

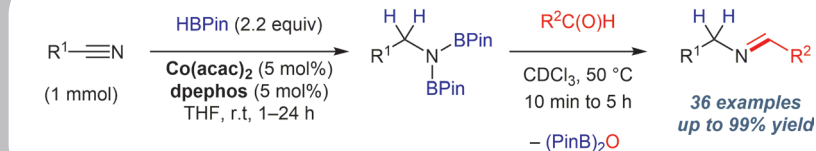
# Synform

People, Trends and Views in Chemical Synthesis

2020/09

## Efficient Co-Catalyzed Double Hydroboration of Nitriles: Application to One-Pot Conversion of Nitriles into Aldimines

Highlighted article by K. A. Gudun, A. Slamova,  
D. Hayrapetyan, A. Y. Khalimon



### Contact

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

## Dear Readers,

I hope you all managed to have some holidays – or at least some rest – despite the unsettling and unprecedented summer we have been living this year. I bet that most of us have re-discovered places which are not too far from home, and have travelled less, which is not necessarily a bad thing. In case you decided to give up on holidays entirely, I hope this new issue of SYNFORM will bring you at least a quantum of solace, to quote Ian Fleming's secret agent... We start with a Young Career Focus interview with I. Vilotijević (Germany) who discusses his career aims and achievements so far, as well as his views on the art of organic synthesis. Another interview comes next, this time with the new Editorial Board Member of *Organic Materials*, Professor Xiaozhang Zhu (P. R. of China). The first Literature Coverage article covers the work of D. Hayrapetyan and A. Y. Khalimon (Kazakhstan) who recently published a clever new methodology for performing the one-pot conversion of nitriles into aldimines. Last but not least, the work of W. Qu (U.S.A.) with a ground-breaking radiolabelling strategy for preparing  $^{11}\text{C}$ -labelled PET tracers via desilylation of organosilanes.

Stay safe and enjoy your reading!!



### In this issue

#### Young Career Focus

**Young Career Focus: Prof. Dr. Ivan Vilotijević (Friedrich Schiller University Jena, Germany)** ..... A126

#### Editorial Board Focus

**Editorial Board Focus: Prof. Xiaozhang Zhu (Institute of Chemistry, Chinese Academy of Sciences, P. R. of China)** ..... A129

#### Literature Coverage

**Efficient Co-Catalyzed Double Hydroboration of Nitriles: Application to One-Pot Conversion of Nitriles into Aldimines** ..... A130

#### Literature Coverage

**A General  $^{11}\text{C}$ -Labeling Approach Enabled by Fluoride-Mediated Desilylation of Organosilanes** ..... A133

Coming soon ..... A137

### Contact

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

## Young Career Focus: Prof. Dr. Ivan Vilotijević (Friedrich Schiller University Jena, Germany)

**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 Prof. Dr. Ivan Vilotijević (Friedrich Schiller University Jena, Germany).

### Biographical Sketch



Prof. Dr. I. Vilotijević

**Ivan Vilotijević** was born and raised in Serbia. He studied chemistry at the University of Belgrade (Serbia), Ohio State University (USA) and the University of Illinois at Urbana-Champaign (USA), and learned the ropes of scientific research with Prof. Leo Paquette and Prof. David Gin. He earned his Ph.D. in organic chemistry from Massachusetts Institute of Technology (USA) in 2010 where he developed *endo*-selective epoxide-opening cascade reactions for the synthesis of ladder polyether natural products with Prof. Tim Jamison. He then moved to Max Planck Institute of Colloids and Interfaces (Germany) as a Marie Curie postdoctoral fellow with a focus on synthesis, biological and biophysical studies of complex GPI glycolipids in the Biomolecular Systems department led by Prof. Peter Seeberger. In 2015 he joined the faculty at Friedrich Schiller University Jena (Germany) as an assistant professor where his group works on the design, discovery, and development of novel (catalytic) methods for synthesis of organic molecules.

### INTERVIEW

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

**Prof. Dr. I. Vilotijević** We focus on discovering new and improving the existing patterns of reactivity of organic molecules and use this as a foundation for the development of transformations that will meet the needs of the modern society in biomedical fields, address the environmental challenges related to energy and sustainability and push the limits of what is possible in organic synthesis. The main research activities in the group are in the areas of Lewis base catalysis and organophosphorus chemistry. These core projects are grounded in the fundamental aspects of organic chemistry and guided by sheer scientific curiosity, but they are often inspired and directed by the needs of medicinal chemistry, pharmaceutical, and biomedical research.

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

**Prof. Dr. I. Vilotijević** I have always had an inclination towards natural sciences and I realized early on that chemistry, as the central natural science, was the one that satisfies my natural curiosity the most (and easily connects to all other natural sciences). My decision to become a chemist evolved during participation in the programs at Petnica Science Center, a unique independent institution for extracurricular, formal and informal, science education of high school students. As an undergraduate student, I was drawn to synthesis because of its proactive nature and the opportunity it gives to create, change and manipulate molecules. Working as an undergraduate research intern at OSU and UIUC introduced me to research in organic synthesis and set me on a path to becoming a synthetic organic chemist. Throughout my time as a graduate student at MIT and a postdoc at Max Planck Institute, I remained determined to pursue an independent academic

career as a synthetic chemist. During this time, I have worked on projects close to biological and biophysical fields, which only strengthened my conviction that organic synthesis will remain an integral part of any interdisciplinary effort in chemical sciences.

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

**Prof. Dr. I. Vilotijević** The more you know, the more you know you don't know. This easily applies to organic synthesis. I am sure that many synthetic chemists will agree with the previous statement, but organic chemistry as a mature field must communicate this to other disciplines to debunk the common "anything can be made easily" attitude. For those in the field, a better interpretation of this statement is "the more you know, the more questions you ask" and that means that there is plenty of progress to be made in the field. These questions can be adequately answered by fundamental research and I personally hope for a renaissance of basic organic chemistry research that will provide long-term benefits for the society. Only in this light will organic chemistry remain a leading discipline of scientific research.

