

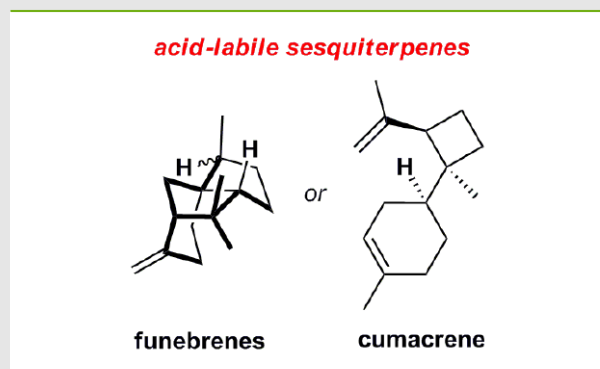
# SYNFORM

People, Trends and Views in Synthetic Organic Chemistry

2013/02

## SYNSTORIES ■ ■ ■ ■

■ Synthesis of Highly Strained Terpenes by Non-Stop Tail-to-Head Polycyclization



■ Hypoiodous Acid Initiated Rearrangement of Tertiary Propargylic Alcohols to  $\alpha$ -Iodoenones

■ Copper-Catalyzed C–H Azidation of Anilines under Mild Conditions

■ Young Career Focus: Dr. Henry Dube (Ludwig-Maximilians-Universität München, Germany)

**CONTACT +++++**

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



Dear readers,

I am writing this editorial soon after the Christmas and New Year's celebrations when, like most of us, I've thoroughly enjoyed eating and drinking too much, although I am now dealing with a slight feeling of stomach

discomfort and a couple of kilograms in excess. The new research year is now looming, with its load of revolutionary projects and ideas which will undoubtedly lead to terrific publications and six or seven-figure grants. At least this is my wish for all of us... What is absolutely sure is that the protagonists of the three **SYNSTORY** articles of this **SYNFORM** issue managed to materialize at least the first part of this wish during the recently archived year 2012. The hypiodite-promoted rearrangement of propargylic alcohols to  $\alpha$ -iodoenones discovered by Dr. W. Moran (UK) opens the issue, followed by the exciting biomimetic synthesis of highly strained terpenes developed by Professor R. A. Shenvi (USA). The third **SYNSTORY** reports on the copper-catalyzed C–H bond functionalization of the *ortho* position of anilines with an azide moiety recently described by Professor N. Jiao (P. R. of China). The issue is completed by a Young Career Focus article dedicated to an up-and-coming young researcher: Dr. H. Dube (Germany) and his work in the area of supramolecular and biomimetic chemistry.

Enjoy your reading!

**Matteo Zanda**

Editor of **SYNFORM**

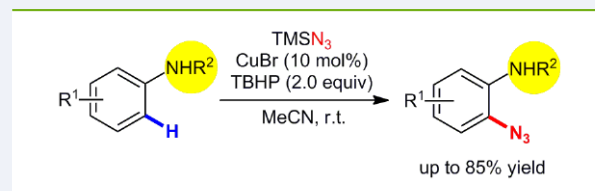
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**CONTACT + + + +**

If you have any questions or wish to send feedback, please write to Matteo Zanda at:  
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NEWS AND VIEWS ■ ■ NEWS AND VIEWS ■ ■ NEWS AND VIEWS ■ ■

## Hypoiodous Acid Initiated Rearrangement of Tertiary Propargylic Alcohols to $\alpha$ -Iodoenones

*Org. Biomol. Chem.* **2012**, *10*, 8590–8592

Iodine is a very useful element that can form compounds with six different oxidation states (-1, 0, +1, +3, +5 and +7). These different iodine species can mediate or catalyze useful processes that might otherwise require expensive or non-sustainable metal salts. Inorganic iodides such as sodium iodide can be oxidized to new iodine species with higher oxidation states that, normally, are only observed in organic iodine compounds such as *N*-iodosuccinimide (+1) and iodobenzene diacetate (+3). One new item was recently added to the list of reactions promoted by iodine species, in this case I(+1) or hypoiodite: the conversion of tertiary propargylic alcohols into 1-iodo-enones.

