

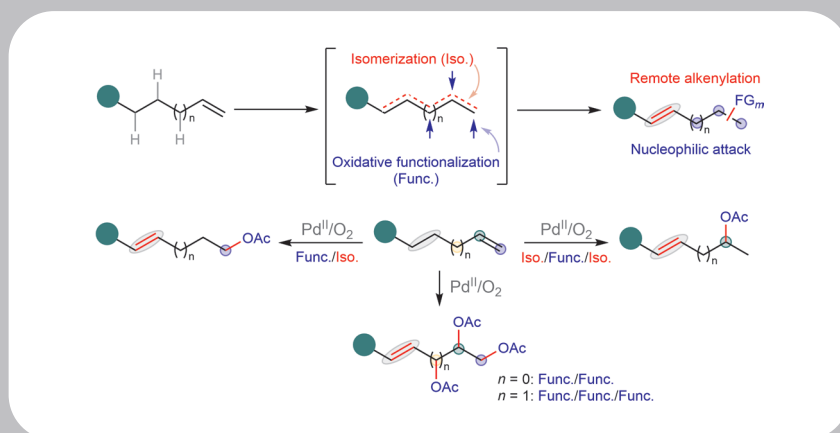
# Synform

People, Trends and Views in Chemical Synthesis

2023/12

## Multi-site Programmable Functionalization of Alkenes via Controllable Alkene Isomerization

Highlighted article by Z. Wu, J. Meng, H. Liu, Y. Li, X. Zhang, W. Zhang



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## Dear Readers,

There is currently a massive debate on how we should deal with generative artificial intelligence (Gen-AI), defined as those algorithms (such as ChatGPT) that can be used to create new content, including audio, images, text, simulations, videos and much more. This debate is very timely, as the topic is particularly sensitive and somehow slippery for its implications in the areas of scientific publishing, grant writing and even peer reviewing. And even for its influence on the creative process at the basis of every aspect of scientific research. A number of questions arise: are we still able to identify which ideas are genuinely original and stemming from an individual's intellect alone, from those which are partly or entirely generated with the aid of Gen-AI? Is it fair to use tools such as ChatGPT for writing manuscripts and grant applications, or is it an unacceptable aid, a way to deceive and cut corners? In fact, not everyone is of the opinion that making use of Gen-AI is unfair, some people believe we should not even bother to check. At the end of the day, ChatGPT is just a tool to distil information from the vast ocean of data and narrative present in the web, it should be how we use it that really matters. Don't we all get inspiration from what we see, hear, read and experience around us? So, what's different with Gen-AI, which just offers a quicker, more accessible and personalised way to streamline and customise information from a universe of data and sources, which are already out there, available and free to be used? And finally, is there even a way to regulate the use of Gen-AI? How do we know if someone is using it, if this use is not self-declared? These are tough questions that sooner or later we will have to answer once and for all, and decide where the red line is, if there is one. Meanwhile, Gen-AI's development is so fast that it is outpacing our capacity to cope with it and fully understand its implications. My opinion is that the only sensible way to deal with Gen-AI is to accept it and find a way to adapt to it (not vice-versa, as I suspect it is already too late for adapting Gen-AI to us), as trying to impose red tape to its use is simply unrealistic. It is already here, it is an integral part of our life and work, it will grow bigger and bigger, and eventually it will be simply essential. If you disagree or have different thoughts about the use of Gen-AI in Chemistry and Research, please write to SYNFORM, as we are keen to hear about the opinions of our readership, especially on this topic.

Going back to this issue of SYNFORM, I hope there will be a unanimous verdict that the science featured herein is world-class and ground-breaking. We start with a Young Career Focus interview with the 2023 Thieme Chemistry Journals Awardee Y. Yang (USA), who tells us how his group is integrating chemistry,

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biology and AI. Next, we have an interview with Prof. Daniele Leonori (Germany), who joined the Editorial Board of SYNTHESIS with effect of November 2023. The following Literature Coverage article comes from the group of W. Zhang (P. R. of China) and covers their recent *Nat. Chem.* paper on the exciting multi-site programmable functionalization of alkenes, which was achieved via controllable alkene isomerization. I am particularly thrilled to introduce the next article, as it covers a great paper published in SYNTHESIS by K. Toshima and D. Takahashi (Japan) on exciting work toward avian pathogenic *Escherichia coli* O1 vaccine development. Last but not least, the issue is closed by another Literature Coverage article, this time from the group of S. Chang (South Korea) on a recent *Science* article where the authors took mechanistic snapshots of rhodium-catalyzed acylnitrene transfer reactions.

Enjoy your reading!



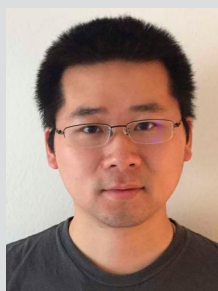
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## Young Career Focus: Assistant Professor Yang Yang (University of California Santa Barbara, USA)

**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 Assistant Professor Yang Yang (University of California Santa Barbara, USA).

### Biographical Sketch



Asst. Prof. Y. Yang

**Yang Yang** obtained his B.S. in chemistry from Peking University (P. R. of China) in 2011. He received his Ph.D. in organic chemistry in 2016 under the guidance of Prof. Steve Buchwald at MIT (USA). In the Buchwald lab, he developed CuH-catalyzed methods for the asymmetric hydrofunctionalization of simple olefins. As an NIH Postdoctoral Fellow working with Prof. Frances Arnold at Caltech (USA), Yang studied biocatalysis and protein engineering and developed biocatalytic asymmetric C–H amination. Yang started his independent career in the Department of Chemistry and Biochemistry at the University of California Santa Barbara (USA) in 2020. By integrating organic chemistry, biocatalysis and protein engineering, the Yang group is reprogramming nature's biosynthetic machineries to address challenging problems in synthesis and catalysis. The Yang group recently coined and implemented two new concepts in biocatalysis, including metalloradical biocatalysis and pyridoxal radical biocatalysis, to enable otherwise challenging asymmetric radical transformations. Yang is a recipient of the Regent's Junior Faculty Fellowship Award (2021), Faculty Career Development Award (2022), NSF CAREER Award (2022), NIH Maximizing Investigators' Research Award (2022), the Thieme Chemistry Journals Award (2023) and the Army Research Office Young Investigator Award (2023).

### INTERVIEW

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

**Asst. Prof. Y. Yang** By integrating chemistry, biology and artificial intelligence, our group is developing novel enzymatic strategies to tackle daunting challenges in synthesis and catalysis. First, we are addressing long-standing problems in asymmetric catalysis by taking advantage of the intimate enzyme–substrate interaction that can be easily tuned via directed evolution. Second, by synergistically merging small-molecule catalysis and biocatalysis, we are advancing novel biocatalytic processes that are both new-to-biology and new-to-chemistry. Third, we are developing machine learning and laboratory automation methods to accelerate the development of customized biocatalysts with tailored synthetic applications. Collectively, these efforts will provide insight into fundamental synthetic chemistry and enzymology, allowing for the rapid assembly of small molecules and macromolecules of use.

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

**Asst. Prof. Y. Yang** When I was in high school, I found an electronic copy of Nicolaou and Sorensen's book *Classics in Total Synthesis*. The beautiful structures and elegant syntheses in this book spurred my early interest in organic synthesis. Throughout my career, I have had the privilege to work with the best mentors who have been incredibly supportive. My experience working with them fostered my passion for organic synthesis. Working with Professor Jianbo Wang at Peking University as an undergraduate student, I developed a good understanding of organic reaction mechanisms. My summer research with Professor Neil Garg at UCLA allowed me to see the synergy between total synthesis and synthetic method-

ology. My graduate research with Professor Steve Buchwald at MIT led me to appreciate the power of impactful fundamental research in solving real-world problems. Working closely with Steve also prompted me to maintain a high standard in my own research. Furthermore, my postdoctoral training with Professor Frances Arnold at Caltech prepared me to tackle difficult problems in organic synthesis using an interdisciplinary approach combining protein engineering and enzymology. Frances' vision for directed evolution and biocatalysis has always been extremely inspiring.

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

**Asst. Prof. Y. Yang** I think that organic synthesis remains a central discipline to discover fundamentally new reactivity that can both satisfy our curiosity and find utility in the real world. In my opinion, new concepts of catalysis and new catalyst development remain the central innovation engine in modern organic synthesis. It is new concepts of catalysis and new forms of catalysts that differentiate us from organic chemistry pioneers, when it comes to what types of new reactions that could not be imagined a few decades ago. To push organic chemistry to the next level of sophistication and practicality, it is imperative for us to innovate, and not just to revisit what was discovered a few decades ago. As researchers and educators, it is our responsibility to convey the excitement of fundamental organic chemistry research to the new generation of students. Organic chemistry is fun, not only because it is useful in the pharmaceutical and agrochemical industries, but also because it can be rationalized and there remain new exciting reactivities to be discovered.

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

**Asst. Prof. Y. Yang** Since we started at the University of California Santa Barbara in 2020, my group has made contributions to two areas of stereoselective radical biocatalysis, including metalloradical biocatalysis and pyridoxal radical biocatalysis.

In the first area, by leveraging the unique redox property of first-row transition-metal cofactors spanning a wide potential window, we repurpose and evolve natural metalloenzymes to catalyze unnatural free-radical reactions in a stereocontrolled fashion. Our group is the first to coin and implement the general concept of "metalloradical biocatalysis" to impose stereocontrol over fleeting radical intermediates.<sup>1-3</sup> Using metalloradical biocatalysis, we developed atom-

transfer radical reactions, whose asymmetric catalysis has long eluded synthetic organic chemists.

