Direct Radical Functionalization of Native Sugars

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Carbohydrates exist ubiquitously in numerous living organisms, and their conjugates mediate various crucial biological processes. In these roles, carbohydrate-based compounds therefore gain and drive altered biological functions simply through the attachment of a substituent (small and large) at the anomeric C-1 carbon. However, the low abundance and extraction challenges associated with many bioactive sugar-based molecules found in natural sources, coupled with their enormous heterogeneity, consequentially hamper systematic biological studies. To 'plug this gap', synthetic carbohydrate chemistry has evolved as a branch of organic chemistry to be one of the most reliable technologies, albeit specialized, to attain notable quantities of carbohydrates and their derivatives, as well as useful analogues. Among various glycosides, *C*-glycosyl compounds, as counterparts to natural *O*-glycosides, are considered rarer yet prominent, due to their stability towards hydrolytic enzymes. These have, for example, been used as potential surrogates of *O*-glycosides in developing sugar-based therapeutics. However, unlike enzymatic *C*-glycosylation in which the glycosyl moiety of an unprotected nucleotide sugar donor is precisely transferred to an acceptor through anomeric functionalization with exceptional regio- and stereoselectivity, currently established non-enzymatic *C*-glycosylation mostly relies on a sequential protection, functionalization and deprotection strategy to transfer native sugars into tailored chemical glycosyl donors for subsequent C–C bond coupling delivering targeted *C*-glycosyl compounds. "The long reaction sequence of these approaches inevitably compromises the efficiency and essentially prevents further application in complicate biological milieu," said Prof. Ming Joo Koh from the National University of Singapore, whose research group has a strong interest in the synthesis of complex carbohydrates. He added: "Many research groups, including ours, have endeavoured tirelessly to conceive a protecting-group-free chemical glycosylation approach that can directly transform native sugars into the desired glycosides by selective functionalisation at the anomeric position. However, this has proven to be extremely challenging."

Inspired by biological *S*-glycosylation, a biomimetic 'cap and glycosylate' strategy to directly transfer native sugars into various classes of glycosides and glycoconjugates, thereby bypassing unnecessary protecting group manipulation, has been recently revealed by Prof. Benjamin G. Davis (the Rosalind Franklin Institute and University of Oxford, both in the UK) and Prof. Ming Joo Koh. This direct radical functionalization approach now provides a streamlined access to what the authors consider is essentially equivalent to a 'clean', unprotected glycosyl moiety that allows diverse and robust formation of *C*-, *S*-, *Se*-glycosides, as well as *O*-glycosides. Moreover, because of its aqueous- and bio-compatibility, this protocol can be readily and seamlessly applied even to biomacromolecules, realizing the direct post-translational chemical glycosylation of proteins from sugars that come directly from nature.

Prof. Davis said: "Our group has spent a number of years exploring the idea of inserting information into biological molecules, such as proteins and sugars, to alter their function. One of the things that we have found is that carbon-centred radicals are wonderfully useful yet benign reactive intermediates for achieving new chemistries in biological systems. In this research, by generating free glycosyl radicals as intermediates directly from native sugars, we are trying to mimic what is happening in biology to make the synthesis of these glycosides and glycoproteins far more efficient. This efficient 'harvesting' of native sugars that can be plugged directly into new glycoconjugates has the potential to open up a number of different avenues, including the development of diverse sugar-based therapeutics."

Considering the efficiency, benign reaction conditions and exceptional biocompatibility of this protocol, Prof. Koh concluded: "We believe that this biomimetic 'cap and glycosylate' technology would pave the way towards modernizing carbohydrate and glycoconjugate synthesis without the need for protecting groups. This would bring enormous benefits in saving costs, time and manpower, empowering researchers to rapidly access saccharides and offering a practical platform to introduce fully unprotected glycosyl groups into biological systems."

