

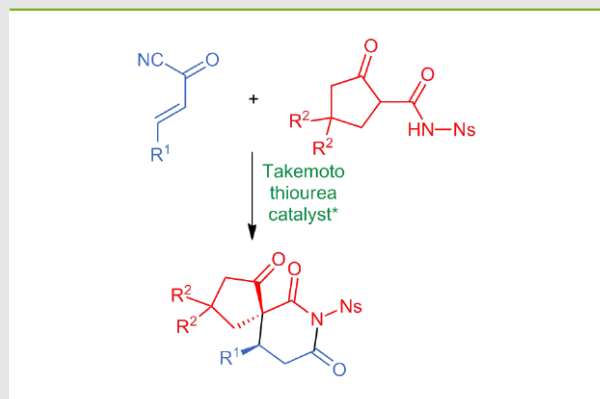
# SYNFORM

People, Trends and Views in Synthetic Organic Chemistry

2014/04

## SYNSTORIES ■ ■ ■ ■

■  $\alpha,\beta$ -Unsaturated Acyl Cyanides as New Bis-Electrophiles for Enantioselective Organocatalyzed Formal [3+3]-Spiroannulation



■ Total Synthesis and Anti-Hepatitis C Virus Activity of MA026

■ Rapid Assembly of Complex Cyclopentanes Employing Chiral,  $\alpha,\beta$ -Unsaturated Acylammonium Intermediates

■ Young Career Focus:  
Dr. Alexander Breder  
(Georg-August-Universität  
Göttingen, Germany)

CONTACT ++++

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



### Dear Readers,

Do you remember the good old times when authors were dealing with Editors, Deputy Editors, Assistants and other human beings working for journals and we had a chance to discuss reviews and rebuttals, ask for additional reviewers, negotiate the option of transferring manuscripts to other journals at the same publisher and much more? Well, I do and I really miss that, because nowadays the situation is very different... Most journals (with the notable exception of Thieme Chemistry's ones, of course!!) have become impact-factor factories, and the only thing that actually matters is to publish mainstream research that produces short-term citations and leads to bigger impact factors. In contrast, the human factor is almost completely disappeared. When I submit a manuscript and, after a while, I get back the review, I don't have the impression that I am dealing with humans but with a bunch of dumb machines that can only answer yes or no, operating exclusively through clickable links, with absolutely no chance to discuss anything with anyone or find tailored solutions for my manuscript. At this point, I would like to make an example: recently I got one manuscript rejected from a journal published by a major chemical society, and the email I got back from them had just two clickable options: transfer your manuscript to another journal (same publisher, of course, but lower impact factor) or decline (i.e. send your non-mainstream rubbish to some other publisher). No apparent third option. I didn't give up and I took about one hour of my time to write an email and make a compelling case for my manuscript, making clear that the reviewers were absolutely right and made very useful comments, and eventually asking whether I could make the necessary corrections and resubmit to the same journal. The reply I got after a couple of days left me completely dumbstruck: a clearly pre-drafted and standardized email saying that they were sorry that I was unsatisfied with the decision to reject my manuscript and offering a further review by a senior adjudicative referee. It had nothing to do with what I wrote!!! And clearly they didn't even read my email, because those dumb machines cannot read anything, they can only offer clickable options!! So, after 10 minutes of depression I decided to give up, I clicked one of the two links provided in the original email, and went back to my research with a deep sense of discomfort, and really missing the good old times when people in flesh and bones, and not clickable cybernetic organisms, were running journals. Luckily, there are no heartless machines here at **SYNFORM** and all of our contributors would be able to confirm that!!! Including

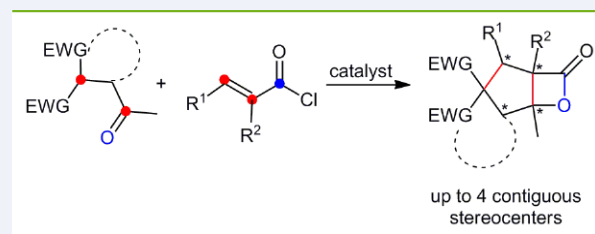
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If you have any questions or wish to send feedback, please write to Matteo Zanda at:  
[Synform@chem.polimi.it](mailto:Synform@chem.polimi.it)

those featured in this new issue, who are: Professor F. Sugawara (Japan) with his total synthesis of a highly complex anti-hepatitis decapeptide, Professor J. Rodriguez (France) and his organocatalyzed enantioselective spiroannulation, Professor D. Romo (USA) with his spectacular synthesis of cyclopentane-fused  $\beta$ -lactones, and Dr. A. Breder (Germany) who is the protagonist of a new Young Career Focus.

Enjoy your reading!

**Matteo Zanda**  
Editor of **SYNFORM**

## Total Synthesis and Anti-Hepatitis C Virus Activity of MA026

*J. Am. Chem. Soc.* **2013**, *135*, 18949–18956

■ Depsipeptides are fascinating natural compounds closely resembling peptides where one or more peptide bonds CO–NH are replaced by ester functions CO–O. Cyclic depsipeptides are frequently encountered as metabolites of bacteria and marine organisms, and very often these compounds display potent biological activities. Recently, Professor Fumio Sugawara's group at the Tokyo University of Sciences (Japan) described the first total synthesis of MA026, a structurally complex and synthetically challenging antiviral lipocyclodepsipeptide.

Professor Sugawara said: "We originally isolated MA026 from the fermentation broth of *Pseudomonas* sp. RtIB026 found in the digestive tract of rainbow trout (*Oncorhynchus mykiss*). In rainbow trout aquaculture, an outbreak of infectious hematopoietic necrosis virus (IHNV) can cause extensive economic loss, and surveys were conducted. Our previous studies revealed that rainbow trout with resistance to IHNV infection live in symbiosis with *Pseudomonas* sp. RtIB026 in their digestive tracts." Anti-IHNV bioassay-guided fractionation of organic extracts from the culture fluid of *Pseudomonas* sp. RtIB026 resulted in the isolation of a new lipocyclodepsipeptide, designated MA026, as a principal active constituent. MA026 displays antiviral activity against not only IHNV but also hepatitis C virus (HCV).

