

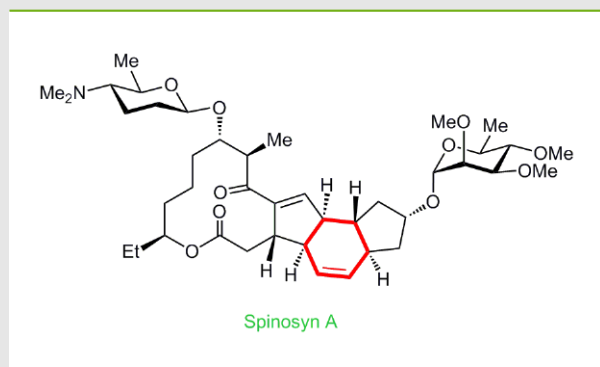
# SYNFORM

People, Trends and Views in Synthetic Organic Chemistry

2011/10

## SYNSTORIES ■ ■ ■ ■

■ **Enzyme-Catalyzed [4+2] Cycloaddition is a Key Step in the Biosynthesis of Spinosyn A**



■ **Copper-Catalyzed Aerobic Oxidation of Hydroxamic Acids Leading to a Mild and Versatile Acylnitroso Ene Reaction**

■ **Pd-Catalyzed Ring-Contraction and Ring-Expansion Reactions of Cyclic Allyl Amines**

**CONTACT ++++**

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Dear readers,

This issue of **SYNFORM** is packed full of great science, as it features three **SYNSTORY** articles covering recent breakthroughs in the area of organic chemistry. The first one tells a fascinating story bridging organic synthesis

with biotechnology that was recently published in a *Nature* paper by the group of Professor H. Liu (USA): the discovery of an enzymatic [4+2] cycloaddition as the key step in the synthesis of spinosyn A, a complex tetracyclic macrocycle with a selective and environmentally benign insect control activity produced by some bacterial organisms. In the second **SYNSTORY**, Professor J. Read de Alaniz (USA) discloses how his group was able to develop a straightforward method to produce highly reactive acylnitroso compounds and use them for an efficient acylnitroso-ene reaction producing allylic hydroxamic acids and oxime derivatives. Last but not least, in the third **SYNSTORY**, Professor A. K. Yudin (Canada) tells us about his recently discovered acid-promoted Pd-catalyzed skeletal rearrangement of cyclic amine substrates producing a ring contraction leading to cyclic allyl amines.

Enjoy your reading!

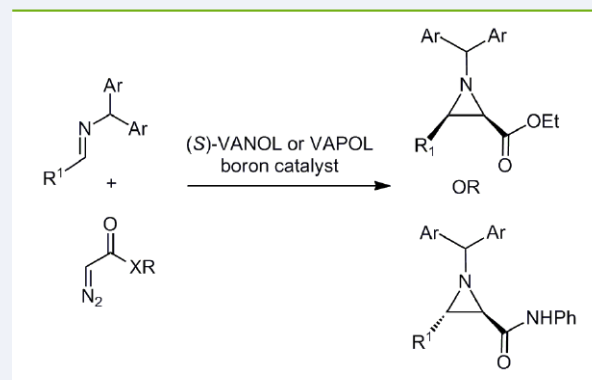
**Matteo Zanda**

Editor of **SYNFORM**

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### CONTACT + + + +

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[Synform@chem.polimi.it](mailto:Synform@chem.polimi.it)

