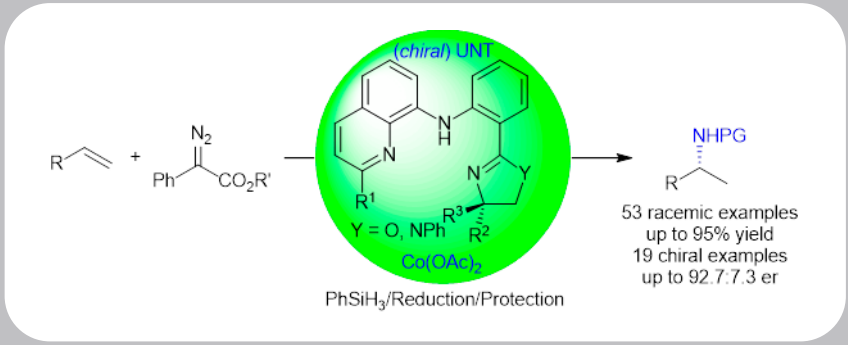
Synform

People, Trends and Views in Chemical Synthesis

2020/06

Ligand-Promoted Cobalt-Catalyzed Radical Hydroamination of Alkenes

Highlighted article by X. Shen, X. Chen, J. Chen, Y. Sun, Z. Cheng, Z. Lu



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Dear Readers,

I wish I could write this Editorial without mentioning the coronavirus, but the problem is that nothing else seems to be happening anymore: no sport, no politics, no research, no gossip, zero. The entire world is still mostly on lockdown – in the UK we do not even have an exit date or plan yet – and very few of us have been allowed back to our beloved labs and work. We cannot travel, we cannot meet friends or colleagues, we cannot even plan for the future, because nobody has the faintest idea of how the future is going to be. So, what are we supposed to talk about when everything seems to revolve around this single element, which has swallowed every other aspect of our lives, just like a giant coronavirus-shaped black hole? Perhaps we should simply strive to think positively and consider this emergency as an opportunity to delete and restart – when we are allowed to – with a different, more environmentally compatible and less hectic lifestyle, making the most of what we have learned during these unprecedented times. First and foremost, all that travelling – especially flying – we used to do may not be entirely necessary after all, and could well be replaced – to some extent at least – by virtual meetings and events. Personally, I am not a great fan of online lecturing, but now we know it can be done with some degree of effectiveness, if required. And some work-related meetings can be effectively conducted virtually, although online workshops and conferences – especially large ones – are not that exciting, are they... And what about working from home? Well, it can be done and – oh yes – it can even be productive and time effective. Less travelling will undoubtedly come at a cost for the economy, but would hopefully have a positive environmental effect and result in a less stressful and hectic lifestyle for many of us. After all this gazing into the crystal ball, let's move on to something rock-solid: a new issue of SYNFORM! The start is more exciting than the three rounds of Marvin 'Marvelous' Hagler vs. Thomas 'Hitman' Hearns: Professor Phil Baran's interview on his SYNLETT Best Paper Award: Electrochemical C(sp^3)–H Fluorination! The second article is certainly not disappointing either: a Literature Coverage piece on Z. Lu's excellent *Nat. Commun.* paper on the radical hydroamination of alkenes, from P. R. of China. The third article is another Literature Coverage of ... – drumroll – the elegant study on the carboimination of alkenes by F. Glorius (Germany). And – icing on the cake – the issue is wrapped up by a Young Career Focus interview with Tatiana Besset (France).

Enjoy your reading!!

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

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SYNLETT Best Paper Award 2019: Electrochemical C(sp^3)–H Fluorination

Synlett **2019**, *30*, 1178–1182

Background. Thieme Chemistry and the Editors of SYNTHESIS and SYNLETT present the 'SYNTHESIS/SYNLETT Best Paper Awards'. These annual awards honor the authors of the best original research papers in each of the journals, considering their immediate impact on the field of chemical synthesis.

Professor Phil S. Baran and co-workers from The Scripps Research Institute, USA, as well as from industrial companies in Ukraine, China and Japan, are the recipients of the SYNLETT Best Paper Award 2019. The authors are recognized for their stereospecific approach to alkylamines. Benjamin List, Editor-in-Chief of SYNLETT, noted: "This is a truly outstanding paper in which the authors apply electrochemistry as a rising technology to activate aliphatic C–H bonds, delivering highly important fluorinated molecules. In addition, the method is scalable, has a very large scope, and can be applied to late-stage functionalizations of pharmaceuticals and natural products. Awesome work!"

