

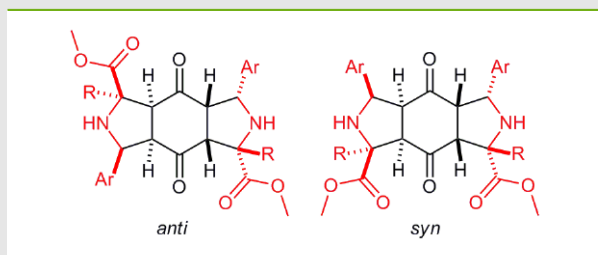
# SYNFORM

People, Trends and Views in Synthetic Organic Chemistry

2012/08

## SYNSTORIES ■ ■ ■ ■

■ Programmable Enantioselective One-Pot Synthesis of Molecules with Eight Stereocenters



■ Catalytic Asymmetric Mono-Fluorination of  $\alpha$ -Keto Esters: Synthesis of Optically Active  $\beta$ -Fluoro- $\alpha$ -hydroxy and  $\beta$ -Fluoro- $\alpha$ -amino Acid Derivatives

■ Young Career Focus:  
Professor Cristina Nevado  
(University of Zürich, Switzerland)

CONTACT ++++

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



**Dear readers,**

I've just spent ten minutes looking at my laptop without being able to write a single word, without energy, just dripping in sweat and then I decided to write about this: the heat. It's June 30th and here in the north of Italy

today it is nearly 35 °C. Two days ago I was in Scotland, with fog and 12 °C. The change has been dramatic and my brain is refusing to work in these conditions... I think I'll head to the fridge shortly, and get a cold beer, perhaps this would help? Perhaps not, I am afraid I would sweat even more, and then I will need to jump into the shower. OK, I am afraid I will have to accept the situation, I can't think of anything that is not a beach or a swimming pool, no way to formulate anything related to chemistry in these conditions. So let's just summarize what's in this exciting new issue of **SYNFORM** (but I mustn't get too excited or I would sweat even more...). The first **SYNSTORY** reports on a highly sophisticated stereodivergent tandem double cycloaddition reaction leading to libraries of stereodefined compounds with eight stereogenic centers, developed by Professor H. Waldmann and Dr. A. Antonchick (Germany). The second **SYNSTORY** is about the synthesis of  $\beta$ -fluoro  $\alpha$ -amino acid derivatives via catalytic asymmetric fluorination of  $\alpha$ -keto esters, as described by Professor M. Sodeoka (Japan). The issue is completed by a Young Career Focus article presenting Professor C. Nevado (Switzerland).

I am still sweating; it's not getting any better. I think I am about to open the fridge and grab that cold beer...

Enjoy your reading!

**Matteo Zanda**

*Editor of SYNFORM*

## IN THIS ISSUE

### SYNSTORIES ■ ■ ■ ■

**Programmable Enantioselective One-Pot Synthesis of Molecules with Eight Stereocenters** ..... **A77**

**Catalytic Asymmetric Mono-Fluorination of  $\alpha$ -Keto Esters: Synthesis of Optically Active  $\beta$ -Fluoro- $\alpha$ -hydroxy and  $\beta$ -Fluoro- $\alpha$ -amino Acid Derivatives** ..... **A80**

**Young Career Focus: Professor Cristina Nevado (University of Zürich, Switzerland)** ..... **A82**

**COMING SOON** ..... **A84**

### CONTACT + + + +

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)

## Programmable Enantioselective One-Pot Synthesis of Molecules with Eight Stereocenters

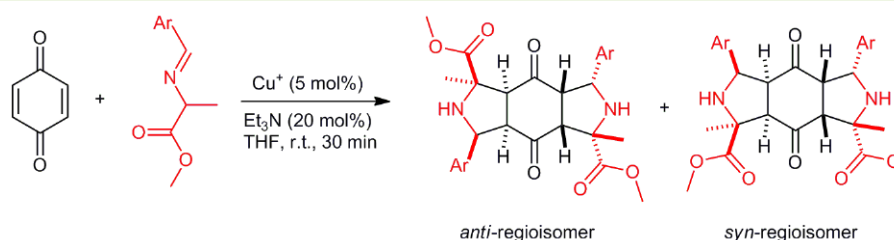
*Nat. Chem. Biol.* **2012**, *8*, 428–430

