

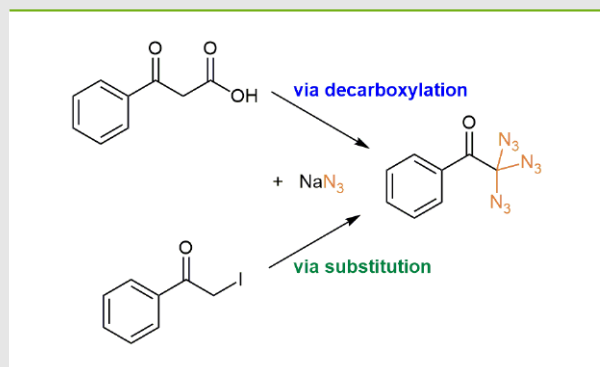
# SYNFORM

People, Trends and Views in Synthetic Organic Chemistry

2014/11

## SYNSTORIES ■ ■ ■ ■

■ The Synthesis of  $\alpha$ -Azidoesters and Geminal Triazides



■ A Biocompatible Alkene Hydrogenation Merges Organic Synthesis with Microbial Metabolism

■ Iron-Catalyzed Intermolecular Hydroamination of Styrenes

■ Young Career Focus:  
Dr. Jackson D. Leow (National Tsing-Hua University, Hsinchu, Taiwan)

**CONTACT +++++**

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



**Dear Readers,**

This is my first editorial after the referendum for Scottish Independence, which had global coverage by world's media. I am not willing to write about politics and in any case I do not think this would be the right place for doing

so, however, as a scientist, I am glad that Scottish science will continue to be part of British science because I firmly believe that neither creating barriers nor losing critical mass is good for science and research, and this is true in general, not just in this country. In fact, I also believe that the European dimension is a fantastic opportunity for developing cutting-edge science and maximizing the positive impact of research in the Old Continent and beyond. I would love to see more opportunities for collaboration among scientists from all over the world – which is exactly what Europe's Horizon 2020 is already trying to do by opening a number of funding schemes to extra-European countries and researchers – and I think we scientists should consider the globalization of research as a fundamental goal we need to achieve and we should lobby as hard as possible with our politicians to convince them that “Better Together” is true everywhere, not just here in Scotland. Is it just Utopia? I don't think so, not when it comes to science at least, because science has an immense power, it can do miracles and it can bring peace where otherwise there is war. There are so many examples of scientists who keep talking and collaborating even when their respective governments don't or are even fighting each other. In science the whole is always much greater than the sum of its parts, that's why we need to stay and work together, in Scotland, in the UK, in Europe, and in the World. And this issue of **SYNFORM** mirrors very well the global nature of science, as at least three continents are represented in the four articles of this issue. We start from the USA, where E. Balskus takes us through the biocompatible chemical transformations developed by her group, and we continue with Europe and Germany, where S. F. Kirsch found an ingenious way to prepare geminal triazides and  $\alpha$ -azidoesters. We then go back to the USA, where J. Yang explains how his group designed and achieved a novel hydroamination of styrenes. This month's journey ends in Asia, and more precisely in Taiwan, where J. D. Leow, the protagonist of a new Young Career Focus, is based. Wherever you are... have a nice read!!!

Enjoy your reading!

**Matteo Zanda**

Editor of **SYNFORM**

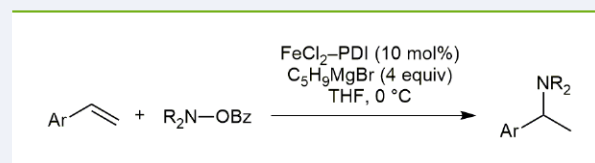
## IN THIS ISSUE

### SYNSTORIES ■ ■ ■ ■

**A Biocompatible Alkene Hydrogenation Merges Organic Synthesis with Microbial Metabolism** .....A145

**The Synthesis of  $\alpha$ -Azidoesters and Geminal Triazides** .....A147

**Iron-Catalyzed Intermolecular Hydroamination of Styrenes** .....A150



**Young Career Focus: Dr. Jackson D. Leow (National Tsing-Hua University, Hsinchu, Taiwan)** .....A152

**COMING SOON** .....A155

**CONTACT + + + +**

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

## A Biocompatible Alkene Hydrogenation Merges Organic Synthesis with Microbial Metabolism

*Angew. Chem. Int. Ed.* **2014**, *53*, 7785–7788

■ The metabolism of living organisms, such as microbes, is a powerful tool for producing small molecules directly from fermentations in an efficient and environmentally compatible manner. However, the potential of microbial metabolism would be dramatically boosted if ‘traditional’ organic synthesis could be efficiently combined with enzymatic methods in living organisms. This remains a challenging endeavor owing to the non-aqueous solvents, extreme temperatures, and reactive intermediates generally used in non-enzymatic synthesis. Recently, a paper published by the research group of Professor Emily Balskus, Harvard University (USA), described a novel approach to this problem and their subsequent successful effort to actually integrate a reaction from synthetic organic chemistry with the chemistry that happens in the biological realm for the purposes of small molecule synthesis. Professor Balskus gave some background on this topic: “I fell in love with chemistry as a high school student and kept pursuing it into my graduate studies, which focused on a mix of asymmetric catalysis and natural product total synthesis. As a post-doc, I became interested in studying the chemistry that happens in biological systems, and for my independent career I wanted to focus on innovative science that can weave these

two threads together. My lab’s research merges chemical and biological synthesis in multiple ways.”

