

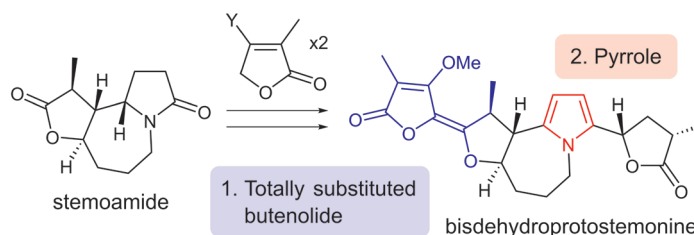
Synform

People, Trends and Views in Chemical Synthesis

2024/08

SYNTHESIS Best Paper Award 2023: Total Synthesis and Anti-inflammatory Activity of Stemoamide-Type Alkaloids Including Totally Substituted Butenolides and Pyrroles

Highlighted article by Y. Soda, Y. Sugiyama, S. Sato, K. Shibuya, J. Saegusa, T. Matagawa, S. Kawano, M. Yoritake, K. Fukaya, D. Urabe, T. Oishi, K. Mori, S. Simizu, N. Chida, T. Sato



SAR study of the anti-inflammatory activities

Contact

Your opinion about Synform is welcome, please correspond if you like:
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Dear Readers,

In this August issue of SYNFORM we celebrate the other 2023 Best Paper Award winners. In the July issue we interviewed Professor Santanu Mukherjee and co-author from The Indian Institute of Science, Bangalore (India), who were the recipients of the SYNLETT Best Paper Award 2023. In this issue we have the great honour to feature the interview with Professor Takaaki Sato and collaborators, a team from Keio University and Toyama Prefectural University (Japan), who are the recipients of the SYNTHESIS Best Paper Award 2023 for their article “Total Synthesis and Anti-inflammatory Activity of Stemoamide-Type Alkaloids Including Totally Substituted Butenolides and Pyrroles” (*Synthesis* **2023**, *55*, 617–636). The interview provides an account on their prize-winning research, besides covering current research activities ongoing in the group. The other articles in this issue are an interview with the recent Thieme Chemistry Journals Awardee Akihito Konishi (Japan), followed by the first of two Literature Coverage articles: the versatile deacylative arylation and alkynylation of unstrained ketones developed by the group of X. Zhang (P. R. of China). The second one covers the intriguing catalytic 1,1-diazidation of alkenes reported by the group of X. Zhao and L. Liao (P. R. of China).

Enjoy your reading!



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

SYNTHESIS Best Paper Award 2023: Total Synthesis and Anti-inflammatory Activity of Stemoamide-Type Alkaloids Including Totally Substituted Butenolides and Pyrroles

Synthesis **2023**, *55*, 617–636

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

A collaborative team from Keio University and Toyama Prefectural University (Japan) led by Takaaki Sato have been awarded the SYNTHESIS Best Paper Award 2023. The authors are recognized for their detailed synthetic study of the stemoamide class of heterocycles including tricyclic, tetracyclic and pentacyclic frameworks. The paper includes a stereodivergent strategy in the creation of a fully substituted butenolide. A comprehensive investigation that outlines several optimization reactions, careful structure elucidation and discussion, and anti-inflammatory assays, are highlights on this exciting study. This paper was the subject of a previous *SYNFORM News* announcement and a *SYNTHESIS Highlight* article (*Synform* **2022**, *12*, A202; DOI: 10.1055/s-0040-1720579) wherein the background and research were discussed in more detail.

SYNFORM spoke with Professor Takaaki Sato, who was happy to both share some additional insight into the prize-winning paper and to answer a few other questions on research in his group and total synthesis in general.

Biographical Sketch



Top, from left: Yasuki Soda, Yasukazu Sugiyama, Kana Shibuya, Shunsei Sato, Junya Saegusa, Tomoe Matagawa, Sayaka Kawano
Bottom, from left: Prof. Makoto Yoritate, Prof. Keisuke Fukaya, Prof. Daisuke Urabe, Dr. Kento Mori, Prof. Siro Simizu, Prof. Noritaka Chida, Prof. Takaaki Sato (Dr. Takeshi Oishi not shown)

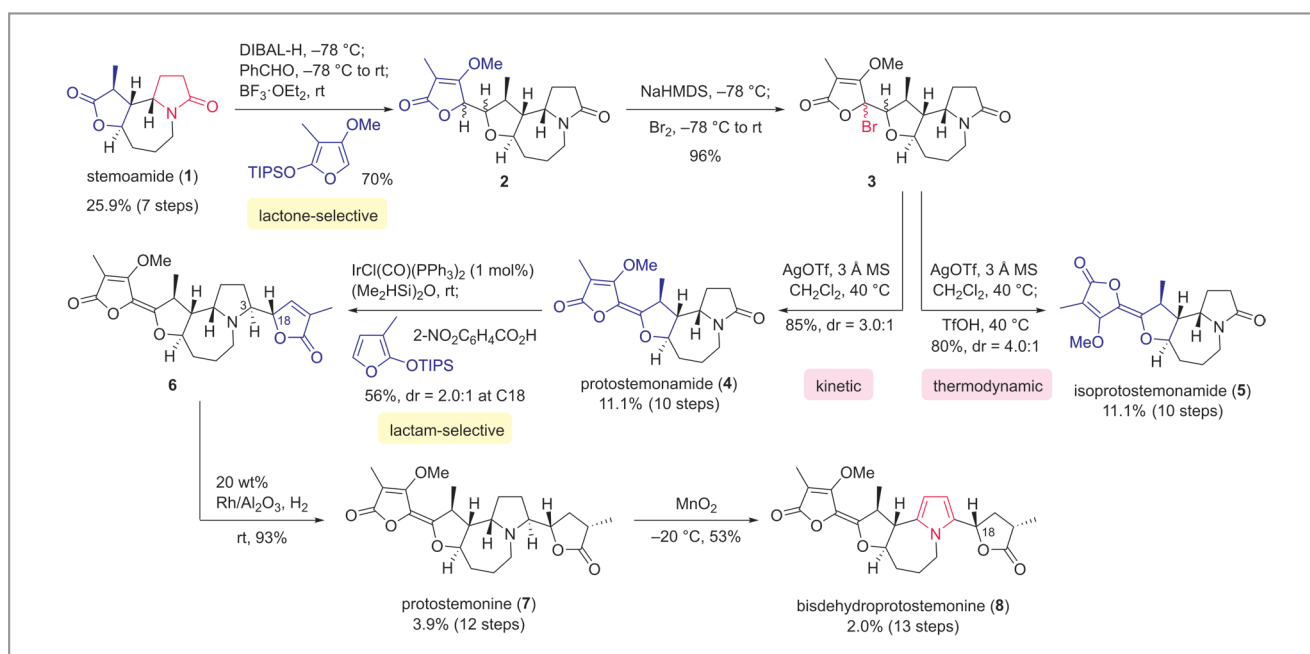
Takaaki Sato received his B.Sc. degree in 2001 from Tohoku University (Japan), and his Ph.D. in 2006 from the same university (Professor Masahiro Hirama). He spent two years in Professor Larry E. Overman's group at the University of California, Irvine (USA) as a JSPS fellow. He joined the Department of Applied Chemistry, Keio University (Japan) as an assistant professor in 2008 and was promoted to associate professor in 2016. In 2022, he started his independent career at Keio University. He was awarded the Otsuka Pharmaceutical Co. Award in Synthetic Organic Chemistry, Japan in 2008, the Young Scientist's Research Award in Natural Product Chemistry in 2014, the Incentive Award in Synthetic Organic Chemistry, Japan in 2016, and a Thieme Chemistry Journals Award in 2019.

