

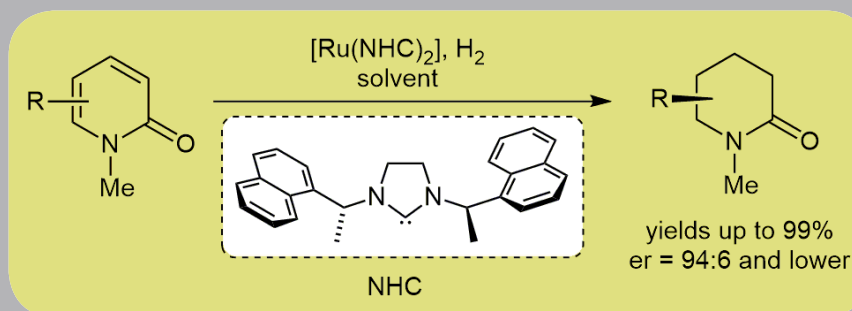
Synform

People, Trends and Views in Chemical Synthesis

2016/05

SYNLETT Best Paper Award 2015: Asymmetric Homogeneous Hydrogenation of 2-Pyridones

Highlighted article by J. Wysocki, C. Schlepphorst,
F. Glorius



Contact

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Dear Readers,

This May 2016 issue of SYNFORM opens with an interview to Professor Frank Glorius (Germany) who is the winner of the first SYNLETT Best Paper Award. The 2015 winner received € 3000 and a framed certificate, which are obviously negligible achievements compared to the honor of being featured in SYNFORM! I have to admit that I am a bit jealous of Professor Glorius and I promised to myself that this year I will submit more and better manuscripts to try to secure either the SYNLETT or SYNTHESIS Best Paper Award 2016! Quoting the SYNLETT Editor-in-Chief – Professor Ben List – Glorius' winning article “stands for what we expect from the best SYNLETT papers: To provide an original solution to a significant synthetic problem. The work of the Glorius team represents a new approach to the asymmetric hydrogenation of 2-pyridones and provides an elegant access to enantiopure 2-piperidones.” So the competition for the next year's Award is open and I am pretty sure that the bar will be even higher in 2016. The second article is a Young Career Profile interview with M. Gulías (Spain) who tells us about his research plans and ideas. The third story of this issue comes from the big pharma and specifically from A. Tsai (Pfizer, USA) who guides us through his recent one-step, efficient and simple method for achieving the synthesis of sulfonamides from *N*-tosylhydrazones. The issue is completed by a report on the elegant total synthesis of racemic alstoscholarisine A developed by F. Bihelovic and Z. Ferjancic (Serbia).

Enjoy your reading!



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If you have any questions or wish to send feedback, please write to Matteo Zanda at: synform@outlook.com

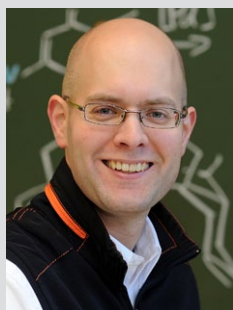
SYNLETT Best Paper Award 2015: Asymmetric Homogeneous Hydrogenation of 2-Pyridones

Synlett 2015, 26, 1557–1562

Background and Purpose. Thieme Chemistry and the Editors of SYNLETT and SYNTHESIS present the ‘SYNTHESIS/SYNLETT Best Paper Awards’. These annual awards honor the authors of the best original research papers in each of the journals, considering their immediate impact on the field of chemical synthesis. Frank Glorius and his co-workers from the University of Münster (Germany) have won the inaugural SYNLETT Best Paper Award for the year 2015. The authors are honored for their work on the asymmetric homogeneous hydrogenation of 2-pyridones. Benjamin List, Editor-in-Chief of SYNLETT, praised the paper as a publication that “stands for what we expect from the best SYNLETT papers: To provide an original solution to a significant synthetic problem. The work of the Glorius team represents a new approach to the asymmetric hydrogenation of 2-pyridones and provides an elegant access to enantiopure 2-piperidones.”

SYNFORM talked to Frank Glorius who was happy to share some background information regarding the prize-winning paper as well as his current research activities.

Biographical Sketch



Prof. F. Glorius

Frank Glorius was born in Germany in 1972 and educated in chemistry at the Universität Hannover (Germany), at Stanford University (USA) with Professor Paul A. Wender, at the Max-Planck-Institut für Kohlenforschung (Mülheim/Ruhr, Germany) and the Universität Basel (Switzerland) with Professor Andreas Pfaltz, and at Harvard University (USA) with Professor David A. Evans. In 2001, he began his independent research career at the Max-Planck-Institut für Kohlenforschung and in 2004 was promoted to Associate Professor for Organic Chemistry at the Philipps-Universität Marburg (Germany). Since 2007, he has been Full Professor at the Westfälische Wilhelms-Universität Münster. His research program focuses on the development of new concepts for catalysis and their implementation in organic synthesis. The group is especially interested in the chemistry of N-heterocyclic carbenes (NHCs), C–H activation, asymmetric arene hydrogenation, (asymmetric) NHC organocatalysis, photoredox catalysis, heterogeneous catalysis with common and with tailor-made, surface-modified nanoparticles, and the