In the second area, by converting natural two-electron pyridoxal enzymes to catalyze single-electron processes, we develop pyridoxal radical biocatalysis to enable the stereoselective synthesis of valuable non-canonical amino acids (ncAAs), including those possessing multiple contiguous stereocenters that are difficult to prepare by other means (Scheme 1). Our group is the first to design and implement "synergistic photoredox-pyridoxal radical biocatalysis" as a general strategy for convergent ncAA synthesis without protecting groups through a radical mechanism.<sup>4</sup>

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

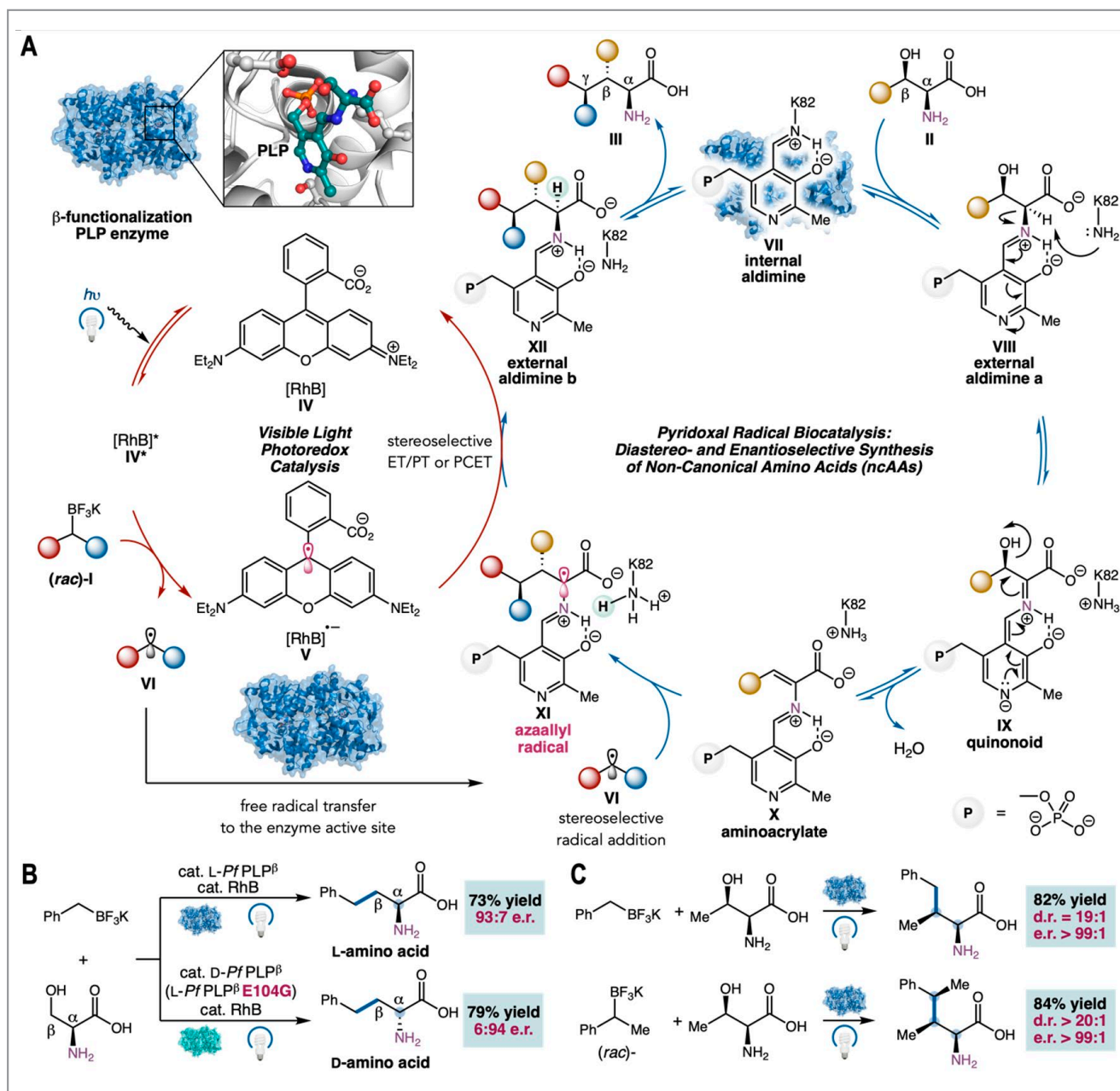
**Asst. Prof. Y. Yang** In my mentored research with Professor Steve Buchwald at MIT, I made contributions to copper(I) hydride catalyzed asymmetric hydrofunctionalization of olefins. Working closely with other labmates, I developed a CuH-catalyzed asymmetric hydroamination of unactivated internal olefins.<sup>5,6</sup> Working with my long-term computational collaborator Prof. Peng Liu at the University of Pittsburgh, I rationalized the unusual ligand effect involving DTBM-SEGPHOS by attractive dispersion interactions.<sup>6</sup> I also developed a set of Cu-catalyzed methods for the asymmetric addition of olefin-derived nucleophiles to carbonyls and imines.<sup>7-12</sup> These methods allow abundant olefins to be used as latent organometallic reagents in carbonyl and imine addition chemistry. Together, these methods allowed for a range of amines and alcohols, including those possessing multiple contiguous stereogenic centers, to be prepared with excellent stereocontrol.

In my independent research, my group developed two new modes of stereoselective radical biocatalysis. Our metalloenzyme work allowed atom-transfer reactions that were not previously known in the biological world to be developed with evolved metalloproteins.<sup>1-3</sup> These stereocontrolled biotransformations provided a new means to impose stereocontrol over free-radical intermediates. By synergistically merging photoredox catalysis and pyridoxal radical biocatalysis, we advanced a new mode of catalysis which is not known in either synthetic organic chemistry or biochemistry.<sup>4</sup> Pyridoxal radical biocatalysis has the potential to furnish a wide range of non-canonical amino acids with excellent diastereo- and enantiocontrol.

**SYNFORM** *What is the most exciting aspect of your job, the one you like the most?*

**Asst. Prof. Y. Yang** The most exciting aspect of my job as a researcher is to work with talented young students and post-docs. They contribute key ideas to our ongoing program and get challenging projects to work. None of my published work at UCSB would be possible without

*Mattias Fomale*



## REFERENCES

- (1) Q. Zhou, M. Chin, Y. Fu, P. Liu, Y. Yang *Science* **2021**, *374*, 1612–1616.
- (2) Y. Fu, H. Chen, W. Fu, M. Garcia-Borràs, Y. Yang, P. Liu *J. Am. Chem. Soc.* **2022**, *144*, 13344–13355.
- (3) W. Fu, N. M. Neris, Y. Fu, Y. Zhao, B. Krohn-Hansen, P. Liu, Y. Yang *Nat. Catal.* **2023**, *6*, 628–636.
- (4) L. Cheng, D. Li, B. K. Mai, Z. Bo, L. Cheng, P. Liu, Y. Yang *Science* **2023**, *381*, 444–451.
- (5) Y. Yang, S.-L. Shi, D. Niu, P. Liu, S. L. Buchwald *Science* **2015**, *349*, 62–66.
- (6) G. Lu, R. Y. Liu, Y. Yang, C. Fang, D. S. Lambrecht, S. L. Buchwald, P. Liu *J. Am. Chem. Soc.* **2017**, *139*, 16548–16555.
- (7) Y. Yang, I. B. Perry, G. Lu, P. Liu, S. L. Buchwald *Science* **2016**, *353*, 144–150.
- (8) Y. Yang, I. B. Perry, S. L. Buchwald *J. Am. Chem. Soc.* **2016**, *138*, 9787–9790.
- (9) R. Y. Liu, Y. Yang, S. L. Buchwald *Angew. Chem. Int. Ed.* **2016**, *55*, 14077–14080.
- (10) E. Y. Tsai, R. Y. Liu, Y. Yang, S. L. Buchwald *J. Am. Chem. Soc.* **2018**, *140*, 2007–2011.
- (11) R. Y. Liu, Y. Zhou, Y. Yang, S. L. Buchwald *J. Am. Chem. Soc.* **2019**, *141*, 2251–2256.
- (12) C. Li, R. Y. Liu, L. T. Jesikiewicz, Y. Yang, P. Liu, S. L. Buchwald *J. Am. Chem. Soc.* **2019**, *141*, 5062–5070.
- (13) B. K. Mai, N. M. Neris, Y. Yang, P. Liu *J. Am. Chem. Soc.* **2022**, *144*, 11215–11225.

## Editorial Board Focus: Professor Daniele Leonori (RWTH Aachen University, Germany)

**Background and Purpose.** From time to time, SYNFORM portraits 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 Daniele Leonori (RWTH Aachen University, Germany) who joined the Editorial Board of SYNTHESIS with effect of November 2023.

### Biographical Sketch



Prof. D. Leonori

**Daniele Leonori** obtained his PhD at the University of Sheffield (UK) under the supervision of Prof. Iain Coldham and carried out post-doctoral studies at RWTH Aachen University (Germany) and the Max Planck Institute for Colloids and Interfaces (Germany) under the supervision of Profs. Magnus Rueping and Peter Seeberger, respectively. After a Research Officer position at the University of Bristol (UK) under the mentorship of Prof. Varinder Aggarwal FRS, Daniele started his independent career at the University of Manchester (UK) in 2014 where he was promoted to Reader in 2018 and Professor in 2020. In 2022 Daniele and his group moved to the RWTH Aachen University, where he is a W3 Chair of Organic Chemistry. Research in the Leonori group focuses on the development of novel methods exploiting the reactivity of radical and photoexcited species.