INTERVIEW

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

Prof. T. Sato The stemoamide-type alkaloids have been recognized as one of the most popular synthetic targets due

to recent biological studies involving anti-inflammatory effects such as LPS-induced acute lung injury in mice. However, the structure–activity relationship (SAR) had not been demonstrated, especially for libraries including pentacyclic natural products. Structurally, stemoamide-type alkaloids consist of various five-membered heterocyclic rings. However, a building block strategy using five-membered rings had not been realized, since differentiation between γ -lactones and γ -lactams was highly challenging. We achieved the collective total synthesis of the stemoamide-type alkaloids by chemo-selective assembly of five-membered building blocks (Scheme 1). The lactone selectivity was relatively easy to achieve by taking advantage of the inherent electrophilicity of the lactone (**1**→**2**). In contrast, the lactam selectivity was realized by iridium-catalyzed reductive nucleophilic addition (**4**→**6**). Another conspicuous transformation was the stereodivergent construction of the totally substituted butenolides. While elimination of bromide **3** with AgOTf under kinetic conditions provided protostemonamide (**4**) as a major product, elimination and subsequent acid-mediated isomerization gave isoprotostemonamide (**5**) as a thermodynamic product. These methods enabled us to determine the systematic SAR, revealing that the pentacyclic framework including the totally substituted butenolide is crucial for anti-inflammatory activities.



Scheme 1 Total synthesis of stemoamide-type alkaloids

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

Prof. T. Sato Currently, one of our research topics is the development of reactions including a crystallization process to control unsolved selectivity, and its application to total synthesis of natural products. When you read a textbook of organic synthesis, you can find two basic approaches to control selectivity. The first one is kinetic control, which favors a product via the most stable transition state under irreversible conditions. The other is thermodynamic control, in which the lowest-energy product predominates under reversible conditions. In total synthesis of complex molecules, we are often faced with reactions showing unfavorable selectivity even if both approaches are attempted. Our focus is to come up with an alternative solution utilizing crystallization. Although crystallization itself is a well-studied process, the combination of a reaction process in solution with simultaneous crystallization could provide new selectivity (for selected examples, see: Walsh & Kitching, *JACS Au* **2022**, *22*, 2235–2250). In addition, these types of reactions result directly in crystallized product, and thus can potentially be applied to process chemistry. Prediction of crystallization from molecular structures remains challenging, requiring trial and error. However, we believe that in the near future, more intentional design of selective reactions – including crystallization process – will be feasible by computational approaches.

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

Prof. T. Sato Total synthesis of natural products has a long history, starting from the synthesis of urea by Wöhler in 1828. One of my favorite syntheses is the total synthesis of reserpine by Woodward in 1958. Although traditional, the area still remains a rich source of discoveries, providing opportunities for significant progress of organic synthesis. Historically, total synthesis has advanced with the development of new methods controlling ‘selectivity’. For example, synthetic chemists in the 1950s and 1960s used the conformation of cyclic compounds to control stereoselectivity. However, direct stereocontrol of acyclic compounds was developed due to the need for the synthesis of products such as polyketides. What I focused on, in the unified total synthesis of the stemoamide-type alkaloids, was ‘chemoselectivity’. While control of stereoselectivity contributes in improving the yield of a reaction itself, control of chemoselectivity not only does that, but may also impact efficiency in the synthetic route, reducing the number of steps required by avoiding inefficient reactions. To be more specific,

transformation of the target functional group in natural products often requires protecting group manipulation of more reactive functional groups, causing an increase in the total steps. However, realization of lactam-selective reductive nucleophilic addition in the presence of more electrophilic lactones acted as a game-changer, which enabled quick access to a variety of tetra- and pentacyclic natural products from simple tricyclic stemoamide. The late-stage oxidation of pyrrolidines to pyrroles without affecting other functional groups was also crucial to the concise total synthesis. Through our work, we were able to demonstrate the effectiveness of chemoselectivity and we are certain that this is one way of opening new and innovative routes in the synthetic world. Reactions in the presence of free alcohols, carboxylic acids and primary amines are still limited for synthetic organic chemists.

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

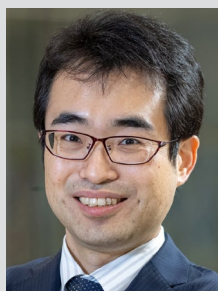
Prof. T. Sato Ultimate goals that lie ahead of total synthesis are contributions to human society, such as human health with medicinal drugs and global food problems with agricultural chemicals. On the other hand, I believe that synthetic organic chemists still enjoy total synthesis, almost as if it is an Olympic event! Who achieved the first total synthesis of this complex natural product in the world? Who developed the shortest synthetic route? Who accomplished it in the highest total yield? Who came up with the most elegant solution? When I came up with the chemoselective assembly of five-membered building blocks to approach stemoamide-type alkaloids, it brought me the feeling that our group may be nominated for a synthetic ‘Olympic event’! It has been more than ten years since our program started in 2013. The project was finally completed with my talented students and wonderful collaborators. We are not sure whether our synthesis is the best or not, but I feel like we won an Olympic medal, being selected as the Synthesis Best Paper Award 2023.