The structure of MA026 was established in 2002 by amino acid composition analyses and NMR analyses with chemical modifications; it was found to consist of a cyclodepsipeptide, a chain peptide, and an N-terminal (*R*)-3-hydroxydecanoic acid. "In total, MA026 contains 14 amino acids, nine of which possess the *d* configuration," explained Professor Sugawara. "The cyclodepsipeptide comprises a 25-membered ring in which the carboxylic group of L-Ile forms a lactone bond with the hydroxyl group of D-Ser." In common with a number of lipocyclodepsipeptides, MA026 possesses a complex structure and interesting activity. In particular, MA026 displays anti-HCV activity that could be used to develop a novel antiviral drug. "In order to reveal the mechanism of antiviral activity," said Professor Sugawara, "it is essential to develop a flexible chemical synthesis of MA026 to facilitate chemical modification of its structure."

Professor Sugawara continued: "After determining the structure of MA026, we started the synthetic study. We chose a solution-phase synthesis in consideration of the structure–activity relationship study. The biggest hurdle was the construction of a cyclodepsipeptide." Professor Sugawara revealed that it was not easy to obtain the cyclodepsipeptide as a pure compound, since in peptide synthesis it is hard to separate the target peptide from by-products as the peptide gets longer. "One member of my research group, the undergraduate student Satomi Shimura, started the synthetic study of MA026 in 2008," he said. "First, she prepared all the components of MA026. Then she tried to construct a cyclodepsipeptide with decadepsipeptide A, but she could not get the cyclodepsipeptide. She tried the macrocyclization over and over. However, it was very difficult to obtain the pure cyclodepsipeptide in enough quantity from decadepsipeptide A." Three years later, now as a PhD student, Satomi decided to change the macrocyclization site. She synthesized a new macrocyclization substrate, decadepsipeptide B, and tried to cyclize the decadepsipeptide again. "Finally, she succeeded in synthesizing and purifying the cyclodepsipeptide," said Professor Sugawara. "By coupling the side chain and the cyclodepsipeptide, she achieved the first total synthesis of MA026."

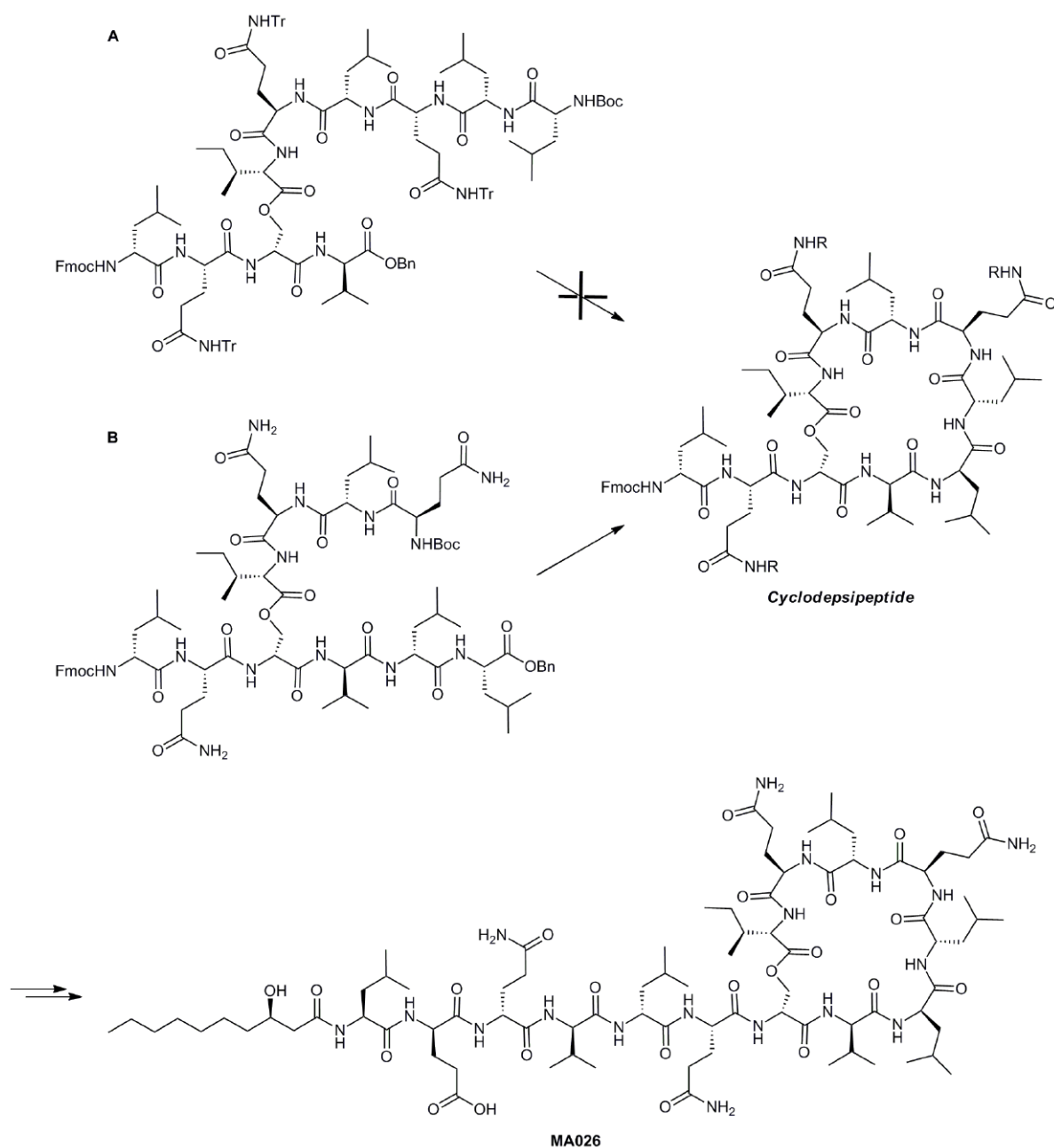
This did not end the investigations into MA026. Satomi performed phage display screening to identify a candidate target protein of MA026 and found claudin-1, an HCV entry receptor, as a candidate target. "At that point, we proposed a hypothesis that MA026 might interact with claudin-1 and thereby suppress HCV infection," said Professor Sugawara. The specific interaction between MA026 and recombinant claudin-1 protein was confirmed by SPR analyses. "However, it is still only a hypothesis that MA026 interacts with claudin-1 specifically," he explained. "Further studies to reveal the detailed mechanism of antiviral activity of MA026 are currently under way."