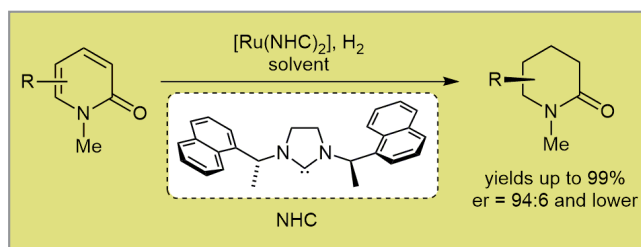
development of useful screening methodology. This work was acknowledged by a couple of distinguished awards, such as the OMCOS award, the Leibniz Award of the DFG (highest German research award), an ERC grant and the 2014 and 2015 Thomson Reuters Highly Cited Researcher acknowledgment.

INTERVIEW

SYNFORM Could you highlight the value of your award-winning paper with respect to the state-of-the-art, potential or actual applications, and explain the origin, motivations and strategy used for conducting the research?

Prof. F. Glorius Asymmetric transition-metal-catalyzed hydrogenation is a very attractive tool to produce enantiomerically pure organic molecules and, actually, in 2001 the Nobel Prize was given in part for this (to Ryoji Noyori and the late Robert Knowles). However, one great challenge remains: the efficient asymmetric hydrogenation of aromatic and heteroaromatic substrates. This kind of transformation would convert flat molecules into three-dimensional ones, a direction pharma industry would like to go with their drug candidates.

In recent years, several research groups around the world have contributed to this challenging transformation and great progress has been made. Still, the scope and efficiency of these transformations generally remain quite limited. In 2011, we were fortunate to develop a ruthenium–NHC based catalyst system that has proved to be a privileged system. Several different classes of heteroarenes could be successfully reduced, such as benzofurans, thiophenes, chromones and indolizines. In the SYNLETT paper highlighted here, we reported our results on the asymmetric hydrogenation of 2-pyridones, nice precursors towards piperidine product motifs (2-piperidones, specifically). But to be fair, many things still need to be improved and we feel that a deeper understanding of the catalyst system would be the ideal next step. We hope that this work will inspire other groups and especially the younger generation to address this long-standing synthetic challenge.

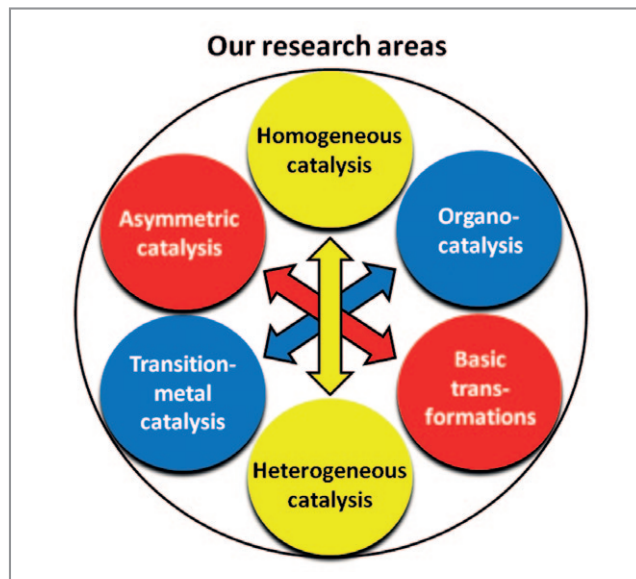


SYNFORM What is the focus of your current research activity, both related to the award paper and in general?

Prof. F. Glorius Characteristic for the Glorius group is the broad range of topics within the field of catalysis (see image below). In terms of this kind of hydrogenation technology, we try to elucidate the structure and mode of action of the active catalyst – a truly challenging endeavor. In addition, the group is also very active in other fields of NHC catalysis, including organocatalysis and the use of NHCs for the modification of catalytically active metal nanoparticle surfaces. Moreover, we also have very active research programs on C–H activation chemistry [utilizing Rh(III) and Co(III) catalysts] and photocatalysis, especially cooperative systems. Finally, we also try to develop smart screening technologies, beneficial for many different fields.

SYNFORM What do you think about the modern role, major challenges and prospects of organic synthesis?

Prof. F. Glorius The field of organic chemistry is up and running. We can be proud of the many achievements of the past, but I also project a glorious future, since (organic) chem-



istry is the central science! But I am very critical of the increasing pressure from politicians and society (maybe also by fellow scientists?) to do 'something useful', pushing scientists more towards applied research. Don't get me wrong, applied research is extremely important and has its place, but we have to leave room for exploratory, basic research. Freedom of scientists is so important, because we are at our best when we can do what we want. Wherever I can, I try to advertise for freedom in science/chemistry, because I am convinced that this will lead to truly spectacular breakthroughs and game-changing developments.

