Remote Steric Control for Undirected *meta*-Selective C–H Activation of Arenes

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According to Dr. Laurean Ilies, from the RIKEN Center for Sustainable Resource Science (Saitama, Japan), a major goal of modern synthetic chemistry is the creation of organic molecules in the most straightforward and efficient manner possible. "For this purpose, the use of a metal catalyst to directly introduce functionality into a simple or complex organic molecule (transition-metal-catalyzed C–H activation) has received much attention," said Dr. Ilies. "However, a serious problem arises: even simple organic molecules have many C–H bonds, and steering the catalytic species towards the desired site is difficult. This problem is familiar even to students of introductory basic organic chemistry, who often encounter questions about *ortho*/*meta*/*para* selectivity in the reaction of arenes." The research described in a recent article published in Science by the Ilies group provides a new solution to the selectivity problem. Inspired by the lock-and-key model of enzymatic catalysis, the authors designed a new catalytic system which creates a molecular pocket that fits an arene substrate only in a determined orientation, thus controlling the selectivity. They demonstrated this concept for the meta-selective functionalization of simple arenes such as alkylbenzenes, anilines, and phenols, and for the late-stage selective functionalization of complex drug molecules.

"It can be said that the seeds of this project were planted more than 10 years ago, when I was an assistant professor at the University of Tokyo in Japan (working with Prof. Eiichi Nakamura), and Sobi Asako was a Ph.D. student in the same group (2009–2014)," said Dr. Ilies. He continued: "We were working on iron-catalyzed functionalization of C–H bonds,[1] and found that the key to controlling these reactions was the use of a rather complicated 'directing group': an organic group (in this case an amide bearing 8-aminoquinoline) that must be installed onto the substrate to coordinate the metal catalyst and facilitate reactivity and selectivity."

In 2018, Dr. Ilies started a new research group at RIKEN, and one major idea was to get rid of the directing group and achieve a more general strategy for the selective functionalization of various organic molecules. But despite many attempts, success was elusive. "Dr. Asako was at that time assistant professor at Okayama University (Japan), working on a different chemistry (molybdenum catalysis and organosodium chemistry), but I convinced him to join the new team at RIKEN," remarked Dr. Ilies. By chance, also in 2018 the late Prof. Daisuke Uemura, whom Dr. Ilies knew from his student days when they were playing tennis together, asked them to write a book on C–H activation. "While building up the laboratory there was plenty of time to think about the contents of the book, and to analyze in more depth the unsolved problems in C–H activation and the known strategies in the literature," explained Dr. Ilies. He continued: "At this point I would like to acknowledge Dr. Takumi Yoshida, the first member of the Ilies team, who brought significant contributions both to the

