The Suzuki–Miyaura Coupling of Nitroarenes

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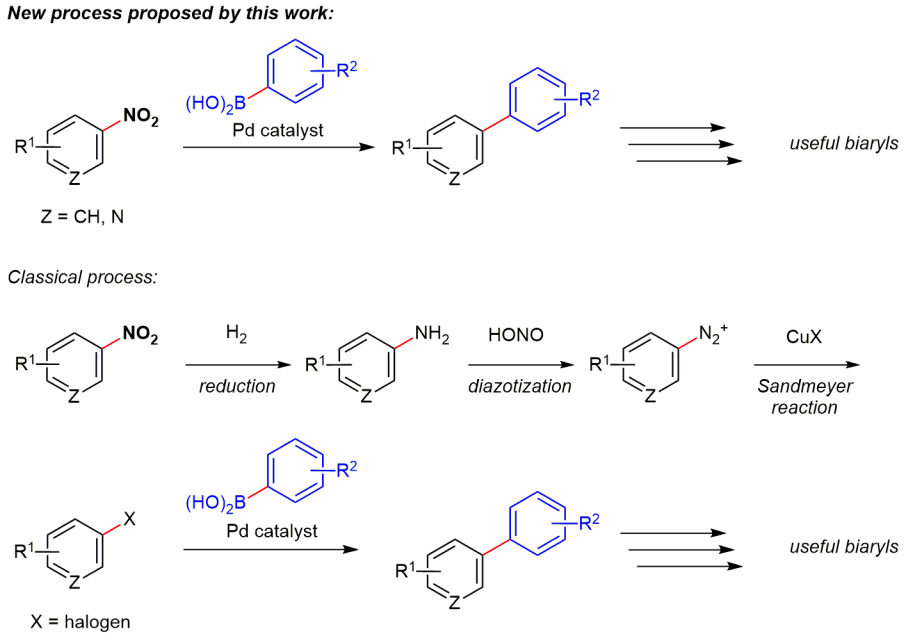
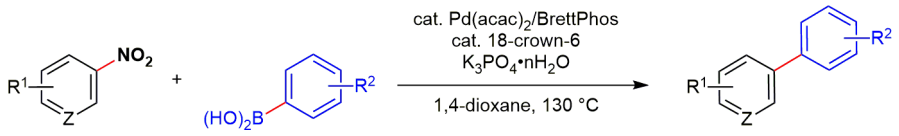
The Suzuki–Miyaura cross-coupling reaction is an indispensable synthetic tool for modern organic synthesis to assemble biaryls, which are ubiquitous in useful substances such as pharmaceuticals, agrochemicals, and materials. One avenue of ongoing research to improve the practicality of the transformation is to seek aryl electrophiles alternative to aryl halides to avoid halogen contaminations in products and wastes as well as to streamline and diversify chemical processes to access biaryls. While many different aryl electrophiles such as aryl esters, aryl ethers, aryl carboxylic acid derivatives, and aryl ammonium salts have been introduced for the Suzuki–Miyaura cross-coupling in the last decade, no successful report has been available for the use of nitroarenes as the coupling partner. Recently, a research endeavor led by Professor Shigeyoshi Sakaki (Fukui Institute for Fundamental Chemistry, Kyoto University, Japan) and Professor Yoshiaki Nakao (Kyoto University, Japan) showed for the first time that nitroarenes can be viable aryl electrophiles for the Suzuki–Miyaura cross-coupling reaction. "Nitroarenes are common synthetic building blocks in chemical processes and often serve as starting materials to derivatize aromatic compounds because nitration is one of the most reliable and established methods to functionalize arenes," said Professor Nakao. Classical processes involving nitration followed by reduction, diazotization, and the Sandmeyer reaction are still running in the chemical industry. "For this reason, the use of nitroarenes for the cross-coupling chemistry is highly desirable because the method could exclude the classical multi-step processes to functionalize arenes (Scheme 1)," said Mr. Takanori Miyazaki from the TOSOH corporation, one of the co-authors of this work.

