People, Trends and Views in Chemical Synthesis

2021/06

SYNTHESIS Best Paper Award 2020: A Bond-Weakening Borinate Catalyst that **Improves the Scope of the Photoredox** α-C–H Alkylation of Alcohols

Highlighted article by K. Sakai, K. Oisaki, M. Kanai



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



Dear Readers,

Recently I did a check on how many of our invitations to contribute to SYNFORM are successful, which turned up an amazing ~60% acceptance rate! I believe this is truly great news, especially considering that only very busy authors of top articles published in the highest impact journals get a SYNFORM invitation. There is a nearly identical situation for the acceptance rate of our Young Career Focus interviews to Thieme Chemistry Journals Awardees, who are often super-busy early-stage academics with extremely packed diaries. And even more excitingly, on average each SYNFORM article is read and downloaded many hundreds of times within weeks of its online publication. This exceptional level of interest by our readership spurs us to constantly improve the quality of SYNFORM's articles, with the aim to serve the organic chemistry community by reporting on the newest scientific advances, facts, people, as well as international conferences. Unfortunately, coverage of the latter has been somewhat discontinued during the pandemic, but it will hopefully resume very soon and with renewed enthusiasm!! The cutting-edge quality of the science covered in this June 2021 issue is testament to the passion for chemistry we have at SYNFORM. The start could not be more pyrotechnic, with the very interesting SYNTHESIS Best Paper Award interview to the 2020 winners, K. Oisaki and M. Kanai (Japan), for the paper "A Bond-Weakening Borinate Catalyst that Improves the Scope of the Photoredox α-C-H Alkylation of Alcohols." The next article is a Young Career Focus interview with V. Pace (Italy), who elaborates on his group's research activity and contributions to the advancement of organic synthesis. The first Literature Coverage article comes next, with the highly innovative iron-catalysed asymmetric carboazidation of styrenes published in Nature Catalysis by X. Zhang and H. Bao (P. R. of China). Last but not least,

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the very intriguing work by J. Kanazawa, K. Miyamoto and M. Uchiyama (Japan) on the synthesis and α -cyclodextrin encapsulation of bicyclo[1.1.1]pentane derivatives.

Thank you so much for your continuing interest and enjoy your reading!!



Contact

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

SYNTHESIS Best Paper Award 2020: A Bond-Weakening Borinate Catalyst that Improves the Scope of the Photoredox α -C–H Alkylation of Alcohols

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Synthesis 2020, 52, 2171–2189

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

Professor Motomu Kanai, Dr. Kounosuke Oisaki and Mr. Kentaro Sakai from the Graduate School of Pharmaceutical Sciences at The University of Tokyo, Japan, are the recipients of the SYNTHESIS Best Paper Award 2020. The authors are recognized for their article '*A Bond-Weakening Borinate Catalyst that Improves the Scope of the Photoredox* α -*C*-*H Alkylation of Alcohols*' (Scheme 1). In announcing the award, Paul Knochel, Editor-in-Chief of SYNTHESIS, mentioned that the selection committee was impressed by the comprehensive study, including the history, optimizations, scope and limitations, of this conceptually new approach. This catchy C–H activation by the addition of a bond-weakening catalyst is expected to be used extensively by the synthetic community.

SYNFORM spoke with Professor M. Kanai, Dr. K. Oisaki and Mr. K. Sakai, who were happy to share some background information regarding the prize-winning paper as well as current research activities ongoing in their group.

his

Biographical Sketches



Professor M. Kanai

doctoral studies with Professor Laura L. Kiessling. In 1997, he returned to Japan and joined Professor Masakatsu Shibasaki's group at UTokyo as an assistant professor. After working as a lecturer (2000–2003) and an associate professor (2003–2010), he became a professor at UTokyo in 2010. He served as a principle investigator at ERATO Kanai Life Science Project (2011–2017), and is currently the head investigator of MEXT Grant-in-Aid for Scientific Research on Innovative Areas, 'Hybrid Catalysis' (2017–2022). He is a recipient of The Phar-

Motomu

Kanai

bachelor's degree from The Univer-

sity of Tokyo (UTokyo) in 1989 under

the direction of the late Professor

Kenji Koga. He obtained an assistant

professor position at Osaka Univer-

sity under the direction of Professor Kiyoshi Tomioka in 1992. He obtained his Ph.D. from Osaka University in

1995, and then moved to the Uni-

versity of Wisconsin, USA, for post-

received

maceutical Society of Japan Award for Young Scientists (2001), the Thieme Journals Award (2003), the Merck-Banyu Lectureship Award (MBLA) (2005), the Asian Core Program Lectureship Award (2008 and 2010, from Thailand, Malaysia, and China), the Thomson Reuters 4th Research Front Award (2016), and the Nagoya Silver Medal (2020). His research interests encompass the design and synthesis of functional molecules