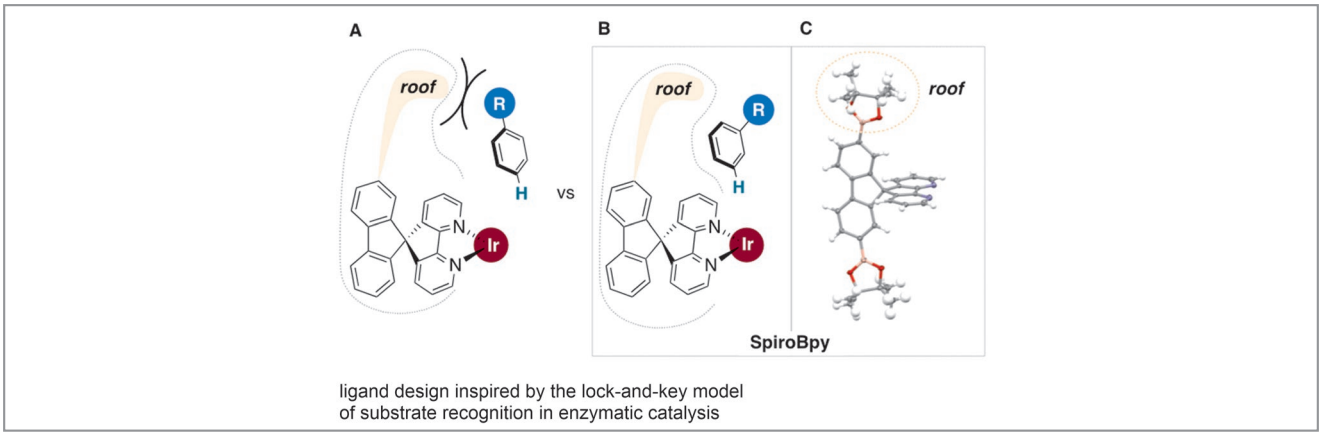

Figure 1 The design of the spirobipyridine (SpiroBpy) ligand

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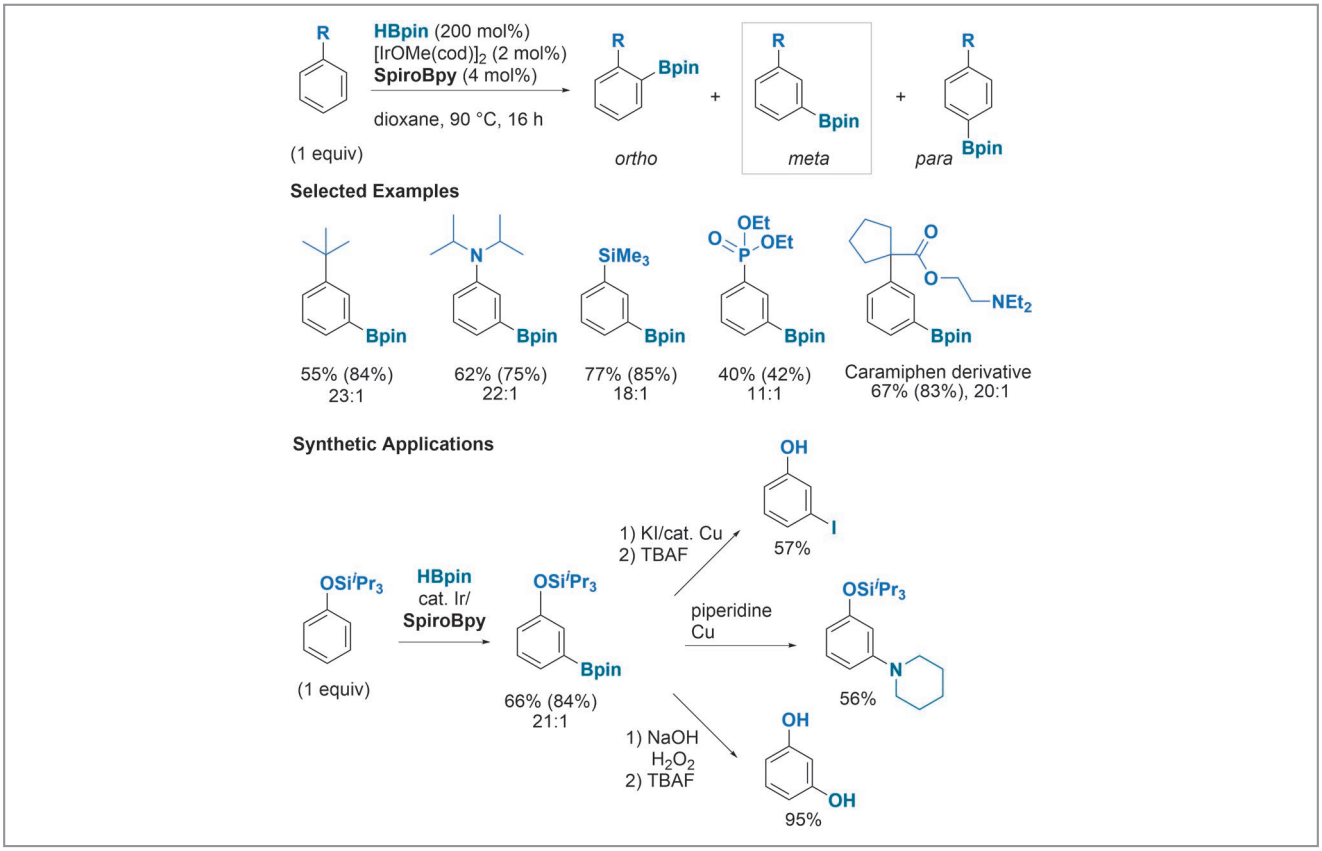
book, and to preliminary ligand designs and trials." By 2019, the book was ready,[2] the laboratory was functional, and Dr. Asako was using his skills in molecular modeling and DFT calculation to come up with the first ligand design. Dr. Ramadoss joined the group and tried making this initial ligand, but the synthesis turned out to be quite challenging. Dr. Asako recalls: "After struggling for a while with little progress, a eureka moment came unexpectedly from my work on a different project, molecular modeling of some gigantic hollow molecules (resembling an enzyme). Thus, I designed the bifunctional spirobipyridine (SpiroBpy) ligand for remote steric control (Figure 1). The spirobipyridine has been used for materials science and its synthesis was known, but surprisingly it has never been used for catalysis despite the prevalence of 2,2′-bipyridine as a useful ligand. The idea was to attach a molecular 'roof' to the spirobipyridine and create a molecular pocket that allows the substrate to approach the catalytic center only in the *meta* orientation (Figure 1, B). Importantly, this 'roof' is placed remotely from the coordination site, rather than in its proximity as with conventional bulky ligands, enabling both selectivity control and high reactivity." Dr. Ramadoss made the first spirobipyridine ligand having a phenyl group as the 'roof', and initial studies showed that selective reaction of *tert*-butylbenzene through remote steric control is indeed possible. After spending a long time trying various organic groups as the 'roof', they found out that using a boronic ester group (Bpin) is the best choice (Figure 1, C), probably because this moiety gives a planar alignment in the transition state to effectively block the *para* approach of the substrate. Dr. Ilies commented: "Incidentally, at the same time, mechanistic studies suggested that *in situ* borylation of the ligand may be the key for achieving selectivity for a different project, the borylation of fluoroarenes.[3] Finally, in 2021, Dr. Jin joined the group and helped to complete the project, notably the synthetic applications of the reaction for late-stage functionalization of drug molecules and the synthesis of phenol derivatives."