Matthew Tanaka

Young Career Focus: Professor Akihito Konishi (Osaka University, Japan)

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 Akihito Konishi (Osaka University, Japan).

Biographical Sketch



Prof. A. Konishi

Akihito Konishi received his Ph.D. in 2013 from Osaka University (Japan) under the supervision of Prof. Takashi Kubo. In 2010, he spent three months with Prof. Rik R. Tykwinski as a visiting researcher at the University of Erlangen–Nuremberg in Germany. During 2014–2015, he worked as a high school teacher in Hyogo prefecture (Japan). After returning to Osaka University, he was appointed Assistant Professor at the Department of Applied Chemistry of Osaka University in 2015. He is currently interested in the synthesis and characterization of novel π -conjugated molecules. He is also investigating the development of Lewis acid catalyzed reactions using main group metals. His awards and honors include: 2020 Young Scholar Lectures of CSJ; 2023 Commendations for Science and Technology Young Scientists' Award in MEXT; 2023 Incentive Award in Synthetic Organic Chemistry; 2023 Chemist Award BCA of MSD Life Science Foundation, Public Interest Incorporated Foundation; and 2024 Thieme Chemistry Journals Award.

INTERVIEW

SYNFORM Which field of organic chemistry are you interested in the most and why?

Prof. A. Konishi My favorite field of organic chemistry is physical and structural organic chemistry, because a beautiful molecule showing an unusual reactivity and having a fascinating geometry always suggests an intrinsic feature of the chemical bond.

SYNFORM Following that, what is the focus of your current research activity?

Prof. A. Konishi My current curiosity is synthesizing and characterizing novel non-benzenoid hydrocarbons having anti-aromatic and open-shell characteristics (Figure 1). Especially, polycyclic hydrocarbons containing non-alternant hydrocarbons such as azulene, pentalene, and heptalene have been my synthetic targets. The related molecules have a long history, and abundant achievements have been demonstrated by many legendary pioneers. Still, many molecules remain elusive even though they should exhibit fascinating electronic features. Characterizing an unreachable molecule should open the door to exciting chemistry based on its molecular framework. Strong cooperation of experimental studies with theoretical investigations will elaborate on the above issues, and the interesting structural and electronic features of non-benzenoid hydrocarbons will attract much attention from various branches of chemistry.

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

Prof. A. Konishi That is a critical point in researching organic chemistry. I believe that organic chemistry can solve many global problems, such as climate change, food supply

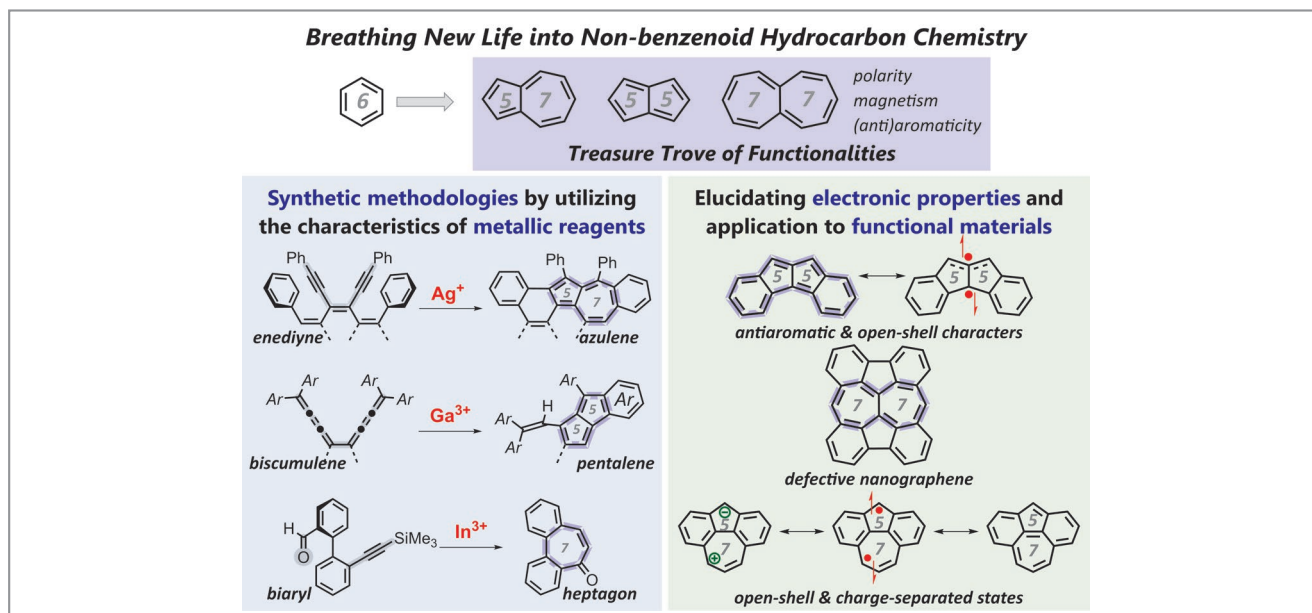


Figure 1 Summary of research interests

problems, depletion of petroleum resources, and so on. From the academic viewpoint, the balance between academic curiosities and awareness of social implementation is essential in order to enhance the possibilities offered by organic chemistry.

SYNFORM Which difficulties are there for young upcoming chemists in your field? Do you have any tips?

Prof. A. Konishi The decreasing number of academic positions and research funding is one of the most challenging points. As one tip to overcoming the situation, connections and exchanges among researchers are important.