Dr. K. Oisaki

Kounosuke Oisaki was born in 1980 in Tokushima, Japan, and received his Ph.D. from The University of Tokyo (UTokyo) in 2008 under the direction of Professor Masakatsu Shibasaki. He then moved to the University of California-Los Angeles, USA, for postdoctoral studies with Professor Omar M. Yaghi. In 2010, he returned to Japan and joined Professor Motomu Kanai's group at UTokyo as an assistant professor. He is currently working as a lecturer (since 2016). He has received The Pharmaceutical Society of Japan Award for Young Scientists (2018), the Mitsui Chemicals Catalysis Science Award of Encouragement (2018), the Chemist Award BCA (2018), and the Thieme Chemistry Journals Award (2019). His current research interest is directed toward the development of new synthetic organic chemistry, with a focus on organoradical-based chemoselective reagents/ catalysis for $C(sp^3)$ –H functionalizations and peptide/protein modifications.

Mr. K. Sakai

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Kentaro Sakai was born in 1994 and raised in Tochigi, Japan. He obtained his bachelor's degree (2017) and master's degree (2019) under the direction of Professor Motomu Kanai at The University of Tokyo. He is currently a Ph.D. student at the Graduate School of Pharmaceutical Sciences, The University of Tokyo. His current research focuses on the development of a new methodology for selective $C(sp^3)$ –H functionalization under visible-light irradiation.

INTERVIEW

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

Prof. M. Kanai, Dr. K. Oisaki and Mr. K. Sakai Over the decades, C–H functionalization has attracted much attention in organic synthesis to open underexplored synthetic routes of functional materials and drugs, enabling short synthesis of complex molecules and late-stage functionalization. A hybrid catalysis comprising visible-light photoredox catalysis and hydrogen-atom-transfer catalysis (PC-HAT) is particularly suitable for $C(sp^3)$ –H activation and functionalization. The PC-HAT system generates intermediary carbon radical species with a mild and green energy input (i.e., visible light), which is beneficial for achieving high functional-group tolerance. Previously reported PC-HAT systems, however, often suffer-

ed from moderate to low site-selectivity. Only the innately weakest or most hydridic $C(sp^3)$ –H bond was preferentially activated among multiple C–H bonds in a substrate organic molecule. Catalyst-controlled, on-demand site-selective $C(sp^3)$ –H functionalization is a long-standing challenge.

In this award-winning study, we conducted DFT-guided screening of bond-weakening catalysts (BWCs), which lowered the bond-dissociation energy (BDE) of alcoholic α -C(*sp*³)–H bonds via selective recognition. We identified a novel electron-deficient borinate catalyst combined with a PC-HAT system. The ternary hybrid catalysis promoted α -alkylation of alcohols containing various functional groups and innately weaker C–H bonds, such as a cyclic ethers and amides (Scheme 1). The substrate scope covered not only simple primary and secondary alcohols, but also a serine derivative and a homoserine-containing dipeptide, indicating potential applicability to late-stage functionalization of complex molecules.



Scheme 1 α-C–H Alkylation of alcohols promoted by PC-HAT-borinate BWC hybrid catalysis

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

Prof. M. Kanai, Dr. K. Oisaki and Mr. K. Sakai We originally aimed at developing site-selective $C(sp^3)$ -H functionalization by devising a new PC-HAT binary hybrid catalysis. However, we faced the general tendency that a $C(sp^3)$ -H bond containing the lowest BDE reacted. Therefore, we switched our strategy to develop a BWC that can lower the BDE of a specific $C(sp^3)$ -H bond. Assisted by DFT calculations, we discovered the first-generation BWC for alcoholic α -C(sp³)–H bonds, Martin's spirosilane (Adv. Synth. Catal. 2020, 362, 337–343).

The utility of our first-generation ternary hybrid catalysis was quite limited, however. This system was only applicable to primary alcohols and required highly oxidizing photoredox catalyst. Martin's spirosilane lowered the BDE value of alcoholic α -C(*sp*³)–H bonds by up to 2.3 kcal/mol. A more active BWC producing greater bond-weakening effects would broaden the scope. The DFT-guided screening of organoborons led us to identify borinate as a potent BWC in a very short period, exhibiting bond-weakening effects as large as 5.3 kcal/ mol. During the study, Taylor's group reported an excellent example of a ternary hybrid catalysis comprising PC-HAT and a borinic acid BWC, enabling site-selective α -C(sp³)–H alkylation of alcohols and sugars (J. Am. Chem. Soc. 2019, 141, 5149-5153).