SYNFORM spoke with Professor Phil S. Baran, who was happy to share some background information regarding the prize-winning paper as well as current research activities ongoing in his group.

Left to right: Pavel Mykhailiuk, Hugh Nakamura, Byron K. Peters, Yu Kawamata, Solomon H. Reisberg, and Yusuke Takahira

Biographical Sketch

Phil S. Baran is a Professor in the Department of Chemistry at Scripps Research (USA). He completed his undergraduate education at New York University (USA) in 1997. After earning his Ph.D. at The Scripps Research Institute (TSRI) in 2001, he pursued postdoctoral studies at Harvard University (USA) until 2003, at which point he returned to TSRI to begin his independent career. He is currently the Darlene Shiley Professor of Chemistry. The mission of his laboratory is to educate students at the intersection of fundamental organic chemistry and translational science.

INTERVIEW

SYNFORM *Could you highlight the value of your award-winning paper with respect to the state-of-the-art, as well as the potential or actual applications?*

Prof. P. S. Baran Achieving site-selective exchange of a C–H bond for a C–F bond has value for those interested in making biologically active substances (for medicinal or agricultural uses for example). This is because such perturbations will often block those sites for metabolism or alter the physical and electronic properties of a substrate in a desirable way. One can envisage that this method for C–H fluorination could have utility in many subfields of chemistry and at small or large scales (Scheme 1).

SYNFORM *Can you explain the origin, motivations and strategy used for conducting the award-winning research?*

Prof. P. S. Baran This problem was initially brought to our attention by our collaborators (co-authors) at Eisai when they were experiencing difficulties in executing photochemical and chemical strategies for C–H fluorination. We simply wanted to see if electrochemical means for achieving such a transformation would be beneficial in certain contexts. It turns out that there are many cases, either in a medicinal or process setting, where this electrochemically driven radical process holds tangible advantages over the state-of-the-art.

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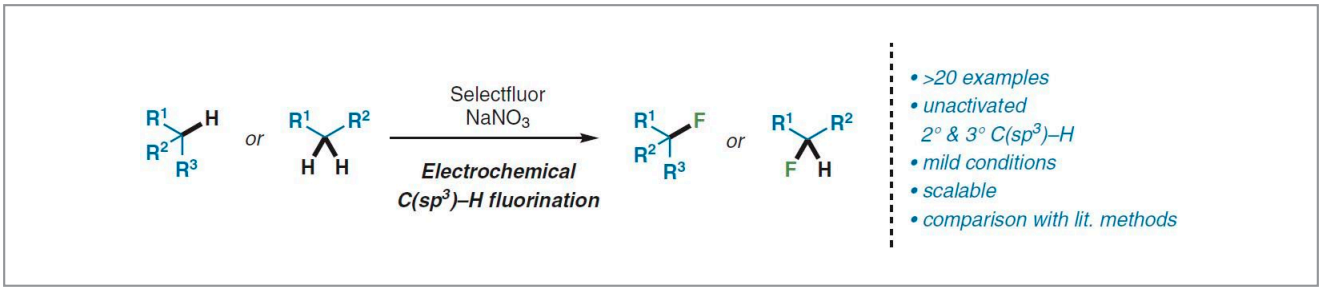

Scheme 1

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

Prof. P. S. Baran Our lab is always interested in making complex things attainable more simply. It can be in the context of natural products (which more than half the lab continues to focus on) or unanswered challenges in medicinal/process chemistry (which we love exploring in collaboration with industrial colleagues). We are agnostic to the approach used to solve such problems and in this case electrochemistry seemed to be an underexplored avenue for C–H fluorination and one that has actual pragmatic benefits.

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

Prof. P. S. Baran Organic chemistry has as bright of a future as it did several decades ago. Many new technologies emerge and some consistently believe that one of them will somehow diminish interest in this core area of the life sciences. Those predictions have so far been shown to be wrong. The number and quality of young scientists captivated by this field has not gone down over the past few decades. The desire of industry to hire such students has only increased. This trend will probably continue for years to come because organic chemistry is indelibly tied to human creativity and imagination. One can create, be artistic, explore, and the product of those efforts can often have direct and rapid impact in so many fields. The major challenge of organic chemistry, indeed its charm and appeal, continues unchanged: to access targets more quickly and more simply and to do so directly without waste. Aiming for ideality is fun because such an aspirational goal requires the invention of new strategies and methods.

