

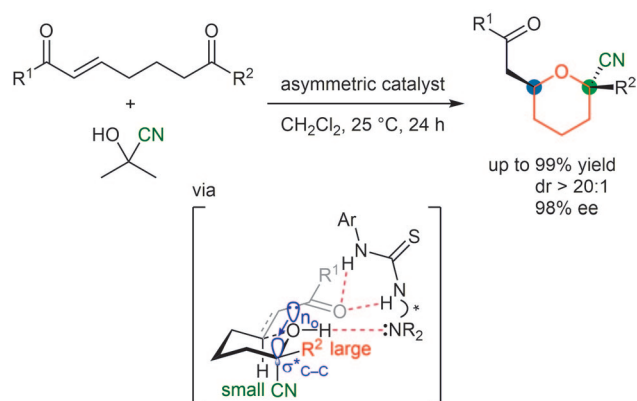
# Synform

People, Trends and Views in Chemical Synthesis

2018/03

## Organocatalytic Enantio- and Diastereo-selective Cycloetherification via Dynamic Kinetic Resolution of Chiral Cyanohydrins

Highlighted article by N. Yoneda, Y. Fujii, A. Matsumoto, K. Asano, S. Matsubara



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## Dear Readers,

The progress in synthetic methodology development continues at a frantic pace, with hundreds – or even thousands – of publications every month reporting more or less innovative methods and modifications of known reactions for producing a range of organic molecules of any kind. But do we actually need more synthetic methods, or is the arsenal of reactions available to organic chemists nowadays more than sufficient, and should we rather at this point focus on the applications, namely using the available methods for the synthesis of useful target molecules, possibly in close collaboration with biologists, material scientists and physicists who can use them? I remember almost 30 years ago, one of my organic chemistry professors – an eminent synthetic chemist – used to argue that there were already enough reactions and methods to synthesize pretty much every molecule we wanted or needed to. Thousands of new synthetic methods and countless publications later, the field is still thriving and the brightest chemists around the world continue to discover and report new reactions. But is it just for the sake of publishing articles or is there a real need and appetite for new synthetic methods? In a nutshell, is the tax-payers' money still well spent on doing research in synthetic methodology development, or not? I am not going to disclose my personal opinion in this brief editorial, but I would love to get your thoughts – dear readers – on the topic. Whatever your opinion is, I guess we can all agree that this new issue of SYNFORM is packed full of a wealth of novel and scientifically exciting synthetic methods! For example, the organocatalytic cycloetherification developed by S. Matsubara and K. Asano (Japan) or the *gem*-difluoropropargylation using alkylzinc reagents reported by X. Zhang (P. R. of China), not to mention the Pd-catalyzed *syn*-1,4-carboamination of aromatic compounds, occurring with

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concomitant dearomatization, as described by D. Sarlah (USA). And finally, there is the work of a young up-and-coming researcher, A. W. H. Speed (Canada) who is the protagonist of the Young Career Focus interview. Very nice and exciting work indeed. But do we need more synthetic methods or should we rather focus on using the existing synthetic technology for producing new and better therapeutics, diagnostics, agrochemicals and useful materials?

Enjoy your reading!

### Contact

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

# Organocatalytic Enantio- and Diastereoselective Cycloetherification via Dynamic Kinetic Resolution of Chiral Cyanohydrins

*Nat. Commun.* **2017**, *8*, 1397

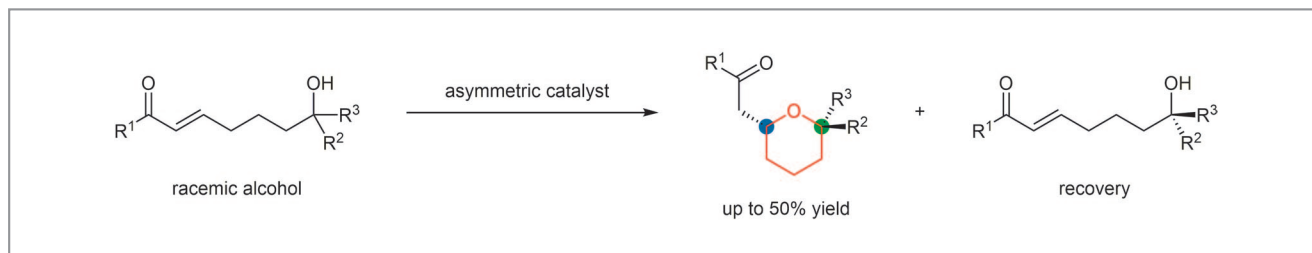
Enantioselective synthetic approaches to six-membered oxacycles are in high demand to enable the discovery of new potential therapeutic agents and bioactive molecules. However, the lack of a simple robust method for such enantioselective syntheses has limited their development. In particular, as the enantio- and diastereoselective construction of multiple stereocenters in a single operation often poses a formidable challenge, it remains desirable to develop a concise efficient method for the asymmetric installation of more than one chiral center in tetrahydropyrans. Recently, the group of Professors Sejiro Matsubara and Keisuke Asano at Kyoto University (Japan) discovered a concise organocatalytic cycloetherification for the highly enantio- and diastereoselective synthesis of tetrahydropyrans, involving simultaneous construction of two stereogenic centers, one of which is fully substituted. This method involves dynamic kinetic resolution of reversibly generated chiral cyanohydrins.

Professor Asano said: “For some time we have been interested in the synthesis of heterocyclic compounds via asymmetric intramolecular hetero-Michael addition with bifunctional organocatalysts, which selectively recognizes a specific conformation of substrates or intermediates. In particular, we have recently tackled the construction of multiple stereogenic centers in a single reaction. We previously reported an asymmetric cycloetherification of secondary or tertiary alcohols bearing an  $\alpha,\beta$ -unsaturated carbonyl moiety affording tetrahydropyrans containing two stereogenic centers via kinetic resolution of the racemic alcohols (*Chem. Lett.* **2016**, *45*, 1300, *Scheme 1*).”

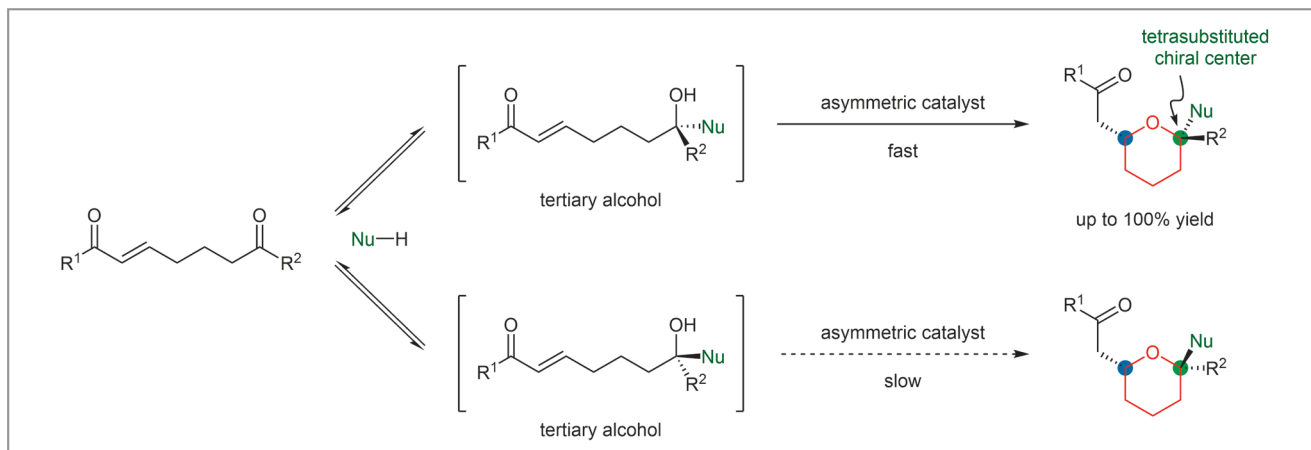
The group then wondered whether the methodology could be extended to cyclization via dynamic kinetic resolu-