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

Prof. M. Kanai, Dr. K. Oisaki and Mr. K. Sakai We are currently expanding BWC-promoted site-selective C(sp³)-H functionalization reactions beyond alkylation. Although carbon radicals are versatile active species for bond formation, reaction patterns are limited. Furthermore, catalyst-controlled stereoselective radical reaction is difficult. Our laboratory is incorporating a transition-metal-complex catalysis to PC-HAT systems, achieving radical polar crossover and metal-complexcatalyzed asymmetric reactions from C(sp³)–H bonds. Our lab reported that allyl radicals were generated from hydrocarbon feedstock alkenes through allylic $C(sp^3)$ -H activation by a PC-HAT. The thus-generated allyl radicals were trapped by a chiral chromium-complex catalyst to generate organochromium species, which were effective for asymmetric addition to carbonyl compounds (Chem. Sci. 2019, 10, 3459-3465; J. Am. Chem. Soc. 2020, 142, 12374–12381; Org. Lett. 2020, 22, 8584-8588). Our goal is to unify the controlled siteselectivity of BWC and diverse reaction patterns and stereoselectivity of metal-complex-catalysis within the framework of PC-HAT hybrid catalysis, enabling catalyst-controlled latestage diversification of complex multifunctional molecules, including proteins and sugars.

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

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> Prof. M. Kanai, Dr. K. Oisaki and Mr. K. Sakai Organic synthesis allows us to design and create new molecules, such as functional materials, pharmaceuticals, and agrochemicals, which are indispensably supporting our lives. Meanwhile, we need to protect the Earth by supplying molecules with high total efficiency and minimal waste in energy-saving and timeeconomical ways. Photoredox C-H functionalization is an approach that can meet such demands. The development of new catalytic C-H functionalization reactions with high site-, chemo-, and stereoselectivity will continue to boost complex molecule synthesis.

> Chemical modifications of biomacromolecules, such as nucleic acids, proteins, and polysaccharides, to produce hypernatural functions, is another challenge in current organic synthesis. These are not only chemically challenging, but also foreshadowing a great impact on life science. Radical chemistry is promising in this research direction due to its orthogonality to polar functional groups in biomacromolecules and compatibility with aqueous media. As the reaction scope of PC-HAT hybrid catalysis expands, we expect continuous advances in not only efficient molecular synthesis, but also functionalization of biomacromolecules. These are our goals for the future.

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

Prof. M. Kanai, Dr. K. Oisaki and Mr. K. Sakai The paper has postulated a new strategy for site-selective C-H functionalization using a PC-HAT catalytic system combined with a borinate BWC, clearly demonstrating substrate generality, selectivity, and mildness of the conditions.

SYNTHESIS is a prestigious journal with great history for more than a half century. We experienced, several times in the past, being saved by methods reported in SYNTHESIS when projects were blocked in every direction. Therefore, receiving the SYNTHESIS Best Paper Award 2020, named after the journal, is a great honor for us. The award will highlight the value of our research and expose our findings to a wider range of readers. We are highly encouraged by receiving this award to continue our research by doing many more experiments and calculations.

Another famale

Young Career Focus: Prof. Vittorio Pace (University of Torino, Italy)

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Background and Purpose. SYNFORM regularly meets young up-and-coming researchers who are performing exceptionally well in the arena of organic chemistry and related fields of research, in order to introduce them to the readership. This Young Career Focus presents Prof. Vittorio Pace (University of Torino, Italy).

Biographical Sketch



Prof. V. Pace

Vittorio Pace graduated in Pharmacy at the University of Perugia (Italy) in 2005 and received a PhD in Chemical Sciences from the Complutense University of Madrid (Spain) under the guidance of Prof. A. R. Alcántara and J. V. Sinisterra in 2010. In 2009 he also obtained a postgraduate MSc in Drug Design and Development from the University of Pavia (Italy). He realized three postdoctoral experiences

at the University of Vienna (Austria; Prof. Holzer, 2010– 2011 – Mach fellow), The University Manchester (UK; Prof. Procter, 2011–2013) and Stockholm University (Sweden; Prof. Olofsson, 2013–2014). Then he started his independent career at the University of Vienna in August 2014 as Group Leader in Synthetic Chemistry, receiving his Habilitation for Pharmaceutical Chemistry from the University of Vienna in 2016. After being promoted to tenure-track professor in Drug Synthesis in 2018, in 2020 Prof. Pace became Chair of Organic Chemistry at the University of Torino (Italy). He realized several placements as visiting scientist/professor at Perugia, Sassari, Palermo, Keio (Japan), Barcelona, and Thandavur (India) – among others.

During his career, Prof. Pace has been awarded several prizes including the Vincenzo Caglioti by the Accademia Nazionale dei Lincei, the Ciamician Medal by the Division of Organic Chemistry of the Italian Chemical Society, the Innitzer Award, the Young Investigator Award by the Faculty of Life Sciences of the University of Vienna, the La Roche–Hoffman Prize by the European Federation of Medicinal Chemistry, the Habilitation Award of the Austrian Chemical Society and the Thieme Chemistry Journals Award – among others. During his career, Prof. Pace has supervised 8 PhD theses and several postdoctoral associates, besides MSc and BSc students. He has been a full professor of Organic Chemistry at the Uni-

versity of Torino since March 2020.

