

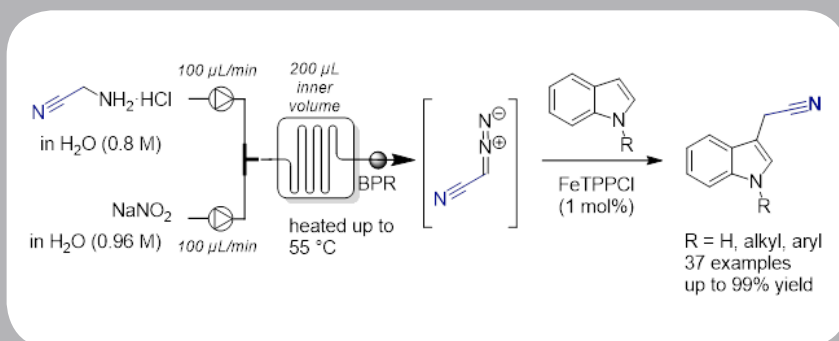
# Synform

People, Trends and Views in Chemical Synthesis

2019/07

## Tryptamine Synthesis by Iron Porphyrin Catalyzed C–H Functionalization of Indoles with Diazoacetoneitrile

Highlighted article by K. J. Hock, A. Knorrscheidt, R. Hommelsheim, J. Ho, M. J. Weissenborn, R. M. Koenigs



### Contact

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

## Dear Readers,

Functionalization of C–H bonds using a range of different catalysts and/or photoactivation methods continues to be a vibrant and timely research area, which is attracting an enormous – and still increasing – amount of interest. Indeed, activation of C–H bonds has long been indicated as the ultimate challenge for synthetic organic chemists in both academia and industry. Progress in the field is nowadays impressive and some of the new methods appear to be more efficient, straightforward and have higher environmental sustainability and compatibility – especially those relying on photocatalysis or enzymes, often involving radical chemistry – than the more traditional multi-step synthetic methods that require stoichiometric amounts of organometallic reagents or Lewis acids/bases. Two examples of this amazing progress in direct C–H activation chemistry are featured in this new issue of SYNFORM. The first example is the synthesis of  $\alpha$ -functionalized alcohols by light-induced radical chemistry which can be used to prepare heterocyclic carbinols, as reported by A. Lei (P. R. of China). The second example, described by R. M. Koenigs (Germany), involves the use of an iron porphyrin and can be applied to the functionalization of indoles and related heterocycles with a  $\text{CH}_2\text{CN}$  residue. Sandwiched between these two methodological papers, there is a good old and inspiring total synthesis of some complex naturally occurring bowl-shaped macrocycles, called Herqulines B and C, developed by the group of C. Schindler (USA). A Young Career Focus interview with J. Campos (Spain) has the key role of wrapping up and closing the issue.

Enjoy your reading!!!



### In this issue

- Literature Coverage  
**Visible-Light-Induced Direct  $\alpha$ -C–H Functionalization of Alcohols**.....A99
- Literature Coverage  
**Total Syntheses of Herqulines B and C**..... A102
- Literature Coverage  
**Tryptamine Synthesis by Iron Porphyrin Catalyzed C–H Functionalization of Indoles with Diazoacetonitrile**.. A106
- Young Career Focus  
**Dr. Jesús Campos (Spanish National Research Council (CSIC), Sevilla, Spain)**..... A109
- Coming soon ..... A112

### Contact

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

## Visible-Light-Induced Direct $\alpha$ C–H Functionalization of Alcohols

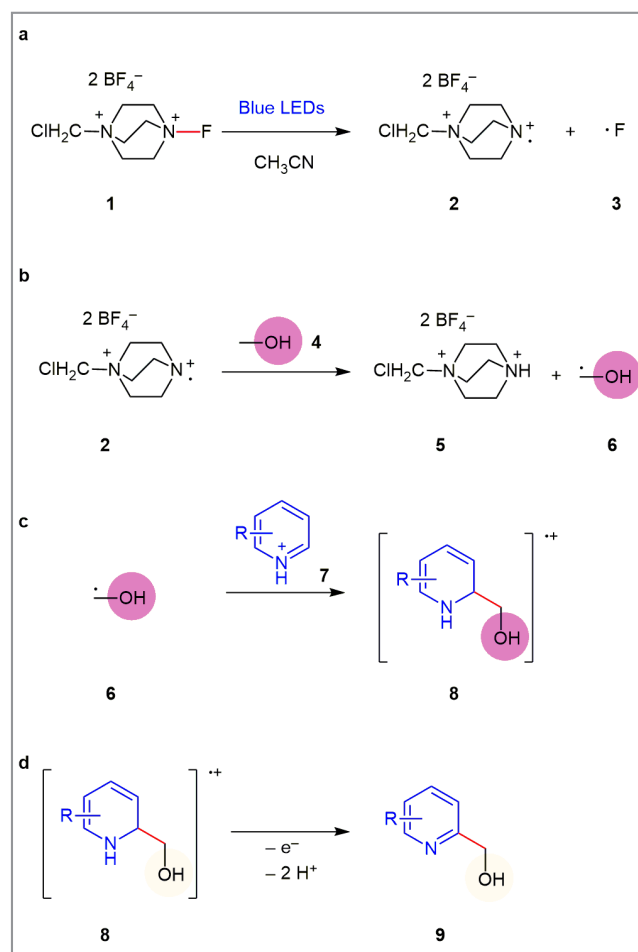
*Nat. Commun.* **2019**, *10*, 467

Alcohols are ubiquitous and widely used raw starting materials with broad applications in organic chemistry, the pharmaceutical industry and chemical engineering, to name just a few. For this reason, having ready access to a broad range of alcohols through the selective  $\alpha$  C–H functionalization of alcohols would be of great significance. “The photocatalytic oxidative  $\alpha$   $sp^3$  C–H arylation of alcohols is still a challenge, especially in the presence of ethers also having  $\alpha$   $sp^3$  C–H bonds,” said Prof. Aiwen Lei, from The College of Chemistry and Molecular Sciences, Institute for Advanced Studies, Wuhan University (P. R. China). According to Professor Lei, although much attention has been paid to the oxidative  $\alpha$   $sp^3$  C–H arylation of ethers with electron-deficient heteroarenes under a photocatalytic oxidation system, it is notable that the analogous reaction of alcohols had not yet been demonstrated. “Therefore, visible-light-induced oxidative  $\alpha$   $sp^3$  C–H arylation of alcohols with electron-deficient heteroarenes to introduce an active alcoholic hydroxyl group is of great synthetic significance,” he added. Selectfluor is well known as a powerful fluorination reagent and oxidant, frequently used in combination with a metal catalyst or photocatalyst. “The N–F bond breaking of Selectfluor can be achieved by electron donation from an external reductant. Conversely, direct visible-light-induced N–F activation of Selectfluor is desirable but rarely described. We hypothesized that activated Selectfluor may exhibit different selectivity for oxidative  $sp^3$  C–H  $\alpha$ -arylation of alcohols and ethers,” said Professor Lei, whose research group recently reported that Selectfluor – under visible-light irradiation – can effectively promote the oxidative cross-coupling between alcohols and heteroarenes, without external photocatalysis, leading to the selective  $\alpha$   $sp^3$  C–H arylation of an alcohol, even in the presence of an ether.