SYNFORM *What does this award mean to you/your group?*

Prof. P. S. Baran We are humbled and honored to receive this recognition and the funds are being used to support our weekly group meetings, the slides of which can be found online.

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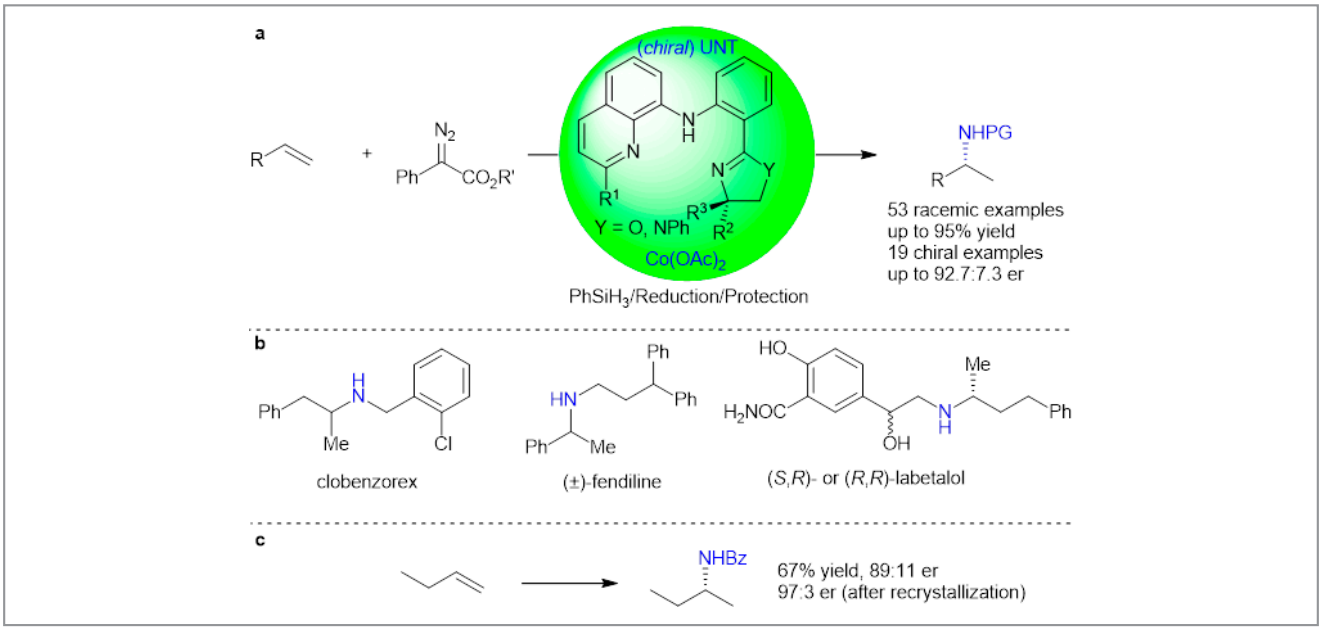
Ligand-Promoted Cobalt-Catalyzed Radical Hydroamination of Alkenes

Nat. Commun. **2019**, DOI: 10.1038/s41467-020-14459-x

Amines and their derivatives are ubiquitous compounds of great value and paramount importance in a number of areas, including agrochemicals, pharmaceuticals and materials. The development of highly efficient and selective methods to introduce amine groups into organic molecules remains therefore a vibrant area of research in organic synthesis. Since the carbon–carbon double bond is one of the most common structural motifs in organic molecules, highly regio- and enantioselective intermolecular hydroamination of alkenes seems an ideal strategy to access chiral amines. "Probably the most important unsolved problem of the hydroamination reaction is the use of aliphatic terminal alkenes without any activating groups or chelating groups as substrates," said Professor Zhan Lu (Zhejiang University, Hangzhou, P. R. of China). He added: "The hydroamination of alkenes via metal-hydride-catalyzed hydrogen atom transfer (HAT) has been studied in detail for its excellent regioselectivity and functional group tolerance. However, due to formation of radical intermediates and the lack of suitable chiral ligands, a successful asymmetric transformation has not been reported yet."

