

Single-Carbon-Atom Transfer to α,β -Unsaturated Amides from N-Heterocyclic Carbenes

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The issue of how to improve efficiency in increasing structural complexity of molecules is a major focus in organic chemistry. The group of Professor Mamoru Tobisu at Osaka University (Japan) has been working on the problem and this paper in *Science* describes their recently developed method, which allows for the four chemical bonds to be formed at a carbon center in a single step, thereby shortening the chemical processes that are traditionally used in classical methods for constructing more elaborate structures.

Professor Tobisu said: “Our findings (Figure 1) show that a simple thermal reaction between α,β -unsaturated amides and N-heterocyclic carbenes (NHCs) results in the formation of homologated γ -lactams. In this reaction, NHC serves as an atomic carbon equivalent. This means that four new chemical bonds are formed at a single carbon center in a single process. These findings are important from a fundamental point

of view because an atomic carbon is too unstable to be used in organic synthesis. This reaction successfully employs stable precursors to an atomic carbon, thus providing a practical method for single-carbon-atom doping reactions.” The synthetic scope of the method is shown in Scheme 1.

Professor Tobisu revealed some background to their work. He told SYNFORM: “We were originally investigating a reaction using NHC as a catalyst (*Org. Lett.* **2021**, 23, 1572–1576). During the course of that study we isolated a byproduct, the molecular weight of which was larger than that of the starting material by 12, suggesting incorporation of a single carbon atom. This was completely unexpected and was a great surprise for us.”

Starting from that serendipitous finding, the methodology was subsequently developed and optimized, while also investigating the mechanism of the process. To that end, the group