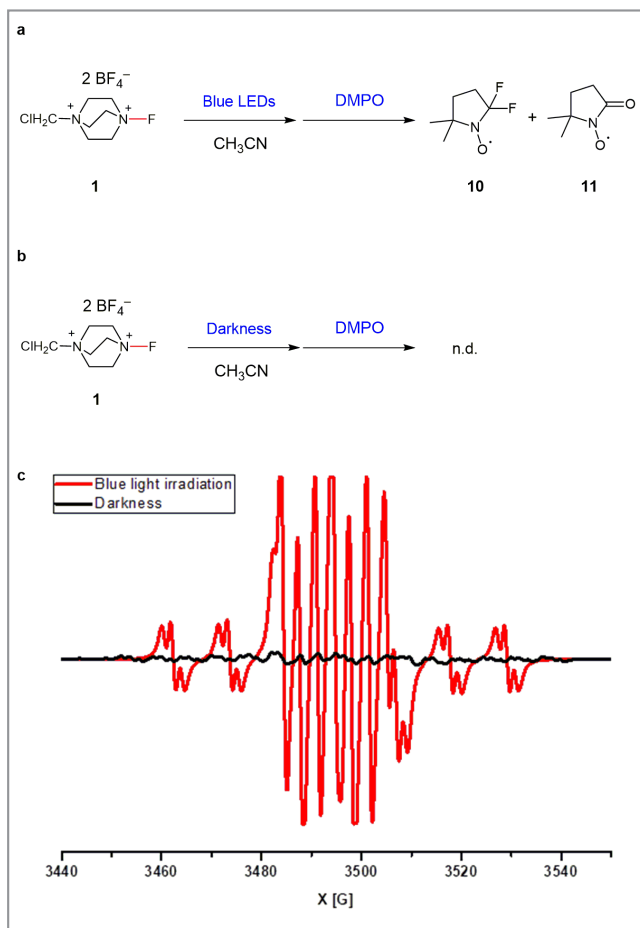
“At first, we questioned whether visible-light irradiation could induce the N–F activation of Selectfluor to directly yield the corresponding N radical cation and F radical (Scheme 1a),” said Mr. Linbin Niu, a co-author of this study. He continued: “The generated N radical cation is responsible for the fission of an  $\alpha$   $sp^3$  C–H bond of the alcohol to form the hydroxyalkyl radical (Scheme 1b). Afterwards, the electron-deficient heteroarenes – protonated by an acid – can capture the relatively nucleophilic radical and deliver the corresponding radical adducts (Scheme 1c). The oxidation and deprotonation of this radical adduct by another Selectfluor molecule would then afford the  $\alpha$ -arylated product (Scheme 1d).” Under the de-

signed oxidation conditions, the spin center shift process of the intermediate can be avoided and the carbinolic hydroxyl group is unaffected, leading to the oxidative  $\alpha$   $sp^3$  C–H functionalization of alcohols with heteroarenes.

“This assumption that the N–F activation of Selectfluor could be achieved by blue-light irradiation was subsequently confirmed by electron paramagnetic resonance (EPR) experiments,” added Mr. Niu. Two kinds of radical signals were observed, when Selectfluor in acetonitrile was irradiated by blue LEDs and when 5,5-dimethyl-1-pyrroline *N*-oxide (DMPO) was employed as a radical scavenger (Schemes 2a and 2c). Another co-author, Mr. Shengchun Wang, explained: “One of



**Scheme 1** The designed reaction pathways



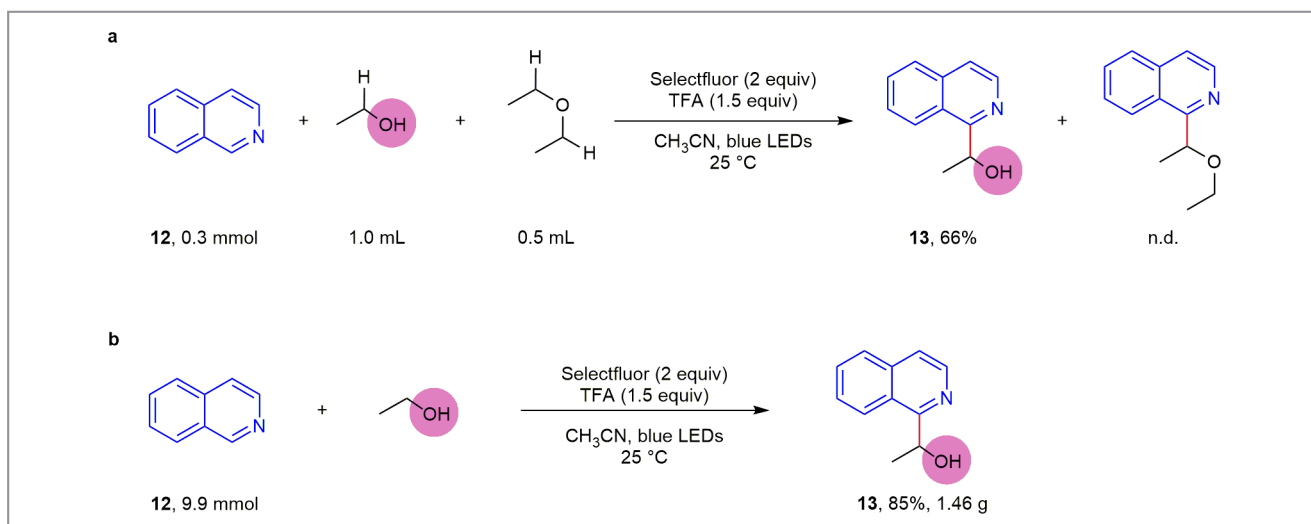
**Scheme 2** The electron paramagnetic resonance (EPR) experiments

the radicals, **10**, was confirmed as the radical adduct between two fluorine radicals and DMPO, while the other one, **11**, resulted from the oxidation of DMPO, where the ratio of **10**:**11** is 3:8.” In contrast, the team did not detect the radical adduct between two fluorine radicals and DMPO under darkness (Schemes 2b and 2c).

“It is significant that the single selectivity and good yield for the oxidative  $\alpha$   $\text{sp}^3$  C–H arylation of alcohols in the presence of an  $\text{sp}^3$  C–H of an ether were observed (Scheme 3a),” said Mr. Niu, continuing: “The gram-scale experiment carried out by Jiamei Liu demonstrates the potential utility of this protocol (Scheme 3b).”

“In summary,” said Prof. Lei, “we have developed a visible-light-induced oxidative  $\alpha$   $\text{sp}^3$  C–H arylation of alcohols with heteroarenes, which is promoted by Selectfluor under blue LED irradiation. What is essential for this protocol is the N–F activation of Selectfluor achieved by blue-light irradiation. These observed reactivities may have significant implications for further chemical transformations.”

*Matters female*



**Scheme 3** Investigation and application of this protocol. (a) Intermolecular competition experiment. (b) Gram-scale synthesis experiment.

## About the authors



L. Niu

**Linbin Niu** was born and grew up in Zhengzhou, Henan Province (P. R. of China). He received his B. S. degree from Zhengzhou University (P. R. of China) in 2015 before moving to Wuhan University (P. R. of China) to further his studies in organic chemistry, directed by Prof. Aiwen Lei. Now, he is a PhD student and his research interests are photocatalysis, electrocatalysis, and nanocatalysis.



X.-A. Liang

**Xing-An Liang** comes from Liuzhou, Guangxi Province (P. R. of China). He obtained his B.S. degree from Wuhan University (P. R. of China) in 2017 before joining Prof. Aiwen Lei's group as a PhD candidate. He is working on electrocatalysis and nanocatalysis.



J. Liu

**Jiamei Liu** was born and grew up in Shenyang, Liaoning Province (P. R. of China). She obtained her B.S. degree from Wuhan University, Hongyi Class (P. R. of China) in 2018. She joined Aiwen Lei's group for extracurricular research during the period 2015–2018. She then continued her studies and joined Prof. Xuechen Li's group in The University of Hong Kong (P. R. of China) and is now working on bioorganic chemistry.