In a recent paper, which represents a breakthrough in the field, Professor Lu's group developed a ligand-promoted cobalt-catalyzed Markovnikov hydroamination of alkenes via HAT process (Scheme 1a). "A wide variety of alkenes could be transformed into the corresponding amine derivatives under this mild protocol, with superb Markovnikov-type selectivity and great functional group tolerance. The newly designed unsymmetric NNN-tridentate (UNT) ligands play a key role in this transformation. Importantly, the asymmetric intermolecular hydroamination of unactivated terminal alkenes has also been achieved using chiral UNT ligands, affording good enantioselectivity," remarked Professor Lu, who continued: "This protocol shows significant functional group tolerance under mild conditions, which offers an opportunity for late-stage hydroamination of structurally complex molecules. Besides, the products could be used to construct nitrogen-containing heterocycles and drugs, which demonstrates the usefulness of this protocol in medicinal chemistry (Scheme 1b). Additionally, simple α-olefins produced in petroleum cracking, such as but-1-ene, could be converted into chiral products with good



Scheme 1 Ligand-promoted selective hydroamination of alkenes via HAT process

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enantioselectivity (Scheme 1c). After simple recrystallization, chiral amine derivatives could be easily obtained with excellent enantiomer excess."

Professor Lu concluded: "This study not only establishes a pathway to solve the long-standing problem in enantioselective hydroamination of aliphatic alkenes but also suggests a potentially general strategy for asymmetric transformation of substrates without any activating or chelating groups by using earth-abundant transition metal catalysis."

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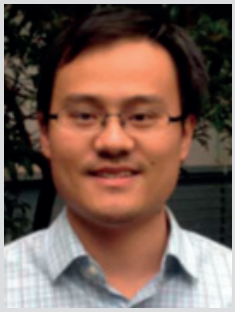


Prof. Z. Lu

Zhan Lu was born in 1981 in Zhejiang Province (P. R. of China). He received a BSc (2003) and a PhD degree (2008) in chemistry under the supervision of Professor Shengming Ma at Zhejiang University (P. R. of China). After postdoctoral research with Professor Shannon S. Stahl and Professor Tehshik P. Yoon at the University of Wisconsin-Madison (USA), he returned to Zhejiang University in 2012 and joined the chemistry faculty. Currently his research interests focus on asymmetric catalysis via earth-abundant transition metals and radical chemistry.

X. Shen

Xuzhong Shen was born in 1994 in Zhejiang Province (P. R. of China). He received his BSc degree in macromolecular materials and engineering from Zhejiang University (P. R. of China). He then joined Professor Zhan Lu's group at the same university to start his PhD studies. His research interests focus on earth-abundant transition-metal-catalyzed asymmetric transformations of alkenes.

Dr. X. Chen

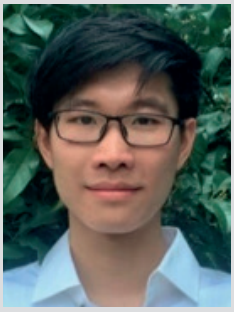
Xu Chen was born in YiYang (P. R. of China). He received his BSc degree in pharmaceutical engineering from Hunan Normal University (P. R. of China). In September 2011, he began his graduate studies under the supervision of Professor Chuanming Yu at Zhejiang University of Technology (P. R. of China). In 2014, he joined Professor Zhan Lu's group and started his PhD studies on Fe- and Co-catalyzed asymmetric synthesis based on ligand design. After earning his doctoral degree in 2018, he began postdoctoral studies in the same group. His research projects focus on the design and synthesis of chiral nitrogen-containing ligands and their application to Fe- or Co-catalyzed asymmetric transformations.

J. Chen

Jieping Chen received his BSc degree in chemical engineering from Tianjin University (P. R. of China). In 2018, he moved to Zhejiang University (P. R. of China) and joined Professor Zhan Lu's group to start his MSc studies. His research project focuses on hydrofunctionalization of alkynes.

