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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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.

Biographical Sketches

Professor M. Kanai

Motomu Kanai received his bachelor's degree from The University of Tokyo (UTokyo) in 1989 under the direction of the late Professor Kenji Koga. He obtained an assistant professor position at Osaka University under the direction of Professor Kiyoshi Tomioka in 1992. He obtained his Ph.D. from Osaka University in 1995, and then moved to the University of Wisconsin, USA, for postdoctoral 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 Pharmaceutical 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

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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

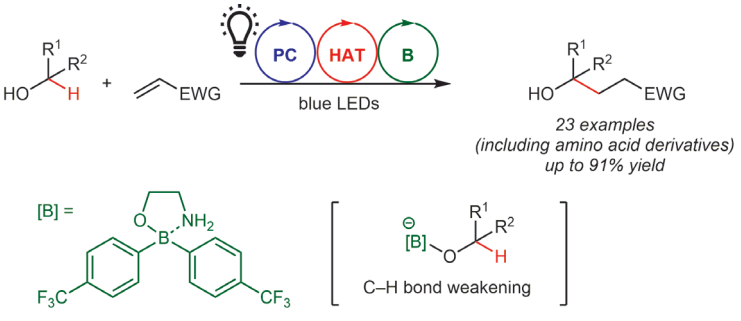
Kentaro Sakai was born in 1994 and raised in Tochigi, Japan. He obtained his bachelor's degree (2017) and master's degree (2019) under the direction of Professor Motomu Kanai at The University of Tokyo. He is currently a Ph.D. student at the Graduate School of Pharmaceutical Sciences, The University 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 award-winning 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 suffered 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

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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(sp^3)–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(sp^3)–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(sp^3)–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-complex-catalyzed asymmetric reactions from C(sp^3)–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 site-selectivity of BWC and diverse reaction patterns and stereoselectivity of metal-complex-catalysis within the framework of PC-HAT hybrid catalysis, enabling catalyst-controlled late-stage 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?*

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 time-economical 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.

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