

SYNFORM

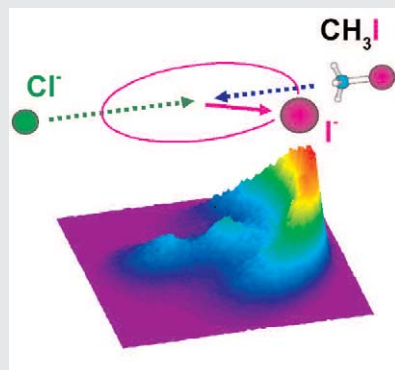
People, Trends and Views in Synthetic Organic Chemistry

2008 / 04

SYNSTORIES ■ ■ ■ ■

■ Combinatorial Synthesis of Peptide Arrays onto a Microchip

■ Imaging Chemical Reactions: Uncovering the Dynamics of Exchange Reactions



■ Enantioselective, Organocatalytic Oxy-Michael Addition to γ/δ -Hydroxy- α,β -enones: Boronate-Amine Complexes as Chiral Hydroxide Synthons

CONTACT ++++

Your opinion about SYNFORM is welcome, please correspond if you like:
marketing@thieme-chemistry.com



Dear readers,

this time I am writing while on sabbatical at the University of Toronto in Canada, hosted by one of the editors of **SYNTHESIS**, Professor Mark Lautens. The University of Toronto offers a vibrant scientific atmosphere, and, together with my family, I am enjoying the warm hospitality provided by both the faculty members and the students. I hope this will have a positive effect on the forthcoming issues of **SYNFORM** that are currently in preparation, and, of course, on this issue that features three **SYNSTORY** articles. The first of these reports on a new technology developed in Germany for the fabrication of peptide arrays on a microchip. The second covers another breakthrough achievement coming from Germany that demonstrates that even those aspects of chemistry that seem to be very well established and taught in every basic organic chemistry course, such as the nucleophilic substitution reaction (S_N2), may be the source of unexpected and fundamental new discoveries. The third **SYNSTORY** deals with a new and efficient strategy developed at the University of Texas Southwestern (USA), for performing a rather difficult reaction, the oxy-Michael reaction, in enantioselective fashion. I hope you enjoy the read!

Matteo Zanda

Editor of SYNFORM

CONTACT ++++

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Synform@chem.polimi.it

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Combinatorial Synthesis of Peptide Arrays onto a Microchip

Science 2007, 318, 1888

■ **Background and Purpose.** Peptide arrays are composed of a large number of diverse peptidic molecules and enable high-throughput screening of compounds that may interact with one or more peptides in the array. Thus, an array of peptidic molecules potentially suitable as ligands for a particular biological receptor or an enzyme may be prepared and “screened” with respect to interaction partners. Another option is that arrays of peptide antigens may be used to screen a patient’s sera for antibodies that are related to any kind of disease. This would allow the use of peptide arrays by clinicians to determine whether or not a patient has developed antibodies to particular peptidic antigens. It is possible as well to use combinations of proteins to screen for molecules which interact or are part of a similar metabolic pathway. Although peptidic arrays are very promising, their potential so far has not been fully realized, and this is in large part due to manufacturing challenges. Now, Dr. Frank Breitling, Dr. F. Ralf Bischoff, Dr. Volker Stadler and coworkers from the Chip-Based Peptide Libraries research group of the German Cancer

Research Center (GCRC), in collaboration with Prof. Volker Lindenstruth, Chair of Technical Computer Science, and coworkers from the Kirchhoff-Institute of Physics (KIP), both in Heidelberg (Germany), have developed a new technology that holds promise to represent a real breakthrough in this competitive field. In this multidisciplinary project, the GCRC group developed the so-called “amino acid particles”, performed the combinatorial synthesis based on custom-made microchips, and stained the peptide arrays. In addition, the group coated the microchips with a specific graft polymer film, which on one hand enables peptide synthesis, and on the other hand prevents non-specific protein adsorption on the array chip surface. The KIP group designed the microchips and helped the partners to charge and deposit the amino acid particles. Hence, this project has a pronounced multidisciplinary character with biologists, chemists, physicists, computer scientists, and engineers among the authors of the Science paper. Volker Stadler, Ralf Bischoff, and Frank Breitling agreed to be interviewed by **SYNFORM**.