Y. Sun

Yufeng Sun received his BSc degree from the School of Chemistry and Chemical Engineering at Shandong University (P. R. of China) in 2018. He then joined Professor Zhan Lu's group at Zhejiang University (P. R. of China) to start his PhD studies. His research interests lie in earth-abundant transition-metal-catalyzed dihydrofunctionalization of alkynes.



Z. Cheng

Zhaoyang Cheng was born in Zhejiang Province (P. R. of China) in 1994. He received his BSc degree in pharmaceutical engineering from Zhejiang University of Technology in 2017 (P. R. of China). At present, he is conducting his PhD research in Professor Zhan Lu's group at Zhejiang University. His research interests focus on earth-abundant transition-metal-catalyzed asymmetric hydrofunctionalization of alkenes and alkynes.

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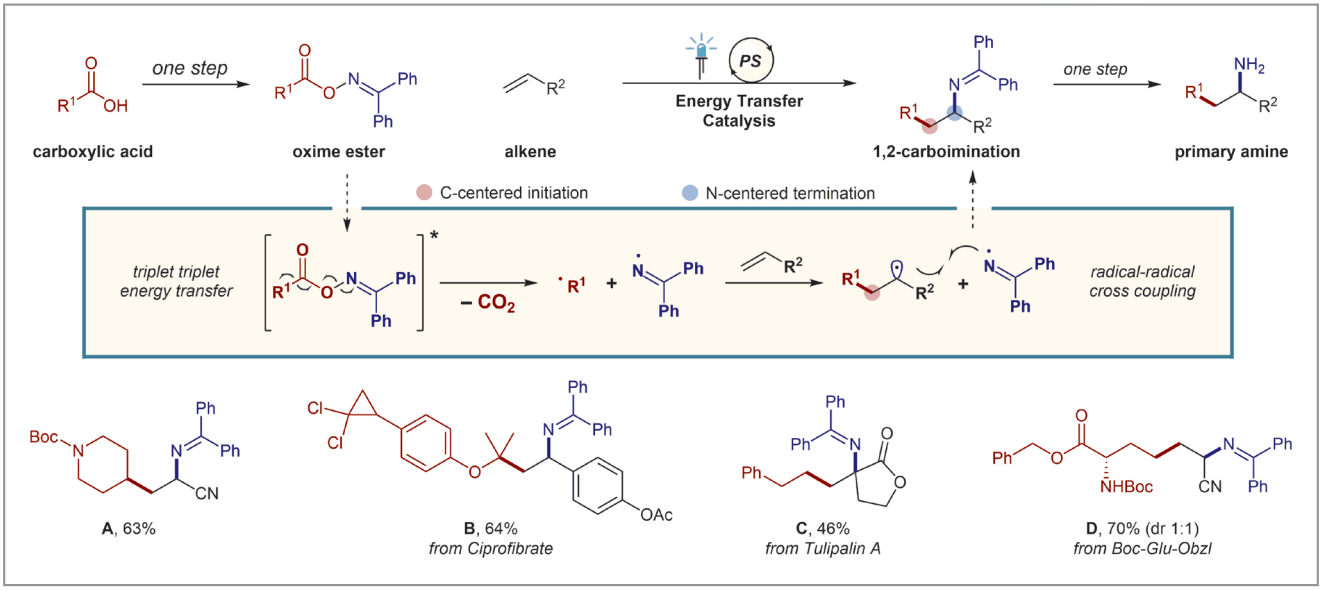
Photosensitized Intermolecular Carboimination of Alkenes through the Persistent Radical Effect

Angew. Chem. Int. Ed. **2020**, *59*, 3172–3177

Aliphatic amines are amongst the most prevalent functionalities in organic molecules, including natural products, drugs, peptides, bioactive compounds and agrochemicals. Owing to their favorable physical and chemical properties, the introduction of amine functionalities in small molecules can increase their likelihood of success as pre-clinical candidates. "In this regard, a powerful strategy to synthesize complex primary amines from accessible feedstocks is even more important, since primary amines are the common precursor for amides as well as for secondary and tertiary amines," said Professor Frank Glorius from the Westfälische Wilhelms-Universität Münster (Germany). "In this work, we developed a 1,2-carboimination strategy for alkenes, resulting in the concurrent installation of both carbon and nitrogen functionalities on the alkenyl framework. For this purpose, we used benzophenone-based oxime esters as bifunctional C- and N-radical sources." He continued: "Expediently, these oxime esters can be easily prepared from highly abundant and inexpensive aliphatic carboxylic acids to afford the corresponding C-radicals. The N-centered benzophenone iminyl radical is concurrently generated, to participate in a radical–radical cross-coupling process providing the final 1,2-carboiminated product. Importantly, the benzophenone iminyl functionality can be readily converted into primary amines by hydrolysis."