Over millions of years of evolution, nature has developed elaborate synthetic machinery which uses a few ‘building blocks’ to produce a great and diverse collection of natural products under different physiological conditions. “Natural products are a proven and rich source of drugs and of efficient tools and reagents for the study of biological phenomena,” said Professor Herbert Waldmann, director of the Max Planck Institute of Molecular Physiology (Dortmund, Germany). “They are complex compounds, present in highly enantio-enriched forms, and it is known that enantiomers may have different roles in biological systems,” he continued. Professor Waldmann explained that complex products exist in various configurations and generally only one of them is essential to evoking a biological response. “Also, there are numerous natural products with the same constitution, derived from the same biosynthetic pathway but demonstrating different behavior in biological systems, for example, the various terpenes derived from isoprenyl phosphate,” he said. Therefore, according to Professor Waldmann, high levels of regio-, diastereo- and enantiocontrol are essential for nature’s synthetic machinery. “Conversely, the methods of classical organic chemistry, based on stepwise creation of complexity of natural products, are dramatically less efficient compared to nature’s synthetic machinery,” added Dr. Andrey Antonchick, group leader at the Max Planck Institute of Molecular Physiology.

In order to address these drawbacks that affect most synthetic methods, intensive groundbreaking studies have recently been performed in the fields of domino (cascade) and tandem reactions as well as multicomponent reactions. However,

according to Dr. Antonchick, these methods have limited application for the synthesis of complex molecules with multiple stereocenters, and the development of efficient methods to obtain such compounds is required. “In 2008, organocatalytic formation of one out of 64 possible stereoisomers was demonstrated by cascade reaction,” he acknowledged. “More recently, David MacMillan and co-workers demonstrated an enantioselective cascade polyene cyclization inspired by the biosynthesis of terpenes.<sup>3</sup> The group of Dieter Enders developed a two-step, one-pot procedure for direct entry to tricyclic frameworks with eight stereocenters,” continued Dr. Antonchick. “However, the transformations developed are limited to the formation of only one possible isomer and do not allow the formation of different regio- or diastereoisomers.”

Recently, in order to establish the synthesis of complex molecules bearing multiple stereocenters, the research group led by Dr. Antonchick and Professor Waldmann proposed the catalytic tandem dicycloadition of azomethine ylides to 1,4-benzoquinone. “Asymmetric catalytic 1,3-dipolar cycloaddition of azomethine ylides to various dipolarophiles in the synthesis of polysubstituted pyrrolidines is well described,” said Dr. Antonchick. “However, no attempts at tandem double cycloaddition were reported,” he continued. “The application of tandem conditions may be advantageous for the controllable synthesis of various complex isomeric products in comparison to the domino process, where multiple stereocenters are generated in a stepwise fashion, based on asymmetric induction or on the use of the same catalyst.”