## NEWS AND VIEWS ■ ■ NEWS AND VIEWS ■ ■ NEWS AND VIEWS ■ ■

## Enzyme-Catalyzed [4+2] Cycloaddition is a Key Step in the Biosynthesis of Spinosyn A

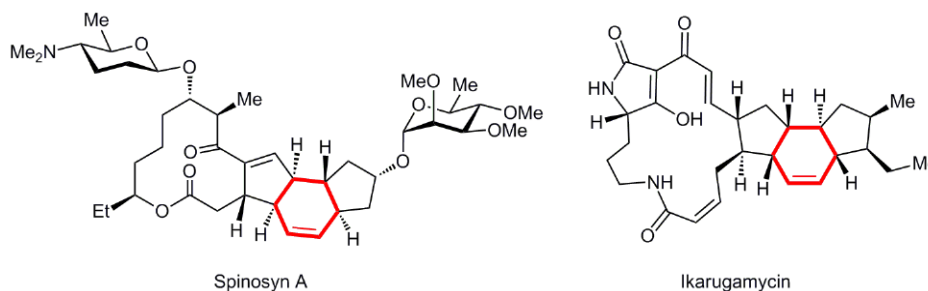
*Nature* **2011**, *473*, 109–112

■ The spinosyns constitute an important class of potent and selective insect control agents featuring a benign environmental profile. From the structural point of view, the spinosyns consist of a macrocyclic core carrying a forosamine residue and a permethylated rhamnose unit. Different total syntheses of spinosyns have been published (see for example: *J. Org. Chem.* **2008**, *73*, 1818 and references therein), but how the tetracyclic macrocycle of the spinosyn A aglycone is biosynthesized by the soil microbe *Saccharopolyspora spinosa* remained essentially obscure and has been the subject of much speculation. Recently, the group of Professor Hung-wen Liu from the University of Texas at Austin (USA) was able to shed light on the spinosyn A aglycone biosynthetic pathway, demonstrating that an enzyme-catalyzed [4+2] cycloaddition is a key step in the process.

According to Professor Liu, his group was initially drawn to the biosynthesis of spinosyn A due to the relatively complex carbon framework it possesses. “As a polyketide natural product, this framework originates through successive Claisen condensations of acyl coenzyme A monomers catalyzed by polyketide synthases (PKS),” he explained. “However, at some point a series of intramolecular C–C bond-formation events must occur in order to generate the unique tetracyclic architecture of the final aglycone in which a 12-membered lactone ring is fused with a perhydro-*as*-indacene moiety.” According to Professor Liu, this type of complex bond rearrangement of a carbon backbone is most commonly associated with terpene biosynthesis. However, the polyketide

rather than isoprene nature of spinosyn A suggested that a new type of chemistry, at least with respect to biochemical transformations, might be involved. “Of particular interest is the presence of a cyclohexene ring at the aglycone core suggestive of a [4+2] cycloaddition reaction and the possible involvement of Diels–Alder chemistry,” he said.

“Our investigation began with the identification of four genes from the spinosyn A biosynthetic gene cluster that were believed to be likely responsible for the cyclization events”,<sup>1</sup> said Professor Liu. However, these genes, *spnF*, *spnJ*, *spnL* and *spnM*, had been annotated according to bioinformatic surveys with functions that did not appear to be consistent with the type of chemical transformations expected for the post-PKS tailoring reactions of the aglycone. It was therefore necessary to verify the intermediacy of a monocyclic macro-lactone product (**1**) of the PKS reactions and characterize the activity of the identified gene products *in vitro*. “A combined multidisciplinary approach involving organic synthesis, molecular biology and enzymology helmed by a very talented graduate student in our group, Hak Joong Kim, was recognized as the only way in which to do so successfully,” continued Professor Liu. “This effort led to the identification of the precursor to the cyclization events (**2**) and characterization of the *spnJ* gene product as a flavin-dependent dehydrogenase, responsible for oxidizing the hydroxy group at the C-15 position to the ketone of the final product.<sup>2</sup> SpnJ was thus considered to catalyze the first modification of **1** and set the stage for subsequent cyclization reactions.”