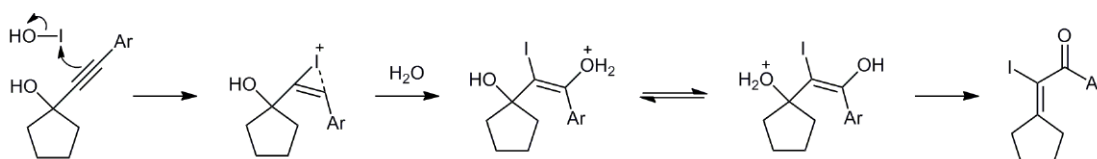
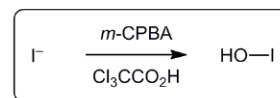
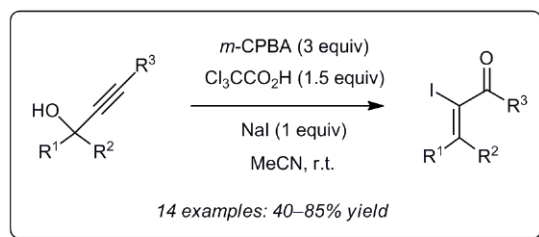
In fact, Dr. Wesley Moran and Dr. Arantxa Rodríguez of the Department of Chemical and Biological Sciences at the University of Huddersfield (UK) recently described their research in accessing an inorganic iodine species in the +1 oxidation state from sodium iodide and investigating its reactivity with propargyl alcohols.

Dr. Moran said: “Our initial intention was to investigate the reactivity of in situ generated organic iodine(III) species on propargyl alcohols along the lines of our previously published work; however, no reaction was observed under these conditions.” Whilst investigating other unusual iodine species they

came across the transformation outlined in the scheme. “With judicious choice of oxidant, acid and solvent, sodium iodide was oxidized into hypoiodous acid, which effected the rearrangement of tertiary propargyl alcohols into  $\alpha$ -iodoenones,” Dr. Moran continued. “Stronger acids than trichloroacetic acid were found to lead to elimination of water from the propargyl alcohols to form the corresponding enynes, while weaker acids led to little or no conversion of the starting material.” Hypoiodous acid is an unstable species that readily disproportionates into iodine and iodic acid (HIO<sub>3</sub>); however, this study suggests that hypoiodous acid is the reactive species in this process. Dr. Rodríguez concluded: “Further work in this area is under way in our laboratory; indeed, an unusual oxidative rearrangement of propargyl alcohols to enoic acids will be reported shortly. Our long-term aim is to develop a suite of useful reactions employing iodine species with different oxidation states. Of particular interest is the development of enantioselective processes.”

Clearly, more exciting and novel organic reactions promoted by iodine species are just around the corner. ■

Matteo Zanda



*About the authors**Dr. W. Moran*

**Wesley Moran** was born in 1978 in Birmingham (UK). He received his PhD (2004) from the University of Sheffield (UK) under the direction of Professor Joseph Harrity. This was followed by postdoctoral research positions with Professor James Morken at The University of North Carolina at Chapel Hill (USA) and Professor Jonathan Clayden at The University of Manchester (UK). He became a Lecturer at the University of Huddersfield in 2007 and was promoted to Senior Lecturer in 2009. His current research interests are concerned with using polyvalent iodine species in synthesis.

*Dr. A. Rodríguez*

**Arantxa Rodríguez** was born in 1974 in Pola de Allande, Asturias (Spain). She received her PhD (2004) from the University of Sheffield under the supervision of Professor Richard Jackson. She undertook postdoctoral research under the guidance of Professor Jetze Tepe at Michigan State University (USA), Professor Michel Gagné at The University of North Carolina at Chapel Hill (USA) and Professor Philip Hodge at The University of Manchester (UK). In 2007 she joined the University of Huddersfield as a Research Fellow. Her research interests include gold catalysis and polyvalent iodine chemistry.

