



INSTITUTE OF CHEMICAL SCIENCES AND ENGINEERING

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ÉCOLE POLYTECHNIQUE  
FÉDÉRALE DE LAUSANNE

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## MESSAGE FROM

# ISIC DIRECTOR PAUL DYSON



FROM LEFT TO RIGHT: PAUL DYSON, DIRECTOR OF THE INSTITUTE – SANDRINE GERBER, DEPUTY DIRECTOR – SANDRA JEANNERET, ADMINISTRATOR – MADELEINE STEFFEN, ADMINISTRATOR

During the 12 months since the publication of our first newsletter we have seen many positive changes in ISIC. Perhaps the most significant changes have taken place in organic chemistry, with the arrival of two new professors, Nicolai Cramer and Jieping Zhu, who complement Kai Johnsson, Jérôme Waser and Christian Heinis, combined with the imminent arrival of Elena Dubikovskaya, who will hold a chair in bio-organic chemistry and is our fifth female professor in the institute. A satellite laboratory of the Ludwig Institute for Cancer Research, focusing on medicinal organic chemistry, has also been established in ISIC. Indeed, I am hearing from people outside our institute that organic chemistry has never been stronger in Lausanne. The newest chair in bio-organic chemistry comes in response to a National Center of Competences in Research in Chemical Biology headed jointly by EPFL and the University of Geneva. This project provides a considerable amount of funding and will stimulate some outstanding research and lead to many discoveries. ISIC is also significantly involved in another such National Center of Competences in Research on Molecular Ultrafast Sciences and Technology.

## ISIC'S PUBLICATION RECORD SINCE 2008

- 1,210 Total number of publications since 2008
- 13 in *Nature* and *Nature* sub-journals, e.g. *Nature Chemistry*, *Nature Chemical Biology*, etc.
- 5 in *Science*
- 46 in *Angewandte Chemie*
- 46 in *Journal of the American Chemical Society*
- 7 in *Proceedings of the National Academy of Sciences*

Indeed, the last year has been phenomenal in terms of external funding obtained. Despite the trend of many organizations to increasingly fund applied research, we have managed to maintain an excellent blend of fundamental and applied work, and thus continue to demonstrate that the creation of new knowledge helps to solve real-world problems.

Once again, I hope you enjoy reading this newsletter. Your comments are welcome, sent either by e-mail to [secretariat.isic@epfl.ch](mailto:secretariat.isic@epfl.ch) or by regular mail to me at the address below. Please visit our website for more detailed information and news on forthcoming events, including a number of special activities to celebrate the International Year of Chemistry, that might be of interest:

<http://isic.epfl.ch>.

Ecole Polytechnique Fédérale de Lausanne  
EPFL SB ISIC-Direction  
CH B3 391  
Station 6  
CH-1015 Lausanne

# SYNTHETIC ORGANIC CHEMISTRY

including Jieping Zhu, Jérôme Waser and Nicolai Cramer

While ISIC's organic chemistry program took a hit with the retirement of eminent scientists Manfred Schlosser, Pierre Vogel and Manfred Mutter, recent additions of prize-winning professors Jieping Zhu and Nicolai Cramer, who complement Kai Johnsson, Jérôme Waser and Christian Heinis, mean the department has quickly regained momentum. With a focus on the synthesis of natural products, catalytic methods for the synthesis of bioactive compounds, and the synthesis of enantioenriched molecules, the three professors are leading groups that are already providing new tools for the creation of medicines and in some cases even new drug candidates themselves.



## Laboratory of Synthesis and Natural Products

### – Prof. Jieping Zhu

Many medicines on the market today, especially those used to fight cancer and infectious disease, have their origins in natural products; chemical compounds or substances produced by living organisms. Total synthesis – the process of making these complex organic

compounds from simpler, smaller molecules – was initially developed as a way of determining exact structures and developing an alternative supply of these sometimes rare substances. Today, the focus is rather on developing new methods that can save money and time and cut down on the amount of waste produced.

New reactions are also being used to expand the portfolio of compounds that drugmakers can investigate. In recent work, Zhu and colleagues developed an efficient method of synthesizing complestatin, a peptide that shows promise as an antibiotic and HIV-fighting agent.

Another main focus of the group is work on multi-component reactions, reactions in which three or more initial materials react to form a product and where most, or preferably all, of the atoms contribute to the end product.

Dr. MER Sandrine Gerber is a senior scientist and Dr. Qian Wang is a research and teaching associate in the lab, which also has 1 post-doc and 12 doctoral students, and continues to grow rapidly.

### About Jieping Zhu

Jieping Zhu was appointed full professor at EPFL last year. Zhu, a French citizen, studied at Hangzhou Normal University and Lanzhou University in China and earned a master's degree in 1987. After finishing his doctorate at Université de Paris-Sud, he joined the French National

Center for Scientific Research (CNRS). He was hired as a research fellow by the Institute for the Chemistry of Natural Substances in Gif-sur-Yvette, France, where he developed a highly innovative research program for the synthesis of complex molecules. He was the CNRS research director at ICSN between 2000 and 2010 and headed a laboratory of 25 doctoral students, postdoctoral fellows and researchers there. He has won a number of awards, including most recently the 2009 CNRS Silver medal and the 2010 French Chemical Society-Division of Organic Chemistry award.



## Laboratory of Catalysis and Organic Synthesis

### – Prof. Jérôme Waser

Meanwhile, Jérôme Waser's group is developing new catalytic methods for use in the synthesis of bioactive molecules. This might eventually lead to compounds that can be used to fight cancer, neglected diseases or neurological disorders.

"We're doing the kind of research that the pharma industry won't do," Waser said. "They are working under high pressure to bring new drugs to the market, they have no time for developing synthetic methods and just use what is already working well."

Scientists working in industry now have "the same set of 100 reactions" and it's becoming increasingly difficult to find new drugs as everybody concentrates on the same structures and techniques, he said. True to the maxim that "an unexpected result in industry is a catastrophe, in academia it's a discovery," Waser's group rather looks at reactions that aren't working well and tries to figure out why. This way, they can create new tools that allow the synthesis of new structures with unprecedented properties.