The optimized reaction is shown in Scheme 1. Initial studies focused on alkylbenzenes, because these simple sub-



Scheme 1 Iridium/SpiroBpy-catalyzed *meta*-selective borylation of arenes. The following data are shown: isolated yields; total reaction yield, e.g. including all the different isomers formed in the reaction, as measured by GC or ^{1}H NMR (in brackets); the selectivity (*meta*-isomer + bis-*meta*-isomer)/*para*-isomer, as measured by GC or ^{1}H NMR.

strates lack functionality capable of strong electronic interactions, and therefore their selective activation through other methods is difficult. “The strategy proved quite general, and important classes of molecules, such as anilines and phenols, could be selectively borylated at the meta position,” revealed Dr. Ilies, who continued: “It should be noted that such selectivity had not yet been achieved by any other method: electron-rich arenes react under electrophilic substitution conditions at the ortho and para positions, and functionalization of the meta position of phenol or aniline compounds is an undergraduate-level organic chemistry problem that requires multiple steps.”

According to the authors, this reaction has the potential to efficiently produce molecules of interest for medicinal chemistry, materials science, etc., and to create new, unexplored chemical space for drug discovery or the development of functional materials. “The remote steric control strategy can in principle be applied to other C–H activation reactions, and the ligand ‘roof’ can be designed to fit a substrate in various orientations to target different C–H bonds,” said Dr. Asako. Dr. Ilies concluded: “There are many more possibilities to be explored in addition to C–H activation: thinking about the prevalence of bipyridine in catalysis, spirobipyridine ligands are expected to be effective for various other catalytic reactions. The Ilies group is actively working on these developments at the moment.”