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

Prof. A. Konishi I would like to nominate two recent achievements. The first is the first synthesis and characterization of bis-periazulene (*J. Am. Chem. Soc.* **2022**, *144*, 3370). The pursuit of the non-alternant isomers of pyrene, which has seven possible non-alternant isomers, has been the most significant related project. Through enormous dedication by many pioneering works, six of the seven possible non-alternant isomers of pyrene have been isolated and characterized as stable aromatic molecules, differentiating themselves from pyrene in terms of optoelectronic properties. However, the

only unsynthesized isomer, bis-periazulene (cyclohepta[def]fluorene), had remained an uncharacterized hydrocarbon until 2022, despite many synthetic and theoretical investigations since it was first reported in 1955. My group synthesized and characterized triaryl derivatives that exhibited the superimposed electronic structures of peripheral, polarized, and open-shell π -conjugated systems. In contrast to previous theoretical predictions, bis-periazulene derivatives were in the singlet ground state. Changing an aryl group controlled the energy gap between the lowest singlet–triplet states. My group unveiled that the double *peri*-benzoannulation into an azulene core provides fascinating electronic features.

The second is characterizing the pseudo Jahn–Teller effect (PJTE) of $4n\pi$ -conjugated system (*J. Am. Chem. Soc.* **2023**, *145*, 20595). Although PJTE is an essential effect to provide the attractive characteristics of $4n\pi$ systems, an understanding of the structure–property relationship derived from the PJTE for planar $4n\pi$ electron systems is still in its infancy. Our experimental and theoretical investigations through diareno[*a,f*]pentalenes concluded that their largest anti-aromaticity and moderate open-shell character are derived from the small energy barrier E_a^\ddagger for the bond-shift valence tautomerization. The energy profile of the single crystal of the molecule showed the temperature-dependent structural variations assigned to the dynamic mutual exchange between the two C_s -symmetric structures, which was also supported by the spectroscopic measurements in the solution phase. The find-

ings of this study advance the understanding of antiaromaticity characterized by the PJTE by controlling the energy barrier for bond-shift valence tautomerizations, potentially leading to the rational design of optoelectronic devices based on novel antiaromatic molecules possessing the strong contributions of their highly symmetric geometries.

SYNFORM *Could you tell us something about yourself outside the lab, such as your hobbies or extra-work interests?*

Prof. A. Konishi I enjoy spending time with my family.

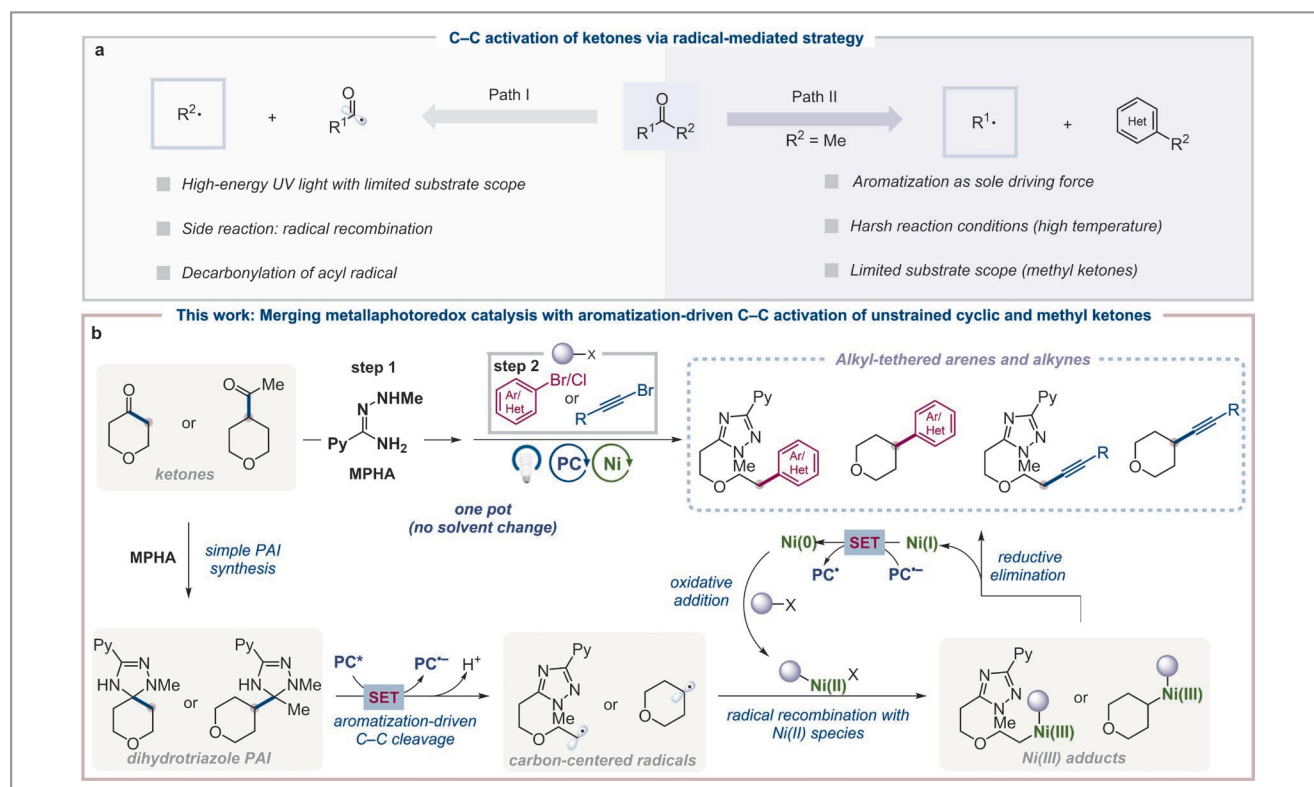


Deacylative Arylation and Alkynylation of Unstrained Ketones

Sci. Adv. **2024**, *10*, eado0225

The majority of organic compounds are comprised of carbon–hydrogen (C–H) and carbon–carbon (C–C) bonds, which represent the two pivotal units in organic chemistry and whose synthetic modification constitutes a central aspect in organic synthesis. “Complementary to altering existing frameworks through late-stage C–H functionalization, the selective C–C bond activation offers unique opportunities for constructing diverse organic molecule backbones. However, it has still been challenging to develop general and practical methods for C–C bond activation,¹” said Professor Xiaheng Zhang from Hangzhou Institute for Advanced Study, University of Chinese Academy of Sciences (Hangzhou, P. R. of China.). He continued: “The carbonyl group of ketones is an important structural motif in bioactive natural products and pharmaceuticals. Additionally, as one of the most prevalent and easily accessible functional groups, it serves as an excellent platform for C–C bond activation reactions.”