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**THE TEAM HAS NONETHELESS ALREADY SEEN SUCCESS, WITH THE "HYPERVALENT IODINE" REAGENT TIPS-EBX, WHICH BECAME COM-MERCIALY AVAILABLE FROM SIGMA ALDRICH IN NOVEMBER 2010.**

While making new compounds is generally easy, Waser said, the trick is to make them efficiently. Increasing the rate of a chemical reaction through catalysis, instead of using large amounts of toxic reagents, is one of the best ways to reach this goal. And reducing several steps in a reaction to one or two through the discovery of new processes could also have a huge positive environmental impact. About two times the mass of products is generated in waste in the manufacture of bulk chemicals, but that ratio goes up to 1,000 in the production of pharmaceutical products, Waser said, making some compounds expensive and environmentally damaging to produce.

While the new reagents and catalysts need to make synthesis more efficient, they also have to have the right properties, he said;

researchers should be able to mix them in the air and it's generally better to work in water when working with biomolecules. "And ideally you can give it to the next grad student that comes into your lab, and it works perfectly the first time he or she tries," he said. "If it's too high tech, industry won't use it."

The group's main interest is in the ability of catalysis to promote carbon-carbon bond formation, which in turn allows for rapid, efficient improvement in the complexity of the molecules produced. The researchers, aiming to achieve "unprecedented reactivity," are approaching the problem in two steps.

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## **"WHAT WE'RE DOING IS CONTRARY TO THE CLASSICAL WAY AND IT'S CHALLENGING," WASER SAID. "THERE ARE VERY FEW PRECEDENTS."**

The first involves synthetic modification, or tweaking, of classical functional groups to create molecules with new reactivity. The second step involves revealing the reactivity using a catalyst to form new carbon-carbon bonds in a way never achieved before.

The main focus so far is on alkynes, hydrocarbons that have a triple bond between two carbon atoms, and cyclopropanes, the smallest ring in organic chemistry (3 carbon atoms), which is an energy-loaded molecule. Alkynes are widely used in organic synthesis because they can be further modified in a wide variety of reactions to produce many different substances. They also have exceptional structural and electronic properties that are widely used in fields such as biochemistry and material sciences.

Methods now used to elaborate alkynes have limitations though; they're quite rich in electrons and so are generally transferred to a substance poor in electrons. Many functional groups in organic chemistry or in biomolecules such as proteins are electron-rich too and the traditional method of introducing alkynes is limited here. The Waser group wants to make alkyne-transfer reagents that are electron poor so that they can be added to the electron-rich functionalities of biomolecules.

"What we're doing is contrary to the classical way and it's challenging," Waser said. "There are very few precedents."

The team has nonetheless already seen success, with the "hypervalent iodine" reagent TIPS-EBX, which became commercially available from Sigma Aldrich in November 2010. Waser and colleagues made the initial discoveries in fall 2008 and have since used it in three reactions that are important for medicinal and synthetic chemistry, he said. Results were published in the journal *Angewandte Chemie*.

A new technique, which came out of the group's other main focus – the application of catalytic methods in the synthesis of bioactive compounds – produced a molecule that's now being examined for anti-cancer properties by biochemists at the University of Bern.

The molecule, goniomitine, was synthesized using a new method that came out of the group's research on polycyclic structures, molecules that have two or more atomic rings and are omnipresent in natural products and bioactive compounds. These structures are usually generated through a process that makes use of activating agents and so results in a considerable amount of waste. Waser's

group experimented with a way of producing intermediates for the synthesis of polycyclic structures under mild conditions, using the strain of cyclopropane rings.

"I think it's important for us to make the first step of transfer," Waser said. "We have to demonstrate that we can make a bioactive natural product using our method. If it's just a fundamental reaction, people will fail to realize the application."

The lab, made up of 1 post-doc and 5 doctoral students, is continuing its efforts in the development of reagents, catalytic methods and complex structures inspired by natural product that might eventually help with drug discovery, Waser said.

### **About Jérôme Waser**

Waser was born in Sierre in October 1977. From 1997 to 2001, he studied chemistry at ETH Zurich. After a summer internship at Lonza AG in Visp in 2000, he chose organic chemistry as a specialization and obtained his diploma under the supervision of Prof. Erick M. Carreira and Dr. Christian Fischer in 2001. In 2002, he started his PhD studies at ETH Zurich also under the supervision of Prof. Carreira. During his PhD, he worked on the development of new metal-catalyzed amination reactions, which culminated in a new access to azides and hydrazines directly from olefins. After obtaining his PhD in 2006, he then joined the group of Prof. Barry M. Trost at Stanford University as a postdoctoral fellow. While at Stanford, he worked on the total synthesis of Pseudolaric Acid B, a diterpene natural product displaying interesting antifungal, antifertility and antitumor activity. Waser has won a number of awards and fellowships, including most recently an unrestricted research grant from drugmaker Roche Holding AG.



### **Laboratory of Asymmetric Catalysis and Synthesis**

#### **– Prof. Nicolai Cramer**

Nicolai Cramer likes to cook, "just like a lot of chemists," he says. It's this process of creation that first drew him to the field and keeps him interested.

Cramer and his students are aiming to generate efficient catalytic cascade reactions that work through new modes of activation and can be used, for example, to synthesize bioactive natural products.

The current research focus is on the development of novel metal-catalyzed functionalization reactions mainly using rhodium-, palladium-, iridium- and copper-complexes. These metal complexes are designed to selectively activate carbon-hydrogen and carbon-carbon bonds. These bonds are by far the most abundant in almost any organic molecule, and the chemist's toolbox can so far address and modify only a small fraction of them, Cramer says.

"Convincing" them to react is a challenge because they're among the least reactive bonds. And poor reactivity isn't the only problem. Researchers also need to come up with set of rules to predict what part of the molecule reacts.

"If you can't control it, it's worthless," Cramer said. The magic lies in finding the right ligand, which gives the central metal atom the required properties.

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**“IN CHEMISTRY YOU CAN IMAGINE A MOLECULE, THEN MAKE IT AND HAVE SOMETHING THAT HAS NEVER BEEN ON EARTH BEFORE,” CRAMER SAID. “THAT’S EXCITING.”**

“This makes all the difference,” he said. “It’s as simple as if you were just dressed in shorts, trying unsuccessfully to enter a fancy nightclub. If you wear your best tuxedo it changes everything.”

Getting the properties of the ligand right is not a trivial issue though. Cramer likens it to prospecting for gold: “You may be in a promising area, but it isn’t payday until you hit the big vein,” he said.

The group, which now includes five PhD students and one post-doc, will eventually apply these methods to the synthesis of molecules that have interesting pharmacological properties.

“In chemistry you can imagine a molecule, then make it and have something that has never been on Earth before,” Cramer said. “That’s exciting.”