tion involving racemization of chiral alcohols, thus potentially enabling quantitative yields of the desired product. “In order to construct a tetrasubstituted chiral carbon center, racemization of tertiary alcohols is necessary; however, redox processes cannot be employed in such cases and these racemizations typically require harsh reaction conditions that are not suitable for asymmetric catalysis,” explained Professor Asano. He continued: “Thus, to achieve the cyclization of chiral tertiary alcohols via dynamic kinetic resolution, I discussed with Mr. Yoneda for several hours in front of a glass board, which we often use to draw chemical structures for discussion. After an hour, we first hit on the idea that a process involving reversible addition of a carbon nucleophile to ketones may result in formal racemization of tertiary alcohols under mild conditions (*Scheme 2*). Actually, we previously utilized an analogous process for the asymmetric synthesis of spiroketals involving reversible generation of chiral hemiacetals from ketones with alcohols as the nucleophile (*Angew. Chem. Int. Ed.* **2015**, *54*, 15497).”

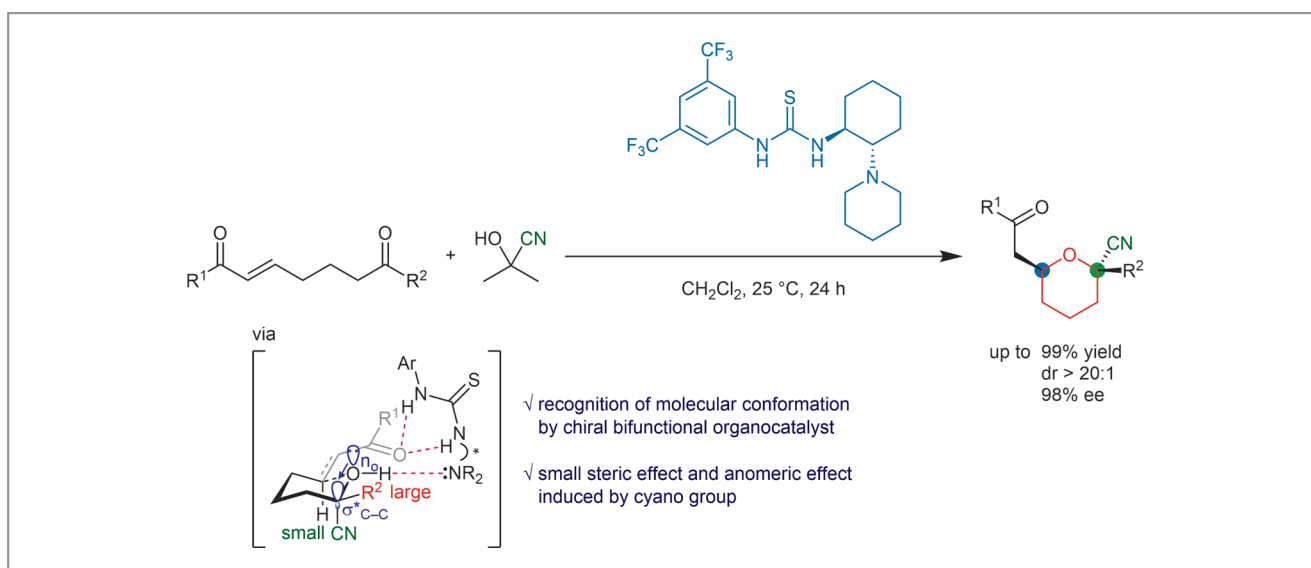
Next, the two researchers asked each other what would be suitable as the carbon nucleophile. The solution they reached after additional discussion was the use of cyanation, as it might be reversible. “Based on the discussion, Mr. Yoneda initiated the investigations for optimizing the reaction conditions including cyanide sources, catalysts, and so on,” said Professor Asano, continuing: “Although the desired product was not initially obtained at all, after dedicated efforts he identified acetone cyanohydrin as a useful cyanation reagent and managed to optimize the effective catalyst structure (*Scheme 3*).”



**Scheme 1** Cycloetherification via kinetic resolution of racemic alcohols



**Scheme 2** Cycloetherification via dynamic kinetic resolution involving reversible addition of a carbon nucleophile to ketones



**Scheme 3** Organocatalytic enantio- and diastereoselective cycloetherification via dynamic kinetic resolution of chiral cyanohydrins

Regarding the excellent enantio- and diastereoselectivities, the pair had further brainstorming sessions and noticed that in this reaction the anomeric effect induced by the electronegative character of the cyano group was likely to have an important effect on the stereoselectivity with respect to the tetrasubstituted chiral carbon. “At that stage, unfortunately, Mr. Yoneda left our group to join a company, where he is currently working. Thus, further studies for the mechanistic insights and the derivatization of a reaction product were taken over by Ms. Fujii and Mr. Matsumoto. They revealed, experimentally, the importance of the cyano group for the excellent stereoselectivities as well as the synthetic useful-

ness of the cyano group, which can be further transformed to install various important functional groups on the tetrasubstituted chiral center,” said Professor Asano.

Professor Matsubara realized the importance of this transformation soon after the discovery, encouraging the group and giving numerous pieces of fruitful advice during the course of the study. “We also appreciated comments from one of the manuscript’s referees, pointing out the large impact of the small A value of the linear cyano group on weak 1,3-diaxial interactions in a six-membered chair-like conformation. Because of them, we could plausibly rationalize the stereoselectivities of the reactions,” explained Professor Asano.

“We consider that this strategy provides a platform to design efficient approaches to a wide range of optically active tetrahydropyrans, which are otherwise synthetically challenging materials,” remarked Professor Asano. He continued: “In addition, Mr. Matsumoto is currently trying to develop additional efficient synthetic reactions on the basis of this methodology. We are further aiming for the application of this catalytic system to the development of synthetic transformations involving simultaneous formation of more stereogenic centers and a versatile methodology for the construction of tetrasubstituted stereogenic carbons.”

Professor Asano concluded: “Finally, it is notable that the discussions we had with many people contributed strongly to improving this study. In particular, the initial long discussion with Mr. Yoneda opened the door to this successful research project. I thus realized that many hours spent on discussions and brainstorming sessions over research issues can then be rewarded by several years of brilliant results!”

*Matthew Farnok*

### About the authors



N. Yoneda

**Naoki Yoneda** completed his B.S. (2013) and M.S. (2015) degrees at Kyoto University (Japan) under the supervision of Professor Seiji Matsubara, and he is currently working at DKS Co., Ltd. (Japan).