INTERVIEW

SYNFORM What is the focus of your current research activity?

Prof. V. Pace Since the launching of my research group in Vienna in 2014 we have been actively engaged with the development of homologation tactics for selectively introducing functionalized methylene (CH₂) fragments into a given organic array. To this end, we take advantage of the intrinsic nucleophilic behavior of the so-called lithium carbenoid reagents, which deliver the methylenic fragments with high efficacy and chemocontrol onto a proper carbon electrophilic platform. Furthermore, we became interested in designing synthetic transformations whose initial step is represented by the homologation event and, upon modulating the reaction conditions, rearrangement sequences may be effectively triggered. At the same time, the high significance of fluorinated scaffolds - as optimal modulators of physical-chemical properties - inspired us to undertake studies for the introduction of fluorine-containing carbanions in nucleophilic regime.

SYNFORM When did you get interested in synthesis?

Prof. V. Pace During my MSc in Pharmacy at the University of Perugia (Italy) I developed a strong interest in synthesis, which guided the orientation of my subsequent studies. I received my PhD at the Complutense University of Madrid (Spain) with Profs. Alcántara and Sinisterra, working on the synthesis of enantiopure haloketone precursors of biologically relevant structures. A short-term placement as a PhD visiting student in the laboratory of Prof. De Kimpe in Gent (Belgium) introduced me to the prototypal C1-synthon - diazomethane and I would consider that my first touch with homologation chemistry. Later, I expanded my knowledge in synthesis during my postdocs at Vienna (Prof. Holzer), Manchester (Prof. Procter) and Stockholm (Prof. Olofsson). Together, these experiences provided me with the skills for starting my independent career in Vienna in 2014, culminating with the Habilitation in 2016 and the Chair in Organic Chemistry at the University of Torino in March 2020.

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

Prof. V. Pace Organic synthesis plays a central role in modern society: there is almost no field of our life that doesn't benefit from the contributions of the art of making molecules. This is particularly evident in biomedical research but also encompasses materials and agrochemical sciences. *inter alia*. Accessing optically active substances continues to fascinate chemists and, in my opinion, there is a huge need to implement strategies for this purpose: it would elevate the chemical lab towards the ideal lab, namely live organisms! Both systems are based on the same chemical rationale and, if we were able to fully understand and explain a biochemical cascade, why not attempt to emulate it in vitro? I am fully convinced that the canonical nucleophilic-electrophilic paradigm could still drive new directions of synthesis with a touch of fantasy added by scientists... As a chemist working with carbanions, I am excited to see complex syntheses solved with concepts introduced by Grignard more than a century ago. In summa, these are only a few of the seminal works directing our imagination and stimulating our research! Critical for the operator and his/ her success is making them flexible to current needs. This is what I try to apply to my own work. Nada más...

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

Prof. V. Pace As briefly mentioned above, we are interested in formally introducing single (functionalized) carbon atoms into an organic skeleton, using halocarbenoids as C1delivery synthons (Scheme 1). Some crucial aspects of their reactivity are worth mentioning: a) they manifest ambiphilic reactivity (nucleophilic vs. electrophilic), tunable by properly selecting the metal, with lithium analogues having predominant carbanion-like features; b) the constitutive instability has historically represented the Achilles heel of these species and taming or eliminating it is often a critical part of our studies. For the sake of clarity, recent studies by others indicate that microfluidic techniques could prevent these degradative phenomena. Although the initial applications of carbenoids in synthesis date back to the 1960s, later searches for new elements of reactivity have focused mainly on the homologation of heteroatoms. The venerable Matteson reaction is one of the most beautiful examples, as recently documented in brilliant works by Aggarwal and Blakemore.

In this context, my group looks at developing new reactions of carbenoids with carbon electrophiles: previously, these species have been studied only marginally and thoroughly applied to intuitive transformations such as the carbonylepoxide conversion, the synthesis of α -haloketones from esters, inter alia. We recognized that a plethora of carbon-centered electrophilic manifolds could be reacted with carbenoids and, upon the proper modulation of the conditions, complex architectures could be accessed through a single synthetic operation. This is because, besides what we call the interrupted homologation - i.e. the final compound features the unmodified inserted fragment during the homologation event the innate reactivity of a given CHXY motif represents an inspirational element for elaborate unusual rearrangements and sequential reactions. This is, at the moment, one of the hottest topics that we are pursuing.