A particular emphasis of the group is on asymmetric catalysis, which aims to solve the problem of chirality. Most complex natural products are chiral; they can’t be superimposed on their mirror images. The two hands of a molecule are called enantiomers and problems can arise when drugs are made of chiral molecules because the two can have completely different effects.

In earlier days, methods of synthesis were simpler and targeted equal mixtures of the two enantiomers and both were then administered to the body. One of the most infamous examples of two active enantiomers is the molecule thalidomide, also known by the brand name Contergan. One of them is a sedative, the other can lead to defects in fetuses.

Since these issues came to light, pharmaceutical companies have been cautious about delivering the correct enantiomer in a pure form. The common technique is still to make both, though now chemists need to separate out the desired molecule. Synthesizing selectively only the desired one would be “much more efficient” and “you would reduce the generated waste by half and need only half the amount of resources,” Cramer said.

The group also aims to apply the methods to synthesize bioactive natural products.

“You can win twice: first, others see that your methods work in more complex and real life problems and start considering it for their own work,” Cramer said. “But additionally, you are one of a few people in the world that have access to that molecule and can study its activities.”

#### **About Nicolai Cramer**

Nicolai Cramer was born and raised in Stuttgart, Germany. He studied chemistry at the University of Stuttgart and received his diploma degree in 2003. He stayed there and earned his PhD in 2005 under the guidance of Professor Sabine Laschat for a total synthesis of the cytotoxic tetramic acid lactam Cyindramide. After a short research stint at Osaka University, Japan, he joined the group of Professor Barry M. Trost at Stanford University as a postdoctoral fellow in 2006, where he worked on palladium-catalyzed asymmetric TMM-cycloadditions and their use in the total synthesis of the alkaloid Marcfortine B. Endowed with a Liebig fellowship, he worked on his habilitation from 2007–2010, mentored by Professor Erick M. Carreira at ETH Zurich. He joined EPFL last fall. Cramer has won a number of awards, including the ADUC price and the ORCHEM Award from the German Chemical Society and, most recently, the Bayer Early Excellence in Science Award and the Gold Medal of the Euchems European Young Chemist Award.

EDCH

# THE DOCTORAL SCHOOL

**EPFL has been training and educating PhD students for decades, but the enhanced doctoral program in Chemistry and Chemical Engineering (EDCH) is just eight years old. Nonetheless, it’s already attracting growing numbers of world-class students who go on to take top research posts, jobs in industry and faculty positions across the globe.**

The EDCH program was established in January 2003 as part of EPFL’s drive to centralize the recruitment and administration of graduate students while still encouraging the trans-disciplinarity and cross-fertilization of ideas that the university is known for. In the past three years, the program has grown by 20 percent, and now includes 151 PhD students from 25 different nations. Some 37 percent of students are women.

The admission rate suggests that the program is very competitive: just above 10 percent are admitted. Those selected joined a group of students coming from Switzerland and Europe, but also India, China, Iran and beyond. Indeed, applicants from Indian institutes are the most strongly represented.

Of the students who fulfilled the requirements of the program, almost all successfully obtain their PhDs, mostly within 4 years. Of the 33 PhD students that graduated in 2010, more than 50% are pursuing postdoctoral positions in academia, while others are now working in industry.

Our program is proud that one of the EPFL best thesis awards for 2010 was given to Dr. Bruce Yoder (Laboratory of Molecular Physical Chemistry under the supervision of Professor Rainer Beck) for his thesis entitled “Steric Effects in the Chemisorption of Vibrationally Excited Methane on Nickel” (see page 10 for details). Yoder has been a postdoctoral researcher at University of British Columbia (UBC) since January and received a postdoctoral fellowship from the Swiss National Science Foundation.

The EDCH offers an exciting environment in which to conduct research in the chemical sciences and engineering. While all classical areas of chemistry and chemical engineering (analytical, biological, computational, inorganic, organic, physical, biochemical and bio-molecular, catalysis, materials, thermodynamics, and transport) are represented in the program, the research activities are at the forefront of modern chemistry and also include chemical biology, drug discovery, diagnostics, biomaterials, solar cells, protein engineering, supramolecular chemistry and nanoscience.

The program’s faculty members, i.e. the ISIC faculty, are leaders in their research areas, as demonstrated by the international awards they receive every year, their role as editors in academic journals, and the number of invited lectures they deliver annually.

The PhD students also organize several events every year to strengthening the links within the community at EPFL, promoting the collaboration between the different laboratories and the doctoral school and creating a link with former PhD students who have continued their careers in Swiss industry.



Through different programs, the EPFL doctoral school offers a large number of courses, which are open to every graduate student. This allows EDCH's students to broaden their knowledge from courses in physics, computer- and computational sciences, life sciences, energy and the environment. Students can also take courses at partner institutions including the neighboring Universities of Geneva and Lausanne and the ETH Zurich. In addition, students have access to a huge range of courses that allows them to broaden skills in everything from languages and communication to management and leadership.

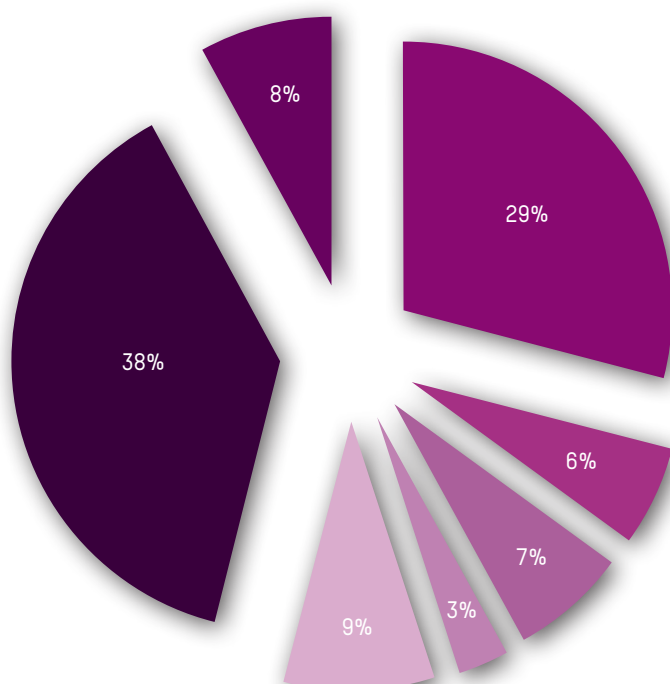
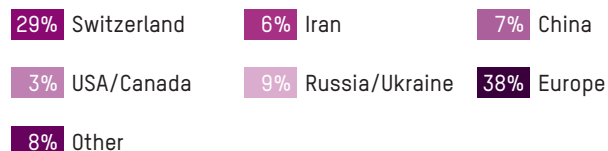
And this prepares them well for whatever they go on to do. Some of last year's graduates continued in research as post-docs at leading universities including Oxford University, Imperial College, Caltech, MIT, UC San Francisco... and the University of Tokyo. Others are pursuing different adventures: Dr. Katrin Anne Thommes is volunteering at a marine conservation project in Mexico while Dr. Bin Fan went on to start his own company.