It has been noted that ketones traditionally participate in a limited number of organic transformations, including the Baeyer–Villiger oxidation, the Beckmann rearrangement, and the Schmidt reaction. Transition-metal-catalyzed C–C activation reactions, which offer a feasible approach to simplifying the synthesis of complex molecules, have contributed significantly to the functionalization of ketone substrates over the past decade.² Nevertheless, the C–C activation of ketones via a radical-mediated strategy remains largely unexplored, possibly due to the lack of appropriate radical precursors. This limitation also restricts the effective conversion of ketones and their utilization in organic synthesis. According to Professor Zhang, the Norrish–Young reaction represents a potent method to cleave C–C bonds of ketones, yet its synthetic application has been constrained by issues of selectivity and practicality (Scheme 1a, left).³ “To date, three representative types of radical precursors, namely dihydroquinazolinone,⁴

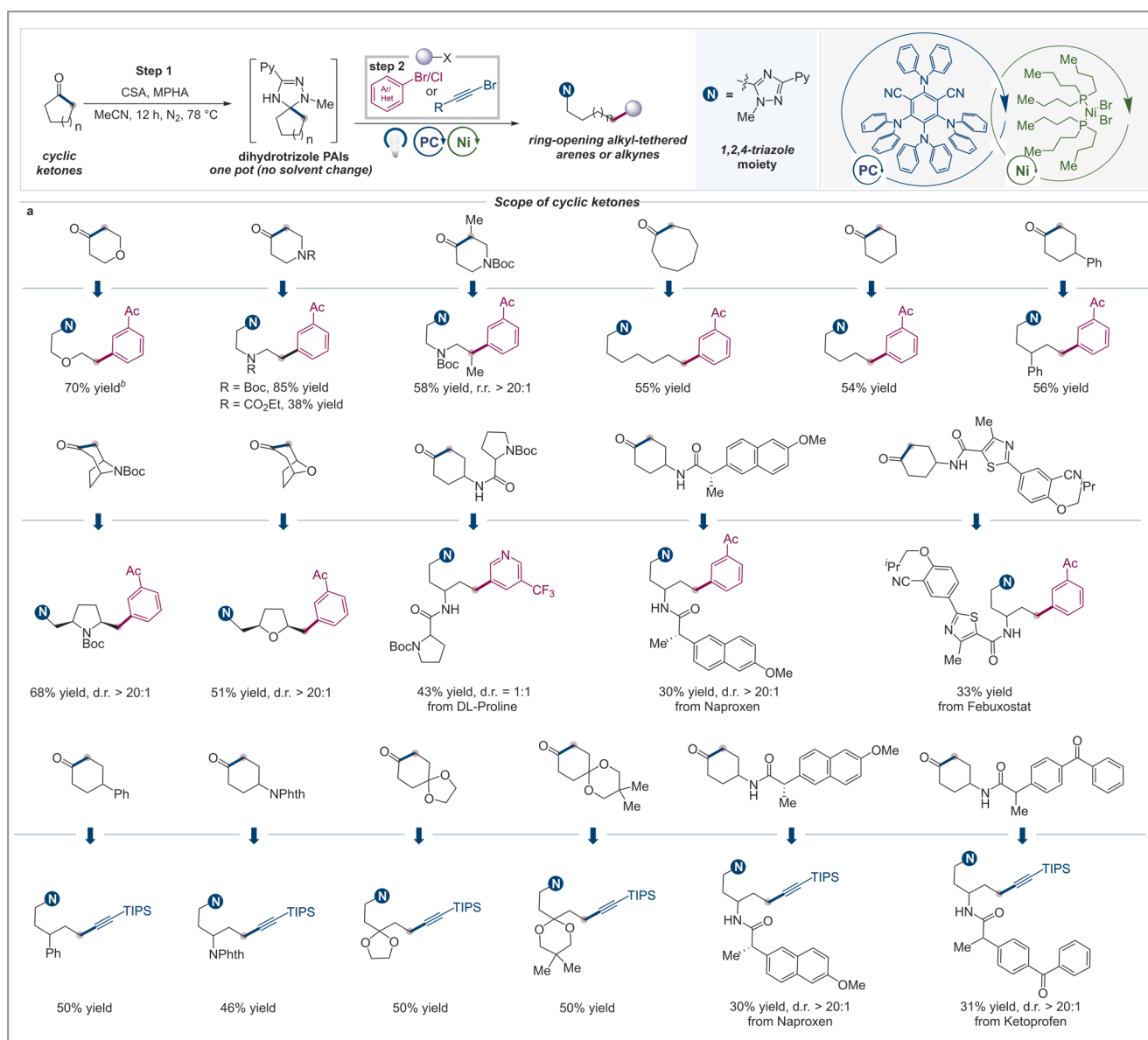


Scheme 1 C–C activation of ketone derivatives

dihydropyrazole⁵ and dihydrotriazole⁶ derivatives, have been employed to enable C–C activation of ketones. Nonetheless, the harsh reaction conditions and intricate substrate synthesis have strongly limited the substrate scopes and the reaction types (Scheme 1a, right),” explained Professor Zhang, who continued: “Our research focuses on addressing those key challenges associated with this methodology: 1) identifying a mild catalytic system to generate carbon-centered radicals; 2) simplifying substrate synthesis and realizing one-pot operations; and 3) expanding substrate scopes and reaction

types. Drawing inspiration from metallaphotoredox catalysis, we have successfully achieved the deacylative arylation and alkynylation of unstrained ketones under dual nickel/photo-redox catalysis, providing a reliable method for the preparation of structurally diverse alkyl-tethered arenes and alkynes.”