Prof. K. Asano

**Keisuke Asano** completed his Ph.D. at Kyoto University (Japan) in 2012 under the supervision of Professor Seiji Matsubara. He was appointed as an Assistant Professor at Kyoto University in 2012 and joined the group of Professor Jun-ichi Yoshida before moving back to the group of Professor Seiji Matsubara in 2013. He received The 30th Inoue Research Award for Young Scientists (2014), the Eisai Award in Synthetic Organic Chemistry, Japan (2014), and was a Special Young Lecturer in the 95th CSJ Annual Meeting (2015).



Y. Fujii

**Yuki Fujii** completed her B.S. (2015) and M.S. (2017) degrees at Kyoto University (Japan) under the supervision of Professor Seiji Matsubara, and she is currently working at KURARAY Co., Ltd. (Japan).



Prof. S. Matsubara

**Seiji Matsubara** was educated in chemistry at Kyoto University (Japan), completing his Ph.D. in 1986 with Professors Hitoshi Nozaki and Kimitiro Utimoto, and at the Université de Lausanne (Switzerland) where he was a Ph.D. course student with Professor Manfred Schlosser. He was appointed as an Assistant Professor at Kyoto University in 1986. After postdoctoral research with Professor Barry M. Trost at Stanford University (USA) in 1988–1989, he became an Associate Professor at Kyoto University in 1995. In 2006, he became a Full Professor at Kyoto University. He received The 3rd Inoue Research Award for Young Scientists (1987), the Incentive Award in Synthetic Organic Chemistry, Japan (1998), the Asian Core Program Lectureship Award, Korea and Malaysia (2014), and The 34th Chemical Society of Japan Award for Creative Work (2017).



A. Matsumoto

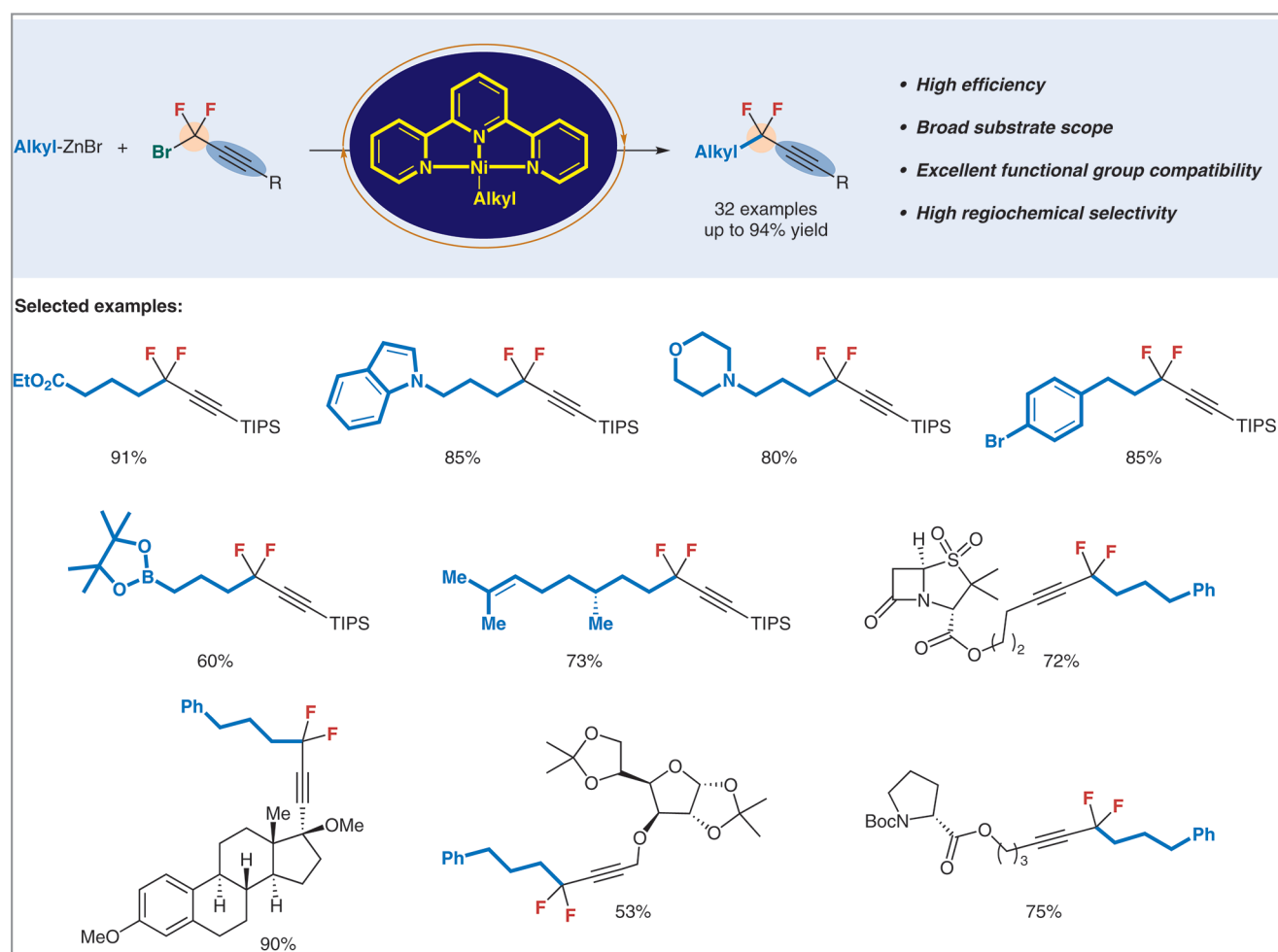
**Akira Matsumoto** completed his B.S. (2014) and M.S. (2016) degrees at Kyoto University (Japan) under the supervision of Professor Seiji Matsubara, and he is currently pursuing his Ph.D. studies.

# Highly Selective *gem*-Difluoropropargylation of Unactivated Alkylzinc Reagents Catalyzed by Nickel

*Nat. Commun.* **2017**, *8*, 1460

With increasing demands from both life and materials science sectors, the controllable introduction of fluorine atom(s) into organic molecules has become an attractive strategy to modulate physical and biological properties of functional molecules, owing to the unique characteristics of fluorine atom(s) and C–F bond.<sup>1</sup> Over the past decade, tremendous efforts have been made in developing new and general methods for site-selective fluorination and fluoroalkylations. Among the developed methods, transition-metal-catalyzed fluoroalkylations

have become a useful strategy for the construction of C–R<sub>f</sub> (R<sub>f</sub> = CF<sub>3</sub>, CF<sub>2</sub>R) bonds.<sup>2</sup> However, most of these methods rely on the construction of Ar–R<sub>f</sub> bonds, whereas it remains a challenge to adapt the same strategy to form C<sub>sp3</sub>–R<sub>f</sub> bonds. Recently, the research group of Professor Xingang Zhang at Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences (P. R. of China) demonstrated the feasibility of forming C<sub>sp3</sub>–CF<sub>2</sub>R bonds by employing a transition-metal-catalyzed difluoroalkylation strategy (Scheme 1).