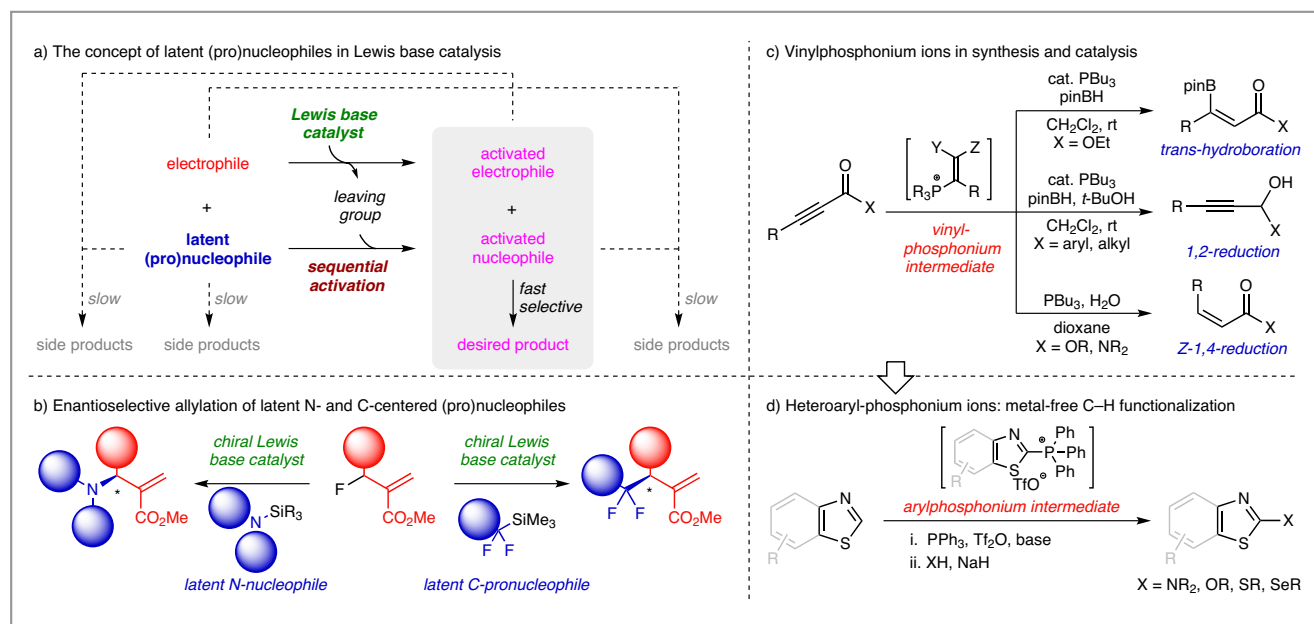
In applied organic synthesis, it is easy to see the ever-increasing need for more diverse and more complex organic molecules in virtually all branches of industry and research which is why organic synthesis is here to stay. The real

question is who will do organic synthesis in the future and how will it be done. I believe that we need to embrace new technologies like automation and artificial intelligence and use them as tools to solve scientific problems and gain further knowledge. The more diversity we have in the technical set-ups we use, the better! Finally, the environmental impact of organic synthesis and its sustainability will be central in any future synthetic efforts at scale.

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

**Prof. Dr. I. Vilotijević** We are committed to discovering new patterns of reactivity that will enable practical and more sustainable synthetic methods. Most of our efforts are in organocatalysis and in making bridges between main group chemistry and organic synthesis. Our focus on studying the underexplored/underutilized intermediates in Lewis base catalysis led our current research in two general directions: Lewis base catalysis and organophosphorus chemistry. In both fields, our approach is similar and based on a detailed analysis and understanding of the reaction mechanisms and the reactivity of intermediates.

In the field of Lewis base catalysis, we have established the concept of latent nucleophiles where we start the reaction with capped molecules of diminished nucleophilicity and require the interdependent sequential activation of the



**Scheme 1** The work of Vilotijević group in Lewis base catalysis and organophosphorus chemistry

electrophile and the nucleophile (Scheme 1, a).<sup>1</sup> Our studies have shown that this concept allows for a much broader scope and improved selectivities in Lewis base catalyzed enantioselective allylations (Scheme 1, b).<sup>2</sup> Furthermore, we are exploring the reactivity of non-traditional frustrated Lewis pairs in the context of Lewis base catalysis. In this area, we have developed hydroboration and reduction protocols that involve vinylphosphonium intermediates (Scheme 1, c).<sup>3</sup> Moving from the vinyl- to arylphosphonium ions has resulted in the development of the C–H functionalization protocols which are the basis of the broader transition-metal-free platform for functionalization and cross-coupling of N-heterocycles (Scheme 1, d).<sup>4</sup> In the area of organophosphorus chemistry, we also focus on P(III)–P(V) cycling and the development of new phosphorus-containing functional materials and fluorophores.<sup>5</sup> Lastly, we have a strong connection to biological research and collaborative projects where our chemistry is used in the synthesis of natural products, biosynthetic intermediates and other bioactive molecules and probes for biological research.

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

**Prof. Dr. I. Vilotijević** My group is very excited about the concept of latent (pro)nucleophiles which we have recently outlined and used to address the specific challenges in enantioselective Lewis base catalysis. Not only does this concept enable expanded scope for Lewis base catalyzed reactions, but it may also lead to improvements in other fields of catalysis in general and be applicable to transition-metal-catalyzed reactions. With that said, I like to think that our most important scientific achievements are still ahead of us.



## REFERENCES

- (1) M. Lange, Y. Zi, I. Vilotijević *Synlett* **2020**, submitted for publication.
- (2) (a) Y. Zi, M. Lange, C. Schultz, I. Vilotijević *Angew. Chem. Int. Ed.* **2019**, *58*, 10727–10731. (b) M. Lange, Y. Zi, I. Vilotijević *J. Org. Chem.* **2020**, *85*, 1259–1269. (c) Y. Zi, M. Lange, P. Schüler, S. Kriek, M. Westerhausen, I. Vilotijević *Synlett* **2020**, *31*, 575–580. (d) Y. Zi, M. Lange, I. Vilotijević *Chem. Commun.* **2020**, *56*, 5689–5692.
- (3) (a) F. Schömberg, Y. Zi, I. Vilotijević *Chem. Commun.* **2018**, *54*, 3266–3269. (b) Y. Zi, F. Schömberg, F. Seifert, H. Görls, I. Vilotijević *Org. Biomol. Chem.* **2018**, *16*, 6341–6349.
- (4) (a) Y. Zi, K. Wagner, F. Schömberg, I. Vilotijević *Org. Biomol. Chem.* **2020**, in press. DOI: 10.1039/D0OB00684J. (b) Y. Zi, F. Schömberg, K. Wagner, I. Vilotijević *Org. Lett.* **2020**, *22*, 3407–3411.
- (5) M. Sauer, V. Nasufovic, H.-D. Arndt, I. Vilotijević *Org. Biomol. Chem.* **2020**, *18*, 1567–1571.

