# SYNFORM People, Trends and Views in Chemical Synthesis

# 2015/04

# SYNSTORIES

Synthesis of Chiral Heterocycles by Ligand-Controlled Regiodivergent vs sp<sup>2</sup> C–H Bonds with Pd(II) and Enantiospecific Suzuki-Miyaura **Cross-Coupling** 



Chemoselective Activation of sp<sup>3</sup>

Highly Enantioselective Synthesis of 3,4-Dihydropyrans through a Phosphine-Catalyzed [4+2] Annulation of Allenones and **β**,γ-Unsaturated α-Keto Esters

# CONTACT ++

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Young Career Focus: **Dr. Ivana Fleischer** (University of Regensburg, Germany)



# **SYNFORM**



# Dear Readers,

During particularly busy times my editorial activity for **SYNFORM** has to coexist with my other academic duties, so occasionally I have to squeeze it between meetings or during lunch times. This is exactly one such busy

situation, so I am typing this editorial with just one finger while holding a sandwich (or what remains of it) in the other hand. I know it is not a healthy habit, in fact it is not even a habit for me, but it happens and I just have to live with that, and so does my digestion, which – I bet – will haunt me during the next meeting and throughout the afternoon ahead...

OK, so what do we have in this new issue of **SYNFORM**? Well, the usual load of high quality organic chemistry, of course! Starting from the synthesis of chiral heterocycles via Suzuki–Miyaura cross-coupling developed by D. Hall (Canada) and continuing with the Young Career Focus of which I. Fleischer (Germany) is the protagonist. The third **SYNSTORY** covers a novel chemoselective activation of C–H bonds described by M. C. Kozlowski (USA). The issue is completed by the enantioselective approach to 3,4-dihydropyrans stemming from the work of Y. Lu (Singapore).

Meanwhile I have already experienced the first signs of hiccup... Enjoy your reading!!

Matteo Zanda

Editor of SYNFORM

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

# Young Career Focus: Dr. Ivana Fleischer (University of Regensburg, Germany)

**Background and Purpose.** From time to time **SYN**-**FORM** 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 **SYNSTORY** with a Young Career Focus presents Dr. Ivana Fleischer (University of Regensburg, Germany).

# **BIOGRAPHICAL SKETCH**



Ivana Fleischer was born and raised in Poprad, (Czecho)Slovakia. She studied chemistry at the Commenius University in Bratislava (Slovakia), where she conducted her Diploma thesis under the supervision of Professor Štefan Toma in the field of ferrocene synthesis. Following a family break, she moved to Basel (Switzerland) to work with Professor Andreas Pfaltz on mass spectrometric

Dr. I. Fleischer

screening methods for chiral organocatalysts. After receiving her PhD in 2010, she joined the group of Professor Matthias Beller at the Leibniz Institute for Catalysis in Rostock (Germany) as a postdoctoral fellow of the Swiss National Science Foundation, where she spent three years. She developed new ruthenium-based catalysts for hydroformylation reactions. Since September 2013, she is a group leader at the University of Regensburg (Germany) and Liebig Fellow of the Fonds der chemischen Industrie. Her research interests center on the field of homogeneous catalysis and organic synthesis with emphasis on method development.

# INTERVIEW

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

**Dr. I. Fleischer** Our research focuses on the development of new catalytic transformations for organic synthesis. The main subjects of our investigations are non-classical C1 building blocks for various metal- and organocatalyzed reactions. We are interested in the whole picture: from the mechanistic understanding of the reactions to useful synthetic applications.

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

**Dr. I. Fleischer** In secondary school, I participated in the chemistry olympiad and I enjoyed, most of all, topics in organic chemistry – primarily at the theoretical level. I was fascinated by its logic and ease of comprehension. The attraction of science of organic synthesis persisted throughout my studies, and was even strengthened by the exciting and multifaceted laboratory work. I was lucky to be taught by amazingly gifted teachers and lecturers, whom I would like to thank at this point.

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

**Dr. I. Fleischer** Recent years have shown that catalysis has played a central role in the progress of modern organic synthesis. The current focus lies in the development of efficient, selective and sustainable chemical transformations for the synthesis of value-added chemicals, materials and natural compounds. The interest in utilization and transformation of renewable raw materials is growing and requires new methods. Theoretical chemistry and spectroscopic methods will become more important tools in the elucidation of reaction mechanisms and design of catalyst structures. But still, I think that serendipity will continue to surprise us and provide the most astonishing discoveries.