### INTERVIEW

**SYNFORM** *What fascinates you most about organic chemistry and synthesis?*

**Prof. D. Leonori** Organic chemistry is really about discovering new ways to make interesting molecules. Improving the ways we make molecules is fundamental to the discovery, manufacture and evolution of almost all products we encounter in our daily life like drugs, agrochemicals, perfumes... Organic chemistry will always be integral to our wellbeing.

**SYNFORM** *Tell us more about your current research activities.*

**Prof. D. Leonori** My group's research activity is mostly based on the development of novel chemical reactions. We are interested in the discovery of new activation modes that allow us to assemble chemical bonds in unprecedented manners.

**SYNFORM** *What do you think about the modern role and prospects of synthetic chemistry?*

**Prof. D. Leonori** I think synthetic chemistry will play an increasingly important role to our society. We now face many new challenges in terms of the types of molecules we want to make but also how we make them. Continuous developments in synthesis have strong potential to impact our wellbeing but also address aspects related to sustainability and waste detoxification.

**SYNFORM** *What would you consider your most important scientific achievement to date and why?*

**Prof. D. Leonori** It is too early to say but I think my group has demonstrated several novel concepts for either bond

formation or cleavage that provide novel and orthogonal opportunities in chemical synthesis.

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

**Prof. D. Leonori** I will be mostly involved in helping SYNTHESIS in evaluating new research manuscripts.

**SYNFORM** *How do you describe the value of a resource like SYNTHESIS to the chemistry community?*

**Prof. D. Leonori** SYNTHESIS is an invaluable resource in organic synthesis where new and modern chemical reactions appear daily. It is also a journal with a fast turnaround of articles so that urgent discoveries can be published in a timely fashion.

**SYNFORM** *Finally, on a personal note, what do you do in your free time?*

**Prof. D. Leonori** I enjoy trying new cooking recipes with my wife and our little daughter. I also like to study astronomy and how it has impacted the development of ancient cultures – my favorite constellation is Orion.





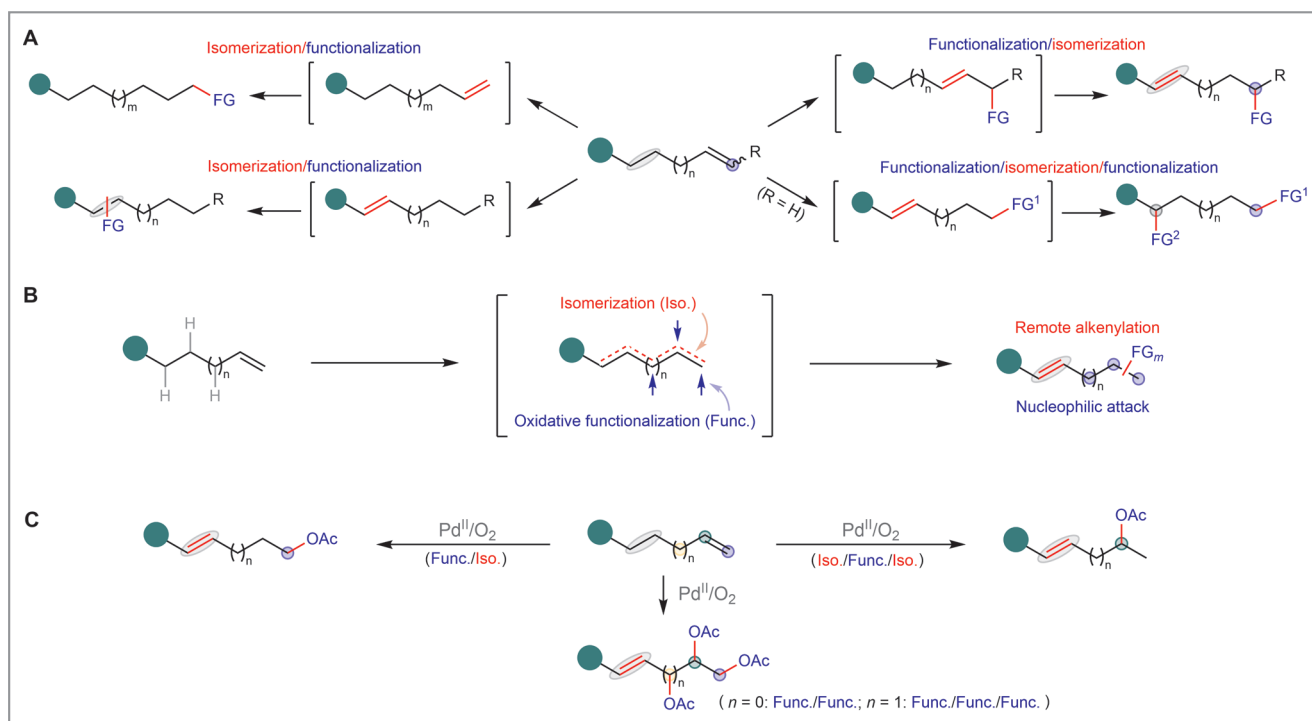
# Multi-site Programmable Functionalization of Alkenes via Controllable Alkene Isomerization

*Nat. Chem.* **2023**, *15*, 988–997

The direct and selective functionalization of hydrocarbon chains, including their multi-functionalization, is a fundamental challenge in modern synthetic chemistry.<sup>1,2</sup> Conventional functionalization of C=C double bonds and C(sp<sup>3</sup>)-H bonds provides some solutions, but site diversity remains an issue. “The merging of alkene isomerization with (oxidative) functionalization provides an ideal method for remote functionalization, which would provide more opportunities for site diversity,<sup>3,4</sup>” said Professor Wanbin Zhang, from Shanghai Jiao Tong University (Shanghai, P. R. of China), who added: “However, the reported functionalized sites are still limited, essentially consisting in a specific terminal position and internal site; thus new site-selective functionalization, including multi-functionalization, remains a largely unmet challenge (Scheme 1A).<sup>3,4</sup>” The research described in a recent article published in *Nature Chemistry* by the Zhang group provides a new solution for the diverse functionalization of

flexible olefins. The authors designed a new catalytic system which controls the reaction sequence between alkene isomerization and oxidative functionalization, thus achieving multi-site programmable functionalization of terminal alkenes (involving the C=C double bond and multiple C(sp<sup>3</sup>)-H bonds), accompanied by controllable remote alkenylation (Schemes 1B and 1C). “Specifically, aerobic oxidative 1-acetoxylation (anti-Markovnikov), 2-acetoxylation, 1,2-diacetoxylation and 1,2,3-triacetoxylation have been realized,” said Professor Zhang. The authors demonstrated that this method can enable the conversion of readily available terminal olefins from petrochemical feedstocks into unsaturated alcohols and polyalcohols, and particularly into different monosaccharides and C-glycosides.

Professor Zhang remarked: “In fact, the study began as early as in 2013, when Zhengxing Wu (the first author of the title article) was still a doctoral student in my group. At that



**Scheme 1** Remote functionalization of alkenes

time, he was focusing on the aerobic oxidative difunctionalization of conjugated dienes, which was a good method for obtaining multifunctional compounds, because of the presence of an easily convertible double bond in the functionalized product. Considering that the preparation of conjugated dienes is not easy, and our group has accumulated experience in the oxidative functionalization of mono-alkenes, we discussed whether it was possible to obtain the product identical to that resulting from the difunctionalization of conjugated dienes from readily available unactivated mono-alkenes." Dr. Wu recalled: "In the preliminary reaction design, we initiated the process with an easily monitored terminal alkene, namely 5-phenylpent-1-ene. The reaction was designed to proceed through tandem oxidative acetoxylation to afford the 1,2-difunctionalized products while preserving the double bond. These reactions were then conducted using palladium as the catalyst, acetic acid as the nucleophile, and oxygen as the oxidant. Interestingly, after exploring various reaction conditions, we did not obtain the desired 1,2-diacetoxylation product; instead, we observed a small number of 1- and 2-acetoxylation products, accompanied by the isomerization of the double bond to the conjugated position with the phenyl group. Additionally, we also observed that changing the acidity of the sodium acetate/acetic acid buffer had a significant impact on the ratio of 1- and 2-acetoxylation products, although the ratio was not particularly high (3:1~1:2). We realized that this is a very interesting phenomenon, so the reaction mechanism was studied further. Through the mechanism studies, we learned that both 1-acetoxylation and 2-acetoxylation involve alkene isomerization and oxidative functionalization (the oxidative functionalization is facilitated by  $\text{Pd}^{\text{II}}\text{X}_2$ , while alkene isomerization is facilitated by *in situ* generated  $\text{Pd}^{\text{II}}\text{-H}$  species). The distinct reaction sequence between alkene isomerization and oxidative functionalization leads to the formation of different 1- and 2-acetoxylation products." At that point, after further discussions, the authors had a breakthrough idea: "Drawing inspiration from computer programming languages using 0 and 1, we thought that if we can precisely control the sequence of alkene isomerization and oxidative functionalization, similarly to programming commands, the diversity of functionalized sites could, in theory, be significantly enriched." While the idea was promising and offered rich possibilities, finding a suitable catalytic system to precisely control the reaction sequence turned out to be extremely challenging. After more than a year of exploration (until 2015), the research had successfully achieved 1-acetoxylation with good yield and selectivity; however, further significant progress could not be achieved regarding the control of the reaction sequence. On the other hand, Zhengxing Wu began preparing for his doc-