"In our laboratory, there are three groups working on isolation and structure determination of natural products, synthesis of organic compounds, and target identification of biologically active compounds, respectively," said Professor Sugawara. "MA026 is a representative example that under-

went all three processes. We performed the study of MA026 both chemically and biologically. This is the value of this paper.”

However, the synthetic route of MA026 reported in the article presents some problems for large-scale synthesis, as recognized by Professor Sugawara, who added that there are a few low-yielding sequences where improvements should be made. Nonetheless, this convergent, flexible, solution-phase

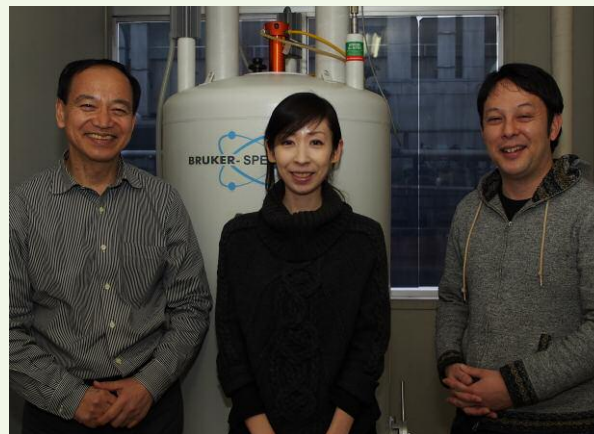
synthesis is useful for generating MA026 derivatives for structure–activity relationship studies and further biological investigations. “We think it is important to understand the behavior of MA026, chemically and biologically,” said Professor Sugawara. “The chemical knowledge is essential, or at least useful, when we interpret the results of biological experiments. On the other hand, the biological knowledge is important when we make a decision about synthetic targets.



The biological activity is a significant property of organic compounds. To fully appreciate the biological activity and the mechanism of action of a given organic compound, a broad perspective across chemistry and biology is necessary.” ■

*Matteo Zanda*

### About the authors



From left: Prof. F. Sugawara, Dr. S. Shimura, Dr. S. Kamisuki

**Fumio Sugawara** was born in 1950 and received his Ph.D. in 1979 from Tohoku University (Japan). From 1979 to 1995 he worked as Vice Chief Scientist at RIKEN (Japan). During that time he conducted postdoctoral research at Montana State University (USA) from 1983–1985. In 1996, he was promoted to his current position as a Full Professor at the Tokyo University of Science (Japan). He received the Young Scientists Award from The Japan Bioscience, Biotechnology and Agrochemistry Society in 1986 and the Special Award for Excellent Scientists from Tokyo University of Science in 2008, and served as an editorial board member of *Chemistry & Biology* from 1994 to 2004.

**Shinji Kamisuki** was born in 1977 in Tokyo (Japan). He received his Ph.D. from Tokyo University of Science under the supervision of Professor Fumio Sugawara in 2005. Then, he worked with Professor Motonari Uesugi as a postdoctoral fellow at Baylor College of Medicine (Houston, USA) and Kyoto University (Japan) from 2005 to 2009. After postdoctoral study for two more years (2009–2011) with Mikiko Sodeoka, Chief Scientist at RIKEN (Japan), he joined Tokyo University of Science as an assistant professor in 2011.

**Satomi Shimura** was born in 1986 in Tokyo (Japan). She studied for her B.Sc. and M.Sc. degrees at Tokyo University of Science (Japan), obtaining her M.Sc. in 2011. She remained at the same institution for Ph.D. studies, and received her Ph.D. under the supervision of Professor Fumio Sugawara in 2014. She is currently a postdoctoral fellow at the National Institute of Infectious Diseases (Japan).

## $\alpha,\beta$ -Unsaturated Acyl Cyanides as New Bis-Electrophiles for Enantioselective Organocatalyzed Formal [3+3]-Spiroannulation

*Chem. Eur. J.* **2014**, *20*, 410–415

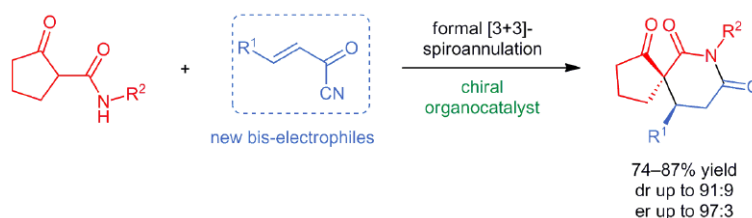
The synthesis of stereodefined all-carbon quaternary centers, such as spirocyclic systems, continues to represent a formidable challenge in organic synthesis. Recently, the group of Professor Jean Rodriguez at the Aix Marseille Université (France), reported the first utilization of  $\alpha,\beta$ -unsaturated acyl cyanides as efficient bis-electrophiles, and the authors have exploited their intriguing reactivity in a formal enantioselective organocatalyzed synthesis of synthetically valuable aza-spiro[4,5]decanones. From a synthetic point of view, this methodology represents the first direct enantioselective method to construct glutaramide derivatives, a structural motif found in many biologically active molecules (natural products as well as drugs).