"We have come up with very simple reaction conditions employing Buchwald's BrettPhos as a key ligand to enable the palladium-catalyzed Suzuki–Miyaura cross-coupling reaction of nitroarenes (Scheme 2)," explained Mr. Miyazaki. He continued: "The reaction requires a relatively higher temperature compared to the cross-couplings of aryl halides due to reluctant oxidative addition of the C–NO_2 bond of nitroarenes, but



Scheme 1 Comparison of chemical processes to access biaryls starting from nitroarenes



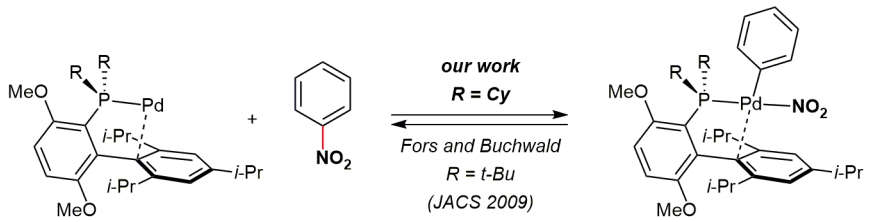
Scheme 2 The Suzuki–Miyaura cross-coupling of nitroarenes

no exotic or complex reagents or conditions have been utilized to achieve the new reaction. We indeed planned to develop this reaction as a user-friendly process as we knew the potential value of the methodology, if available." Never imagining that standard cross-coupling conditions would work, and since many papers had already been published showing that nitroarenes are poor substrates for the reaction, one of the other authors, Dr. M. Ramu Yadav, started to screen more sophisticated systems such as the use of other transition metals and multiple metal catalysts to tackle the reaction.

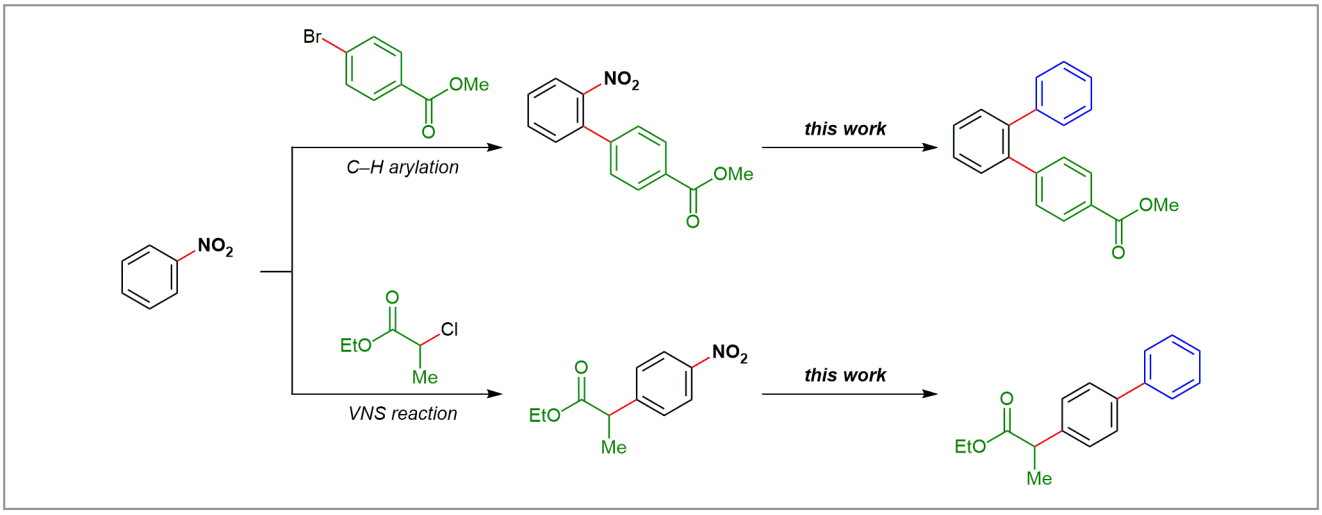
"There was actually a key finding available in the literature, previously described by the Fors and Buchwald group, who reported the nitration of aryl halides by palladium/*t*-Bu-BrettPhos catalysis (*J. Am. Chem. Soc.* **2009**, *131*, 12898)," said Professor Nakao. "In that reaction – which is the reverse reaction of the desired oxidative addition of Ar–NO_2 (Scheme 3) – the reductive elimination of the Ar–NO_2 bond via the intermediate palladium complex is a product-forming step, whereas in our case it is a key elemental step of the cross-coupling, as experimentally probed by Dr. Nagaoka." He continued: "It is interesting to note that the cleavage/formation equilibrium of the Ar–NO_2 bond may be controlled by a subtle change (Cy or *t*-Bu) of the phosphorus ligands, BrettPhos or *t*-Bu-BrettPhos (Scheme 3). This aspect is currently under theoretical investigation by Professor Sakaki and Dr. Zhong, who have revealed a full catalytic cycle of the Suzuki–Miyaura cross-coupling of nitroarenes using calculations supported by some experimental work executed by Dr. Nagaoka, Mr. Kashihara, and myself."