In this, the International Year of Chemistry, the EDCH at EPFL is proud to celebrate its growth into one of the best doctoral programs in the world, creating knowledge and preparing bright young people for successful careers.

Please see the website for more information:

<http://phd.epfl.ch/edch>

#### ORIGIN OF CURRENT PhD STUDENTS



**MS BO RAM LEE, FROM SOUTH KOREA, SAYS SHE CHOSE THE EPFL PROGRAM RATHER THAN ONE CLOSER TO HOME BECAUSE CHEMISTRY**

**IS EXCELLENT AT EPFL, THE FACILITY IS OUTSTANDING, AND, OF COURSE, THE COUNTRY IS BEAUTIFUL.**

## EDCH MAINTAINS CLOSE TIES TO INDUSTRY

EPFL is surrounded by chemical and pharmaceutical companies that have been providing jobs to chemistry PhD students for a long time. The EDCH strives to maintain close ties with these companies.

The Chemical Engineering Day is jointly organized by PhD students and EDCH with the aim of strengthening the links within the chemical engineering community at EPFL, promoting the collaboration between the different labs working in the field and the doctoral school, and keeping in touch with former chemical engineering PhD students who have continued their careers in Swiss industry. It's also a good opportunity to present the doctoral program to current master students.

Last year's event, held on November 18<sup>th</sup>, featured presentations from a variety of industries, ranging from pharmaceuticals (Merck Serono SA and Novartis Consumer Health SA) and flavors/fragrances (Givaudan Suisse SA and Firmenich SA) to the food industry (Nestle SA). The third annual Chemical Engineering Day will be held this autumn and is being organized by Anne-Laure Dessimoz and Micaela Crespo Quesada of the Group of Catalytic Reaction Engineering.

The goal of the EPFL Organic Chemistry Symposium, which will be held for the first time in November, is to bring together the EPFL organic chemistry community and the chemical and pharmaceutical industries. The symposium will promote the doctoral program, maintain ties with industry and present different opportunities for master's and PhD students. The symposium is being organized by Françoise Borcard of the Laboratory of Synthesis and Natural Products and Jonathan Brand of the Laboratory of Catalysis and Organic Synthesis.

# TOWARDS CHEMISTRY NEAR ABSOLUTE ZERO

Attracted by biochemistry in high school, Andreas Osterwalder knew he'd need to fully understand chemistry. While studying chemistry, he realized he needed to delve into physics: but an undergrad class at EPFL during an exchange year from ETHZ made him realize that it was the physical aspect of chemistry that interested him most. Stopping just short of studying physics instead, Osterwalder is now developing methods that will help to improve understanding of chemical reactions at the most fundamental level.

A key to this type of research is producing molecules at very low temperatures, Osterwalder says. While his main interest is in the chemistry of the cold systems – there are specific features such as tunneling, the phenomenon in which a particle moves through a barrier that it couldn't surmount if following the rules of classical mechanics, or the wave-like nature of matter – the techniques he is developing may eventually also be used in quantum computation, in high-resolution spectroscopy, or in a fundamental study of molecular scattering.

But it's all easier said than done.

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**“IN TERMS OF COMPLEXITY, THE MOLECULES THAT THE ORGANIC CHEMISTS IN ISIC WORK WITH OBVIOUSLY ARE ON AN ENTIRELY DIFFERENT LEVEL. THE LARGEST MOLECULE THAT I HAVE PRODUCED AT A TEMPERATURE BELOW 1 K IS AMMONIA.”**

Researchers have been able to produce cold samples of molecules for several decades, but these molecules generally move at very high speed. For the research areas mentioned above it is crucial to produce cold molecules that on average have zero velocity. By now there is an array of about 15 methods that reach this goal, but there is a general limitation to many of them: the relatively low number density of molecules produced is less than ideal if one is looking to observe collisions. Scientists are also looking for even lower temperatures than current methods produce. Those two goals can be summed up as a quest for increased phase-space density, or the density of the cloud of molecules in a six-dimensional space defined by the three momentum coordinates and the three Cartesian coordinates.

In view of collision experiments, any new method should also be more general, Osterwalder says. No one of the existing methods is really general in terms of the types of cold molecules it's able to produce.

“And from a chemical point of view, they're all quite limited,” Osterwalder said. “In terms of complexity, the molecules that the organic chemists in ISIC work with obviously are on an entirely different level. The largest molecule that I have produced at a temperature below 1 K is ammonia. For chemistry studies, one would like to have access also to more complex molecules with atmospheric or interstellar relevance.”

That's why Osterwalder and colleagues are now pursuing three different possible methods of cooling elusive molecules.

One method aims to attain cold molecules by filtering them. The technique makes use of the fact that molecules move at many different velocities, including low ones, in a thermalized gas. One way

to get cold molecules is then to filter out the slow-moving ones and discard the rest. Researchers have constructed a filter that's able to guide only the slow moving molecules – those that have a certain maximum velocity that corresponds to a temperature of a few Kelvin – to the end of the guide. A key advantage of this method is that the initial sample could be as warm as room temperature.

Another project, being carried out with the Fritz-Haber-Institute of the Max Planck Society in Berlin, is looking at improving on a current method called Stark deceleration. Stark deceleration uses electric fields to reduce the central velocity of packets of molecules: such fields, if shaped the right way, can reduce the kinetic energy of a polar molecule. Because only a small amount of kinetic energy can be removed with each pass through a strong electric field, so-called Stark decelerators are made up of 100 or so stages, each of which slows the molecule down a bit more. The final “product” is a packet of molecules with a central velocity around zero. Osterwalder, along with colleagues in Berlin, has designed and constructed a new type of decelerator that operates by having traps made from electric fields. The traps move at high speed initially, and they can be slowed down; the researchers trap the fast-moving molecules and then reduce the velocity of the traps. Osterwalder likens it to using a moving bucket to try to catch water from a jet by moving the bucket backwards; some will spill over as you slow the bucket down, but some will stay.