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In parallel, the group looks at some additional aspects of carbenoid-like reactivity: a) the implementation of the stability of halomethyl-type metal units through formal transmetalations to Sn, Se, Si or Ge (we refer to these as shuttle reagents); b) the use in nucleophilic mode of fluorinated elements, usually considered elusive species in preparative processes, being the commercially available and easy-tomanipulate liquid fluoroiodomethane (bp 52 °C), an excellent F-containing C1 source amenable for metalation, deprotonation or nucleophilic substitution; c) the outstanding performance of Weinreb amides as acylating placeholders for a wide series of functionalized organolithiums; we succeeded in isolating and characterizing for the first time the putative hemiaminal-type tetrahedral intermediates; d) the forging of (thio)amide linkages through nucleophilic additions of formal carbanions to heterocumulenes. Discovered by Gilman in the early 1920s, these processes provide extremely versatile strategies whose efficiency favorably compares with more sophisticated techniques, thus showing once again that the nucleophile-electrophile classical reactivity still drives the new horizons in synthesis!

Finally, I am delighted to edit for Wiley a book on the topic – Homologation Reactions. Reagents, Applications and Mechanisms – in which 25 world-leading chemists bring together the most recent advances on the exciting formal targeted delivery of single C1 atoms.

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

Prof. V. Pace The merging of homologation events with conceptually distinct transformations is undoubtedly our most significant contribution to synthesis. I am referring to the operationally simple conversion of an unsaturated ketone to the corresponding homologated fully α -substituted aldehyde: indeed, the design of a chemical sequence constituted by three completely disconnected events (homologation -Meinwald rearrangement – aldenolate electrophilic trapping) enables the rapid access to complex motifs in just one pot. Also, we build up robust telescoped homologations on the reactivity of trifluoromethyl chloroimidates with carbenoids, establishing genuine chemoselective processes tunable at the operator's wish (nature of the halogen of the carbenoid): so, treating the same starting material with different carbenoids (or modulating the stoichiometry) results in different products, as a result of the diverse chemical pathways triggered by the conditions. In this section, I cannot forget to mention the first direct fluoromethylation tactic with fluoromethyllithium: in collaboration with my friend and colleague - Prof. Renzo Luisi, Univ. Bari (Italy) – we recognized how to lithiate ICH_2F and then played around with the delivery of nucleophilic CH_2F to several electrophiles. Indeed, that was the missing piece in lithium carbenoid chemistry: the preparative use of the fluorinated analogue for introducing the fluoromethyl fragment in a highly convenient and straightforward way. Having developed this concept means having removed *de facto* unnecessary operations: installation and removal of stabilizing elements on the F-carbanion.



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Iron-Catalysed Asymmetric Carboazidation of Styrenes

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Nat. Catal. 2021, 4, 28-35

Professor Hongli Bao (Fujian Institute of Research on the Structure of Matter, Chinese Academy of Sciences, P. R. of China) recalls that one particular research question puzzled her at the onset of the research program that eventually led to the title paper: What will happen when a carbon radical meets a metal species? "Three scenarios are detailed in Professor Jav K. Kochi's paper (Scheme 1),¹" explains Professor Bao: "i) singleelectron transfer from the radical to the metal-ligand (M-G) species, forming a carbon cation which is subsequently either deprotonated or attacked by nucleophiles in the reaction environment; ii) ligand (G) transfer from the metal species M-G to the radical without obvious interaction between two reactants; this process is also called outer-sphere group transfer or radical substitution mechanism by other chemists; iii) the radical combines with the M-G metal species forming a high-valent metal species M(n+2), which undergoes reductive elimination to deliver a product; the latter reaction mode is known as an inner-sphere pathway.2"

According to Professor Bao, among these three modes, normally the inner-sphere pathway is utilized in asymmetric synthesis, given that the C–M bond brings two coupling partners close in a chiral environment. She continued: "Conversely, due to the lack of moderate/strong interactions – e.g. covalent, dative, ionic, or hydrogen bonds – between two reaction partners, the stereocontrol through the outer-sphere pathway is extremely challenging, if not entirely impossible to achieve. But as Louis Pasteur once said: 'The universe is asymmetric and I am persuaded that life, as it is known to us, is a direct result of the asymmetry of the universe or of its indirect consequences.' So, at the very beginning of the chirality-preference determination, a well-defined chiral environment with strong interaction was unlikely to exist and a weak interaction was therefore more likely to be a trigger." Professor Bao and her research group are extremely interested in seeking to achieve stereocontrol in the outer-sphere radical reactions by harnessing weak interactions. Professor Bao said: "Before we began our exploration, there was only one successful precedent of stereoselective outcome involving a free untethered radical in enantioselective Kharasch addition reactions, which was reported by Professor Joseph Ready.³"

"Our journey in this field began by studying radical azidation, which is a powerful approach to incorporate the nitrogen element," explained Professor Bao (Scheme 2). She continued: "Although many achiral or racemic versions of radical azidations have been developed, the catalytic chiral radical azidation with high levels of enantiocontrol is unprecedented. Many previous studies on azidation reactions indicated that metal-catalyzed radical azidation often involves intermolecular transfer of an azido group from the metal catalyst to a carbon radical.⁴ Such radical group transfer reactions do not involve interactions between metal species and radicals, therefore few believed that this type of transformation could be enantioselective."