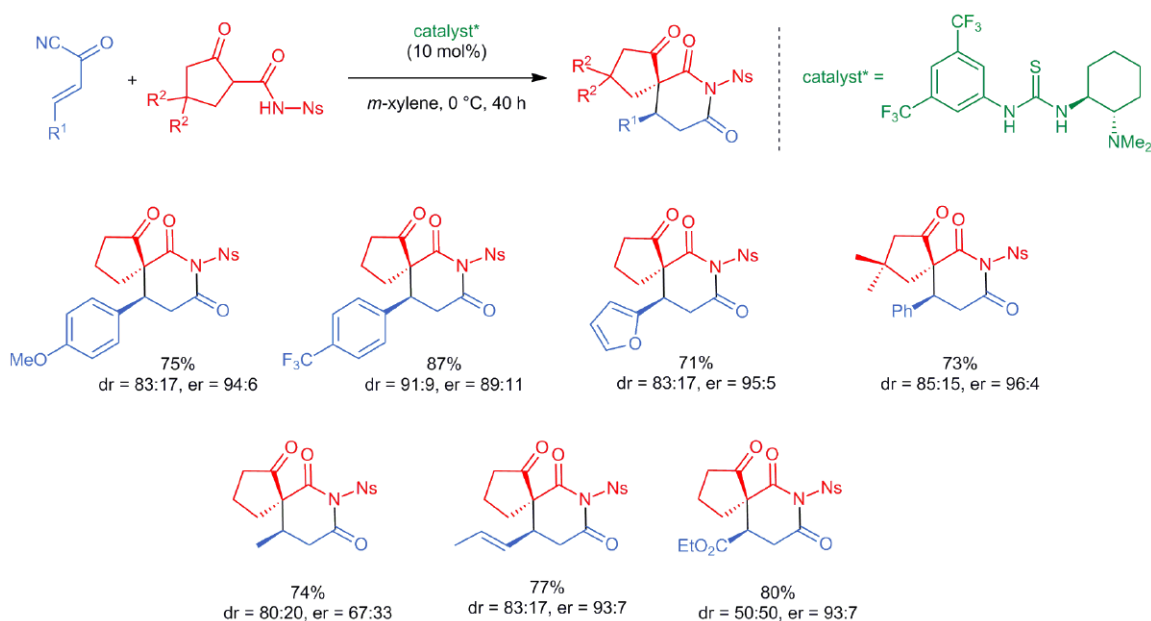
Professor Rodriguez' group has pioneered the use of  $\alpha$ - and  $\beta$ -ketoamides as pronucleophiles in enantioselective organocatalyzed Michael additions. They successfully underwent reactions with nitroalkenes (*Org. Lett.* **2010**, *12*, 5246, *Adv. Synth. Catal.* **2012**, *354*, 3523), were involved in domino sequences with  $\alpha,\beta$ -unsaturated carbonyls (*Org. Lett.* **2011**, *13*, 3296), or behaved as bis-nucleophiles in multicomponent reactions with enals (*Angew. Chem. Int. Ed.* **2013**, *52*, 14143). However, reactions with carbonyl electrophiles were restricted to  $\beta$ -unsubstituted substrates. Professor Rodriguez said: "To expand the synthetic usefulness of these transformations, we turned our attention towards more activated Michael acceptors." Sébastien Gouedranche, a PhD student involved in this project, tackled this problem and proposed to evaluate the reactivity of various Michael acceptors including the scarcely used  $\alpha,\beta$ -unsaturated acyl cyanides. Professor Rodriguez explained that these species are easily obtained by

reaction of copper cyanide with the corresponding  $\alpha,\beta$ -unsaturated acyl chloride in refluxing acetonitrile. "When reacting them with a  $\beta$ -ketoamide in the presence of a bifunctional organocatalyst (Takemoto thiourea catalyst), Sébastien observed the formation of a spirocyclic compound by a Michael heterocyclization domino sequence, with participation of the amide nitrogen atom as nucleophile," revealed Professor Rodriguez. Hence, these unfamiliar Michael acceptors not only reacted as simple electrophiles, but also proved to be efficient 1,3-bis-electrophiles that could take part in domino reactions. Professor Rodriguez continued: "We then investigated this formal [3+3]-spiroannulation by optimizing the reaction conditions and testing our methodology on various acyl cyanides." Representative examples are presented in the following scheme. "The methodology proved to be quite general with respect to the starting acyl cyanide, as various types of substituents (aryl, heteroaryl, alkyl, vinyl, ester) are well tolerated, affording the desired product in good yields, diastereo- and enantioselectivities," said Professor Rodriguez.

With this new reactivity in hand, additional experimental work was conducted in order to answer the following two questions: a) Is the reactivity of acyl cyanides in this reaction specific? and b) What is the mechanism of this reaction explaining the stereochemical outcome?

Professor Rodriguez remarked: "We clearly identified the specificity of unsaturated acyl cyanides by comparing their reactivity with other potential 1,3-bis-electrophiles that are cinnamaldehyde, cinnamoyl chloride and 4-nitrophenyl cinnamate. No reaction occurred in any of these three cases."





Concerning the reaction mechanism, two possible activation modes could, in theory, explain the observed stereoselectivities. Complementary NMR and HRMS studies clearly showed the formation of an uncommon acyl ammonium intermediate between the catalyst and the acyl cyanide in polar solvents. “This kind of chiral  $\alpha,\beta$ -unsaturated acylammonium intermediate has recently been exploited by Romo and co-workers for the enantioselective synthesis of various heterocycles (see *Angew. Chem. Int. Ed.* **2013**, *52*, 13688),” Professor Rodriguez acknowledged. “At this point, we are not certain whether the reaction is going through a transition state involving this cationic intermediate or through a more ‘classical’ transition state where both partners are activated by the bifunctional catalyst through a well-ordered hydrogen-bond network,” he continued. “Additional experimental work and theoretical calculations are currently being conducted in our laboratory to gain further insight into this intriguing mechanism.” Professor Rodriguez concluded: “We also expect that the functional compatibility and the versatility of  $\alpha,\beta$ -unsaturated acyl cyanides will allow their application in reactions with other bis-nucleophiles.”