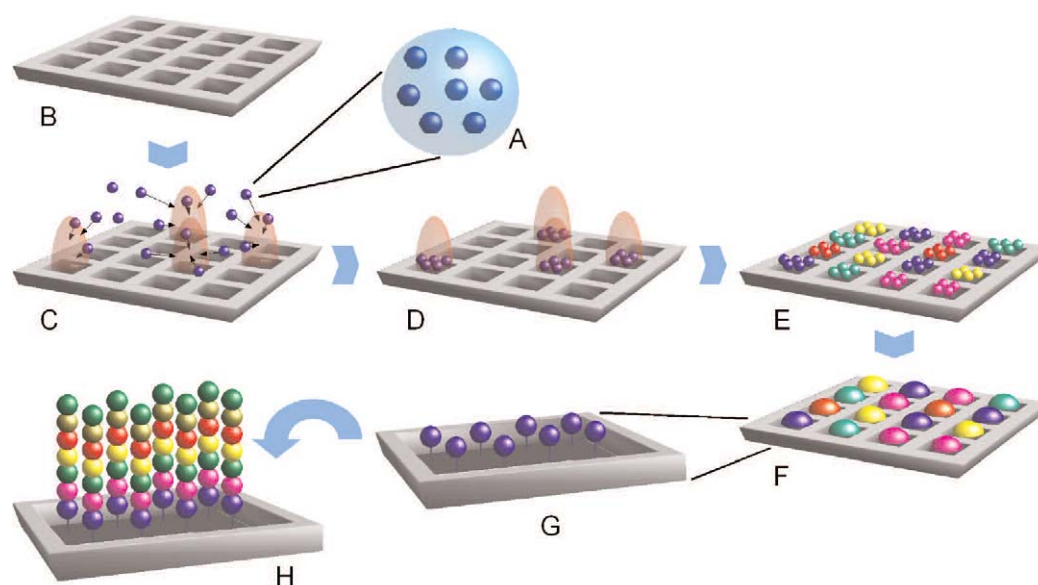


Figure A Synthesis of peptide arrays on microchips: Activated amino acids are embedded within particles (A) that are addressed onto a chip’s surface (B) by electrical fields generated by individual pixel electrodes (C, D). A whole layer of consecutively addressed “amino acid particles” (E) is melted at once to induce the coupling reaction (F). After washing and deprotection steps as a matter of routine (G), repetitive coupling cycles finally generate a peptide array (H).

INTERVIEW

(Questions by **SYNFORM**, answers by Dr. V. Stadler, Dr. R. Bischoff, and Dr. F. Breitling)

Question | What about the applications for high-density peptide arrays?

Answer | For example, to target a highly expressed protein in cancer cells with D-peptides that specifically bind to that target protein. We need D-peptides (= mirror-image peptides of L-peptides) for that because naturally occurring L-peptides are simply digested, i.e. don't reach the tumor. Depending on the targeted protein, sometimes it is sufficient to block/compete for the binding of that target protein to another protein to get a therapeutic effect. This can be exemplified by HPV's oncogenic E6 protein, which blocks apoptosis of deregulated cells by degrading p53 in cervical cancer. There is an L-peptide, which in turn blocks E6 restoring apoptosis, but it is digested much too fast to be used as a therapeutic. Here, peptide arrays can be used (a) to do binding-pocket mapping to identify the less important positions in this L-peptide, (b) to exchange these positions with D-amino acids, and (c) to identify E6 binders of these stabilized D/L-peptides as therapeutic lead structures for cervical cancer therapy.

Do the same as above with L-peptide arrays, but use a mixture of antibody molecules, i.e. the serum antibodies of a patient that recently overcame a severe disease, or, to the

contrary, suffers especially from the very same disease. You would like to know which antibodies – if any – are responsible for that. Maybe you find out that way, i.e. find a panel of peptides that each define one of the patient's antibodies. You can use these peptides to verify your results, i.e. ask the question: does a certain pattern of antibodies correlate with a specific problem?

