THE INSIDE STORY

The Impact of REACh on the Chemical Enterprise

SYNSTORIES

- Total Synthesis of (±)-Merrilactone A via Catalytic Nazarov Cyclization
- Assigning the Configuration of Cryptochiral Small Molecules
- Enantioselective Petasis-Type Reaction of Quinolines Catalyzed by New Thiourea Catalysts

CONTACT

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

The REACh (Registration, Evaluation and Authorisation of Chemicals) is the new regulatory framework on Chemicals that came into force on June 1, 2007. According to the European Commission “The aim of REACh is to improve the protection of human health and the environment through the better and earlier identification of the properties of chemical substances” (http://ec.europa.eu/environment/chemicals/reach/reach_intro.htm), so it is generally welcome by the European citizens.

However, the REACh is also raising legitimate industry concerns in Europe as well as in America and Asia. The new INSIDE STORY presents a “face-to-face” between Dr. Geert Dancet, the interim Executive Director of the European Chemicals Agency, ECHA, and two experts from the world of industry, Mr. Steven Russell, Senior Director for Health, Products and Science Policy of the American Chemistry Council (ACC) and Dr. Martin Kayser, Head Product Safety of BASF AG.

The three SYNSTORY articles deal with new exciting developments of organic chemistry. Professor Werner Hug and Dr. Christian Bochet (Switzerland) bring us to the known limits of the universe of chirality. Professor Alison Frontier (USA) discloses some very interesting “behind-the-scenes” in her recent elegant synthesis of racemic merrilactone A. Last but not least, Professor Yoshiji Takemoto (Japan) elaborates on a new enantioselective Petasis-type reaction promoted by thiourea catalysts, within the frame of a Special Topic on “Thiourea as Catalyst” to be published in SYNTHESIS issue 16/2007.

We hope you will appreciate this fourth issue of SYNFORM. Thanks for reading

Matteo Zanda
Editor of SYNFORM

CONTACT

If you have any questions or wish to send feedback, please write to Matteo Zanda at: Synform@chem.polimi.it
The Impact of REACh on the Chemical Enterprise

ABSTRACT

What are the objectives and scope of REACh? The EU’s new chemicals legislation REACh stands for the Registration, Evaluation, Authorisation and Restriction of Chemicals, and it came into force on June 1, 2007. The objectives of REACh are to:

- Protect human health and the environment
- Maintain and enhance the competitiveness of the EU chemicals industry
- Prevent the fragmentation of the internal market
- Increase transparency
- Integrate with international efforts
- Promote non-animal testing
- Comply with EU international obligations under the WTO.

By creating an EU-wide system for the management of chemicals REACh will bring together the EU chemicals legislation. REACh will no longer differentiate between so-called “existing” and “new” chemicals.

Previously, all chemicals put onto the market before 1981 were called “existing” chemicals while chemicals introduced after 1981 were termed “new” chemicals. New chemicals had to be tested quite rigorously under the legislative provisions, which are repealed by REACh. There were no such provisions for “existing” substances. As a result, knowledge on properties and uses of “existing” substances is rather limited.

Under REACh, the burden of proof for demonstrating the safe use of chemicals will be transferred from Member States to industry. ECHA is the new European Chemicals Agency based in Helsinki. It has marked its start-up with the launch of its website (http://echa.europa.eu) on June 1, 2007, the day of implementation of the REACh Regulation, and will become fully operational by June 1, 2008. ECHA will manage and coordinate the registration, evaluation, authorization, and restriction processes of chemical substances under the REACh Regulation to ensure consistency in the management of chemicals across the European Union. The Agency will provide Member States and EU institutions with scientific and technical advice on chemicals covered by the Regulation.

Further information about REACh can be found on the website http://ec.europa.eu/enterprise/reach/index_en.htm.

INTERVIEWEE

Geert Dancet, PhD
Interim Executive Director of the European Chemicals Agency, ECHA

Geert Dancet studied economics, econometrics and philosophy at the University of Louvain (Belgium).