The final project is looking at a completely new method: using negative ions to produce cold molecules. The method, which first occurred to Osterwalder while he was on a post-doc at the University of California in Berkeley, seems promising because it's much easier to manipulate the motion of ions than that of neutrals because stronger forces can be produced.

The basic idea is to first generate a negatively charged precursor to the neutral. This anion would then be decelerated in an electrostatic field and neutralized by laser photo-detachment. This would produce a neutral sample at the same translational temperature. Collision processes could then be studied by crossing the sample with other molecules at variable kinetic energy. The big advantage of that method is that it would be much more general.

Osterwalder and colleagues haven't yet been able to show that it works though. The method is complicated by the need to produce a very clean sample of ions; the velocity has to be well defined.

“Because ions are so sensitive to fields, you need the maximum possible control,” Osterwalder said. “The smallest deviation from the ideal field would produce an increase in temperature.”



#### About Andreas Osterwalder

Osterwalder completed his Diploma in chemistry at ETHZ in 1998 and continued on to complete his PhD in the group of Frédéric Merkt in 2002. He was a post-doc in the group of Daniel Neumark at the University of California, Berkeley from 2002 until 2005, and was also a fellow of the Swiss National Science Foundation in 2002-2003. Osterwalder was a project leader at the Department for Molecular Physics by Gerard Meijer at the Fritz-Haber-Institute of the Max Planck Society in Berlin from 2005 until 2009. Since 2009, he has been a SNSF-funded professor at EPFL.



## CYSVIEW GETS U.S. REGULATORY APPROVAL

# FDA APPROVES CANCER IMAGING PRODUCT DEVELOPED BY VAN DEN BERGH TEAM

The U.S. Food and Drug Administration has approved Cysview, a compound originally developed by a team led by Hubert van den Bergh, director of the EPFL's Medical Photonics Group and faculty member at ISIC and STI. The team also includes researchers from the University of Lausanne and the Centre hospitalier universitaire vaudois, or CHUV.

**"I COUNT BRINGING A DRUG LIKE CYSVIEW TO THE MARKET, WHERE IT REALLY HELPS PATIENTS, AS ONE OF THE MOST IMPORTANT RESULTS OF MY WORK."**

The optical imaging product, sold by GE Healthcare under license from PhotoCure ASA, was approved for the detection of non-muscle invasive papillary bladder cancer in patients suspected or known to have lesions. These cases account for about 70 percent of all bladder cancers, which together represent the 4<sup>th</sup> most common malignancy in men and the 8<sup>th</sup> most common in women in the western world.

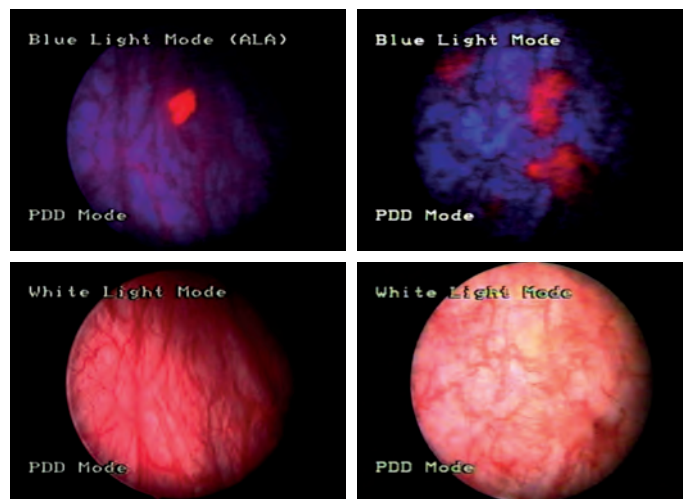
"Accompanying a medical research project through essentially all the steps, from the first ideas and experiments, to the clinical testing, and finally to the market, was a particularly rewarding experience, with of course occasionally a quite steep learning curve for me," van den Bergh said.

Blood in the urine is often the first sign of bladder tumors. Patients who have this symptom usually then undergo urine cytology and cystoscopy – an endoscopy of the bladder via the urethra. Before the development of Cysview, this endoscopy was carried out using white light, and some lesions, particularly flat ones, were difficult to see. The use of cystoscopy with Cysview, known as Hexvix in Europe, has significantly improved detection of non-invasive papillary cancer and flat carcinoma in situ compared with standard white-light cystoscopy, and has also been linked to a reduction in tumor recurrence at nine months.

A clinical study showed that Hexvix-guided fluorescence cystoscopy detected tumors that had not been seen with conventional cystoscopy in 16% of the patients with certain kinds of malignancies. Of the tumors only seen using Hexvix cystoscopy, 59% were medium-grade tumors and many were tumors of high risk of recurrence and progression. Some 32% of the patients with carcinoma in situ, a high-grade, aggressive cancer, were identified only by Hexvix-guided cystoscopy.

Nonetheless, these results likely under-represent the actual benefit that Cysview offers, van den Bergh said. That's because the trials were carried out by senior urologists with many years of experience in spotting cancerous growth using the classical white-light method. "For them, our method is better, but not hugely better," he said. "But for someone with less experience in the endoscopic identification of the very small or flat lesions in the bladder, our method can be a major improvement".

Cysview – an ester of the heme precursor aminolevulinic acid – is first instilled in the bladder. It then enters into the mucosal cells of the bladder wall, where it is used in the formation of the photoactive intermediate protoporphyrin IX (PpIX) and other photoactive porphyrins (PAPs). Due to mainly differences in enzyme activity between the cancers and the normal tissue, PpIX and PAPs accumulate more in the cancer



BLADDER WITH EARLY STAGE CANCERS FLUORESCING IN RED (TOP) AND CORRESPONDING WHITE LIGHT IMAGE (BOTTOM)

cells than in the normal urothelium. After excitation with blue light PpIX and other PAPs will fluoresce. This eases the detection of lesions, which appear bright red and well demarcated against a dark blue background of normal tissue.

Cysview helps not only in diagnosing cancer, but is also used by the urologists to ensure that all malignant cells are removed during transurethral bladder resection, a critical step towards reducing the recurrence of tumors. While the urologist needs to remove all of the cancerous cells, it's also important to avoid puncturing the wall of the bladder. Cysview allows the surgery to be as minimally invasive as possible; doctors remove tissue until all bits of red fluorescence are gone.

