

# SYNFORM

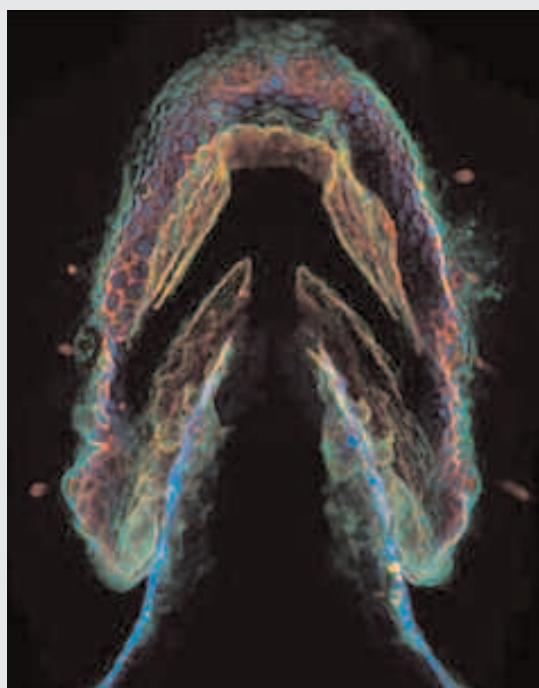
People, Trends and Views in Synthetic Organic Chemistry

2008 / 11

## SYNSTORIES ■ ■ ■ ■

■ An Expedient Asymmetric Synthesis of Platencin

■ Second-Generation Difluorinated Cyclooctynes for Copper-Free Click Chemistry



■ Direct and Stereospecific Synthesis of Allenes via Reduction of Propargylic Alcohols with  $\text{Cp}_2\text{Zr}(\text{H})\text{Cl}$

■ From Windmill to Nanomill: Altitudinal Molecular Motors on Surfaces

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**Dear readers,**

This last 2008 issue of *SYNFORM* comes in a period of deep global financial depression. It is not clear yet how and how much the crisis will affect scientific research, but in the long run one could expect hard times

in terms of further tightening of resources and funding, particularly in those countries (such as my own) where science is considered all but a priority. Fortunately the crisis does not involve the creativity of scientists, particularly of those who are protagonists of the *SYNSTORIES* featured in this issue of *SYNFORM*. Indeed, great creativity is one of the many merits of Professor C. Ber tozzi (USA) who recently discovered how to harness the potential of click chemistry in in vivo systems. And creativity is one of the main components in the total synthesis of the antibiotic platencin, developed by the group of Dr. D. Chen and Professor K. C. Nicolaou (Singapore/USA). When it comes to design a novel stereocontrolled synthetic approach to allenes, creativity becomes a key element of success, as demonstrated by the work of Professor J. M. Ready (USA). Last but not least, how much creativity is needed to miniaturize a windmill to a nanomill, as exemplified in a communication presented at the ACS Philadelphia meeting by Professor B. L. Feringa and coworkers (The Netherlands)? A lot, I guess...

Enjoy your reading!!!

**Matteo Zanda**

*Editor of SYNFORM*

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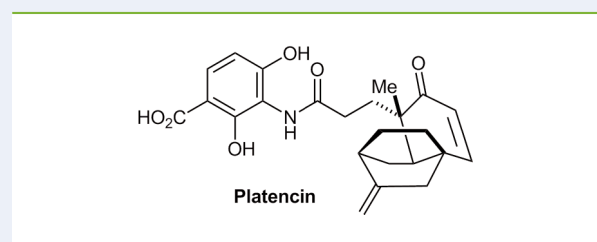
If you have any questions or wish to send feedback, please write to Matteo Zanda at:  
[Synform@chem.polimi.it](mailto:Synform@chem.polimi.it)

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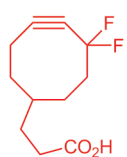
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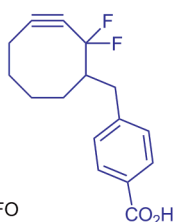
## Second-Generation Difluorinated Cyclooctynes for Copper-Free Click Chemistry

*J. Am. Chem. Soc.* **2008**, *130*, 11486–11493

■ Site-selective labeling of biomolecules *in vitro* and *in vivo* represents an important tool for the study of their function and cellular fate. Among the synthetic strategies that can be used to achieve this goal, click chemistry {a Cu(I)-catalyzed [3+2] cycloaddition of terminal alkynes with azides} is particularly attractive because of its mildness, selectivity and the biostability/inertness of the resulting 1,2,3-triazole. The use of copper, however, is incompatible with living systems owing to the toxicity of the metal. Recently the group of Professor Carolyn R. Bertozzi from the University of California, Berkeley (USA), introduced a difluorinated cyclooctyne reagent having enhanced reactivity toward azides. This first generation reagent, dubbed DIFO, was demonstrated to undergo reaction with azides on intact proteins even in the absence of Cu(I), at a comparable rate to that of Cu(I)-catalyzed click chemistry. The main drawback of DIFO was represented by its difficult preparation, comprising 12 overall steps and an overall yield of about 1%. Recently, Professor Bertozzi and co-workers reported the second-generation DIFO reagents, featuring a greatly simplified synthesis and holding a strong potential to become very important tools for the site-selective labeling of biomolecules.



