N-Heterocyclic Carbene- and Organic Photoredox-Catalysed *meta*-Selective Acylation of Electron-Rich Arenes

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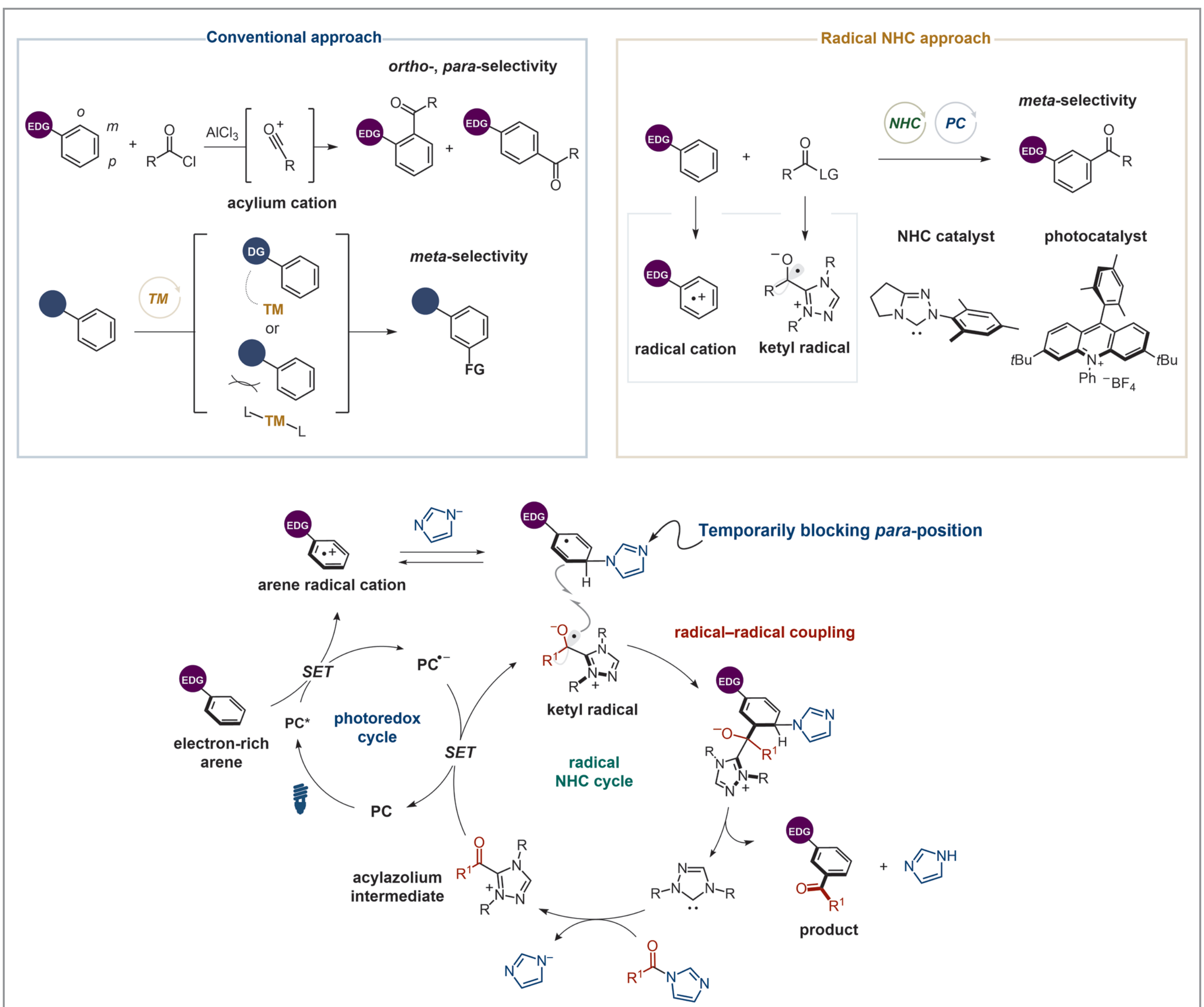
The Friedel–Crafts reaction serves as a highly useful chemical process, featured prominently in organic chemistry literature and textbooks. Since the initial report from Friedel and Crafts on the acylation of aromatic rings in 1877 (see also the Name Reaction Bio article, *Synform* **2018**, A49–A52), this methodology has found widespread applications, extending seamlessly from the laboratory to industrial level, for the synthesis of materials, natural products, and pharmaceutical agents.