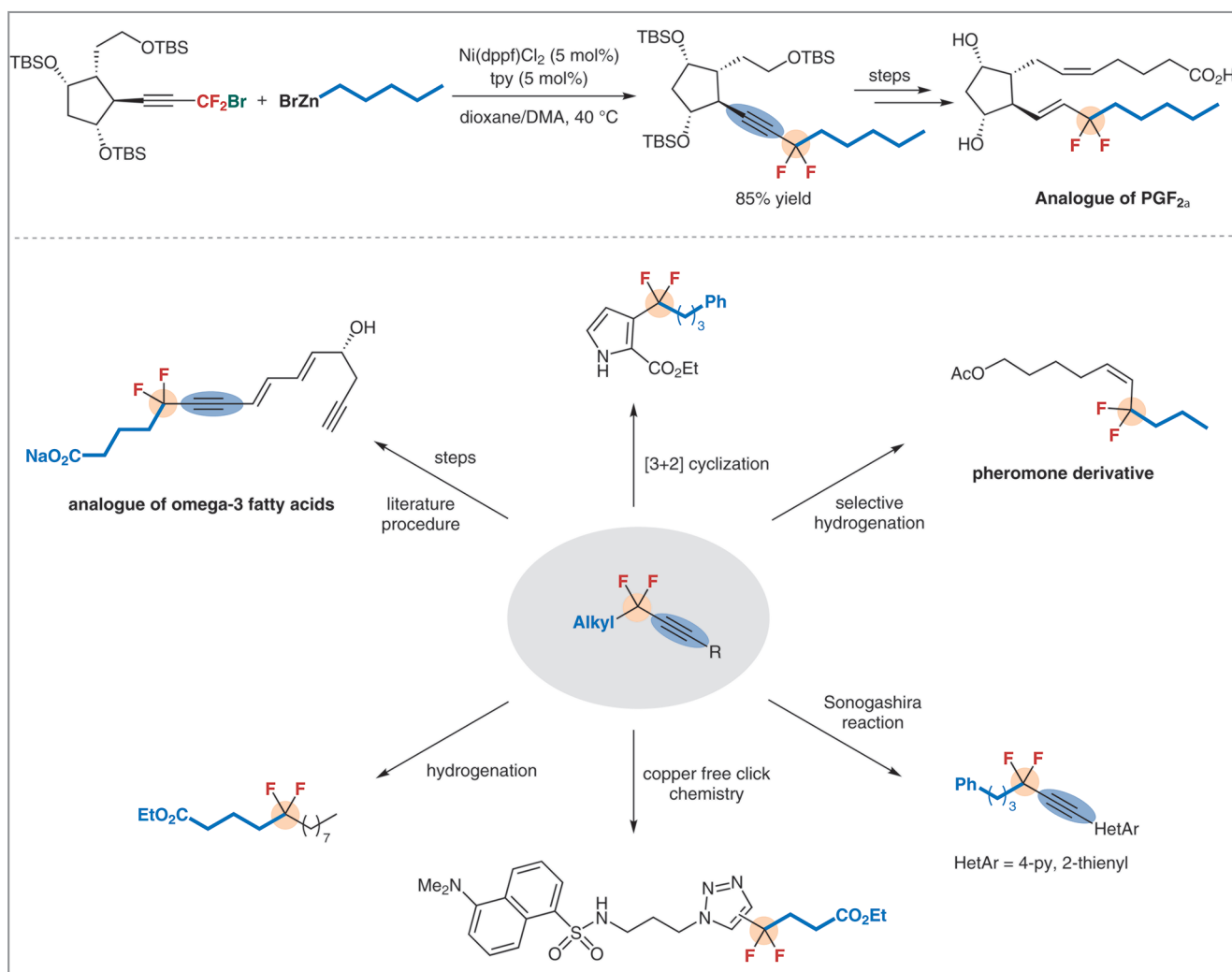
**Scheme 1** Highly selective Nickel catalyzed *gem*-difluoropropargylation of unactivated alkylzinc reagents

“We had focused on transition-metal-catalyzed reactions for the direct introduction of fluorinated groups into organic molecules since we set up our group in 2008,<sup>3</sup>” explained Professor Zhang. He continued: “Although transition-metal-catalyzed cross-coupling reactions are one of the most powerful and efficient strategies to construct C–C bonds, some specific challenges remain unsolved in the construction of C–R<sub>f</sub> bonds, such as the site-selective construction of C<sub>sp<sup>3</sup></sub>–R<sub>f</sub> bonds. Our main contribution to the area in this work is the site-selective introduction of a CF<sub>2</sub> group into an aliphatic chain in a straightforward manner.” The new method designed by Professor Zhang led to *gem*-difluoropropargylated alkanes under mild reaction conditions with high efficiency, broad substrate scope and excellent functional group tolerance, even towards complex natural products (Scheme 1).

Transformations of the resulting difluoroalkylated products could produce a variety of analogues of biologically active molecules, including pheromones, omega-3 fatty acids and prostaglandin F<sub>2α</sub> (PGF<sub>2α</sub>), the active principle of eye drops used for sterilization treatment (Scheme 2).

“This reaction protocol thus serves as a general approach to accessing difluoroalkylated alkanes. Since the C–C triple bond is a versatile functional group, the resulting *gem*-difluoropropargylated alkanes provide good opportunities for applications in medicinal chemistry,” said Professor Zhang.

He also emphasized: “Although mechanistic investigations of nickel-catalyzed Negishi cross-couplings of alkyl electrophiles have been reported, the general catalytic pathway of these couplings remains uncertain and the outcome depends on the nickel catalysts and alkyl electrophiles used.<sup>4</sup> To the



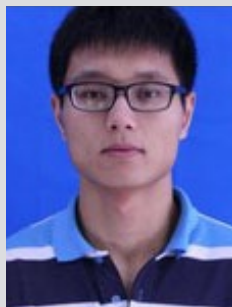
**Scheme 2** Synthetic transformations of *gem*-difluoropropargylated alkanes

best of our knowledge, the mechanistic study of the Negishi cross-coupling of fluoroalkyl halides has not been documented so far.” Based on their preliminary mechanistic studies, Professor Zhang and coworkers revealed that a Ni(I/III)-catalytic cycle is involved in the reaction, which is initiated by the transmetalation of Ni(I) with alkylzinc to generate an alkyl nickel complex [alkylNi(tpy)].

Professor Zhang concluded: “An efficient method to site-selectively synthesize difluoroalkylated alkanes has been developed through a nickel-catalyzed cross-coupling reaction. In the near future, we are looking to use abundant and inexpensive industrial raw materials, such as small molecule fluoroalkanes,<sup>5</sup> as fluorine sources to stereoselectively introduce fluorinated groups into organic molecules. We hope our long-

term efforts will provide cost-efficient and straightforward approaches for applications in the production of pharmaceuticals, agrochemicals and advanced functional materials.”