After a short academic career and an assignment in Latin America for UNIDO, he joined the European Commission in 1986 and was Administrator, Head of Sector and Deputy Head of Unit at the Directorate-General for Competition in charge of sectorial State aid in industries covered by special rules.

In July 1997 he became Head of Unit at the Directorate-General for Industry of the coordination unit in charge of the industrial aspects of competition policy and structural measures. When creating the Enterprise DG in January 2000, the Commission confirmed him as Head of Unit in charge of the enterprise aspects of competition, the mirror unit for competition policy.

In March 2004 he was nominated Head of Unit of the newly established REACh Unit in the Enterprise DG. This involved taking the REACh proposal through the regulatory process in the Council and European Parliament as well as developing and implementing an interim strategy, including the preparations for the new Chemicals Agency.

In January 2007, the Commission nominated him as the interim Executive Director of the European Chemicals Agency, ECHA. He has taken office in the agency in Helsinki on June 1, 2007, the date of implementation of the new REACh Regulation, adopted in December 2006.
One of the stated objectives of REACh is to protect the competitiveness of the European industry. Many people outside the EU interpret this as a fairly straightforward admission and that REACh is in fact a protectionist regime. This view is reinforced by the requirement of importers to register monomers in imported polymers, and by the initial reports from some companies that the scope of work and potential liability is making it difficult (as a practical matter) to find sufficient “only representative” service providers. How do you react to that view?

According to the first recital of the Regulation, the aims of REACh are to ensure a high level of protection of human health and the environment as well as the free movement of substances (on their own, in preparations and in articles) while enhancing the competitiveness and innovation. The second recital stresses that the efficient functioning of the internal market for substances can be achieved only if requirements for substances are harmonized across the EU. The third recital stipulates that the legislation should be applied in a non-discriminatory manner whether substances are traded on the internal market or internationally in accordance with the Community’s international commitments. The Regulation is thus not protecting the EU market but creating a level-playing field throughout the Community and for all players, local manufacturers and importers alike.

As it is known, polymers have been exempted from registration but not from restriction or authorization. In order to know what substances are contained in polymers, it was agreed in co-decision procedure on REACh to require the registration of monomers from EU producers and importers. The requirement to register monomers in a polymer is driven by workability concerns. It is well known that the number of polymers is extraordinary high. It is much more reasonable to register the more limited number of monomers than polymers themselves.

In the Agency or Commission we are unaware that companies from third countries would have difficulties in finding firms providing “only representative” services. ECHA helpdesk has already clarified at several occasions that these service providers can outsource specialized expertise in the handling of chemicals, which should facilitate their identification.

Steven Russell, Esq.  
American Chemistry Council

Steven Russell joined the American Chemistry Council (ACC) in 1995 and currently serves as Senior Director for Health, Products and Science Policy. In that capacity Mr. Russell provides strategic guidance and counsel on chemical management policy at the state, federal and international venues. Mr. Russell has also provided legal counsel on the US Toxic Substances Control Act (TSCA) as well as other US federal and state chemical control laws.

Mr. Russell helped to develop and guide the chemical industry’s proactive response to a report by Environmental Defense and a widely publicized challenge by the US EPA to make test data on chemicals publicly available. That program – the High Production Volume (HPV) Chemical Challenge Program – resulted in commitments to provide the public with safety data and other information for more than 95% by volume of chemicals in commerce. The HPV Chemical Challenge Program is widely agreed to be the most successful voluntary chemical safety program of its kind, involving the mobilization and organization of more than 300 companies. Mr. Russell also was instrumental in conceiving and delivering a voluntary industry-led extension of that program in 2005.

Mr. Russell has helped to represent the interests of US business abroad, including active participation in various chemicals-related work programs of the Organization for Economic Cooperation and Development. Mr. Russell has also served as the Chairman of the Business Industry Advisory Committee’s (BIAC) Chemicals Committee to the OECD since 2005. More recently Mr. Russell participated on behalf of the ACC in the process which led to the adoption of REACh to ensure that decision makers understood the potential impacts on non-EU industries, and in particular provide examples from experience on how to meet the objectives of REACh while avoiding unnecessary barriers. His work in that area continues, including contributions to development of many of the REACh guidance documents, and helping ACC member companies prepare to implement REACh.

