Deacylative Arylation and Alkynylation of Unstrained Ketones

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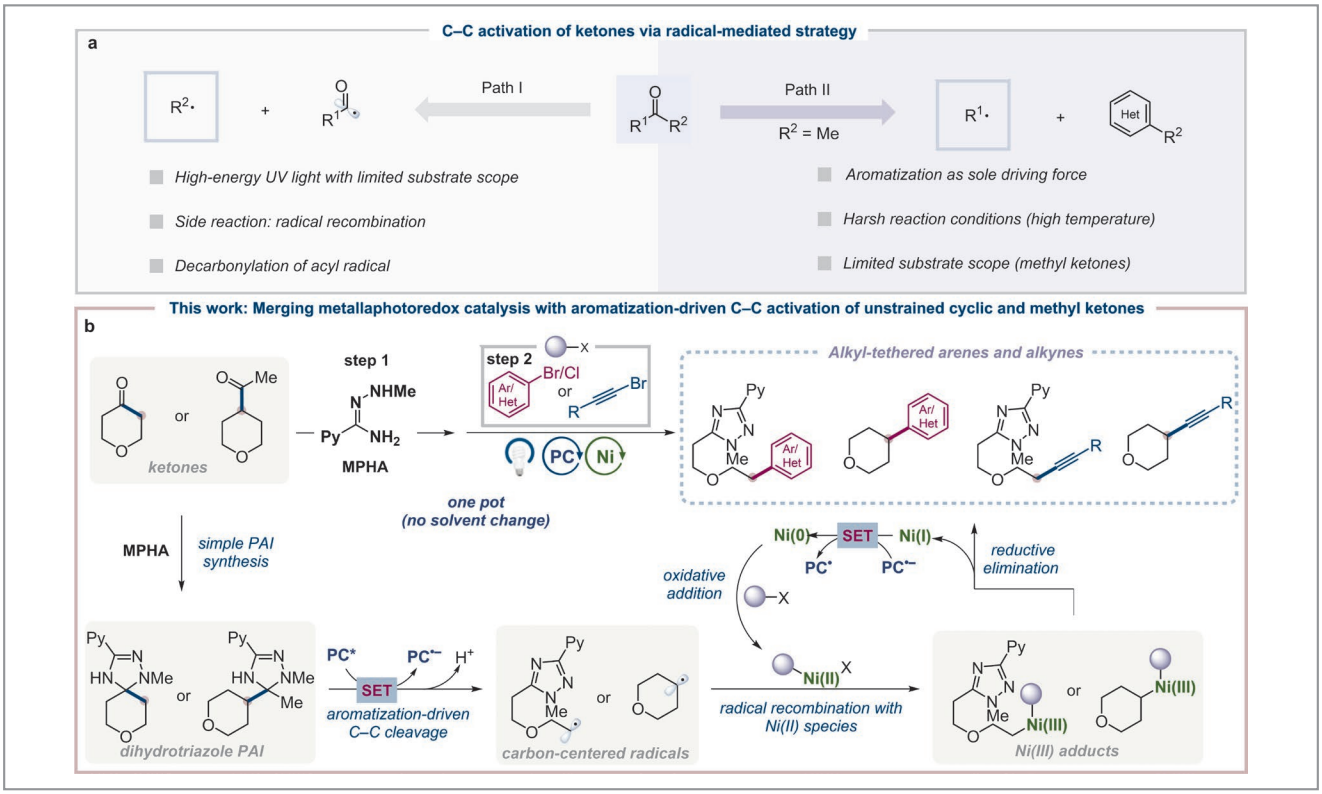
The majority of organic compounds are comprised of carbon–hydrogen (C–H) and carbon–carbon (C–C) bonds, which represent the two pivotal units in organic chemistry and whose synthetic modification constitutes a central aspect in organic synthesis. "Complementary to altering existing frameworks through late-stage C–H functionalization, the selective C–C bond activation offers unique opportunities for constructing diverse organic molecule backbones. However, it has still been challenging to develop general and practical methods for C–C bond activation,[1]" said Professor Xiaheng Zhang from Hangzhou Institute for Advanced Study, University of Chinese Academy of Sciences (Hangzhou, P. R. of China.). He continued: "The carbonyl group of ketones is an important structural motif in bioactive natural products and pharmaceuticals. Additionally, as one of the most prevalent and easily accessible functional groups, it serves as an excellent platform for C–C bond activation reactions."