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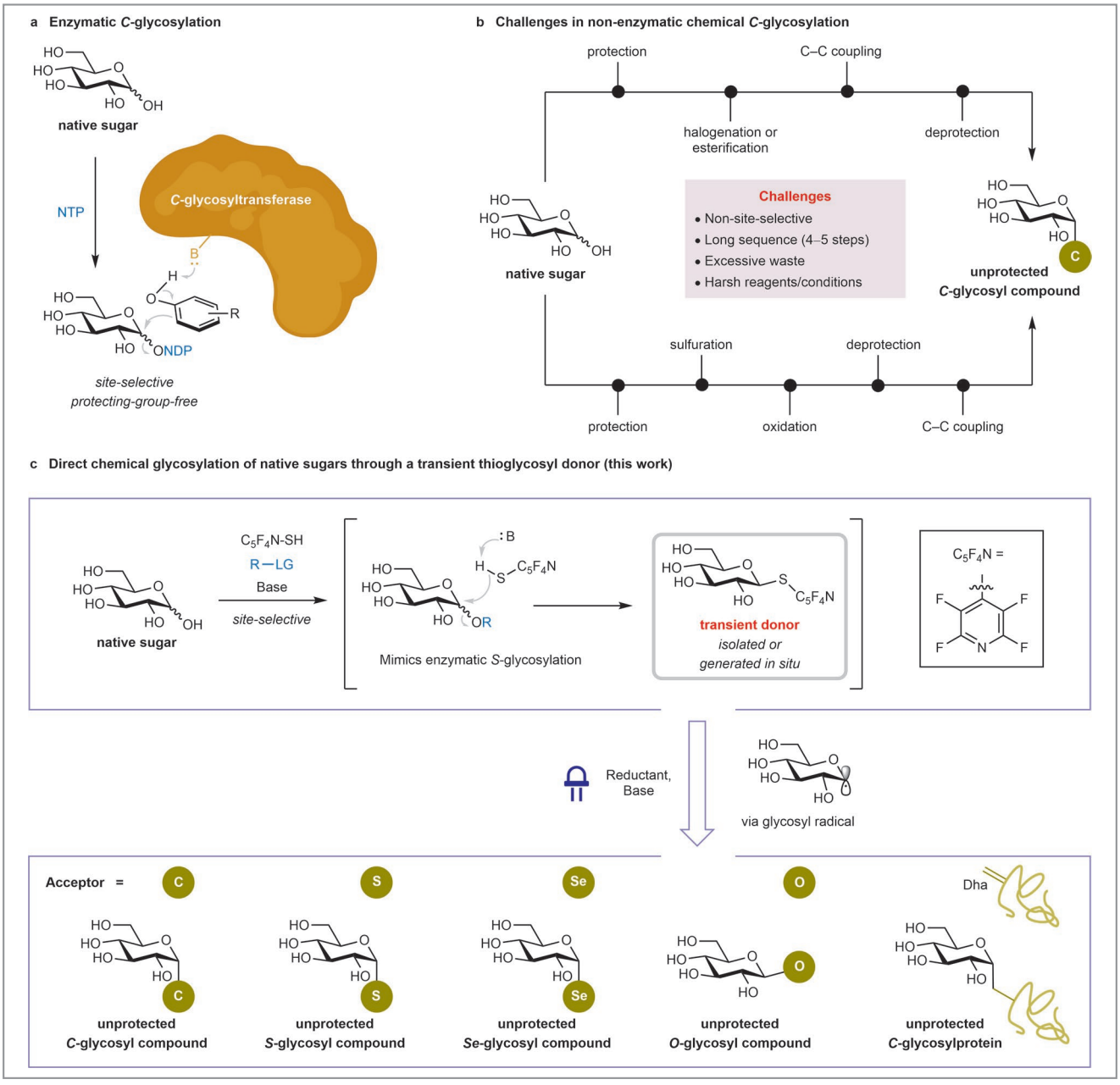

Figure 1 Design of a 'cap and glycosylate' strategy for functionalization of native sugars [credit: Jiang et al., *Nature* **2024**, *631*, 319–327]

About the authors

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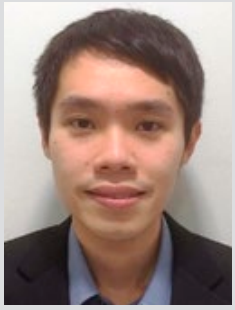
Yi Jiang obtained his B.S. and M.S. degrees from Lanzhou University, P. R. of China. After that, he pursued his Ph.D. studies at the National University of Singapore (Singapore) under the supervision of Prof. Ming Joo Koh and secured his Ph.D. in 2023. In the same year, he joined Prof. Benjamin G. Davis's group at University of Oxford (UK) and the Rosalind Franklin Institute (UK) for postdoctoral studies. His research interests revolve around post-translational mutagenesis of proteins by chemical methods.

Dr. Y. Wei

Yi Wei obtained her Ph.D. in 2019 at Central China Normal University (P. R. of China) under the supervision of Prof. Liang-Qiu Lu and Prof. Wen-Jing Xiao. Starting in 2020, she carried out postdoctoral research at the National University of Singapore (Singapore) with Prof. Ming Joo Koh for three years. Since then, she has begun her independent career at South-Central Minzu University (P. R. of China). Her research interests are mainly focused on light-driven radical-mediated glycosylation.

Prof. B. G. Davis

Benjamin G. Davis received his B.A. (1993) and D.Phil. (1996) at University of Oxford (UK) where he studied carbohydrates with George Fleet. After influential periods at the University of Toronto (Canada) and the University of Durham (UK), he moved to Oxford in 2001 and was promoted to Professor in 2005. In 2019 he became the Science Director for Chemistry at the Rosalind Franklin Institute (UK). The Davis group's research centers on the chemical understanding and exploitation of biomolecular function with an emphasis on carbohydrates and proteins. In 2015, he was elected to the Royal Society.



Prof. M. J. Koh

Ming Joo Koh obtained his Ph.D. with Prof. Amir H. Hoveyda at Boston College (USA) in 2017 and carried out postdoctoral studies in the same group. He joined the Department of Chemistry at the National University of Singapore as an Assistant Professor in 2018 and was promoted to Associate Professor in 2023. Research in the Koh group focuses on developing sustainable and practical transformations that address critical challenges in chemical synthesis through base-metal catalysis, radical chemistry and cross-coupling.

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