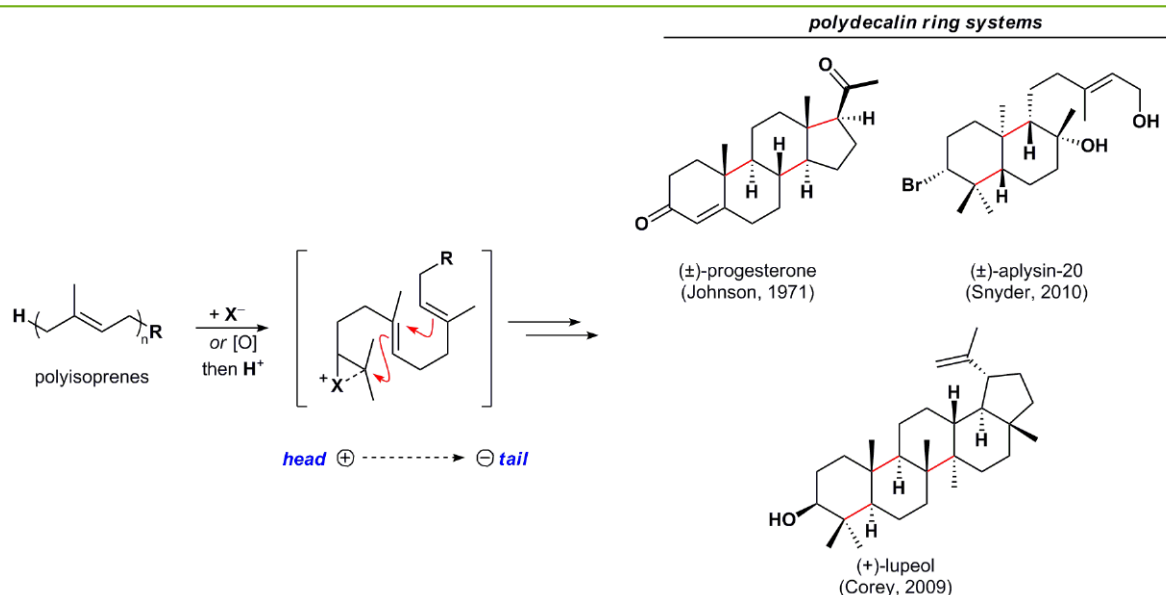
# Synthesis of Highly Strained Terpenes by Non-Stop Tail-to-Head Polycyclization

*Nature Chem.* **2012**, *4*, 915–920

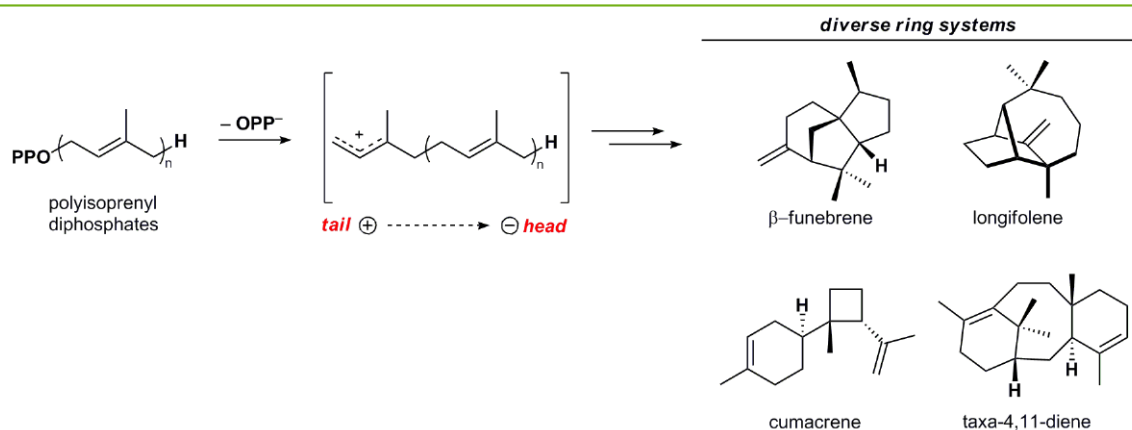
Terpenes are widespread organic compounds (more than 23,000 terpenes are known) that contain the fundamental isoprene unit  $C_5H_8$ . Larger terpenes are constituted by several isoprene units, which are usually linked head-to-tail. In the 1950s, Albert Eschenmoser, working in the laboratory of Leopold Ruzicka at ETH Zurich (Switzerland), realized that tail-to-head (TH) carbocationic polycyclizations of poly-isoprenes could explain the biogenesis of all sesquiterpenes, and