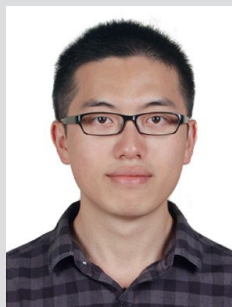
### About the authors



L. An

**Lun An** was born in Shandong (P. R. of China) in 1990. He obtained his BSc degrees in chemistry and marine chemistry from Ocean University of China (P. R. of China) in 2013. With a strong interest in organic chemistry, he then moved to Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences (P. R. of China) and began his graduate research under the supervision of Professor Xingang Zhang. His research interests are focused on site-selective

base-metal-catalyzed fluoroalkylation reactions and developing new and general methods to enantioselective fluoroalkylations.



C. Xu

**Chang Xu** was born in Kunming (P. R. of China) in 1992. He obtained his BSc degree in basic pharmacy from China Pharmaceutical University (P. R. of China) in 2015. With an interest in organic chemistry and medicinal chemistry, he then began his graduate studies at Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences (P. R. of China) under the supervision of Professor Xingang Zhang. His research interests are focused on the activation and transformations of small-molecule fluoroalkylanes and their applications in medicinal chemistry.



Prof. X. Zhang

**Xingang Zhang** was born in Xinjiang (P. R. of China) in 1975. He graduated in 1998 from Sichuan University (P. R. of China) and received a PhD in 2003 at Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences (P. R. of China). After his postdoctoral work at the University of Illinois at Urbana Champaign (USA) guided by Professor Wilfred A. van der Donk, he joined the faculty team of Shanghai Institute of Organic

Chemistry as a research associate professor in 2008, and became research professor in 2012. His current research interests are focused on organofluorine chemistry and chemical biology. He received the Thieme Chemistry Journals Award in 2014, the 2015 RSC Fluorine Chemistry Prize and 2015 Fifth Chinese Chemical Society (CCS)-Royal Society of Chemistry (RSC) Young Chemist Award.



## REFERENCES

- (1) K. Müller, C. Faeh, F. Diederich *Science* **2007**, *317*, 1881.
- (2) For selected reviews, see: (a) T. Furuya, A. S. Kamlet, T. Ritter *Nature* **2011**, *473*, 470; (b) O. A. Tomashenko, V. V. Grushin *Chem. Rev.* **2011**, *111*, 4475.
- (3) (a) X. Zhang, S. Fan, C.-Y. He, X. Wan, Q.-Q. Min, J. Yang, Z.-X. Jiang *J. Am. Chem. Soc.* **2010**, *132*, 4506; (b) Z. Feng, F. Chen, X. Zhang *Org. Lett.* **2012**, *14*, 1938; (c) Z. Feng, Q.-Q. Min, Y.-L. Xiao, B. Zhang, X. Zhang *Angew. Chem. Int. Ed.* **2014**, *53*, 1669.
- (4) (a) G. D. Jones, J. L. Martin, C. McFarland, O. R. Allen, R. E. Hall, A. D. Haley, R. J. Brandon, T. Konovalova, P. J. Desrochers, P. Pulay, D. A. Vici *J. Am. Chem. Soc.* **2006**, *128*, 13175; (b) X. Lin, D. L. Phillips *J. Org. Chem.* **2008**, *73*, 3680; (c) N. D. Schley, G. C. Fu, *J. Am. Chem. Soc.* **2014**, *136*, 16588.
- (5) Z. Feng, Q.-Q. Min, X.-P. Fu, L. An, X. Zhang *Nat. Chem.* **2017**, *9*, 918.

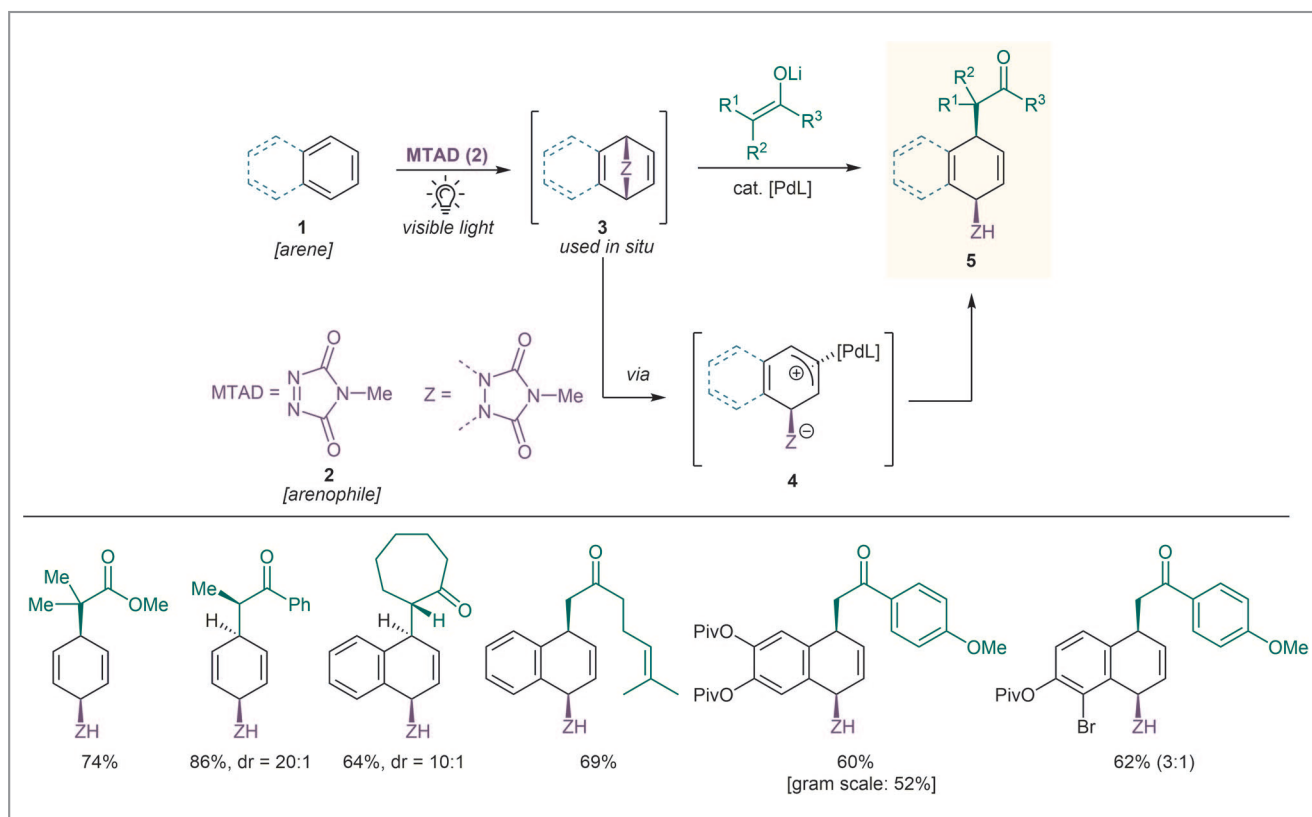
## Palladium-Catalyzed Dearomative *syn*-1,4-Carboamination

*J. Am. Chem. Soc.* **2017**, *139*, 17787–17790

Arenes constitute one of the most abundant classes of compounds, and are often associated with structural planarity, exceptional stability, and chemical inertness. While most of the reactions involving arenes as substrates result in net conservation of aromaticity, there are several reactions that result in loss of aromaticity, known as dearomatizations. Such transformations play an important role in synthetic organic chemistry as they present a direct link between readily available arenes and high-value-added synthetic intermediates. However, many dearomatization reactions do not introduce functionalities, and further transformations are often required to install desired reactive groups or molecular handles. Thus, the development of novel dearomative functionalizations continues to be an active area of research as it could expand the synthetic utility of arenes and provide more direct access to valuable building blocks.