Mattias Forkle



The Glorius Group *Left:* official group photo. “Everyone is alert and looks strong: strong individual scientists enjoying freedom of research,” commented Professor Glorius.” *Right:* Photo taken during the preparation for the official photo. “It is spontaneous, a serendipitous photo. It represents the interaction between the group members,” said Professor Glorius, who concluded: “The two photos displayed sequentially give you the impression of a movie. I like this combination very much. The interplay between freedom and interaction is something I am advocating for and I try to bring it to life in my group.”

Young Career Focus: Professor Moisés Gulías (Universidade de Santiago de Compostela, Spain)

Background and Purpose. SYNFORM regularly meets 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 Young Career Focus presents Professor Moisés Gulías (Universidade de Santiago de Compostela, Spain).

Biographical Sketch



Prof. M. Gulías

Moisés Gulías was raised in Pontevedra, Galicia, a small town located on the northwest coast of Spain. He studied chemistry at the Universidade de Santiago de Compostela (Spain), where he also obtained his PhD in 2006 under the supervision of Professor Mascareñas. During his PhD he completed a pre-doctoral stay at Stanford University (USA) with Professor Barry Trost. He was a Marie-Curie postdoctoral fellow during 2007–2009 in the research group of Professor Matthew J. Gaunt at the University of Cambridge (UK). In 2010, he obtained a Parga Pondal position at the Universidade de Santiago de Compostela and in 2016 he was promoted to Assistant Professor. He has received the Sigma-Aldrich prize by the Spanish Royal Society of Chemistry (RSEQ) and the Thieme Chemistry Journals Award in 2015. For details about his independent research, please see: <http://gulias-group.com/>.

INTERVIEW

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

Prof. M. Gulías Enhancing the efficiency of assembling relatively complex organic products from simple and non-expensive precursors constitutes one of the most exciting challenges for a synthetic chemist. Within this objective, our research program is dedicated to the development of new metal-catalyzed reactions involving the activation of C–H bonds that result in rapid increases in molecular and/or stereochemical complexity and match the requirements of atom economy, selectivity and minimization of chemical waste.

SYNFORM *When did you get interested in synthesis?*

Prof. M. Gulías I have been always very passionate about learning new things, which causes me to have a wide range of interests. Science has always interested me, and chemistry in particular was my favorite subject as far back as I can remember. I really liked how chemistry allowed scientists to become molecular architects, so I chose to study chemistry at university. Later, I became fascinated by the ability of metal complexes to carry out unique transformations, so I pursued my PhD in this field.

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

Prof. M. Gulías Organic synthesis remains central to the advancement of science and improvements in quality of life since it provides an ideal platform for progress in other sciences and for fostering new technological applications. On one hand, organic synthesis plays an important role in the progress of many other areas of science such as biochemistry, medicine, materials science, agriculture, petrol chemistry...

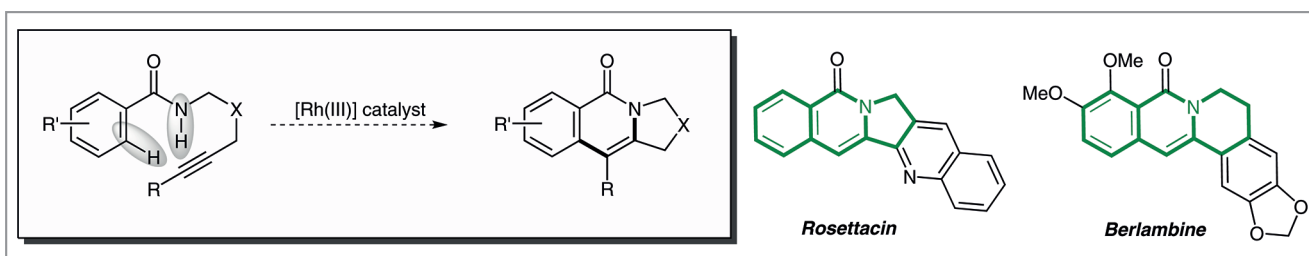
and I think this connection of organic chemistry with the other sciences is a trend that will be increasing in the future. On the other hand, the role of organic synthesis remains the same as always, as a tool for constructing designed molecular structures that modify biological processes and provide new therapeutic opportunities. This is of vital importance since it is among those scientific activities that organic synthesis can have major long-term benefits for humanity.