Professor Zhang explained: “The reaction commences with the *in situ* synthesis of a dihydrotriazole pre-aromatic intermediate (PAI) through the condensation of ketones with *N'*-methylpicolino-hydrazoneamide (MPHA). This is followed by the oxidative single-electron transfer (SET) from the PAI’s



Scheme 2 Selected examples of cyclic and drug-derived ketones

α -C–C bond to generate an alkyl radical, which is subsequently intercepted by Ni(II) species to form organometallic Ni(III) adducts, facilitating the formation of diverse C(sp³)-C(sp²)/C(sp) bonds with remarkable generality (Scheme 1b)."

"The reaction represents a novel approach to the deacylative coupling of unstrained ketones, complementing previous deacylative transformation of ketones," said Dr. Beibei Zhan, a co-corresponding author on the paper, who continued: "This protocol tolerates a wide range of ketones, particularly cyclic and drug-related ketones. Remarkably, the regioselective cleavage of the C–C bond predominantly occurs at a more sterically hindered position when employing an unsymmetrical cyclic ketone. Furthermore, a diverse array of aryl halides and alkynyl bromides bearing various functional groups are all compatible in the reaction (Scheme 2)."

"In the future, we will delve into the deacylative coupling reaction of ketones catalyzed by other transition metals," said Professor Zhang, who concluded: "Given the prevalence of the ketone functional group in organic chemistry, we anticipate

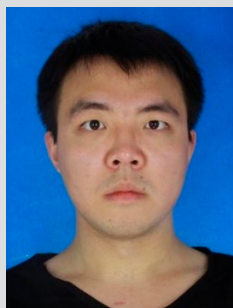
that the C–C bond activation of unstrained ketones could ultimately become a valuable addition to the chemist's toolbox for creating complex molecular scaffolds."

Matt's favorite

REFERENCES

- (1) L. Deng, G. Dong *Trends Chem.* **2019**, *2*, 183–198.
- (2) F. Song, B. Wang, Z.-J. Shi *Acc. Chem. Res.* **2023**, *56*, 2867–2886.
- (3) R. G. W. Norrish, C. H. Bamford *Nature* **1936**, *138*, 1016.
- (4) X.-Y. Lv, R. Abrams, R. Martin *Angew. Chem. Int. Ed.* **2023**, *62*, e202217386.
- (5) Y. Xu, X. Qi, P. Zheng, C. C. Berti, P. Liu, G. Dong *Nature* **2019**, *567*, 373–378.
- (6) X. Zhou, Y. Xu, G. Dong *J. Am. Chem. Soc.* **2021**, *143*, 20042–20048.

About the authors



B. Zhang

Boyi Zhang obtained his bachelor's degree in applied chemistry in 2021 from Tianjin University (P. R. of China). He will obtain his master's degree in 2024 from Hangzhou Institute for Advanced Study, University of Chinese Academy of Sciences (P. R. of China) under the guidance of Prof. Xiaheng Zhang. His research interests focus on C–C bond activation of ketones.



Dr. B. Zhan

Beibei Zhan received his PhD from Zhejiang University (P. R. of China) in 2020 under the supervision of Prof. Bing-Feng Shi. Subsequently, he joined the Hangzhou Institute for Advanced Study (HIAS), University of Chinese Academy of Sciences (P. R. of China) as a postdoctoral fellow in Prof. Biao Yu's group, where he contributed to the development of Cu-catalysed mild glycosylation. In 2022, he joined the HIAS as an assistant research fellow and his current research focuses on the deacylative transformations of ketones under metallaphotoredox catalysis.



Dr. H. Bai

Hui Bai received her bachelor's degree in chemistry in 2014 from China Agricultural University (Beijing, P. R. of China), and her PhD in chemistry in 2021 from the same university. Now, she is a postdoctoral scholar at Hangzhou Institute for Advanced Study, UCAS (P. R. of China) under the supervision of Prof. Xiaheng Zhang. In the Zhang group, she focuses on metallaphotoredox reactions.



K.-H. Wei

Kai-Hang Wei was born in Zhejiang province. He received his BS degree (2022) from Hangzhou Normal University (P. R. of China). He then joined Prof. Zhang's lab at Hangzhou Institute for Advanced Study, University of Chinese Academy of Sciences (P. R. of China) to pursue his MS degree in organic chemistry. His current research interest focuses on photoredox catalysis and transition-metal-catalyzed selective cross-coupling reactions.

*Prof. S. Nie*

Shenyou Nie was born in 1986 and received his BS degree (2009) from Wuhan University (P. R. of China). He completed his PhD (2014) at Shanghai Institute of Organic Chemistry (SIOC, P. R. of China) under the supervision of Prof. Biao Yu. He then worked as a postdoctoral researcher at the labs of Prof. Arun K. Ghosh (Purdue University, USA, 2015–2016) and Prof. Yongcheng Song (Baylor College of Medicine, USA, 2016–2020), respectively. He started his independent research at Chongqing Medical University (P. R. of China) in 2020. His research interests focus on the development of small-molecule inhibitors and degraders targeting ferroptosis and cancer, and construction of diverse compound libraries by employing the Ugi reaction, photoredox catalysis and C–H activation/domino strategies.

*Prof. X. Zhang*

Xiaheng Zhang obtained his PhD in 2015 from Shanghai Institute of Organic Chemistry (SIOC, P. R. of China) with Prof. Biao Yu. He then moved to Princeton University (USA) to pursue postdoctoral studies with Prof. David W. C. MacMillan. He started his independent research at Fudan University (P. R. of China) as an Assistant Professor in 2021. Then he took the position of Associate Professor of Chemistry at Hangzhou Institute for Advanced Study, University of Chinese Academy of Sciences (P. R. of China) at the end of 2021. His research interests include photoredox catalysis and carbohydrate chemistry.

