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Orthogonal Synthesis of Isoindoles and Isoquinolines via 1,3-Dipolar Cycloaddition and Electrocyclization

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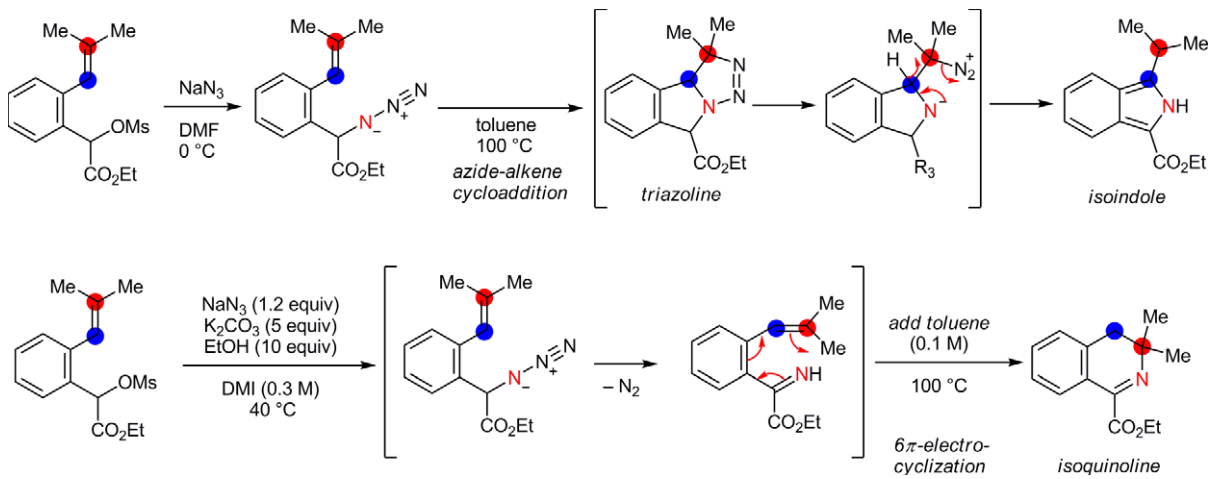
Nitrogen-containing heterocycles (azaheterocycles) are important and widespread structures, present in numerous natural products, potent pharmaceutical drugs, and various kinds of functional materials. Although a number of diverse synthetic approaches toward azaheterocycles have been developed it is still highly desirable to exploit versatile methodologies to construct such molecules with selective control of substitution patterns using readily accessible building blocks. The group of Professor Shunsuke Chiba from the Nanyang Technological University in Singapore has recently been interested in the chemical reactivity of organic azides to synthesize azaheterocycles via various types of C–N bond formations.

"During the course of our studies," explained Professor Chiba, "α-azido carbonyl compounds containing a 2-alkenyl-aryl unit were found to be promising precursors for the synthesis of isoindole and isoquinoline derivatives via 1,3-dipolar cycloaddition of azides onto alkenes and 6π-electrocyclization of *N*–H imine intermediates, respectively." According to Professor Chiba, this methodology exploits orthogonal modes of chemical reactivity of such organic azides, displayed by slight modification of the reaction conditions as shown in the scheme below.

Isoindoles could be accessed by simple heating of the starting organic azides in toluene, whereupon intramolecular azido–alkene cycloaddition and consecutive elimination of dinitrogen from the resulting triazolines would produce isoindoles. "The appeal of isoindoles prepared by this methodology can be attributed to not only their attractive fluorescent and electroluminescent properties but also their versatility as reaction precursors for the synthesis of oligoacenes," said Professor Chiba. "By using newly synthesized isoindoles, we are now aiming to prepare new types of oligoacenes with a range of substituents."

Chiba and Hui discovered the second reactivity pattern of these organic azides – to provide isoquinoline derivatives – serendipitously, when direct conversion of the mesylate into the isoindole was tried using 1.5 equivalents of NaN_3 in DMF at 100 °C via a substitution reaction followed by an azido–alkene 1,3-dipolar cycloaddition (for details, see the original paper). "After understanding that the excess amount of NaN_3 induced the formation of *N*–H imine," he concluded, "we soon elucidated the optimized reaction conditions to provide isoquinolines selectively."

Matteo Zanda



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Shunsuke Chiba was born in Kanagawa (Japan) in 1978. He obtained his B.Eng. degree from Waseda University (Japan) in 2001 and received his Ph.D. degree in 2006 from the University of Tokyo (Japan), the latter under the supervision of Professor Koichi Narasaka. He was appointed as a Research Associate in Professor Narasaka's group at the University of Tokyo in 2005. In 2007, he moved to the Division of Chemistry & Biological Chemistry, School of Physical & Mathematical Sciences, Nanyang Technological University (Singapore) as an Assistant Professor. His research is focused on the development of organic synthetic methodologies and the synthesis of natural and unnatural products.

W.-Q. Hui

Benjamin Wei-Qiang Hui was born in Singapore in 1982 and obtained his bachelor's degree in chemistry from the National University of Singapore (NUS) in 2007. In the same year, he entered the graduate program at Nanyang Technological University (NTU) under the supervision of Professor Shunsuke Chiba. His research focuses on the development of new synthetic methods to access azaheterocyclic compounds.

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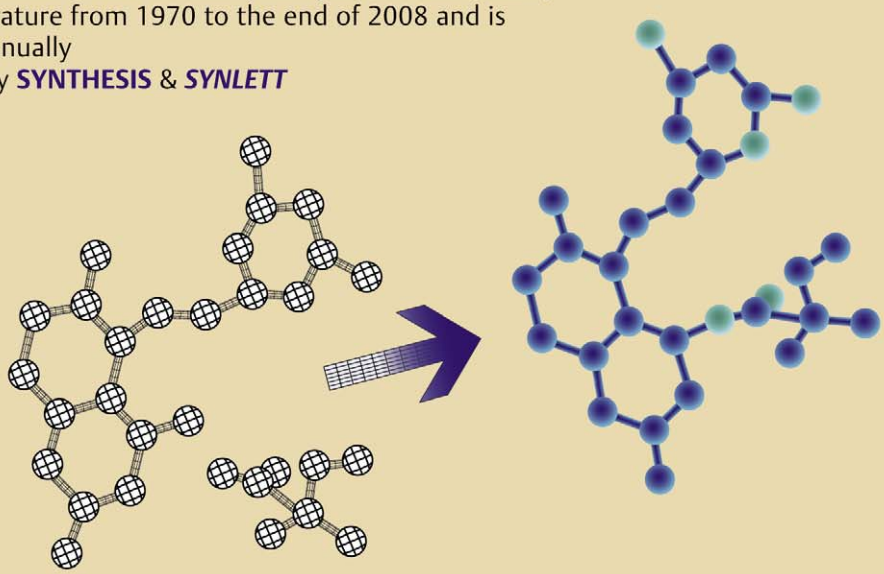

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