PhotoCure and US partner Salix Pharmaceuticals Inc. are also developing the same compound, known chemically as hexaminolevulinate, for use in detecting flat lesions in the colon.

"I count bringing a drug like Cysview to the market, where it really helps patients, as one of the most important results of my work," van den Bergh said. "It is something very real, whereas adding another publication to the literature adds to our knowledge, but often seems a bit more abstract. That is why this event is one of the things which gives me real satisfaction."

#### Some of the other main contributors to the project include:

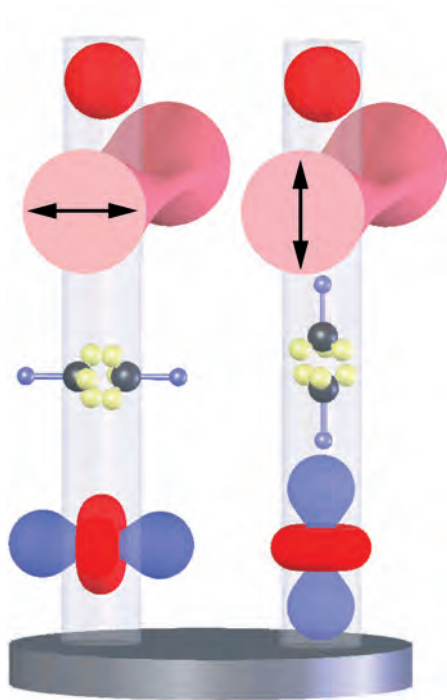
- 1 Prof. P. Jichlinski, CHUV, clinical tests
- 2 Dr. Norbert Lange, UNIGE, chemical synthesis of a compound library, and preclinical as well as clinical tests
- 3 Prof. P. Kucera, UNIL, preclinical tests
- 4 Dr. G. Wagnières, EPFL, technology transfer
- 5 Dr. A. Marti, CHUV, preclinical and clinical tests
- 6 Prof. R. Tyrrell, ISREC, first tests on ALA esters

# KAI JOHANSSON NAMED CO-DIRECTOR OF NCCR



**P**rof. Kai Johansson, head of ISIC's Laboratory of Protein Engineering, was awarded co-directorship of the Swiss National Centre of Competence in Research in chemical biology with the University of Geneva's Howard Riezman. The program grant, which will receive 13.3 million Swiss francs for the first four years from the Swiss National Science Foundation and should run for a total of up to 12 years, is using advances in chemistry to improve our understanding of life at a molecular level. Few technologies have been able to fully characterize the biological activities that make up a living cell, but this is changing with research into new approaches to visualizing biochemical activities in living cells and in vivo. The group aims to develop innovative techniques based on small molecules and proteins to obtain information about biological processes such as signaling, cell division and how membranes control the activity of proteins. The NCCR is also establishing a platform – Academic Chemical Screens in Switzerland, or ACCESS – for chemical screening aimed at developing a new generation of molecules with biological effects. More information can be found at <http://nccr-chembio.ch/>

## RAINER BECK EXAMINES METHANE VIBRATIONS IN *SCIENCE*



METHANE'S REACTIVITY WITH A NICKEL SURFACE DEPENDS NOT ONLY ON ITS KINETIC ENERGY AND VIBRATIONAL STATE, BUT ALSO ON THE DIRECTION OF THE VIBRATIONAL MOTION RELATIVE TO THE PLANE OF THE SURFACE.

**P**rof. Rainer Beck, from the Laboratory of Molecular Physical Chemistry, and colleagues published an article in *Science* describing a discovery that might lead to a better understanding of heterogeneous catalytic conversion. This finding may eventually allow researchers to improve catalysts that are used in more than 90% of all processes in the chemical industry.

One of the most frequently used types of catalysis involves a gas reacting on the surface of a solid catalyst. Such heterogeneous catalysis involves the gaseous reactants diffusing to the catalyst surface and adsorbing onto it through the creation of chemical bonds. After this reaction, the products desorb from the surface and diffuse away. An example is found in exhaust pipes of vehicles: the carbon monoxide and unburned hydrocarbons emitted hit a platinum or palladium surface and are oxidized into carbon dioxide and water. While the process is well-known, the molecular mechanism of the reaction isn't fully understood.

Beck and colleagues looked at the catalytic transformation of water vapor and methane into hydrogen and carbon monoxide through contact with a nickel surface. This process, known as steam reforming, is used extensively in the chemical industry to produce the starting materials for the synthesis of many products as well as to produce hydrogen gas, the clean fuel of the future "hydrogen economy."

Using an infrared laser, the researchers excited methane molecules to vibrate and could also orient the direction of the vibrational motion relative to the surface of the catalyst. To their surprise, the researchers found that methane's reactivity depends strongly on the direction of molecule's vibration.

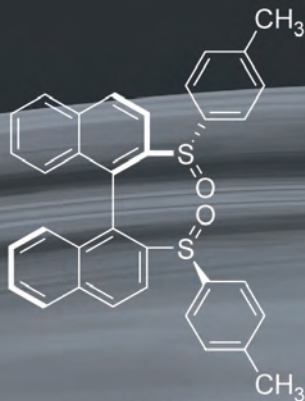
Methane that has its chemical bonds stretched parallel to the surface of the catalyst can be twice as reactive as methane that vibrates perpendicular to the plane of the surface. While the underlying reasons for this alignment-dependence of methane's reactivity are not yet understood, the findings will help to clearly contradict simple statistical theories for the chemisorption reaction and will help to develop more sophisticated and realistic models for this important reaction.

While the method presented in the paper couldn't be used on an industrial scale, the understanding gained may eventually lead to catalytic converters that are more efficient and less expensive.

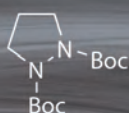
Beck's former PhD student Bruce Yoder, the first author on the *Science* article, was awarded an EPFL doctorate prize for one of the two best PhD theses for the year 2010.

Please see "Steric Effects in the Chemisorption of Vibrationally Excited Methane on Ni(100)" in *Science*, volume 329, for more information.

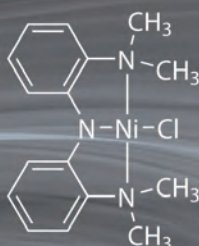
Thanks to Lionel Pousaz for assistance with this story.