Professor Bao and Professor Xinhao Zhang (Peking University Shenzhen Graduate School, P. R. of China) thought differently. "We postulated that the rigid azido group may keep



Scheme 1 Reaction pathways between carbon radicals and metal species







Scheme 2 Radical carbo-azidation reaction



Scheme 3 Mechanism and scope of the new radical azidation reaction of styrenes

two reaction partners at a distance of weak interactions," said Professor Bao. She continued: "This system could then be an opportunity to design an asymmetric outer-sphere pathway. Two brave PhD students, Liang Ge and Huan Zhou, started to work on this project. To solve this problem, the chiral pocketlike catalyst, which contains a quasi-macrocyclic plain structure with an iron atom in the center and bulky groups on the side as steric hindrance, was designed and synthesized. With this catalyst, the first catalytic asymmetric radical carbo-azidation was accomplished. Feedstock chemicals such as CBr₄, CHI₃, CHBr₃ and other alkyl bromides or iodides are suitable carbon sources, while the alkene substrate is limited to styrenes.⁵"

After achieving positive experimental results (Scheme 3), the group conducted mechanistic studies to verify whether this was truly a group transfer reaction. "Many people feel profoundly that enantioselectivity in metal-catalyzed radical reactions indicates instead an inner-sphere, high-valent-metal pathway," said Professor Bao, who went on to explain: "The DFT studies by Dr. M. Chiou supported the proposed group transfer pathway and revealed the origin of the chirality control. This catalyst recognizes the carbon radical by π and van der Waals interactions whose bonding energies are very small and generally less than 3 kcal/mol. The capture of critical intermediates by HRMS studies and other experiments like radical clock also supported the proposed mechanism."

"Many metal-catalyzed radical reactions undergo the group transfer mechanism, and the enantioselective control in these reactions is no longer mission impossible," said Professor Bao, who concluded: "Our work should shed light on asymmetric radical reactions and may well lead to other enantioselective group transfer reactions."

Anattes Janake

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About the authors



Liang Ge graduated from Huainan Normal University (P. R. of China) in 2012 and received his Master's degree in 2016 from Hefei University of Technology (HFUT, P. R. of China) under the guidance of Prof. Yougui Li. He studied as a visiting student at Fujian Institute of Research on the Structure of Matter (FJIRSM), CAS (P. R. of China), under the guidance of research Prof. Hongli Bao from 2014 to 2016. Currently,

L. Ge

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he is carrying out his Ph.D. studies in the same research group at FJIRSM.



Dr. H. Zhou



Dr. M. F. Chiou

Huan Zhou obtained a BS degree in chemistry from Huaiyin Normal University (P. R. of China) in 2014. She did her PhD work under the supervision of Prof. Hongli Bao in 2019 at FJIRSM. Now, she is pursuing postdoctoral research in Prof. Xin-Yuan Liu's research group at South University of Science and Technology (P. R. of China). Her research interest is transition-metalcatalyzed asymmetric radical involved reactions.

Mong-Feng Chiou obtained his B.S. and Ph.D. degrees from Fu Jen Catholic University (P. R. of China) under the supervision of Prof. Wen-Shyan Sheu. His major studies are in the field of physical and computational chemistry, and his research interest is the reaction mechanism of metal-catalyzed organic chemistry for his postdoctoral studies.

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Literature Coverage

Synform



Prof. X. Zhang

Xinhao Zhang studied chemistry at the University of Science and Technology of China (P. R. of China), receiving his diploma in 2002. He did his PhD work under the supervision of Prof. Yun-Dong Wu at the Hong Kong University of Science and Technology (P. R. of China). After graduating in 2007, he received an Alexander von Humboldt Research Fellowship, and pursued postdoctoral research in Prof. Helmut Schwarz's research group at

Technische Universität Berlin (Germany). In 2011, he joined the faculty of Peking University Shenzhen Graduate School (P. R. of China) where he has focused on the understanding of reaction mechanisms in catalysis and developing promising catalysts by combining mass spectrometry and computational chemistry.