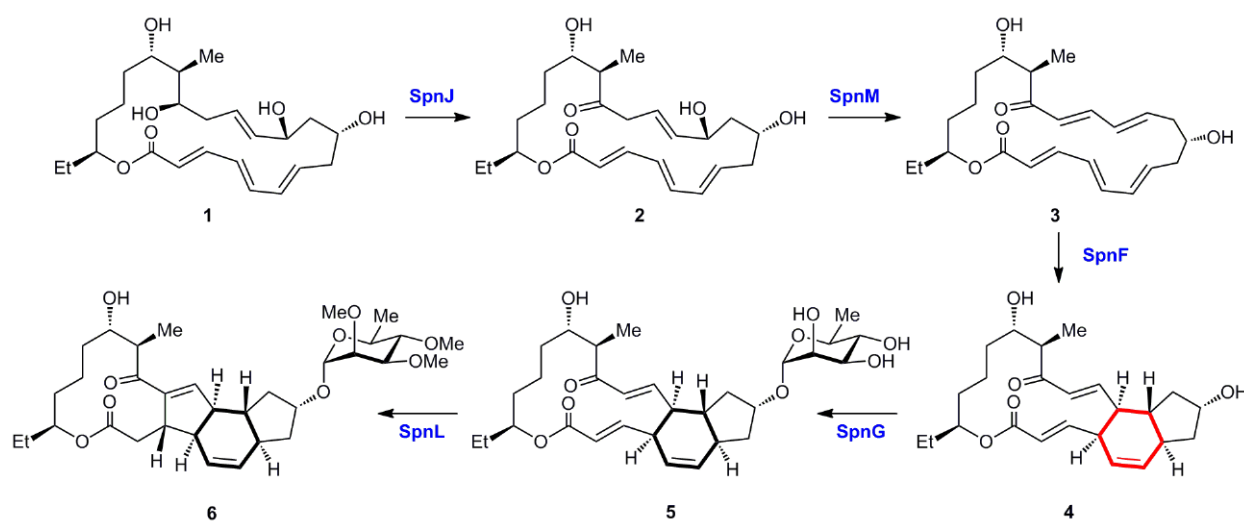
Professor Liu recalled that the progress with the remaining three genes, *spnF*, *spnL*, and *spnM*, was initially slowed since the corresponding gene products either showed no apparent activity with the SpnJ reaction product or simply could not be expressed in a soluble form. “Our first real breakthrough was thus the realization that the annotated *spnM* gene had overlooked a second start codon approximately 200 base pairs upstream of that previously assigned,” revealed Professor Liu. “Expression of the new open reading frame succeeded in producing SpnM in soluble form, and the resulting SpnM was shown to be capable of catalyzing a 1,4-dehydration of the 11-OH group to produce a conjugated  $\pi$ -system in the product **3**, extending from C-11 to the C-15 carbonyl opposite that extending from the C-1 ester moiety to C-7.” The researchers also noticed that the SpnM dehydration product underwent a [4+2] cycloaddition to generate a tricyclic product (**4**) containing the cyclohexene moiety that had initially drawn their interest. “This observation appeared to suggest that biosynthesis of the cyclohexene ring is largely a non-enzymatic event since the rate of cyclization as opposed to dehydration was independent of the SpnM concentration,” said Professor Liu.

“At this point, we felt that we understood the pathway up to the tricyclic lactone and turned our attention to formation of the final C–C bond between C-3 and C-14. We believed that this was logically the next biosynthetic event, because it had been reported by Chiu and co-workers that the rhamnosyl transferase, SpnG, accepted the tetracyclic aglycone as a substrate,”<sup>3</sup> he continued. “Therefore, we began looking into end point assays in which SpnM and its substrate were mixed with either SpnL or SpnF; however, we observed neither the anticipated

tetracyclic core, nor any other new species for that matter.” What Professor Liu and his co-workers observed instead was a more rapid consumption of the SpnM 1,4-dehydration product in the presence of SpnF. “This was subsequently confirmed with more careful kinetic experiments showing that the rate of cyclization in the SpnF active site is approximately 500 times faster than when free in solution,” he said.

As a free enzyme whose only function appears to be the acceleration of a [4+2] cycloaddition, SpnF became the key result and focal point of the biosynthetic investigation carried out by the Texas researchers. “Though several other enzymes had been proposed to catalyze analogous reactions, they are multifunctional, and it has been difficult to specifically discriminate the respective cyclization reaction from their other activities,” explained Professor Liu. “Nevertheless, we should emphasize that the chemical mechanism of the SpnF reaction has yet to be firmly established, that means we still don’t know if it is indeed a *bona fide* ‘Diels–Alderase.’” Before such a distinction can be made, it will be necessary to show that cyclization proceeds through a single pericyclic transition state rather than a series of dipolar or zwitterionic intermediates,” he reckoned. A separate but related question that was also of interest is how exactly the enzyme is able to accelerate the reaction, whether it be concerted or stepwise. “These and other hypotheses are very much of interest to us, and we are looking into ways of testing them,” confirmed Professor Liu.