First generation cyclooctyne reagent DIFO (difficult and low yielding preparation)

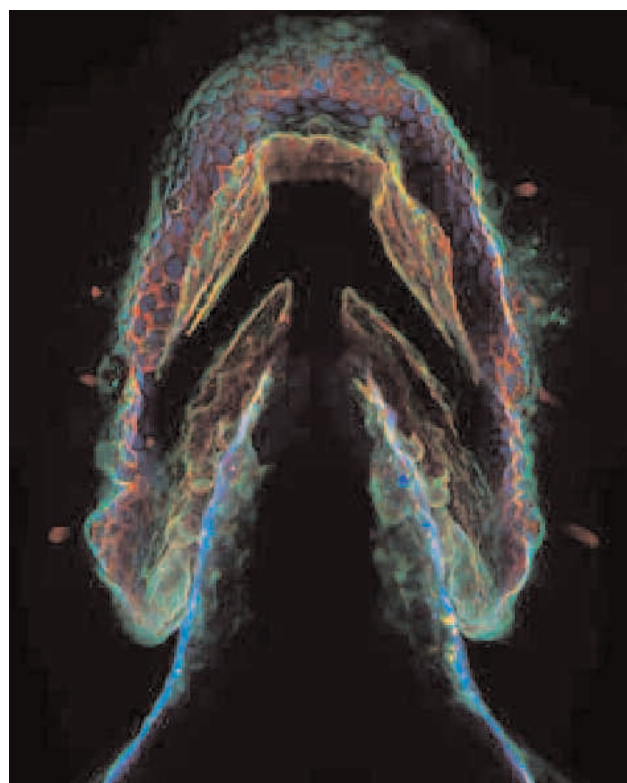


Second generation cyclooctyne reagents (much easier and more efficient preparation)

“The reagents were designed for facile reaction with azides via 1,3-dipolar cycloaddition,” explained Professor Bertozzi. “The reaction requires no exogenous reagents, such as the copper catalyst required for reaction of unactivated terminal alkynes with azides, and is thus compatible with live biological systems. The work follows up on a previous study in which

we used a related difluorinated cyclooctyne conjugated to fluorescent probes for *in vivo* imaging of glycans metabolically labeled with azidosugars. However, that previous compound was a troublesome synthetic target, which we feared would limit its use by biologists.” According to Professor Bertozzi the new reagents presented in this paper solve that synthetic obstacle. “They are easy to prepare in about six steps with minimal chromatography,” she said. “The reagents will soon be commercialized, which will make them that much more accessible to biologists.”

A notable feature of this paper is that the first author, Julian Codelli, was an undergraduate student in Professor Bertozzi's lab. “He was recruited by graduate student Jeremy Baskin, the



Ventral view of a zebrafish embryo in which the glycans are labeled with difluorinated cyclooctyne reagents

second author, who conceived the synthetic route, and assisted by Nick Agard, a former graduate student, who was one of the originators of the cyclooctyne project,” Professor Bertozzi said. “Nick is now a postdoctoral fellow at UCSF in the lab of Professor Jim Wells and Julian is now a first-year PhD student at Caltech. Jeremy is completing his PhD work this year, continuing to use difluorinated cyclooctynes for imaging glycans in developing zebrafish embryos. Together, Julian, Jeremy and Nick were a ‘dream team’ of synthetic chemists and chemical biologists,” she concluded.

According to Dario Neri, Professor of Biomacromolecules from the Institute of Pharmaceutical Sciences of the ETH Zürich (Switzerland) and an expert in the field of site-selective labeling of biomolecules, “the [3+2] cycloaddition of azides and alkynes, which is often performed with copper catalysis (click chemistry), has proven to be an efficient method for the covalent coupling of a variety of different chemical moieties under mild and selective conditions, thus finding applications in several areas, including drug development and chemical modification of biologically active (macro)molecules. However,” continued Professor Neri, “the use of copper catalysts is generally incompatible with living systems. In this new article, the group of Carolyn Bertozzi describes a novel difluorinated cyclooctyne reagent that rapidly reacts with azides without the need for copper. The new reagents promise to find a broad range of applications for the selective chemical modification of certain (macro)molecules in cells and, possibly, more complex living organisms. One such application may be

represented by the two-step modification of certain oligosaccharidic structures. These moieties,” concluded Professor Neri, “could be modified in a first step with reagents which introduce an azide functionality, to be followed by a cycloaddition reaction which mediates the coupling to difluorinated cyclooctyne derivatives of fluorophores, biotin or other molecules useful in the context of bioorganic chemical research.”