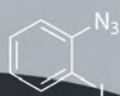
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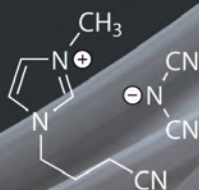
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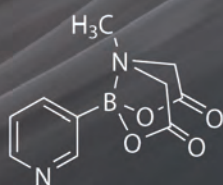
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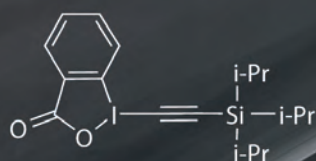
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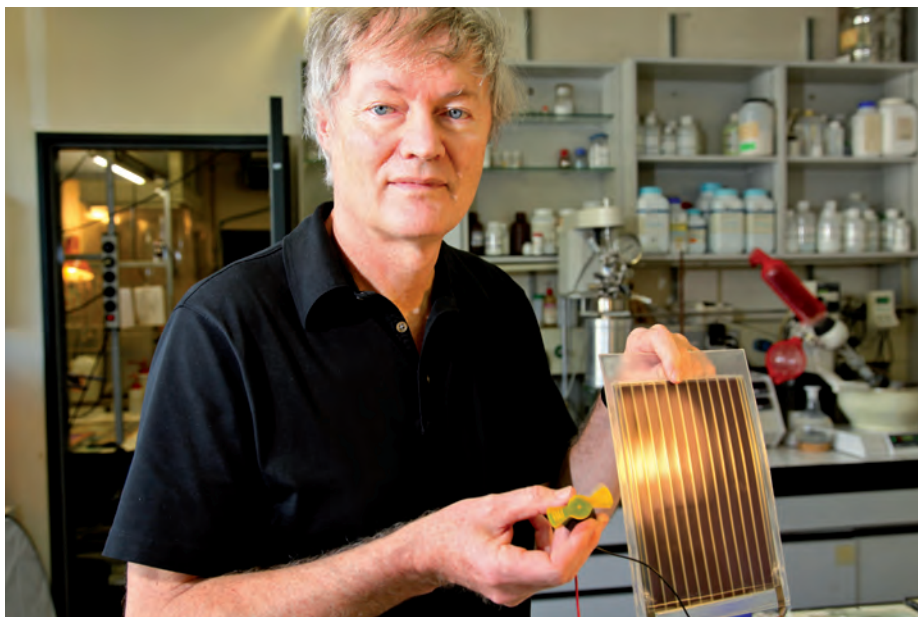
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# MICHAEL GRÄTZEL WINS MILLENIUM GRAND PRIZE

THE 800,000-EURO AWARD, GRANTED BY THE TECHNOLOGY ACADEMY FINLAND, A FINNISH GOVERNMENT AND INDUSTRY GROUP, IS GIVEN FOR INNOVATIVE SCIENTIFIC DISCOVERIES THAT CONTRIBUTE DIRECTLY TO THE WELL-BEING OF ALL.



**P**rof. Michael Grätzel, head of ISIC's Laboratory of Photonics and Interfaces, won the 2010 Millennium Technology Grand Prize. The 800,000-euro award, granted by the Technology Academy Finland, a Finnish government and industry group, is given for innovative scientific discoveries that contribute directly to the well-being of all.

Grätzel's prize was, of course, for his work on dye-sensitized solar cells, also known as Grätzel cells. The award committee found that the price/performance ratio of the cells gives them "major potential" as a future energy technology. Grätzel cells are likely to have an important role in low-cost, large-scale solutions for renewable energy in photovoltaics – the method of generating power by converting solar radiation into electricity using semiconductors that create voltage or electric current upon exposure to light – as well as in batteries and hydrogen production, the Technology Academy found.

"Though DSC cells are still in relatively early stages of development, they show great promise as an inexpensive alternative to costly silicon solar cells and an attractive candidate for a new renewable energy source," the consortium said.

Photovoltaic cells have traditionally been made from silicon. When light hits a cell, some of it is absorbed within the material so that the energy of the absorbed light is transferred to the semiconductor. The energy allows electrons to flow freely, creating a current that can then be drawn off by placing conductive plates on the top and the bottom of the cell.

While traditional photovoltaic cells use silicon as both the source of electrons and

the conductor of the charge carriers, DSC cells separate these two tasks, often leading people to refer to the method as "artificial photosynthesis." In plants, sunlight absorbed in the leaf by chlorophyll converts carbon dioxide and water into oxygen and glucose, providing energy. In Grätzel cells, chlorophyll is replaced by dye molecules and the leaf structure is instead a porous titanium oxide nanostructure. This nanostructure is coated with light-absorbing dye molecules and then placed in an electrolyte solution and either put between two glass plates or enclosed in plastic. Electrons are freed when light strikes the dye and then collected by titanium dioxide particles and transferred to an external circuit, producing a current.

DSC cells are cheaper to make than silicon-based cells, and are made out of materials that are found in relatively great abundance and are largely non-toxic. The cells can also, unlike those that are silicon-based, produce electricity in low-light conditions and can be directly incorporated into buildings by replacing glass panels. Indeed, Grätzel cells "promise electricity-generating windows and low-cost solar panels," the Technology Academy said. Consumers have recently gotten access to the technology in the form of G24 Innovations' Grätzel bag, a backpack coated with a DSC solar cell and used for charging devices such as mobile phones, GPS or iPods while on the go.

Grätzel, who has been professor of Physical Chemistry at EPFL since 1977, is the author of more than 900 publications, two books and the inventor of more than 50 patents. His research has already had 75,000 citations, ranking him among the 10 most highly cited chemists in the world.

# JEAN-CLAUDE BÜNZLI EXPLAINS EUROPIUM IN *NATURE*



**P**rof. Jean-Claude Bünzli, honorary professor and former head of ISIC's Laboratory of Lanthanide Supramolecular Chemistry, last year published an article in *Nature Chemistry* explaining why europium, an element that's neither commonly found in the Earth's crust or involved in biological processes, is nevertheless very interesting.

The critical property of europium, which belongs to a series of elements called lanthanides, is its bright luminescence: the element emits red light in trivalent form and blue light in divalent form. Phosphors based on red and blue europium- as well as green terbium-emitters can convert UV radiation into visible light and have played essential roles in applications such as X-ray-intensifying screens, cathode-ray tube or plasma-display panels, fluorescent lamps and light-emitting diodes.

The luminescence of trivalent europium can be sensitized by organic aromatic molecules, Bünzli writes, making the complexes useful in applications such as security inks and bar codes. Europium also plays a critical role in certain kinds of common biomedical analysis. Fortunately, "one kilogram of europium is sufficient for almost one billion analyses," Bünzli writes; the applications aren't threatened by the feared shortage of rare-earth elements.