Synthetic chemists have made great strides in bringing biological reactivity (e.g. enzymes and biocatalysis) into the chemical realm, and Professor Balskus hopes this paper shows that the reverse may also be possible, i.e. using reactions and catalysts familiar to synthetic organic chemists in the biological realm. “Over the past century, synthetic chemists have made enormous contributions to both science and society, and we now have an amazing capability to access non-natural small molecules,” said Professor Balskus, adding: “Metabolic engineers would like to advance their field to the point where their ability to produce small molecules rivals or surpasses that of synthetic chemists, which is an admirable goal.” Professor Balskus continued: “One of the main obstacles I see to achieving that level of synthetic prowess in the biological realm is that there are certain types of chemical reactivity that have not yet been observed in nature.” Making certain bond connections is not possible using enzymatic chemistry, explained Professor Balskus, and evolving enzymes to carry out these transformations is still a long way off. “This situation is incredibly common when the small

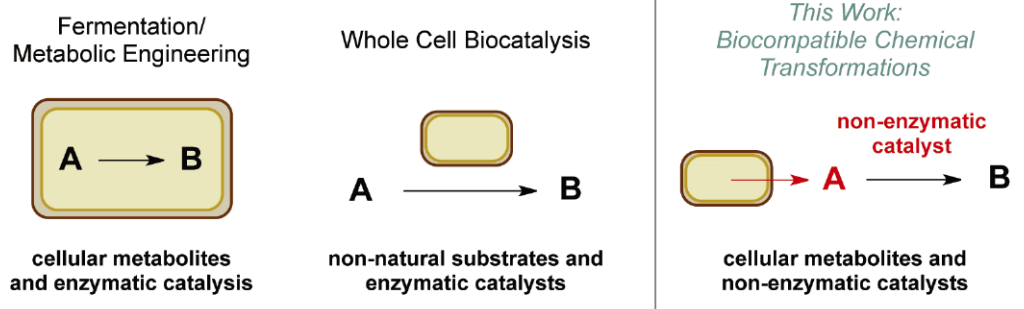
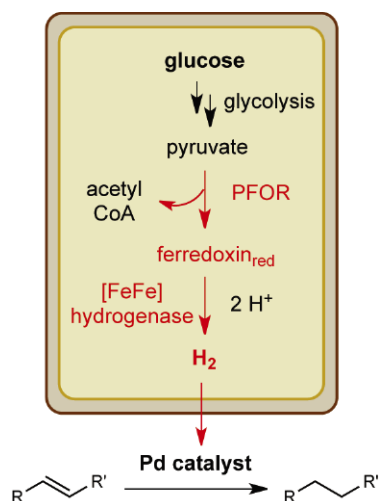


Figure 1 Overview of biocompatible chemistry

molecule target of interest is something like a non-natural pharmaceutical, such as drugs like Lipitor or Januvia,” Professor Balskus noted. “So, for metabolic engineers to actually reach their goal, they will need some way to bring the synthetic chemist’s repertoire into a biological reaction milieu. That is what we describe in this paper,” she explained. “We developed what we have termed ‘biocompatible chemistry’, the interfacing of a non-enzymatic transformation with the metabolism of a living organism (Figures 1 and 2). This report is a demonstration that such a combination is possible, and we hope that it inspires other scientists, both metabolic engineers and synthetic chemists, to think about how they can bring the power of synthetic organic chemistry to bear on difficult metabolic engineering challenges.”



**Figure 2** Bacterially produced hydrogen gas is used in situ for an alkene reduction

In thinking about the specifics of the paper, one thing that surprised Professor Balskus looking back was how similar the process of developing this reaction was to optimizing any other reaction that she and the co-authors of this work, Dr. Gopal Sirasani and Mr. Liuchuan Tong, have worked on. Professor Balskus said: “Our very early experiments showed that the desired reactivity and compatibility were possible, and from there it was a matter of optimizing the catalyst and reaction conditions. To us, it is very encouraging that many of the reaction conditions we tried did indeed yield product, we didn’t just happen upon the one set of conditions that would work in some unique way. The approach we took to reaction

development is familiar to all organic chemists, which is why I’m optimistic others will join us in exploring this new frontier in synthesis,” she concluded. ■

**Matteo Zanda**

### About the authors



*Prof. E. Balskus*

**Emily Balskus** was born in Cincinnati, Ohio (USA) and became interested in chemistry as a high school student. She graduated from Williams College (USA) in 2002 as valedictorian with highest honors in chemistry. After spending a year at the University of Cambridge (UK) as a Churchill Scholar in the lab of Professor Steven Ley, she pursued graduate studies in the Department of Chemistry and Chemical Biology (CCB) at Harvard University (USA), receiving her PhD in 2008. Her graduate work with Professor Eric Jacobsen focused on the development of asymmetric catalytic transformations and their application in the total synthesis of complex molecules. From 2008–2011 she was an NIH postdoctoral fellow at Harvard Medical School in the lab of Professor Christopher T. Walsh. Her research in the Walsh lab involved elucidating and characterizing biosynthetic pathways for the production of small molecule sunscreens by photosynthetic bacteria. She also received training in microbial ecology and environmental microbiology as a member of the Microbial Diversity Summer Course at the Marine Biology Lab at Woods Hole during the summer of 2009.