delineated these relationships in his PhD thesis. Subsequently, both Eschenmoser and Gilbert Stork proposed a mechanistic and stereochemical model for the biosynthesis of steroids and triterpenes via head-to-tail (HT) cationic polyolefin cyclizations of squalene, a hypothesis which has proven to be correct.

Although HT polycyclizations have been reproducible in the flask for several decades (Figure 1), there have been no reports of truly biomimetic, non-stop cationic cascade cycli-



**Figure 1** Head-to-tail polycyclization: reproducible in bulk solvent



**Figure 2** Tail-to-head polycyclization: NOT reproducible in bulk solvent

zations along the TH pathways (Figure 2). However, recent developments in the chemistry of carbocations (carbonium ions), particularly by manipulation of their counter-anions, have begun a modest renaissance in carbocation chemistry. Inspired by the recent contributions of Toste, List, and Jacobsen to carbocation chemistry, the laboratory of Professor Ryan Shenvi [(Department of Chemistry, The Scripps Research Institute, La Jolla (USA))] embarked on a quest to explore the elusive TH polycyclization pathways of sesquiterpenes with the goal of developing a chemical system to study and eventually manipulate these sequences in bulk solvent.

Professor Shenvi explained: “Carbocations can be rapidly quenched by elimination (E1) of adjacent protons, and unfortunately attract to themselves the anionic species that cause this very elimination. As a result, the anti-Markovnikov cyclizations or Wagner–Meerwein shifts that occur in enzymatic mediation of TH pathways are outcompeted by E1 elimination when these cyclizations are attempted in bulk solvent.” He continued: “In our recent paper in *Nature Chemistry*, Sergey Pronin and I propose that sequestration of the counter-anion

away from the highly acidic intermediate carbocations (or carbonium ions) is necessary for propagation of cationic charge along biosynthetic reaction pathways (Figure 3). We show how implementation of this strategy is competent to produce strained sesquiterpenes that do not form when the counter-anion is mobile, and decompose using the vigorously acidic conditions for cyclization reported in the past.”

A key step in these cascades involves a Wagner–Meerwein hydride shift, which may be influenced by Coulombic attraction to the sequestered anion. Recently, Reuben Peters and Dan Thomas Major have proposed that Coulombic (electrostatic) influence of the counter-anionic pyrophosphate within cyclase enzymes’ active sites also influence cyclization outcomes. Professor Shenvi concluded: “We anticipate that our observations and techniques for reproducing TH polycyclizations in bulk organic solvent will lead to greater insights into these and other inner workings of nature’s most complex chemical reactions.”

Matteo Zanda

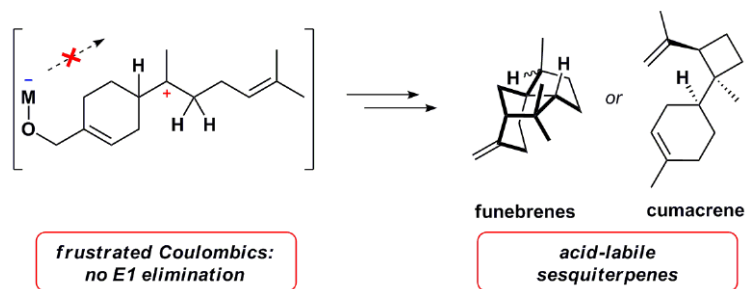


Figure 3 Anion sequestration allows tail-to-head polycyclization in bulk solvent

### About the authors



Prof. R. A. Shenvi

**Ryan A. Shenvi** was born and raised in Wilmington, DE (USA) and received his BSc degree in chemistry from Penn State University (USA), where he was a research student in the laboratories of John R. Desjarlais and Raymond L. Funk. He earned his PhD with Phil S. Baran at The Scripps Research Institute, and then joined the laboratory of E. J. Corey at Harvard University (USA) as a post-doctoral fellow. Since 2010, he has

been an Assistant Professor in the Department of Chemistry at The Scripps Research Institute.