SYNFORM *Your research group is active in the field of metal catalysis. Could you tell us more about your research and its aims?*

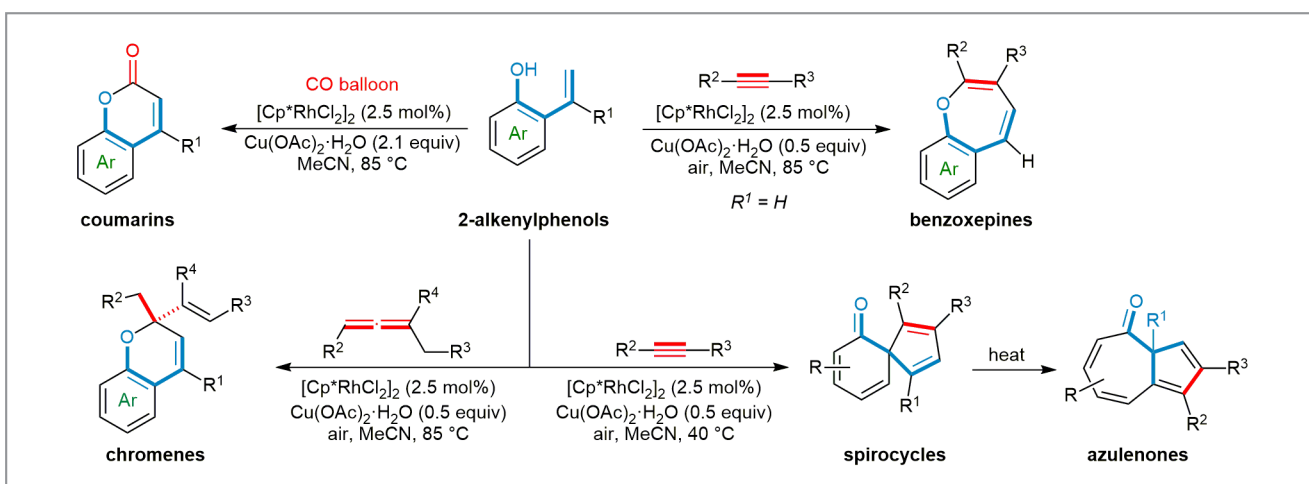
Prof. M. Gulías As I have mentioned before, we seek to transform simple molecules into complex products by the functionalization of C–H bonds with metal catalysts. While most of the C–H functionalization is related to cross-coupling transformations, our group works in the development of new types of cycloadditions which involve the cleavage of C–H bonds in order to form cyclic systems from otherwise unreactive acyclic precursors.

For instance, we have shown how benzamides can react intramolecularly with alkynes, leading to the formation of tricyclic isoquinolinic structures which form the core of many bioactive molecules (see Scheme 1).¹ We also have shown how 2-alkenylphenols – which are prepared in one step from commercially available compounds – can be transformed into a variety of interesting cyclic structures (Scheme 2). Thus, Rh(III) complexes catalyze the reaction of these substrates with alkynes, leading to benzoxepines² or spirocycles³ – which rearrange into azulenones by simple heating – under mild conditions. The 2-alkenylphenols can also react with carbon monoxide to produce very appealing coumarin products,² while reaction with allenes leads to the formation of chromene products which are heterocycles present in many bioactive molecules.⁴

Lately we have also been working on the development of asymmetric reactions involving C–H bond activations. Another important aim in our group is to deepen the understanding of the mechanism of these transformations, so we like to go through both complex mechanistic experiments and DFT calculations.



Scheme 1 Rh(III)-catalyzed intramolecular annulation between benzamides and alkynes



Scheme 2 Rh(III)-catalyzed intermolecular annulations of 2-alkenylphenols

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

Prof. M. Gulías My independent career is just starting, so the list of achievements of our group is still short. We like to think that our best work is yet to come. However, our work in the Rh(III)-catalyzed annulation of 2-alkenylphenols with alkynes is the one I am most proud of because it allowed our group to be considered an actor in the field, and helped us to get some recognition.