Emily joined the CCB faculty in 2011. She is also an Associate Member of the Broad Institute of Harvard and MIT and is a Faculty Associate of the Microbial Sciences Initiative at Harvard. Her independent research has been recognized with multiple awards, including the 2011 Smith Family Award for Excellence in Biomedical Research, the 2012 NIH Director’s New Innovator Award, and the 2013 Packard Fellowship for Science and Engineering. She is also a 2012 Searle Scholar.

## The Synthesis of $\alpha$ -Azidoesters and Geminal Triazides

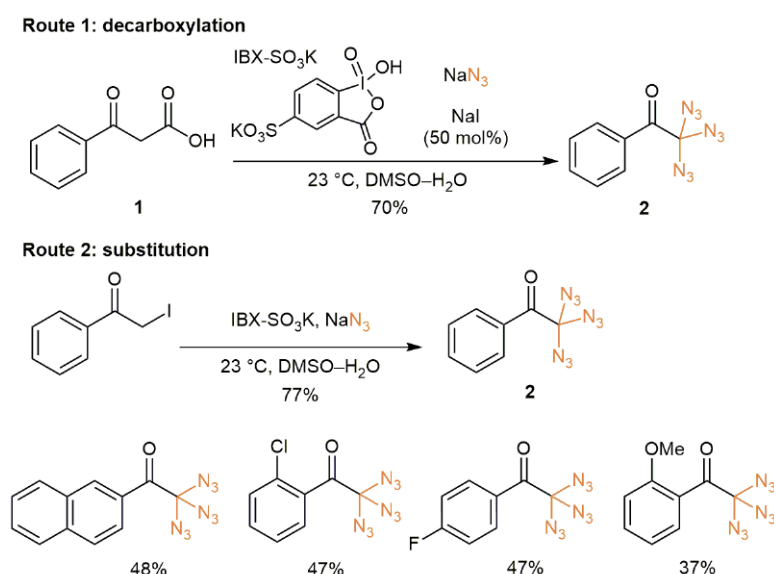
*Angew. Chem. Int. Ed.* **2014**, *53*, 7913–7917

■ The use of organic azides is ubiquitous in the functionalization of biomolecules through click chemistry, and also has many applications in materials science. These aspects led Professor Stefan Kirsch and his research group at the Bergische Universität Wuppertal (Germany) to develop an interest in the direct installation of the azide moiety through the oxidative functionalization of enolizable compounds with a simple azide source, preferably sodium azide. Professor Kirsch explained: “When we began our studies, the major goal was to achieve the azidation reaction in a highly chemoselective manner. To this end, a sulfonylated derivative of 2-iodoxybenzoic acid, IBX-SO<sub>3</sub>K, was developed that, in combination with sodium iodide, showed a perfectly balanced oxidation power to convert 1,3-dicarbonyls into their mono- and diazides in the presence of numerous functional groups. This method allowed the exchange of all hydrogens for azides at the easily enolizable position.”

Upon publication of their results (see: *Chem. Eur. J.* **2012**, *18*, 1187), they wondered whether the same azidation strategy could lead to azidated carbonyl compounds through a concomitant decarboxylation when malonic acid monoesters

were employed. Indeed, Dr. Philipp Klahn was able to show that the reaction of malonic acid monoesters with NaN<sub>3</sub> in the presence of IBX-SO<sub>3</sub>K and substoichiometric amounts of NaI in aqueous DMSO led directly to the formation of  $\alpha$ -azidoesters, a class of compounds that might be of future interest as potential precursors of  $\alpha$ -amino acids. Next they turned their attention to the decarboxylative azidation of the very similar 3-oxocarboxylic acids (such as **1**), where Professor Kirsch expected to find the azidoacetophenone **3** as the azidated product, or even higher azidated derivatives thereof. Professor Kirsch recalled: “However, the mono-azidated compound was not formed, and instead Philipp isolated, after work-up, column chromatography and concentration with the rotary evaporator, the novel azide-containing compound **2**. I was quite puzzled when the <sup>1</sup>H NMR spectrum of **2** did not show a single hydrogen at the  $\alpha$ -position, thus revealing a quaternary carbon.”