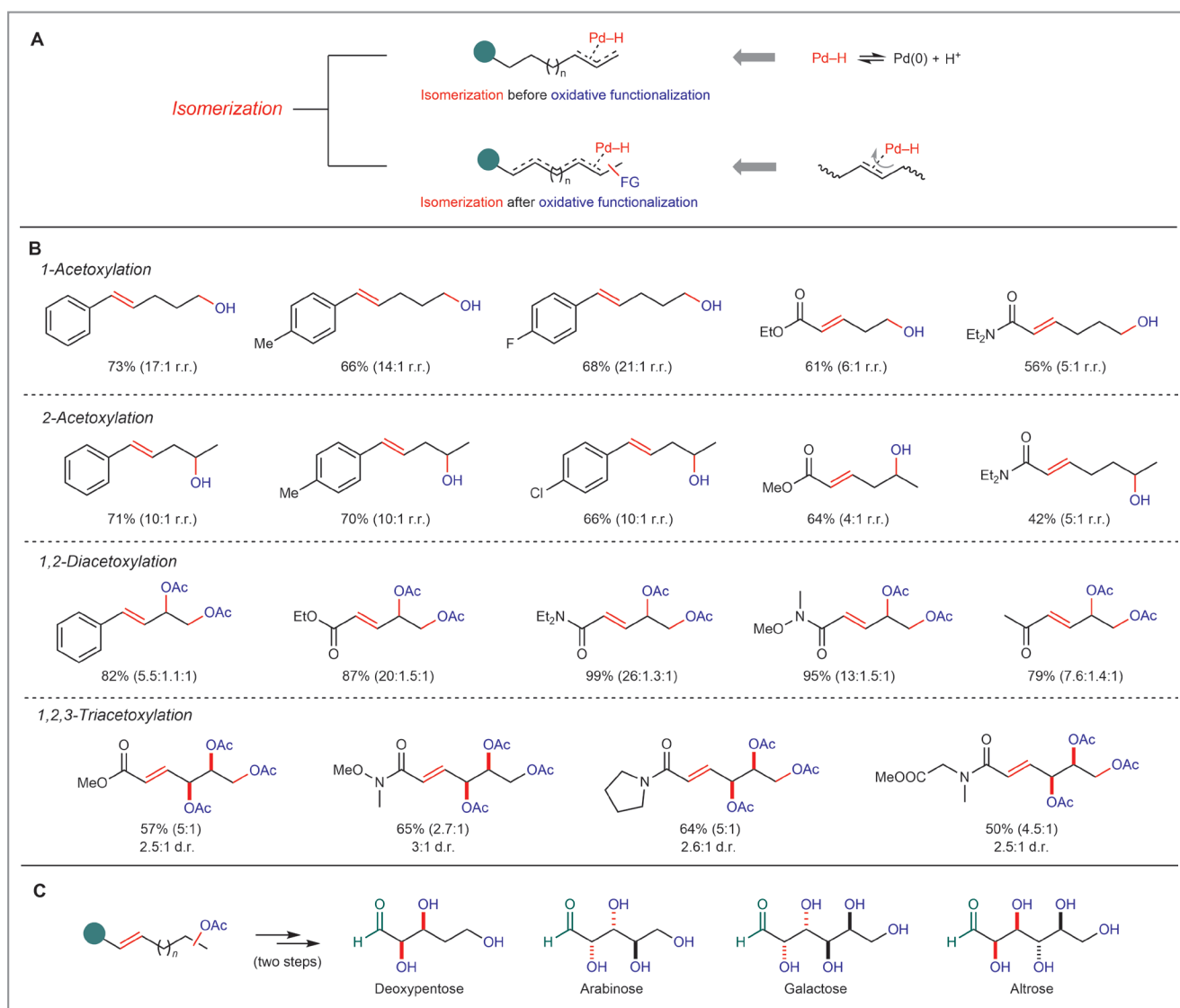
toral graduation. Hence, it was agreed that the research would be temporarily placed in stand-by, for more systematic development when the timing was appropriate.

Dr. Wu remained in Professor Zhang's group as an assistant research fellow after graduating in 2017, and then the study was resumed. "Some things cannot be expected to be accomplished overnight; after pausing for some time, we may gain new perspectives and ideas when we look back," said Professor Zhang. Indeed, after in-depth analysis of the body of data accumulated from the past, the authors realized that many factors can simultaneously affect the rate of alkene isomerization and oxidative functionalization in the catalytic reaction, which makes it difficult to design suitable reaction conditions. Professor Zhang continued: "To make progress, we needed to simplify the problem and identify the main conflicting elements. This would help us gain a clear direction to move forward." Dr. Wu recalled: "After thorough considerations, we came to the conclusion that alkene isomerization is more challenging to control compared to oxidative functionalization. To address this, we simplified the rate of oxidative functionalization to be constant, while the focus shifted to controlling alkene isomerization, which was deemed to be the key challenge in solving the problem." Furthermore, the authors broke down the control of alkene isomerization on the hydrocarbon chain into two parts: alkene isomerization before oxidative functionalization, and alkene isomerization after oxidative functionalization. This rationalization allowed for a more systematic approach to tackle the challenge of controlling the reaction sequence. After finalizing the research idea, Professor Zhang and co-authors conducted a comprehensive analysis of the impact of various factors on alkene isomerization based on existing literature. They also designed a series of experiments to observe the influence of different factors on the two types of alkene isomerization. "One year later, we had made significant progress and essentially determined that the alkene isomerization before oxidative functionalization could be primarily controlled by the stability of the  $\text{Pd}(\text{II})\text{-H}$  species in the catalytic system," recalls Professor Zhang. This stability was found to be influenced by the acidity of the reaction system (Scheme 2A, top).<sup>5,6</sup> The isomerization after oxidative functionalization, enabled by  $\text{Pd}(\text{II})\text{-H}$ , was found to be predominantly controlled by  $\text{Pd}(\text{II})\text{-H}$  coordination with the alkene chain and the rotation of the coordinating bond. These processes were found to be influenced by the synergistic coordinating effects of the amide solvent and chloride ion (Scheme 2A, bottom).<sup>7-10</sup> "By utilizing the aforementioned factors to control the reaction sequence, as of 2019, we achieved 1-acetoxylation (anti-Markovnikov), 2-acetoxylation, 1,2-diacetoxylation, and even 1,2,3-triacetoxylation of alkenes," said

Professor Zhang. “These transformations were accompanied by controllable remote alkenylation as shown in Scheme 2B. Notably, for the 1,2,3-triacetoxylation, five sequential site activations on the hydrocarbon chain (one C=C double bond and three C(sp<sup>3</sup>)-H bonds) in a one-step reaction was achieved.” In the following year, the authors of this study continued to deepen their understanding of the mechanism and further expanded the method’s scope. “After successfully achieving further dihydroxylation of the unsaturated bond in our catalytic product, we came to the realization that this could be a promising approach to constructing sugars,” Professor Zhang remarked. “Based on this, one of the most efficient syntheses

of pentose and hexose sugars (including some rare ones) with different configurations was achieved via a two-step route from the catalytic products (Scheme 2C).”

Professor Zhang concluded: “The study period was quite extensive, and we encountered countless difficulties throughout the research process. There were even moments when the idea of giving up halfway was contemplated. However, fortunately, we persevered and overcame the challenges. This methodology allows for the diverse functionalization of flexible olefins, which has the potential to efficiently produce compounds that are needed in medicinal chemistry and materials science. We firmly believe that the controllable



**Scheme 2** Selected catalytic products of aerobic oxidative acetoxylation and their application

reaction sequence strategy still holds significant potential for exploring new functionalized sites on the hydrocarbon chain. With this in mind, we are committed to continuing our efforts in this direction and further advancing these developments.”

Matthews female

## REFERENCES

- (1) R. I. McDonald, G. Liu, S. S. Stahl *Chem. Rev.* **2011**, *111*, 2981–3019.
- (2) S. E. Mann, L. Benhamou, T. D. Sheppard *Synthesis* **2015**, *47*, 3079–3117.
- (3) A. Vasseur, J. Bruffaerts, I. Marek *Nat. Chem.* **2016**, *8*, 209–219.
- (4) Y. Li, D. Wu, H.-G. Cheng, G. Yin *Angew. Chem. Int. Ed.* **2020**, *59*, 7990–8003.
- (5) E. Larionov, H. Li, C. Mazet *Chem. Commun.* **2014**, *50*, 9816–9826.
- (6) C. M. Frech, G. Leitus, D. Milstein *Organometallics* **2008**, *27*, 894–899.
- (7) I. Massad, R. Suresh, L. Segura, I. Marek *Nat. Synth.* **2022**, *1*, 37–48.
- (8) T.-S. Mei, H. H. Patel, M. S. Sigman *Nature* **2014**, *508*, 340–344.
- (9) D. G. Kohler, S. N. Gockel, J. L. Kennemur, P. J. Waller, K. L. Hull *Nat. Chem.* **2018**, *10*, 333–340.
- (10) S. T. Henriksen, D. Tanner, S. Cacchi, P.-O. Norrby *Organometallics* **2009**, *28*, 6201–6205.