Prof. A. Lei

**Aiwen Lei** graduated from Huaibei Normal University (P. R. of China) in 1995 and obtained his PhD at the Shanghai Institute of Organic Chemistry, Chinese Academy of Science (P. R. of China) in 2000, directed by Prof. Xiyan Lu. He worked as a post-doctoral fellow in the Department of Chemistry at Pennsylvania State University (USA), with Prof. Xumu Zhang from 2000 to 2003. Then he joined the group of Prof. James P. Collman at Stanford University (USA) working as a research associate for two years. Finally, he joined Wuhan University (P. R. of China) as a professor in 2005. His research interests are organic synthesis methodology, physical organic chemistry, electrocatalysis, photocatalysis, nanocatalysis and biomimetic catalysis.



S. Wang

**Shengchun Wang** is from Yongzhou, Hunan Province (P. R. of China). He obtained his B.S. degree from Hunan University (P. R. of China) in 2016, then joined Prof. Aiwen Lei's group at Wuhan University as a PhD candidate. He focuses on oxidative radical cross-coupling and nanocatalysis.

## Total Syntheses of Herquelines B and C

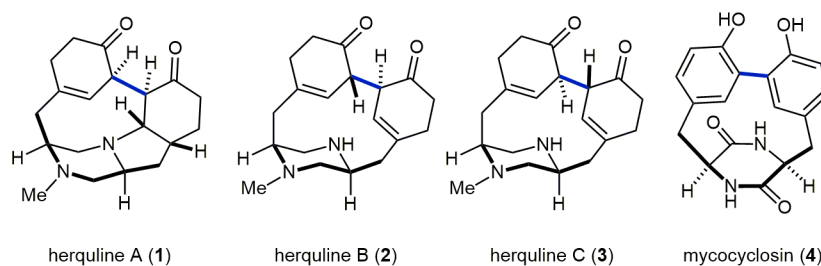
*J. Am. Chem. Soc.* **2019**, *141*, 3409–3413

The herquelines (**1–3**, Figure 1) were initially isolated from *Penicillium herquei* in 1979 by Omura and co-workers (*J. Antibiot.* **1979**, *32*, 786–790). Preliminary biological evaluations of these compounds revealed that the herquiline congeners are effective inhibitors of platelet aggregation and influenza virus replication. Architecturally, these small, highly strained alkaloids bear an unsymmetrical *N*-methyl Lewis basic piperazine core residing at the base of a bowl-shaped macrocycle. Additionally, two bridging  $\beta,\gamma$ -cyclic enones constitute the northern portion of **2** and **3**. The group of Prof. Corinna Schindler at the University of Michigan (USA) became interested in these structures as targets due to the challenge in synthesizing the highly strained core. Professor Schindler remarked: “We postulated that mycocyclosin (**4**) or a related analogue would serve as a key synthetic intermediate towards the herquiline family *via* a series of well-coordinated stereoselective reductions.”

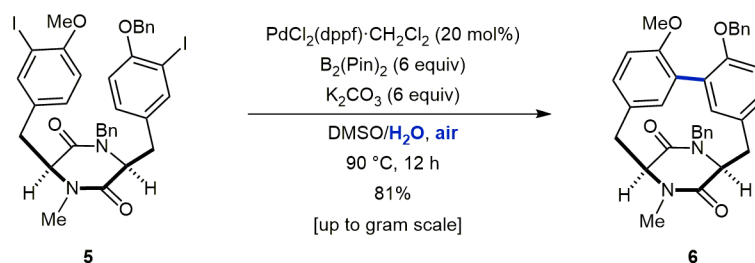
At the outset of their preliminary studies, the group developed a scalable and robust metal-catalyzed biaryl coupling of cyclodipeptide bis-iodides **5** (Scheme 1) to afford the re-

quisite cyclophane on scale. “These cyclodipeptide bis-iodide substrates were readily available from 3-iodo-L-tyrosine,” explained Professor Schindler. She continued: “Our detailed studies (*Org. Lett.* **2018**, *20*, 2862–2866) revealed that the palladium-catalyzed macrocyclization of **5** to **6** benefitted from the addition of exogenous air and water. We postulated that palladium(0) could be oxidized to a palladium(II)-peroxy intermediate by air, while exogenous water would subsequently facilitate the formation of a palladium(II)-hydroxy species suitable for transmetalation of the *in situ* formed bis-borononic ester. Notably, without the addition of air and water to the palladium-catalyzed macrocyclization, the cyclophane products were routinely formed in lower yields and/or the reaction proved not scalable. This carefully optimized biaryl coupling reaction readily afforded mycocyclosin derivatives on gram scale, which proved suitable to advance to the herquiline natural products.”

With a suitable synthetic strategy in hand to attain mycocyclosin derivatives on scale, the group’s next challenge was to evaluate the highly strained biaryl system’s compatibility



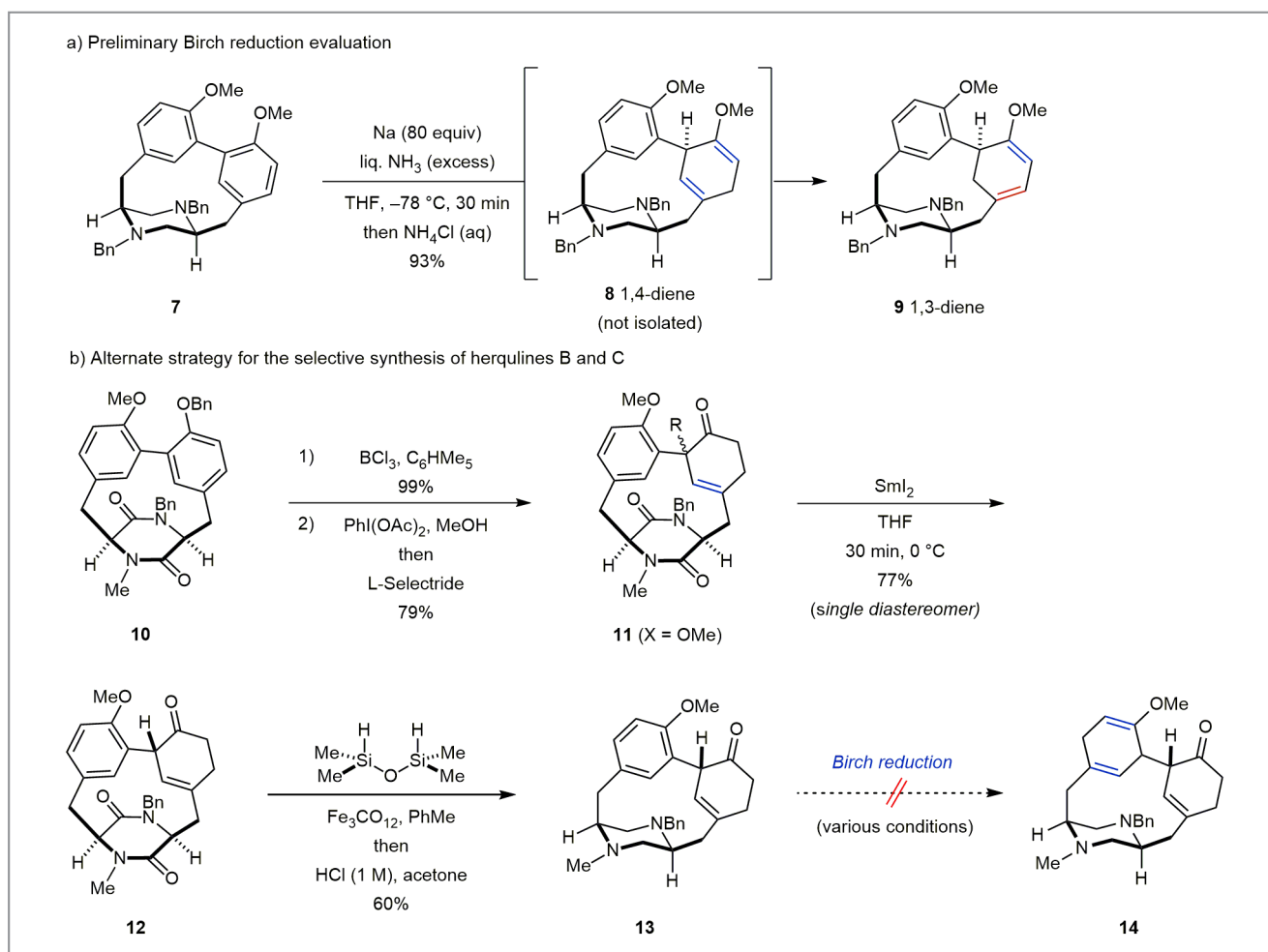
**Figure 1** Structures of herquelines A–C (**1–3**) and mycocyclosin (**4**)