*Matteo Zanda*



*Prof. C. R. Bertozzi*

## An Expedient Asymmetric Synthesis of Platencin

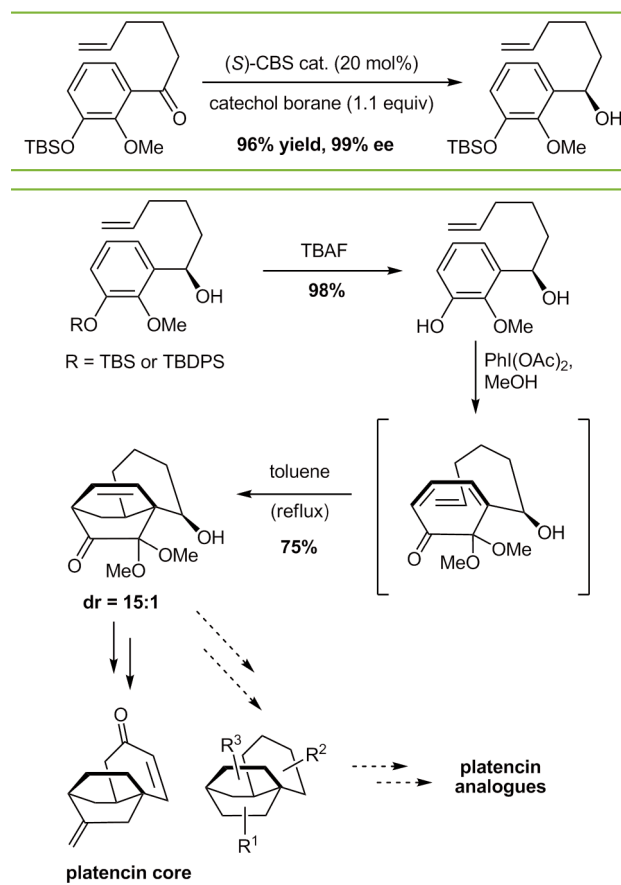
*J. Am. Chem. Soc.* **2008**, *130*, 11292–11293