Matteo Zanda

### About the authors



S. Gouedranche

**Sébastien Gouedranche** was born in Mulhouse (Alsace, France) in December 1988. In 2011, he obtained his MSc (synthetic organic chemistry) from Université de Haute-Alsace (France). He is now pursuing his PhD under the supervision of Professor Thierry Constantieux and Dr. Damien Bonne in the STeRéO group at Aix-Marseille Université (France). His research focuses on the development of new organocatalyzed methodologies.



Dr. X. Bugaut

**Xavier Bugaut** was born in Saint-Rémy (France) in 1982. After graduating from the Ecole Nationale Supérieure de Chimie de Montpellier (France), he carried out his doctoral work on the synthesis of landomycinone under the supervision of Dr. Emmanuel Roulland at the Institut de Chimie des Substances Naturelles (Gif-sur-Yvette, France). He then joined the group

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of Professor Frank Glorius at the Westfälische Wilhelms-Universität Münster (Germany) as a postdoctoral fellow, focusing on the development of new NHC-catalyzed transformations. In October 2011, he was appointed maître de conférences (equivalent to assistant professor) at Aix-Marseille Université (France) in the group of Professors Jean Rodriguez and Thierry Constantieux. His current research interests include enantioselective organocatalysis, with a focus on its application to multicomponent reactions and the development of new modes of action for organocatalysts.



Prof. T. Constantieux

Thierry Constantieux was born in Pau (France) in 1968. After studying chemistry at the University Bordeaux I, he completed his PhD under the supervision of Drs. J.-P. Picard and J. Dunoguez in 1994. He completed his habilitation in 2004 at Aix-Marseille Université (France), where he is currently professor of organic chemistry. His main research interest is focused on the development of new eco-compatible synthetic methodologies, especially enantioselective organocatalyzed cascades and domino multicomponent reactions from 1,3-dicarbonyl compounds, and their applications in heterocyclic chemistry.



Dr. D. Bonne

Damien Bonne was born in Epinal (France) in 1979. After studying chemistry at the Ecole Supérieure de Chimie de Lyon (CPE Lyon, France), he completed his PhD in 2006 under the supervision of Professor Jieping Zhu working on isocyanide-based multicomponent reactions. He then moved to the University of Bristol (UK) to join the group of Professor Varinder Aggarwal as a postdoctoral associate.

Since 2007, he has been working as an assistant professor with Professor Jean Rodriguez at Aix-Marseille Université (France). His research interests include the development of new asymmetric organocatalyzed methodologies and their applications in stereoselective synthesis.



Prof. J. Rodriguez

Jean Rodriguez was born in Cieza (Spain) in 1958 and in 1959 his family emigrated to France. After studying chemistry at the University of Aix-Marseille (France), he completed his PhD as a CNRS researcher with Professors B. Waegell and P. Brun in 1987. He completed his habilitation in 1992, also at Marseille, where he is currently professor and director of the UMR-CNRS-7313-iSm2. His research interests include the development of domino and multicomponent reactions and their applications in stereoselective organocatalyzed synthesis. In 1998 he was awarded the ACROS Prize in Organic Chemistry, in 2009 the Prize of the Division of Organic Chemistry from the French Chemical Society, and in 2013 he became a 'Distinguished Member' of the French Chemical Society.



# Rapid Assembly of Complex Cyclopentanes Employing Chiral, $\alpha,\beta$ -Unsaturated Acylammonium Intermediates

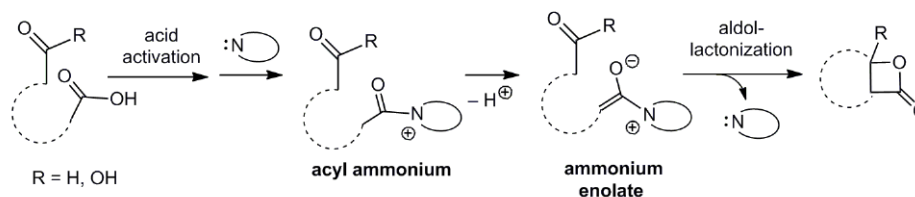
*Nat. Chem.* **2013**, *5*, 1049–1057

Fused  $\beta$ -lactones are important synthetic targets as this structural motif is present in a number of bioactive and natural compounds. For the last 15 years, the Romo group at Texas A&M University (College Station, USA) has been studying methods for the enantioselective synthesis of  $\beta$ -lactones building on the elegant work by Wynberg in the early 1980s (see for example: *J. Am. Chem. Soc.* **1982**, *104*, 166). Professor Daniel Romo said: “In particular, we have developed intramolecular variants of an organocatalyzed aldol-lactoniza-

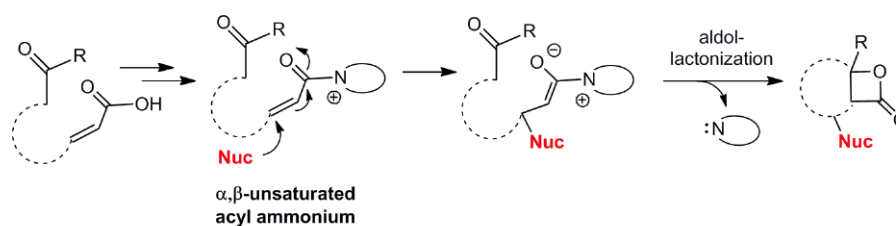
tion process that delivers bicyclic  $\beta$ -lactones in optically active form. Our first publication in this area employing aldehyde substrates (*J. Am. Chem. Soc.* **2001**, *123*, 7945) laid the foundation for further improvements (*J. Org. Chem.* **2005**, *70*, 2835) and developments including the use of keto acid substrates (*Org. Lett.* **2006**, *8*, 4363; *Angew. Chem. Int. Ed.* **2010**, *49*, 9479) which greatly expanded the utility and breadth of what became known as the intramolecular, nucleophile-catalyzed aldol-lactonization (NCAL) process (Scheme 1a).”