**Scheme 1** Scalable Pd-catalyzed oxidative coupling

under Birch reduction conditions. “When symmetrical piperazine **7** (Scheme 2A) was exposed to standard Birch reduction conditions (Na, liq. NH<sub>3</sub>, THF, -78 °C) the biaryl subunit was readily converted into the 1,3-diene **9** in good overall yields,” said Prof. Schindler. “Unfortunately, the incorrect regiochemistry of the requisite olefin (red bond in **9**) was incompatible in terms of further elaboration to the herquelines.” She continued: “We presumed that this undesired Birch product arose from the *in situ* isomerization of 1,4-diene **8** to **9** due to the inherent high ring strain. In a concerted effort to overturn this undesirable reactivity, we evaluated different Birch reduction conditions, including: proton sources, reaction time and temperature, metal equivalences, proton sources, and substrate variations. However, despite extensive evaluation of various reaction conditions we were not able to observe the formation of the desired 1,4-diene product. As such we developed

an alternative strategy to access the herquiline family (Scheme 2B).” Following debenzoylation of **10** (BCl<sub>3</sub>, C<sub>6</sub>HMe<sub>5</sub>), the free phenol was subjected to oxidative dearomatization conditions (PhI(OAc)<sub>2</sub>, MeOH) followed by L-Selectride mediated conjugate reduction to give rise to **11**. Single-electron reduction of **11** with Sml<sub>2</sub> led to **12** as a single diastereomer. The authors were able to confirm by single-crystal X-ray analysis that the corresponding β,γ-enone (**12**) bore the correct unsaturation needed to elaborate to the final targets. At this stage, reduction of the diketopiperazine ring in **12** initially proved difficult. Professor Schindler remarked: “Various standard diketopiperazine reduction conditions were evaluated and led to either no reaction or complete decomposition of the starting material. However, utilizing conditions (Fe<sub>3</sub>(CO)<sub>12</sub>, silanes) initially reported by Beller (*Angew. Chem. Int. Ed.* **2009**, *48*, 9507–9510) we observed that **12** undergoes complete and



**Scheme 2** a) Preliminary Birch reduction evaluation; b) alternate strategy for the selective synthesis of herquelines B and C

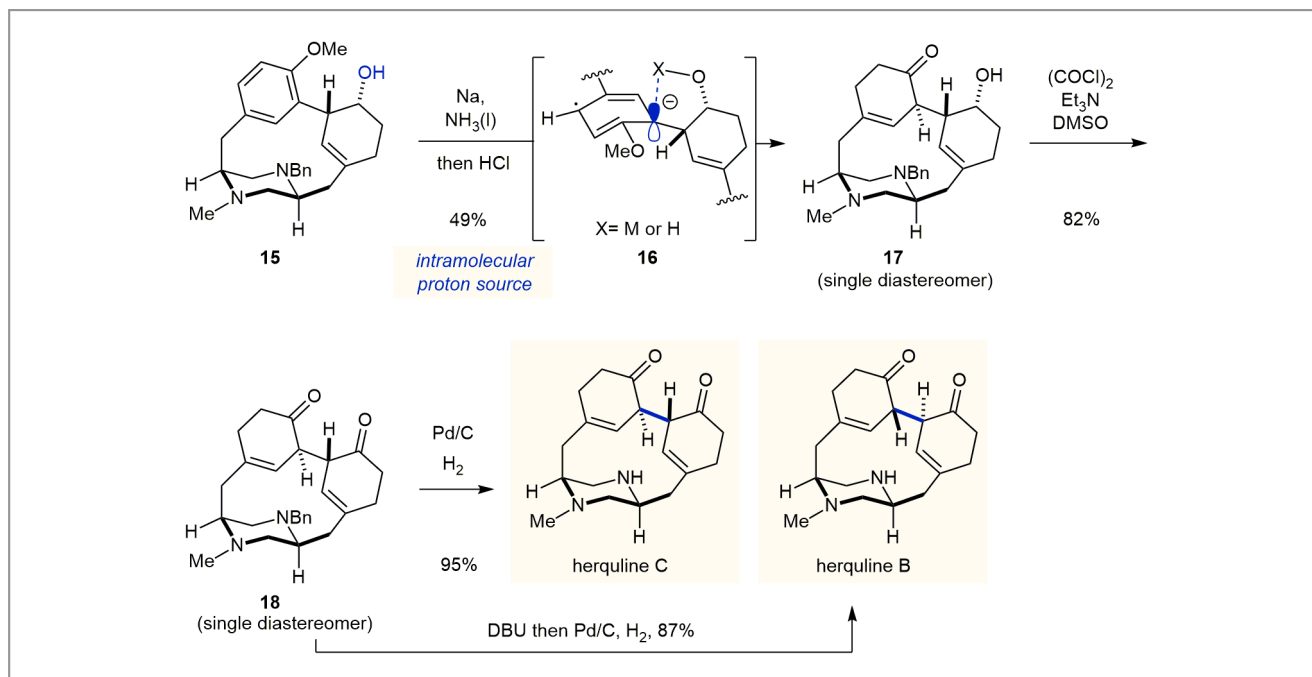
chemoselective reduction to piperazine **13** in the presence of a cyclic ketone. We expect that these reaction conditions will be useful for diketopiperazine reductions in other complex molecular settings.” The selective regiochemical reduction of the remaining aromatic ring was the next objective. When Prof. Schindler and co-authors subjected **13** to a variety of distinct Birch reduction conditions, they observed only reduction of the ketone to the corresponding secondary alcohol (not shown) as well as complex over-reduction mixtures. Furthermore, they found that the corresponding cyclic acetal of **13** proved to be completely recalcitrant under a variety of Birch reduction conditions.

In a final effort to effect reduction of the remaining aromatic ring, the group took inspiration from earlier work by Paddon-Row, who demonstrated that spatially proximate, but remotely connected hydroxyl groups to aromatic rings can facilitate Birch reductions *via* intramolecular protonation (*J. Chem. Soc., Chem. Commun.* **1982**, 1206–1208). “As such, we selectively reduced **13** with NaBH<sub>4</sub> (not shown) to access **15**. Exposure of **15** to Birch reduction conditions, with no exogenous proton sources, led to smooth formation of the desired enone **17** after acidic hydrolysis (Scheme 3),” said Prof. Schindler. She continued: “We hypothesized that not only can an intramolecular protonation occur, but also coordination of a metal to an alkoxy intermediate can help stabilize an inter-

mediate anion (**16**). We were able to complete the synthesis of herquiline C by oxidizing the secondary alcohol to **18**, followed by hydrogenolysis. Furthermore, **18** was readily isomerized with DBU at room temperature, and following hydrogenolysis gave rise to herquiline B.”

Prof. Schindler concluded: “We have been able to complete the total synthesis of herquelines B and C in a concise and efficient approach. Our reported strategy reflects the unique reductive biosynthetic origins of these highly strained natural products by taking advantage of mycocyclusin derivatives as key synthetic intermediates. Our ongoing work in the lab seeks to establish a better understanding of the distinct reactivity of highly strained biaryl systems in the context of natural product total synthesis.”