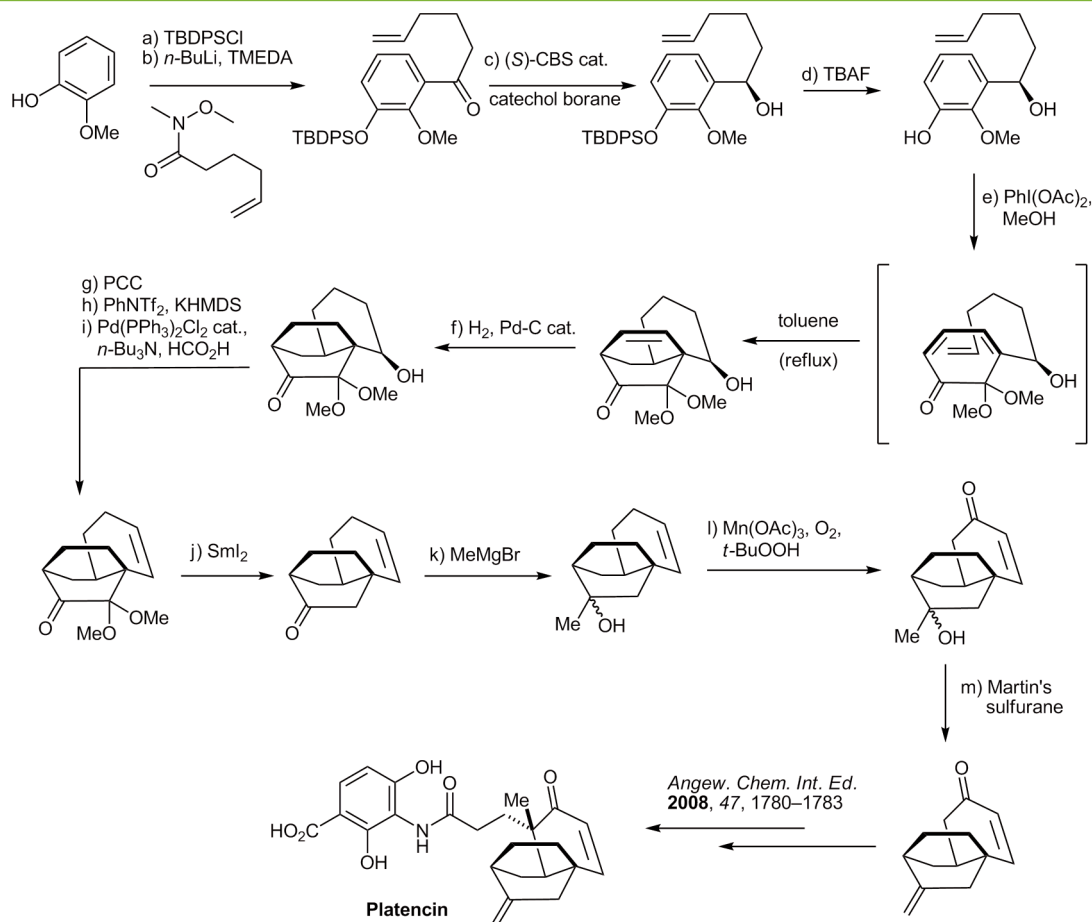
In recent years, the rampant emergence of drug-resistant pathogens has escalated the search of novel antibiotics to new heights, and the discovery of platensimycin and platencin by the Merck team in 2006 generated much excitement within the scientific community. In a combination between classical high-throughput screening and the application of RNA-silencing technology, these compounds were identified as potent and selective inhibitors of the condensing enzymes involved in the bacterial fatty-acid biosynthesis (Fab) pathway. As these targeted enzymes are highly conserved among the clinically important pathogens, the broad-spectrum activities of platensimycin and platencin are particularly noteworthy. Besides their promising therapeutic potentials, according to Dr. David Y.-K. Chen from the Chemical Synthesis Laboratory, Institute of Chemical and Engineering Sciences (ICES) of Singapore the novel molecular architectures endowed by platensimycin and platencin also served as testaments of modern synthetic strategies and technologies, evident from the plethora of publications since their structures were first disclosed. “As a continuation of our platensimycin work reported in early 2008,” said Dr. Chen, “we embarked on the synthetic endeavors towards platencin, a campaign ultimately proved both fulfilling and rewarding from scientific and educational perspectives.” Indeed, Dr. Chen, Professor K. C. Nicolaou, who leads the Chemical Synthesis Laboratory, and attachment student Qiao-Yan Toh recently reported an asymmetric total synthesis of platencin.

“While CSL (Chemical Synthesis Laboratory) is comprised of predominantly postdoctoral researchers,” explained Dr. Chen, “junior attachment students provide a valuable link with the academic sector, at the same time giving the youngsters their first experience in the total synthesis of complex molecules. As any supervisor will know, project selection and assignment, and evaluating its likelihood of success are never trivial tasks, especially when confronted with a fresh newcomer to scientific research.” Ms. Qiao-Yan Toh, who is scheduled to begin her graduate studies under the guidance of Dr. Matthew Gaunt at Cambridge University (UK) in 2009, commenced her work on the platencin project in January 2008. “Full with enthusiasm in her first total synthesis project, unfortunately, the first-generation approach based on an organocatalytic cascade strategy to construct the tricyclic core of platencin immediately met with obstacles,” continued Dr. Chen. “While alternative strategies were being explored, it was the elegant work

reported by Liao and coworkers on the intramolecular Diels–Alder reactions of masked *o*-benzoquinones (*Chem. Commun.* **2001**, 1340) that inspired us to formulate a strategy that ultimately culminated a formal synthesis of platencin.”

The highly efficient Diels–Alder reaction was first validated in the racemic system, but the asymmetric version necessitated some investigation concerning the preparation of the chiral benzylic alcohol precursor. “After carefully examining the reported asymmetric processes (CBS reduction, Nozaki reduction and enantioselective oxidation),” said Dr. Chen, “most recently, we have demonstrated that the CBS reduction can be performed on >10 gram scale in 96% yield and 99% ee. While the intramolecular Diels–Alder reaction represented the highlight of the synthesis, in fact, it was the subsequent functionalization of the Diels–Alder product possessing the tricyclic carbon framework which consumed most of our re-





search efforts. More specifically,” he continued, “carefully orchestrating the synthetic sequence in which the enone and exocyclic olefin were installed, and reductive removal of the gem-dimethoxy functionality were particularly noteworthy. It is also worth mentioning that the low molecular weight of post-Diels–Alder intermediates required careful handling in view of their volatility, especially the final tricyclic enone as we experienced.”