## Evolution of the NCMAL

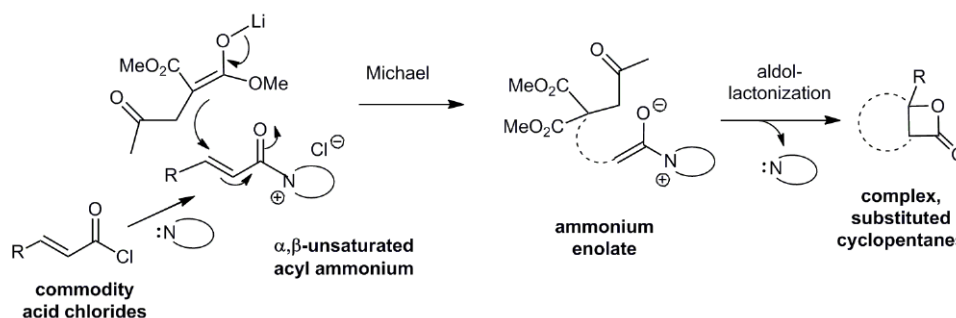
### a) Nucleophile-Catalyzed Aldol-Lactonization (NCAL)



### b) Michael-initiated NCAL



### c) Substrate synthesis via Michael addition $\rightarrow$ Nucleophile-Catalyzed Michael Aldol-Lactonization (NCMAL)



Scheme 1

“In efforts to extend the NCAL process by finding alternative methods to generate the key ammonium enolate intermediate, we considered the application of an initial Michael addition to an unsaturated acylammonium salt leading directly to an ammonium enolate,” said Professor Romo (Scheme 1b). “While this met with some success, a creative graduate student, Gang Liu, recognized the even greater potential of using a Michael addition to not only generate the ammonium enolate but also append the required ketone for the subsequent aldol-lactonization process (Scheme 1c)”. Thus, the Michael addition in essence enables the facile synthesis of substrates for a subsequent intramolecular NCAL. Overall, this provides a rapid assembly of optically active cyclopentanes. This transformation, which became known as the nucleophile-catalyzed Michael aldol-lactonization (NCMAL) organocascade, consistently delivers  $\beta$ -lactone-fused cyclopentanes in a highly enantio- and diastereoselective process from linear or cyclic  $\gamma$ -keto malonates. “Most importantly from a practical perspective, the ability to use commercially available acid chlorides and readily obtained ketomalonate derivatives enables rapid construction of complex cyclopentanes through an organocascade stitching process devoid of specialized reagents,” explained Professor Romo. “In the realm of nucleophilic catalysis by chiral tertiary amines, acylammoniums and ammonium enolates have been the predominant reactive intermediates guiding reaction design, as we employed both of these intermediates in prior NCAL methodology (Figure 1).”

According to Professor Romo, a conceptual extension of this, for example by employing an  $\alpha,\beta$ -unsaturated acylammonium equivalent, would be a very attractive approach to build molecular complexity rapidly from a single reactive

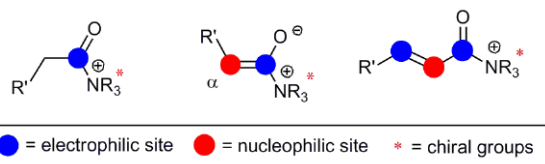


Figure 1

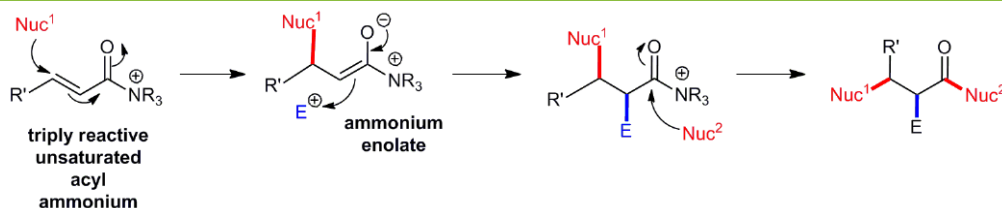


Figure 2

intermediate. Professor Romo explained that little has been done to exploit this concept and that the full potential of forming three bonds by sequentially revealing the unique reactive sites of  $\alpha,\beta$ -unsaturated acylammonium salts had not previously been achieved. He said: “However, Professor Greg Fu (MIT, USA) had demonstrated the potential of this intermediate derived from unsaturated acid fluorides to generate two new bonds (*Chem. Commun.* **2006**, *42*, 2604) and almost simultaneously to our work, Professor Andrew Smith (St. Andrews, UK) had demonstrated the potential for generating two new bonds leading to enol lactones from unsaturated acylammoniums derived from acid anhydrides (*Chem. Sci.* **2013**, *4*, 2193). We targeted the full potential of the triply reactive, unsaturated acylammonium derived from commodity acid chlorides and chiral tertiary amines (Figure 2).”