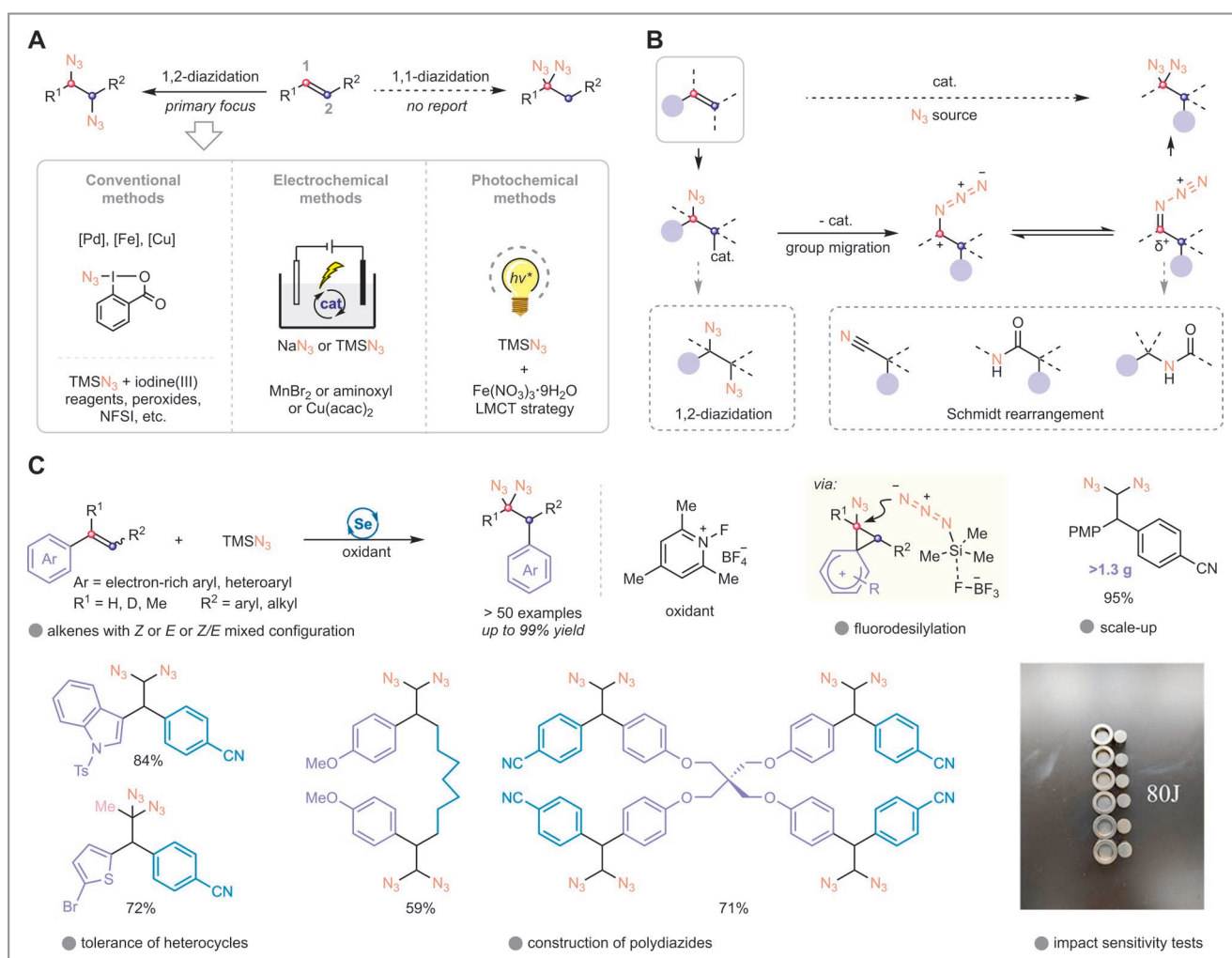
Catalytic 1,1-Diazidation of Alkenes

Nat. Commun. **2024**, *15*, 3632

Organic azides are of great importance in synthetic, materials, and biorthogonal chemistries. Azidative functionalization of alkenes is an important way to produce organic azides, especially alkyl azides. In a recent publication in *Nature Communications*, the group of Professors Xiaodan Zhao and Lihao Liao at Sun Yat-Sen University (P. R. of China) developed a selenium-catalyzed migratory 1,1-diazidation of aryl alkenes for the efficient synthesis of geminal diazides (Schemes 1B and 1C). “Compared to well-developed catalytic 1,2-diazidation of alkenes, the 1,1-diazidation version has not been re-

alized (Scheme 1A), although the obtained geminal diazides can serve as energetic molecules and act as valuable synthetic precursors,” said Professor Zhao. “Developing an efficient approach for 1,1-diazidation of alkenes has been a challenging task in the field of azide chemistry.”

Professor Zhao explained to SYNFORM the background of their work. “One of our research interests is to realize challenging transformations via selenium redox catalysis. Different from other electrophilic catalysts, the involved electrophilic selenium species exhibited the unique properties



Scheme 1 Catalytic diazidation of alkenes

of carbophilicity toward the alkene π bond and a convenient release from the intermediates. As an emerging aspect of main-group-element-based organocatalysis, this technique has become a powerful tool for functionalization of alkenes, especially in allylic functionalization, direct alkenyl C–H functionalization, and 1,2-difunctionalization,” he said, continuing: “Considering the great importance of geminal diazides, we wondered whether these molecules might be constructed in selenium-catalyzed 1,1-diazidation fashion (Scheme 1B), although this type of catalysis had remained elusive for the 1,1-difunctionalization of alkenes. It is gratifying that we have indeed achieved it (Scheme 1C).”