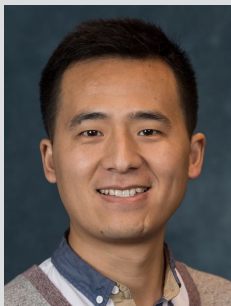
*Matthew Fenske*



**Scheme 3** Completion of the total synthesis of herquelines B and C



## About the authors



Dr. X. Zhu

**Xu Zhu** received his MSc in chemistry from Soochow University (China) under Prof. Shun-Jun Ji in 2011 and started his PhD studies during the same year. In 2015, he obtained his PhD from Nanyang Technological University (Singapore) under the supervision of Prof. Shunsuke Chiba where he studied methodology development for the synthesis of nitrogen heterocycles. Beginning in 2016, he began a postdoctoral stay in Prof.

Corey R. J. Stephenson's group at the University of Michigan (USA) before joining Prof. Corinna S. Schindler's research group at the same university. His current research focuses on total synthesis of resveratrol oligomers and herquiline family natural products.



C. C. McAtee

**Christopher C. McAtee** grew up in Easton, PA (USA) and obtained his B.Sc. (*cum laude*) from Lycoming College (Williamsport, PA, USA) while conducting undergraduate research with Chriss E. McDonald. In 2015, he began his PhD studies in Prof. Corinna S. Schindler's group at the University of Michigan (USA) as an NSF Predoctoral Fellow. His doctoral research focuses on the total synthesis of highly strained alkaloid natural products.



Prof. C. S. Schindler

**Corinna S. Schindler** received her diploma in chemistry from the Technical University of Munich in Germany. After a research stay with Prof. K. C. Nicolaou at the Scripps Research Institute in La Jolla (USA), she joined the group of Erick M. Carreira at ETH Zurich in Switzerland for her graduate studies. She then returned to the USA to conduct postdoctoral studies with Prof. Eric N. Jacobsen at Harvard before starting her independent career at the University of Michigan in 2013.

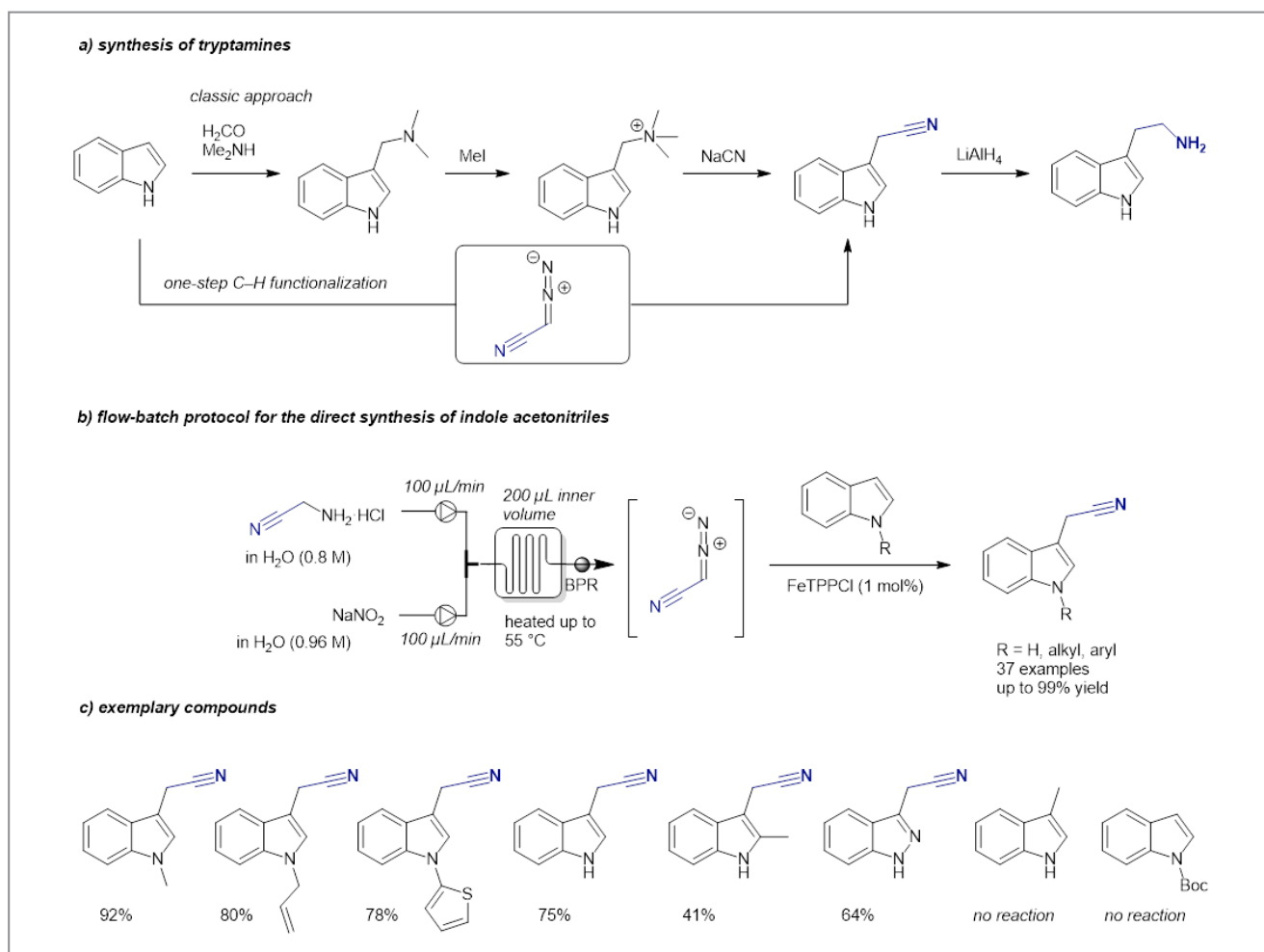
# Tryptamine Synthesis by Iron Porphyrin Catalyzed C–H Functionalization of Indoles with Diazoacetoneitrile

*Angew. Chem. Int. Ed.* **2019**, *58*, 3630–3634

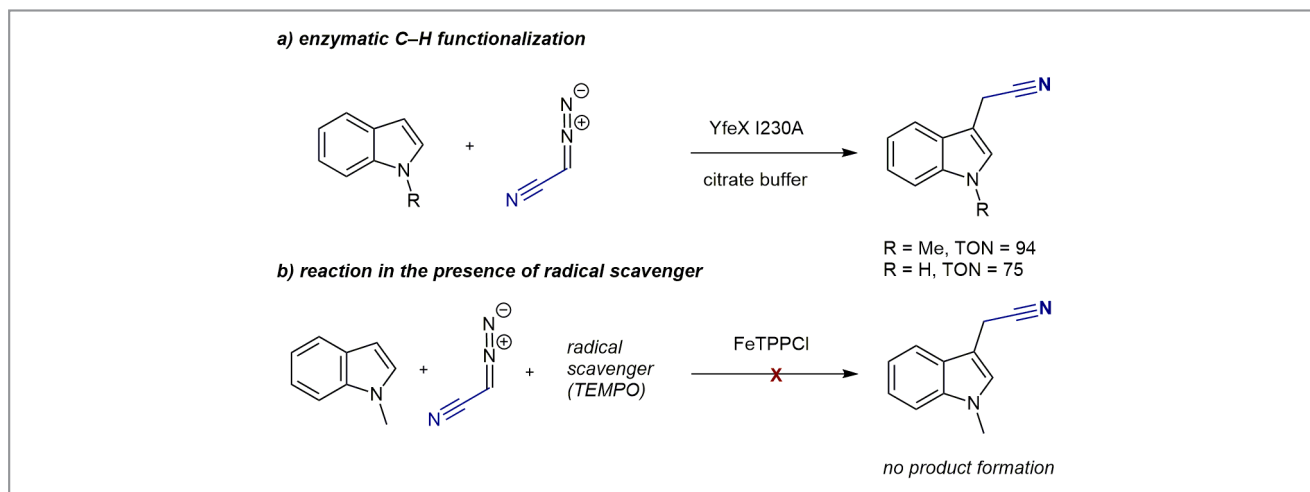
Tryptamines are important endogenous signaling molecules that play a pivotal role in biochemical processes like the regulation of the sleep–wake rhythm. The closely related serotonin possesses key regulatory functions in the cardiovascular system and organ development and plays a central role as a neurotransmitter in the central nervous system. The synthesis of tryptamines is typically conducted following a classic route starting with a Mannich reaction of an indole heterocycle, followed by quaternization of the amine, nucleophilic substitution

with highly toxic cyanide and final reduction (Scheme 1a).