There are also many more possible applications, such as to directly screen for novel antibiotic peptides and catalytically active peptides, to readout the immune response against a pathogen, and so on.

Question | What motivated the study?

Answer | The scientific goal was to obtain affordable high-density peptide arrays at hand for biomedical research (see the applications). The technical goal was to improve the state of the art from currently 22 peptides/cm², which is still defined by Ronald Frank's SPOT synthesis (R. Frank *Tetrahedron* **1992**, *48*, 9217).

Question | What problem or problems were you seeking to address?

Answer | The main technical problem we addressed was to reduce the number of coupling cycles of available technologies to one per layer, and at the same time to significantly enhance the density of peptide arrays. If you look closely at

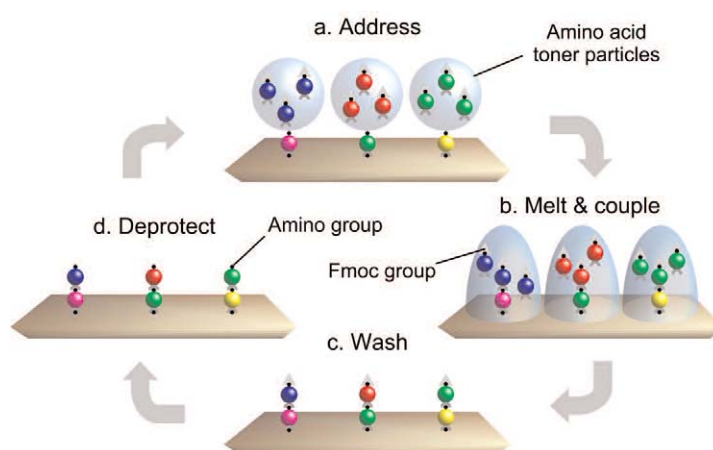


Figure B Particle-based combinatorial Merrifield synthesis: Fmoc-amino-acid-OPfp esters embedded within amino acid particles are addressed onto a solid support (a), where the particles are melted after transfer. This allows the amino acid derivatives to diffuse and couple to the support (b). The cycle is finished when excessive monomers are washed away (c), and the Fmoc protection group is removed (d). Repetitive coupling cycles generate a peptide array.

those papers that tried lithographic methods to synthesize peptide arrays, you perceive one nasty technical problem: intrinsic to their technology they always spatially address only one monomer per coupling cycle, which means that, for example, $20 \times 10 = 200$ coupling cycles have to be done to synthesize an array of decameric peptides. This inevitably leads to an accumulation of time and material, not to mention synthetic artifacts due to inevitable chemical side reactions. Similar arguments highlight the difficulties of other technologies, such as the Nanogen approach (amino acid monomers are picked up by electrical currents from solution to individual pixels; in addition one has to cope with electrolysis).

Question | *What was most novel about the study?*

Answer | The main novelty was to “freeze & package” activated amino acids inside solid particles, which we call “amino acid particles”. Then we delivered these postal packages to individual pixel addresses by electric fields, followed by unpacking a whole layer of postal packages simultaneously just by melting the solid particles. After coupling, we are back again to well-established Merrifield conditions. This principle allows for the miniaturization of the whole process and at the same time reduces the number of coupling cycles to one per cycle. The very same particle-based principle should be feasible for other kinds of combinatorial chemistry; for example, in material sciences.

Question | *What made it possible?*

Answer | The basic principle is that switchable strong electric fields generated by individual pixels direct triboelectrically charged amino acid particles to individual sites, which represent specific addresses for combinatorial array synthesis. Surface tension then transforms melted particles into tiny half-domes, which are somehow both oily and viscous, that reliably cover very small areas, and thereby confine tiny synthesis areas.

Question | *Did you encounter any particular challenges during the study?*

Answer | The biggest challenge was to develop the amino acid particles, which was quite challenging for us biologists and chemists, i.e. getting particles that are chargeable, keep their charge over time, and don't interfere with the chemistry of peptide synthesis (e.g., no functional groups in the matrix material; once melted the particle matrix should behave as a solvent for a chemical reaction). Furthermore, the amino acid particles must not agglomerate; they have to dispose of similar physical properties, that is a narrow size distribution in the micron range as well as largely uniform thermal characteristics.