“Despite our identification of SpnF as what appeared to be a dedicated cyclase, relatively little additional insight was obtained into how the spinosyn A biosynthetic process is to proceed from the tricyclic intermediate,” he continued. “What



we did know, however, was that glycosyl transferases tended to show considerable promiscuity with respect to their substrates.”<sup>4,5</sup> For this reason, Professor Liu and co-workers considered the possibility that SpnG is able to accept both the tricyclic (**4**) as well as the tetracyclic aglycone cores as substrates with only the former being biosynthetically relevant. “This indeed turned out to be the case and led to the finding that the enzyme, SpnL, is responsible for catalyzing the final C–C bond formation in the rhamnosylated tricyclic intermediate (**5**),” he said.

Professor Liu commented that while the SpnF reaction was certainly the key discovery, the SpnL reaction was also of some interest in its own right, as it is reminiscent of an intramolecular Rauhut–Currier reaction. “In these types of transformations an  $\alpha,\beta$ -unsaturated ketone is converted into an enolate through conjugate addition of a nucleophile, whereby the resulting enolate reacts with a second Michael acceptor to create a new C–C bond,” he explained. “To the best of our knowledge, such chemistry is biochemically unprecedented, and confirmation of the proposed Rauhut–Currier mechanism would further expand the mechanistic repertoire of enzyme catalysis.” According to Professor Liu, the essential feature of the proposed mechanism is covalent catalysis to generate the latent enolate. “Hence, identification of a nucleophile, whether it is an amino acid residue of SpnL such as a cysteinyl or an external nucleophile such as glutathione, will be crucial to understanding the chemistry of SpnL catalysis,” he said.

A further element of interest in this research is that in addition to the uncertainty surrounding the detailed mechanisms of SpnF and SpnL, questions have also been raised as to whether similar chemistry is to be expected in other biosyn-

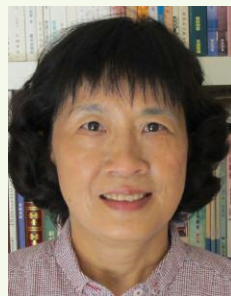
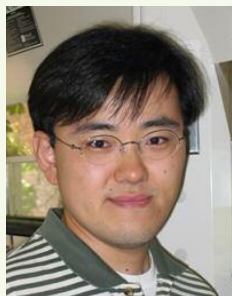
thetic systems. “There are several other natural products structurally related to spinosyn A, and the polyketide natural product ikarugamycin, in fact, also possesses the *as*-indacene moiety,” said Professor Liu. “We plan to identify the biosynthetic gene clusters for these molecules, and we expect the information obtained from the sequence and chemical analyses of SpnF and SpnL to aid in the discovery and characterization of additional enzymes involved in the biosynthesis of complex carbocyclic systems. Furthermore, as the substrate specificity of the enzymes responsible for spinosyn A core maturation is better understood, this information may become useful not only for generating more potent analogues of the parent compound, but also for engineering novel chemical scaffolds through combinatorial biochemical methods,” he concluded. ■

Matteo Zanda

## REFERENCES

- (1) C. Waldron, P. Matsushima, P. R. Rosteck Jr., M. C. Broughton, J. Turner, K. Madduri, K. P. Crawford, D. J. Merlo, R. H. Baltz *Chem. Biol.* **2001**, *8*, 487.
- (2) H. J. Kim, R. Pongdee, Q. Wu, L. Hong, H.-w. Liu *J. Am. Chem. Soc.* **2007**, *129*, 14582.
- (3) Y.-L. Chen, Y.-H. Chen, Y.-C. Lin, K.-C. Tsai, H.-T. Chiu *J. Biol. Chem.* **2009**, *284*, 7352.
- (4) C. J. Thibodeaux, C. E. Melançon III, H.-w. Liu *Angew. Chem. Int. Ed.* **2008**, *47*, 9814.
- (5) C. J. Thibodeaux, C. E. Melançon, H.-w. Liu *Nature* **2007**, *446*, 1008.