According to Professor Hirohisa Ohmiya (Kyoto University, Japan), the Friedel–Crafts acylation reaction, specifically, demonstrates high efficiency in the case of electron-rich arenes, which is achieved through the induction of acylium cations.



Scheme 1 NHC- and organic photoredox-catalysis enabling *meta*-selective acylation

"Electrophilic aromatic substitution reactions typically introduce acyl groups to the *ortho*- and *para*-positions to electron-donating groups on aromatic rings," he explained. "This *ortho*- and *para*-selectivity has enabled the construction of complex aromatic compounds. However, challenging this norm by achieving *meta*-selective aromatic substitution reactions on electron-rich arenes is a difficult yet powerful process, offering a valuable toolbox for organic synthesis."

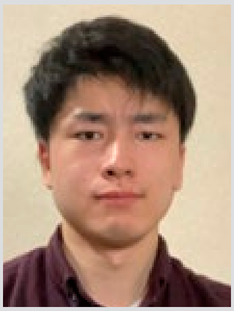
This *Nature Synthesis* paper by Goto, Sano, Sumida and Ohmiya described the N-heterocyclic carbene (NHC) and organic photoredox cooperative catalytic *meta*-selective acylation of electron-rich arenes. "The catalytic system involves a nucleophilic addition of an azolide anion to the radical cation species produced by single-electron oxidation of the electron-rich arenes," said Professor Ohmiya, corresponding author of this paper. He continued: "The nucleophile, the azolide anion, is delivered from the acylation reagent, acyl imidazole, via addition/elimination with an NHC catalyst. The desired *meta*-acylation was achieved based on the cross-selective radical–radical coupling of the cyclohexadienyl radical formed by the nucleophilic addition with the persistent radical, the ketyl radical, via single-electron reduction of the acyl azolium intermediate (Scheme 1)."

Dr. Yuto Sumida, co-corresponding author on the paper, told SYNFORM: "This reaction pathway involves a unique route of functionalization to aromatic rings by radical–radical coupling via attaching and detaching of azolide anion. This catalytic pathway opens up the possibility of radical NHC catalytic systems." Dr. Sumida went on: "This project was accomplished by two promising students: Yamato Goto discovered the reaction through extensive experiments and demonstrated the validity of the plausible mechanism using computational chemistry. Masaki Sano also greatly accelerated the project with countless experiments and analyses."

Dr. Sumida added that the developed method enables modification of a broad range of substances from *meta*-acylation of simple electron-rich arenes, such as anisole, to biologically active molecules having complex structures, such as SN-38, that are difficult to achieve via the conventional approach.

Prof. Ohmiya commented: "In recent years, several *meta*-functionalizations of arenes have been reported using transition-metal catalysts with directing groups or specially designed ligands, but most of them yield products with a small amount of mixed regioisomers. Conversely, our reaction is innovative because it proceeds with almost perfect selectivity based on the mechanistic principle of radical NHC catalysis." Prof. Ohmiya concluded: "We hope that this discovery will be a stepping stone for further regioselective functionalization of aromatic rings."

About the authors



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Yamato Goto received his B.S. degree from Kanazawa University (Japan) in 2021. He then started his MS degree studies under the supervision of Professor Hirohisa Ohmiya. His research interests focus on the development of novel methodology based on radical process under N-heterocyclic carbene catalysis.

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Yuto Sumida received his PhD from Kyoto University (Japan) in 2010 under the supervision of Professor Koichiro Oshima. He spent nine months as a JSPS postdoctoral fellow in the group of Professor Daniel Kahne at Harvard University (USA). In 2011, he became an Assistant Professor at Tokyo Medical and Dental University (TMDU, Japan) working with Professor Takamitsu Hosoya. He moved to RIKEN Kobe (Japan) as a Research Scientist in 2014. He became an Assistant Professor at Kanazawa University (Japan) working with Professor Hirohisa Ohmiya in 2019. He has been an Associate Professor at TMDU working with Professor Takamitsu Hosoya since 2023.

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Hirohisa Ohmiya is a Professor at Kyoto University (Japan). He received his Ph.D. from the same university in 2007 under the supervision of Professor Koichiro Oshima. He spent one year as a JSPS postdoctoral fellow in the group of Professor Timothy F. Jamison at Massachusetts Institute of Technology (USA). In 2008, he became an Assistant Professor at Hokkaido University (Japan) working with Professor Masaya Sawamura. He was promoted to Associate Professor in 2010. He began his professorial career at Kanazawa University (Japan) in 2017 before moving to Kyoto University in 2022.