Professor Koenigs (RWTH Aachen University, Germany) and co-workers previously reported on carbene transfer reactions of the underexplored and explosive diazoacetoneitrile reagent (*Green Chem.* **2017**, *19*, 2118–2122; *Chem. Commun.* **2017**, *53*, 6577–6580). Prof. Koenigs and Katharina J. Hock – a PhD student in the Koenigs group – explained: “We were intrigued by this small fascinating reagent and wanted to find



**Scheme 1** a) Strategies for the synthesis of tryptamines. b) Realization of a flow-batch protocol for the synthesis of diazoacetoneitrile and subsequent iron(III)-catalyzed direct C–H functionalization of indole heterocycles. c) Selected examples of the substrate scope.



**Scheme 2** a) Enzymatic C–H functionalization reaction with the YfeX enzyme. b) Reaction in the presence of a radical scavenger.

solutions to make it commonly available for organic synthetic chemists.” Building on their experience in continuous-flow chemistry and the handling of highly reactive diazoalkanes (*Chem. Eur. J.* **2016**, 9542–9545), the team set up the goal of exploring C–H functionalization reactions. Prof. Koenigs hypothesized that the reaction of diazoacetone nitrile with indole heterocycles should provide a streamlined and unprecedented access to tryptamines and their precursors.

Quite unexpectedly, the team identified a simple iron porphyrin catalyst to be highly efficient in the direct C–H functionalization of protected and unprotected indole heterocycles with diazoacetone nitrile (Scheme 1b and 1c), and they demonstrated the applicability of this transformation even on gram-scale. Prof. Koenigs explained that the limitations of the existing methods lay with the necessity of having either expensive catalysts or cyclopropanation reactions of the indole heterocycle with acceptor-only diazo compounds. “The synthesis of diazoacetone nitrile using flow technology was crucial for obtaining high yields and circumventing risks associated with handling this explosive diazoalkane, as the reactive diazoalkane is directly consumed by the catalyst after addition to the reaction mixture and only diminutive amounts are present in the flow reactor,” commented Katharina J. Hock.

Prof. Koenigs teamed up with Jun.-Prof. Martin J. Weissenborn (Leibniz Institute of Plant Biochemistry and Martin-Luther University Halle-Wittenberg, Germany) who had previously shown a carbene-transfer reaction (*ChemCat-Chem* **2016**, 8, 1636–1640), and Dr. Junming Ho (University of New South Wales, Sydney) to next investigate biocatalytic C–H functionalization reactions with an iron–heme-containing

enzyme and to gain an understanding of the reaction mechanism of this transformation.

Jun.-Prof. Weissenborn and Anja Knorrscheidt – a PhD student in the Weissenborn group – studied the reaction of acceptor-only diazoalkanes with indole heterocycles using the enzyme YfeX. “YfeX is a remarkably stable enzyme with an impressive expression rate. The site-specific mutagenesis in the active site improved the biocatalytic C–H functionalization reaction to more than 90 turnovers (Scheme 2a),” commented Jun.-Prof. Weissenborn.

The reaction mechanism of this C–H functionalization reaction was studied by using deuterium labeling experiments, which however did not provide a clear mechanistic picture. “Maybe there is a radical pathway involved in this C–H functionalization reaction,” suggested Dr. Ho. Indeed, reactions in the presence of radical scavengers did not provide the desired reaction product (Scheme 2b), thus supporting the hypothesis of a radical pathway.

Prof. Koenigs concluded: “This protocol opens up not only the possibility of pursuing safe applications of hazardous diazoacetone nitrile but also provides a new, operationally simple route to important tryptamines starting from simple, commercially available reagents, also on gram-scale. Simple organometallic or enzymatic iron catalysts were identified as being highly efficient in this reaction and first experiments showed an intriguing aspect of iron-catalyzed carbene-transfer reactions. The latter are currently under further investigations from an experimental and theoretical perspective to gain a better understanding of the underlying reaction mechanism.”

*Martin J. Weissenborn*

## About the authors



K. J. Hock

**Katharina J. Hock** studied chemistry at the Goethe University Frankfurt am Main (Germany). She did her Masters thesis in the group of Dr. Georg Manolikakes and moved to RWTH Aachen University (Germany) in January 2016 to pursue her PhD thesis with Prof. Koenigs working on safe applications of small and reactive diazoalkanes in carbene-transfer reactions and cycloaddition reactions.



A. Knorrscheidt

**Anja Knorrscheidt** received her BA in chemistry from the Martin Luther University Halle-Wittenberg (Germany) in the group of Prof. Csuk in 2014. In 2016 she completed her study in chemistry with her MSc at the Leibniz Institute of Plant Biochemistry (Germany) under the supervision of Prof. Wessjohann in 2016. At the same institute she continued as a PhD student in the beginning of 2017 to work in the group of Jun.-Prof.

Weissenborn, focusing her research on enzyme-catalyzed carbene-transfer reactions.



R. Hommelsheim

**Renè Hommelsheim** was born in 1995 in Aachen (Germany). He received his BSc in chemistry from the RWTH Aachen University in 2017. During his Bachelor and Master studies, he worked on the synthesis and applications of diazoalkanes under the supervision of Prof. Koenigs.



Dr. J. Ho

**Junming Ho** completed his PhD (2011) from the Australian National University under the mentorship of Prof. Michelle Coote and Prof. Christopher Easton. From 2013 to 2017, he was an A\*STAR International Fellow at Yale University (USA), and research scientist in the Institute of High Performance Computing (Singapore). In 2017, he moved to the University of New South Wales (Australia), where he currently leads the computational chemistry group focusing on multi-scale simulations and physical organic chemistry.



Prof. M. J. Weissenborn

**Martin J. Weissenborn** completed his MSc in 2008 at the University of Lund, Sweden, and his Chemistry Diploma (Dipl.-Chem.) in 2009 at the University of Kiel, Germany. His diploma thesis was under the supervision of Prof. Thisbe Lindhorst. From 2009–2012 he did his PhD at the Manchester Institute of Biotechnology (UK) in the lab of Prof. Sabine Flitsch. In 2012 he moved to Stuttgart, Germany, and carried out postdoctoral studies in the group of Prof. Bernhard Hauer. In 2016 he had a research stay in the lab of Prof. Don Hilvert at the ETH Zürich, Switzerland. Since autumn 2016 he is jointly appointed Junior-Professor at the Martin Luther University Halle-Wittenberg, Institute of Chemistry, and the Leibniz Institute of Plant Biochemistry (Germany). His research interests focus on discovery and directed evolution of novel non-natural enzymatic reactions.



Prof. R. M. Koenigs

**Rene M. Koenigs** obtained his PhD in 2011 from RWTH Aachen University (Germany) under the guidance of Prof. Magnus Rueping. He subsequently moved to Grunenthal GmbH (Germany), working as a medicinal chemist on GPCR and ion channel targets. In 2015 he was appointed as Junior-Professor at RWTH Aachen University. His research interests focus on applications of carbene transfer reactions, continuous-flow chemistry and fluorine chemistry.