Mr. Russell earned a BA from the University of Kansas in 1984, and a JD from California Western School of Law in 1987. He is a member of the bar in California, Virginia and the District of Columbia.
Question 2 (S.R.) | In previous response to questions regarding whether REACH presented WTO concerns, the Commission seemed to suggest that if other countries harmonized their laws to REACH any competitiveness concerns would be addressed. Since that time EU representatives in the US, China and elsewhere have been reaching out to governments and NGOs to promote REACH. Is this strategy an admission that REACH presents technical barriers to trade?

Answer 2 | No, the EU has assessed the WTO concerns on REACH and these assessments have shown that REACH does not present a technical barrier to trade. The EU manufacturers and importers have identical REACH obligations in relation to their chemical substances. The EU representatives have been interacting with their counterparts in the US, China and other countries to keep them informed on the REACH regulation.

Question 3 (S.R.) | Compliance with REACH is obviously a huge issue for US companies that export chemicals and articles to Europe. REACH runs nearly 850 pages, and at last count there were nearly 7,500 pages of technical guidance documents, only a handful of which had input from outside the EU. Currently helpdesks are only being established in EU Member States. What does the Commission or ECHA plan to do to help non-EU entities comply with REACH, and what assurances should those companies have that enforcement of REACH will not be directed at non-EU companies?

Answer 3 | The REACH regulation published on May 29 is in total 278 pages out of which about 60 are the body text, 70 are the annexes I–XVI and 150 pages are the annex XVII which list the substances with restrictions on marketing and use.

It is true that the REACH technical guidance counts for several thousand pages. We are foreseeing it becoming somewhat more concise when it is finalized but it will stay extensive. This is due to the fact that the guidance needs to address the specificities of all substances and situations covered by the new Regulation and provide advice not only to chemicals manufacturers/importers but also to the users and competent authorities; therefore, the number of pages is high. Everybody should however realize that nobody would need to read all of the pages.

The guidance which is accessible on the European Chemicals Agency website includes also IT tools to help companies. For example, the Navigator-tool is a question- and answer-based tool for companies, in particular SMEs, which will guide the users directly to the information most relevant to them. As the guidance and tools are on the ECHA website they can be accessed easily by any company regardless of its location in the world.

The REACH helpdesks in the 27 EU Member States and the Agency will also assist companies in finding the most relevant guidance and tools for their situation. One should also remember that many industry sectors and also some non-EU countries are considering providing REACH services and often direct assistance to companies.

Enforcement of REACH, just like any other EU legislation, is the responsibility of the EU Member States. To enhance harmonized implementation of the new Regulation the Agency will coordinate the Forum, a network of Member State inspectors of the REACH Regulation.
Question 4 (M.K.) | After ECHA has been established, for the first time there is a single European Agency responsible for the uniform risk assessment of chemicals. This is a significant step forward towards equal opportunities for all manufacturers in the EU. But how wants the Commission also ensure a uniform level of enforcement in the Member States?

Answer 4 | As said before, through the Forum Member States can coordinate their enforcement activities in order to achieve harmonization of these activities. The Commission has recognized at an early stage the need to accelerate the preparation of the Forum by establishing a CWG Subgroup on Enforcement in early 2006.

Question 5 (M.K.) | Now that REACh has come into force, the clock has started ticking. However, important guidance from the REACh Implementation Projects is still missing. Furthermore, not even the draft of the European version of the Globally Harmonized System for Classification and Labeling – which has a significant impact on the content of the chemical safety reports – has been published. Was it really necessary to set such tight deadlines, which add enormous pressure especially to manufacturers with a large substance portfolio?

Answer 5 | The REACh registration deadlines for phase-in substances had been chosen, considering the large number of phase-in substances and the need to ensure that the process is manageable for the industry, Agency and Member State authorities.