Dr. S. V. Pronin

**Sergey V. Pronin** received his Specialist degree in chemistry from Moscow State University (Russian Federation), where he was a research student in the laboratory of Valentine G. Nenajdenko and Elizabeth S. Balenkova. He earned his PhD degree from The University of Chicago (USA) under the supervision of Sergey A. Kozmin. In 2011 he joined the laboratory of Ryan A. Shenvi at The Scripps Research Institute as a postdoctoral associate.

## Copper-Catalyzed C–H Azidation of Anilines under Mild Conditions

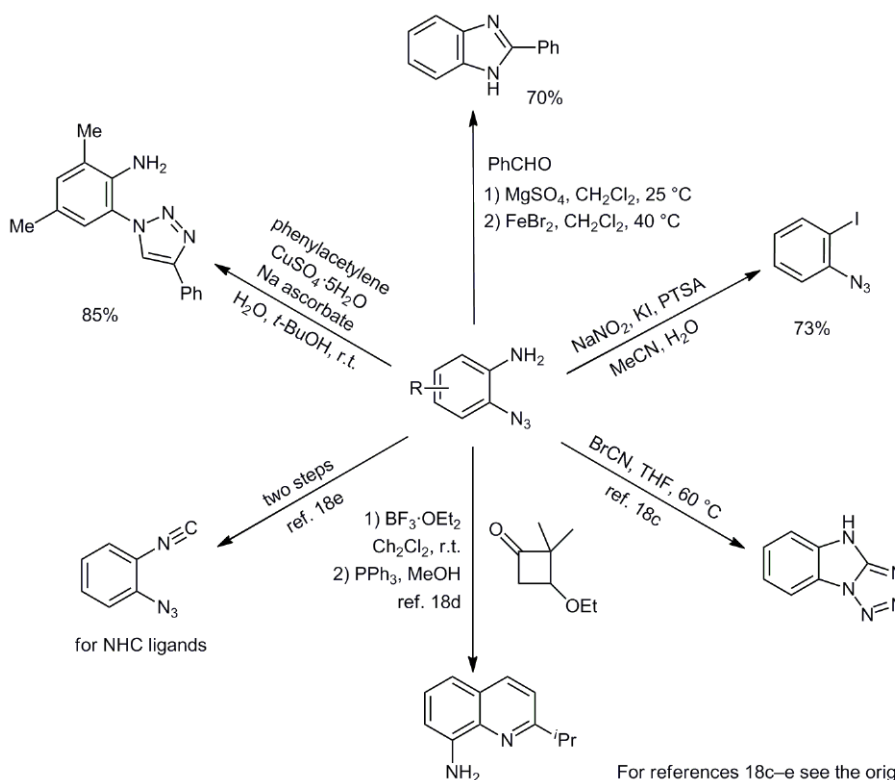
*J. Am. Chem. Soc.* **2012**, *134*, 18924–18927

■ Aryl azides are widely used in organic synthesis as valuable intermediates and building blocks, particularly in the synthesis of nitrogen-containing heterocycles, in peptide chemistry, materials science, polymer chemistry and drug discovery. Moreover, aryl azides have found biological use as photoaffinity labelling agents. Thus, organic azides have assumed an important position at the interface between chemistry, biology, medicine and materials science.

Recently, Professor Ning Jiao and Conghui Tang at the State Key Laboratory of Natural and Biomimetic Drugs, Peking University (P. R. of China) developed a concise and efficient route for the synthesis of aryl azides. This novel approach to aryl azides is based on copper-catalyzed selective *ortho* C–H azidation of aniline derivatives. Professor Jiao said: “The significance of the present chemistry is threefold: 1) this is a novel amino group directed *ortho* C–H functionalization of



simple and readily available anilines; 2) although various C–C and C–heteroatom bond formations via C–H activation have been successfully achieved, the directed *ortho* C–H azidation of arenes was unprecedented; and 3) this process is simple, proceeds under mild conditions, makes use of inexpensive copper catalysts rather than employing expensive transition-metal catalysts, and forms valuable products.” Therefore,





according to Professor Jiao, the reaction represents a good example of a simple, highly efficient and very convenient procedure yielding high-added-value products.