As eluded earlier, while decorating the tricyclic Diels–Alder adduct with the desired functionalities for platencin necessitated some detailed investigation; at the same time, this exercise also provided valuable insights concerning the chemistry and reactivity of the tricyclic core. “Furthermore,” said Dr. Chen, “the Diels–Alder adduct is rich in functionalities (contains an olefin, a ketone, a hydroxyl group and gem-dimethoxy substituents) which offered versatile handles in the chemical-biology and pharmacological investigations of platencin with the constructions of rationally designed analogues. This work is currently being carried out by Ms. Qiao-Yan Toh, together with her colleagues Ms. Sanny Ing and Ms. Hao Li (both yet to commence their graduate studies). It is

with great anticipation that this work will advance beyond our academic curiosities,” concluded Dr. Chen, “and ultimately find application as the next generation of antibiotics.”

**Matteo Zanda**



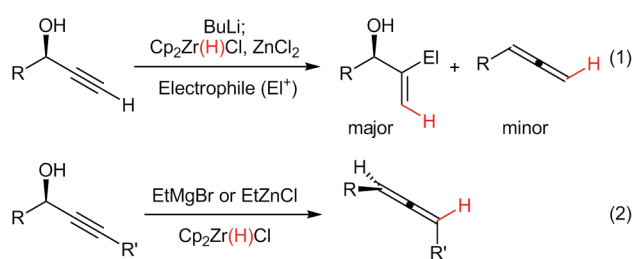
From left: H. Li, S. Ing, Dr. D. Chen, Q.-Y. Toh

## Direct and Stereospecific Synthesis of Allenes via Reduction of Propargylic Alcohols with $\text{Cp}_2\text{Zr(H)Cl}$

*J. Am. Chem. Soc.* **2008**, *130*, 10874–10875

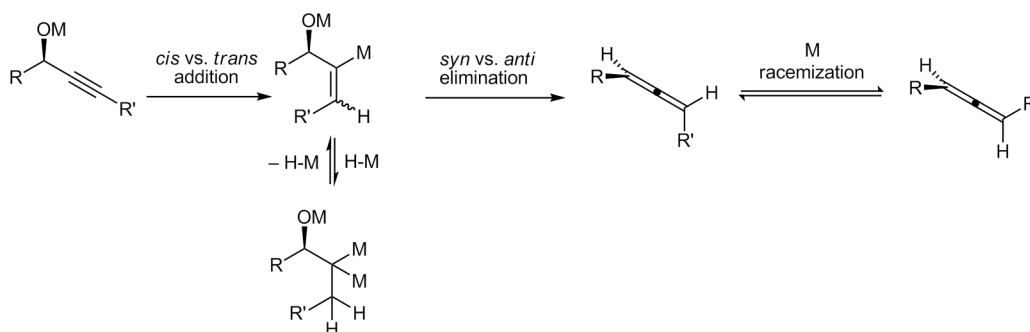
■ Allenes are cumulated dienes endowed with a rigid and linear double bond array, and a very interesting and rather peculiar reactivity. However, the synthesis of allenes, particularly in stereodefined manner, poses some challenges despite the presence of some versatile methodology in the arsenal of the synthetic chemist. Recently, Professor Joseph M. Ready and postdoctoral fellow Xiaotao Pu, both from the University of Texas Southwestern Medical Center in Dallas (USA), reported a significant advancement in the field.

“We previously found that the hydrozirconation of propargylic alcohols was subject to directing group effects,” explained Professor Ready (*J. Am. Chem. Soc.* **2007**, *129*, 12088; *Tetrahedron* **2008**, *64*, 6955). “In fact, under optimized conditions, we observed complete regioselectivity favoring the formation of the more hindered, internal vinyl metal species.” Subsequent work by the group of Professor Ready showed that these organometallic reagents could be trapped by a variety of useful electrophiles (see Scheme 1, equation 1). “However, we occasionally observed small amounts of an allene that would have resulted from a net  $\text{S}_{\text{N}}2'$  addition of hydride to the propargylic alcohol,” continued Professor Ready. “In light of the current interest in allenes, we were eager to optimize this transformation, but decided to focus on the preparation of disubstituted allenes – i.e. allenes derived from internal, chiral propargylic alcohols (Scheme 1, equation 2).” The key issue here, according to Professor Ready, was the conversion of central chirality to axial chirality. Several methods exist to reduce propargylic alcohols, but the hydride-based approaches usually result in a loss in optical purity.