In the final stage of the co-decision procedure, it was decided to prolong the first registration deadline from 3 to 3.5 years in order to facilitate the SIEF formation, data sharing and joint registration process. This also facilitates the adoption process of the GHS regulation considering that it is one of the main objectives of that regulation to avoid the classification and labeling notification according to two different C&L systems.

The Commission proposal for the new EU Classification and Labeling Regulation which will introduce GHS to the Community legislation was published on June 27 and it is now going through the legislative process in the Parliament and Council. It is expected that the new EU Classification and Labeling Regulation are adopted in time. Until then the current classification rules apply to in the chemical safety report.

Question 6 (M.K.) | The whole European Industry was involved into the preparation of REACh. Many experts, well experienced by their daily practical work gave input to help to optimize the legislation and make it workable. How does the European Chemicals Agency plan to proceed with this exchange of expertise?

Answer 6 | The participation of the industry and other stakeholders has been very active and productive in the projects preparing for REACh. The expert contributions of future users of the guidance and tools have been and still are helping us to tailor them to be relevant and as easy to use as possible.

From the Agency’s perspective, the networks and working relationships, which have been established during the past years, are extremely valuable and we want to keep them alive. For that reason we will have a Stakeholder Team in the Agency who will interact with industry and other stakeholders and maintain the already established relationships.

Matteo Zanda
The “Molecule of the Month” (MOM) competition in the Trost Research Group at Stanford University (California, USA) is held four times a year. Each of the four teams of 10–12 people are expected to develop a synthetic strategy for the chosen target molecule that is creative, novel and experimentally feasible. For each team, a postdoctoral researcher and a graduate student are appointed “leaders,” and are expected to present the team’s route at a group meeting held to discuss, criticize, compare and contrast the four approaches proposed by the four teams. Thus, the leaders most directly suffer the humiliation of a poorly conceived strategy, and this serves as a powerful motivating force. In the spring of 2001, merrilactone A was the target molecule chosen for the MOM competition.

The leaders of one of the teams were Alison Frontier, now Assistant Professor of Chemistry at the University of Rochester (USA), and Matthew Crawley. “Every day Matthew asked me if I had started to think about the problem,” recalled Professor Frontier. “Every day I said ‘no, not yet,’ and one day a coworker mentioned to me that Matthew had said that I seemed pretty disorganized. The fundamental truth beneath that statement got me so annoyed that I not only started to think about the problem, but felt it necessary to propose a complete solution because how dare someone suggest I might be disorganized, even if I was.” And so, at the first meeting of the team, a route was proposed involving, as the key step, a catalytic asymmetric Nazarov cyclization of a silyloxyfuran using a chiral Lewis acid.

The strategy remained virtually unchanged, and was presented and defended successfully at the final MOM meeting of the four teams two weeks later. “When I started my independent career at the University of Rochester the following January (2002), studies of catalytic Nazarov cyclization commenced,” Professor Frontier said. The first catalytic Nazarov cyclization was finally accomplished by graduate student Wei He in the summer of 2003, and the first silyloxyfuran cyclization was executed in January 2004 by postdoctoral researcher Xiufeng Sun. Four months later, after several changes in substrate substitution pattern and additional catalyst screening, a cyclization that delivered a bona fide advanced intermediate relevant to merrilactone A was achieved by Wei He. After rapid assembly of the third ring, the project was detained for more than a year by an unexpected complication that prevented formation of the fourth ring. “The molecule, in its infinite wisdom, had decreed that Wei He should learn a great deal about Weinreb amides as strategic intermediates, E- and Z-isomerism in vinyl furanyl ketones, and the behavior of the entire family of carbonate derivatives under acidic and basic conditions before he would be allowed to move forward in his synthetic quest,” explained Professor Frontier. Fortunately, Wei He and postdoctoral researcher Jie Huang solved the problem of the fourth ring in the summer of 2006, and the synthesis was completed on September 15, 2006.