In a recent *JACS* paper from Professor David Sarlah's group at the University of Illinois at Urbana-Champaign (USA) a novel palladium-catalyzed transformation was devised to perform a net *syn*-1,4-carboamination with enolates as nucleophilic counterparts (see Scheme 1). "In a two-step, one-pot process we were able to introduce two functionalities on a wide range of conveniently accessible arenes, in a highly diastereo- and enantioselective fashion," commented Professor Sarlah. "Our approach features an addition of enolates, derived from either ketones or esters, to the proposed electrophilic intermediate **4** that was generated from compound **3** and catalytic amounts of a Pd catalyst. Catalyst loadings could be as low as 2.5 mol%."

It has recently been shown by Professor Sarlah and co-workers (see the references in the original paper for more information) that MTAD (4-methyl-1,2,4-triazoline-3,5-dione, **2**) underwent a cycloaddition reaction with a range of arenes



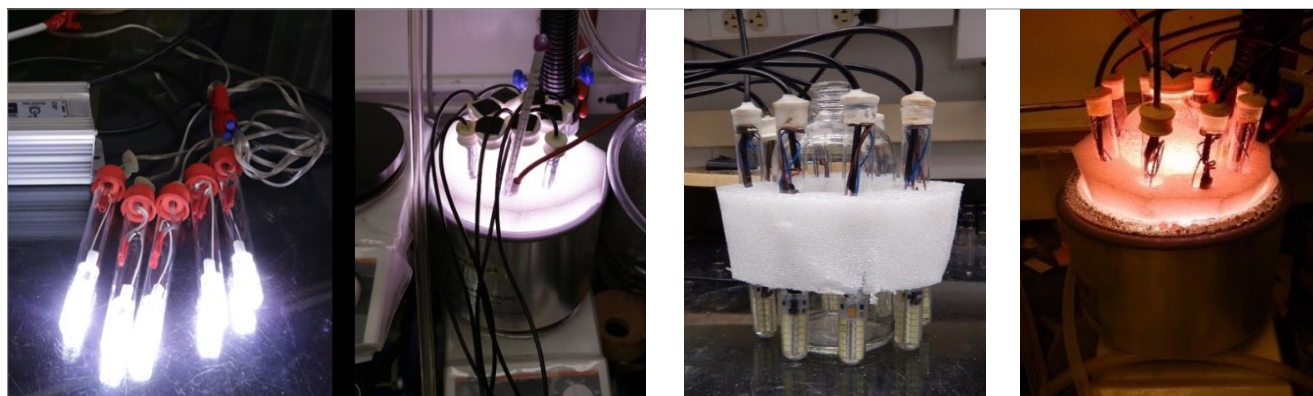
**Scheme 1** Net *syn*-1,4-carboamination of arenes, proposed intermediate and selected products

upon illumination with visible white light (see photos in Figure 1). “We deliberately used the commercial-grade LED and homemade photoreactors to demonstrate the practical ease of getting reliable and reproducible results with this chemistry,” remarked Professor Sarlah.

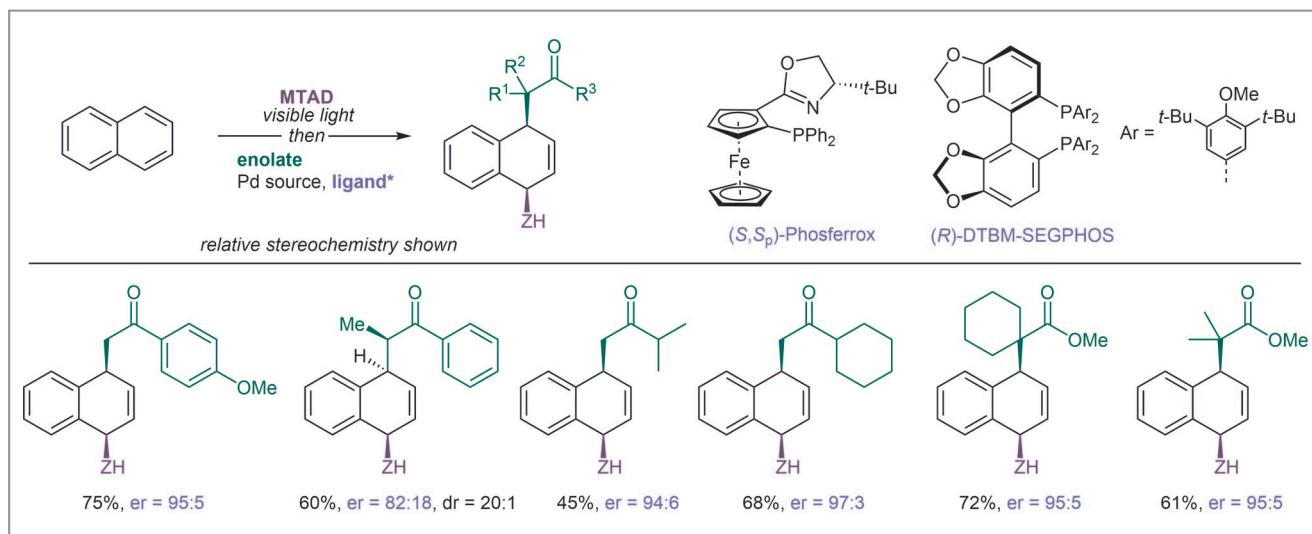
The resulting cycloadducts **3**, common intermediates in Professor Sarlah’s transformations, were unstable and, except in some cases, could not be isolated. “Several compounds of type **3** have been previously reported by Sheridan. We were surprised that no one had transformed this early finding into a synthetic methodology,” explained Professor Sarlah. “It was later found that there were more molecules of similar structures that were also able to undergo these reactions. Analogously to the Diels–Alder reaction where TAD derivatives are

a well-known class of *dienophiles*, we decided to refer to those molecules as *arenophiles* to emphasize their unique ability of reacting with arenes.”

The reactivity of intermediates **3** is being thoroughly studied in Professor Sarlah’s laboratory. “When we just started establishing the arenophile-mediated chemistry, we focused on derivatization of the double bond. However, it was also important to explore different modes of reactivity,” said Professor Sarlah. “It was interesting to find out that somewhat analogous to Tsuji–Trost allylations, our intermediate can undergo oxidative addition to Pd(0) complexes that results in the formation of electrophilic allyl species **4**. We assume their formation happens primarily because of the regioselectivity and exceptional diastereoselectivity of the process. *syn*-Selectivity



**Figure 1** Visible-light LEDs and typical photochemical setup for MTAD-based cycloadditions; commercial-grade visible-light LEDs and normal media bottle were used to assemble the photoreactor.



**Scheme 2** Enantioselective *syn*-1,4-carboamination of arenes

arises from a classical double-inversion pathway. The process is exceptionally well controlled inherently, as we never observed any other constitutional isomers.”