Much analytical work was required to accurately determine the structure of the geminal triazide **2**, since determination of the accurate mass of the molecule ion failed, and less azidated species were also possible. Professor Kirsch

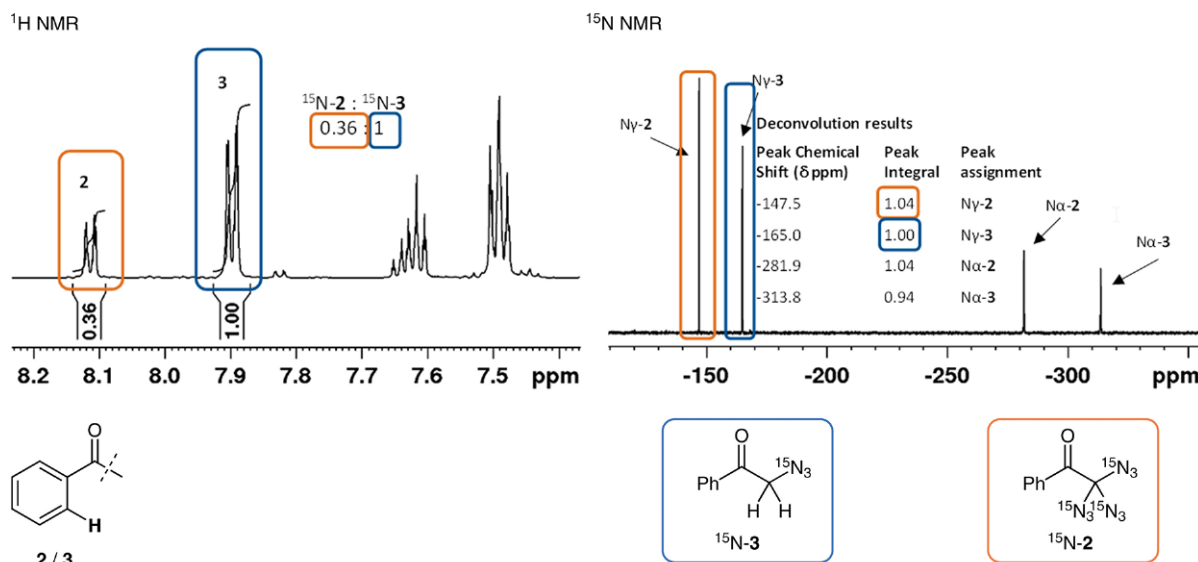


remarked: “Moreover, we were quite reluctant in the beginning to accept the structure of the geminal triazide, because we did not expect that these nitrogen-rich compounds were stable enough to be isolated with the standard experimental repertoire of synthetic chemists.” He continued: “Our first analytical proof for the triazide structure was from the reaction with cyclooctyne that gave the corresponding tris-1,2,3-triazole derivative through triple click reaction.” Two other members of the group, Dr. Andreas Kotthaus and Hellmuth Erhardt, then planned an exciting NMR experiment to directly determine the degree of azidation of **2** by studying a mixture of  $^{15}\text{N}$ -labelled **2** and **3**. Professor Kirsch said: “They obtained the  $^1\text{H}$  and  $^{15}\text{N}$  NMR data and were able to calculate from the integrals in both spectra that **2** has a nitrogen content three times as high as that of the known monoazide **3**: it was clear that the new compound **2** we had synthesized and isolated was the geminal triazide.”

When Dr. Klahn was able to develop a more straightforward route toward this new class of compounds that did not rely on a decarboxylation step, a simple access to a broad range of previously unknown triazides was found. Several  $\alpha$ -iodomethyl aryl ketones were successfully poly-azidated in the presence of IBX- $\text{SO}_3\text{K}$  and  $\text{NaN}_3$  in aqueous DMSO.

Professor Kirsch concluded: “Geminal triazides are not substances that everybody would work with, and one should always take appropriate caution before handling them. However, this is a new class of compounds that might have useful properties, for example as energetic plasticizers. The unusual structure of the triazide functionality holds great potential for discovering even more interesting chemistry.”

Matteo Zanda





### About the authors



Prof. S. F. Kirsch

Stefan F. Kirsch received his undergraduate education at Philipps-Universität Marburg (Germany) and obtained the Diploma degree in 2000. After his PhD thesis at Technische Universität München (Garching, Germany) with Professor Thorsten Bach (2000–2003), he moved as a postdoctoral fellow to the University of California at Irvine (USA) to work with Professor Larry E. Overman. In 2005, he returned to Technische Universität München. In 2011, he accepted an offer as Full Professor in Organic Chemistry at Bergische Universität Wuppertal (Germany). His work focuses on the development of new transition-metal-catalyzed domino reactions, oxidative functionalizations, and their applications in total synthesis.



Dr. P. Klahn

Philipp Klahn worked from 2002–2005 as laboratory technician at Altana Pharma (Germany). He received his undergraduate education at Technische Universität München and obtained his MSc in 2010. Afterwards he completed his PhD in the research group of Professor Stefan F. Kirsch in München and Wuppertal, dealing with, among others, the development of novel azidation protocols for carbonyl compounds. He is currently a Feodor-Lynen postdoctoral fellow at Rice University (USA) where he is working with Professor K. C. Nicolaou on the total synthesis of complex natural products.