According to Professor Frontier, the key Nazarov cyclization could only be achieved using a custom-designed iridium(III) complex developed by the Eisenberg research group at the University of Rochester. “If Rich Eisenberg had not invited me to lunch one day in early 2003, the synthesis of merrilactone A using a catalytic Nazarov cyclization might never have become a reality,” she explained. “The final synthetic sequence is the result of many experiments and many thoughtful suggestions. I would like to express my gratitude to everyone who helped us think about the steps of this synthesis,” concluded Professor Frontier.

In a comment about this work, Dr. Michael Greaney from
MOM

Wednesday, May 9, 2001

MERRILACTONE A
(neurotrophic agent from Illicium merrillianum)

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Order of presentation 1) Team A, 2) Team B, 3) Team C, 4) Team D

Trost “Molecule of the Month” handout with date, target and list of teams
Assigning the Configuration of Cryptochiral Small Molecules

Nature 2000, 446, 526–529

A chirally deuterated neopentane has never been prepared before, neither in enantiopure nor racemic form. The chirality of this molecule arises from the unsymmetrical isotope distribution around the carbon atoms. Concerning the detection of the chirality of the molecule, since the deuterium and the hydrogen are almost identical, any method based on group differentiation by size would almost certainly fail. Now, these extremely challenging tasks have been successfully achieved by the groups of Professors Werner Hug and Christian Bochet from the Department of Chemistry of the University of Fribourg (Switzerland).

The limit of knowledge in the recognition and understanding of its nature by human beings has been stretched far beyond the ancient world of the senses by the introduction of new, sophisticated technological tools. “Although it is well known from the theory of the tetrahedral asymmetric carbon that, when the four substituents on a carbon center are different from each other, the carbon atom becomes stereogenic, the experimental recognition of chirality remains, I would say, in a primitive stage,” said Professor Kenso Soai, an expert in stereochemistry and stereoselective synthesis from the Tokyo University of Science (Japan). “Saturated quaternary hydrocarbons with four very similar substituents and a sample with extremely tiny enantioenrichment with the order of 0.00005% are examples of cryptochirality whose chirality cannot be discriminated by any conventional method. Asymmetric autocatalysis with amplification of chirality serves as an efficient method to discriminate these cryptochiral compounds.”

According to Professor Hug, “The chirally deuterated neopentane is of interest in several respects:

– The central atom of the molecule represents the archetype of a carbon atom asymmetrically rendered exclusively by a chiral mass distribution. Despite its character as a model molecule, it had never been considered by stereochemists.
– Except for a slight difference in the length of the C–H and...
C–D bonds, the site symmetry of the molecule is Td and the electron distribution is symmetric. Thus, the molecule’s diastereomeric interaction with chiral matter appears at present to be unmeasurable. The experimental proof that the enantiomers of this mass-chiral molecule can be distinguished through vibrational optical activity was therefore of basic interest.”

Concerning computations and measurements, Professor Hug said that “the two sister methods of vibrational optical activity are vibrational circular dichroism (VCD) and Raman optical activity (ROA). In view of both the small amount of sample (a few mg) available and its physical properties (a gas at room temperature), ROA, for which measurements in capillaries had previously been demonstrated, appeared as the better option.”

Professor Hug explained that the computations led to the prediction that ROA measurements would be possible but difficult, due to mutual cancellation of the ROA of the nine rotamers of the molecule. “The measurements were done with an optical multi-channel instrument newly constructed at the University of Fribourg by Dr. J. Haesler, with the same design as a ROA instrument built earlier at the University of Zurich by myself. A decisive aspect of these instruments is the elimination of offsets through the optical creation of the properties of the enantiomeric sample from the those physically present. Measurements confirmed the theoretical predictions, and the absolute configuration deduced from the synthetic pathway.”