Transition-metal-catalyzed *ortho*-selective C–H functionalizations have begun to emerge in recent years by introducing the directing group strategy. “Although different directing groups have been developed for C–H functionalization, we still need to find some transformable or removable directing groups, so as to remove the directing group from the final product,” explained Professor Jiao. “In this work, a primary amino group acts as the directing group, and can be converted into a Cl, Br, I, CN, OH, or H substituent simply by Sandmeyer reaction.”

After optimization of the reaction conditions, the researchers expanded the scope of this method to a series of substituted anilines, which showed excellent functional group tolerance. Moreover, they looked toward applying the aryl azide products in other transformations. “From the results, we can see that the aryl azides can serve as versatile synthons in click, Sandmeyer, and annulation reactions to form benzimidazole, tetrazole, 8-aminoquinoline or other biologically important compounds,” explained Professor Jiao.

To conclude, Professor Jiao said: “A novel and practical Cu-catalyzed *ortho* C–H azidation of anilines has been developed. This azidation reaction is regiospecific at the amino group’s *ortho* position with broad substrate scope.” This chemistry expands the scope of directing groups, and will also very likely promote the application of azide reagents in organic synthesis. ■

Matteo Zanda

### About the authors



From left: Prof. N. Jiao, C. Tang

**Ning Jiao** received his PhD in 2004 from the Shanghai Institute of Organic Chemistry (P. R. of China) with Professor Shengming Ma. He was an Alexander von Humboldt Post-doctoral Fellow (2004–2006) with Professor Manfred T. Reetz at the Max Planck Institute für Kohlenforschung (Germany). In 2007, he joined the faculty at Peking University as an Associate Professor, and was promoted to Full Professor in 2010. His current research is focused on single-electron-transfer processes, aerobic oxidations and oxygenation, nitrogenations, the activation of inert chemical bonds, and protein hybrid catalysts.

**Conghui Tang** was born in Hubei Province (P. R. of China) in 1991. He received his BSc degree in 2011 from Huazhong University of Science and Technology (P. R. of China), under the supervision of Professor Yanlong Gu. He then joined Professor Ning Jiao’s group at Peking University, and is currently a second-year PhD student.



## Young Career Focus: Dr. Henry Dube (Ludwig-Maximilians-Universität München, Germany)

■ **Background and Purpose.** *SYNFORM* will from time to time meet young up-and-coming researchers who are performing exceptionally well in the arena of organic chemistry and related fields of research, in order to introduce them to the readership. This *SYNSTORY* with a **Young Career Focus** presents Dr. Henry Dube, Ludwig-Maximilians-Universität München, Germany.

### BIOGRAPHICAL SKETCH



Dr. H. Dube

**Henry Dube** was born in Halle/Saale (Germany) in 1978. He studied chemistry at the Philipps-Universität Marburg (Germany) and the Ludwig-Maximilians-Universität München (Germany). During his diploma thesis with Professor Knochel he applied a copper-catalyzed, three-component reaction to the enantioselective synthesis of chiral pyrimidines. In 2004 he joined the group of Professor

Diederich at the ETH Zürich (Switzerland) for his PhD. There he worked on synthetic models for heme proteins. Henry then moved to The Scripps Research Institute in La Jolla (USA) as a postdoctoral research fellow to pursue his interest in supramolecular self-assembly and host-guest chemistry in the group of Professor Rebek, Jr. Since 2011 he is an independent research group leader at the LMU in München. His research focuses on functional supramolecular systems, biomimetic chemistry and photochemistry.