## Editorial Board Focus: Prof. Xiaozhang Zhu (Institute of Chemistry, Chinese Academy of Sciences, P. R. of China)

**Background and Purpose.** From time to time, SYNFORM portrays Thieme Chemistry Editorial Board or Editorial Advisory Board members who answer several questions regarding their research interests and revealing their impressions and views on the developments in organic chemistry as a general research field. This Editorial Board Focus presents Professor Xiaozhang Zhu [Institute of Chemistry, Chinese Academy of Sciences (ICCAS), P. R. of China] who joined the Editorial Board of ORGANIC MATERIALS with effect of July 2018.

### Biographical Sketch



Prof. X. Zhu

**Xiaozhang Zhu** was born in August 1978 in Jiangsu Province, P. R. of China. He graduated from Jinlin University (P. R. of China) in 2001. He received his Ph.D. from Institute of Chemistry, Chinese Academy of Sciences (ICCAS, P. R. of China) in 2006. He was successively assigned as an AvH (Alexander von Humboldt Foundation) and a JSPS (the Japan Society for the Promotion of Science) Research Fellow at Ulm University (Germany) and the University of Tokyo (Japan), respectively. Since 2012, he has been a Professor in ICCAS under the support of the Chinese Recruitment Program of Global Youth Experts. His research interests include design and synthesis of organic  $\pi$ -functional materials and their applications in organic optoelectronic devices. He has published over 100 papers in refereed journals. He is one of the co-editors of Organic Materials (Thieme Publishing Group).

### INTERVIEW

**SYNFORM** Please comment on your role as a member of the Editorial Board of ORGANIC MATERIALS.

**Prof. X. Zhu** Besides the daily work of processing the submitted papers, I normally spend much time on the invitation of high-quality original papers from those renowned scholars. I also use every possibility to advocate our journal.

**SYNFORM** How do you describe the value of a journal such as ORGANIC MATERIALS to the chemistry community?

**Prof. X. Zhu** The journal focuses on the publication of reviews and original papers in the multidisciplinary subjects based on organic substances, which represents the tendency of science and technology in the current era and is expected to make a profound contribution to the development of the research field of organic materials.

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

**Prof. X. Zhu** I am focused on the development of new organic conjugated materials based on quinoid-resonance effect for applications in organic optoelectronics such as organic photovoltaic and thermoelectric devices.

**SYNFORM** You are a leading researcher with regard to organic materials chemistry. Could you tell us more about how important you perceive this particular topic to be?

**Prof. X. Zhu** Compared with the traditional inorganic counterparts, organic optoelectronics exhibit great potential in the electronic market because of low cost, large-area fabrication, and intrinsically high flexibility, which has attracted wide interests ranging from academic to industrial communities. Many obscure but interesting scientific problems and the expectation of promising commercial applications bring about the continuous prosperity of this field, which has lasted through the last several decades and will continue beyond.

*Xiaozhang Zhu*

## Efficient Co-Catalyzed Double Hydroboration of Nitriles: Application to One-Pot Conversion of Nitriles into Aldimines

*Chem. Eur. J.* **2020**, *26*, 4963–4968

The development of new transformations allowing for selective synthesis of amines from readily accessible precursors continuously attracts significant attention from the synthetic chemistry community, since amines play an indispensable role as building blocks for the synthesis of many natural products, biologically active molecules, pharmaceutical compounds, agrochemicals, etc. In this regard, catalytic reduction of readily available simple feedstock molecules, such as nitriles, to amines using abundant first-row transition metal catalysts (base metals, such as Fe, Co, Ni) represents an attractive alternative to conventional wasteful stoichiometric reduction methods and catalytic reductions with precious metal catalysts, which are limited in supply and expensive. However, examples of such base metal catalytic systems for efficient and selective room-temperature reduction of nitriles to amines are still scarce and generally require rather sophisticated ligands, the cost of which should not be underestimated. The research group of Professor Andrey Khalimon at Nazarbayev University (Kazakhstan) is interested in the development of economical and readily available abundant transition metal pre-catalysts for reduction of challenging unsaturated molecules and application of such transformations in the synthesis of more complex organic molecules.

“Recently, we have reported a rare example of room-temperature deoxygenative hydrosilylation of tertiary amides to the corresponding amines using bench-stable and commercially available  $\text{Co}(\text{acac})_2$  ligated with commercially available phosphines, i.e.  $\text{PPh}_3$  and bis[(2-diphenylphosphino)phenyl] ether (dpephos)<sup>1</sup>,” said Professor Khalimon. He continued: “The  $\text{Co}(\text{acac})_2/\text{dpephos}$  system also showed moderate catalytic activity for the deoxygenative hydrosilylation of several primary amides. Since previous studies suggested that deoxygenative reduction of primary amides proceeds via dehydration of primary amides to nitriles, followed by their reduction to amines,<sup>2</sup> the  $\text{Co}(\text{acac})_2/\text{dpephos}$  system was tested to perform hydrosilylation of nitriles; however, to our surprise, it was found to be inactive in these transformations.” The group then hypothesized that the reduction of nitriles could be achieved with hydroboranes, which in comparison with the silicon center of hydrosilanes typically possess a more Lewis acidic boron center, as well as a B–H bond having higher hydride character relative to the Si–H bond. Besides, nitrile

hydroboration products such as *N,N*-diborylamines have been recently shown to be promising reagents for the construction of C–N bonds via B–N bond cleavage. However, examples of such transformations are still scarce, since the first synthetic routes to *N,N*-diborylamines have been developed only recently. “In 2012, our group reported the first examples of dihydroboration of nitriles with HBCat (Cat = catechol) using a Mo(IV) imido hydrido–chloride complex  $(2,6\text{-}i\text{Pr}_2\text{PhN=})\text{Mo}(\text{H})(\text{Cl})(\text{PMe}_3)_3$ ,” explained Professor Khalimon. Although the turnover frequencies were low (TOF up to  $1.7\text{ h}^{-1}$ ), this work constituted a valuable proof of principle. Professor Khalimon said: “In the same report, we demonstrated the first example of reactivity of  $\text{PhCH}_2\text{N}(\text{BCat})_2$  with benzaldehyde to afford *N*-benzylidenebenzylamine under mild conditions (r.t., 1 h). A similar transformation with  $\text{PhCH}_2\text{N}(\text{BPin})_2$  (Pin = pinacol) was disclosed by Szymczak and Geri in 2015;<sup>4</sup> however, the reaction required addition of 5 mol% of KHMDS (potassium hexamethyldisilazide) and prolonged heating (up to 18 h) at  $150\text{ }^\circ\text{C}$ . In 2019, Tobita and co-workers reported Ru-catalyzed hydroboration of nitriles to *N*-borylimines and *N,N*-diborylamines and their application in subsequent Pd-catalyzed cross-coupling reactions with aryl bromides.<sup>5</sup> More recently, Baik, Trovitch and co-workers described the reactions of *N,N*-diborylamines with aromatic carboxylic acids at  $120\text{ }^\circ\text{C}$  to afford secondary carboxamides.<sup>6</sup>”