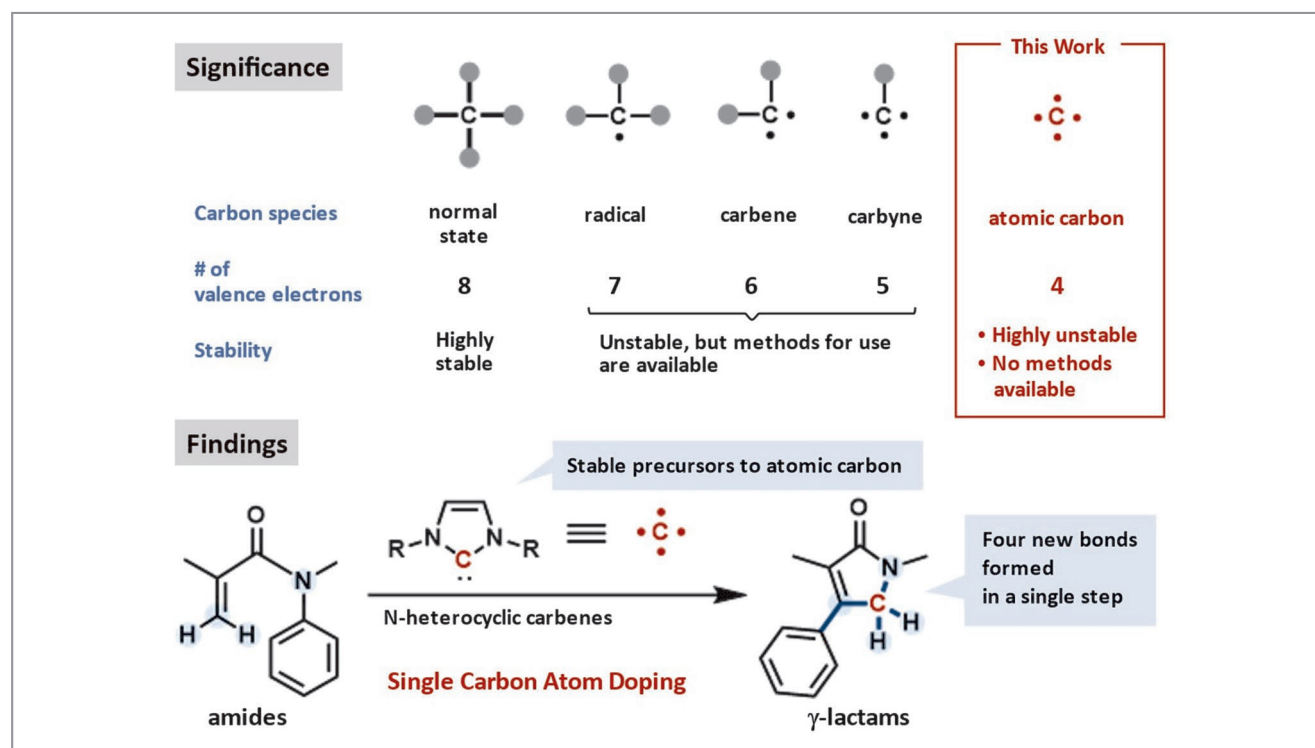
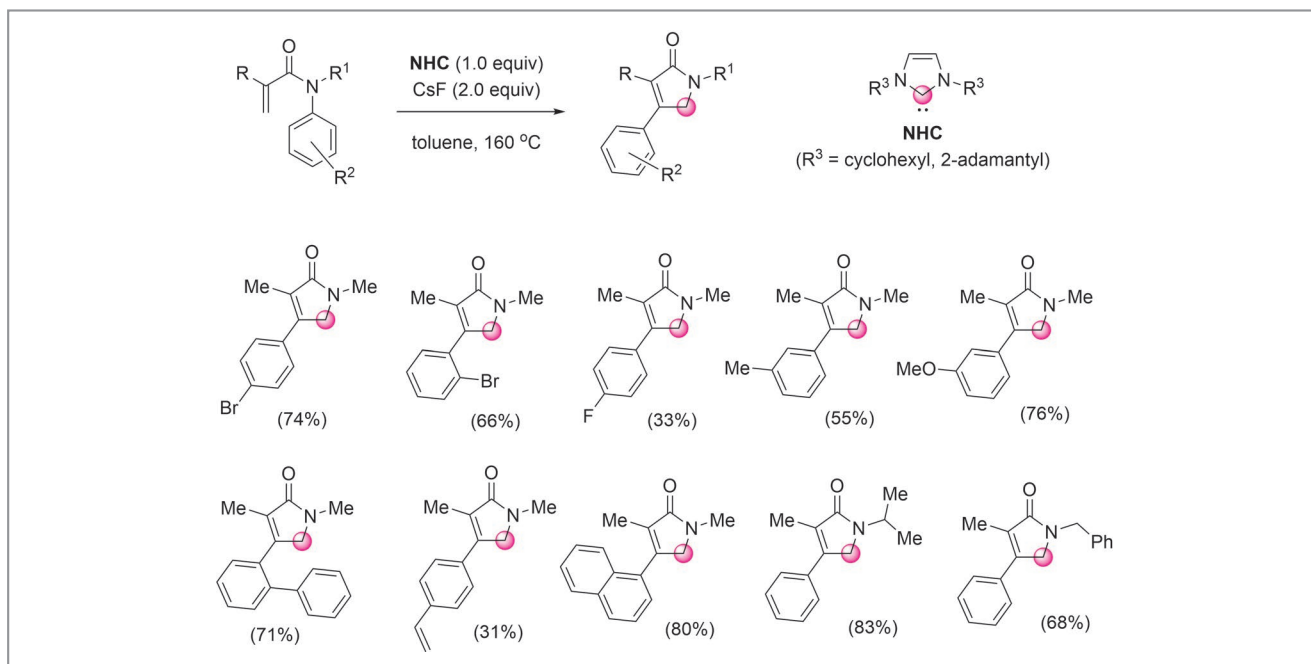


Figure 1 The single-carbon-atom doping reaction



Scheme 1 Scope and applications of the methodology

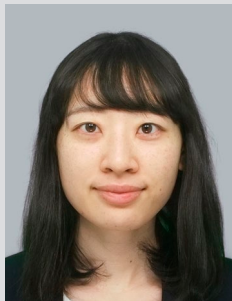
performed a number of experiments, such as using an NHC labelled at the C2 position with ^{13}C , which resulted in the formation of the corresponding γ -lactam incorporating ^{13}C at the C5 position. Furthermore, deuterium labelling experiments and preparation/reaction of the intermediate imidazolium salt further confirmed the proposed mechanistic pathway.