## About the authors



From left: Dr. H. J. Kim, Dr. M. Ruszczycky, S.-h. Choi, Dr. Y.-n. Liu, Prof. H.-w. Liu

## Copper-Catalyzed Aerobic Oxidation of Hydroxamic Acids Leading to a Mild and Versatile Acylnitroso Ene Reaction

*J. Am. Chem. Soc.* **2011**, *133*, 10430–10433

■ Acylnitroso compounds [RC(O)–N=O] are very reactive electrophiles that have mainly been employed as dienophiles in hetero-Diels–Alder reactions, whereas much less is known about the acylnitroso-ene reaction which can be used to produce allylic hydroxamic acids and oxime derivatives. Recently, the group of Professor Javier Read de Alaniz from the University of California, Santa Barbara (USA) devised a novel synthetic strategy to produce acylnitroso compounds from hydroxamic acids and to use them in an efficient and mild ene reaction.

“Our research group is interested in developing new reactions with an electrophilic source of nitrogen,” said Professor Read de Alaniz. “Specifically, we are interested in understanding and utilizing acylnitroso compounds as the electrophilic nitrogen synthon. We began this program in the fall of 2009 with two first-year graduate students, Charles Frazier and Jarred Engelking.” Professor Read de Alaniz explained that acylnitroso intermediates are exceptionally reactive electrophiles with a rich history in the hetero-Diels–Alder reaction. “We felt they were underutilized for the general construction of carbon–nitrogen bonds, despite their potential,” he confirmed. Due to their high reactivity, acylnitroso intermediates can only be generated in situ and are conveniently obtained from the oxidation of hydroxamic acid derivatives using ‘harsh’ oxidants. “A possible reason for the slow advance of the acylnitroso chemistry has been an inability to identify a general and practical oxidant,” said Professor Read de Alaniz. With the aim of developing acylnitroso chemistry beyond the synthetically useful Diels–Alder reaction, the UCSB researchers sought to uncover a mild, chemoselective oxidation protocol that would enable acylnitroso compounds to be generated in situ from the corresponding hydroxamic acid and that would thus circumvent typical problems associated with their use.

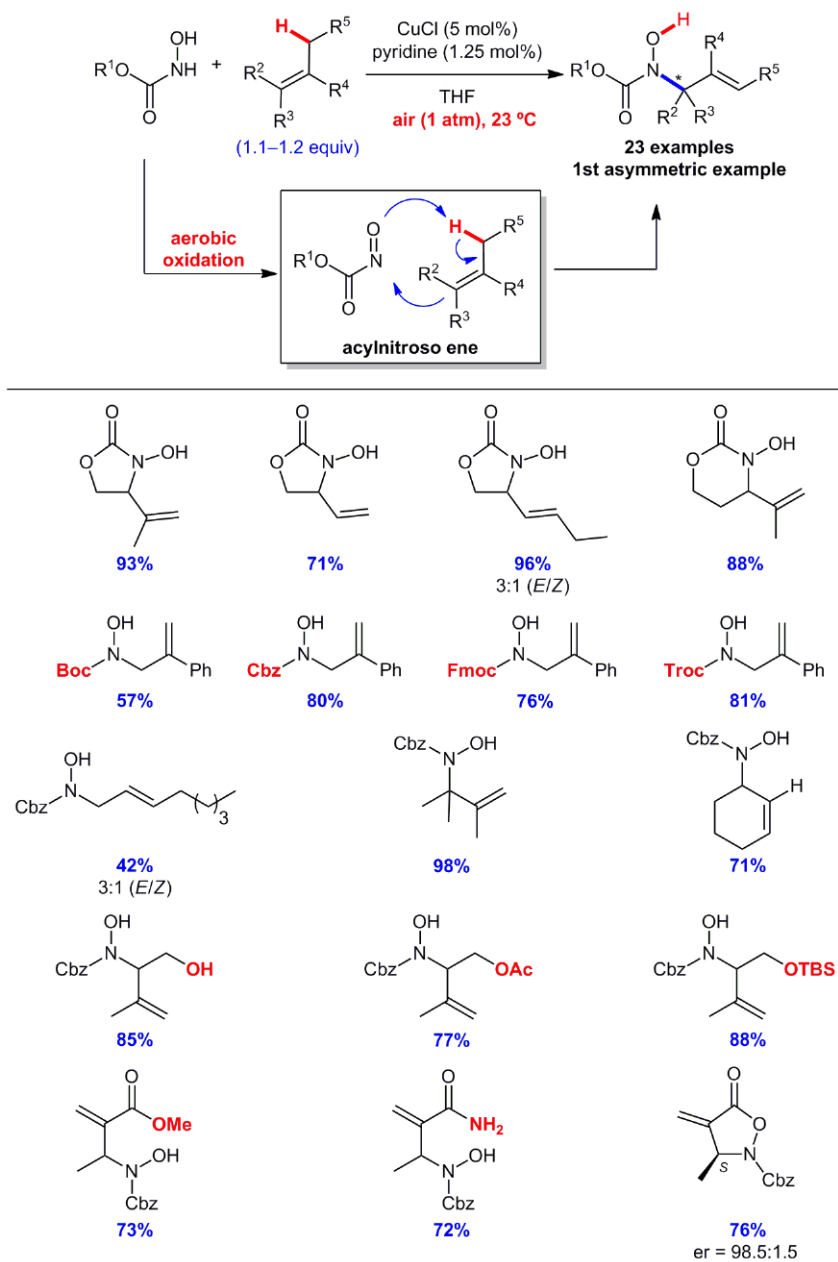
“As a starting point, we decided to focus on the previously developed acylnitroso-ene reaction because the initially formed hydroxylamine-ene products were known to be susceptible to decomposition pathways caused by the oxidant,” recalled Professor Read de Alaniz. “Thus, we felt that this would be an ideal platform to identify the ‘mild’ oxidation conditions we desired. From the onset, this project was inspired by the work of Whiting, Iwasa, and Shea,” he acknowledged. “Their work led us to focus on using metal-oxo com-