Inspired by these examples of reactivity of *N,N*-diborylamines, the group set up a research program directed at the development of simple, economical and efficient catalytic systems for selective and mild hydroboration of nitriles with HBPIn to give *N,N*-bis(pinacolboryl)amines, which can be used in situ for C–N bond construction reactions (Scheme 1, A). “Rewardingly, the commercially available and bench-stable  $\text{Co}(\text{acac})_2/\text{dpephos}$  system turned out to mediate a variety of hydroboration reactions of nitriles under mild conditions, working equally well for substrates bearing electron-withdrawing and electron-donating substituents (Scheme 1, B). Since many reduction reactions suffer from selectivity issues, one of the most intriguing questions for us was whether we could perform hydroboration of nitriles chemoselectively, in the presence of other functional groups prone to reduction,” remarked Professor Khalimon. He continued: “To our delight  $\text{Co}(\text{acac})_2/\text{dpephos}$  allowed for chemo-

selective hydroboration of cyano groups in the presence of halide, ether, ester, lactone, amide and unactivated alkene functionalities (Scheme 1, B). Interestingly, depending on reaction conditions (temperature and HBPIn concentration), chemodivergent hydroboration was observed for cinnamitrile. At room temperature, using 2.5 equivalents of HBPIn, the reaction selectively afforded the product of the C=C bond reduction, e.g. 3-phenylpropionitrile (52% conversion by NMR; Scheme 1, C). In contrast, treatment of cinnamitrile with 5 equivalents of HBPIn at 50 °C resulted in reverse selectivity and gave primarily the *N,N*-diborylcinnamylamine (78% by NMR; Scheme 1, C). This result was totally unexpected but it represents a beautiful example of kinetic control of the reaction, depending on experimental conditions.”

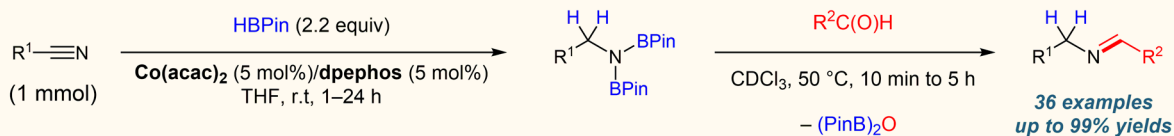
The group found that the resulting *N,N*-bis(pinacolboryl) amines could be converted in situ into a variety of aldimines. “This latter transformation works well for both aliphatic and aromatic *N,N*-diborylamines and aldehydes, and tolerates a wide range of common functional groups having different electronic properties, such as heterocycles, alkenes, alkynes, ketones carboxylic acids, amides and others (Scheme 1, B).

Thus, combining the efficient and economical method for generation of diborylamines from nitriles and selective reactions of diborylamines with aldehydes, the overall protocol represents the first practical, synthetically valuable approach to aldimines from readily available nitriles, without the use of dehydrating agents,” said Professor Khalimon. He went on to explain that the selectivity of the overall transformation is limited only by the chemoselectivity of the hydroboration step and the reactions can be performed selectively with the substrates bearing lactone, ester, carboxamide and unactivated alkene functionalities, which are often not tolerated during reduction of nitriles.

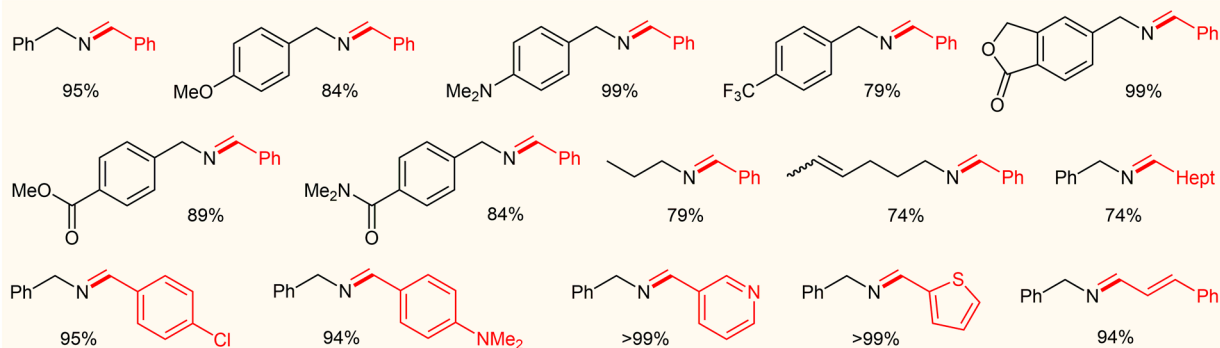
“This study further illustrates that borylamines, which can be easily accessed from readily available nitriles using economical and abundant transition metal catalysts, may serve as powerful reagents for C–N bond construction reactions,” said Professor Khalimon. He concluded: “We are currently examining the potential of this methodology in the synthesis of other nitrogen-containing organic molecules and expect more reports on reactivity of borylamines to appear in the research literature in the near future.”

*Mattes female*

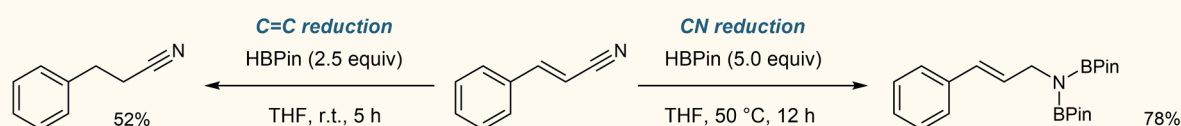
#### A: Overall sequential one-pot transformation



#### B: Scope examples (isolated yields)



#### C: Chemodivergent hydroboration of cinnamitrile (NMR yield)



**Scheme 1** (A) One-pot transformation of nitriles into aldimines. (B) Examples of reaction products with isolated yields. (C) Temperature-dependent chemodivergent hydroboration of cinnamitrile.