## About the authors



Dr. Z. Wu

**Zhengxing Wu** received a BS degree from Donghua University (P. R. of China) in 2009, and a PhD degree from Shanghai Jiao Tong University (P. R. of China) in 2017 under the supervision of Professor Wanbin Zhang. He was appointed as assistant research fellow at Shanghai Jiao Tong University in 2018. His current research interests focus on functionalization of alkenes.



J. Meng

**Jingjie Meng** received her BS degree from Anhui Normal University (P. R. of China) in 2018. In the same year, she joined Professor Wanbin Zhang's group at Shanghai Jiao Tong University (P. R. of China). Currently, she is pursuing her Ph.D. degree in organic chemistry and her research interests focus on the palladium-catalyzed functionalization of alkenes.



H. Liu

**Huikang Liu** received a BS degree from Shanghai Jiao Tong University (P. R. of China) in 2019, and an MS degree from the same university in 2022 under the supervision of Professor Wanbin Zhang. Currently, he is pursuing his Ph.D. degree in the same research group, and his research interests focus on functionalization of alkenes.



Y. Li

**Yunyi Li** was born in Hengshui (P. R. of China). After completing a BSc (2016) in chemistry from Ocean University of China (P. R. of China), she received her MSc in 2019 from Shanghai Jiao Tong University (P. R. of China) under the guidance of Professors Hongjin Chen and Wanbin Zhang. During her postgraduate studies, her research focused on Pd(II)-catalyzed oxyamination of conjugated dienes.



Dr. X. Zhang

**Xiao Zhang** was born in Shanghai (P. R. of China). She completed her BSc in chemistry in 2017 from Shanghai Jiao Tong University (P. R. of China) and worked as an undergraduate research assistant in the lab of Professor Wanbin Zhang from 2014 to 2017. In 2017, she moved to the USA and started her PhD studies in chemistry at Columbia University (USA) with Professor Tomislav Rovis, and obtained her PhD in 2023. Her research interests have covered transition-metal catalysis, photocatalysis and polymer upcycling.



Dr. W. Zhang

**Wanbin Zhang** received his BS and MS degrees from East China University of Science and Technology (P. R. of China) in 1985 and 1988, respectively. From 1994–1997, he undertook PhD studies at Osaka University (Japan) under the supervision of Professor Isao Ikeda. He then worked as an assistant professor at Osaka University until 2001 and then as a research fellow at Mitsubishi Chemical Corporation (Japan). Since 2003, he has worked as a professor in the School of Chemistry and Chemical Engineering at Shanghai Jiao Tong University (P. R. of China). He was promoted to the position of Distinguished Professor in 2013 and the position of Chair Professor in 2021. Professor Zhang's current research interests include asymmetric catalysis and pharmaceutical process chemistry.

# Synthesis and Immunological Evaluation of *Escherichia coli* O1-Derived Oligosaccharide–Protein Conjugates toward Avian Pathogenic *Escherichia coli* O1 Vaccine Development

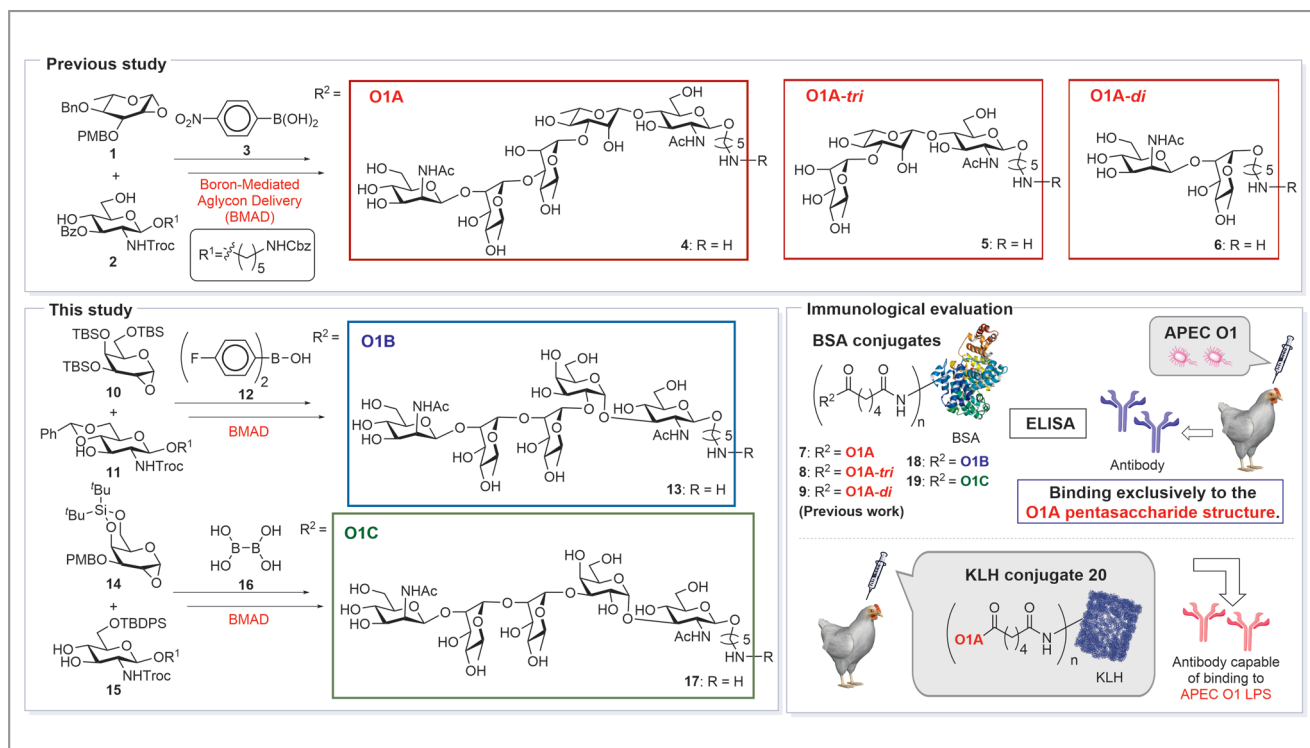
*Synthesis* **2023**, in press; DOI: 10.1055/a-2152-0255

Avian *Escherichia coli* O1 (APEC O1) is a pathogenic bacterium that causes significant economic losses to the poultry industry and is also feared to cause zoonotic infections due to its genomic similarity to human pathogenic *E. coli*. In addition, the emergence of drug-resistant strains is a concern and the development of a glycoconjugate vaccine with a high safety profile would be strongly desirable. However, the glycan structures of APEC O1 antigen have not been clarified yet, which does not help the development of such a vaccine.

The group of Professor Kazunobu Toshima and Associate Professor Daisuke Takahashi at Keio University (Yokohama, Japan) has been studying this area, focusing on the three glycan structures O1A, O1B, and O1C, reported to be present in *E. coli* O1. Professor Takahashi said: “We hypothesized that the

O1A antigen structure, which has been reported to be pathogenic, may be important as a potential glycocone for APEC O1.”

“In our previous studies, we first synthesized complex glycoconjugates with O1A pentasaccharide, trisaccharide, and disaccharide structures using our boronic acid catalyzed BMAD (boron-mediated aglycon delivery) method (*Angew. Chem. Int. Ed.* **2015**, *54*, 10935–10939; *Chem. Commun.* **2017**, *53*, 3018–3021; *J. Am. Chem. Soc.* **2018**, *140*, 3644–3651; *Angew. Chem. Int. Ed.* **2018**, *57*, 13858–13862; *Nat. Commun.* **2020**, *11*, 2431; *Chem. Eur. J.* **2020**, *26*, 10222–10225; *Angew. Chem. Int. Ed.* **2023**, in press, DOI: 10.1002/anie.202307015),” said Professor Takahashi. He continued: “We evaluated their immunological activities to identify candidate glycans for the APEC O1 antigen, and revealed for the first time that the O1A



**Scheme 1** State of the art and main results of the study

pentasaccharide structure is the glycotope of APEC O1 (*Angew. Chem. Int. Ed.* **2021**, *60*, 1789–1796).”

In this study, the authors first synthesized complex glycoconjugates with O1B and O1C pentasaccharide structures using borinic acid catalyzed and diboron-catalyzed BMAD methods (for borinic acid catalyzed methods see: *Org. Lett.* **2016**, *18*, 2288–2291; *Org. Lett.* **2016**, *18*, 5030–5033; *J. Org. Chem.* **2018**, *83*, 7281–7289; for diboron-catalyzed method see: *J. Org. Chem.* **2020**, *85*, 16254–16262) and evaluated their immunological activities. Professor Takahashi remarked: “Interestingly, it was clearly shown that only the O1A pentasaccharide, incorporating a  $\beta$ -rhamnoside structure, is important as a potential glycotope for APEC O1.” He continued: “Furthermore, we also synthesized a KLH-O1A pentasaccharide conjugate and evaluated its antigenicity. ELISA tests confirmed the efficient production of antibodies capable of binding to both APEC O1 LPS and O1A-pentasaccharide structures, indicating that the glycoconjugate with O1A pentasaccharide is a promising vaccine candidate against APEC O1.”

Professor Takahashi told SYNFORM: “One of the most impressive results is that we were able to demonstrate that only the O1A pentasaccharide containing the  $\beta$ -rhamnoside structure among O1A, B, and C is useful as an epitope, as per the working hypothesis. The other remarkable result is that KLH-O1A pentasaccharide conjugate produced antibodies that bind to APEC O1 LPS and O1A-pentasaccharide structures.”