plexes to oxidize the acylnitroso precursors, but the use of stoichiometric peroxides as the terminal oxidant proved problematic and high yields were substrate-dependent. It was clear at this stage that we needed to identify a new oxidant.”

“From the beginning, we were interested in using air as the terminal oxidant because it is green, mild and readily available, but identifying the optimal aerobic oxidation conditions required a bit of luck and good attention to detail, as is often the case,” continued Professor Read de Alaniz. “The second experiment that Charles set up as a graduate student utilized air as the terminal oxidant in refluxing THF. Unfortunately, he only isolated 8% of the desired acylnitroso-ene product from a complex reaction mixture, but he noticed that all the starting material was consumed during the reaction,” he revealed. “He speculated that the highly reactive acylnitroso intermediate was being generated but decomposed under the reaction conditions. Investigating this observation further, he discovered that heat was detrimental,” said Professor Read de Alaniz. The acylnitroso-ene product could be isolated in >70% yield if the reaction was conducted at ambient temperature; however, the reaction took more than 48 hours to complete. “Equally fortunate was an observation made by Jarred that the rate of the acylnitroso-ene reaction under the aerobic oxidative conditions varied depending on the batch of carbobenzyloxy (Cbz)-protected hydroxylamine used,” he continued. It was subsequently discovered that a trace amount of pyridine was responsible for the rate enhancement because excess pyridine was initially used for the synthesis of the Cbz-protected hydroxylamine starting material. “We quickly leveraged these key observations and developed a mild and versatile acylnitroso-ene reaction using a copper-catalyzed aerobic oxidation of hydroxamic acids with a pyridine additive,” said Professor Read de Alaniz, who added that the new strategy is operationally simple and provides a practical solution for the acylnitroso-ene reaction. “Importantly, reagent-grade solvents and cheap, commercially available copper(I) chloride can be used, and since air is the terminal oxidant, water is the only by-product,” he said. “In addition, the mild reaction conditions enabled the first asymmetric acylnitroso-ene reaction using a traceless chiral auxiliary.”