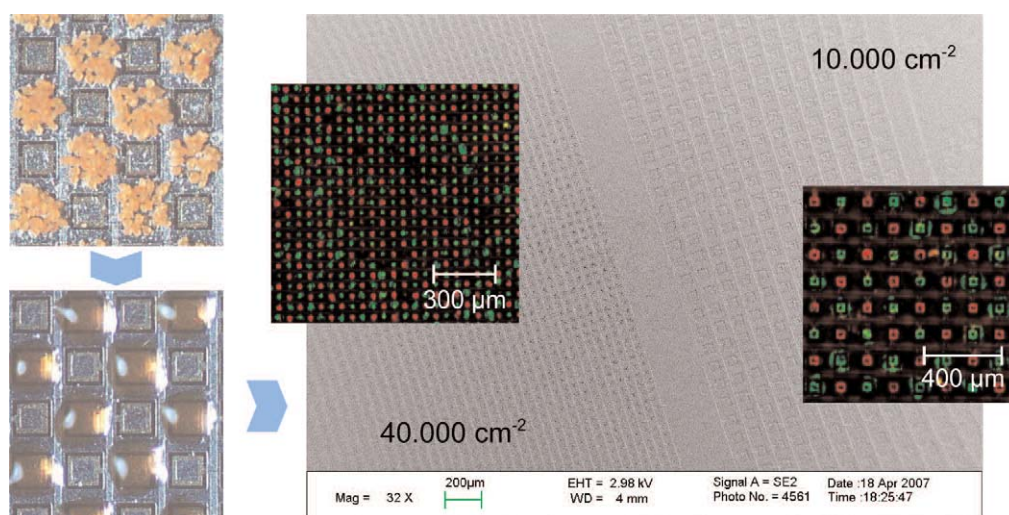


Figure C Synthesis of peptide arrays on microchips: Activated amino acids are addressed onto a chip's surface, where they are melted to induce the coupling reaction. Melted particles delimit individual coupling areas. For better visualization, pixel areas are overloaded (left). Repetitive coupling cycles finally generate a peptide array on the microchip's surface. Particle-based *in situ* synthesis of chessboard-arranged Flag (green) and HA epitopes (red) yielded arrays with densities of 10 000 and 40 000 cm^{-2} , respectively. The peptides were stained with fluorescently labeled specific antibodies (right).

Question | *How did you overcome them?*

Answer | We used another approach, which cannot be disclosed right now, to learn about the physical properties that our amino acid particles should have. Then we tried different ingredients that are used to manufacture such particles for interference with our peptide synthesis. Finally, we found a formulation that had the physical properties of a commercial laser printer toner and at the same time didn't impact our coupling reactions.

Question | *What are the next steps necessary for moving these findings closer to clinical development and ultimately commercialization?*

Answer | There are two crucial steps we are currently working on: (a) An in situ purification of synthesized peptides to homogenize peptide concentrations over the whole array and to remove artifacts; and (b) automation of the synthesis and the routine washing steps to speed up array synthesis. Nevertheless, our peptide arrays, which we produce by means of our amino acid particles and a similar approach on glass

slides, dispose of up to 160 000 different peptides and can already be used for the screening of protein binders. The quality of the peptide arrays on microchips still has to be improved for commercialization.

Question | *Has the research been patented?*

Answer | Yes, it has, the patent family is EP1140977B1.

Question | *Is it available for license?*

Answer | No. We founded a company (PEPperPRINT Ltd.) with the goal to commercialize the technology on our own. This company has not started its operational business yet, but we are looking for venture capital. If someone is interested, he should feel free to contact us.



The Chip-Based Peptide Libraries research group of the German Cancer Research Center (GCRC): the first author of the Science paper, M. Beyer, is the first on the left, F. Breitling is in the last row, wearing glasses, R. Bischoff is in the middle of the last row with the plaid shirt, and V. Stadler is the first from the right.