The authors believe that since the vaccine candidate against APEC O1 discovered in this study is not made from the pathogen, but has chemically synthesized homogeneous sugar chains that are less likely to cause adverse reactions, this makes it potentially valuable from a practical standpoint.

“We were able to demonstrate the viability of our BMAD methods through the efficient synthesis of O1B and O1C pentasaccharides. Therefore, the broad application of this method to the synthesis of antigenic glycan candidates holds great promise for the development of new glycoconjugate vaccines against various pathogens,” said Professor Takahashi. He concluded: “In addition, if APEC with O1B and O1C pentasaccharide structures are expressed in the future, the glycoconjugates synthesized in this study may become vaccine candidates.”

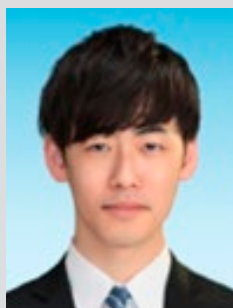
*Mattias Forsell*

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**Katsunori Seki** received a bachelor's degree in 2020 and a master's degree in 2022 from Keio University (Japan) under the supervision of Professor Kazunobu Toshima and Associate Professor Daisuke Takahashi, focusing on the development of glycoconjugate vaccines using boron-mediated aglycon delivery. He is currently working for Astellas Pharma Inc. (Japan).



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**Takumi Makikawa** received a bachelor's degree in 2022 and is pursuing his master's degree under the supervision of Professor Kazunobu Toshima and Associate Professor Daisuke Takahashi at Keio University (Japan), focusing on the development of glycoconjugate vaccines and biologically active glycosides using boron-mediated aglycon delivery.



Prof. K. Toshima

**Kazunobu Toshima** received his Ph.D. in 1988 from Keio University (Japan) under the supervision of Professors Mitsuhiro Kinoshita and Kuniaki Tatsuta. He spent one year in Professor K. C. Nicolaou's group at the University of Pennsylvania (USA) as a postdoctoral fellow. He was appointed as Lecturer of the Department of Applied Chemistry at Keio University in 1989. There, he was promoted to Assistant Professor in 1994, Associate

Professor in 1996, and Full Professor in 2003. He was awarded The Chemical Society of Japan Award for Young Chemists in 1995, Taro Yamashita Academic Award in 1996, The Chemical Society of Japan Award for Creative Work in 2014, and SSOCJ Daiichi-Sankyo Award for Medicinal Organic Chemistry in 2015.



Prof. D. Takahashi

**Daisuke Takahashi** received his Ph.D. in 2006 from Tokyo Institute of Technology (Japan) under the supervision of Professor Takashi Takahashi. He spent two years in Professor Ole Hindsgaul's group at the Carlsberg Laboratory in Denmark as a JSPS fellow and as a postdoctoral fellow. He was appointed as a research associate of the Department of Applied Chemistry at Keio University (Japan) in 2008, where he was promoted to

Assistant Professor in 2012 and Associate Professor in 2016. He was awarded the Incentive Award from the Japanese Society of Carbohydrate Research in 2016, the Incentive Award from Synthetic Organic Chemistry, Japan in 2016, and The Carbohydrate Research Award in 2021.



# Mechanistic Snapshots of Rhodium-Catalyzed Acylnitrene Transfer Reactions

*Science* **2023**, *381*, 525–532

Catalytic C–N bond formation stands as a crucial and highly sought-after process in the realms of synthetic, medicinal, and materials chemistry, offering a pathway to valuable nitrogen-containing compounds. While the Buchwald–Hartwig coupling method has emerged as a practical approach for furnishing valuable amine products,<sup>1,2</sup> catalytic C–H amination is also considered as an attractive strategy, obviating the demand for pre-functionalized substrates and directly converting hydrocarbon precursors into the desired amine products.<sup>3,4</sup> “Transition-metal-catalysis platforms have been devised to facilitate hydrocarbon aminations through metal–nitrenoid transfer routes, employing nitrene precursors, most notably organic azides,” said Professor Sukbok Chang, from the Institute for Basic Science and Korea Advanced Institute of Science and Technology (IBS and KAIST, Daejeon, South Korea). He further noted: “While integrating *N*-acylamino groups into hydrocarbons is another significant transformation to produce various amido compounds, direct C–H amidation through acylnitrenoid transfer with organic acyl azides poses challenges. This is mainly due to the high temperature requirement and to the unstable nature of acyl azides, which tend to decompose to the corresponding isocyanates by the Curtius-type rearrangement.”

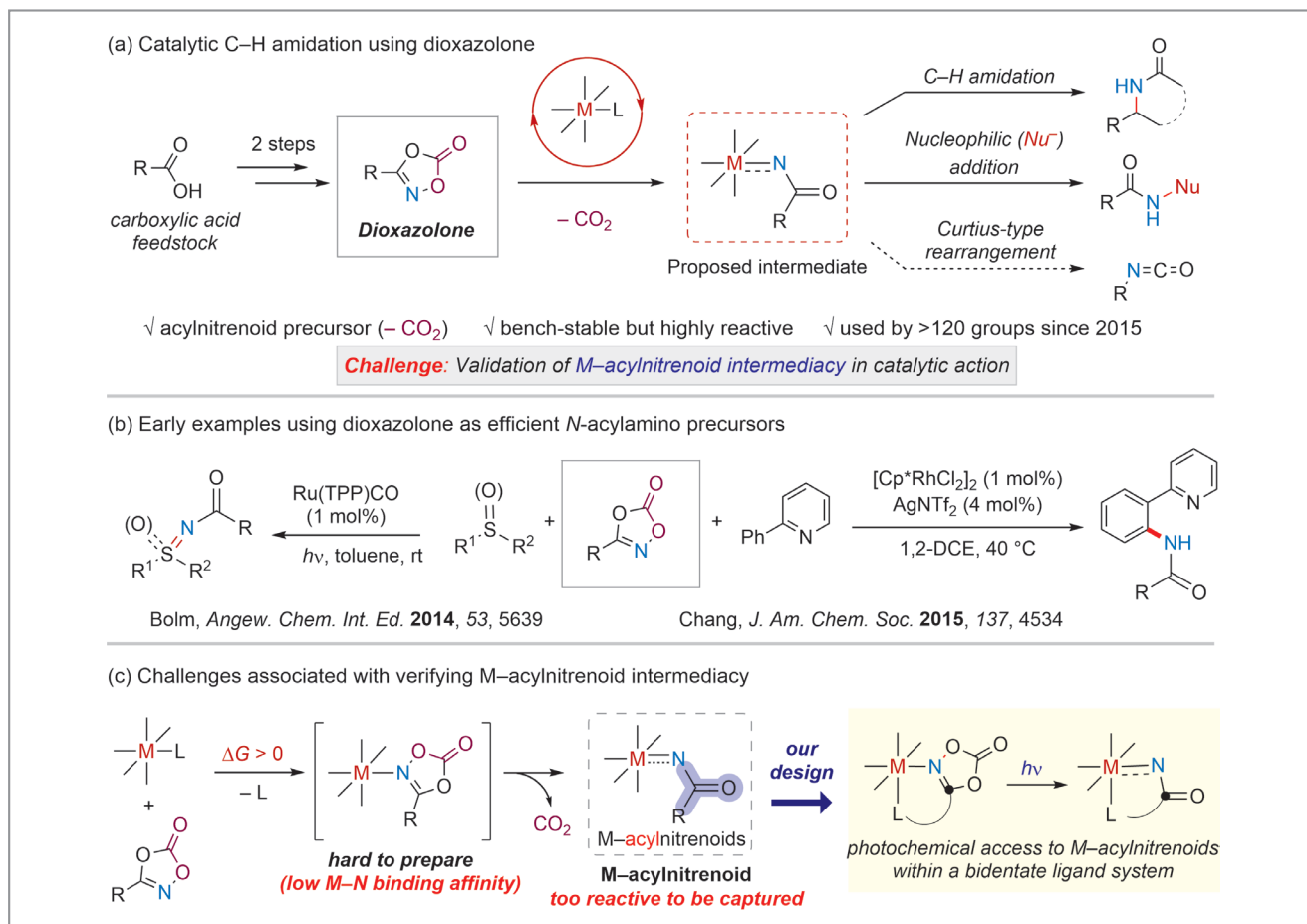
Professor Chang’s group stands at the forefront of research aiming to identify alternative pathways for the challenging C–H amidation. “Recently, instead of using acyl azides as the nitrene precursors, the broader synthetic organic community has shifted its focus to 1,4,2-dioxazol-5-ones (dioxazolones), which have shown promise as user-friendly and highly reactive *N*-acylamino sources (Scheme 1a). Dioxazolones can be easily derived from readily available carboxylic acid feedstocks, and their transformation to acylnitrenoids results in the emission of CO<sub>2</sub> as a sole byproduct,” Professor Chang explained. He continued: “Since Bolm’s efforts with sulfur imidation through ruthenium photocatalysis,<sup>5</sup> and also with our studies on C–H amidation using half-sandwich group *d*<sup>6</sup> transition metal catalysts,<sup>6</sup> dioxazolones have now become popular *N*-acylamino precursors, as more than 120 research groups utilized this strategy from 2015 to 2022 (Scheme 1b).<sup>7,8</sup>” Based on distinct advantages over conventional acyl azides, dioxazolones exhibited remarkable benefits in terms of substrate scope, reactivity, and selectivity. Prof. Chang’s and

other groups exemplified these advantages by utilizing group 9 transition-metal catalysts to leverage the reactivity of anticipated metal–acylnitrenoid species, leading to the creation of value-added products like lactams,<sup>9</sup> arylamines,<sup>6</sup> and hydrazides.<sup>10</sup>

In this regard, Professor Chang explained that the transition-metal–acylnitrenoid species has long been postulated as a key intermediate in catalytic C–H amidation processes, yet has remained uncharacterized due to associated challenges (Scheme 1c). “Since our first discovery in catalytic C–H amidation using dioxazolones as the nitrene precursors in 2015, observing the metal–acylnitrenoid intermediacy has been on our bucket list,” said Prof. Chang. He continued, explaining the key challenges: “However, due to their high reactivity, characterizing these metal–acylnitrenoid species has proven exceedingly difficult. Most representatively, the inherent susceptibility of metal–acylnitrenoids to undergo the Curtius-type rearrangement makes the situation more challenging. Furthermore, the low binding affinity of dioxazolones to transition-metal centers introduces another inherent complication, hindering the preparation of the necessary metal-bound dioxazolone adducts and thereby adding complexity to the exploration of the nitrenoid formation and transfer mechanisms.”