## REFERENCES

- (1) A. Nurseit, J. Janabel, K. A. Gudun, A. Kassymbek, M. Segizbayev, T. M. Seilkhanov, A. Y. Khalimon *ChemCatChem* **2019**, *11*, 790–798.
- (2) A. Y. Khalimon, K. A. Gudun, D. Hayrapetyan *Catalysts* **2019**, *9*, 490.
- (3) A. Y. Khalimon, P. Farha, L. G. Kuzmina, G. I. Nikonov *Chem. Commun.* **2012**, *48*, 455–457.
- (4) J. B. Geri, N. K. Szymczak *J. Am. Chem. Soc.* **2015**, *137*, 12808–12814.
- (5) T. Kitano, T. Komuro, H. Tobita *Organometallics* **2019**, *38*, 1417–1420.
- (6) C. Ghosh, S. Kim, M. R. Mena, J.-H. Kim, R. Pal, C. L. Rock, T. L. Groy, M.-H. Baik, R. J. Trovitch *J. Am. Chem. Soc.* **2019**, *141*, 15327–15337.

## About the authors



Dr. K. A. Gudun

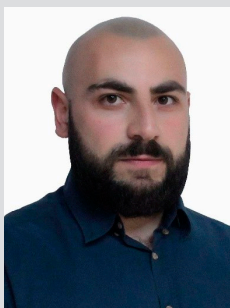
**Kristina A. Gudun** graduated from Karaganda State University (Kazakhstan) with a B.Sc. (2007) and M.Sc. (2009) in chemistry and Ph.D. in chemical technology of organic compounds (2012). In 2017, after a few years in chemical industry, she joined the research group of Prof. Andrey Khalimon at Nazarbayev University (Kazakhstan) as a postdoctoral research assistant. Her work is focusing on nickel and cobalt catalysts for small molecule activation, catalytic reduction of challenging unsaturated organic molecules and carbon dioxide.



A. Slamova

**Ainur Slamova** graduated from E. A. Buketov Karaganda State University (Kazakhstan) with B.Sc. in chemical technology of organic substances in 2013 and received her M.Sc. in chemistry from L. N. Gumilyov Eurasian National University in 2015 (Kazakhstan). Since 2016, she has been working at Nazarbayev University first as laboratory assistant at the Department of Chemistry and then as research technologist in Core Facilities.

In 2019, she joined the group of Prof. Andrey Y. Khalimon working on catalysis with base metal complexes.



Dr. D. Hayrapetyan

**Davit Hayrapetyan** was born and raised in Armenia. He received his Diploma degree in chemistry in 2009 and Ph.D. in organic and organometallic chemistry in 2012 from Lomonosov Moscow State University (Russia). In 2014 he joined Prof. Shu Kobayashi's group at the University of Tokyo (Japan) as a postdoctoral fellow. Then, in 2015 he joined Prof. Kevin Lam's laboratory at Nazarbayev

University (Kazakhstan) and he spent 2016 to 2018 at Ruhr-Universität Bochum (Germany) with Prof. Lukas Gooßen. Since 2019 he has been an independent postdoctoral scholar under The Office of the Provost at Nazarbayev University.



Prof. A.Y. Khalimon

**Andrey Y. Khalimon** was born and raised in Russia. He obtained his Dipl. Chem. degree from Lomonosov Moscow State University (Russia) in 2004 and Ph.D. in chemistry from Brock University (Canada) with Prof. Georgii Nikonov in 2010. Following his graduate studies, he was a postdoctoral associate (2010–2013) in the group of Prof. Warren Piers at the University of Calgary (Canada) and a postdoctoral fellow (2013–2014)

in the Catalysis Research Laboratory (CaRLa; Germany), jointly managed by the University of Heidelberg and BASF SE. In early 2015, he joined Nazarbayev University (Kazakhstan) as an assistant professor of chemistry at the School of Science and Technology, which was then transformed into the School of Sciences and Humanities. In 2018, he also joined the Environment and Resource Efficiency Cluster (EREC) of Nazarbayev University as a principal investigator. His research interests include coordination chemistry, organometallic chemistry and homogeneous catalysis, CO<sub>2</sub> utilization, small molecule activation and development of new abundant metal catalysts for chemo-, regio- and enantioselective transformations of organic substrates into value-added products. A large part of his research is devoted to catalytic reduction of unsaturated organic molecules and understanding the mechanisms of such reactions in order to develop even better systems with predictable properties and reactivity patterns.

# A General $^{11}\text{C}$ -Labeling Approach Enabled by Fluoride-Mediated Desilylation of Organosilanes

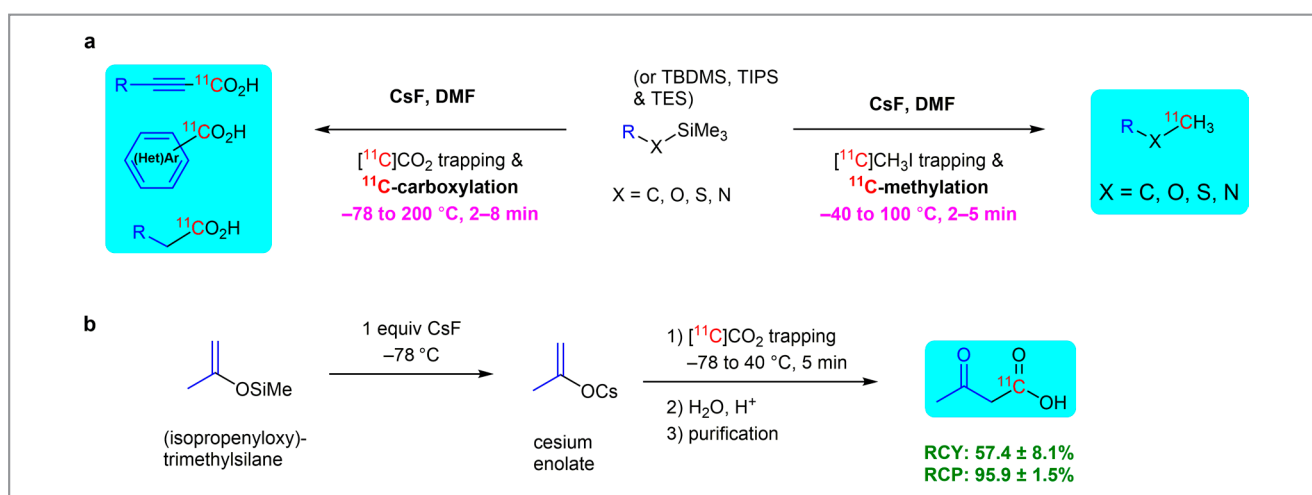
*Nat. Commun.* **2020**, DOI: 10.1038/s41467-020-15556-7