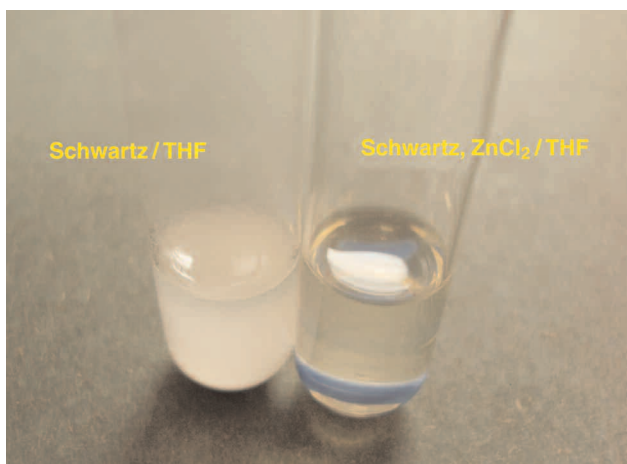


Scheme 1

“Chirality transfer can be compromised in several ways in a hydrometalation/elimination reaction manifold,” said Professor Ready (see Scheme 2). “A competition between *cis* and *trans* addition or *syn* and *anti* elimination could result in erosion of enantioselectivity. Furthermore, reversible formation of bimetallic species or metal-catalyzed racemization could all be deleterious to the reaction,” he continued. “Through some careful experimentation we found that two sets of conditions promoted the reduction of propargylic alcohols to allenes with nearly complete conversion of optical purity.” Both procedures involve treating the propargylic alcohol with base and the Schwartz reagent,  $\text{Cp}_2\text{Zr(H)Cl}$ . “When the alcohol was benzylic or allylic, or if the alkyne was conjugated,  $\text{EtZnCl}$  (from  $\text{Et}_2\text{Zn}$  and  $\text{ZnCl}_2$ ) worked ideally as a base,” said Professor Ready. In other cases,  $\text{EtMgCl}$  appeared preferable. Overall, the transformation provided allenes containing esters, carbamates, alkynes, ethers, and heterocycles.



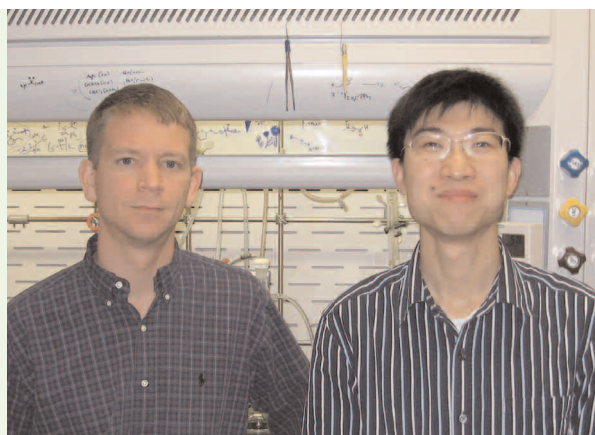
Scheme 2



$\text{Cp}_2\text{Zr(H)Cl}$  with and without  $\text{ZnCl}_2$

The role of the  $\text{EtZnCl}$  appears rather complicated, and is not limited to simply deprotonating the alcohol. “In fact,” confirmed Professor Ready, “zinc salts can interact with a Schwartz reagent in a currently unknown fashion. What we do know is that zinc salts markedly increase the solubility of the  $\text{Cp}_2\text{Zr(H)Cl}$ . At the same time, we found that excess  $\text{ZnCl}_2$  can promote the racemization of disubstituted allenes, so the stoichiometry is crucial to obtaining highly enantioenriched allenes. This observation is intriguing in itself,” he concluded, “and suggests the possibility of developing a dynamic kinetic resolution of allenes – a topic of current investigation in the lab.”

Matteo Zanda



From left: Prof. J. M. Ready, X. Pu



## From Windmill to Nanomill: Altitudinal Molecular Motors on Surfaces

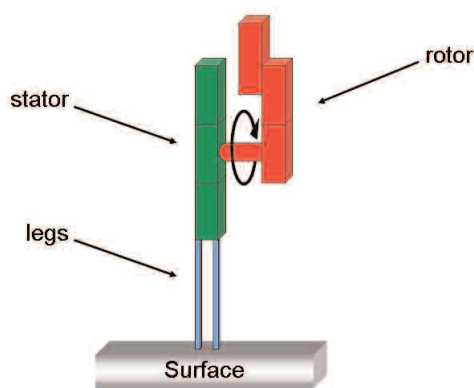
*Selected Presentation from the 236th American Chemical Society National Meeting, Philadelphia (USA), August 17–21, 2008*

■ Biomolecular motors are omnipresent in natural systems where they are used for different tasks. Much of the mechanical work in biological systems is performed by coherent supramolecular structures utilizing the cooperative motion of these motors. The attachment of biological or synthetic rotary motors to solid substrates is considered to be a key step toward the fabrication of nanomechanical devices that exploit the rotational motion generated by the action of these molecules. Additional progress in the field was presented at the Philadelphia ACS meeting by Tatiana Fernández Landaluce, graduate student in the group of Professor Petra Rudolf from the University of Groningen (The Netherlands), in collaboration with Professor Ben L. Feringa from the same university.