H. Erhardt

Hellmuth Erhardt completed his undergraduate studies at the Nuremberg Institute of Technology (Germany) and obtained his MSc in 2013. He then joined the research group of Professor Stefan F. Kirsch at the Bergische Universität Wuppertal where he is currently continuing with his PhD studies in the field of polyazides.



Dr. A. F. Kotthaus

Andreas F. Kotthaus received his PhD in 2005 under the guidance of Professor Hans-Joseph Altenbach at the Bergische Universität Wuppertal. He then moved to the biochemicals company BACHEM (Switzerland) where he worked as a team leader in the production of peptides. In 2008 he returned to Wuppertal as a permanent research associate in the group of Professor Stefan F. Kirsch.

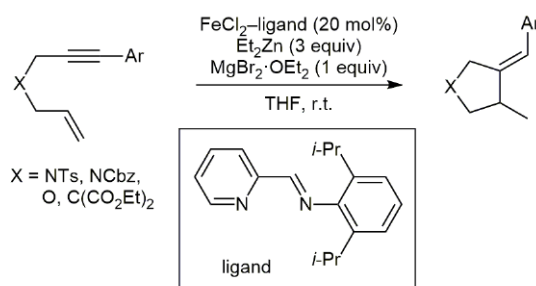
## Iron-Catalyzed Intermolecular Hydroamination of Styrenes

*Org. Lett.* **2014**, *16*, 3620–3623

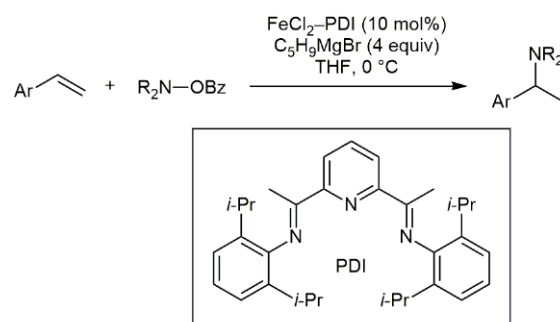
Functionalized benzylamines are important compounds with a number of uses as agrochemicals, intermediates in medicinal chemistry and building blocks in materials science, to cite only a few examples. Therefore, the development of novel methods for accessing this class of compounds in an efficient and economically sustainable manner continues to be an area of great interest in organic chemistry. The group of Professor Jiong Yang at Texas A&M University (USA) has an interest in low-valent iron catalysis that can be traced back to one of their natural product total synthesis projects (see: *Org. Lett.* **2010**, *12*, 5072; *J. Am. Chem. Soc.* **2012**, *134*, 8806). That work made use of a combination of  $\text{FeCl}_2$ – $\text{MeMgCl}$  and  $\text{TMSCl}$  to convert the  $\alpha,\beta$ -unsaturated ketone of carvone into an extended trimethylsilyl dienol ether. Professor Yang said: “Our curiosity about the mechanism of this unusual transformation led us to consider other possibilities of low-valent iron catalysis. Iron played an important role in the early develop-

ment of organometallic chemistry, but it has been overshadowed by late transition metals such as Pd, Rh, Ru, etc. in recent decades.” According to Professor Yang, despite the recent surge of research activities, such as the chemistry of iron-redox active ligand complexes, iron-catalyzed C–H activation, etc., the chemistry of low-valent iron remains underexplored. “We envisioned that the unique electronic structure of iron and other early transition metals could probably be translated into distinct reactivity that may be explored in transformations that have been difficult with late transition metals,” explained Professor Yang, whose group’s recent efforts have been focused on low-valent iron-catalyzed functionalization of alkenes. In collaboration with postdoctoral research associate Dr. Aijun Lin and postdoctoral fellow Dr. Zhi-Wei Zhang, they recently developed the first iron-catalyzed reductive cyclization of 1,6-enynes (*Org. Lett.* **2014**, *16*, 386).