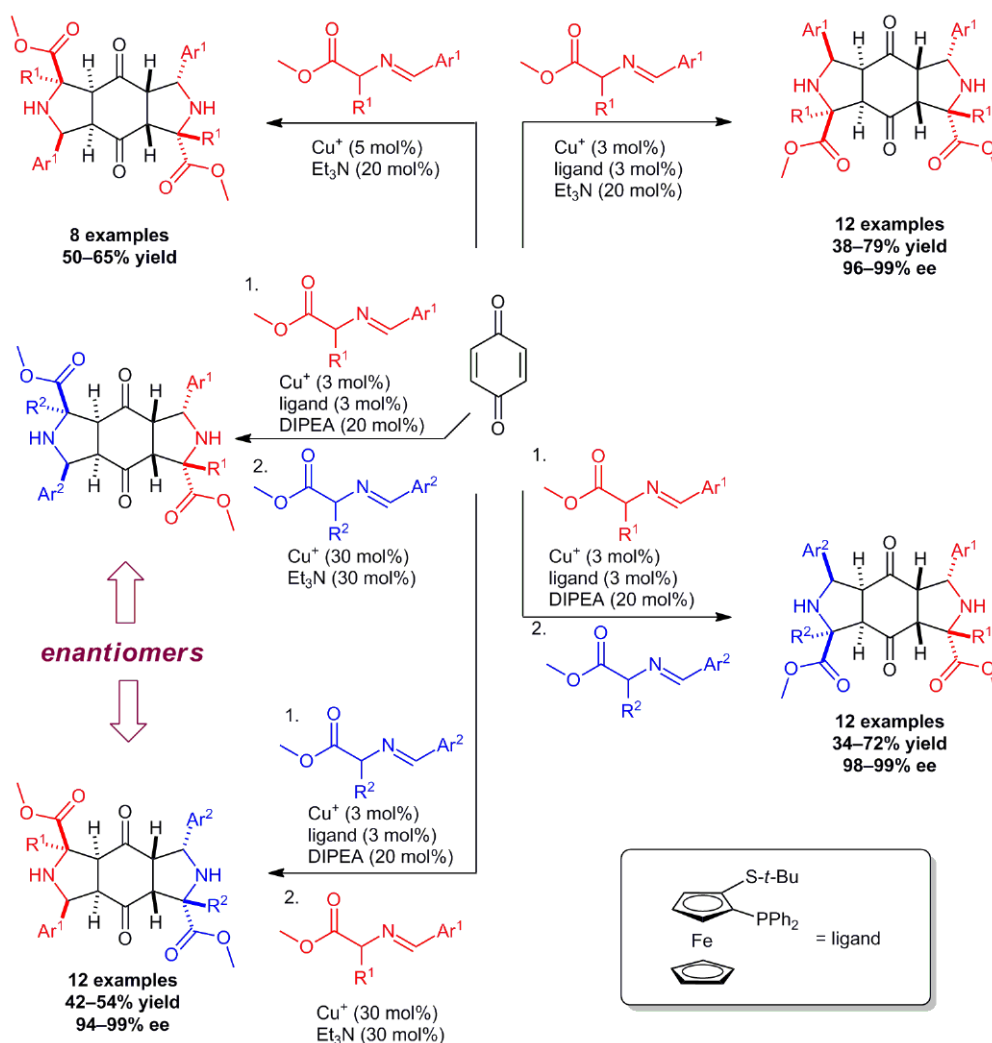


Scheme 1

Professor Waldmann revealed that Marco Potowski, a first-year graduate student, was very intrigued by the possibility of generating four carbon–carbon bonds in a one-pot reaction and his first experiment led to an impressive result. “A mixture of only two regioisomers out of 512 possible compounds (eight stereocenters and two regioisomers =  $2^8$ ) was formed under catalytic conditions (Scheme 1),” recalled Dr. Antonchick. “Furthermore, the transformation discovered was sensitive to changes in reaction conditions that allowed straightforward optimization for the selective synthesis of one desired regioisomer,” he said. Excitingly, cyclohexa-1,4-dione showed a twist-boat conformation in the *syn*-regioisomers obtained. “These compounds do not have an axis of symmetry that allows development of a catalytic enantioselective approach

(Scheme 2),” said Dr. Antonchick. Inspired by these results, the researchers demonstrated that the stepwise addition of two different azomethine ylides led to the formation of a structural complex compound library from a small number of simple starting compounds. “Furthermore,” he added, “application of this methodology enables, for the first time, the synthesis of both enantiomers of the target product using absolutely the same chemicals including the absolute configuration of the chiral ligand. The enantiomers can be accessed simply by changing the sequence of reagent addition,” said Dr. Antonchick.

“We believe that the methodology will inspire further development of efficient cascades and open new opportunities for biological research,” said Dr. Antonchick. “The development



Scheme 2

of efficient and operationally simple methods for the synthesis of complex products will overcome challenges which are not easily met in classical stepwise synthesis.”

