

# Metal-Free Enantioselective Oxidative Arylation of Alkenes: Hypervalent-Iodine-Promoted Oxidative C–C Bond Formation

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The oxidative 1,2-difunctionalization of alkenes with carbon nucleophiles represents a great challenge in synthetic organic chemistry and the development of metal-free reactions capable of efficiently producing complex and functionalized molecules is the object of significant research efforts worldwide.

The group of Professor Morifumi Fujita from the University of Hyogo (Japan) has recently been working on this problem. “In this type of functionalization, the alkene is initially oxidized and then receives nucleophilic attacks,” said Professor Fujita. He continued: “Oxidation of the carbon nucleophile needs to be avoided; however, more reactive carbon nucleophiles are more easily oxidized. Thus, the reactivity of both alkene and carbon nucleophile must be tuned. To enhance the reactivity of the alkene towards oxidation, we focused our attention on achieving nucleophilic assistance in the oxidation.”

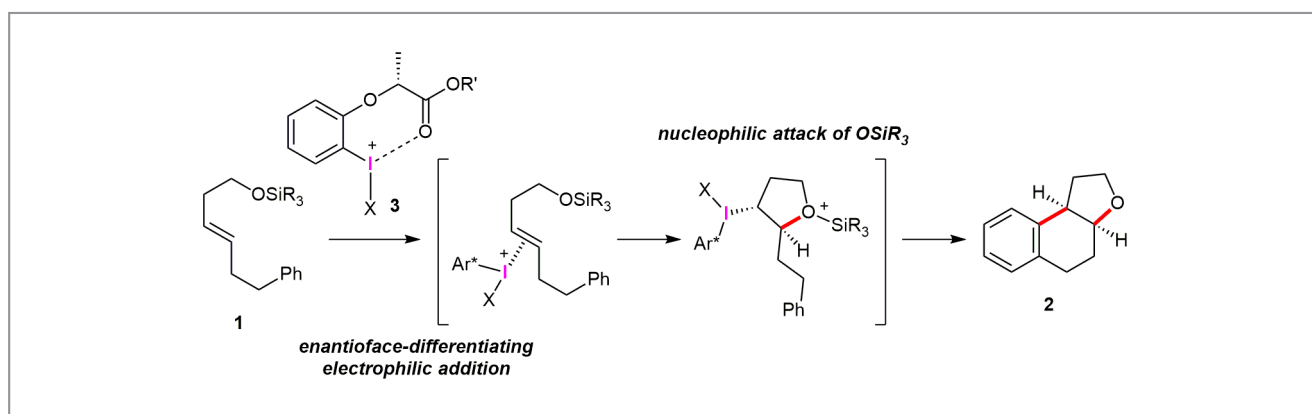
“Our extensive screening of reaction substrates and conditions allowed us to find that 6-phenyl-1-silyloxy-hex-3-ene **1** was the most suitable alkene substrate for the oxidative carbon–carbon bond formation (Scheme 1),” explained Professor Fujita, continuing: “It is remarkable that the silyloxy group does not act as a protection group; however, it preferentially promotes the nucleophilic oxycyclization to yield **2**. The nucleophilic assistance of the silyloxy group was also observed in the dioxycyclization of *ortho*-(4-silyloxybut-1-enyl)benzoate with a hypervalent iodine reagent.<sup>1</sup>”

The oxidative arylation first proceeds through enantioface-differentiating electrophilic addition of lactate-based chiral hypervalent iodine reagent **3** to the alkene (Scheme 1). The following oxycyclization may be accelerated owing to inductive electron-donation of the silyl group. Nucleophilic attack of the phenyl group completes the double cyclization yielding **2**.

