be considered to be the prototypical example of hydrogen-mediated C–C bond formation. Despite this fact, systematic efforts toward the development of hydrogen-mediated couplings that extend beyond carbon monoxide insertion have remained absent from the literature. The Krische Group has shown that it is possible to reductively couple two or more complex organic molecules simply through their exposure to gaseous hydrogen in the presence of a metal catalyst. This finding has led to the development of a new family of "C-C bond forming hydrogenations", adding a new dimension to catalytic hydrogenation – one of Chemistry's oldest and most broadly utilized reactions. In particular Krische described the application of a Rh-Walphos complex to the reductive coupling of conjugated enynes with α-keto esters which proceeds with high enantioselectivity and good chemical yields.

From the many comments both during and after the symposium we can conclude that also the fifth Solvias Science Day was an unqualified success and we have every intention to continue the series.

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