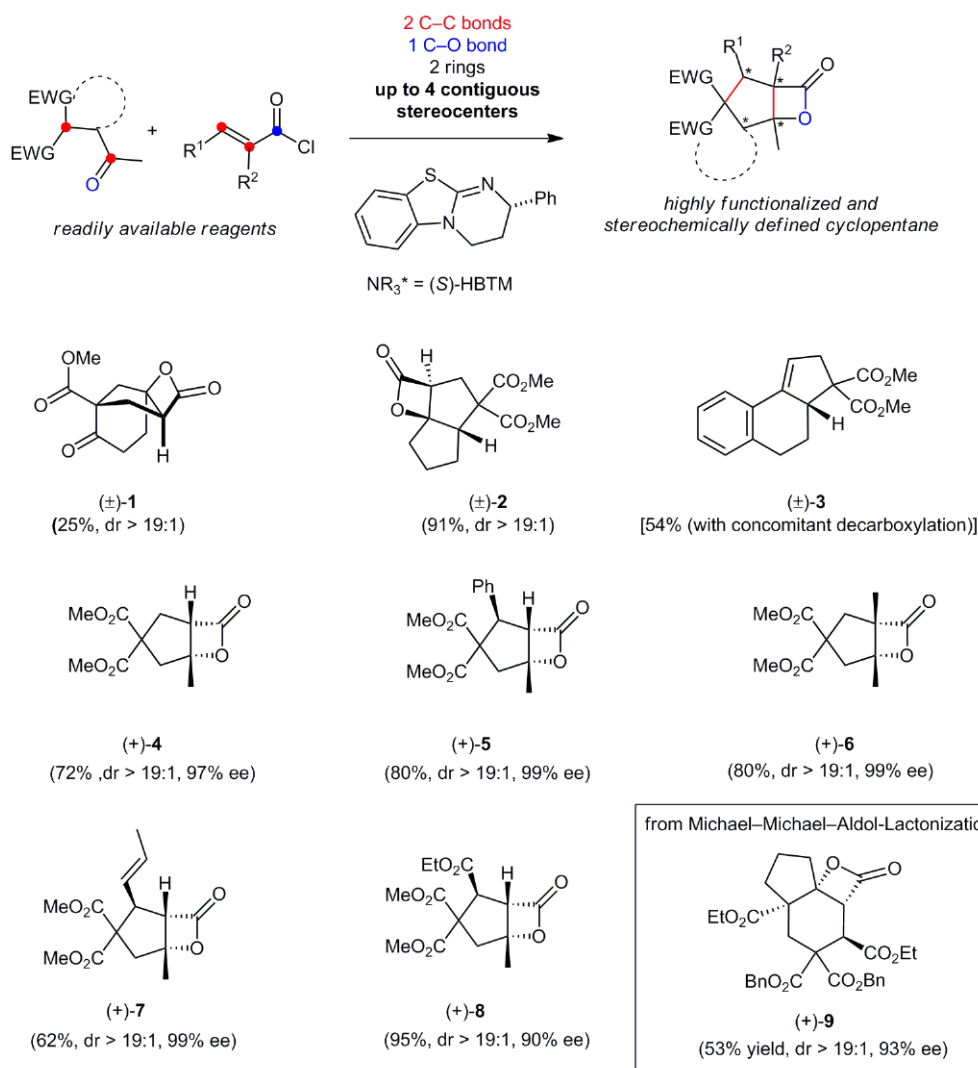
The key to the reaction design was the meticulous selection of suitable nucleophiles and electrophiles that would engage with the three reactive sites of an  $\alpha,\beta$ -unsaturated acylammonium in a chemoselective fashion. “We designed a triply reactive substrate tethering a soft nucleophile, which initiates the tandem process by attacking the  $\beta$ -carbon of the  $\alpha,\beta$ -unsaturated acylammonium, to a ketone group for trapping the resulting ammonium enolate and ensuing acylammonium to form a bicyclic  $\beta$ -lactone,” said Professor Romo.

This strategy proved to be very successful at enabling the construction of two C–C bonds, one C–O bond, two rings and up to three contiguous stereogenic centers, providing rapid access to complex cyclopentanes and cyclohexanes with high levels of relative and absolute stereocontrol employing (*S*)-HBTM as the catalyst (see examples in Scheme 2). “This work demonstrated the power of  $\alpha,\beta$ -unsaturated acylammonium salts for rapid construction of molecular complexity in an asymmetric fashion and in a facile one-pot procedure,” said Professor Romo. “The greater utility of these intermediates was demonstrated by the development of a multi-component Michael–Michael–aldol-lactonization process building from the NCMAL [see Scheme 2, cyclohexane (+)-**9**] providing up to four contiguous stereocenters. Further organocascades can be envisioned and are currently in development

in our laboratory," he concluded. Indeed, another application of these unsaturated acylammonium salts was recently described by the Romo group for the rapid synthesis of several N-heterocycles including several useful intermediates toward

neuroactive drugs or drug candidates (*Angew. Chem. Int. Ed.* **2013**, *52*, 13688).

Matteo Zanda



Scheme 2

*About the authors**G. Liu**Dr. M. E. Shirley**K. N. Van**R. McFarlin**Prof. D. Romo*

## Young Career Focus: Dr. Alexander Breder (Georg-August-Universität Göttingen, 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. Alexander Breder, Georg-August-Universität Göttingen, Germany.

### BIOGRAPHICAL SKETCH



Dr. A. Breder

**Alexander Breder** was born in 1978 in Halle/Westfalen, Germany. He studied chemistry at the Universität Bielefeld (Germany) and received his diploma degree in 2005. Subsequently, he moved to the Swiss Federal Institute of Technology Zurich (ETH), Switzerland, where he joined the group of Professor Erick M. Carreira. During his doctoral studies he worked on the synthesis of oroidin

alkaloids, a bioactive class of marine natural products. In late 2009, Alexander joined the group of Professor Barry M. Trost to pursue postdoctoral studies at Stanford University (USA), where he investigated ruthenium-catalyzed domino and consecutive reactions. Since December 2011, he is an independent research group leader at the Georg-August-Universität Göttingen (Germany). His research interests are located at the interface of synthetic methodology and total synthesis, with a particular emphasis on rational catalyst design, and target-oriented synthesis of biologically relevant molecules.

### INTERVIEW

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

**Dr. Alexander Breder** | One of the key problems we strive to address within our research group is the identification of new, sustainable, and, in part, asymmetric methods for the catalytic oxidative functionalization of simple, non-activated alkenes. In this context, we are interested in a variety of transformations, such as aminations, halogenations, and oxygenation reactions. While there have been outstanding achievements in the realm of transition-metal catalysis throughout the past, cognate procedures on the basis of p-block elements, in particular of chalcogens, have only been exploited to a small extent. Consequently, we are strongly involved in the rational development of novel organochalcogen compounds in order to strategically apply them as redox-active catalysts in alkene functionalization reactions. In so doing, we are not only aiming at broadening the understanding of organochalcogen chemistry but we also seek to provide new synthetic solutions for the rapid construction of molecular complexity derived from simple unsaturated hydrocarbons.