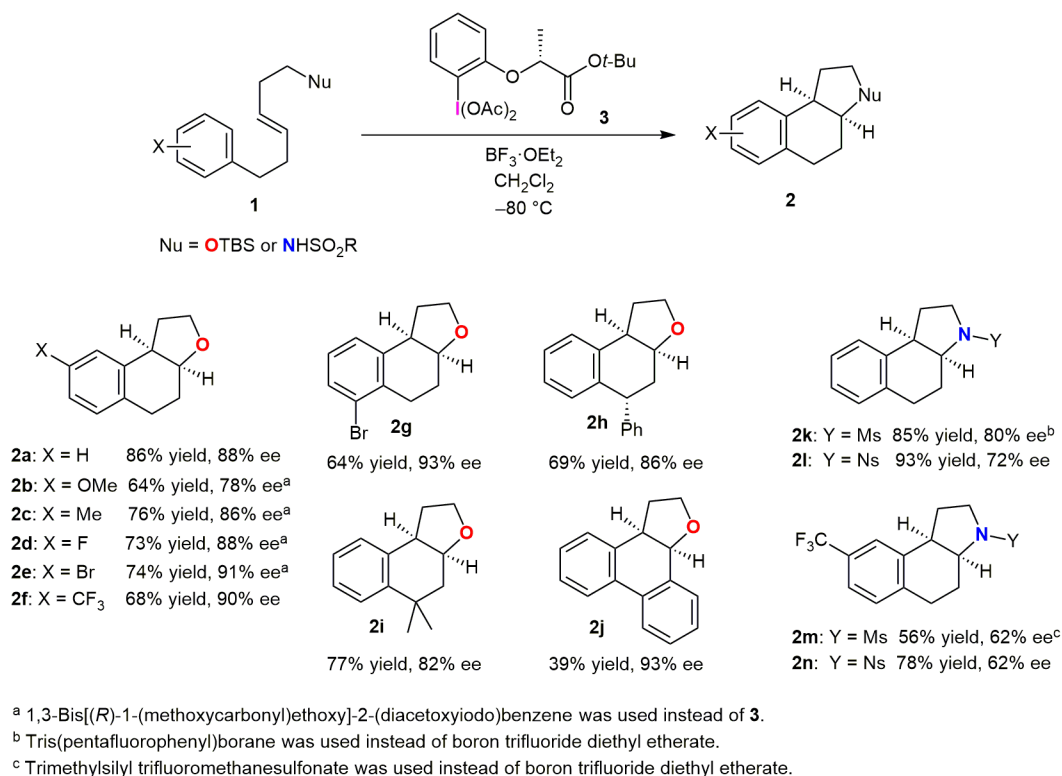
Professor Fujita said: “The lactate-based chiral hypervalent iodine reagent has been used for several types of highly enantioselective oxidations since our research group first reported it in 2007.<sup>2</sup> Electrospray ionization mass spectrometry measurements indicate interaction of the lactate moiety with the electron-deficient iodine atom of **3**.<sup>3</sup> We postulate that the interaction may induce pseudo chirality at the iodine center leading to high enantioselectivity.”

Thanks to the concise preparation of **3** and easy derivatization of the lactate side chain, the reagent design allowed the authors to achieve further development of the enantioselective oxidation with hypervalent iodine.

As shown in Scheme 2, a wide range of both electron-rich and electron-deficient arenes were found to participate in the oxidative arylation. “Although the electron-deficient aryl group has lower reactivity as a carbon nucleophile, even the CF<sub>3</sub> substrate yielded the oxidative arylation product **2f**,” said Professor Fujita. “Desymmetrization in the oxidative arylation was also achieved to yield **2h** as the single diastereomer. Aminoarylation also proceeded to yield methanesulfonyl



**Scheme 1** Plausible mechanism for enantioselective oxyarylation



Scheme 2 Selected scope of the enantioselective oxidative arylation

(Ms) amide **2k** and (2-nitrophenyl)sulfonyl (Ns) amide **2l**. The enantioselective aminoarylation provided optically active hexahydrobenzo[e]indoles, which are candidate agonists/antagonists for dopamine and serotonin receptors.<sup>4</sup>