Professor Glorius noted that in general, almost all known N-centered radicals are highly reactive and tend to add first to the alkene C=C bond, which would require the subsequent addition of carbon functionalities. Professor Glorius said: "In contrast, the realization of relatively long lifetimes of the N-centered benzophenone iminyl radical is remarkable. As a result, selective C-radical addition to the alkene indeed occurs first, followed by the N-radical addition to give an overall regioselectivity switch. Importantly, the overall process is highly atom-economic and generates carbon dioxide as the sole byproduct."

Professor Glorius concluded: "Most radicals generally applied in synthesis are transient (short-lived) in nature. Hence, the key discovery of the high lifetimes of the N-centered benzophenone iminyl radicals has a great potential, as it allows for radical recombinations in alkene difunctionalization chemistry and beyond."



Scheme 1 General strategy for 1,2-carboimination of alkenes using oxime esters as bifunctional reagents, with representative examples

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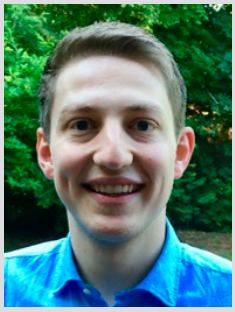
About the authors

Dr. T. Patra

Tuhin Patra obtained his B.Sc. degree in chemistry from University of Calcutta (India). After his M.Sc. in chemistry from Indian Institute of Technology Bombay, in 2011, he joined the group of Prof. Debabrata Maiti to explore the field of distal C–H activation. Soon after the completion of his PhD in 2017 from IIT Bombay (India), he moved to Münster (Germany) to join the group of Prof. Frank Glorius as an Alexander von Humboldt postdoctoral fellow. His postdoctoral research has centered on the development of new methods through visible-light photocatalysis.

P. Bellotti

Peter Bellotti received his B.Sc. degree in chemistry from the University of Milan (Italy) under the supervision of Prof. Cesare Gennari. While completing his M.Sc. in advanced synthesis and catalysis at the University of Regensburg (Germany) in the research group of Prof. Burkhard König working on visible-light carboxylation reactions, he joined Hoffmann–La Roche pRED, Basel (Switzerland) for one year in industry, focusing on cancer and neurodegenerative diseases. In 2019, he started his PhD in the group of Prof. Frank Glorius, focusing on visible-light photocatalysis and N-heterocyclic carbenes (NHCs) on surfaces.



F. Strieth-Kalthoff

Felix Strieth-Kalthoff studied chemistry at the University of Münster (Germany), where he obtained his BSc degree under the supervision of Prof. J. Neugebauer in 2015. After a six-month research stay with Prof. T. F. Jamison at the Massachusetts Institute of Technology (USA), he joined the group of Prof. F. Glorius at the University of Münster, where he received his MSc in 2017. Currently, he is a doctoral student in the same group, focusing on the development of photocatalytic reactions and screening methodologies for their discovery.

Prof. F. Glorius

Frank Glorius is a Full Professor of Organic Chemistry at the Westfälische Wilhelms-Universität Münster (Germany). His research program focuses on the development of new concepts for diverse areas of catalysis such as photocatalysis, C–H activation, smart screening and data-based technologies, and N-heterocyclic carbenes (NHCs) in organocatalysis and as surface modifiers and in (asymmetric) arene hydrogenation.

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Young Career Focus: Dr. Tatiana Besset (CNRS, France)

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. Tatiana Besset (CNRS, France).