### (A) Yang's previous work: Iron-catalyzed reductive cyclization of 1,6-enynes



### (B) This work: Iron-catalyzed intermolecular hydroamination of styrenes

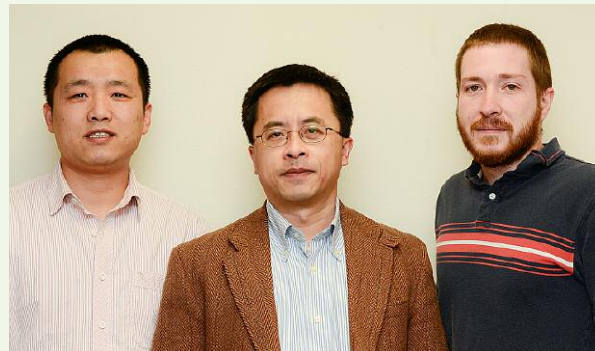




Professor Yang said: “This research project quite naturally led us to become interested in the possibility of low-valent iron-catalyzed hydroamination of alkenes using electrophilic nitrogen sources. Aijun carried out preliminary studies to verify the feasibility of the reaction before the project was transferred to the then graduate student, Bryan Huehls.” One major difficulty at that time, recalled Professor Yang, had been the low conversion of the reaction. Dr. Huehls solved this problem by literally following his nose: a distinct smell of piperidine during reaction work-up suggested that most of the electrophilic nitrogen source (*O*-benzoyl-*N*-hydroxypiperidine) had been consumed by a non-productive reduction pathway. This situation could be effectively corrected by slow addition of the electrophilic nitrogen reagent using a syringe pump. Further optimization of the reaction conditions and testing the scope of the substrates led to this iron-catalyzed intermolecular hydroamination of styrenes. According to Professor Yang, the significance of this research lies in demonstrating the possibility of low-valent iron in catalyzing transformations that have typically been reserved for late transition metals. “We are confident that further development of iron catalysis, such as by inventing new ancillary ligands, developing effective protocols to generate reactive catalytic species, and exploring new reactivities of organoiron complexes, etc. will lead to catalytic systems that are more effective and enable unique transformations that have been difficult or impossible using other transition-metal catalytic systems,” Professor Yang concluded. ■

Matteo Zanda

### About the authors



From left to right: Dr. A. Lin, Prof. J. Yang, C. B. Huehls

**Aijun Lin** was born in Jintan (P. R. of China). He received his Ph.D. from Nanjing University (P. R. of China) in 2011 for his work on asymmetric organocatalysis under the guidance of Professor Chengjian Zhu. After a one-year postdoctoral stint at the same group, he joined the research group of Professor Jiong Yang at Texas A&M University (USA) in 2012 as a postdoctoral research associate.

**C. Bryan Huehls** attended Ball State University, Indiana (USA) where he first began research in synthetic methodology under the guidance of Professor Robert E. Sammelson. After receiving his B.A. in chemistry in 2009, he started his graduate studies at Texas A&M University in spring 2010 and joined the research group of Professor Jiong Yang. His doctoral research focused on developing new methods for synthesis of indolenines and exploring iron-catalyzed transformations.

**Jiong Yang** received his Ph.D. from The Ohio State University (USA) for his work on total synthesis of natural products under the tutelage of Professor Leo A. Paquette. He pursued postdoctoral research in chemical genetics in the laboratories of Professor Peter G. Schultz (The Scripps Research Institute, La Jolla, USA) and then Professor Stuart L. Schreiber (Harvard University/Broad Institute of MIT and Harvard, USA) as an NIH postdoctoral fellow before joining Texas A&M University.

## Young Career Focus: Dr. Jackson D. Leow (National Tsing-Hua University, Hsinchu, Taiwan)

■ **Background and Purpose.** *SYNFORM* will from time to time meet young up-and-coming researchers who are performing exceptionally well in the arena of organic chemistry and related fields of research, in order to introduce them to the readership. This *SYNSTORY* with a Young Career Focus presents Dr. Jackson D. Leow (National Tsing-Hua University, Hsinchu, Taiwan).

### BIOGRAPHICAL SKETCH



Dr. J. D. Leow

**Jackson D. Leow** was born in Singapore in 1981. He received both his undergraduate and Ph.D. degrees from the National University of Singapore (NUS) under the tutelage of Professor Choon-Hong Tan in 2005 and 2009, respectively. His efforts led to the discovery of chiral bicyclic guanidine as a proton shuttle molecular machine for enantioselective

protonation and isomerization reactions. In between, he worked at S\*Bio Pharma and accumulated industrial experience in drug discovery. From 2010–2012, he pursued his postdoctoral studies with Professor Jin-Quan Yu at The Scripps Research Institute in San Diego (USA). There, he was engaged in research at the forefront of activating inert *meta*-C–H bonds, solving one of the most challenging problems in organic synthesis. He established the concept of directed remote *meta*-C–H functionalization which was published in *Nature*. Following that, he returned to Singapore to work at the Agency for Science, Technology and Research (A\*STAR). As a research scientist II, he led a small research team as project leader. He assumed the position of Assistant Professor at the National Tsing Hua University of Taiwan in 2013. His works attracted an average of 58 citations per paper. They were recognized with numerous awards including the Thieme Chemistry Journal Award (2014), Marquis Who's Who in the World (2014), A\*STAR postdoctoral fellowship (2010), and Kiang Ai Kim scholarship (2006). He is an elected Fellow of the World Technology Network as well as the Global Young Academy (GYA). His current research focuses on developing new catalytic processes to control radicals in organic synthesis.

### INTERVIEW

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

**Dr. J. D. Leow** | My current research activity focuses on developing new catalytic processes. Ideally, they should proceed with excellent efficiency, selectivity, and eco-friendliness. From this perspective, classic radical reactions rarely fulfill these criteria. They have been known since their discovery by Professor Moses Gomberg in 1900. They are very reactive, resulting in poor regioselectivity and stereoselectivity. We aim to tap into their unique high reactivity profile while modulating them such that they do not react at random sites. We take on this challenge by using contemporary approaches such as transition-metal catalysis and organo-catalysis.