## Young Career Focus: Dr. Jesús Campos (Spanish National Research Council (CSIC), Sevilla, 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 Dr. Jesús Campos (Spanish National Research Council (CSIC), Sevilla, Spain).

### Biographical Sketch



Dr. J. Campos

**Jesús Campos** was born in Sevilla (Spain), where he studied chemistry (University of Sevilla, 2007, Spain) before moving to the University of Manchester (UK) to work under the guidance of Prof. John D. Sutherland (MPhil, 2008). Upon moving back to Sevilla he joined the group of Prof. Ernesto Carmona to work on fundamental organometallic chemistry, and spent some time as a visiting researcher with Prof. Maurice Brookhart (University of North Carolina, USA, 2010). He returned to the USA later, as a postdoctoral researcher, joining the group of Prof. Robert H. Crabtree at Yale University to work in green catalysis and energy-related transformations (2013–2014). He was awarded a Talentia Postdoc Fellowship for a second postdoctoral period in the laboratory of Prof. Simon Aldridge at the University of Oxford (UK) to focus on bond activation and catalysis with main-group systems (2014–2016). In 2016 he moved back to the University of Sevilla after securing a Marie Curie IF fellowship and one year later he was awarded a permanent position as Tenured Scientist of the Spanish National Research Council (CSIC) to develop his independent career at the Institute of Chemical Research (IIQ) at Sevilla. In 2017 he was awarded an ERC Starting Grant project aiming to develop new strategies in cooperative bond activation and catalysis.

### INTERVIEW

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

**Dr. J. Campos** Our current interests range over a variety of topics within the fields of organometallic chemistry and homogeneous catalysis. We have recently focused on investigating cooperative chemical systems for small-molecule activation, with the final aim of discovering new catalytic processes. As such, we have embarked into the design of frustrated Lewis pairs based on transition metals, as well as other less well-explored bimetallic combinations of transition metals and low-valent main-group elements. The design of exceptionally bulky ligands for these and other purposes has also become a common aim within our group.

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

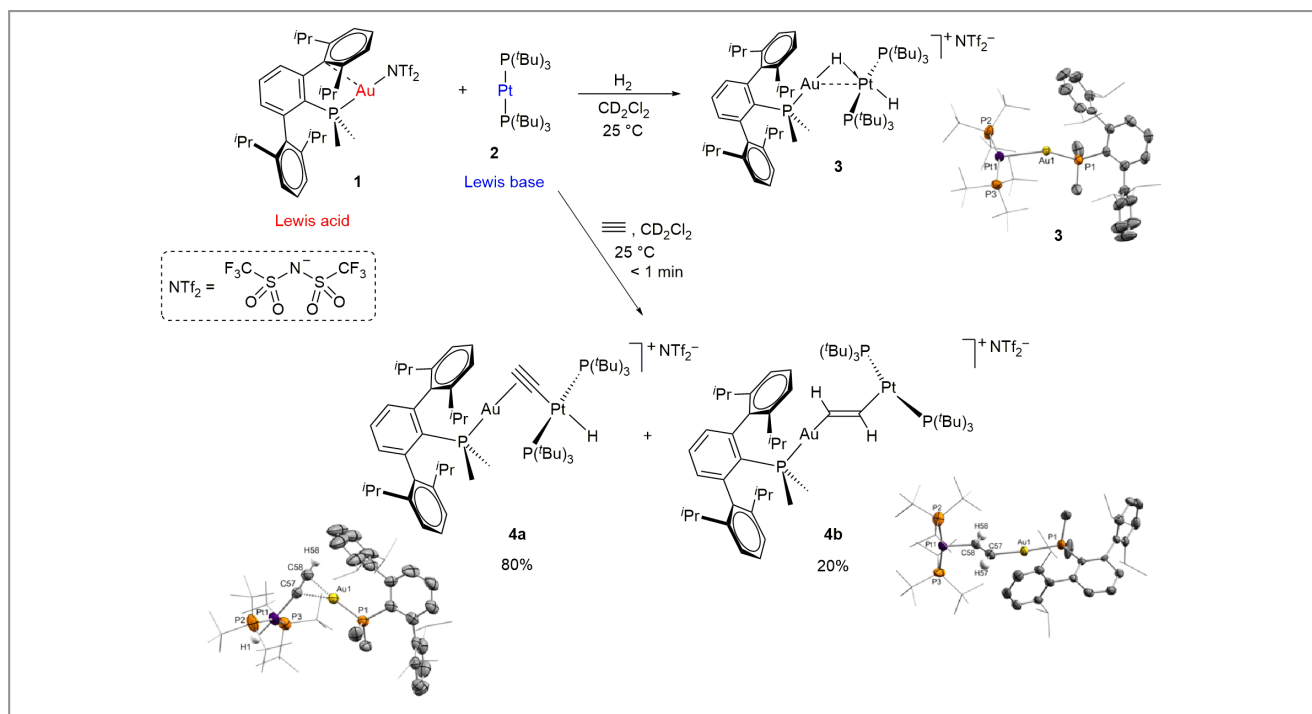
**Dr. J. Campos** I have been fascinated by synthetic chemistry from as far back as I can remember. I have always been truly enthralled by the creativity of synthetic chemists in preparing complex natural products. Connecting and disconnecting chemical fragments by forming and cleaving chemical bonds to access challenging structures constitutes the perfect blend of art and science. But beyond its beauty, the molecules that synthetic chemists can provide have a tremendous impact on our modern life. My first incursions into synthetic challenges came during my master's studies at the University of Manchester (UK), where I prepared a variety of isotopically labelled nucleosides to carry out mechanistic studies in the context of prebiotic chemistry. A decade later, I retain my interest in the analysis of reaction mechanisms but now focus on the role of metal centers to mediate otherwise unattainable transformations.

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

**Dr. J. Campos** Organic synthesis has been at the heart of modern chemistry for the last century and will certainly remain a key interdisciplinary science for the foreseeable future. Despite being a mature discipline there are still many aspects that require improvement. Chemical sustainability is arguably one of the major challenges for the 21<sup>st</sup> century. In fact, our chemical industry needs to be more efficient in terms of energy demands, waste production and sustainable feedstocks. The role of organic chemists, particularly those working on developing new catalysts and catalytic processes, will be essential in achieving these goals. Catalysis already occupies a prominent position in synthetic organic chemistry, both at laboratory scale and in industry, and looking at how Nature does chemistry, I am convinced of the many groundbreaking discoveries in the field of catalysis that will emerge in the years to come, not only applied to organic synthesis, but also to other related areas such as materials science or supramolecular chemistry.

**SYNFORM** Could you tell us more about your group's areas of research and your aims?

**Dr. J. Campos** As mentioned before, our current interests include many aspects of organometallic chemistry and homogeneous catalysis, with particular emphasis on developing cooperative systems based on underexplored concepts. I have the privilege of working with a group of several highly motivated students that certainly enjoy doing science. This allows us to consider not only our initial aims, but also every other aspect that shows up in the course of our investigations. Besides all the nice surprises that we find in these excursions, we are particularly focused on developing several types of cooperative chemical systems for small-molecule activation and, eventually, for their application in the development of new catalytic transformations. The first of these involves the design of frustrated Lewis pairs (FLPs) based on transition metals. The ability of FLPs to activate a wide variety of small molecules has revolutionized the chemistry of the P block elements, which are now capable of mediating bond-activation reactions that were thought to be restricted to transition metals. Catalytic applications of FLPs mainly include hydrogenation and other related transformations. However, the introduction of transition metals into FLP designs can enhance



the catalytic potential of the FLP concept by virtue of the set of elementary reactions that transition metals offer. We expect that metallic FLPs will expand the catalytic usefulness of the concept far beyond their current applications. Our efforts in the field allowed us to describe the first metallic FLP in which the two components of the cooperative pair are based on transition metals, more precisely Au(I) and Pt(0) as the Lewis acid and basic components, respectively (Scheme 1). This pair readily reacts with dihydrogen or acetylene in a cooperative manner, while the individual metallic components exhibit either no or dissimilar reactivity. We are now extending these results to other late-transition metals and exploring their potential in cooperative catalysis.