Matteo Zanda

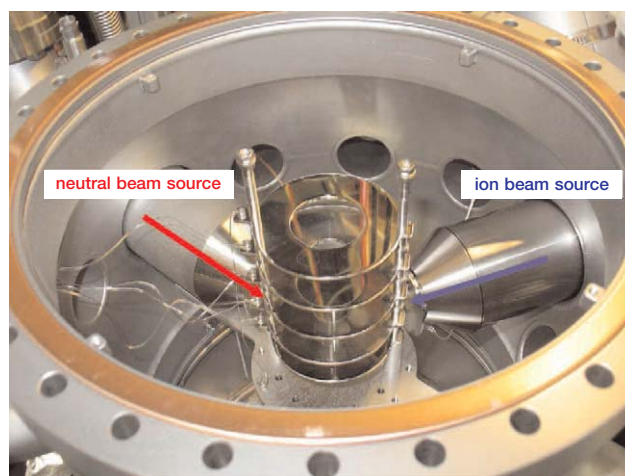
Imaging Chemical Reactions: Uncovering the Dynamics of Exchange Reactions

Science 2008, 319, 183–186

■ The chemical reaction, that means the omnipresent rearrangement of atoms to new molecules, continues to pose many open questions to scientists and engineers. Nowadays a detailed understanding of the mechanisms of chemical reactions is required to optimize the production of synthetics and drugs or to alleviate the destruction of our earth's ozone layer. For his groundbreaking studies of chemical reactions on surfaces, which are important in catalysts, the German physicist Gerhard Ertl was awarded the Nobel Prize in Chemistry in December 2007. One of the most important classes of chemical reactions have now been uncovered in detail in an experiment carried out by scientists at the Physics Institute of the University of Freiburg (Germany) in a collaboration with a chemical dynamics theory group at Texas Tech University (USA). Their work, located at the interface between chemistry and physics, appears in a recent issue of *Science* and shows that the substitution of atoms during the reaction proceeds in a quite different manner than assumed to date (*Science online* January 11, 2008).

Five years ago, Priv.-Doz. Dr. Roland Wester joined the group of Professor Dr. Matthias Weidemüller and started a research project which employs a novel technique in the study of chemical reactions of ions and neutral molecules. Since then, the two experimental physicists and their team of PhD and diploma students have developed a dedicated experimental apparatus that is capable of visualizing reactive collisions between ions and molecules on a single particle level. This can be regarded as watching the collision of billiard balls on a pool table: molecular beams provide the colliding reactants at controlled velocity before the reaction products' scattering angle and velocity are imaged directly with an elaborate camera system. "In the last years we had to cope not only with many unsolved problems, but also with the doubts of our colleagues that this experiment would ever work. With our recent breakthroughs we demonstrated that our unique combination of novel innovative techniques allows us to obtain much deeper insight into many chemical reactions than had been available to date," said Roland Wester proudly and added: "Without the impressive effort of our PhD and diploma students, this would never have worked out."

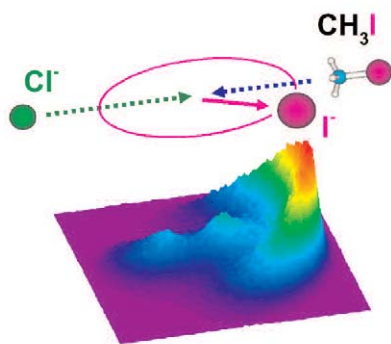
In their most recent work the scientists from Freiburg and Texas have investigated the so-called nucleophilic substitution reaction, a chemical reaction that plays an important role in biology and organic chemistry. When a negatively charged chlorine atom collides with a methyl iodine molecule CH_3I , the iodine atom I is substituted by the chlorine to form a CH_3Cl molecule and a negatively charged iodine atom. The analysis of the camera images, which show the velocity of the reaction product, revealed many unexpected details of the reaction dynamics. Contrary to the simplistic expectation found in chemistry textbooks, this exchange reaction does not solely involve an attack of the CH_3I molecule by the chlorine ion at the reactive center, which drives the iodine atom away on the opposite side. Instead, the reactants stick together at the low velocity of the reaction partners and form a transient complex which undergoes several rotations before the reaction products are formed. On the recorded images, this results in product velocities distributed over all scattering angles. The expected direct mechanism is only established once the reactants carry a significant amount of kinetic energy.