Professor Read de Alaniz explained that Professors Shea and Whiting simultaneously reported a similar copper(II)-



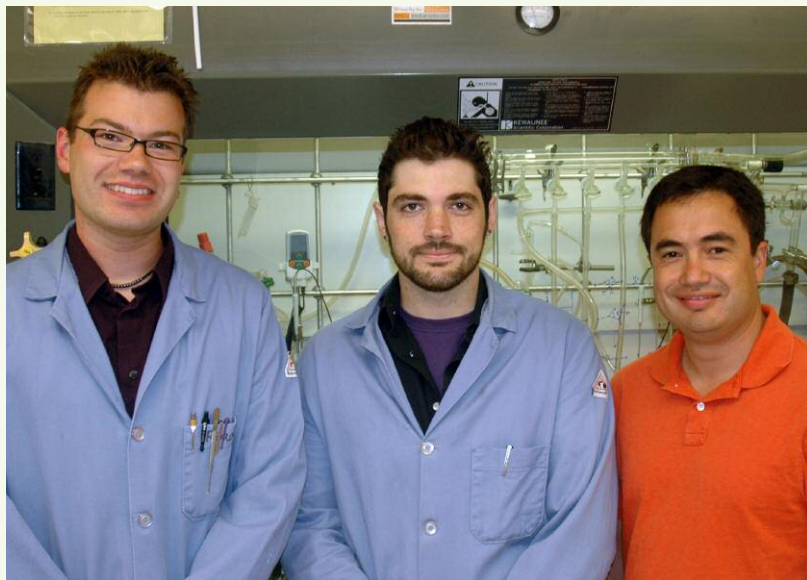


catalyzed aerobic oxidation of hydroxamic acids to acylnitroso intermediates and their Diels–Alder trapping (*Org. Lett.* **2011**, *13*, 3442).

“Currently, we are working on gaining a better understanding of the mechanism, as well as on developing a catalytic asymmetric variant and expanding the acylnitroso chemistry

as a whole. We believe the newly developed copper-catalyzed aerobic oxidation of hydroxamic acids will allow for future advances in acylnitroso chemistry,” Professor Read de Alaniz concluded. ■

Matteo Zanda

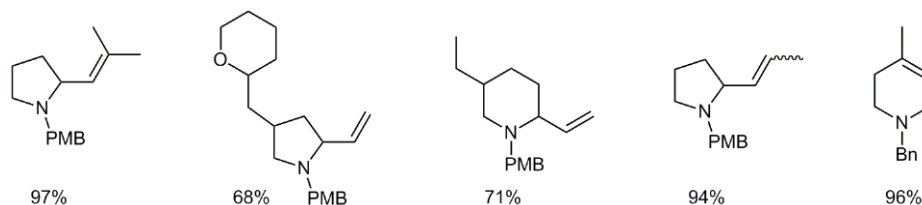
*About the authors*

*From left: J. Engelking, C. Frazier, Prof. J. Read de Alaniz*



## Pd-Catalyzed Ring-Contraction and Ring-Expansion Reactions of Cyclic Allyl Amines

*Angew Chem. Int. Ed.* **2011**, *50*, 5924–5926



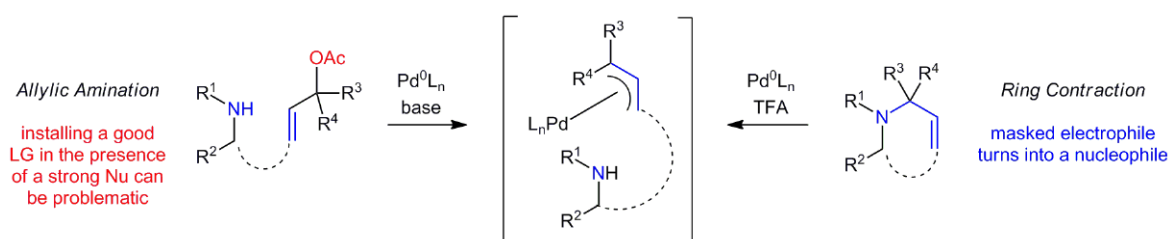
Some of the cyclic allyl amines obtained via Pd-catalyzed ring contraction

Cyclic allyl amines are privileged structural scaffolds in bioactive molecules and for this reason they represent important targets in organic synthesis. A number of methods are available for the synthesis of cyclic allyl amines, including ring-closing metathesis, which is probably the most direct and versatile approach to these compounds. However, the search for new strategies continues and drives the discovery of novel applications and functional structural frameworks containing the cyclic allyl amine templates. A novel promising methodology based on an acid-promoted Pd-catalyzed ring contraction of larger cyclic amines was recently published by the group of Professor Andrei K. Yudin from the University of Toronto (Canada). The reaction holds promise for finding applications in the total synthesis of natural compounds because of the interesting retrosynthetic disconnections that are made possible by the skeletal rearrangement of the starting cyclic amine substrates.