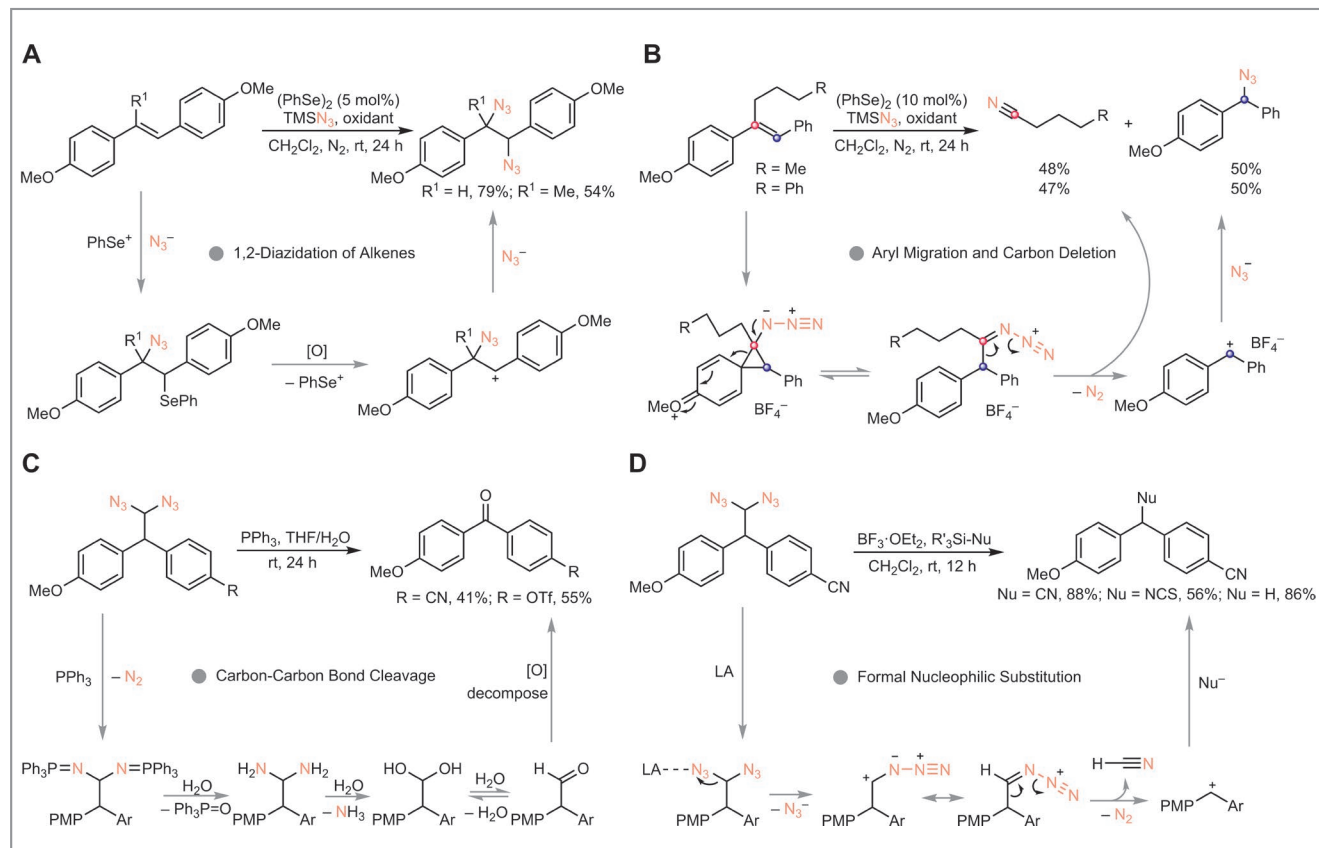
During the evaluation of reaction conditions, the authors discovered some interesting phenomena. “Tetrafluoroborate anion-bearing oxidants were found significantly better than triflate-bearing ones, suggesting that tetrafluoroborate anion might facilitate the release of azide anions from azidotrimethylsilane via fluorodesilylation,” said Professor Liao, adding: “In addition, both *Z*- or *E*-alkenes could be converted into the desired products efficiently, which is of great signi-

ficance for practical organic synthesis, owing to the easy availability of *Z/E* alkene isomers.”

With the optimized conditions in hand, the scope of substrates was evaluated systematically. “1,2-Disubstituted or trisubstituted alkenes with electron-rich aryl or heteroaryl groups could go through the migratory 1,1-diazidation to afford the geminal diazides smoothly,” graduate student Wangzhen Qiu said, continuing: “Besides, oligomeric alkenes could yield polydiazides in this catalytic system without difficulties, which might be attractive in materials science.”

“Compared to the well-developed 1,2-difunctionalization of alkenes, the corresponding 1,1-difunctionalization of alkenes is more challenging,” said Professor Zhao, adding: “It was found that the hypervalent iodine system, an important tool for 1,1-difunctionalization, could not furnish the desired geminal diazides no matter how catalysis or stoichiometry were varied, reflecting the advantages and uniqueness of selenium redox catalysis.”

As the simplest geminal diazide derivative, diazido-methane $\text{CH}_2(\text{N}_3)_2$ is highly explosive and vibration-sensitive.



Scheme 2 Some interesting reactions

To figure out whether the obtained geminal diazides are also so dangerous, the authors conducted a safety evaluation. “TGA-DSC analysis showed that some representative geminal diazides with relatively lower $(N_C+N_O)/N_N$ were stable under 118 °C, and standard fall hammer tests revealed that the most likely ‘dangerous’ sample was insensitive to impact (IS > 80 J),” remarked graduate student Qiu, who continued: “These results indicated that the obtained geminal diazides are relatively safe for conventional use, which might be the reason why the scale-up reactions (using alkenes in several hundred milligrams to one gram scale) could be handled routinely.”

In addition to the pursued catalytic 1,1-diazidation, the authors also observed other interesting reactions when using different substrates. “1,2-Diazidation occurred instead of 1,1-diazidation when stilbene derivatives with two electron-rich aryl groups were utilized as substrates (Scheme 2A), while aryl migration plus carbon deletion was observed when some trisubstituted alkenes were used, and the products were identified as diarylmethyl azides and nitriles (Scheme 2B),” said Professor Liao, adding: “These two reactions further enrich the field of selenium-catalyzed azidations of alkenes.”

Moving away from the conventional reactivities of organic azides, the unique reactivities of geminal diazides were also investigated. “Ketones were formed via carbon–carbon bond cleavage when geminal diazides were treated with triphenylphosphine under Staudinger reduction conditions (Scheme 2C),” Professor Liao said, continuing: “Interestingly, the geminal diazidomethyl moiety could act as a formal leaving group in the presence of a Lewis acid, facilitating the subsequent nucleophilic substitution (Scheme 2D).” The authors believe that these new reactivities might promote new applications of geminal diazides.

“This work represents the first successful example of catalytic 1,1-diazidation of alkenes, which is greatly complementary to the fields of alkene chemistry and azide chemistry,” Professor Zhao concluded, continuing: “It also exhibits the unique advantage of selenium redox catalysis, which offers a basis for the design of new reactions.”

Mattes Fenske

About the authors



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