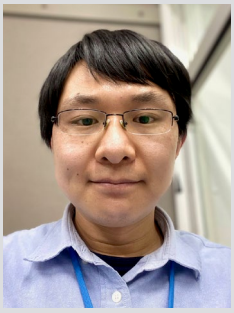
REFERENCES

(1) An overview: L. Ilies *Bull. Chem. Soc. Jpn.* **2021**, *94*, 404–417.
(2) L. Ilies, S. Asako, T. Yoshida *Chemistry Essentials Series*, Vol. 34 *(in Japanese)*; Kyoritsu Shuppan: Tokyo, **2019**.
(3) O. Kuleshova, S. Asako, L. Ilies *ACS Catal.* **2021**, *11*, 5968–5973.

About the authors

Dr. B. Ramadoss

Boobalan Ramadoss was born and grew up in Chengalpattu, India. After completing a BSc (2008) in chemistry from Rajeshwari Vedachalam Government Arts College, Chengalpattu (India), he obtained an MSc (2010) from Gurunanak College, Chennai (India). After that he received his MPhil (2013) in organic chemistry from the University of Madras (India) under the guidance of Dr. A. K. Mohanakrishnan. He received PhD (2018) for his work on C–H bond activation under the supervision of Prof. Chien-Hong Cheng from National Tsing Hua University, Hsinchu (Taiwan). In 2018 he was appointed as a postdoctoral researcher at RIKEN with Dr. Laurean Ilies’s team (Japan). His research interest mainly focuses on C–H functionalization reactions and C–C bond formation using metal catalysis.



Dr. Y. Jin

Yushu Jin was born in Nanjing (China) and grew up in Shanghai (China). He received his MSc in 2015 and PhD in 2018 from Kyushu University (Japan) under the supervision of Prof. Ryoichi Kuwano. In 2015, he was a visiting researcher in Prof. John F. Hartwig’s group at University of California, Berkeley (USA). In 2018, he joined Prof. Nobuharu Iwasawa’s group at Tokyo Institute of Technology (Japan) as a postdoctoral fellow. In 2021, he moved to Prof. Laurean Ilies’s group at RIKEN (Japan) as a postdoctoral researcher. His research has focused on transition-metal-catalyzed reactions, including asymmetric hydrogenation, CO_2 fixation, and C–H functionalization.

Dr. S. Asako

Sobi Asako was born in Yokohama (Japan). He obtained his PhD in 2014 from the University of Tokyo, Japan (advisor: Prof. Eiichi Nakamura), where he developed iron-catalyzed C–H functionalization reactions. In the same year, he was appointed assistant professor at Okayama University (Japan) in

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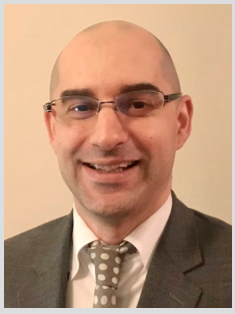
the group of Prof. Kazuhiko Takai, where he started exploring organosodium chemistry using sodium dispersion and molybdenum chemistry for the development of diazo-free reactions using unconventional stable precursors such as carbonyl compounds and cyclopropanes. In 2019, he moved to RIKEN Center for Sustainable Resource Science as a senior scientist to further pursue research along these lines. His research interests cover the exploration of sustainable organic synthesis and the design of conceptually new catalysts for challenging transformations.



Dr. L. Ilies

Laurean Ilies was born and grew up in Transylvania (Romania). He received his BSc (2004), MSc (2006) and PhD (2009) from the University of Tokyo, Japan (advisor: Prof. Eiichi Nakamura), working on the development of new synthetic methods for conjugated heterocyclic compounds and their applications in materials science. In 2009, Laurean was appointed assistant professor at the University of Tokyo (Japan), and in 2014 he was promoted to associate professor. During this time, he mainly investigated catalysis with Earth-abundant metals, especially iron, for C–H functionalization. In 2018, Laurean was appointed team leader at RIKEN, running a research group focused on the development of new synthetic methodologies for C–H functionalization, catalysis with Earth-abundant metals, and organosodium chemistry.

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