In addition to the instrumental performance, the synthesis was itself a real challenge. “When Professor Hug asked me whether my team (together with Ivan Schindelholz and Dr. Emmanuel Riguet) would be capable of making it, like any other synthetic organic chemist, I said ‘Sure, easy!’,” explained Professor Bochet. “The quick and naive retrosynthetic analysis that was first sketched indeed looked very straightforward. At the fifth version some days later, we knew that it would not be that easy! For example, the last step involved the displacement of a mesylate by a hydride at a neopentylic site: this step was a Damocles’ sword above the whole synthesis (however, if one wants to make neopentane, there is no way to avoid dealing with a neopentylic site).”

“It took us a good full year to get the enantiopure compound,” he continued. “We based our strategy on the difference in shape between sp²- and sp³-hybridized carbon atoms...
An additional challenge is that neopentane is a gas at room temperature and pressure; and since we made only a few milligrams, handling it was a real nightmare. It is actually a highly flammable gas; the ROA measurement has to be carried out in a flame-sealed capillary: you can imagine that turning on the Bunsen burner next to our precious chiral sample gave us cold sweats. Thanks to the exceptional skills of the physical chemistry team (in particular Jacques Haesler) we could successfully isolate it for the first time!

“The method of Hug, Bochet and coworkers has expanded the human knowledge of the recognition of cryptochiral compounds,” commented Professor Soai. “The compound they discriminate is neopentane, which is chiral because the four substituents, i.e., CH₃, CH₂D, CHD₂, and CD₃ are different from each other. The compound is apparently an extreme example of cryptochirality due to the saturated quaternary hydrocarbon and the fact that the difference of four substituents is only due to deuterium substitution. They were successful for the first time in discriminating the chirality of this cryptochiral compound by observing the vibrational Raman spectrum. The setup of the highly sensitive instrument for vibrational Raman spectroscopy has been an important factor in their success. One can envisage that the method is applicable to the chiral discrimination of various chiral compounds which have not been able to be discriminated.”

REFERENCES

pounds. Therefore, catalyst 1 could not be applied to achieve stereocontrol in enantioselective Petasis processes using organoboronic acids as nucleophiles. For Petasis processes, we designed the new thiourea catalyst 2, which has a chiral donor group.

In the Petasis reaction, the formation of reactive 'ate' complexes such as A is assumed to play an important role in the reactivity and selectivity. "On the basis of this mechanism, we considered that the catalytic generation of a chiral ternary complex from catalyst 2, electrophile, and organoboronic acids would be crucial for the success of enantioselective transformations," continued Professor Takemoto. "Our newly designed catalyst 2 has a chiral chelating aminoalcohol functionality, which could activate the organoboronic acids by coordinating to the boron center and direct the stereochemical outcome of the reaction."

Professor Takemoto’s group has studied the enantioselective reaction of activated quinolines with vinyl boronic acid. "In our concept, the thiourea moiety of catalyst 2 acts as a Bronsted acid and activates electrophiles such as N-acylated quinolinium salts," he said. "We also expected that the thiourea moiety could control the distribution of s-trans/s-cis isomers of the amide bond in N-phenoxycarbonyl quinolinium salt. Additionally, the greater reactivity of catalyst-activated electrophiles and organoboronic acids could enable reactions at low temperatures. Indeed, catalyst 2 promoted the reaction at −78 °C with phenyl chloroformate as an activating reagent.

We also found that the addition of H₂O increased the enantioselectivity and the addition of NaHCO₃ improved the chemical yield. A remarkable effect of H₂O and NaHCO₃ is assumed to be the in situ regeneration of catalyst 2 promoted by a proton source and removal of the resulting boronic acid by base." The effects of 1,2-amino alcohol and thiourea moieties in catalyst 2 were confirmed by testing several related catalysts. A suitable combination of these functionalities was essential for valuable stereocontrol.