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

**Dr. J. D. Leow** | My high school aspiration was to become a chemist. I am grateful and thankful that I had inspirational chemistry teachers during the formative years of my education. During my undergraduate studies, I chanced upon Professor K. C. Nicolaou's "Classics in Total Synthesis I". I was greatly fascinated by the monumental works of various legendary organic synthetic chemists such as Professor Robert B. Woodward and Professor E. J. Corey. On the other hand, I found them daunting and overwhelming. Luckily, I met a wonderful advisor, Professor Tan, when I started my undergraduate research with him. He has never failed to support and encourage me all these years. I found a sense of achievement and satisfaction whenever a new reaction was discovered. Since I started my undergraduate research in synthesis, I have never looked back. The irony is that I have yet to attempt a total synthesis project. I hope we can apply our new reaction methodologies to the total synthesis of natural products in the near future.

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

**Dr. J. D. Leow** | Carbon is an important element that resulted in the origin of life. It is omnipresent in our daily life, such as food, clothes, plastics, etc. Organic synthesis remains prevalent in our modern society as we advance to the technological era. We have seen the importance of the role that organic synthesis played in the enhancement of living standards. It has become an indispensable tool in industries such as petrochemicals, pharmaceuticals, flavors, fragrances, agrochemicals and others. In the past 13 years or so, this has been recognized with the award of Nobel prizes in the fields of asymmetric synthesis, olefin metathesis, and palladium-catalyzed cross-couplings. We will continue to experience revolutionary technological advancements, which offer greater reaction efficiency and greener solutions. Some of the upcoming exciting areas are asymmetric organocatalysis, transition-metal-catalyzed C–H bond activation, and photoredox catalysis.

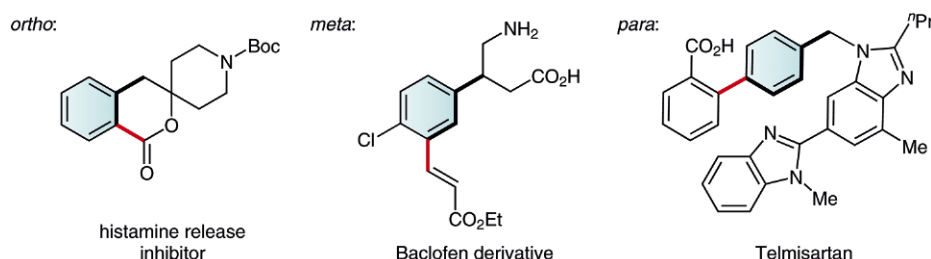
**SYNFORM** | Your research group is active in the area of organic synthesis, particularly C–H bond activation and catalysis. Could you tell us more about your research and its aims?

**Dr. J. D. Leow** | I had a fruitful postdoctoral experience with Professor Yu at The Scripps Research Institute, which naturally trained me to be interested in the field of C–H bond activation. Direct functionalization of unactivated C–H bonds provides a fast and straightforward method for building up complexity in simple molecules. No additional step is required to reinstall the C–X handle and it represents an ideal step economy. However, complications arise when multiple C–H bonds are present in the target molecule, posing a challenge to achieve positional selectivity. For

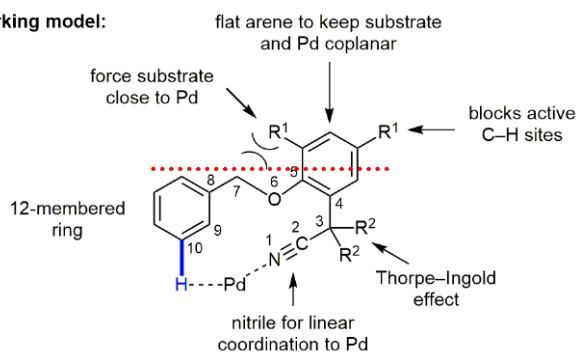
example, there are three different C–H sites on a monosubstituted arene. The regioselectivity is often clouded by the electronic and steric effects from the substituent. One of the classical methods to functionalize an arene C–H bond is the Friedel–Crafts reaction, in which it is heavily dependent on the electronic factor.

There has been a rapid development of  $\alpha$ -chelating groups to direct the transition metal to the *ortho*-position of the arene ring. Using a weak coordination approach, *ortho*-C–H carbonylation of phenethyl alcohols was achieved in the presence of amino acid ligands to accelerate the reaction (*Chem. Sci.* **2011**, *2*, 967). This transformation provided an expedient route to 1-isochromanone motifs, which are common structural elements in natural products and other biologically active compounds (Figure 1). The synthesis of *para*-substituted biaryl compounds poses a significant challenge due to selectivity issues. A highly *para*-selective C–H/C–H cross-coupling of monosubstituted arenes was developed using an electrophilic fluorinating reagent as a bystandant oxidant (*J. Am. Chem. Soc.* **2011**, *133*, 13864).

Although proximity-driven reactivity has found broad applications, the activation of remote *meta*-C–H bonds is unfavorable due to the entropy effect of a large 12-membered ring. Recently, we have designed a class of removable nitrile-based templates tethered to the target arene. By squeezing the Pd and substrate together through steric effects, they are then able to interact with each other. The template makes a molecular U-turn while the nitrile group acts like a linear robotic arm. It swings the Pd out and around to reach the distal *meta*-C–H bonds (more than ten bonds away). This method can be used to functionalize a commercially available drug, Baclofen, to access novel *meta*-substituted molecules for drug screening in a single step. This work was published in the prestigious journal *Nature* (*Nature* **2012**, *486*, 518).