Positron emission tomography (PET) is an important imaging modality for the non-invasive investigation of biochemical and molecular events in living organisms. Because of the ubiquitous presence of carbon atoms in organic molecules, carbon-11 ( $^{11}\text{C}$ ,  $t_{1/2} = 20.4$  min,  $E_{\beta^+} = 1.98$  MeV) labeled organic compounds with well-characterized biological and pharmacological properties (i.e., metabolism, drug pharmacokinetics, receptor binding affinity, enzyme substrate affinity, etc.) could be used for clinical and pre-clinical studies with much fewer hurdles, compared with compounds labeled with other radioisotopes (such as fluorine-18, iodine-123 and bromine-76). In addition, the short half-life of  $^{11}\text{C}$  allows the performance of multiple studies on the same subject in a single site visit, which represents a great advantage in clinical studies. To produce the desired  $^{11}\text{C}$ -labeled compounds in high radiochemical and chemical purities, as well as with high molecular activity, there is a still unmet demand to develop fast and reliable approaches for introducing  $^{11}\text{C}$  into molecules with diversified structures. Among them, the development of a new  $^{11}\text{C}$ -carboxylation approach for the direct use of  $[^{11}\text{C}]\text{CO}_2$  as radiosynthon would be especially attractive. Recently, Professor Wenhao Qu at Stony Brook University (USA) and his colleagues reported a general  $^{11}\text{C}$ -labeling strategy using a fluoride-mediated desilylation (FMDS) process to generate

reactive nucleophiles for nucleophilic  $^{11}\text{C}$ -carboxylation and  $^{11}\text{C}$ -methylation (Scheme 1, a).

In early 2017, during the development of a protocol for preparing  $[^{11}\text{C}]\text{acetoacetic acid}$  to support a clinical imaging study, Professor Qu and his colleagues occasionally noticed an unexpected amount of chemical impurities when they used an existing literature method for the lithium enolate  $^{11}\text{C}$ -carboxylation. "To circumvent this problem, we explored alternative methods and eventually identified conditions for enolate formation mediated by fluoride ion desilylation that could represent a milder and general  $[^{11}\text{C}]\text{CO}_2$  incorporation method," explained Professor Qu. He continued: "The optimal reaction conditions were obtained following careful and extensive modifications and this updated synthesis method led to the formation of  $[^{11}\text{C}]\text{acetoacetic acid}$  with good radiochemical and chemical purities, and also dramatically improved radiochemical yield in a similar production time frame (Scheme 1, b)."

This success triggered the group's interest in employing this FMDS approach for  $^{11}\text{C}$ -carboxylation further, with different organosilanes as labeling precursors. "It turned out that a variety of organosilanes with trialkylsilyl group attached at  $\text{sp}^-$ ,  $\text{sp}^2$ -, and  $\text{sp}^3$ -carbon atoms could all afford the corresponding  $^{11}\text{C}$ -carboxylic acids with fair to excellent yields,"



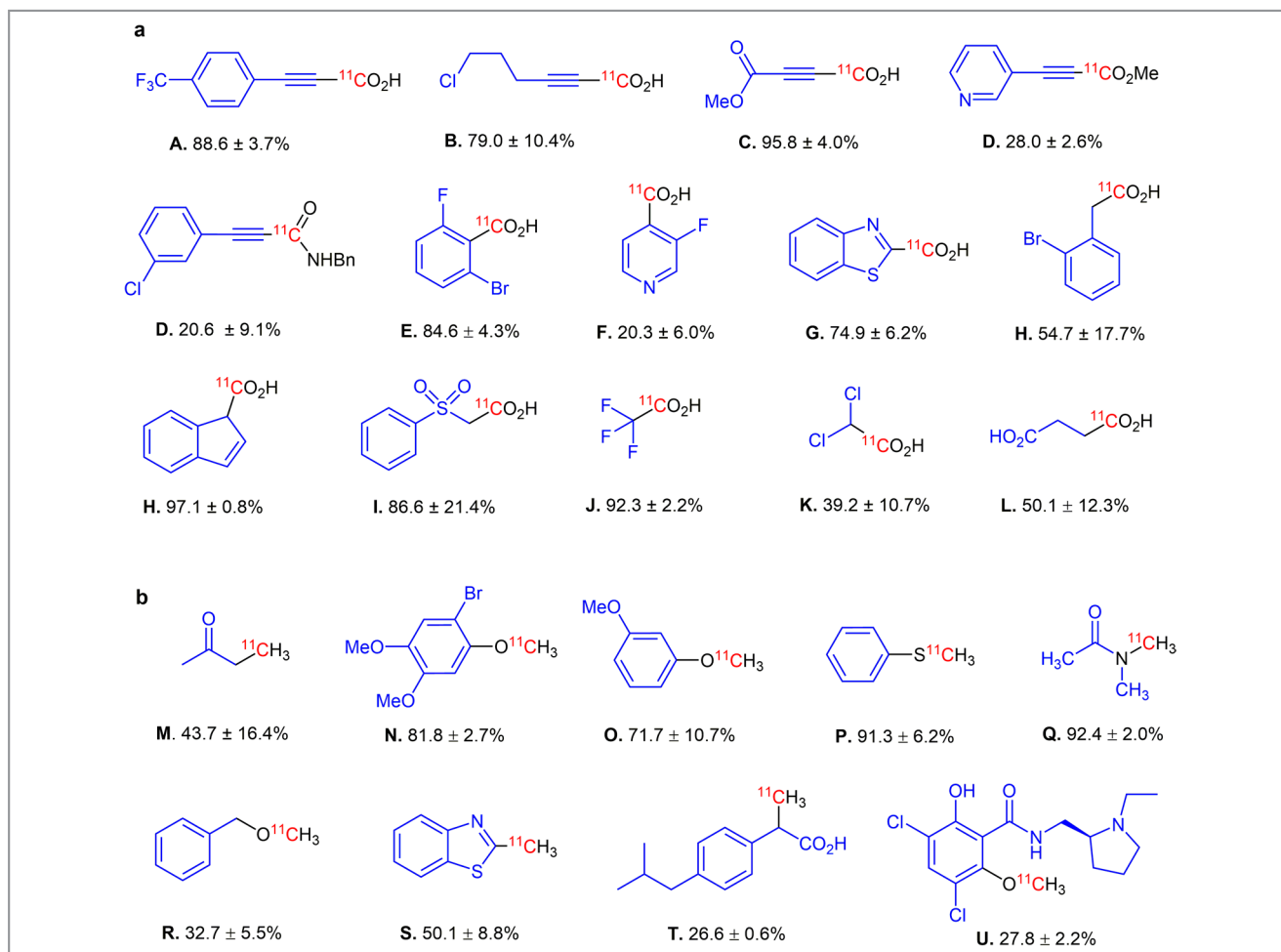
**Scheme 1** Fluoride-mediated desilylation for (a)  $^{11}\text{C}$ -carboxylation and  $^{11}\text{C}$ -methylation of organic molecules and (b) FMDS  $^{11}\text{C}$ -carboxylation for synthesizing  $[^{11}\text{C}]\text{acetoacetic acid}$ .