“Our research focuses on synthetic light-driven unidirectional molecular rotary motors based on over-crowded alkenes that undergo photoisomerization followed by thermal helix inversion,” explained Ms. Fernández Landaluce. “In pursuit of designing systems that can use the photo-induced rotary movement, one half of the motor is attached to the surface of a quartz or silicon substrate.” In such systems different orientations of the rotating part (rotor) relative to the stationary part (stator) can be envisioned. “Here we showed the first demonstration of light-driven rotary motion in an altitudinal system,” she said. “Assemblies of rotary molecules in which the axis of rotation is normal to the substrate may prove to be more useful than previously reported azimuthal systems (rotor parallel to the substrate) to transport material placed on top of the monolayer given the direction of motion at the interface (*Angew. Chem. Int. Ed.* **2007**, *46*, 1278).”

A major hurdle to apply such systems to perform complex tasks is to develop a versatile and stable surface modification method. To overcome that problem, in the group of Professor Feringa enantiopure alkene- and azide-terminated motors were synthesized and subsequently grafted to a variety of surfaces bearing azide or alkene moieties, respectively, via the copper-catalyzed 1,3-dipolar cycloaddition. “Crucially a combination of surface analysis techniques demonstrates the success of the interfacial reaction as well as the fact that the surface-bound motors preserve their light-induced rotary movement. Although we focused on quartz and silicon substrates,” concluded Ms. Fernández Landaluce, “this facile procedure is

expected to be suitable for other materials, including polymers, gels and various self-assembled systems.” ■



*Altitudinal motor on a surface*

### About the authors

Professor **Ben L. Feringa**, Jacobus H. van't Hoff distinguished Professor of Molecular Sciences since 2003, received his Ph.D. degree from the University of Groningen in 1978 with Professor Hans Wynberg on the topic of asymmetric phenol oxidation. He was a research scientist with Royal Dutch Shell, both at the Shell Research Center in Amsterdam and at the Shell Biosciences Laboratories in Sittingbourne (UK) from 1978–1984. He joined the Department of Chemistry at the University of Groningen in 1984 as a Lecturer and was appointed Full Professor at the same university in 1988.

Professor **Petra Rudolf** studied physics at the Università La Sapienza in Rome (Italy) and then had an international career which took her from the TASC-INFM laboratory in Trieste, where she switched to Surface Science, to Bell Labs, NJ (USA), where she pioneered fullerene research,

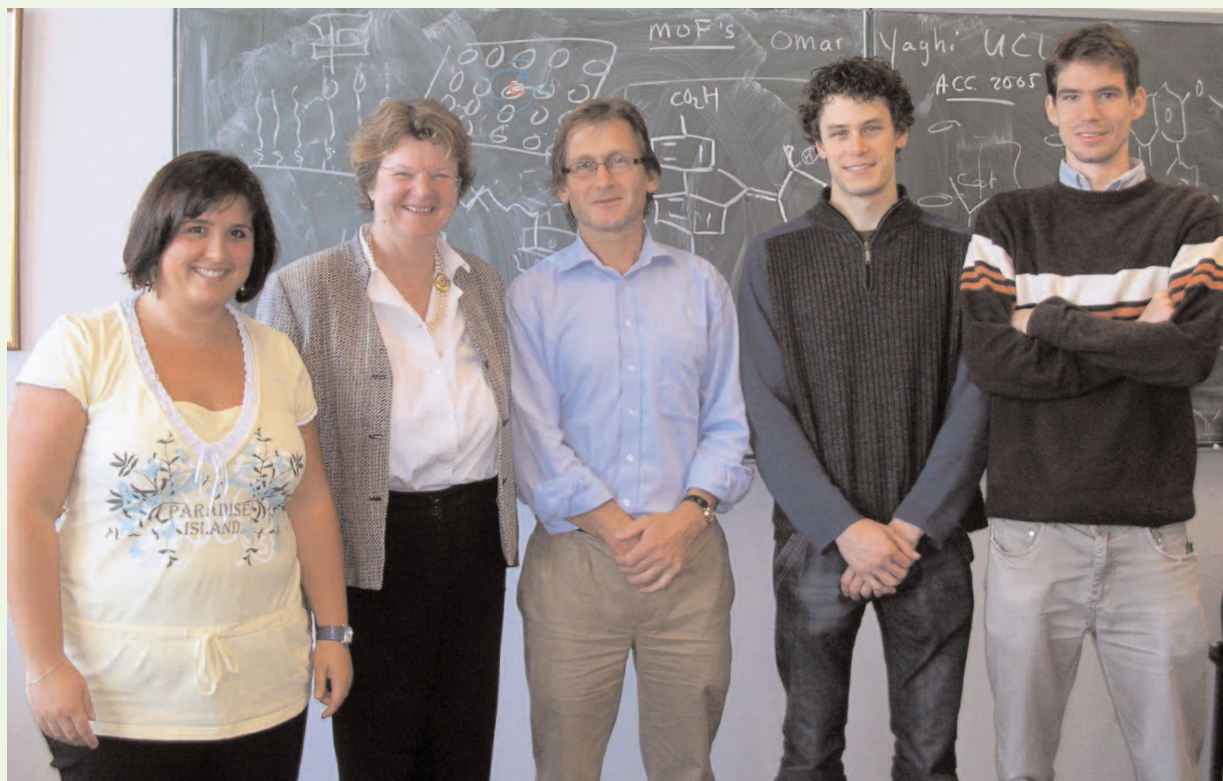
and then to the Facultés Universitaires Notre Dame de la Paix in Namur (Belgium) where she began to work on molecular motors in 1994. Since 2003 she has the Chair in Experimental Solid State Physics at the University of Groningen where she also heads the Surfaces and Thin Films group of the Zernike Institute for Advanced Materials.