Professor Chang went on by explaining that in some cases, transition-metal–nitrenoid intermediates were characterized through the utilization of azides and transition-metal complexes. In previous studies, researchers often designed bulky ligands to protect the metal–nitrenoid structure from reacting with other substrates (Betley,<sup>11</sup> Munz<sup>12,13</sup>). Beyond ligand design strategies, Powers,<sup>14,15</sup> Schneider<sup>16,17</sup> and others utilized photo- or thermal-induced crystallographic approaches, wherein the structure of the metal–nitrenoid could be captured in the crystalline matrix from single crystals of the metal–azide complex upon irradiation or thermal perturbation. “However, the literature precedents all utilized azides to obtain structures of alkyl, aryl, and sulfonyl nitrenes, and still, elucidating the structure of metal–acylnitrenoids using dioxazolones remains a challenge,” Prof. Chang commented.

Professor Chang’s group has now solved this long-standing challenge of characterizing transition-metal–acylnitrenoid species, which resulted in this paper in *Science*.<sup>18</sup> The first



**Scheme 1** Dioxazolones as an efficient amidation source: scope, reactivity, and challenges

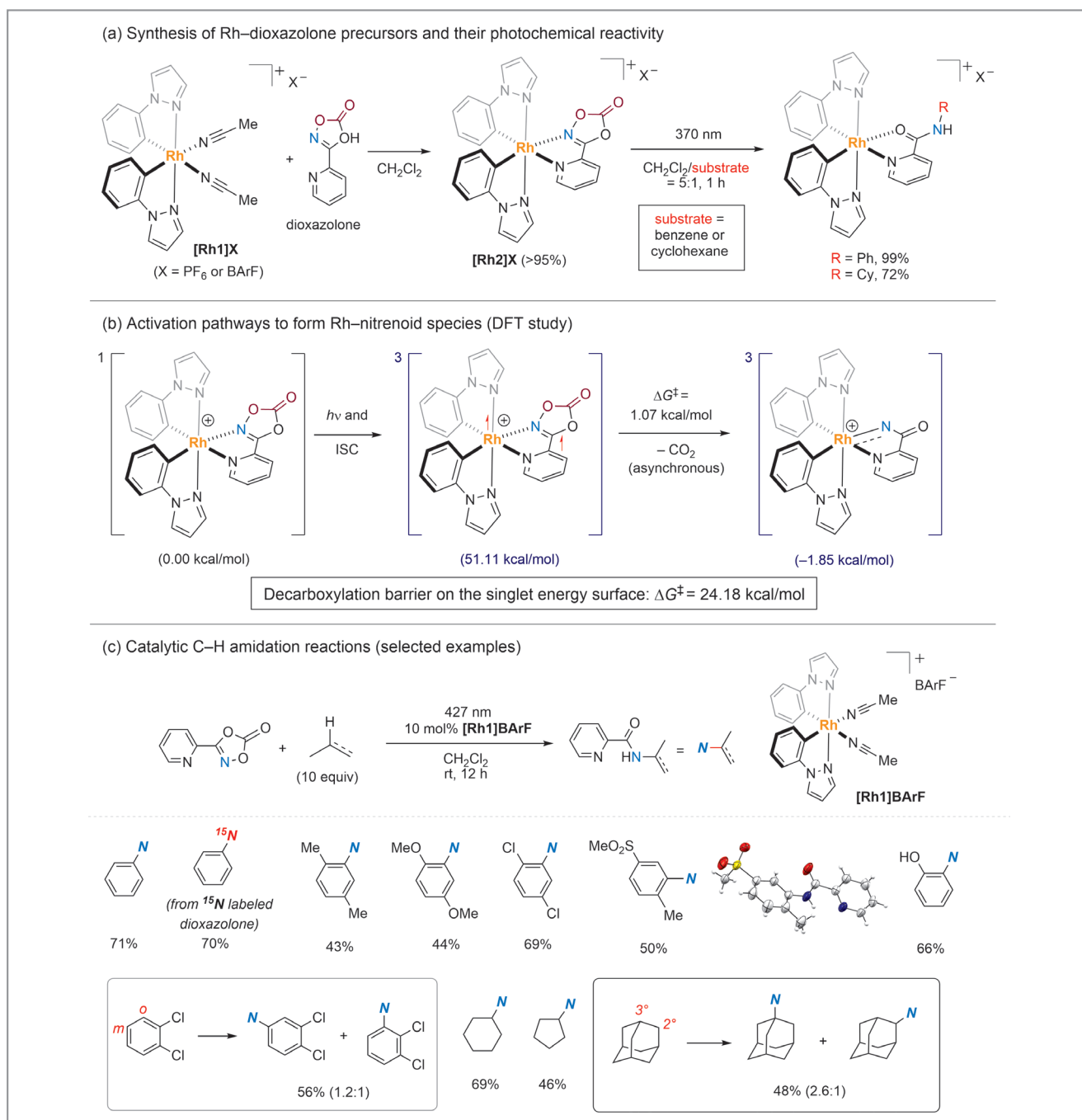
author, Hoimin Jung, explained: “To solve this challenge, we strategically designed a photosensitizable octahedral rhodium complex that coordinates with a bidentate dioxazolone to serve as an *N*-acylamino precursor.” He continued: “We developed a photocatalytic hydrocarbon amidation reaction with a pyridinyl dioxazolone by using an octahedral rhodium catalyst inspired by the Meggers-type photocatalyst.<sup>19</sup> We successfully isolated the rhodium-bound dioxazolone adduct, and further photochemical studies showed that this new platform exhibits photocatalytic nitrene transfer reactivity toward both C(sp<sup>2</sup>)-H and C(sp<sup>3</sup>)-H amidations (Schemes 2a and 2c). Combined experimental and computational studies indicated that photochemical activation of the Rh–dioxazolone adduct could induce the formation of Rh–acylnitrenoid species via metal-to-ligand charge transfer (MLCT) activation of the dioxazolone (Scheme 2b). Also, mechanistic probe experiments and computational studies supported the involvement of singlet Rh–acylnitrene species responsible for nitrenoid transfer.”

Interestingly, the newly prepared rhodium–dioxazolone complex also showed photochemical reactivity in the solid reaction phase. The co-corresponding author Dongwook Kim emphasized: “With the single crystal of Rh–dioxazolone complexes in hand, we investigated the subsequent photoinduced decarboxylation step using an X-ray photocrystallography experiment in the Pohang Accelerator Laboratory (Korea).” He continued: “It was possible to capture the highly reactive species using the synchrotron facility, as the measurements could be finished within a few minutes. When using a Rh–dioxazolone crystal with a bulky tetrakis{3,5-bis(trifluoromethyl)phenyl}borate (BARF) anion, we finally captured and resolved a glimpse of the Rh–acylnitrenoid formation at 100 K upon 370 nm irradiation. After 30 min of irradiation, we found ~33% conversion of the starting rhodium–dioxazolone complex, where the Rh–N bond length contracted significantly from 2.153(2) Å to 2.02(2) Å upon the formation of the Rh–acylnitrenoid species. Remarkably, upon structure analysis, we