“Our current efforts are focused on investigations of the biological activity of the obtained compounds and development of new one-pot methods for the synthesis of complex natural-product-inspired compounds,” concluded Professor Waldmann. ■

## REFERENCES

- (1) (a) J. W.-H. Li, J. C. Vederas *Science* **2009**, *325*, 161;  
(b) D. J. Newman, G. M. Cragg *J. Nat. Prod.* **2007**, *70*, 461.
- (2) S. Bertelsen, R. L. Johansen, K. A. Jørgensen *Chem. Commun.* **2008**, 3016.
- (3) S. Rendler, D. W. C. MacMillan *J. Am. Chem. Soc.* **2010**, *132*, 5027.
- (4) D. Enders, M. R. M. Hüttl, J. Runsink, G. Raabe, B. Wendt *Angew. Chem. Int. Ed.* **2007**, *46*, 467.
- (5) J. Adrio, J. C. Carretero *Chem. Commun.* **2011**, *47*, 6784.

Matteo Zanda

## About the authors



Dr. A. P. Antonchick



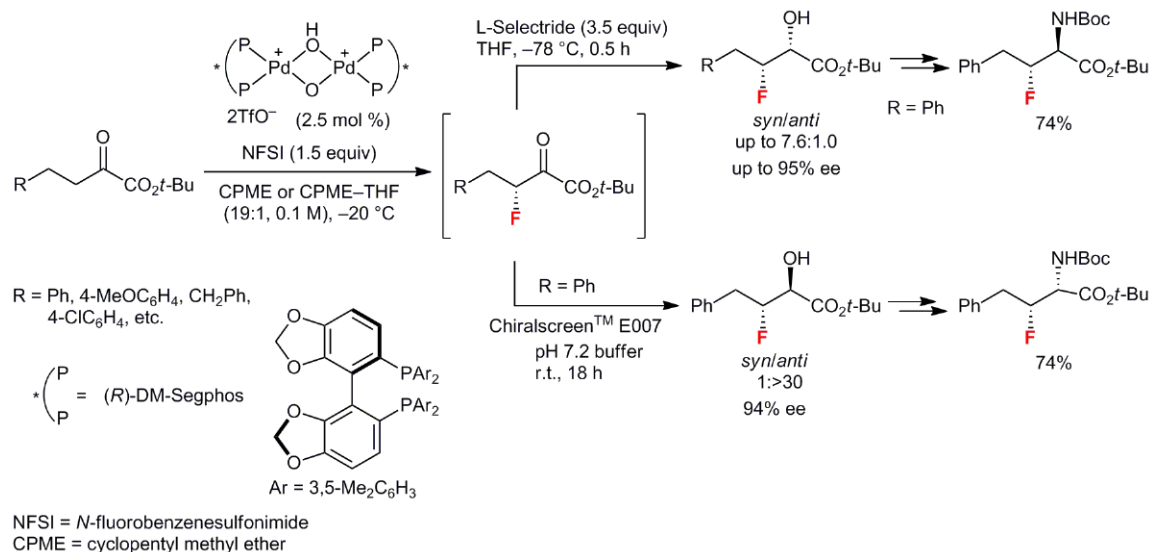
Prof. H. Waldmann



M. Potowski

# Catalytic Asymmetric Mono-Fluorination of $\alpha$ -Keto Esters: Synthesis of Optically Active $\beta$ -Fluoro- $\alpha$ -hydroxy and $\beta$ -Fluoro- $\alpha$ -amino Acid Derivatives

*Angew. Chem. Int. Ed.* **2012**, *51*, 4581–4585



$\beta$ -Fluorinated amino acids and  $\beta$ -fluorinated hydroxy acids are unique chiral building blocks in medicinal chemistry; moreover, some  $\beta$ -fluorinated amino acids alone are biologically active. Therefore, the development of efficient synthetic methods for these key molecules is highly desirable. Known methods generally involve the use of chiral pools and enzymatic reactions, which would limit the scope of the reaction. Recently, the group of Professor Mikiko Sodeoka from RIKEN Advanced Science Institute (Wako, Japan) devised a novel method using catalytic asymmetric reactions for the preparation of a variety of fluorinated  $\alpha$ -functionalized acid derivatives. When asked to explain background and starting point of this research, Professor Sodeoka replied: “Dr. Hamashima, a catalysis project leader in my group, and I have been working on palladium enolate chemistry, which is highly effective for catalytic asymmetric fluorination of acidic substrates (*Adv. Synth. Catal.* **2010**, *352*, 2708). In addition,” she continued, “we have also reported the first example of asymmetric conjugate addition of  $\alpha$ -keto esters to nitroolefins using a chiral nickel complex. We expected that a fusion of these studies

would lead to the development of monofluorination of  $\alpha$ -keto esters, which would provide a basis for the preparation of a variety of optically active fluorinated compounds including amino acid derivatives, as the keto group of the product could be readily transformed into various functional groups,” said Professor Sodeoka.