**Figure 1** Synthesis of novel drug leads via position-selective C–H bond functionalization

**Working model:****Figure 2**

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

**Dr. J. D. Leow** | We are a newly set-up research group in the midst of intense exploration of new exciting chemistry with fervor. Our unpublished data show promising results that can possibly be important contributions to the chemistry community. We focus on unique catalyst and ligand designs that can dictate and tame the radicals towards our target reaction site. They are fine-tuned such that we can hit the sweet spot of our reactions. Our results greatly improve and expand the synthetic utility of radical chemistry. I hope our work will inspire fellow organic chemists to view existing challenges from different angles. ■

**Matteo Zanda**

COMING SOON ►► COMING SOON ►►

SYNFORM 2014/12

is available from November 18, 2014

In the next issues:

## SYNSTORIES ■ ■ ■ ■

■ **Enantioselective Organocatalytic Michael/Aldol Sequence: Anticancer Natural Product (+)-trans-Dihydrolycoricidine**  
(Focus on an article from the current literature)

■ **From Perylene to a 22-Ring Aromatic Hydrocarbon in One-Pot**  
(Focus on an article from the current literature)

■ **ChemSites: Institute of Transformative Bio-Molecules (ITbM), Nagoya University, Japan**  
(NEW! Featured Institute article)

## FURTHER HIGHLIGHTS + + + +

## SYNTHESIS

**Review on: Synthesis of Multiply Arylated Heteroarenes, Including Bioactive Derivatives, via Palladium-Catalyzed Direct C–H Arylation of Heteroarenes with (Pseudo)Aryl Halides or Aryliodonium Salts**

(by R. Rossi, F. Bellina et al.)

## SYNLETT

**Account on: Enamide Derivatives: Versatile Building Blocks for Highly Functionalized  $\alpha,\beta$ -Substituted Amines**

(G. Bernadat, G. Masson)

## SYNFACTS

**Synfact of the Month in category "Synthesis of Natural Products and Potential Drugs": [Syntheses of \(+\)-Flabellidine and \(-\)-Lycodine](#)**

## 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@outlook.com](mailto:synform@outlook.com), fax: +39 02 23993080

## Editor

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

C.N.R. – Istituto di Chimica del Riconoscimento Molecolare  
Via Mancinelli, 7, 20131 Milano, Italy  
Editorial Assistant: Alison M. Sage  
[synform@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 Editor: Selena Boothroyd,  
[selena.boothroyd@thieme.de](mailto:selena.boothroyd@thieme.de)
- Scientific Editor: Stefanie Baumann,  
[stefanie.baumann@thieme.de](mailto:stefanie.baumann@thieme.de), phone: +49 711 8931 776
- Scientific Editor: Michael Binanzer,  
[michael.binanzer@thieme.de](mailto:michael.binanzer@thieme.de), phone: +49 711 8931 768
- Assistant Scientific Editor: Christiane Kemper,  
[christiane.kemper@thieme.de](mailto:christiane.kemper@thieme.de), phone: +49 711 8931 785
- Senior Production Editor: Thomas Loop,  
[thomas.loop@thieme.de](mailto:thomas.loop@thieme.de), phone: +49 711 8931 778
- Production Editor: Helene Ott,  
[helene.ott@thieme.de](mailto:helene.ott@thieme.de), phone: +49 711 8931 929
- Production Editor: Thorsten Schön,  
[thorsten.schoen@thieme.de](mailto:thorsten.schoen@thieme.de), phone: +49 711 8931 781
- Editorial Assistant: Sabine Heller,  
[sabine.heller@thieme.de](mailto:sabine.heller@thieme.de), phone: +49 711 8931 744
- Marketing Manager: Julia Stötzner,  
[julia.stoetzer@thieme.de](mailto:julia.stoetzer@thieme.de), phone: +49 711 8931 771
- Postal Address: SYNTHESIS/SYNNLETT/SYNFACTS, 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 2014 by Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany, and is an additional online service for SYNTHESIS, SYNLETT and SYNFACTS.

## Publication Policy

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

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

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

To order: [customerservice@thieme.com](mailto:customerservice@thieme.com) or use the Web site facilities at [www.thieme-chemistry.com](http://www.thieme-chemistry.com), phone: +1 212 760 0888

Order toll-free within the USA: +1 800 782 3488

Fax: +1 212 947 1112

Periodicals postage paid at Hanover, PA 17331.

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

To order: [customerservice@thieme.de](mailto:customerservice@thieme.de) or use the Web site facilities at [www.thieme-chemistry.com](http://www.thieme-chemistry.com).

Phone: +49 711 8931 421; Fax: +49 711 8931 410

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

## Online Access

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

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

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

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 and SYNLETT

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

## Copyright

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

## Copyright Permission for Users in the USA

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