remarked Professor Qu. He continued: "The presence of different reactivities among these organosilane substrates was readily explained by the  $pK_a$  values of the conjugate acids of these anionic nucleophiles generated by the fluoride-desilylation. In addition, we also found that the newly formed  $^{11}\text{C}$ -carboxylic acids could be converted into the corresponding ester or amide in a simple and fast manner (Figure 1, a)."

Encouraged by the success of using the FMDS  $^{11}\text{C}$ -labeling strategy to afford various  $^{11}\text{C}$ -carboxylic acids, which was even more remarkable considering that previously many of them could be prepared only with difficulty, Professor Qu and his co-workers further extended their FMDS approach for  $^{11}\text{C}$ -methylation. "We found that the  $[^{11}\text{C}]\text{CH}_3^-$  group could be attached to specific positions (oxygen, sulfur, nitrogen and carbon atoms) of organic molecules through a FMDS  $^{11}\text{C}$ -methylation process under very mild reaction conditions in a straightforward manner (Figure 1, b)," explained Professor Qu.

Professor Qu commented: "This FMDS  $^{11}\text{C}$ -labeling approach not only provides radiochemists with a fast and easy access to various  $^{11}\text{C}$ -carboxylic acids, but also presents itself as an ideal alternative for  $^{11}\text{C}$ -methylation of organic molecules with attractive biological activities." He concluded: "In the end, I expect that our group will apply this newly established  $^{11}\text{C}$ -labeling approach to develop synthetic protocols for radiotracers of high clinical interest where regular production is very difficult using currently reported methods."

*Mattias Fank*



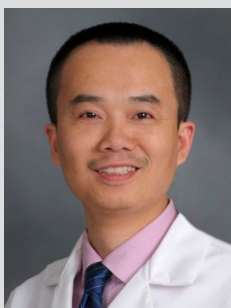
**Figure 1** Selected  $^{11}\text{C}$ -labeling examples and the radiochemical yields (RCYs,  $n = 3$ ).

## About the authors



Prof. W. Qu

**Wenchao Qu** was trained as a synthetic organic chemist and obtained his Ph.D. from the University of Akron, Ohio (USA) in 2006. After a postdoctoral fellowship in Dr. Hank F. Kung's radiopharmaceutical chemistry group at University of Pennsylvania (Upenn, USA) and later a research track assistant professorship at the same university, he joined Dr. Joanna Folwer's PET chemistry program at Brookhaven National Laboratory (USA) as an associate chemist in 2012. Three years later, he moved to Citigroup Biomedical Imaging Center at Weill Cornell Medicine (USA) and became a senior radiochemist and associate professor in radiopharmaceutical sciences research. In November 2019, he started his current position as associate professor and deputy director of PET chemistry at Psychiatry Department, Stony Brook University (SBU, USA). In addition to supervising regular radiotracer productions for supporting clinical and pre-clinical imaging studies at SBU, he is highly interested in developing novel radiopharmaceuticals for diagnosis and treatment of chronic diseases, as well as developing new radiochemistry methodologies for facile and fast incorporation of short half-life radioisotopes (carbon-11, fluorine-18, and other radiohalides) into bioactive molecules.



Dr. B. Hu

**Bao Hu** was born in Hunan, P. R. of China in 1982. He completed his B.E. from Hunan University of Science and Technology (P. R. of China) in 2005. After gaining his PhD with Prof. Zhongwen Wang at Nankai University (P. R. of China) in 2010, he joined Zhejiang University of Technology (ZJUT, P. R. of China) as an Assistant Professor. After a short period of independent research at ZJUT, he moved to the USA in 2012 as a postdoctoral fellow with Prof. Stephen DiMaggio at the University of Nebraska-Lincoln (UNL, USA). He then became a Research Assistant Professor at UNL and University of Illinois at Chicago (USA). In 2017, he moved his family to New York City and joined Weill Cornell Medicine (USA) as an Instructor, where he worked with Prof. John Babich and Prof. Wenchao Qu in the field of radiochemistry. Since early 2020, he has served as an Assistant Professor of Research Psychiatry and the Director of Radiotracer Production at Stony Brook University (USA). His current work at SBU

includes cGMP production of  $^{11}\text{C}$ - and  $^{18}\text{F}$ -labeled tracers for human and animal studies, development of novel radiotracers for imaging and therapeutic applications, and clinical translation of these new radiopharmaceutical candidates.