Which is good because another potential use is emerging: plastics doped with divalent europium and monovalent copper have been shown to convert the UV portion of solar energy into visible light. Using such plastics to cover greenhouses enhances the amount of visible light received by the crops, leading to yields about 10 percent higher, he said.

"Such an increase could cover the growing need for food over several decades without expanding the cultivated surface," Bünzli wrote in *Nature Chemistry*. "Europium is possibly heading towards another bright future."

See *Nature Chemistry*, Vol. 2, August 2010 for the full article.

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## THREE ISIC PROFESSORS WIN EUROPEAN YOUNG CHEMIST ACKNOWLEDGEMENT



Professor Nicolai Cramer won the gold medal and Professor Clémence Corminboeuf the silver at the "European Young Chemists Award" given at the 3rd European Association for Chemical and Molecular Sciences (EuCheMS) Chemistry Congress in Nuremberg last year. Professor Xile Hu was on the shortlist of 13 finalists.

CLOCKWISE FROM  
UPPER LEFT:  
NICOLAI CRAMER,  
CLÉMENCE  
CORMINBOEUF,  
XILE HU



The award, sponsored by EuCheMS, the Italian Chemical Society, the Gesellschaft Deutscher Chemiker, and the European Young Chemists Network was given for the third time last year. It is intended to honor and encourage younger chemists whose current research displays a "high level of excellence and distinction." Organizers received a large number of applications from scientists between the ages of 19 and 34. Though applicants came from 18 different countries, most of them came from Spain, Italy and Germany.

At the conference, Cramer gave a talk on enantioselective rhodium-catalyzed C-C bond activation and its economic and ecological interest. Corminboeuf presented a quantum chemical methodology that enables the direct assessment of pi-conjugation effects on molecular and material properties and can be used to identify systematic strategies for enhancing the functionalities of pi-electron systems. Hu discussed the cross-coupling of non-activated alkyl halides by a well-defined Ni catalyst, using an approach that allows researchers to understand and control the reactivity in a rational manner.

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# COMMINELLIS RECOGNIZED BY SPECIAL ISSUE OF *JOURNAL OF APPLIED ELECTROCHEMISTRY*



The *Journal of Applied Electrochemistry* honored Christos Comninellis with a special issue in commemoration of his 65<sup>th</sup> birthday and 40 years at EPFL. During the four decades, Comninellis has published more than 250 scientific papers, has been granted 15 patents and has been the main advisor for 30 doctoral theses.

Though his research is now focused on environmental electrochemistry, he has been active in electrocatalysis and the development of new electrodes and fuel cells. According to the journal, his biggest success in the field of applied electrochemistry is the development of new electrodes for treating wastewater. The electrodes are coated with artificial diamond doped with boron to make them conductive and enable the destruction of the organic elements in water without producing any pollution.

Described as “friendly, open-minded and humane,” Comninellis officially retired this year, though he will remain very active and continue to teach and research. Comninellis dedicated the volume, *J Appl Electrochem* (2010) 40, to his wife Evangelia and his children Anastasia and Gil.

Please see <http://www.springerlink.com/> for the full issue.



Elena Dubikovskaya has been appointed tenure track assistant professor of bio-organic chemistry. She has developed new and non-invasive imaging techniques for the study of processes that are specifically involved in the growth of cancerous cells. She will perform her research work in the context of the new chair in bio-organic chemistry at ISIC.



Christian Heinis won the 2011 European Federation for Medicinal Chemistry's Prize for Young Medicinal Chemist in Academia. The prize is given annually and consists of a diploma, € 1,000 and an invitation for a short presentation at an EFMC symposium.

## NEW CATALYST MAY REVOLUTIONIZE HYDROGEN PRODUCTION

Hydrogen can be produced from water by electrolysis, but the reaction is slow and platinum – an expensive material that has tripled in price over the last decade – is generally used as a catalyst to speed things up. This means, however, that sustainable production of the gas is a challenge and that the production cost is high. A team led by Prof. Xile Hu, head of ISIC's Laboratory of Inorganic Synthesis and Catalysis, discovered a catalyst based on the abundantly available metal, molybdenum, that is efficient and allows hydrogen

production at room temperature. An international patent based on this discovery, which may significantly lower production costs, has just been filed. “The next stage is to create a prototype that can help to improve sunlight-driven hydrogen production,” Hu says. The paper – Amorphous molybdenum sulfide films as catalysts for electrochemical hydrogen production in water, written by Daniel Merki, Stéphane Fierro, Heron Vrubel and Xile Hu – was published in *Chemical Science* earlier this year ([doi: 10.1039/c1sc00117e](https://doi.org/10.1039/c1sc00117e)).

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Station 6  
1015 Lausanne  
Switzerland  
[secretariat.isic@epfl.ch](mailto:secretariat.isic@epfl.ch)

EDITOR  
Carey Sargent  
[www.sargent-holliger.com](http://www.sargent-holliger.com)

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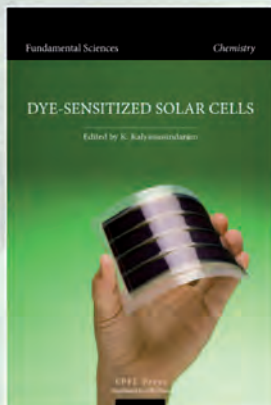
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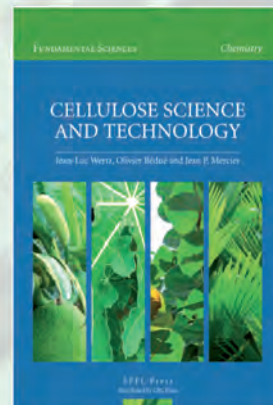
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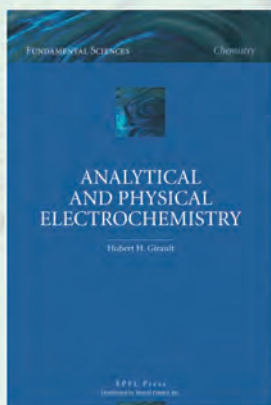
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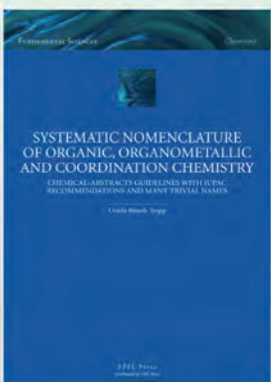
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