One possible big concern of the Japanese researchers was the chemical and optical stability of  $\beta$ -fluorinated  $\alpha$ -keto esters having three electron-withdrawing groups around the stereogenic carbon center. “Nevertheless, our original study on the reaction of aryl acetic acid derivatives led us to think that  $\beta$ -fluorinated  $\alpha$ -keto esters might be optically stable in the reaction mixture (*Angew. Chem. Int. Ed.* **2007**, *46*, 5435),” said Professor Sodeoka. “In addition, successful examples of  $\alpha$ -fluorination of primary aldehydes, which also tend to racemize, reported by Jørgensen and MacMillan gave us the confidence to start this project (*Angew. Chem. Int. Ed.* **2005**, *44*, 3703; *J. Am. Chem. Soc.* **2005**, *127*, 8826),” she added.

Professor Sodeoka recalled that soon after Dr. Suzuki started the experiments, they found that their hypothesis was

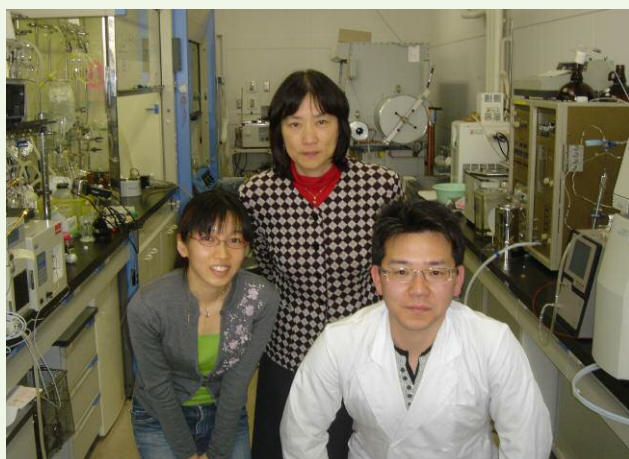
correct, and careful optimization of the reaction conditions improved the enantioselectivity to up to >90%. “Since the  $\alpha$ -keto ester can easily adopt its hydrate form, reaction conditions had to be carefully monitored,” explained Professor Sodeoka. “As it was also difficult to isolate the fluorinated keto esters, the products were isolated after simple reduction. At this stage, we were very excited to find that there had been no precedent in the literature,” she said.

The task to be solved was to improve the diastereoselectivity in the reduction of the fluorinated keto esters, and this, according to Professor Sodeoka, had also remained largely unexplored in the literature. “It took a long time (about six months) to establish the reduction conditions,” she revealed. Indeed, simple screening of the reducing agents and reaction conditions revealed that L-Selectride gave satisfactory syn-selectivity, but the researchers were not able to obtain high anti-selectivity with any chemical reducing agents. “Since enzymatic reduction of  $\alpha$ -keto esters had been reported previously, Dr. Kitamura tried such a reduction,” said Professor Sodeoka. “After screening of the commercially available enzymes, we were very pleased to find that >30:1 anti-selectivity was achieved with E007 as a reduction enzyme.”