Calculations as well as catalytic and stoichiometric experimental mechanistic studies demonstrated that the rate-determining step of the reaction was the oxidative addition step. Professor Nakao explained: "The design of novel metal catalysts will probably be necessary to improve the efficiency of this new bond-activation process, which in turn would lead to an improved overall utility of the new nitroarene-based cross-coupling reaction. This would also likely lead to the possibility of using a greater diversity of nucleophilic coupling partners, in line with the rich chemistry demonstrated in many previous aryl halide based cross-coupling studies."

"Nitroarenes feature a unique reactivity due to the strongly electron-withdrawing nature of the nitro group. For example, *ortho*- and *para*-positions of nitrobenzene can be directly functionalized to install organic substituents via C–H arylation and vicarious nucleophilic substitution (VNS) reactions, respectively," remarked Professor Nakao. He concluded: "Subsequently, the nitro group can be submitted to the coupling reaction developed in this study, enabling the synthesis of disubstituted benzenes (Scheme 4)."



Scheme 3 Oxidative addition/reductive elimination of the Ar–NO_2 bond by Pd/BrettPhos complexes



Scheme 4 Synthesis of disubstituted benzenes through C–H functionalization and the Suzuki–Miyaura coupling reactions of nitrobenzene

About the authors

From left: Dr. M. R. Yadav, Dr. M. Nagaoka, M. Kashihara

M. Ramu Yadav obtained his Ph.D. degree working on metal-catalyzed C–H functionalization of arenes at the University of Hyderabad (India) under the supervision of Professor Akhila K. Sahoo in 2014. He has been a postdoctoral researcher at Kyoto University (Japan) with Professor Yoshiaki Nakao since 2015.

Masahiro Nagaoka obtained his Ph.D. degree working on the synthesis and reactivity of polyhydrido metal clusters under the supervision of Professors Hiroharu Suzuki and Toshiro Takao in 2016 at Tokyo Institute of Technology (Japan). He then joined the research group of Professor Yoshiaki Nakao as a postdoctoral fellow. He is currently a research scientist at Sagami Chemical Research Institute (Japan).

Myuto Kashihara obtained his B.S. degree at Kyoto University (Japan) in 2017 and has just started his graduate study in the group of Professor Yoshiaki Nakao.

T. Miyazaki

Takanori Miyazaki obtained his M.S. degree at Kyushu University (Japan) in 2004. He is currently a senior researcher at TOSOH corporation. He is collaborating with the group of Professor Nakao to develop the new reaction described here and hoping that the novel transformation of nitroarenes will expand.

From left: Prof. S. Sasaki, Dr. R.-L. Zhong

Shigeyoshi Sakaki (Ph.D.; Professor Emeritus) has been a senior research fellow in the Fukui Institute for Fundamental Chemistry, Kyoto University (Japan) since his retirement from a full professor position at Kyoto University. He is working in the theoretical and computational chemistry of d element(s) with much interest in the reaction mechanism of organometallic and catalytic reactions.

Rong-Lin Zhong is a lecturer at the Institute of Theoretical Chemistry, Jilin University (P. R. of China). He obtained his B.S. degree from Northeast Normal University (P. R. of China) in 2010. He then joined Professor Zhong-Min Su's group in Northeast Normal University and obtained his Ph.D. degree in physical chemistry in 2015. He has worked in Professor Sakaki's group as a research fellow in the Fukui Institute for Fundamental Chemistry, Kyoto University (Japan) since 2016.

Prof. Y. Nakao

Yoshiaki Nakao was educated in chemistry at Kyoto University (Japan; Ph.D. with Professors Tamejiro Hiyama and Eiji Shirakawa), Yale University (USA; visiting student with Professor John F. Hartwig), and the Max-Planck-Institut für Kohlenforschung (Germany; visiting scholar with Professor Manfred T. Reetz). He was appointed as an assistant professor at Kyoto University in 2002, and has been a full professor since 2014. He is interested in developing new synthetic reactions by catalysis.