It has been noted that ketones traditionally participate in a limited number of organic transformations, including the Baeyer–Villiger oxidation, the Beckmann rearrangement, and the Schmidt reaction. Transition-metal-catalyzed C–C activation reactions, which offer a feasible approach to simplifying the synthesis of complex molecules, have contributed significantly to the functionalization of ketone substrates over the past decade.[2] Nevertheless, the C–C activation of ketones via a radical-mediated strategy remains largely unexplored, possibly due to the lack of appropriate radical precursors. This limitation also restricts the effective conversion of ketones and their utilization in organic synthesis. According to Professor Zhang, the Norrish–Young reaction represents a potent method to cleave C–C bonds of ketones, yet its synthetic application has been constrained by issues of selectivity and practicality (Scheme 1a, left).[3] "To date, three representative types of radical precursors, namely dihydroquinazolinone,[4]



Scheme 1 C–C activation of ketone derivatives

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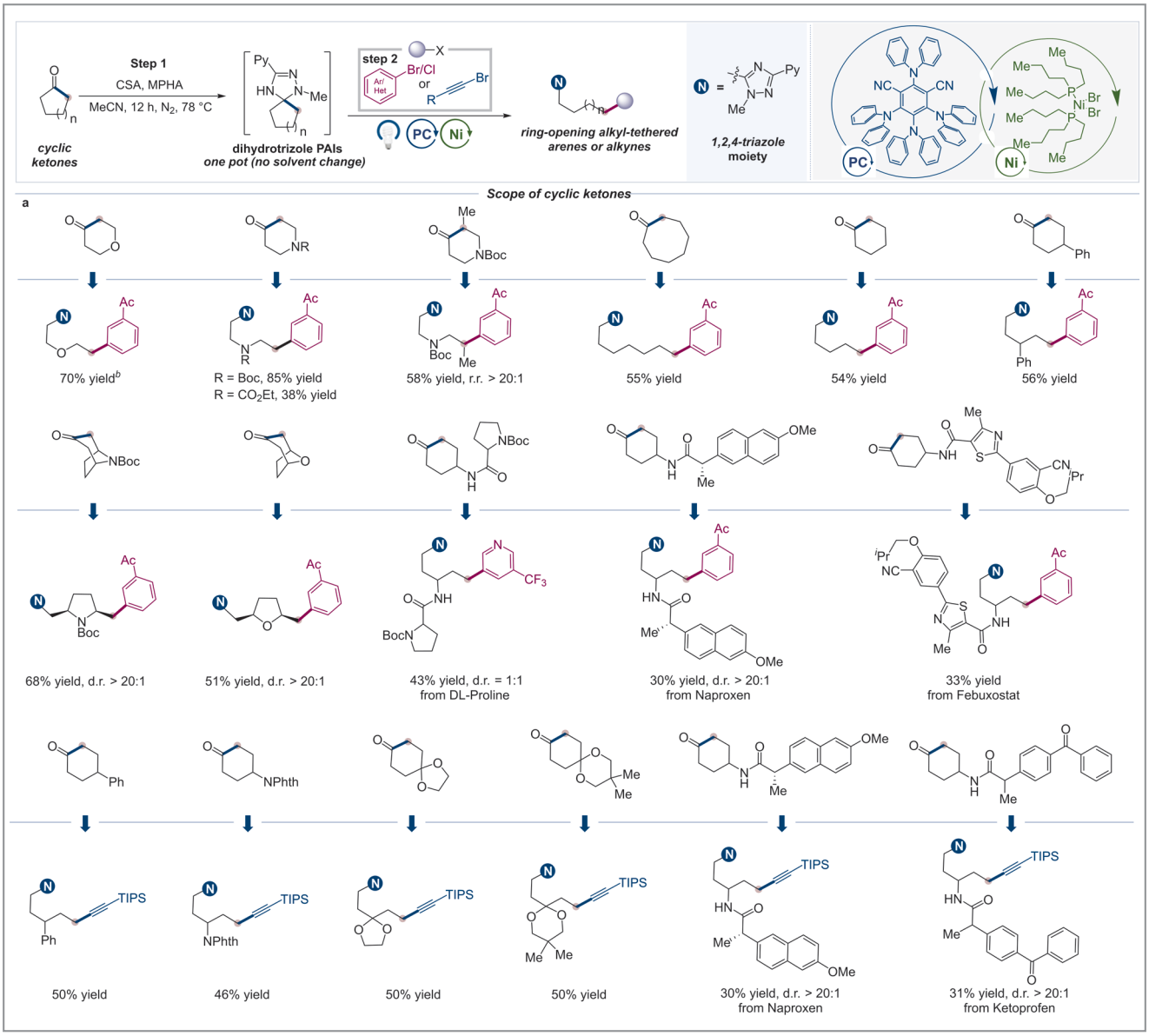
dihydropyrazole[5] and dihydrotriazole[6] derivatives, have been employed to enable C–C activation of ketones. Nonetheless, the harsh reaction conditions and intricate substrate synthesis have strongly limited the substrate scopes and the reaction types (Scheme 1a, right)," explained Professor Zhang, who continued: "Our research focuses on addressing those key challenges associated with this methodology: 1) identifying a mild catalytic system to generate carbon-centered radicals; 2) simplifying substrate synthesis and realizing one-pot operations; and 3) expanding substrate scopes and reaction types. Drawing inspiration from metallaphotoredox catalysis, we have successfully achieved the deacylative arylation and alkynylation of unstrained ketones under dual nickel/photoredox catalysis, providing a reliable method for the preparation of structurally diverse alkyl-tethered arenes and alkynes."