### INTERVIEW

**SYNFORM** | *What is the focus of your current research activity?*

**Dr. Henry Dube** | The focus of my current research is supramolecular and biomimetic chemistry. We are working at the interface of organic synthesis and physical organic chemistry with the long-term goal of creating complex and responsive supramolecular systems that are – at least in part – inspired by the extraordinary complexity found in biology. To this end we use a variety of weak intermolecular interactions to tailor structures and properties not only spatially but also in the time dimension. To achieve control over a heightened level of complexity we integrate different responsive units within one system. After that, we study the interplay of the different responsive units and their behavior towards triggering events. By this research we hope to develop smart materials for applications in sensing, information processing, energy conversion, as well as chemical biology. We believe that one of the most interesting challenges of modern organic chemistry is creating responsive and dynamic interactions between molecules – an endeavor that is just at its beginning.

**SYNFORM** | *When did you get interested in synthesis?*

**Dr. Henry Dube** | My interest in synthesis started during my chemistry studies, I was especially fascinated by the ‘creative power’ to make molecules that did not exist before. During my diploma studies I got more and more interested in the mechanistic aspects of covalent bond making and breaking. Starting with my PhD, the secrets behind intermolecular interactions caught my attention and still keep me busy thinking.

**SYNFORM** | *What do you think about the modern role and prospects of organic synthesis?*

**Dr. Henry Dube** | Covalent organic chemistry is very well developed by now, and gives us unprecedented power to make almost any unimolecular structure that is chemically reasonable. The challenge today is to develop intermolecular interactions – i.e. supramolecular chemistry – to a similar

level of control. I assume that organic synthesis will transform far beyond covalent bond chemistry in the future, making it possible to use weak interactions in a similar way as we use reagents and catalysts for synthesis today. Another important development of the future will be biological synthesis of active molecules, an approach that will rival classical organic synthesis approaches in efficiency and selectivity.

**SYNFORM** | Your research group is active at the intersection of supramolecular, biomimetic and physical organic chemistry. Could you tell us more about your research and its aims?

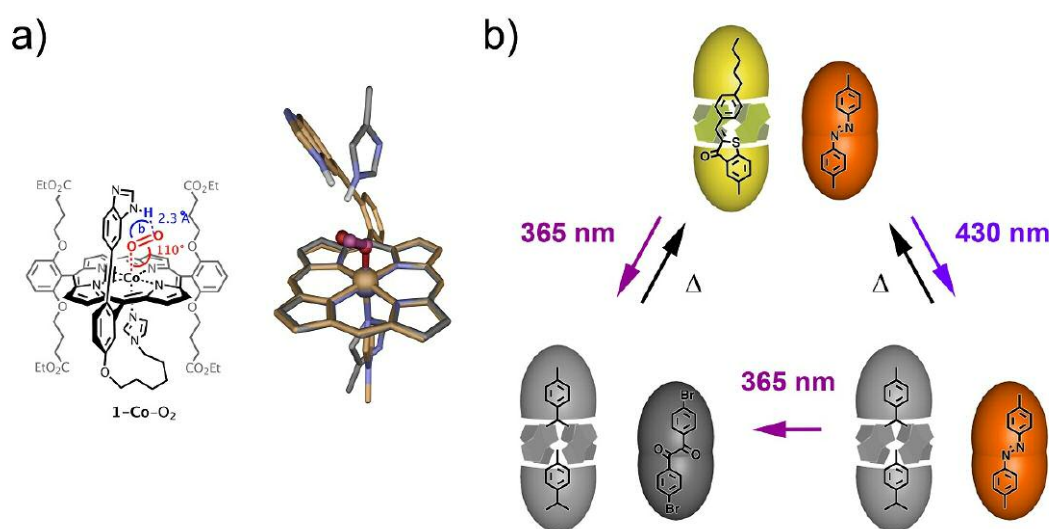
**Dr. Henry Dube** | We are investigating synthetic self-replication as well as responsive self-assembly processes. Self-replication is a composite of autocatalysis and molecular recognition, which allows establishing off-equilibrium states with high efficiency. Such behavior is different from self-assembly processes where most of the time the thermodynamically most stable state is established. Therefore, self-replication can serve as a crude model for biological systems, which also operate far from the equilibrium. Another interesting feature is the nonlinear kinetics that can be used to design dynamic processes with instant responses. In these studies we aim to create evolvable chemical systems that can respond to external chemical signals to study basic evolutionary processes such as mutation events, natural selection, or divergence – and in the end apply them to sensing.