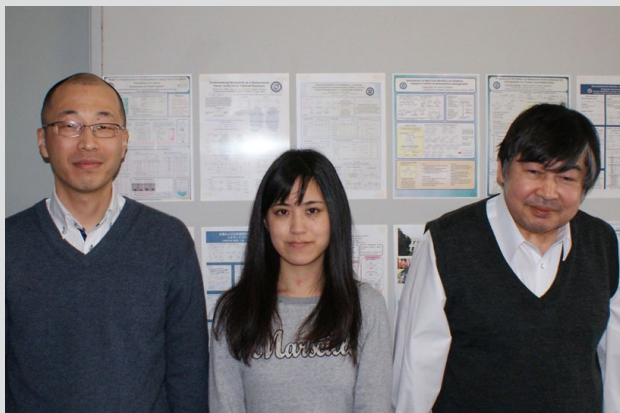
Professor Fujita concluded: “The oxidative arylation provides a single-step construction of the polycyclic skeleton with functional groups in an enantioselective manner. This approach also involves a unique utilization of the silyloxy group. We hope that this concept will find further applications in other reactions.”

*Matthew Farnish*

## REFERENCES

- (1) M. Fujita, K. Mori, M. Shimogaki, T. Sugimura *Org. Lett.* **2012**, *14*, 1294.
- (2) M. Fujita, S. Okuno, H. J. Lee, T. Sugimura, T. Okuyama *Tetrahedron Lett.* **2007**, *48*, 8691.
- (3) M. Fujita, Y. Yoshida, K. Miyata, A. Wakisaka, T. Sugimura *Angew. Chem. Int. Ed.* **2010**, *49*, 7068.
- (4) X. Song, A. M. Crider, S. F. Cruse, D. Ghosh, C. Klein-Stevens, L. Liang, M. A. Scheideler, A. Varming, I. Søjtofte *Eur. J. Med. Chem.* **1999**, *34*, 487.

## About the authors



From left: Prof. M. Fujita, Dr. M. Shimogaki, Prof. T. Sugimura

**Mio Shimogaki** was born in Hyogo (Japan) in 1989. She completed her B.Sc. at the University of Hyogo (Japan) in 2012. Since April 2012 she has been carrying out her graduate studies on the development of novel oxidation reactions with hypervalent iodine and application to asymmetric syntheses of bioactive natural products at the same university. In March 2017 she will complete her doctoral thesis on oxidative cyclization of alkene using chiral hypervalent iodine(III). Her research interest focuses on the development of new strategies for oxidation with hypervalent iodine.

**Morifumi Fujita** studied chemistry at Osaka University (Japan) and received his B.E. in 1991. He continued his graduate work on photo-induced electron transfer chemistry under the super-

vision of Dr. Shunichi Fukuzumi. After completing his M.E. in 1993, he joined the group of Professor Setsuo Takamuku at the same university to carry out his Ph.D. studies as a research fellow of the Japan Society for the Promotion of Science. In 1995, he joined the group of Professor Akira Tai at the Himeji Institute of Technology (Hyogo, Japan) as a research associate. After receiving his doctoral degree from Osaka University in 1997, he carried out postdoctoral work with Professor Steven V. Ley at University of Cambridge (UK) for one year. He returned to the Institute of Technology and began the work on hypervalent iodine chemistry with Professor Tadashi Okuyama. In 2006, he was promoted to Associate Professor at the University of Hyogo. His current research interests focus on the chemistry of reactive intermediates and hypervalent iodine, which are applied to stereoselective reactions and total synthesis.

**Takashi Sugimura** graduated from Osaka University (Japan) in 1979 and received his Ph.D. in 1984 under the guidance of Professor Ichiro Murata. After working as a postdoctoral fellow at Ohio State University (USA) for two years, he moved to the Himeji Institute of Technology (Japan) in 1986. He became an Associate Professor in 1994. He has been a Full Professor at the University of Hyogo (Japan) since 2006. He has been studying in the fields of both organic synthesis and asymmetric hydrogenation catalysis. In 1995, he received the award for Excellent Young Scientists from The Society of Organic Synthetic Chemistry, Japan. In the field of asymmetric hydrogenation, he is known as a record maker of heterogeneous asymmetric catalysis.