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**SYNFORM** Your research group is active in the areas of catalysis and new methodology in organic synthesis. Could you tell us more about your research and its aims?

**Dr. I. Fleischer** Our research aims at the construction of carbonyl compounds, which are among the most versatile synthetic intermediates. Our synthetic approach is based on the use of metal- and organocatalysts for the functionalization of the available feedstock with C1 building blocks. The most attractive and especially challenging C1 source is carbon dioxide, which constitutes an easily accessible and non-toxic gas. Its use would expand the resource base, and valuable products could be produced from this renewable carbon source. However, its reactivity is low and new methods are required for its functionalization. Our strategy is based on a two-step protocol, which consists of two catalytic transformations taking place under mild conditions. We also want to apply the developed methods to the synthesis of natural compounds. Figure 1 depicts the overall conversion of CO<sub>2</sub> to complex molecules. In addition, we are investigating new tandem reactions of carbonyl compounds based on one metal-catalyzed and one organocatalyzed step. Such reaction sequences enable the effective formation of several bonds and are characterized by atom-, step- and redoxeconomy.



Figure 1 Envisioned conversion of carbon dioxide into complex compounds

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

**Dr. I. Fleischer** I stand at the beginning of my independent research career, so it is difficult to answer this question. Nevertheless, the ongoing research of my group is very exciting and I hope we will be able to communicate our results soon. So far, we have developed a convenient protocol for acid-catalyzed hydroarylation of activated alkenes

(*RSC Adv.* **2015**, *5*, 493) and a new defined rutheniumbased catalyst for the alkoxycarbonylation of alkenes using formates (*Org. Biomol. Chem.* **2014**, *12*, 6972).



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# Synthesis of Chiral Heterocycles by Ligand-Controlled Regiodivergent and Enantiospecific Suzuki–Miyaura Cross-Coupling

Nat. Commun. 2014, 5, 5474

Controlling the regioselectivity of an organic reaction at one's discretion while also maintaining full control of the stereochemistry of the process is a luxury in organic synthesis and not many methods are known for achieving such an outstanding level of control in the generation of stereogenic allylic systems. Recently, Professor Dennis Hall and co-workers at the University of Alberta (Canada) described the first example of a Suzuki–Miyaura cross-coupling with allylic boronates where both the configuration of an sp<sup>3</sup> carbon (stereoselectivity) and the regioselectivity of the coupling process are fully controlled by the catalyst and especially the nature of the ligand (Figure 1).

What distinguishes this work from prior contributions is not only the merging of stereo- and regiocontrol, but also the ability to achieve this feat with functionalized allylic boronates. Professor Hall explained: "The heterocyclic allylic boronates employed as substrates contain a conjugated heteroatom and as such are more complex than a majority of chiral secondary allylboronates reported in the literature."

"These chiral heterocyclic allylic boronates are precursors of important varieties of substituted pyran and piperidine



**Figure 1** The regiochemical direction of a stereospecific allylic Suzuki–Miyaura cross-coupling is controlled by a judicious choice of ligand on the palladium catalyst.

units present in a vast number of natural products and drugs," said Professor Hall, continuing: "These key precursors highlight the usefulness (or utility) of the catalytic enantioselec-



Scheme 1 Hall's methodology

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Figure 2 Some of the compounds synthesized using Hall's methodology

tive borylative isomerization that we previously reported and that we also employed in carbonyl allylboration."

According to Professor Hall, this work also highlights the power and complementarity of state-of-the-art ligand systems for cross-coupling reactions, such as the biaryldialkylphosphines (Stephen Buchwald) and the NHC carbene catalysts (Michael Organ).

"All of the experimental work was performed in the skilled hands of 5<sup>th</sup> year graduate student Jinyue Ding and 4<sup>th</sup> year graduate student Taras Rybak," acknowledged Professor Hall. "Shortly after completing this work, Ding defended his PhD thesis and has now taken up a position as a Research Scientist in medicinal chemistry at Inception Sciences in Vancouver."