Professor Zhang explained: "The reaction commences with the *in situ* synthesis of a dihydrotriazole pre-aromatic intermediate (PAI) through the condensation of ketones with *N*′-methylpicolino-hydrazonamide (MPHA). This is followed by the oxidative single-electron transfer (SET) from the PAI's



Scheme 2 Selected examples of cyclic and drug-derived ketones

α-C–C bond to generate an alkyl radical, which is subsequently intercepted by Ni(II) species to form organometallic Ni(III) adducts, facilitating the formation of diverse C(sp^3)–C(sp^2)/C(sp) bonds with remarkable generality (Scheme 1b)."

"The reaction represents a novel approach to the deacylative coupling of unstrained ketones, complementing previous deacylative transformation of ketones," said Dr. Beibei Zhan, a co-corresponding author on the paper, who continued: "This protocol tolerates a wide range of ketones, particularly cyclic and drug-related ketones. Remarkably, the regioselective cleavage of the C–C bond predominantly occurs at a more sterically hindered position when employing an unsymmetrical cyclic ketone. Furthermore, a diverse array of aryl halides and alkynyl bromides bearing various functional groups are all compatible in the reaction (Scheme 2)."

"In the future, we will delve into the deacylative coupling reaction of ketones catalyzed by other transition metals," said Professor Zhang, who concluded: "Given the prevalence of the ketone functional group in organic chemistry, we anticipate that the C–C bond activation of unstrained ketones could ultimately become a valuable addition to the chemist's toolbox for creating complex molecular scaffolds."

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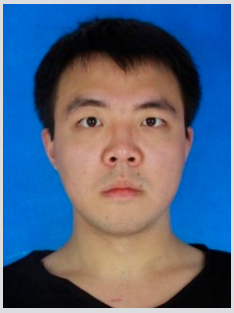
About the authors



B. Zhang

Boyi Zhang obtained his bachelor's degree in applied chemistry in 2021 from Tianjin University (P. R. of China). He will obtain his master's degree in 2024 from Hangzhou Institute for Advanced Study, University of Chinese Academy of Sciences (P. R. of China) under the guidance of Prof. Xiaheng Zhang. His research interests focus on C–C bond activation of ketones.

Dr. H. Bai

Hui Bai received her bachelor's degree in chemistry in 2014 from China Agricultural University (Beijing, P. R. of China), and her PhD in chemistry in 2021 from the same university. Now, she is a postdoctoral scholar at Hangzhou Institute for Advanced Study, UCAS (P. R. of China) under the supervision of Prof. Xiaheng Zhang. In the Zhang group, she focuses on metallaphotoredox reactions.

Dr. B. Zhan

Beibei Zhan received his PhD from Zhejiang University (P. R. of China) in 2020 under the supervision of Prof. Bing-Feng Shi. Subsequently, he joined the Hangzhou Institute for Advanced Study (HIAS), University of Chinese Academy of Sciences (P. R. of China) as a postdoctoral fellow in Prof. Biao Yu's group, where he contributed to the development of Cu-catalysed mild glycosylation. In 2022, he joined the HIAS as an assistant research fellow and his current research focuses on the deacylative transformations of ketones under metallaphotoredox catalysis.

K.-H. Wei

Kai-Hang Wei was born in Zhejiang province. He received his BS degree (2022) from Hangzhou Normal University (P. R. of China). He then joined Prof. Zhang's lab at Hangzhou Institute for Advanced Study, University of Chinese Academy of Sciences (P. R. of China) to pursue his MS degree in organic chemistry. His current research interest focuses on photoredox catalysis and transition-metal-catalyzed selective cross-coupling reactions.

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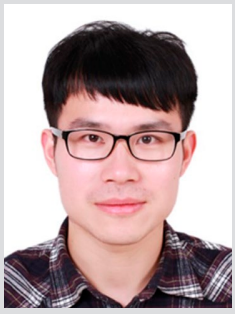
Prof. S. Nie

Shenyou Nie was born in 1986 and received his BS degree (2009) from Wuhan University (P. R. of China). He completed his PhD (2014) at Shanghai Institute of Organic Chemistry (SIOC, P. R. of China) under the supervision of Prof. Biao Yu. He then worked as a postdoctoral researcher at the labs of Prof. Arun K. Ghosh (Purdue University, USA, 2015–2016) and Prof. Yongcheng Song (Baylor College of Medicine, USA, 2016–2020), respectively. He started his independent research at Chongqing Medical University (P. R. of China) in 2020. His research interests focus on the development of small-molecule inhibitors and degraders targeting ferroptosis and cancer, and construction of diverse compound libraries by employing the Ugi reaction, photoredox catalysis and C–H activation/domino strategies.



Prof. X. Zhang

Xiaheng Zhang obtained his PhD in 2015 from Shanghai Institute of Organic Chemistry (SIOC, P. R. of China) with Prof. Biao Yu. He then moved to Princeton University (USA) to pursue postdoctoral studies with Prof. David W. C. MacMillan. He started his independent research at Fudan University (P. R. of China) as an Assistant Professor in 2021. Then he took the position of Associate Professor of Chemistry at Hangzhou Institute for Advanced Study, University of Chinese Academy of Sciences (P. R. of China) at the end of 2021. His research interests include photoredox catalysis and carbohydrate chemistry.

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