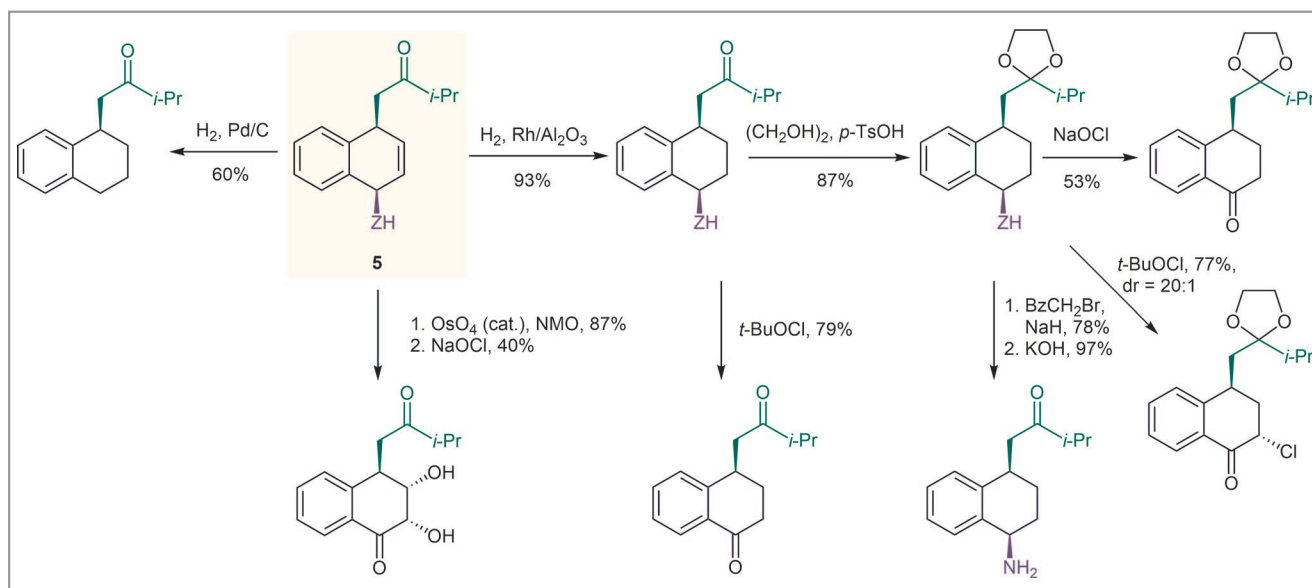
Having the substrate scope in hand, the authors sought to develop an enantioselective process (see Scheme 2). Professor Sarlah remarked: “It was quite unexpected that the (*S,S*)<sub>p</sub>-*t*-Bu-Phosferrox ligand turned out to be the optimal one for the reaction with ketone enolates. Previously, we established a different nickel-catalyzed carboamination with Grignard reagents as nucleophilic counterparts that featured the same ligand scaffold. As for the ester enolates, additional optimization of conditions resulted in changing the metal source to allylpalladium chloride and using DTBM-SEGPHOS as a ligand.”

Apart from establishing a selective dearomative difunctionalization, the authors also managed to perform a series of derivatizations of the product **5** (see Scheme 3), demonstrating the broader utility of this method.

Concerning future directions, Professor Sarlah remarked: “Despite having made a good start with the palladium-catalyzed reactions of the arene–arenophile cycloadducts, there is still plenty of work that needs to be done. First, we will explore a range of different nucleophiles. Second, we are working to get a more comprehensive picture of the mechanism behind these transformations. Last, but not less important, this methodology still has to be tested in a synthesis to demonstrate its true potential.” He then concluded: “Arenes are among the most abundant and cheapest materials in organic chemistry, yet their full synthetic potential is still underexplored. For the

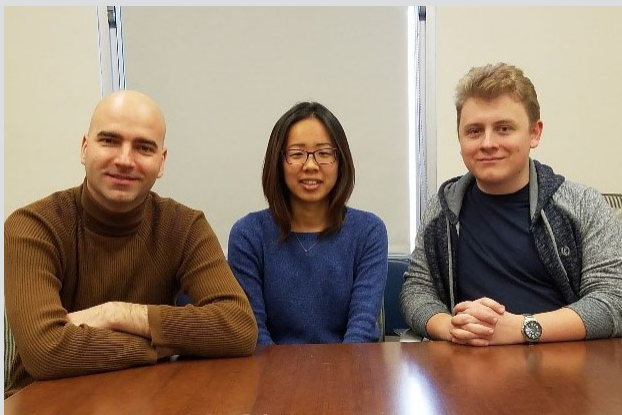
first time we have demonstrated that it is possible to transform a wide variety of aromatic systems without substrate-dependent methods or stoichiometric amounts of transition metals, by using a small organic molecule as the key mediator. We hope that this method will be recognized as a useful synthetic tool in both academic and industrial environments.”

*Matthew Fenske*



**Scheme 3** Further derivatizations of product **5**

## About the authors



From left: Prof. D. Sarlah, M. Okumura, A. Shved

**David Sarlah** is an assistant professor in the Department of Chemistry at the University of Illinois at Urbana-Champaign (UIUC, USA). He was born in Slovenia, where he earned his B.S. degree from the University of Ljubljana. He obtained his Ph.D. in 2011 with Professor K. C. Nicolaou at The Scripps Research Institute (USA), and then joined the laboratory of Professor Erick M. Carriera at ETH Zürich (Switzerland). In 2014, David returned to the USA to start his own laboratory at the University of Illinois, which explores both chemical synthesis of biologically active natural products and methods development.

**Mikiko Okumura** was born and raised in Japan. She received her B.S. (2012) and M.S. (2014) in chemistry at the University of Tokyo (Japan) working with Professor Shū Kobayashi. She began her graduate studies in the Sarlah group at UIUC (USA) in the fall of 2014, and is currently working on developing new dearomatization strategies.

**Alexander Shved** was born and raised in Moscow (Russia). He obtained his M.S. degree in 2016 from the Moscow University of Chemical Technology of Russia, Higher Chemical College of the Russian Academy of Sciences (RAS). Before graduation, he worked in Professor Sema L. Ioffe's group at the Zelinsky Institute of Organic Chemistry RAS (Russia) where he studied the chemistry of nitronates. In autumn 2016, Alex joined Professor David Sarlah's group at the UIUC (USA) as a research assistant working on dearomative methodologies. In the beginning of 2018 he joined the group again, this time as a graduate student. His current research interests involve in-depth studies of reaction mechanisms, computational chemistry and development of new methodologies. In his spare time Alex enjoys cooking, fishing and travelling.