"Ironically, the most difficult part of the project often was not the actual reaction, but the development of chiral HPLC conditions to measure the enantioselectivity of the reaction," continued Professor Hall. "In some cases, the preparation of derivatives of the products was necessary. On the other hand, these derivatization reactions and the synthetic application to anabasine and paroxetine further exhibit the versatility of the cross-coupling products." The group is now investigating the application of their methodology on other heterocyclic allylboronates and finetuning the regioselectivity with other unexplored ligands. "We would like to further demonstrate the value of this methodology towards the synthesis of other natural products and valuable drug targets that are currently difficult to access," said Professor Hall, concluding: "Future work will also include the mechanistic study of stereoselective and regioselective Suzuki–Miyaura reactions. Based on the mechanistic understanding, more novel and practical reactions could be developed."

Matteo Zanda

# About the authors



From left: T. Rybak, Dr. J. Ding, Prof. D. Hall

**Dennis Hall** was born in Baie-Comeau, Province of Québec (Canada) in 1968. In 1991, he enrolled in graduate studies under the guidance of Professor Pierre Deslongchamps at Université de Sherbrooke (Canada). His graduate research project involved new synthetic methods and strategies applicable to natural product synthesis. His work culminated on the development of a new tandem transannular [4+2]/aldol approach to diterpenes such as Aphidicolin, and on new findings on the mechanism of the Diels–Alder reaction. After obtaining his PhD degree in 1995, Hall moved on to explore new areas of investi-

gation such as bioorganic chemistry and combinatorial chemistry, working as an NSERC Postdoctoral Fellow in the laboratory of Professor Peter G. Schultz, then at the Department of Chemistry at UC Berkeley (USA). In his postdoctoral stay from 1995–1997, he was involved in various projects and learned to apply his knowledge of organic synthesis to problems in bioorganic chemistry. In August 1997, he returned to Canada to take an academic position at the Department of Chemistry, University of Alberta. He was promoted to Professor of Chemistry level in July 2005.

**Jinyue Ding** was born in Henan (P. R. of China). He obtained his BSc at Zhengzhou University in 2008 in the same province. He moved to Canada in 2009 and obtained his PhD at the University of Alberta in 2014 under the supervision of Professor Dennis Hall. He is currently living in Vancouver and employed as a Senior Scientist I at Inception Sciences Canada.

**Taras Rybak** was born in Hamilton (Canada) in 1985. He received his BSc degree in Honours Chemistry at the University of Waterloo (Canada). He is currently a PhD student at the University of Alberta under the supervision of Professor Dennis Hall. His research focuses on the development of new methods for preparing and functionalizing pyran compounds towards the synthesis of medicinally relevant natural products.

# Chemoselective Activation of sp<sup>3</sup> vs sp<sup>2</sup> C–H Bonds with Pd(II)

J. Am. Chem. Soc. 2015, 137, 18-21

Oxidative C-H activation is the most atom-economical process for the construction of carbon-carbon bonds. Yu, White, Sanford, Fagnou and Davies (for references see the original article) have pioneered the activation of  $C(sp^3)$ -H bonds with directing groups (heteroatom, allyl, carbene, etc.). The ability of some metals, such as Pd catalysts, to insert selectively into C-H bonds has provided a host of new, useful methods for the synthesis of organic molecules. Considering as an example the Pd-mediated carboxylation of toluene, selective insertion into  $C(sp^2)$ -H bonds (110–115 kcal/mol) by palladium is remarkable when considering bond strengths of the competing  $C(sp^3)$ -H bonds (benzylic 85–90 kcal/mol). Typically, the arene  $\pi$ -system positions the metal carboxylate for a favorable deprotonative insertion that relies on forming the stronger  $C(sp^2)$ -Pd bonds.

The group of Professor Marisa C. Kozlowski at the University of Pennsylvania (USA) has had an ongoing interest in oxidative C–H activation. Initial studies on the chemoselective activation of toluene arose from a serendipitous discovery; in the course of attempting an arylation of azlactones, an unusual benzyl product was observed (Scheme 1). "This is a perfect example of how chance favors the prepared mind," said Professor Kozlowski. "Since the targeted compound was not observed, many scientists would have moved on. Only the curiosity and diligence of the graduate student undertaking the experiments, Dr. John Curto, brought this result to light. Upon further study, we discovered that a selective insertion into the benzylic position of toluene was occurring under conditions that would typically cause insertion into one of the arene C–H bonds." In fact, methyl and other alkyl sub-

stituents on arenes have been shown to be compatible to many Pd-catalyzed  $C(sp^2)$ -H insertions. "Thus, this discovery represents a novel mode of reactivity for Pd," added Professor Kozlowski, who explained that toluene derivatives are the ideal benzylation reagent because they are stable, commercially available, and easy to handle, while being far more atom-economical than the corresponding benzyl halides.