Another part of our studies deals with implementing photoresponsive elements into self-assembling monomers and studying their structures, their responsiveness, and their physical properties. Using light as a trigger to change molecular structures and assemblies is appealing because it introduces no further components into the system and allows easy spatial and temporal control of the signal. We develop new photochromics to address current problems in materials science as well as chemical biology. Together with physicists we also study the basic mechanisms of photochromism of these molecules to gain a deeper basic understanding of their properties and to learn how to tailor these properties by structural variations.

**SYNFORM** | What is your most important scientific achievement to date and why?

**Dr. Henry Dube** | My most important scientific achievements were the deciphering of hydrogen bonding towards bound dioxygen in myoglobin using synthetic model complexes during my PhD and the development of a multi-photoresponsive host–guest system in solution during my postdoctoral studies.

Hydrogen bonding in myoglobin and hemoglobin has been proposed for a long time as the crucial mechanism by which the proteins are able to distinguish between the two gaseous ligands O<sub>2</sub> and CO. Within a series of model compounds we



**Figure 1** a) Hydrogen bonding to bound dioxygen in a synthetic model complex for myoglobin and hemoglobin. b) Three encapsulation states are accessible in solution depending on the sequence of irradiation with 365 nm and 430 nm light and heating.

could elucidate the geometrical prerequisites for a hydrogen bond interaction between a hydrogen bond donor and bound dioxygen. In collaboration with the groups of Professor Schweiger and Professor Jeschke it was possible to devise a suitable EPR method to measure this interaction directly. That study showed again the power of synthetic model complexes for studying biological processes.

With the multi-photoresponsive host–guest system, the most complex control over the encapsulation state of molecules in solution was achieved. Typically, host–guest complexes in solution offer no easy means to control guest exchange processes *after* the initial assembly is formed. We used two photoisomerizable dyes – an azobenzene and a hemithioindigo – as ‘dummy’ guests for two different molecular capsules. Stable host–guest assemblies with these two dyes are formed even in the presence of other prospective guest molecules in solution. Irradiation of this solution with light of different wavelengths leads to isomerization of the dyes and their breaking out of the capsular compartments. This provides access to three different encapsulation states in solution depending on the sequence of irradiation. Such multi-responsive systems are of high interest for molecular computing, sensing, as well as smart drug release. ■

**Matteo Zanda**



COMING SOON ►► COMING SOON ►►

## SYNFORM 2013/03

is available from  
February 15, 2013

In the next issues:

## SYNSTORIES ■ ■ ■ ■ ■

■ **Palladium-Catalyzed *N*-(2-Pyridyl)sulfonyl-Directed C(sp<sup>3</sup>)-H  $\gamma$ -Arylation of Amino Acid Derivatives**  
(Focus on an article from the current literature)

■ **Construction of an All-Carbon Quaternary Stereocenter by the Peptide-Catalyzed Asymmetric Michael Addition of Nitromethane to  $\beta$ -Disubstituted  $\alpha,\beta$ -Unsaturated Aldehydes**  
(Focus on an article from the current literature)

■ **One-Pot Catalyst-Free Synthesis of  $\beta$ - and  $\gamma$ -Hydroxy Sulfides Using Diaryliodonium Salts and Microwave Irradiation**  
(Focus on an article from the current literature)

## FURTHER HIGHLIGHTS + + + +

## SYNTHESIS

**Review on: Multimetallic Schiff Base Complexes as Cooperative Asymmetric Catalysts**  
(by S. Matsunaga, M. Shibasaki)

## SYNLETT

**Cluster on "Process Research" in issue 03/2013**

## SYNFACTS

**Synfact of the Month in category "Synthesis of Natural Products and Potential Drugs": [Synthesis of a Glucagon Receptor Antagonist](#)**

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