Prof. H. Bao

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Hongli Bao received her B.S. degree in chemistry from the University of Science & Technology of China (P. R. of China) in 2002. She obtained her Ph.D. from the joint program of the Shanghai Institute of Organic Chemistry (P. R. of China) and the University of Science & Technology of China (P. R. of China) in 2008 with Professor Kuiling Ding and Professor Tianpa You. She joined the Tambar lab in 2009 and received the UT South-

western Chilton Fellowship in Biochemistry in 2012. She started her independent career in 2014 at FJIRSM, Chinese Academy of Science. She is interested in developing new metal-catalyzed reactions and asymmetric catalysis.

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α-Cyclodextrin Encapsulation of Bicyclo[1.1.1]pentane Derivatives: A Storable Feedstock for Preparation of [1.1.1]Propellane

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[1.1.1]Propellane is a highly strained molecule that represents the most convenient starting material for the synthesis of the bicyclo[1.1.1]pentane (BCP) unit, which is now widely recognized as a three-dimensional (3D) bioisostere of the benzene ring. Replacement of *para*-phenyl derivatives with 1,3-disubstituted BCP scaffolds can improve metabolic stability, solubility, and membrane permeability (Scheme 1A).¹ However, the lack of straightforward and versatile synthetic methodologies to access multi-functionalized BCP derivatives is a significant impediment to realizing the full potential of this promising scaffold.² To address this synthetic challenge and to contribute to the field of drug discovery, the group of Professor Masanobu Uchiyama from The University of Tokyo (Japan) started a project to develop innovative synthetic tools to access a variety of BCP derivatives.

"Synthetic methodologies that can access 3D drug-like scaffolds are very important in modern drug discovery," said Professor Uchiyama. "In particular, 3D scaffolds with higher Fsp³ (fraction of sp³ carbon atoms) values let us escape from the landscape of "flat" molecules and open up a much larger structural space, contributing to the development of drugs with superior physical properties and improved safety.³"

Professor Uchiyama explained that [1.1.1]propellane, which is now recognized as the key precursor of BCPs, features a remarkable inverted tetrahedral geometry at the bridgehead carbons. "The nature of the bond between the bridgehead carbons (covalent, charge-shift bond, singlet biradicaloid, or no bond) of [1.1.1] propellanes has been addressed in a number of theoretical and experimental studies, which have sometimes led to conflicting conclusions," said Professor Uchiyama: "In 2017, we reported a radical multicomponent carboamination of [1.1.1]propellane to form C-C and C-N bonds simultaneously on a BCP scaffold for the first time.⁴ This reaction provides easy access to a wide range of novel multi-functionalized BCP derivatives. These products are easily transformed into a variety of synthetically useful drug-like 3-functionalized BCPamines. Thus, this methodology opened up previously inaccessible drug-like chemical spaces."

"In subsequent work, we focused on the creation of a versatile synthetic platform for BCP scaffolds. Commonly used BCP intermediates have symmetrical structures, and multiple synthetic operations are needed to transform them into unsymmetrically functionalized BCP derivatives," said Professor Uchiyama. He continued: "In 2020, we developed a silaboration of [1.1.1]propellane, enabling direct introduction of B and Si functional groups onto the BCP scaffold.⁵ The silylborated BCP can be obtained on a gram scale in a single step without the need for column-chromatographic purification, and is storable as well as easy to handle. Thus, it serves as a versatile synthetic intermediate, whose B–C and Si–C bonds can be used as footholds to access unsymmetrically 1,3-disubstituted BCP scaffolds."

The next challenge for the group was an efficient preparation of [1.1.1]propellane, which remains the most important precursor for BCP derivatives.⁶ According to Professor Uchiyama, little progress has been made in the preparation of [1.1.1]propellane since the first practical synthesis in 1985 by Szeimies,⁷ and several fundamental issues remain to be addressed (Scheme 1B). He then went on to list them: "(1) [1.1.1] propellane is currently synthesized from tetrahalide 1 and 2 equivalents of highly active organolithium reagent (MeLi or PhLi), and the reaction conditions must be strictly controlled; (2) [1.1.1]propellane thus synthesized is isolated by distillation and hence is obtained as an ethereal solution (normally in Et₂O), which can be problematic if the subsequent reaction requires a different solvent; (3) [1.1.1]propellane is thermally and chemically labile, so its solution should, in principle, be freshly prepared prior to use. In our paper, we describe α -cyclodextrin (α -CD) encapsulation of BCP derivatives, providing a bench-top-storable format for these derivatives," explained Professor Uchiyama. He continued: "We also developed simple protocols for deiodination reaction of 1,3-diiodo BCP (I-BCP-I) to afford [1.1.1]propellane. Together, these findings provide for the first time a simple methodology for on-demand preparation of [1.1.1]propellane in a wide range of solvents (protic/aprotic/polar/non-polar) under mild conditions (Scheme 1C)."