Professor Kozlowski said: "Our initial success with the selective C(sp<sup>3</sup>)-H bond activation of tolyl and methylnaphthyl analogues prompted our exploration of secondary benzylic C-H bonds. Extension of the alkyl chain on benzene to ethyl, propyl and butyl most surprisingly gave rise to the terminal alkylated product (Scheme 2, top). This chemoselectivity provides access to chemical space that would not be feasible via a radical-mediated process." A mechanism consistent with the C-H activation step involving a benzylic metalation is supported by kinetic isotope effect studies performed by Professor Kozlowski and Dr. Curto. For ethylbenzene, deuterium scrambling supports a zipper mechanism, involving  $\beta$ -hydride elimination and rearrangement of a benzylic palladium species (Scheme 2, bottom). "If the conditions that permit this novel pathway of alkyl benzene activation can be understood, then similar migrations could be achieved in a broad range of known Pd-catalyzed coupling processes," said Professor Kozlowski.

Upon discovering this novel  $C(sp^3)$ -H activation of alkyl arene bonds, a primary goal for the Kozlowski group was to identify catalytic conditions, which would greatly expand the utility of this transformation. "We utilized the UPenn High-Throughput Experimentation Center, one of the few academic



Scheme 1

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#### Scheme 2

centers with this technology, to screen multiple variables and rapidly identify trends," said Professor Kozlowski. "Parallel microscale experimentation (Scheme 3, left) revealed that most transition-metal oxidants used extensively in the Pd-catalyzed  $C(sp^2)$ –H processes were ineffective in this transformation. The highlighted oxidants were identified as potential leads and eventually led to the discovery of catalytic conditions using fewer equivalents of the alkyl benzene reaction partner (Scheme 3, right)."

"In summary, a novel reactivity mode for alkyl arenes was discovered from the investigation of a serendipitous result," said Professor Kozlowski. With a simple system consisting of  $Pd(OAc)_2$  and pivalic acid, catalytic dehydrogenative crosscoupling with a carbon nucleophile occurs readily for the terminal methyl positions of methyl, ethyl, propyl and butyl arenes. Notably, selective  $C(sp^3)$ -H insertion is observed in benzylic systems even though  $Pd(OAc)_2$  typically causes arene  $C(sp^2)$ -H insertion. Double C-H activation to form a C-C bond is a difficult transformation because two different C-H bonds need to be activated in a selective manner. "We hope to extend the scope of this technology and are exploring other acidic C-H partners. Although the full mechanistic details of this transformation remain to be elucidated, our ongoing efforts lend support for a mechanism that represents a shift in our understanding of Pd," concluded Professor Kozlowski.

Matteo Zanda



Scheme 3

#### About the authors



Dr. J. Curto

synthesis of  $\alpha, \alpha$ -disubstituted  $\alpha$ -amino acids and studies on the Pd-catalyzed C(sp<sup>3</sup>)-H activation of alkyl arenes. John and his wife Barb currently live in Connecticut where John has begun his career as a medicinal chemist.

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 Kevin Quinn on the synthesis of small natural products. In 2014, John graduated from the University of Pennsylvania (USA) with a PhD under the guidance of Professor Marisa Kozlowski on the asymmetric



Prof. M. Kozlowski

design of new catalysts and transformations. She has also coauthored 'Fundamentals of Asymmetric Catalysis' with Patrick Walsh.

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Marisa Kozlowski received an A.B.