“This project was started by Igor Dubovyk, who was previously working on palladium-catalyzed regioselective allylic amination,” said Professor Yudin. “In his earlier work, Igor

developed a system where the branched regiochemistry of the resulting allyl amine was dictated by how well the resulting acid formation was being suppressed by the exogenous base (*J. Am. Chem. Soc.* **2007**, *129*, 14172). According to Professor Yudin, in the absence of base, the linear allyl amine was forming as a result of an acid-promoted palladium-catalyzed isomerization. “Later, instead of suppressing this isomerization, we set out to turn it into a useful process for the synthesis of substituted saturated heterocycles,” he continued. “This methodology now allows for the preparation of a wide range of heterocycles.” Professor Yudin told *SYNFORM* that Dmitry Pichugin later joined the group as an undergraduate research assistant and helped with the preparation of substrates.

“The advantage of this method over the classical intramolecular allylic amination is that there is no need to install a leaving group in a substrate that contains an amine nucleophile within its scaffold,” explained Professor Yudin. “Instead, the leaving group can be generated in situ by the protonation of the tertiary amine, which, subsequently, becomes a nucleophile and closes the ring by attacking the  $\pi$ -allyl Pd complex.”

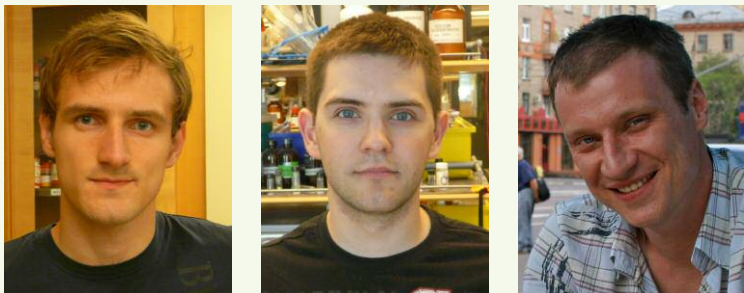


Complementarity of the novel synthetic methodology with the Pd-catalyzed allylic amination

“We discovered that the highest yields were obtained in the presence of both trifluoroacetic acid and either morpholine or *N*-methylmorpholine, which led us to believe that morpholinium trifluoroacetate was the active acid,” he said. “This approach significantly simplifies strategic planning by avoiding the issue of functional group incompatibility, especially if our methodology is used in multistep syntheses. We are now particularly encouraged about the prospects of using this reaction in syntheses employing non-obvious disconnections that involve allyl amine hydrogenation as the first retrosynthetic step,” concluded Professor Yudin. ■

*Matteo Zanda*

#### About the authors



From left: I. Dubovyk, D. Pichugin, Prof. A. K. Yudin

COMING SOON ►► COMING SOON ►►

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In the next issues:

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(Focus on an article from the current literature)

■ **sp<sup>3</sup>-C–H Bond Activation with Ruthenium(II) Catalysts and C(3)-Alkylation of Cyclic Amines**  
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■ **Highly Diastereoselective and Enantioselective Synthesis of  $\alpha$ -Hydroxy  $\beta$ -Amino Acid Derivatives**  
(Focus on an article from the current literature)

■ **Dr. Tanja Gaich (Leibniz University of Hannover, Germany)**  
(Young Career Focus)

### FURTHER HIGHLIGHTS + + + +

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(by Y. Nakao)

#### SYNLETT

**Account on: Adventures in Total Synthesis: A Personal Account**  
(by D. Y.-K. Chen)

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**Synfact of the Month in category “Polymer-Supported Synthesis”:** [Cycloaddition of Tetramethyldisiloxane to Alkynes with \[Au\]/TiO<sub>2</sub>](#)

### 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  
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