The group investigated host–guest complex formation with various host molecules (α -/ β -/ γ -CDs, calix[n]arenes (n = 4-6), pillar[n']arenes (n' = 5, 6), or 18-crown-6-ether), and serendipitously found that only α -CD gave a complex of I–BCP–I encapsulated in two molecules of α -CD. Surprisingly, the α -CD supramolecular capsule could incorporate a wide range of BCP derivatives: the corresponding ternary complexes of



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Scheme 1 (A) Pharmaceutical applications of the bicyclo[1.1.1]pentane (BCP) scaffold. (B) Preparation of [1.1.1]propellane by Szeimies *et al.* (C) This work.



Scheme 2 (A) Encapsulation of α -CD and BCP derivatives. (B) X-ray crystal structure of $(\alpha$ -CD)₂ \supset Ac-BCP-Ac (CCDC 2036538). (C) Sublimability of $(\alpha$ -CD)₂ \supset Br-BCP-Br and Br-BCP-Br at 25 °C. (D) Photostability of $(\alpha$ -CD)₂ \supset I-BCP-I and I-BCP-I under ambient air and fluorescent lighting conditions. (E) Release from α -CD capsule and optimized protocols for the preparation of [1.1.1]propelane.

other 1,3-disubstituted BCPs (X-BCP-Y) were obtained in high vields (81–95%) (Scheme 2A). Professor Uchiyama remarked: "These complexes were precipitated in water and readily collected by simple filtration. A single-crystal X-ray diffraction analysis clearly showed the complete uptake of 1 equivalent of Ac–BCP–Ac inside the head-to-head dimeric α -CD capsule (Scheme 2B). Encapsulation affords great benefits to the synthetic chemistry of BCPs by overcoming the intrinsic disadvantages of BCP synthons, such as volatility, sublimability, and low boiling point. For example, encapsulation converted Br-BCP-Br, which is oily and volatile at room temperature, into a stable and easy-to-handle powder (Scheme 2C). In addition, the photostability of I-BCP-I was greatly improved by encapsulation (Scheme 2D). Thus, α-CD encapsulation endows BCPs with unprecedented chemical, thermal, photo-, and airstability, and provides the first bench-top-storable source for these derivatives. Finally, we confirmed that the encapsulated I–BCP–I could be converted into [1.1.1]propellane, the goldstandard intermediate for BCP synthesis. As a result of various investigations, we developed a method for quantitative decapsulation and conversion of I–BCP–I to [1.1.1]propellane under mild conditions, enabling on-demand preparation of [1.1.1] propellane in a wide range of solvents (protic/aprotic/polar/ nonpolar) (Scheme 2E).⁸"

Professor Uchiyama concluded: "We believe this methodology represents an important advance in the synthetic chemistry of BCPs and related 3D structures, and will expand the chemical space available for medicinal chemistry, synthetic chemistry, and materials sciences."



Biographical Sketches



From left: Prof. Dr. K. Miyamoto, Prof. Dr. M. Uchiyama, Prof. Dr. J. Kanazawa

Junichiro Kanazawa received his B.Sc. in 2011 and his M.Sc. in 2013 from The University of Tokyo (Japan) under the direction of Professor Masanobu Uchiyama. He has worked as a medicinal chemist at Japan Tobacco Inc. (Japan) from 2013, and has been a visiting researcher at RIKEN (Japan) since 2015. He received his Ph.D. in 2018 from the University of Tokyo under the direction of Professor Masanobu Uchiyama. He has been an Assistant Professor at the Graduate School of Pharmaceutical Sciences, The University of Tokyo since 2019. His research interests include the development of new reactions, and computational chemistry.

Kazunori Miyamoto received his Ph.D. in 2008 from the University of Tokushima (Japan). He was appointed as an Assistant Professor at the Graduate School of Pharmaceutical Sciences, University of Tokushima, in 2005. He moved to the Graduate School of Pharmaceutical Sciences, The University of Tokyo (Japan), as a Lecturer in 2014 and was promoted to Associate Professor in 2019. His research interests include hypervalent halogen compounds and the development of organic reactions based on the unique characteristics of the elements and compounds.

Masanobu Uchiyama received his Ph.D. in 1998 from The University of Tokyo (Japan). He was appointed as an Assistant Professor at the Department of Pharmaceutical Sciences, Tohoku University (Japan), in 1995. He moved to the Graduate School of Pharmaceutical Sciences, The University of Tokyo, as an Assistant Professor in 2001 and was promoted to Lecturer in 2003. He moved to RIKEN (Japan) as an Associate Chief Scientist (PI) in 2006. He has been a Professor at The University of Tokyo since 2010. He was promoted to Chief Scientist at RIKEN in 2013 (Joint Appointment), and is also a Professor of Research Initiative for Supra-Materials (RISM) at Shinshu University, Japan (Cross Appointment). His research interests include the development of new reactions, new materials, and new functions based on the integration of theoretical calculations and synthetic chemistry.

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