In a related line of research that we started very recently, we are pursuing the design of hybrid systems that incorporate a low-valent main-group element and a transition-metal center in close proximity. We expect that the ability of the former to activate a wide variety of polar bonds, along with the chemical richness of the latter, will permit the discovery of new ways of bond activation and catalysis. In addition, we have lately begun to explore other bimetallic and multimetallic systems that operate under synergistic mechanisms for the activation of small molecules. A common aspect shared by the three lines of research described is ligand design, particularly those that provide sufficient steric protection to modulate the balance between metal–metal interaction and frustration and to kinetically stabilize unsaturated species.

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

**Dr. J. Campos** Our team started as an independent research group very recently and thus our most important scientific contributions are yet to come. That being said, I am most proud of my first report in the field of transition-metal FLPs, which I developed myself and published two years ago as a single-author paper (*J. Am. Chem. Soc.* **2017**, *139*, 2944–2947). This work laid the foundation for one of our most productive research lines at the moment and, I would like to believe, it will motivate other research groups to develop these types of cooperative systems and exploit their potential in catalysis.



## Coming soon

### Articles with focus on the American Chemical Society Spring 2019 National Meeting, Orlando (USA)

#### ■ Name Reaction Bio

### Carbocation Rearrangements: The Pinacol, Wagner–Meerwein, Demjanov, and Tiffeneau–Demjanov Rearrangements

#### Further highlights

##### **Synthesis** Review: Rhodium-Catalyzed Allylation Reactions

(by M. B. Thoke and Q. Kang)

##### **Synlett** Account: Cp\*Co<sup>III</sup>-Catalyzed C–H Functionalization and Asymmetric Reactions Using External Chiral Sources

(by T. Yoshino and S. Matsunaga)

##### **Synfacts** Synfact of the Month in category “Synthesis of Natural Products and Potential Drugs”: Total Synthesis of (+)-Flavisiamine F

For current SYNFORM articles, please visit [www.thieme-chemistry.com](http://www.thieme-chemistry.com)  
SYNFORM issue 2019/08 is available from July 18, 2019  
at [www.thieme-connect.com/ejournals](http://www.thieme-connect.com/ejournals)

#### Editor

Matteo Zanda, Chair in Biomolecular Imaging, Centre for Imaging Science, Department of Chemistry, School of Science, Loughborough University, Leicestershire, LE11 3TU, UK and  
C.N.R. – Istituto di Chimica del Riconoscimento Molecolare  
Via Mancinelli, 7, 20131 Milano, Italy  
Editorial Assistant: Alison M. Sage  
[synform@outlook.com](mailto:synform@outlook.com); fax: +39 02 23993080

#### Editorial Office

- Managing Editor: Susanne Haak,  
[susanne.haak@thieme.de](mailto:susanne.haak@thieme.de), phone: +49 711 8931 786
- Scientific Editors:  
Stefanie Baumann, [stefanie.baumann@thieme.de](mailto:stefanie.baumann@thieme.de), phone: +49 711 8931 776  
Selena Boothroyd, [selena.boothroyd@thieme.de](mailto:selena.boothroyd@thieme.de)  
Michael Binanzer, [michael.binanzer@thieme.de](mailto:michael.binanzer@thieme.de), phone: +49 711 8931 768  
Giuliana Rubulotta, [giuliana.rubulotta@thieme.de](mailto:giuliana.rubulotta@thieme.de), phone: +49 711 8931 183  
Kathrin Ulbrich, [kathrin.ulbrich@thieme.de](mailto:kathrin.ulbrich@thieme.de), phone: +49 711 8931 785
- Senior Production Editors:  
Thomas Loop, [thomas.loop@thieme.de](mailto:thomas.loop@thieme.de), phone: +49 711 8931 778  
Thorsten Schön, [thorsten.schoen@thieme.de](mailto:thorsten.schoen@thieme.de), phone: +49 711 8931 781
- Production Manager: Sophia Hengst,  
[sophia.hengst@thieme.de](mailto:sophia.hengst@thieme.de), phone: +49 711 8931 398
- Production Assistant: Tobias Brenner,  
[Tobias.brenner@thieme.de](mailto:Tobias.brenner@thieme.de), phone: +49 711 8931 769
- Editorial Assistant: Sabine Heller,  
[sabine.heller@thieme.de](mailto:sabine.heller@thieme.de), phone: +49 711 8931 744
- Marketing Director: Julia Stötzner,  
[julia.stoetznern@thieme.de](mailto:julia.stoetznern@thieme.de), phone: +49 711 8931 771
- Postal Address: Chemistry Journals, Editorial Office, Georg Thieme Verlag KG,  
Rüdigerstraße 14, 70469 Stuttgart, Germany,
- Homepage: [www.thieme-chemistry.com](http://www.thieme-chemistry.com)

#### Publication Information

Synform will be published 12 times in 2019 by Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany, and is an additional online service for Synthesis, Synlett and Synfacts.

#### Publication Policy

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

#### Ordering Information for Print Subscriptions to Synthesis, Synlett and Synfacts

The Americas: Thieme Publishers New York, Thieme Medical Publishers, Inc., 333 Seventh Avenue, New York, NY 10001, USA.  
Via e-mail: [customerservice@thieme.com](mailto:customerservice@thieme.com)  
Via website: [www.thieme-chemistry.com](http://www.thieme-chemistry.com)  
Phone: +1 212 760 0888; Fax: +1 212 947 1112  
Order toll-free within the USA: +1 800 782 3488

Europe, Africa, Asia, and Australia: Thieme Publishers Stuttgart, Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany.  
Via e-mail: [customerservice@thieme.de](mailto:customerservice@thieme.de)  
Via website: [www.thieme-chemistry.com](http://www.thieme-chemistry.com)  
Phone: +49 711 8931 421; Fax: +49 711 8931 410

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

#### Online Access

The online versions of Synform as well Synthesis, Synlett, Synfacts and SynOpen are available through [www.thiemeconnect.com/products/ejournals/journals](http://www.thiemeconnect.com/products/ejournals/journals) where it is also possible to register for a free trial account. For information on multi-site licenses and pricing for corporate customers as well as backfiles, please contact our regional offices:

The Americas: [esales@thieme.com](mailto:esales@thieme.com), phone: +1 212 584 4695  
Europe, Africa, Asia, and Australia: [eproducts@thieme.de](mailto:eproducts@thieme.de), phone: +49 711 8931 407  
India: [eproducts@thieme.in](mailto:eproducts@thieme.in), phone +91 120 45 56 600  
Japan: [brhosoya@poplar.ocn.ne.jp](mailto:brhosoya@poplar.ocn.ne.jp), phone +81 3 3358 0692

#### Manuscript Submission to Synthesis, Synlett, and SynOpen

Manuscript submissions will be processed exclusively online via <http://mc.manuscriptcentral.com/synthesis>, <http://mc.manuscriptcentral.com/synlett> and <http://mc.manuscriptcentral.com/synopen>, respectively. Please consult the Instructions for Authors before compiling a new manuscript. The current version and the Word template for manuscript preparation are available for download at [www.thieme-chemistry.com](http://www.thieme-chemistry.com).

#### Copyright

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

#### Copyright Permission for Users in the USA

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