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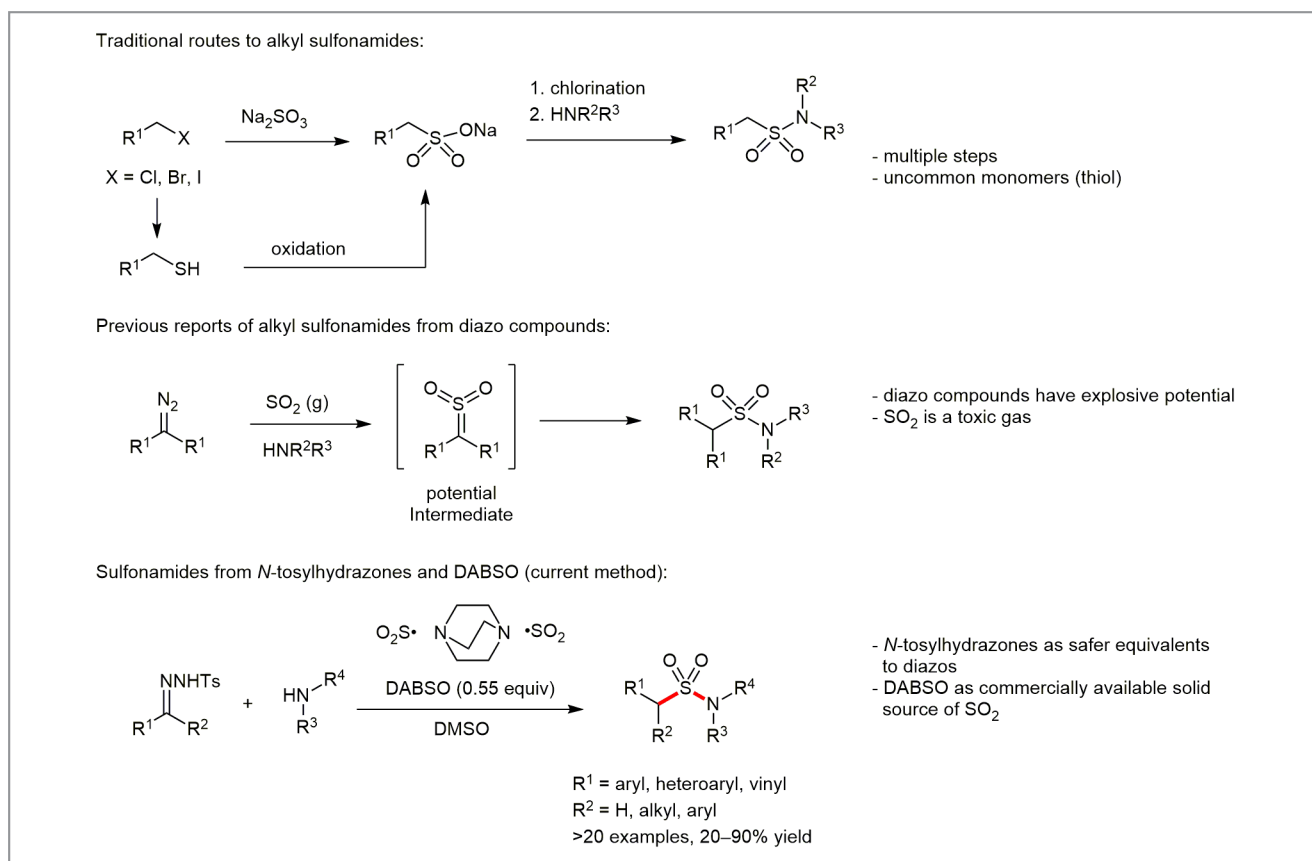
One-Step Synthesis of Sulfonamides from *N*-Tosylhydrazones

Org. Lett. **2016**, *18*, 508–511

Since the discovery of the sulfa antibiotics in the 1930s, the sulfonamide motif has been a prevalent pharmacophore found in many medicines and drug candidates. Thus, sulfonamide formation is commonly sought after to explore structure–activity relationships (SAR) during drug discovery efforts. While traditional syntheses of sulfonamides are straightforward from sulfonyl chlorides and amines, several steps are generally required to prepare the necessary sulfonyl chloride. To address the limitations from these early methodologies, recent work from Pfizer and other groups led to the development of convenient one-pot methods to obtain sulfonamides starting from a large pool of readily available reactants such as (hetero)aryl/alkyl halides or (hetero)arylboronic acids and amines (see the original article for references). One particular project called for the synthesis of a variety of alkyl sul-

fonamides. Following from their previous work in the Pfizer laboratories, Dr. Andy Tsai and his co-workers at Pfizer Worldwide Medicinal Chemistry (Groton, USA) sought to develop novel methods for accessing alkyl sulfonamides from other commonly encountered starting materials.

“In thinking about a new method to make alkyl sulfonamides, several features were important,” said Dr. Tsai. “First is that the reaction leverages commonly encountered reactants, which is important for parallel synthesis application and to support rapid SAR exploration.” Dr. Tsai continued: “Operational simplicity is also of paramount importance, especially in the context of parallel synthesis setting. With these factors in mind, of particular interest to us were decades old reports that showed alkyl sulfonamides could be obtained from alkyl diazo compounds, SO₂ (gas), and amines.” These



Scheme 1

reports approached the reaction largely as a curiosity: the mechanism was explored but their synthetic value was not, which may not be surprising as diazo species are explosive and SO_2 is a toxic gas. However, in the intervening decades since these reports, *N*-tosylhydrazones have been appreciated as safer equivalents to diazo compounds and DABSO {1,4-diazabicyclo[2.2.2]octane bis(sulfur dioxide) adduct} has been developed as a convenient solid source of SO_2 gas. “With the consideration that *N*-tosylhydrazones are simply obtained from condensation using commonly encountered ketones and aldehydes, we reckoned that the reaction held the potential of a novel route to sulfonamides,” said Dr. Tsai.