The experimental setup

At these higher scattering energies the scientists found a big surprise. "We were puzzled by an additional prominent feature in our data that appeared besides the direct reaction mechanism and for which we had no explanation," said Dr.

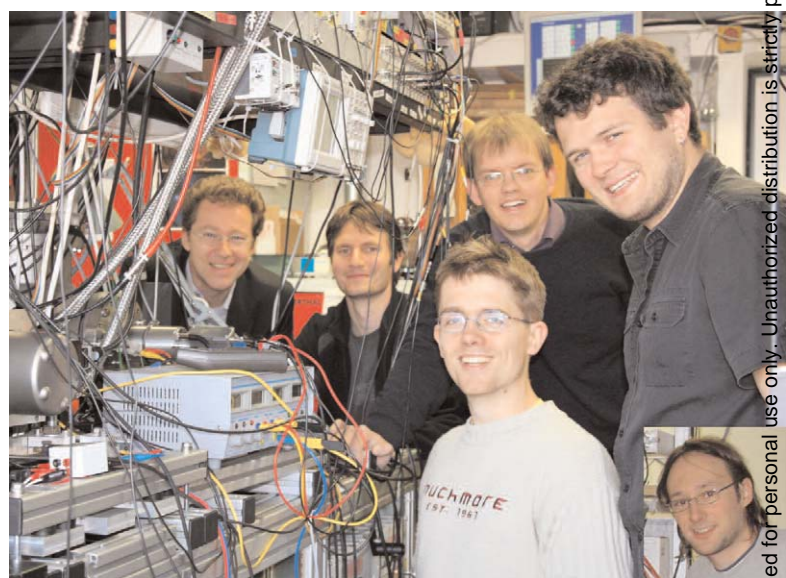
Jochen Mikosch, who earned his doctorate recently on the experimental work in Freiburg. To explain the measured velocity of the reaction products in detail, precise computer-based simulations by Professor Dr. Bill Hase, one of the pioneers in this research field, and his coworkers at Texas Tech University were undertaken. These simulations show, in agreement with the experiment, that in the direct reaction mechanism only a small fraction of the translational energy of the reaction partners is transferred to internal vibration of the product molecule. Since the total energy is conserved, this results in a high velocity of the iodine atom produced in the reactive encounter. Even in the computer calculations, a previously completely unknown type of interaction was observed in which the CH_3I molecule is kicked by the impacting chlorine ion, such that it spins around before the reaction proceeds. “The simulations of our coworkers agree remarkably well with our experimental observations. This suggests a novel reaction mechanism at high relative energy of the reactants which transfers much more of the available energy into internal vibration as in the direct reaction mechanism,” added Jochen Mikosch. The new mechanism was named ‘roundabout’ mechanism. It might be of much more general importance and could appear in other chemical reactions as well.



Three-dimensional center-of-mass images of the I^- reaction product velocity from the reaction of Cl^- with CH_3I at 1.90 eV relative collision energy (E_{rel})

“Nucleophilic substitution reactions are most important in water and likely to play a key role in living organisms. Therefore the scientists plan to study what changes when water molecules are stuck on the reactants one at a time. This will provide better predictions of the course of technologically important reactions and a deeper insight into chemical processes in cells,” Wester said. Matthias Weidemüller and Roland Wester are convinced that the interface between phys-

ics, chemistry and biology holds many more surprises by the conjuncture of complexity and quantum theory. “Our understanding of modern quantum physics is currently undergoing a paradigm shift. So far it was assumed that quantum effects do not have a significant influence in complex and biological systems. However, the progress in understanding complex quantum systems has broadened our perspective and I’m sure that in the near future, evidence of phenomena will appear where quantum physics plays an important role in living systems,” pointed out Matthias Weidemüller. To discover them is the big challenge for the Freiburg scientists. ■