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

**Dr. Alexander Breder** | As an undergraduate student I attended a very impressive lecture on natural product synthesis at the University of Michigan, Ann Arbor, USA. At that very instant I became fascinated by the creative power and pervasive logic inherent to organic synthesis. This fascination was even amplified throughout my graduate studies, as I became more fully aware of the virtues of organic methodology and catalysis. To this day I am enthralled by the fact that we, as scientists, are able to purposefully interconvert matter in order to implement discretionary, macroscopic properties into molecular architectures.

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

**Dr. Alexander Breder** | In my opinion, one of the most critical objectives within modern organic synthesis is the tar-

geted construction of molecular frameworks with simultaneous consideration of all facets of chemical economy and sustainability. This ultimate goal includes not only the development of new, minimally dissipative organic reactions but also the design of novel concepts for the stereo- and/or regioselective manipulation of inert C–H bonds. The latter aspect is of particular importance as it fundamentally influences the way complex molecules can be derived from structurally simple starting materials. In the recent past, there have been numerous landmark achievements in the context of catalytic C–H bond functionalization reactions, which are predominantly facilitated by rare and costly transition metals, such as palladium and ruthenium. In this regard, future endeavors will focus on the identification of more abundant and cost-efficient elements as catalytically active species to enable cognate transformations.

**SYNFORM** | Your research group is active in the area of total synthesis and development of novel synthetic methodology. Could you tell us more about your research and its aims?

**Dr. Alexander Breder** | Throughout the last two years we have been investigating oxidative functionalization reactions, such as allylic and vinylic aminations, halogenations, and oxygenations of simple alkenes using organochalcogen catalysts (chalcogen = S, Se). The central mechanistic aspect of our endeavors towards the design of new synthetic methods is the Lewis base facilitated activation of precursors to formal electrophiles such as halonium or nitrenium ions. Certain sulfur and selenium compounds can efficiently stabilize this type of reactive intermediate, which is key to their controlled conversion with simple alkenes. In this context, we are par-

ticularly interested in the rational development of new chiral organochalcogen catalysts that permit the direct installation of heteroatom-ligated, stereogenic centers into the framework of simple, unsaturated hydrocarbon precursors.

In the course of our investigations we discovered that substoichiometric amounts (5 mol%) of diphenyldiselenide can efficiently catalyze oxidative C(sp<sup>2</sup>)-H amination reactions of cyclic (hetero)alkenes and styrene derivatives using only 1.1 equivalents of *N* fluorobenzenesulfonimide (NFSI) as the terminal oxidant and nitrogen source. Furthermore, we demonstrated that the same catalyst system is suitable for oxidative allylic aminations of acyclic, non-conjugated alkenes. In contrast to cognate palladium-catalyzed reactions, which generally furnish linear allylic amine derivatives, our method permits access to branched products.

In the long term, we aim for the implementation of these catalysis concepts into chemically economic syntheses of biologically relevant natural and anthropogenic compounds. In so doing, we wish to fruitfully combine fundamental organic methodology with pharmacological research.

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

**Dr. Alexander Breder** | I truly hope that it is too early to have a definitive answer to this fundamental question. Nonetheless, I believe that our discoveries on oxidative functionalization reactions of alkenes facilitated by simple and inexpensive chalcogen catalysts will set the stage for a new chapter in organocatalysis. Eventually, however, it will be up to the scientific community to judge upon the contextual impact of our achievements. ■

Matteo Zanda

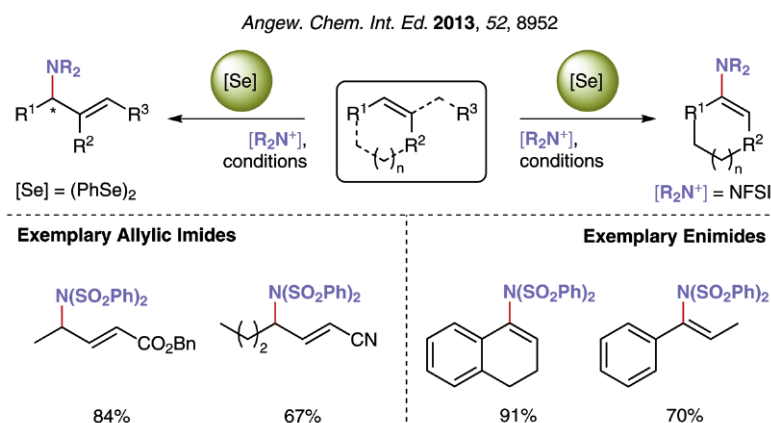


Figure 2

COMING SOON ►► COMING SOON ►►

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is available from April 17, 2014

In the next issues:

## SYNSTORIES ■ ■ ■ ■

■ Nickel-Catalyzed Site-Selective Alkylation of Unactivated C(sp<sup>3</sup>)-H Bonds*(Focus on an article from the current literature)*

## ■ Ascorbic Acid as an Initiator for the Direct C-H Arylation of (Hetero)Arenes with Anilines Nitrosated in situ

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

## ■ Click to Release: Instantaneous Doxorubicin Elimination upon Tetrazine Ligation

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

## FURTHER HIGHLIGHTS + + + +

## SYNTHESIS

## Review on: Asymmetric Cyclopropanation Reactions

*(by R. Dalpozzo et al.)*

## SYNLETT

Account on: Palladium-Catalyzed Decarboxylative Cross-Coupling of  $\alpha$ -Oxocarboxylic Acids and Their Derivatives*(by J. Miao, H. Ge)*

## SYNFACTS

## Synfact of the Month in category "Synthesis of Natural Products and Potential Drugs": Synthesis of Chemokine Receptor Antagonist NIBR-1282

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