Biographical Sketch

Dr. T. Besset

Tatiana Besset obtained her PhD in chemistry (2009) at Grenoble University (France) with Dr. Greene. She then moved to the Westfälische Wilhelms Universität Münster (Germany) as a postdoctoral fellow in the group of Prof. Frank Glorius (Rh C–H bond activation). In 2011, she joined the group of Prof. Joost N. H. Reek at the University of Amsterdam (The Netherlands), as a postdoctoral fellow in collaboration with the Eastman company where she was working on supramolecular encapsulated rhodium catalysts for branched selective hydroformylation of alkenes. Since 2012, she has been a CNRS Associate Researcher in the "Fluorinated Biomolecules Synthesis" group in Rouen, France. In 2017, she was awarded an ERC Starting Grant. In 2018, she defended her habilitation, received the CNRS Bronze medal and the "J.-P. Sauvage" prize (SCF). Her research involves the design of new transformations involving transition-metal catalysis (C–H bond activation) and the development of new strategies in organofluorine chemistry.

INTERVIEW

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

Dr. T. Besset Since the beginning of my career, I have focused on solving synthetic problems by the development of new methodologies for unprecedented organic transformations. Aiming at accessing original scaffolds, our research is dedicated to the elaboration of new tools for the selective C–Rf (Rf = various fluorinated groups) and C–X bond formation by transition-metal-catalyzed C–H activation under mild reaction conditions with a special interest towards C(sp^3)–H bonds. In addition, the design of original fluorinated reagents and their applications for the synthesis of fluorinated molecules, compounds of interest, is also part of our research program.

SYNFORM *When did you get interested in synthesis?*

Dr. T. Besset I have to admit that my interest in synthesis was a rather long journey until today, although I am still in an early stage of my career. I discovered organic chemistry in high school and since then, I have been always fascinated by its omnipresence in our daily life. Throughout my different professional experiences, I confirmed my interest in synthesis and I have learnt to appreciate it by becoming more persistent and curious. Moreover, my background in organic chemistry in various fields, gained in the course of my doctorate and post-doctoral studies, gave me an idea of the incredible possibility of the research in synthesis in organic chemistry.

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

Dr. T. Besset Sometimes underestimated compared to other research areas in chemistry, organic chemistry is the foundation of chemistry: it always was and will continue to be a very active and key research field. Indeed, beyond offering constantly original, efficient and useful synthetic tools

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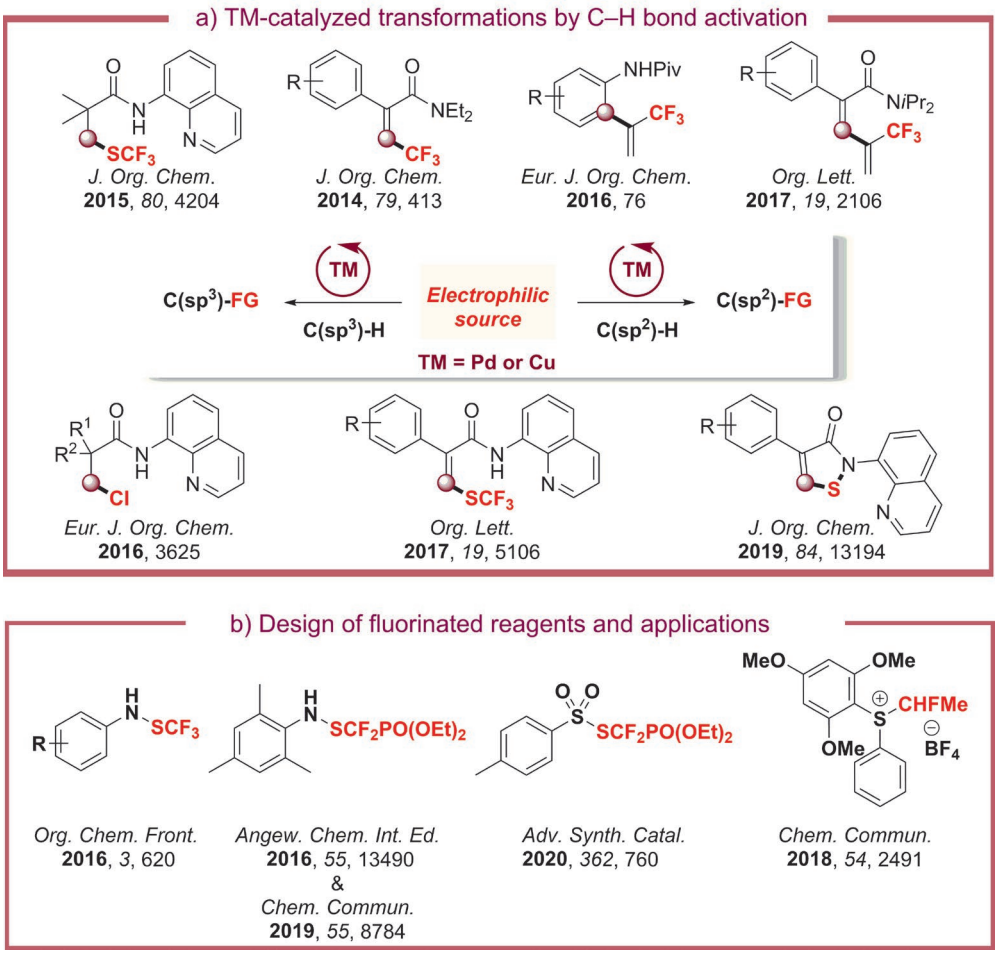
for materials, agrochemicals and pharmaceutical industries as well as access to complex molecules for instance, organic chemistry is a fascinating research field thanks to its infinite possibilities to synthesize molecules. Despite the tremendous advances made over the years, major synthetic challenges are still persistent and stimulate the imagination of the scientific community to push forwards the boundaries of knowledge and to bring cutting-edge technologies to change the way molecules are made. Especially, innovation in the development of more sustainable and efficient solutions with high selectivity will definitively offer groundbreaking achievements.