Preliminary experiments showed that mixing the *N*-tosylhydrazone, DABSO, and an amine in DMSO provided the desired sulfonamide. After some optimization, the substrate

scope was defined. “Our current work is to extend the scope to include non-aromatic *N*-tosylhydrazones,” said Dr. Tsai. “To guide us to this goal, we hope to be able to use react-IR and in-situ NMR to identify key intermediates in the reaction to help elucidate the mechanism.”

Dr. Tsai concluded: “In summary, this method provides a novel route to sulfonamides from aldehydes and ketones (via their condensation with *N*-tosylhydrazide). The simple reaction setup and ready availability of diverse building blocks provide a basis for compound libraries to explore SAR in future drug discovery efforts.”

Matthew Fenske

About the authors



Dr. A. Tsai

Andy Tsai graduated with a B.S. in chemistry from University of Michigan (USA). Subsequently, he studied under the direction of Professors Jonathan Ellman and Robert Bergman at the University of California, Berkeley (USA) in the area of C–H activation. Upon receiving his Ph.D in 2011, he moved down to the Scripps Research Institute in Jupiter, Florida (USA) where he worked as a postdoctoral associate with Professor William Roush. He is currently a medicinal chemist at Pfizer.

and his wife Barb currently live in Connecticut where John has begun his career as a medicinal chemist.



Dr. B. N. Roche

Benjamin N. Roche was born and raised near Peoria, IL (USA). In 2004, he received a B.S. in chemistry from the University of Illinois at Urbana-Champaign (USA), where his research in the lab of Professor Gregory S. Girolami resulted in an award-winning thesis. Since then, he has been employed by Pfizer in Groton, CT (USA). His work has contributed to the advancement of several molecular entities as clinical candidates for the treatment of type II diabetes or cardiovascular disorders. Ben enjoys tuning and repairing pianos in his spare time, as well as spending time with his family.



Dr. J. Curto

John Curto was born and raised in western Massachusetts (USA). He obtained his undergraduate degree at the College of the Holy Cross in Worcester, MA (USA), where he was first introduced to research while working for Professor Kevin Quinn on the synthesis of small natural products. In 2014, John graduated from the University of Pennsylvania (USA) with a Ph.D. under the guidance of Professor Marisa Kozlowski on the asymmetric synthesis of α, α -disubstituted α -amino acids and studies on the palladium-catalyzed $\text{C}(\text{sp}^3)\text{--H}$ activation of alkyl arenes. John



Dr. A.-M. Dechert Schmitt

Anne-Marie Dechert Schmitt obtained her B.S. degree in chemistry from the University of Georgia (USA), and completed undergraduate research under the direction of Professor Tim Dore. From there, Anne-Marie moved to the University of North Carolina (USA) to complete her graduate work. Her work focused on the synthesis of polyketide natural products under the tutelage of Professor

Michael Crimmins. She joined Professor Michael Krische as a postdoctoral researcher in 2011, and studied Ir-catalyzed C–C bond-forming reactions. She currently works at Pfizer in Groton, CT (USA) as a senior scientist in the CVMET group.



Dr. G. Ingle

Gajendra Ingle was born in India and after completing his undergraduate degree, he moved to Utah State University in Logan, UT (USA) for his Master's degree in chemistry. In 2007, Gajendra joined Professor Jon Antilla's laboratory at University of South Florida, Tampa, FL (USA) for graduate studies, where he investigated chiral phosphoric acid/metal phosphate catalyzed transformations of imines and epoxides. As a postdoctoral scholar

in Professor Dean Toste's laboratory at University of California, Berkeley (USA), he worked on the chiral phosphate anion catalyzed macrocyclization reaction of malonate-appended diazonium salts. He joined Pfizer in December 2014, and is currently working as a Senior Scientist in CVMET in Groton, CT (USA).



Dr. V. Mascitti

Vincent Mascitti received his diploma in chemical engineering from the ECPM (Strasbourg, France). He then completed his Ph.D. with Professor Stephen Hanessian (University of Montreal, Canada) on the total synthesis of natural products bearing deoxypropionate motifs (e.g., dolicolide and borrelidin), and the synthesis of bioactive oligosaccharides. He did his postdoctoral studies in the laboratories of Professor E. J. Corey where he

completed the first total synthesis of the ladderane-containing natural product pentacycloanammoxic acid. Vincent joined Pfizer in 2006, where as a medicinal chemist in the CVMED chemistry department he contributed to various diabetes- and obesity-related projects. In particular, Vincent was the driving force behind the design and synthesis of SGLT2 inhibitor Ertugliflozin (PF-04971729), a clinical candidate currently in development and being evaluated for type II diabetes treatment. Vincent is the (co)author of over 40 publications and patent applications. He is currently a Senior Director at Pfizer in the CVMET medicinal chemistry department.