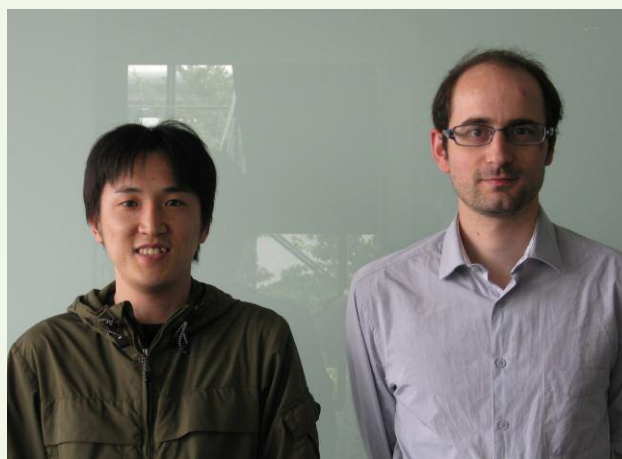
In spite of their efforts, Professor Sodeoka and her co-workers failed to achieve direct conversion of fluorinated keto esters into the corresponding amino acids using enzymatic reductive amination. “However, Dr. Lectard established a step-by-step procedure for conversion of an  $\alpha$ -hydroxy ester into an  $\alpha$ -amino ester in remarkable yield. Importantly, the combination of artificial catalytic reaction and natural enzymatic reduction allows, in principle, the preparation of all possible stereoisomers (enantiomers and diastereomers) of fluorinated amino acids,” said Professor Sodeoka. “Our research is the first example of the catalytic asymmetric fluorination of  $\alpha$ -keto esters,” she continued. “This reaction allows access to medicinally interesting, but so far less available compounds. We are confident that fluorinated amino acid derivatives will be quite useful in medicinal studies. To meet the requirements for various compounds in such studies, we need to further investigate in order to improve the scope of the reaction and reaction efficiency,” concluded Professor Sodeoka. ■

Matteo Zanda

### About the authors



From left: Dr. S. Suzuki, Prof. M. Sodeoka, Dr. Y. Hamashima



From left: Dr. Y. Kitamura, Dr. S. Lectard

## Young Career Focus: Professor Cristina Nevado (University of Zürich, Switzerland)

■ **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 Professor Cristina Nevado, University of Zürich, Switzerland.

### BIOGRAPHICAL SKETCH



Prof. C. Nevado

**Cristina Nevado** was born in Madrid in 1977. She studied chemistry at the Autónoma University of Madrid graduating in 2000. In October 2004 she received her PhD in organic chemistry at the same university working with Professor Antonio M. Echavarren on the cyclization of 1,6-enynes catalyzed by late transition metals. In December 2004 she joined the lab of Professor Alois Fürstner at the Max-Planck-Institut für Kohlenforschung (Germany) working on the total synthesis of bioactive marine macrolides. Since May 2007 she is Assistant Professor at the Organic Chemistry Institute of the University of Zürich (Switzerland). Her research interests involve the development of new methodologies based on late transition metals and their application in the total synthesis of complex natural products.

### INTERVIEW

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

**Professor Nevado** | Our group is interested in the synthesis of naturally occurring molecules by means of chemical methods. We believe natural products provide an enormous synthetic challenge for organic chemists. In contrast to primary metabolites, available through the assembly of their corresponding building blocks in a chemical laboratory, the synthesis of natural products is far from routine. The reason is directly related to the immense structural complexity and diversity that nature is able to introduce in its secondary metabolites. This highly varied structural scenario demands from organic chemists the development of new reactions, reagents and catalysts to achieve our targets.

In the past five years, our group has developed a multidisciplinary research program supported on three pillars: first, the development of new methodologies for the synthesis of C–C and C–X bonds based on late transition metal catalysis, with special focus on gold; second, the application of such methods to streamline the synthesis of complex natural products; and third, the study at a molecular level, both computational and experimentally, of relevant biological processes influenced by these complex organic molecules, including cancer progression, cancer metastasis and cell motility.

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

**Professor Nevado** | I felt fascinated by the power of organic synthesis as an undergraduate student. At that time, I used to read articles reporting the total synthesis of complex natural products, and found myself unable to recognize many of the reactions that were employed. However, I was able to appreciate the challenge and beauty in the construction of molecular complexity impregnating many of those reports. After a PhD focused on methodology development, I wanted to “learn by doing” and explore complex natural product synthesis during my time as a post-doctoral associate.



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

**Professor Nevado** | I truly believe that the development of new methodologies is fully worthy when coupled to the resolution of challenging, previously unsolved, synthetic problems. Connecting both methodology development and complex organic synthesis is a challenging but extremely attractive endeavor, to which our research group aims to contribute.