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

Dr. T. Besset Our research group is focused on the development of efficient and more sustainable synthetic tools to access unprecedented organic scaffolds. With that aim, we have developed innovative strategies for the synthesis of organic compounds and especially fluorine-containing molecules by transition-metal catalysis. Regarding this last aspect, two complementary approaches were elaborated: 1) the development of transition-metal-catalyzed transformations for the introduction of fluorinated groups via eco-friendlier strategies (e.g. C–H bond activation) and 2) the use of fluorinated building blocks to build up compounds of interest. More recently, the design of new reagents for the introduction of highly functionalized fluorinated groups has emerged as an important part of our research program. Special attention was



Scheme 1 Recent synthetic methodologies developed in the Besset lab

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also paid to the construction of C–X and C–S bonds by C–H bond activation, especially on C(sp^3) centers, and taking benefit from the tools we developed, our goal is to further explore this chemistry towards enantioselective processes.

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

Dr. T. Besset My most important achievement to date was the development of a methodology for the trifluoromethylthiolation of aliphatic derivatives by Pd-catalyzed C–H bond activation. This approach offered an original tool to functionalize primary C(sp^3) centers with the emergent SCF_3 group to access important fluorinated molecules (*J. Org. Chem.* **2015**, *80*, 4204). This piece of work is a cornerstone in our research. This was our first contribution to the construction of transition-metal-catalyzed C–S bond formation by C–H bond activation, so far restricted to a handful of examples. Moreover, this study constituted a starting point in our group to develop innovative synthetic solutions to achieve value-added scaffolds by combining organofluorine chemistry and C–H bond activation. Hence, these results paved the way to various perspectives and we are expecting future achievement in catalysis and organofluorine chemistry.

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Coming soon

SYNTHESIS Highlight

SYNTHESIS Best Paper Award 2019: Enantioselective Synthesis of *cis*- and *trans*-Borocyclopropylmethanol: Simple Building Blocks To Access Heterocycle-Substituted Cyclopropylmethanols

Literature Coverage

Catalytic C(sp^3)–H Bond Activation in Tertiary Alkylamines

Literature Coverage

Metal-Free Photoredox-Catalysed Formal C–H/C–H Coupling of Arenes Enabled by Interrupted Pummerer Activation

Further highlights

Synthesis **Review: Recent Advances in the Synthesis of Enantiomerically Enriched Diaryl, Aryl Heteroaryl, and Diheteroaryl Alcohols through Addition of Organometallic Reagents to Carbonyl Compounds**
(by R. S. Schwab, S. Narayanaperumal, and co-workers)

Synlett **Account: Synthesis of Aromatic and Aliphatic Di-, Tri-, and Tetrasulfonic Acids**
(by J. Christoffers, M. S. Wickleder)

Synfacts **Synfact of the Month in category "Polymer-Supported Synthesis": An Atomically Dispersed Platinum Catalyst for the Catalytic Diboration of Alkynes**

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Impressum

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