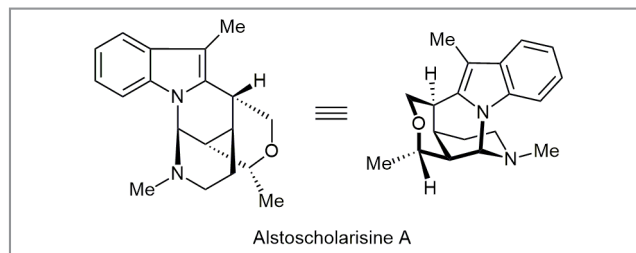
Total Synthesis of (±)-Alstoscholarisine A

Angew. Chem. Int. Ed. **2016**, *55*, 2569–2572

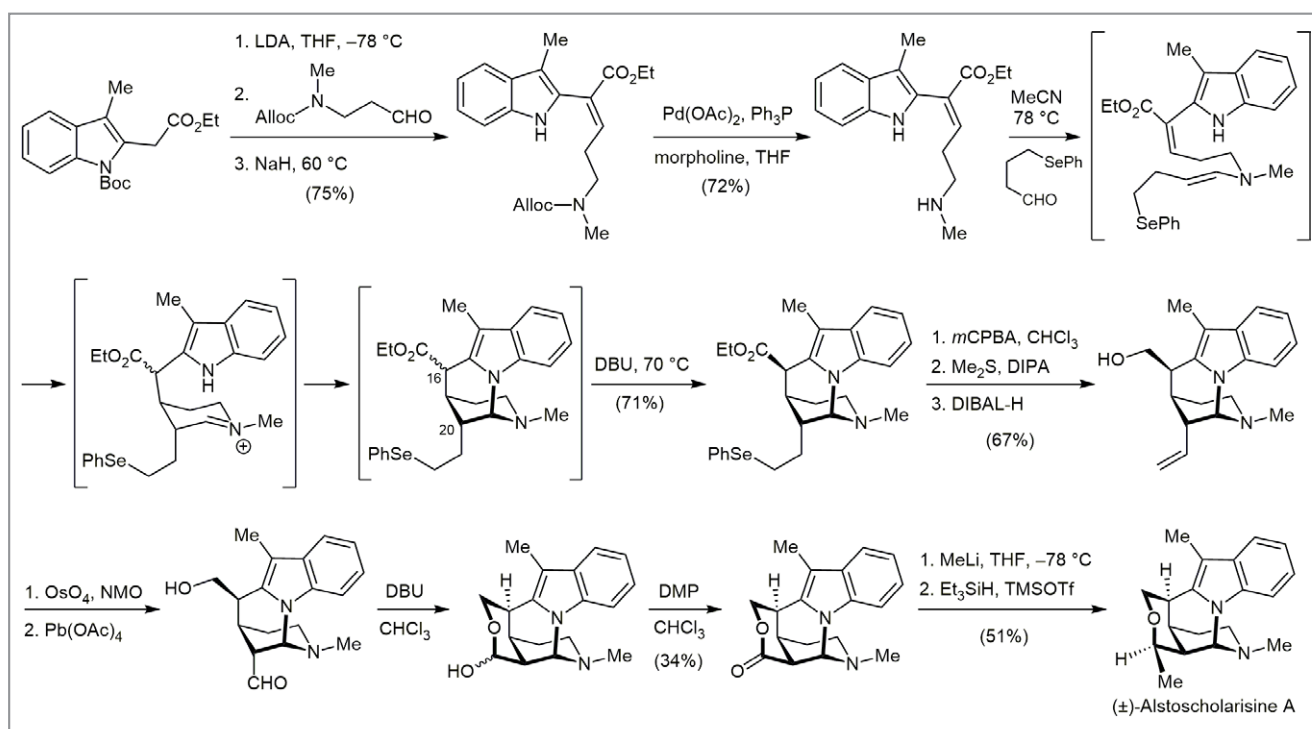
Alzheimer's, Parkinson's and Huntington's disorders, as well as amyotrophic lateral sclerosis, are the most common examples of currently incurable neurodegenerative diseases, characterized by a progressive loss of neuronal function. It has been estimated that Alzheimer's disease alone affects more than 44 million people globally, and this number is rapidly growing. In recent years, it has been realized that small molecules could promote adult neuronal stem cell (NSC) proliferation and differentiation, which could have important therapeutic applications for addressing unmet medical needs such as neurodegeneration.

In 2014, five indole alkaloids were isolated from *Alstonia scholaris*, and alstoscholarisine A was shown to significantly promote adult NSC proliferation and differentiation (see the original paper for references).