To further demonstrate the synthetic potential of the methodology, the γ -lactam primary products were subjected to a series of transformations – such as hydrogenation, dehydrogenation and further homologations – which led to an array of functionalized pyrrole, pyrroline and pyrrolidine derivatives.

Professor Tobisu concluded: “Our next goal is to extend the concept of the carbon-atom doping reactions to be a general tool in organic synthesis by developing diverse types of transformations.”

Mattias Fomok

About the authors



M. Kamitani

Miharu Kamitani received her MS degree from Osaka University (Japan) under the direction of Prof. Mamoru Tobisu (2021). She is currently working for DAIKIN INDUSTRIES, LTD (Japan).



B. Nakayasu

Bunta Nakayasu received his B.S. degree from Osaka University (Japan) under the direction of Associate Professor Toru Amaya (2021). He then started his MS degree studies at the same university, under the direction of Prof. Mamoru Tobisu. His research interests include the development of new synthetic methods using N-heterocyclic carbenes.



Prof. H. Fujimoto

Hayato Fujimoto received his B.Sc. degree from Osaka University (Japan) under the supervision of Prof. Toshiyuki Moriuchi and Prof. Toru Amaya (2017). He obtained his M.Sc. (2017) and Ph.D. (2022) degrees from the same university under the supervision of Prof. Mamoru Tobisu. In 2022, he joined Prof. Tobisu's group as an assistant professor at Osaka University. His research interests focus on the development of new catalytic reactions and synthetic methods.



Prof. K. Yasui

Kosuke Yasui received his B.Sc. (2015) and M.Sc. (2017) degrees from Osaka University (Japan) under the supervision of Prof. Naoto Chatani, and Ph.D. (2020) degree from the same university under the supervision of Prof. Mamoru Tobisu. In 2018, he joined the group of Prof. Phil S. Baran in Scripps Research, USA, as a visiting student for 6 months. In 2020, he started his academic career

as a program-specific assistant professor in the group of Prof. Aiko Fukazawa in Kyoto University (Japan). He then moved to Prof. Koji Hirano's group at Osaka University as an assistant professor in 2023. His research interests include the development of new catalytic reactions and novel π -conjugated systems.



Prof. T. Kodama

Takuya Kodama received his Ph.D. from Osaka University (Japan) under the supervision of Prof. Takashi Kubo (2018). During his Ph.D. studies, he also worked with Prof. Masayoshi Nakano for three months (2013) at Osaka University and Prof. Michael M. Haley at the University of Oregon, USA (2017) for three months as a visiting student. He started his academic career at Osaka University in 2018 as an assistant professor with Prof.

Mamoru Tobisu. His research interests include structural and physical organic chemistry, in particular, syntheses, properties, and reactivities of new organic and organometallic compounds with unprecedented electronic structures.



Prof. M. Tobisu

Mamoru Tobisu received his Ph.D. from Osaka University (Japan) under the direction of Prof. Shinji Murai (2001). During his Ph.D. studies, he also worked with Prof. Gregory C. Fu as a visiting scientist for five months at the Massachusetts Institute of Technology, USA (1999). Following a period as a scientist at the Takeda Pharmaceutical Company, Japan (2001–2005), he started his academic career at Osaka University in 2005 as

an assistant professor with Prof. Naoto Chatani. He was then appointed as an associate professor at the same university in 2011 and was promoted to full professor there in 2017. Since 2020, he has also served as a director of Innovative Catalysis Science Division of the Institute for Open and Transdisciplinary Research Initiatives at Osaka University. His research interests center on synthetic organic chemistry and homogeneous catalysis.