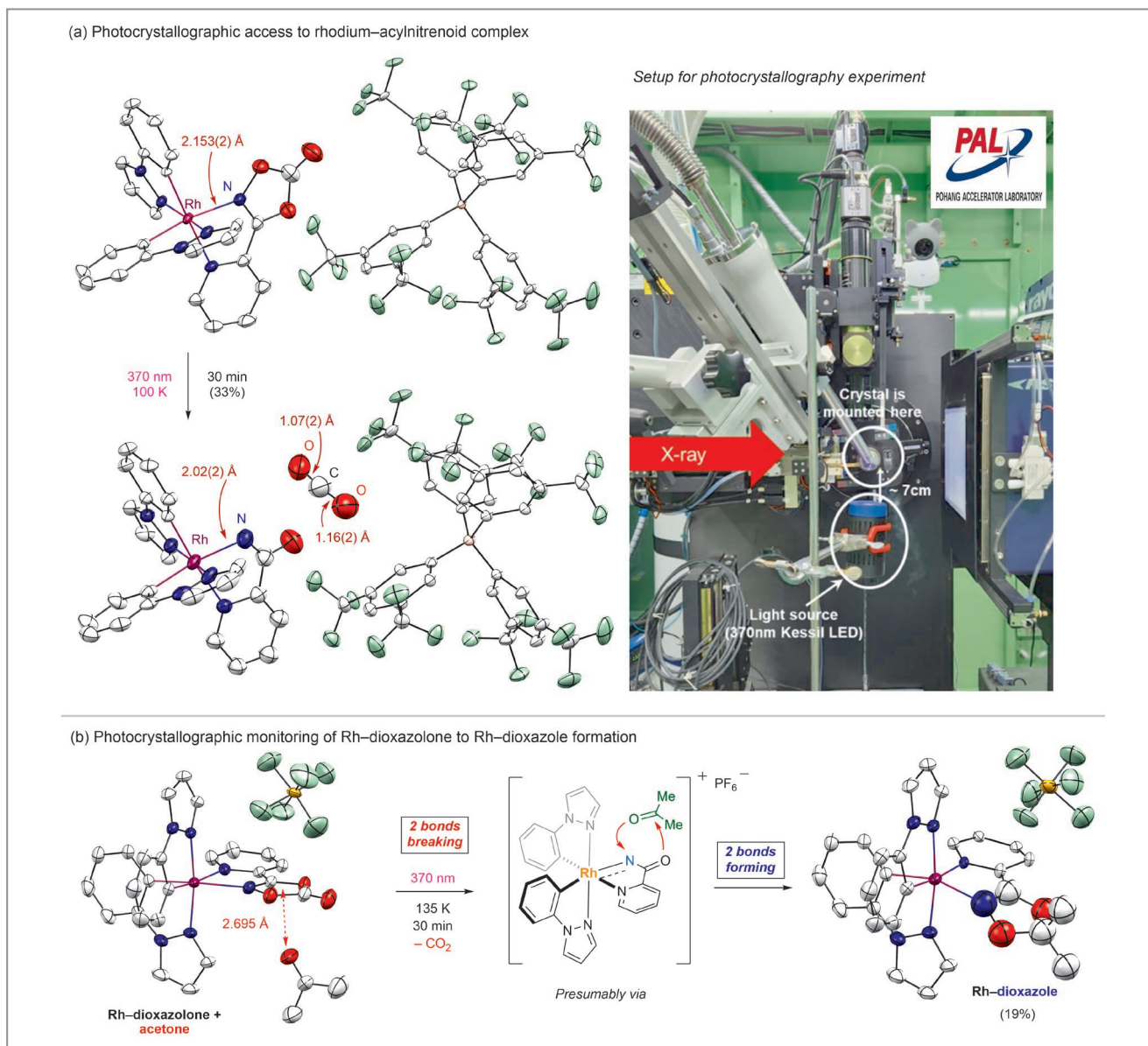
observed the extruded CO<sub>2</sub> molecule naturally (without geometrical restraints), which resides between the bulky BARf anion and the Rh–acylnitrenoid fragment (Scheme 3a)."

However, observing the rhodium–acylnitrenoid structure itself may not be sufficient to fully understand its catalytic

reactivity. Hence, the authors designed another photo-crystallography experiment that could directly support the reactivity nature of the sought-after rhodium–acylnitrenoid complex (Scheme 3b). First author Dr. Jung said, "By switching the counter anion to a smaller PF<sub>6</sub> anion, we prepared a



**Scheme 2** Synthesis of rhodium–dioxazolone coordination complexes and their photochemical reactivity



**Scheme 3** Photocrystallographic access to rhodium–acylnitrenoid species and crystallographic reaction monitoring

co-crystal of Rh–dioxazolone with one acetone molecule in the crystalline matrix, where the acetone was found very close to the dioxazolone moiety (2.695 Å).” Dr. Kim continued by explaining: “When subjecting this acetone co-crystal to the X-ray photocrystallographic analysis, we were able to observe significant residual electron densities, indicating the formation of the corresponding Rh–dioxazole molecule as the photoproduct, wherein acetone is incorporated into the *in situ* generated Rh–acylnitrenoid in the solid state. For this experiment, a slightly higher temperature of 135 K was op-

timal to induce the change, and 19% of Rh–dioxazole structure was observed after 30 minutes irradiation with the 370 nm light source.” Professor Chang further highlighted: “With this series of X-ray photocrystallographic analyses, we captured the complete mechanistic snapshot of acylnitrene transfer, which includes the two-bond-breaking decarboxylation and two-bond-associating dioxazole formation. In addition to the structural characterization of the Rh–acylnitrenoid intermediate, we also found experimental evidence on the electrophilic nature of such intermediates.”

Professor Chang concluded: “We have solved the long-standing challenge of identifying metal–acylnitrenoid intermediacy in the catalytic C–H amidation process. Our study represents a significant breakthrough in catalytic hydrocarbon amidation, offering new insights into the mechanism of this crucial reaction and presenting a strategic avenue for characterizing metal–acylnitrenoid intermediates and their electrophilic nature. The isolation and characterization of the Rh–acylnitrene complex serve as a long-sought-after key mechanistic motif, furnishing vital new perspectives for the design of more efficient and selective catalytic systems.”

*Matters female*

## REFERENCES

- (1) F. Paul, J. Patt, J. F. Hartwig *J. Am. Chem. Soc.* **1994**, *116*, 5969–5970.
- (2) A. S. Guram, S. L. Buchwald *J. Am. Chem. Soc.* **1994**, *116*, 7901–7902.
- (3) Y. Park, Y. Kim, S. Chang *Chem. Rev.* **2017**, *117*, 9247–9301.
- (4) T. Rogge, N. Kaplaneris, N. Chatani, J. Kim, S. Chang, B. Punji, L. L. Schafer, D. G. Musaev, J. Wencel-Delord, C. A. Roberts, R. Sarpong, Z. E. Wilson, M. A. Brimble, M. J. Johansson, L. Ackermann *Nat. Rev. Methods Primers* **2021**, *1*, 43.
- (5) V. Bizet, L. Buglioni, C. Bolm *Angew. Chem. Int. Ed.* **2014**, *53*, 5639–5642.
- (6) Y. Park, K. T. Park, J. G. Kim, S. Chang *J. Am. Chem. Soc.* **2015**, *137*, 4534–4542.
- (7) K. M. van Vliet, B. de Bruin *ACS Catal.* **2020**, *10*, 4751–4769.
- (8) S. Y. Hong, Y. Hwang, M. Lee, S. Chang *Acc. Chem. Res.* **2021**, *54*, 2683–2700.
- (9) S. Y. Hong, Y. Park, Y. Hwang, Y. B. Kim, M.-H. Baik, S. Chang *Science* **2018**, *359*, 1016–1021.
- (10) H. Wang, H. Jung, F. Song, S. Zhu, Z. Bai, D. Chen, G. He, S. Chang, G. Chen *Nat. Chem.* **2021**, *13*, 378–385.
- (11) K. M. Carsch, I. M. DiMucci, D. A. Iovan, A. Li, S.-L. Zheng, C. J. Titus, S. J. Lee, K. D. Irwin, D. Nordlund, K. M. Lancaster, T. A. Betley *Science* **2019**, *365*, 1138–1143.
- (12) A. Grünwald, N. Orth, A. Scheurer, F. W. Heinemann, A. Pöthig, D. Munz *Angew. Chem. Int. Ed.* **2018**, *57*, 16228–16232.
- (13) A. Grünwald, B. Goswami, K. Breitwieser, B. Morgenstern, M. Gimferrer, F. W. Heinemann, D. M. Momper, C. W. M. Kay, D. Munz *J. Am. Chem. Soc.* **2022**, *144*, 8897–8901.
- (14) A. Das, Y.-S. Chen, J. H. Reibenspies, D. C. Powers *J. Am. Chem. Soc.* **2019**, *141*, 16232–16236.
- (15) A. Das, C.-H. Wang, G. P. Van Trieste III, C.-J. Sun, Y.-S. Chen, J. H. Reibenspies, D. C. Powers *J. Am. Chem. Soc.* **2020**, *142*, 19862–19867.
- (16) J. Sun, J. Abbenseth, H. Verplancke, M. Diefenbach, B. de Bruin, D. Hunger, C. Würtele, J. van Slageren, M. C. Holthausen, S. Schneider *Nat. Chem.* **2020**, *12*, 1054–1059.
- (17) T. Schmidt-Räntsch, H. Verplancke, J. N. Lienert, S. Demeshko, M. Otte, G. P. Van Trieste III, K. A. Reid, J. H. Reibenspies, D. C. Powers, M. C. Holthausen, S. Schneider *Angew. Chem. Int. Ed.* **2022**, *61*, e202115626.
- (18) H. Jung, J. Kweon, J.-M. Suh, M. H. Lim, D. Kim, S. Chang *Science* **2023**, *381*, 525–532.
- (19) L. Zhang, E. Meggers *Acc. Chem. Res.* **2017**, *50*, 320–330.

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Dr. D. Kim

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(South Korea), and now he has been promoted to a senior research fellow at the same research center. He is interested in the structural investigation of intermediates of organic, organometallic, and inorganic compounds and their analytical evaluation using single-crystal X-ray diffraction.



Prof. S. Chang

**Sukbok Chang** is a Director at the Institute for Basic Science (IBS, South Korea) and also a Distinguished Professor of Chemistry at KAIST (South Korea). He earned his Ph.D. in organic chemistry in 1996, at Harvard University (USA) under the guidance of Professor Eric N. Jacobsen. After one and half years of postdoctoral experience with Professor Robert H. Grubbs at Caltech (USA), he joined Ewha Womans University in Seoul, Korea,

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