Synthetic chemists Professor Filip Bihelovic and Professor Zorana Ferjancic at the University of Belgrade (Serbia) were also impressed by the unique molecular structure of alstoscholarisine A and therefore started a synthetic project aimed at developing a concise yet flexible synthesis, which would also allow the researchers to synthesize its analogues



for SAR studies. Professor Bihelovic said: "We kept in mind a statement by Professor Mulzer, who said: "In fact, the total synthesis of complex natural products has often resulted in unacceptably long and low-yielding unpractical sequences" (*Nat. Prod. Rep.* **2014**, *31*, 595–603)." Consequently, in order to achieve a short synthesis, the researchers considered domino reactions, where the molecular complexity could dramatically increase in a single step. After developing their initial synthetic plan, they commenced their synthesis from skatole. "However, it was an unpleasant surprise when we realized that we didn't have this particular substance in our collection and that it would take more than a month to get it delivered to Serbia,"



remarked Professor Bihelovic. "So we made it and everything was ready for a real beginning."

Although the pair thought that synthesis of the amine for the key domino reaction would be a trivial task, it took a considerable amount of time to get these first steps to work. "The major difficulty was to properly select the aldehyde component for the aldol condensation," explained Professor Bihelovic. Interestingly, *N*-Boc-, *N*-Cbz- and *N*-Alloc-protected 3-aminopropanal all gave different products under the same reaction conditions. "Only *N*-Alloc-protected aldehyde reacted in a feasible way, reminding us again what we usually take for granted when planning synthesis: much more attention should be paid to a proper choice of a protecting group," said Professor Bihelovic.

To their delight, the key cyclization step was amazingly smooth and high-yielding, requiring no catalyst at all. Out of four theoretical stereoisomers, the authors of this study obtained only two, and none had a properly oriented substituent on C-20 at the newly formed bicyclic core. "Aside from elements of bad luck, this wasn't so surprising or disappointing, as we already recognized this possibility during our retrosynthetic analysis," remarked Professor Bihelovic. The first epimerizable stereocenter (C-16) was easily rectified in situ, through a DBU-catalyzed thermodynamic isomerization. A correction of the second stereocenter was more challenging, and they isomerized it also under basic conditions, but it was necessary to intramolecularly trap the thermodynamically less stable aldehyde in form of a hemiacetal, thus completely shifting the equilibrium. "The rest of the synthesis was straightforward and we were very excited to see that the NMR spectrum of the synthetic material matched the reported spectrum of the natural product," said Professor Bihelovic.

"We believe the problems emphasized by Professor Mulzer could be avoided by applying efficient domino reactions, as we hopefully demonstrated in our total synthesis of alstoscholarisine A," said Professor Bihelovic, who concluded: "Additionally, our work could provide a solid basis for easy preparation of new alstoscholarisine A analogues, which would represent a valuable contribution to SAR studies and hopefully help in understanding mechanisms of regulation of adult neural stem cells."

Mattias Ferjanek

About the authors



Prof. F. Bihelovic

Filip Bihelovic was born and raised in Belgrade (Serbia). After earning his BSc degree in chemistry (2005) from the University of Belgrade (Serbia), he joined the laboratory of Professor Radomir N. Saicic for PhD studies. Upon completion of his PhD in 2011, he joined Professor Dirk Trauner at Ludwig-Maximilians-Universität München (Germany) for postdoctoral studies. In 2014, he was promoted to Assistant Professor at the University of Belgrade. His main research interests lie in the area of natural products total synthesis.



Prof. Z. Ferjancic

Zorana Ferjancic was born in Belgrade (Serbia). She obtained her BSc (1996), and MSc (2000) from the University of Belgrade (Serbia). She received her PhD degree from the same institution in 2006 under the supervision of Professor Radomir N. Saicic. During 2007, she carried out postdoctoral research at the Ecole Polytechnique (Palaiseau, France) in Professor Samir Zard's group. In 2008, she was appointed Assistant Professor at the University of Belgrade and then promoted to the position of Associate Professor in 2014. Her main research interest is the synthesis of natural products and biologically active molecules.

Coming soon

Literature Coverage

Nitro-polyols via Pyridine-Promoted C=C Cleavage of 2-Nitro-glycols. Application to the Synthesis of (-)-Hyacinthacine A1

Literature Coverage

Myoglobin-Catalyzed Olefination of Aldehydes

Literature Coverage

Chemoselective Palladium-Catalyzed Deprotonative Arylation/[1,2]-Wittig Rearrangement of Pyridylmethyl Ethers

Further highlights

Synthesis Short Review: **Diversity-Oriented Synthesis of Macrocyclic Libraries for Drug Discovery and Chemical Biology**

(by D. R. Spring and co-workers)

Synlett Account: **Synthesis of Benzo-Fused Cyclic Compounds via Intramolecular Cyclization of Aryltriazenes**

(by H. Ren and co-workers)

Synfacts Synfact of the Month in category "Organo- and Biocatalysis": **A Silylated C-H Acid Catalyst for the Asymmetric Diels-Alder Reactions of Cinnamates**

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