**SYNFORM** | *Your research group is active at the frontier of organic synthesis and catalysis. Could you tell us more about your research and its aims?*

**Professor Nevado** | We have taken advantage of gold complexes as soft carbophilic Lewis acids to activate propargylic carboxylates generating non-classical gold-stabilized carbocations. These electron-deficient species are able to store the stereochemical information of the starting material, enabling the stereocontrolled formation of five-, six- and seven-membered rings. These methods have offered us a straightforward access to the enantioselective syntheses of natural products such as frondosins, carvones, etc. In parallel, we have also

targeted the development of Au(I)/Au(III) redox catalytic cycles to trigger novel C–H functionalizations, C–F bond-forming reactions and flexible alkene difunctionalizations.

Our group has also reported the first total synthesis of iriomoteolide 3a, a novel marine macrolide with a promising biological profile. Our work has enabled the in-depth study of the cellular targets of this molecule, revealing the iriomoteolides as effective tools to study the cellular cytoskeleton.

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

**Professor Nevado** | I feel the most important contribution is still to come: we have shown that new gold reactivity can be discovered, enabling both previously challenging transformations as well as the rapid stereocontrolled construction of molecular complexity. In the future, our research will aim to embrace a more ambitious goal that transcends the individual disciplines: the design and efficient synthesis of organic molecules and their use as molecular probes to understand/modulate biologically relevant processes. ■

**Matteo Zanda**

COMING SOON ►► COMING SOON ►►

## SYNFORM 2012/09

is available from  
August 21, 2012

In the next issues:

### SYNSTORIES ■ ■ ■ ■ ■

#### ■ Preparation of Alkylmagnesium Reagents from Alkenes through Hydroboration and Boron–Magnesium Exchange

*(Focus on an article from the current literature)*

#### ■ Urea Activation of $\alpha$ -Nitro diazoesters: An Organocatalytic Approach to N–H Insertion Reactions

*(Focus on an article from the current literature)*

### FURTHER HIGHLIGHTS + + + +

#### SYNTHESIS

Special Topic on “Continuous-Flow and Microreactor Chemistry” in issue 16/2012

#### SYNLETT

Account on: Stereocontrol Strategies in the Asymmetric Bioreduction of Alkenes

*(by K. Faber, M. Hall et al.)*

#### SYNFACTS

Synfact of the Month in category “Metal-Catalyzed Asymmetric Synthesis and Stereoselective Reactions”:  
[Ion-Paired Ligands for Palladium-Catalyzed Asymmetric Allylation](#)

### CONTACT + + + +

Matteo Zanda,  
NRP Chair in Medical Technologies  
Institute of Medical Sciences  
University of Aberdeen  
Foresterhill, Aberdeen, AB25 2ZD, UK  
and  
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, NRP Chair in Medical Technologies, Institute of Medical Sciences, University of Aberdeen, Foresterhill, Aberdeen, AB25 2ZD, UK and

C.N.R. – Istituto di Chimica del Riconoscimento Molecolare  
Via Mancinelli, 7, 20131 Milano, Italy  
Editorial Assistant: Alison M. Sage  
[Synform@chem.polimi.it](mailto:Synform@chem.polimi.it); fax: +39 02 23993080

#### Editorial Office

- Managing Editor: Susanne Haak,  
[susanne.haak@thieme.de](mailto:susanne.haak@thieme.de), phone: +49 711 8931 786
- Scientific Editor: Selena Boothroyd,  
[selena.boothroyd@thieme.de](mailto:selena.boothroyd@thieme.de)
- Scientific Editor: Stefanie Baumann,  
[stefanie.baumann@thieme.de](mailto:stefanie.baumann@thieme.de), phone: +49 711 8931 776
- Assistant Scientific Editor: Christiane Kemper,  
[christiane.kemper@thieme.de](mailto:christiane.kemper@thieme.de), phone: +49 711 8931 768
- Senior Production Editor: Thomas Loop,  
[thomas.loop@thieme.de](mailto:thomas.loop@thieme.de), phone: +49 711 8931 778
- Production Editor: Helene Deufel,  
[helene.deufel@thieme.de](mailto:helene.deufel@thieme.de), phone: +49 711 8931 929
- Production Editor: 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: Julia Stötzner,  
[julia.stoetznern@thieme.de](mailto:julia.stoetznern@thieme.de), phone: +49 711 8931 771
- Postal Address: SYNTHESIS/SYNNLETT/SYNFACTS, Editorial Office,  
Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany,  
phone: +49 711 8931 744, fax: +49 711 8931 777
- Homepage: [www.thieme-chemistry.com](http://www.thieme-chemistry.com)