**Gregory T. Carroll** received his Ph.D. in Chemistry in 2007 from Columbia University (USA) with Professor N. Turro and subsequently started his post-doctoral research at the Department of Synthetic Organic Chemistry of the University of Groningen.

**Tatiana Fernández Landaluze** received her M.Sc. in Physical Chemistry in 2005 from the University of the Basque Country (Spain), and subsequently started her Ph.D. at the Department of Surfaces and Thin Films at the University of Groningen.

**Gábor London** received his M.Sc. in Organic Chemistry in 2006 from the University of Szeged (Hungary), and subsequently started his Ph.D. at the Department of Synthetic Organic Chemistry at the University of Groningen.

**Michael M. Pollard** received his Ph.D. in Organic Chemistry in 2003 from the University of Alberta (Canada), after which he joined the group of Professor Feringa at the University of Groningen. In summer of 2008 he started as an Assistant Professor at York University (Canada).



From left: T. Fernández Landaluze, Prof. P. Rudolf, Prof. B. L. Feringa, Dr. G. T. Carroll, G. London

COMING SOON ► ► COMING SOON ► ►

## SYNFORM 2009/1 is available from December 18, 2008

In the next issues:

### SYNSTORIES ■ ■ ■ ■ ■

#### ■ Arylation of Phe and Tyr Side Chains of Unprotected Peptides by a Suzuki–Miyaura Reaction in Water

(Focus on an article from the current literature)

#### ■ Conference Report

(Focus on the 2<sup>nd</sup> EuCheMS Chemistry Progress, Turin, Italy, September 16–21, 2008)

### FURTHER HIGHLIGHTS + + + +

#### SYNTHESIS

**Review on: One-Pot Cyclizations of (2,4-Dioxobutylidene)-phosphoranes and (2-Alkoxy-4-oxo-but-2-enylidene)-phosphoranes**

(by H. Feist, P. Langer)

#### SYNLETT

**Account on: Complex Systems from Simple Building Blocks via Subcomponent Self-Assembly**

(by V. E. Campbell, J. R. Nitschke)

#### SYNFACTS

**Synfact of the Month in category "Polymer-Supported Synthesis":  
A Bimetallic, Heterogeneous, Multifunctional Catalyst**

### CONTACT + + + +

**Matteo Zanda,**  
C.N.R. – Istituto di Chimica del Riconoscimento Molecolare,  
Via Mancinelli, 7, 20131 Milano, Italy,  
e-mail: [Synform@chem.polimi.it](mailto:Synform@chem.polimi.it), fax: +39 02 23993080

#### Editor

Matteo Zanda, C.N.R. – Istituto di Chimica del Riconoscimento Molecolare  
Via Mancinelli, 7, 20131 Milano, Italy  
[Synform@chem.polimi.it](mailto:Synform@chem.polimi.it)  
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#### Editorial Office

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[susanne.haak@thieme.de](mailto:susanne.haak@thieme.de), phone: +49 711 8931 786
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- Production Assistant: Thorsten Schön,  
[thorsten.schoen@thieme.de](mailto:thorsten.schoen@thieme.de), phone: +49 711 8931 781
- Editorial Assistant: Sabine Heller,  
[sabine.heller@thieme.de](mailto:sabine.heller@thieme.de), phone: +49 711 8931 744
- Marketing: Thomas Krimmer,  
[thomas.krimmer@thieme.de](mailto:thomas.krimmer@thieme.de), phone: +49 711 8931 772
- Postal Address: SYNTHESIS/SYNLETT/SYNFACTS, Editorial Office,  
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