## Young Career Focus: Professor Alexander W. H. Speed (Dalhousie University, Canada)

**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 Professor Alexander W. H. Speed (Dalhousie University, Canada).

### Biographical Sketch



Prof. A. W. H. Speed

**Alex Speed** was born and raised in Liverpool, Nova Scotia, on the east coast of Canada. His BSc degree (2006) at Dalhousie University, in Halifax, Nova Scotia (Canada) provided his first exposure to chemistry research on a variety of summer projects, first with Professor James Pincock, then with Professor Jean Burnell. In 2008, he joined the Evans group at Harvard for his PhD, where he worked on the synthesis of the natural products peloruside A and spiro-prorocentrimine. In 2012 he began a postdoctoral stay in the group of Professor Amir Hoveyda at Boston College (USA), where he explored the application of Z-selective olefin metathesis to the synthesis of disorazole C1. In the summer of 2015, Alex returned to Dalhousie University as an assistant professor, initiating a program to explore main-group chemistry in organic synthesis. Outside of chemistry, Alex's interests include the outdoors, botany, art, LP records, craft beer, and history.

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

**Prof. A. W. H. Speed** Having a father who was an engineer/woodworker, and a mother who is an artist/musician/teacher, I was raised in a creative household. I had a chemistry set as a child, but rather than reading the accompanying book, I just mixed and observed, fortunately with no big mishaps! Later on, I developed an interest in biology. The chemical structures captivated me, and learning how they were put together led to my interest in organic chemistry. After my first year at Dalhousie, I was fortunate to work in the Pincock lab, which focused on mechanistic photochemistry. We irradiated substrates that took a few steps to make, so I had some great early exposure to synthesis. In subsequent years, I worked in the Burnell lab, whose program focused on stereochemistry and natural product total synthesis. The communication between the students was great, so I learned much beyond my own project. I was definitely hooked on synthesis at that point.

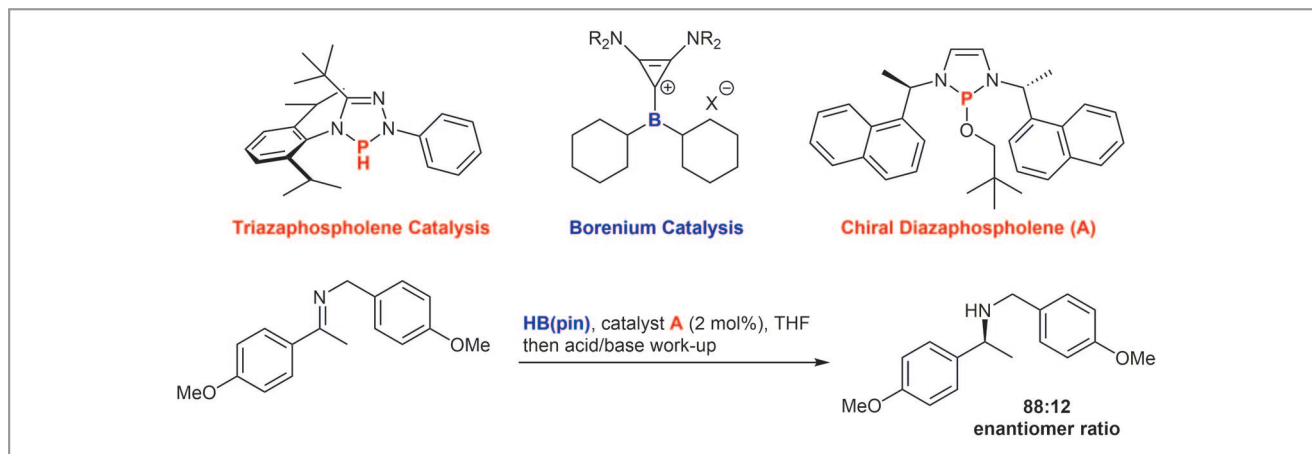
**SYNFORM** *What do you think about the modern role and prospects of organic synthesis?*

**Prof. A. W. H. Speed** Materials generated through organic synthesis underpin our modern society, from medicine to electronics. Developing tools to make molecules more efficiently, or make previously inaccessible molecules will always be in demand. The complexity of some new pharmaceuticals is astounding to me, and the fact they are made on scale is awe-inspiring. Working on small scales, it is tough to predict what might be practical on larger scales, but honest assessment of scope and limitations takes a lot of uncertainty away from potential adopters. Almost all practical advances come from building on somebody else's fundamental research, so preserving basic research is vital, a huge source of stress in today's funding climate. Advances are increasingly interdisciplinary; more researchers today are using light, electrons, or bespoke enzymes in reactions. Absorbing the immense

### INTERVIEW

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

**Prof. A. W. H. Speed** My group is interested in helping to bring some concepts from main-group chemistry to organic synthesis, with the hopes of eventually uncovering types of reactivity and selectivity inaccessible to current technologies. My background in the total synthesis of complex molecules helps teach me appreciation for how a larger chemical toolbox enables new strategies for synthesizing molecules.



Scheme 1

amount of literature from multiple fields is challenging, so there is tremendous potential for artificial intelligence to help. Unfortunately, solutions considered well known to one set of experts are often off the radar of experts from another field. Better communication there is key. Making these disparate connections will also increasingly be suited to computational analysis. Finally, looking after mental health, and work-life balance is something that is being addressed more and more in the organic synthesis community, which is a positive direction from times past.

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

**Prof. A. W. H. Speed** For now, my group is focusing on figuring out how to make some interesting phosphorus and boron compounds (Scheme 1). We are attempting to catalyze rearrangements, and addition of nucleophiles to alkenes. We try a lot of reactions containing motifs that would poison most metal-containing catalysts, to find best-in-class applications. However, organometallic chemistry is amazingly efficient, and some of the compounds we make turn out to be decent ligands for metals as well. I hope this direction of research will grow in my group. My dream from any of those directions is to find a reaction robust and useful enough for widespread adoption by the community. Eventually, with the appropriate funding, I would also like to apply our discoveries to some total synthesis ideas for simple biologically active targets.

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

**Prof. A. W. H. Speed** I am excited about our asymmetric imine hydroboration with diazaphospholenes (Scheme 1). This built on seminal work by Professor Dietrich Gudat (Stuttgart, Germany) and Professor Rei Kinjo (Nanyang Technological University, Singapore), and to the best of my knowledge is the first example of an asymmetric reaction catalyzed by a diazaphospholene. Despite modest enantioselectivity, the low loading and ease of synthesis of these catalysts is nice. We are working on second-generation catalysts to improve selectivity. Diazaphospholenes have fascinating reactivity, and I hope they will take off as tools in synthesis because of their modularity and ease of assembly. I consider myself fortunate to have entered this area of research near the ground floor.

*Matthew Fenske*

## Coming soon

### — Name Reaction Bio

#### Charles Friedel (1832–1899) and James Mason Crafts (1839–1917): The Friedel–Crafts Alkylation and Acylation Reactions

### — Literature Coverage

#### A Unifying Paradigm for Naphthoquinone-Based Mero-terpenoid (Bio)synthesis

### — Literature Coverage

#### Ruthenium(II)-Catalyzed Olefination via Carbonyl Reductive Cross-Coupling

## Further highlights

### **Synthesis** Review: Remote C–H Functionalization via Selective Hydrogen Atom Transfer

(by D. A. Nagib and co-workers)

### **Synlett** Account: The Hitchhiker's Guide to Organophosphate Chemistry

(by H. J. Jessen)

### **Synfacts** Synfact of the Month in category "Metal-Catalyzed Asymmetric Synthesis and Stereoselective Reactions": Enantioselective Cycloaddition of Cyclopropylcarboxamides to Alkynes

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