#### Publication Information

SYNFORM will be published 12 times in 2012 by Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany, and is an additional online service for SYNTHESIS, SYNLETT and SYNFACTS.

#### Publication Policy

Product names which are in fact registered trademarks may not have been specifically designated as such in every case. Thus, in those cases where a product has been referred to by its registered trademark it cannot be concluded that the name used is public domain. The same applies as regards patents or registered designs.

#### Ordering Information for Print Subscriptions to SYNTHESIS, SYNLETT and SYNFACTS

The Americas: Thieme Publishers New York, Thieme Medical Publishers, Inc., 333 Seventh Avenue, New York, NY 10001, USA.

To order: [customerservice@thieme.com](mailto:customerservice@thieme.com) or use the Web site facilities at [www.thieme-chemistry.com](http://www.thieme-chemistry.com), phone: +1 212 760 0888  
Order toll-free within the USA: +1 800 782 3488  
Fax: +1 212 947 1112

Airfreight and mailing in the USA by Publications Expeditors Inc., 200 Meacham Ave., Elmont NY 11003. Periodicals postage paid at Jamaica NY 11431.

Europe, Africa, Asia, and Australia: Thieme Publishers Stuttgart, Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany.

To order: [customerservice@thieme.de](mailto:customerservice@thieme.de) or use the Web site facilities at [www.thieme-chemistry.com](http://www.thieme-chemistry.com).  
Phone: +49 711 8931 421; Fax: +49 711 8931 410

Current list prices are available through [www.thieme-chemistry.com](http://www.thieme-chemistry.com).

#### Online Access via Thieme-connect

The online versions of SYNFORM as well SYNTHESIS, SYNLETT and SYNFACTS are available through Thieme-connect ([www.thieme-connect.com/ejournals](http://www.thieme-connect.com/ejournals)) where you may also register for free trial accounts. For information on multi-site licenses and pricing for corporate customers as well as backfiles please contact our regional offices:

The Americas: [esales@thieme.com](mailto:esales@thieme.com), phone: +1 212 584 4695

Europe, Africa, Asia, and Australia: [eproducts@thieme.de](mailto:eproducts@thieme.de), phone: +49 711 8931 407

#### Manuscript Submission to SYNTHESIS and SYNLETT

Please consult the Instructions for Authors before compiling a new manuscript. The current version and the Word template for manuscript preparation are available for download at [www.thieme-chemistry.com](http://www.thieme-chemistry.com). Use of the Word template helps to speed up the refereeing and production process.

#### Copyright

This publication, including all individual contributions and illustrations published therein, is legally protected by copyright for the duration of the copyright period. Any use, exploitation or commercialization outside the narrow limits set by copyright legislation, without the publisher's consent, is illegal and liable to criminal prosecution. This applies translating, copying and reproduction in printed or electronic media forms (databases, online network systems, Internet, broadcasting, telecasting, CD-ROM, hard disk storage, microcopy edition, photomechanical and other reproduction methods) as well as making the material accessible to users of such media (e.g., as online or offline backfiles).

#### Copyright Permission for Users in the USA

Authorization to photocopy items for internal or personal use, or the internal or personal use of specific clients, is granted by Georg Thieme Verlag KG Stuttgart · New York for libraries and other users registered with the Copyright Clearance Center (CCC) Transactional Reporting Service, provided that the base fee of US\$ 25.00 per copy of each article is paid directly to CCC, 22 Rosewood Drive, Danvers, MA 01923, USA, 0341-0501/02.