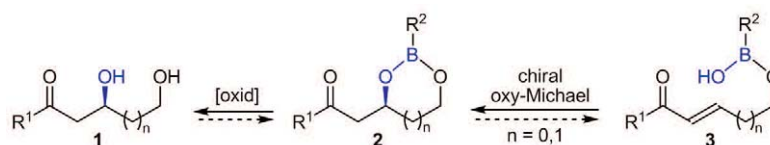


From left: Prof. M. Weidemüller, P. Hlavenka, R. Otto, Dr. R. Wester, S. Trippel and Dr. J. Mikosch (inset)

Matteo Zanda

Enantioselective, Organocatalytic Oxy-Michael Addition to γ/δ -Hydroxy- α,β -enones: Boronate-Amine Complexes as Chiral Hydroxide Synthons

J. Am. Chem. Soc. **2008**, *130*, 46–48

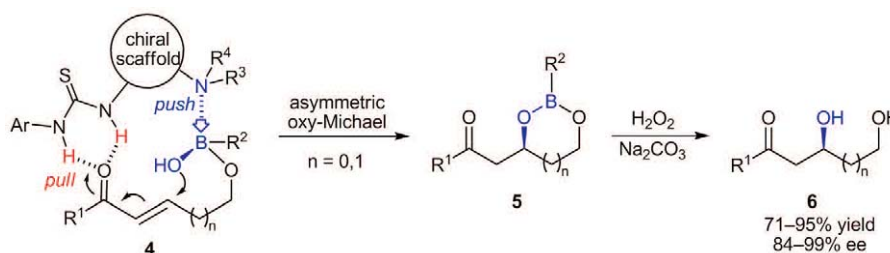


■ Structural motif **1** is present in a wide range of natural products and synthetic intermediates. While Michael additions of hydroxide or synthetic equivalents to α,β -unsaturated carbonyls represent an attractive approach to this moiety, the strong basicity of the former and generally poor nucleophilicity or lability of the latter often render this option problematic. In its place, the intramolecular oxy-Michael addition of hemiacetal/hemiketal-derived alkoxides has emerged as a popular alternative strategy, although the resultant cyclic acetals/ketals can be difficult to remove. Recently Professor J. R. Falck and Dr. D. Li from the University of Texas Southwestern Medical Center, Dallas (USA) reported a new strategy based on the use of boronate-amine complexes as chiral hydroxide equivalents.

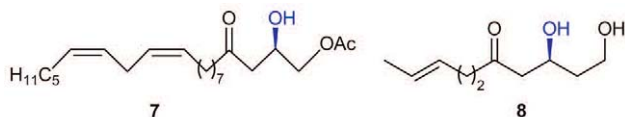
“We envisioned that the boronic acid hemiester **3**, formed in situ, could be induced to undergo intramolecular oxy-Michael addition leading to boronate esters **2**,” explained Professor Falck. “Removal of the boronate via exchange or mild oxidation affords diol **1**. Despite expectations, when

model compound (*E*)-4-hydroxy-1-phenylbut-2-en-1-one was mixed with equimolar amounts of phenylboronic acid and activated 4 Å molecular sieves, no intramolecular Michael addition was observed.” After surveying a variety of reaction conditions, Falck and Li were pleased to note that amines (e.g., Et_3N , *i*- Pr_2NH) readily catalyze the reaction. “We attribute this dramatic difference to the in situ formation of a nucleophilic, pyramidized quaternary boronate complex,” said Professor Falck. “Inspired by the pronounced success of push/pull-type bifunctional organocatalysts, we developed an asymmetric version of the addition. Coordination of the carbonyl by the thiourea (the pull) and complexation of the tertiary nitrogen with boron (the push) were expected to simultaneously enhance the nucleophilicity of the boronate oxygen as well as envelop the enone in a chiral environment.”