Dr. J. W. Babich

**John W. Babich** is a native of New York City (USA) where he received his early education before attending St. John's University (USA) for his B.S. in pharmaceutical sciences. He received his Master's degree in radiopharmacy from the University of Southern California in Los Angeles (USA) and his doctoral degree in radiopharmaceutical chemistry from The Institute of Cancer Research (ICR) of the University of London (UK), under the supervision of Prof. R. J. Ott. He began his research career at Brookhaven National Laboratory (USA) working with Powel Richards and Suresh Srivastava on technetium-99m labeling of red blood cells. He then joined NASA in Houston, TX (USA), where he was developing a Tungsten-178/Tantalum-178 radionuclide generator for cardiovascular imaging in humans and later joined the faculty at Baylor College of Medicine (USA). He moved to the UK in 1984 to pursue his PhD at the ICR and also worked full time in the Department of Physics where he was responsible for the radiopharmaceutical research program which focused on the use of monoclonal antibodies for cancer imaging, radiometals for positron emission tomography and targeted radiotherapy of neuroblastoma. In 1990 he moved to Boston to take a position at Massachusetts General Hospital (USA) and joined the faculty of Harvard Medical School (USA) where he was Assistant Professor of Radiology. Here he developed his interest in Technetium-99m labeled peptides for disease detection focusing on infection and breast cancer imaging. In 1998 he co-founded Molecular Insight Pharmaceuticals (MIP) where he was CSO and head of Research and Development until the company was acquired in January 2013. At MIP he oversaw the clinical development of seven novel radiopharmaceuticals, including the world's first imaging and therapy of human prostate cancer using small-molecule inhibitors of PSMA. In 2013 he joined the faculty at Weill Cornell Medical College (USA) where he is currently Chief of Radiopharmaceutical Sciences in Radiology. Babich's research interests include the design of molecular imaging probes and metabolic substrates for unmet needs in cancer, heart disease and neurological disease. Dr. Babich's contributions are reported in 220 peer-reviewed articles and 40 issued patents.

*N. Waterhouse*

**Nicole Waterhouse** was born in 1993 in Markham, Ontario (Canada), and grew up in nearby Richmond Hill, before moving to Ho-Ho-Kus, New Jersey (USA). She graduated with a BSc degree in chemistry from Manhattan College (USA) in 2016. Currently, she is enjoying working in radiochemistry at Weill Cornell Medicine (USA) under Dr. John Babich, while studying to earn her MS in chemistry from New Jersey Institute of Technology (USA).

*J. Urgiles*

**Julie Urgiles** received her BA degree in chemistry in 2017 from Cornell University (USA) where she worked under Prof. Justin J. Wilson. She then worked as a research assistant for a year under Dr. John Babich at Weill Cornell Medicine (USA). She is currently enrolled in Harvard Medical School (USA) where she completed a research assistantship in Dr. Angela Koehler's lab at MIT in 2019.

*M. Dooley*

**Marybeth Dooley** was born in 1993 in Queens, New York (USA) and lived there before moving to Rockland County, NY (USA) where she grew up. She graduated from Manhattan College (USA) with a BS in chemistry in 2015. Having previously worked as a Research Technician for four years at Weill Cornell Medicine (USA), she is now working in the pharmaceutical industry as a QC Chemist.

*Dr. S. Ponnala*

**Shashikanth Ponnala** earned his doctoral degree from Central Drug Research Institute (CDRI, India) under the supervision of Dr. Devi Prasad Sahu and received his Ph.D. in 2009. He worked as an Associate Scientist at GVK Biosciences (India) before moving to the USA to pursue his postdoctoral studies in 2010 with Prof. Wayne Harding (Hunter College, CUNY, USA) and Prof. Jason Lewis (Memorial Sloan Kettering Cancer

Center, USA). He subsequently joined Dr. John Babich's group at Weill Cornell Medicine, NY (USA) as a Research Associate, where he worked on the design and synthesis of PSMA-targeting ligands in prostate cancer PET imaging and therapy. At present he is working as a Senior Scientist at Angion Biomedica Corp, NY (USA) on small-molecule therapy for liver and kidney fibrosis.

## Coming soon

### — Literature Coverage

#### Allyl 4-Chlorophenyl Sulfone as a Versatile 1,1-Synthon for Sequential $\alpha$ -Alkylation/Cobalt-Catalyzed Allylic Substitution

### — Literature Coverage

#### Stain Protocol for the Detection of N-Terminal Amino Groups during Solid-Phase Peptide Synthesis

### — Literature Coverage

#### Asymmetric One-Pot Transformation of Isoflavones to Pterocarpans and Its Application in Phytoalexin Synthesis

## Further highlights

### **Synthesis** Review: Non-Classical Amide Bond Formation: Transamidation and Amidation of Activated Amides and Esters by Selective N–C/O–C Cleavage

(by G. Li and M. Szostak)

### **Synlett** Account: Manganese-Catalyzed Dehydrogenative/Deoxygenative Coupling of Alcohols

(by Y. Wang and Q. Liu)

### **Synfacts** Synfact of the Month in category “Organo- and Biocatalysis”: Identification of the First Stand-Alone Inter-molecular Diels–Alderase

For current SYNFORM articles, please visit [www.thieme-chemistry.com](http://www.thieme-chemistry.com)  
SYNFORM issue 2020/10 is available from September 17, 2020  
at [www.thieme-connect.com/ejournals](http://www.thieme-connect.com/ejournals)

### Editor

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

### Editorial Office

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

### Publication Information

Synform will be published 12 times in 2020 by Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany, and is an additional online service for Synthesis, Synlett and Synfacts.

### Product Names

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 to labels, names or other signs.

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

The Americas: Thieme New York, 333 Seventh Avenue, New York, NY 10001, USA.  
Via e-mail: [customerservice@thieme.com](mailto:customerservice@thieme.com)  
Via website: [www.thieme-chemistry.com](http://www.thieme-chemistry.com)  
Phone: +1 212 760 0888; Fax: +1 212 947 0108  
Order toll-free within the USA: +1 800 782 3488

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

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

### Online Access

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

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

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

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

### Ownership and Copyright

© Georg Thieme Verlag KG Stuttgart · New York 2020  
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 in particular to photocopy reproduction, copyright, cyclostyling, mimeographing or duplication of any kind, translating, preparation of microfilms, and electronic data processing and storage (CD-ROM, DVD, USB memory stick, databases, cloud-based service, ebook and other forms of electronic publishing) as well as making it available to the public (e.g., internet, intranet or other wired or wireless data networks), in particular by displaying on stationary or mobile visual display units, monitors, smart phones, tablets or other devices by download (e.g., e-pub, PDF, App) or retrieval in any other form.

### 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; [www.copyright.com](http://www.copyright.com). For reprint information in the USA, please contact: [journals@thieme.com](mailto:journals@thieme.com)