The electrophiles of choice were the quinoline derivatives, since products such as tetrahydroquinoline derivatives are important synthetic intermediates and structural units of alkaloids and biologically active compounds. However, enantioselective nucleophilic addition to quinolines is less explored and is limited to the addition of RLi or TMSCN, because resonance stability of heteroaromatic compounds might impede the enantioselective transformation. Additionally, these reactions are frequently plagued by the generation of regio-
isomeric 1,2- and 1,4-adducts. In one of the few related examples, an organocatalyst has recently been reported by Jacobsen’s group to promote the enantioselective addition of silylketene acetal to isoquinoline (*Angew. Chem. Int. Ed.*, 2005, 44, 466–468). “It is particularly important to stress that our catalyst provides a powerful method for enantio- and regioselective synthesis of 1,2-adducts without the formation of 1,4-adducts,” concluded Professor Takemoto. “In the last decade, various types of organocatalysts have been developed and proved to be applicable to a wide range of asymmetric reactions. However, there are still a limited number of organocatalytic reactions that have general and successful application, in comparison with the metal-catalyst-mediated reactions. Therefore, we should design new and multi-functional organocatalysts for this purpose, based on the reaction mechanism of enzyme-mediated reactions as well as that of recently developed organocatalyzed reactions.” The above-mentioned reaction would be one example of such a frontier in organocatalysis. Many asymmetric reactions, which might be accelerated with organocatalysts, remain to be solved.

According to Dr. Stephen Connon, an expert in thioureas as organocatalysts from the Trinity College Dublin (Ireland) said: “Professor Takemoto’s team has developed a potentially very useful organocatalytic asymmetric Petasis-type reaction. While traditional approaches to nucleophile activation using thiourea-based bifunctional catalyst design usually rely on general base catalysis,” he concluded, “the in situ formation of ‘ate’ complexes potentially allows for the catalytic manipulation of more diverse pronucleophiles for the formation of carbon–carbon bonds (without requiring an acidic methylene/methane group) with high levels of stereocontrol and, as such, is a very interesting concept.”

**About the authors.** *Yoshiji Takemoto* is Professor at the Graduate School of Pharmaceutical Sciences, Kyoto University (Japan) since 2000. He received his BSc (1983) and PhD degrees (1988) from Osaka University. He worked as a post-doctoral fellow with Professor R. A. Holton at Florida State University in 1988 and with Dr. S. Terashima at Sagami Chemical Research Center in 1989. He joined the Faculty of Pharmaceutical Sciences, Osaka University, as an Assistant Professor in 1990. He moved to the Graduate School of Pharmaceutical Sciences, Kyoto University, as an Associate Professor in 1998. *Hideto Miyabe* is Professor at the School of Pharmacy, Hyogo University of Health Sciences (Japan) since 2007. He received his BSc (1991) and PhD degrees (1996) from Osaka University. He joined Kobe Pharmaceutical University (Professor Takeaki Naito’s group) as an Assistant Professor in 1996. He worked as a JSPS postdoctoral fellow with Professor Mukund P. Sibi at North Dakota State University in 2001. He moved to the Graduate School of Pharmaceutical Sciences, Kyoto University, as an Assistant Professor in 2002 and was promoted to Associate Professor in 2004.
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(by D. J. Ramón, M. Yus)

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CONTACT ▶▶▶▶
Matteo Zanda,
C.N.R. – Istituto di Chimica del Riconoscimento Molecolare,
Via Mancinelli, 7, 20131 Milano, Italy
E-mail: Synform@chem.polimi.it, Fax: +39 02 23993080

Editorial Office
- Managing Editor: Susanne Haak, susanne.haak@thieme.de, phone: +49 711 8931 786
- Editorial Office: Selena Boolaudy, selena.boolaudy@thieme.de, phone: +49 711 8931 776
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- Production Editor: Herbert Krieg, herbert.krieg@thieme.de, phone: +49 711 8931 781
- Production Assistant: Helene Deufel, helene.deufel@thieme.de, phone: +49 711 8931 929
- Editorial Assistant: Sabine Heller, sabine.heller@thieme.de, phone: +49 711 8931 744
- Marketing: Thomas Krimmer, thomas.krimmer@thieme.de, phone: +49 711 8931 772
- Postal Address: SYNTHESIS/SYNLETT/SYNFACTS, Editorial Office, Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany, phone: +49 711 8931 744, fax: +49 711 8931 777
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