To validate the applicability of the foregoing methodology in natural products total synthesis, acetate **7**, an extraordinarily potent antifungal/hepatic protective agent isolated from

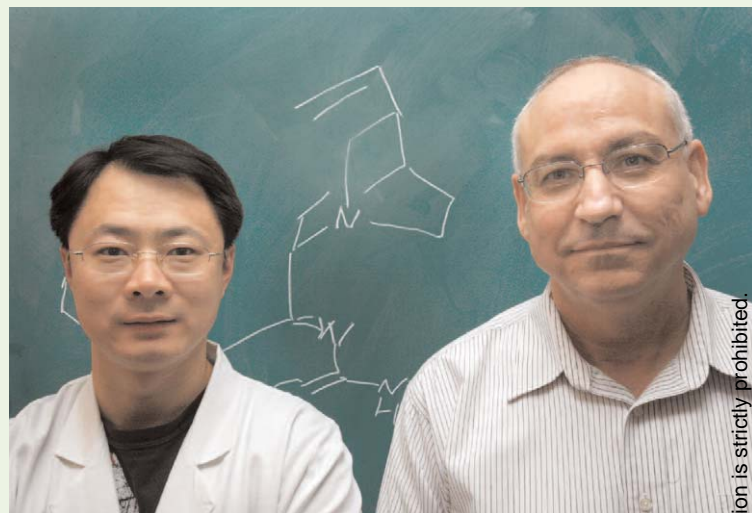


avocado, and (+)-(*S*)-streptenol A (**8**), an inhibitor of cholesterol biosynthesis and tumor cells, were prepared in good overall yields and enantiomeric excesses.



“Boronic acids have a remarkably rich and often unique chemistry, yet typically play a passive role in organic synthesis, for example, as a leaving group in the Suzuki cross-coupling,” said Professor Falck. “In this study, we cogently demonstrate that the boronic acid moiety can directly participate in the reaction and that the boron can be reversibly complexed with a catalytic chiral amine to induce useful enantioselectivity. Recently, we successfully extended these concepts to a highly diastereoselective oxy-Michael addition using secondary alcohols as well as an enantioselective carbonyl reduction. These results and others,” he concluded, “will be published in the near future.” ■

Matteo Zanda



From left: Dr. D. Li, Prof. J. R. Falck

ABOUT THE CORRESPONDING AUTHORS

Derun Li was born in Yantai (P. R. of China) in 1978. He received his B.Sc. (1999) from Lanzhou University under the direction of Professor Yongqiang Tu, and his Ph.D. (2004) from SIOC (Shanghai Institute of Organic Chemistry) under the direction of Professors Guoqiang Lin and Weishan Zhou, where he completed the total synthesis of phorbaxazole B. In 2005, he joined Professor Falck's group at UTSW as a postdoctoral fellow, where he is working on asymmetric boron chemistry.

J. R. Falck was born in Fairbanks, Alaska (USA) in 1948. He earned his B.Sc. (1970) and Ph.D. (1973) at Colorado State University where he developed an electrochemical synthesis of morphine alkaloids. Following postdoctoral training with Derek H. R. Barton (Imperial College, UK), Theodore Cohen (University of Pittsburgh), and E. J. Corey (Harvard University), he joined the faculty at the University of Texas Southwestern where he is currently the Robert A. Welch Distinguished Chair in Chemistry. His research interests include natural products total synthesis, asymmetric synthetic methodology, inositol pyrophosphates and eicosanoids.

COMING SOON ► ► COMING SOON ► ►

SYNFORM 2008/05 is available from APRIL 23, 2008

In the next issues:

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► Chemistry in Singapore

SYNSTORIES ■ ■ ■ ■

■ Modular Syntheses of Polyene Natural Products
via Iterative Cross-Coupling

(Focus on an article from the current literature)

■ An Enantioselective Organocatalytic Oxidative
Dearomatization Strategy

(Focus on an article from the current literature)

FURTHER HIGHLIGHTS + + + +

SYNTHESIS

Review on: Osmium and Palladium:
Complementary Metals in Alkene Activation and Oxidation
(by S. D. R. Christie and A. D. Warrington)

SYNLETT

Cluster on "Acetylene and Allene Chemistry" in issue 5/2008

SYNFACTS

Synfact of the Month in category "Organo- and Biocatalysis":
[Tripeptides: Efficient Catalysts for 1,4-Addition Reactions to Nitroolefins](#)

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