in Chemistry from Cornell University

(USA) in 1989 and a PhD under the

direction of Paul Bartlett from the

University of California at Berkeley

(USA) in 1994. After an NSF postdoc-

at Harvard University (USA), she joined

sylvania (USA) in 1997 and is currently

Professor of Chemistry. The Kozlowski

group's research focuses on the

toral fellowship with David A. Evans

the faculty at the University of Penn-

# Highly Enantioselective Synthesis of 3,4-Dihydropyrans through a Phosphine-Catalyzed [4+2] Annulation of

J. Am. Chem. Soc. 2015, 137, 54–57

■ Phosphine-catalyzed cyclization reactions are of enormous synthetic value, evidenced by the ubiquitous presence of ring structures in natural products and bioactive molecules. Over the last few years, the group of Professor Yixin Lu at the National University of Singapore has been interested in developing novel and versatile organic catalysts that can be readily derived from amino acids. Thus, explained Professor Lu, one of the main research efforts of his group is to devise powerful approaches to access chiral ring motifs, especially those structures that are not yet accessible via existing methods, and the dihydropyrans synthesized in this paper are important skeletons of biological significance. Professor Lu said: "In the area of phosphine catalysis, we designed a series of amino acid based bifunctional phosphines and demonstrated their effectiveness for a wide range of reactions, including (aza)-MBH

Allenones and β,y-Unsaturated α-Keto Esters

reactions, various [3+2] cycloadditions, [4+2] cyclization, [4+1] annulation, asymmetric allylic alkylation, phosphinemediated Michael addition, and ?-addition. Our catalysts can be easily assembled and the structures are highly tunable, and such features are crucial in asymmetric catalysis as a 'universal' catalyst does not exist."

Professor Lu explained: "In phosphine catalysis, it is imperative to expand the scope of substrates suitable for phosphine activation. While allene esters have been widely employed, utilization of allene ketones is rare. This paper documents an unprecedented utilization of allenones as a reaction partner. The reaction system is complex," continued Professor Lu, "and achieving the desired [4+2] cyclization was quite tricky." Professor Lu explained that the activation of allenones by phosphines creates a phosphonium enolate,





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which possesses different resonance forms. "The subsequent advanced intermediate generated upon addition of the enolate anion to an electrophile also has different reaction pathways. In this paper, we suppressed undesired modes of reaction by careful selection of reaction systems," he added.

This work not only demonstrates an unprecedented utilization of allenones as a reaction partner, but also represents the first asymmetric synthesis of dihydropyrans via phosphine catalysis. "We hope this work will lead to the discovery of more novel approaches to access oxygen-containing ring structures via phosphine catalysis," said Professor Lu.

"The complexity in phosphine-catalyzed reaction systems is challenging, but also truly exciting. Discoveries on new reactions and novel modes of activations are well anticipated, if one can discern subtle mechanistic differences and design catalytic systems accordingly," he concluded.

Matteo Zanda

## About the authors



Dr. W. Yao



Dr. X. Dou



Prof. Y. Lu

Department of Chemistry, NUS, in September 2003 where he is now a professor.

Weijun Yao was born in Zhejiang (P. R. of China) in 1983. He received his B.Sc. and Ph.D. (under the supervision of Professor Cheng Ma) from Zhejiang University in 2006 and 2011, respectively. Currently, he is a postdoctoral follow working with Professor Yixin Lu at National University of Singapore (NUS).

Xiaowei Dou was born in Shandong (P. R. of China) in 1987. He received his B.Sc. from Nanjing University (P. R. of China) in 2009, and he then joined the research group of Professor Lu at NUS. He received his Ph.D. in 2013, and he is now working with Professor Tamio Hayashi as a postdoctoral fellow at NUS.

Yixin Lu received his Ph.D. from McGill University (Montreal, Canada) under the supervision of the late Professor George Just in 2000. He then carried out postdoctoral research with Professor Peter W. Schiller at the Clinical Research Institute of Montreal (Canada), and subsequently worked as an RCMS fellow with Professor Ryoji Noyori at Nagoya University (Japan). He joined the

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The Phosphinoboration Reaction (Focus on an article from the current literature)

Catalytic Enantioselective Synthesis of Indanes by a Cation-Directed 5-endo-trig Cyclization (Focus on an article from the current literature)

# FURTHER HIGHLIGHTS +++

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#### SYNLETT

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**SYNFACTS** Synfact of the Month in category "Metal-Mediated Synthesis": Addition of Carboxylic Acids Using Chiral Lithium Amides as **Auxiliaries** 

# 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, fax: +39 02 23993080

## Editor

Matteo Zanda, NRP Chair in Medical Technologies, Institute of Medical Sciences, University of Aberdeen, Foresterhill, Aberdeen, AB25 2ZD, UK and C.N.R. - Istituto di Chimica del Riconoscimento Molecolare Via Mancinelli, 7, 20131 Milano, Italy

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#### **Editorial Office**

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