SYNLETT Best Paper Award 2022: A Photoenzyme for Challenging Lactam Radical Cyclizations

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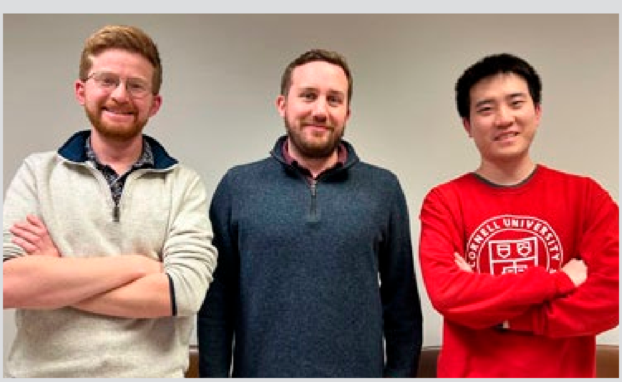
Background. Thieme Chemistry and the Editors of SYNTHESIS and SYNLETT present the 'SYNTHESIS/SYNLETT Best Paper Awards'. These annual awards honor the authors of the best original research papers in each of the journals, considering their immediate impact on the field of chemical synthesis.

Professor Todd K. Hyster, with Bryce T. Nicholls and Tianzhang Qiao, from Cornell University, USA, are the recipients of the SYNLETT Best Paper Award 2022. In disclosing the selection, Benjamin List, Editor-in-Chief of SYNLETT, stated: "Controlling the selectivity of radical reactions is a grand challenge in chemical synthesis and catalysis. By using engineered enzymes that preorganize radical substrates in a confined active site to selectively engage in chemical reactions, Todd Hyster and his team provide a beautiful and general solution to this long-standing problem. In the recognized SYNLETT paper, they courageously underline the power of their photoenzymatic approach by comparing it with traditional tin hydride and more modern methods such as iron hydride and photoredox catalysis, clearly establishing the superiority of radical biocatalysis in reductive radical cyclizations."

SYNFORM spoke with Professor Todd K. Hyster, who was happy to share some background information regarding the prize-winning paper as well as current research activities ongoing in his group.

Biographical Sketches



Left to right: Bryce T. Nicholls, Prof. Todd K. Hyster, Tianzhang Qiao

Todd K. Hyster is an Associate Professor of Chemistry and Chemical Biology at Cornell University (USA). He received his B.S. in chemistry from the University of Minnesota (USA) and did his Ph.D. studies with Tomislav Rovis at Colorado State University (USA). As part of his Ph.D., he was a Marie Curie Fellow with Thomas Ward at the University of Basel (Switzerland), then became an NIH Postdoctoral Fellow with Prof. Frances Arnold at Caltech (USA). He started his independent career at Princeton University (USA) in 2015. His group has developed new methods in photoenzymatic catalysis.

Bryce T. Nicholls was born in Alberton, South Africa. He emigrated to the USA in 2014, and in 2018 he graduated with an A.B. in biochemistry from Kenyon College in Gambier, OH (USA). That same year, he began his Ph.D. studies at Princeton University, NJ (USA) in the research group of Todd Hyster – now at Cornell University in Ithaca, NY (USA). His research focuses on developing new photoenzymatic reactions.

Tianzhang Qiao was born in Qinhuangdao, Hebei Province (P. R. of China). He obtained his B.S. degree in chemistry from Nankai University (NKU, P. R. of China) in 2020. While at NKU, he worked as an undergraduate research assistant in Prof. Shou-Fei Zhu's lab. In 2021, he joined Prof. Todd Hyster's lab at Cornell University (USA) to pursue his Ph.D. in organic chemistry. Tianzhang is interested in biocatalysis, and his current research focuses on ene-reductase-catalyzed non-natural photoenzymatic reactions.

INTERVIEW

SYNFORM *Could you highlight the value of your award-winning paper with respect to the state-of-the-art, as well as the potential or actual applications?*

Prof. T. K. Hyster Our group has been focused on developing methods for synthesizing nitrogen-containing heterocycles because of their prevalence in pharmaceutical and agricultural molecules. One possible strategy is to cyclize acyclic amides. The problem is that rotation around the amide C–N bond is slower than the rate of radical termination. Consequently, most traditional methods for radical cyclization give a mixture of cyclized and acyclic products. In contrast, our photoenzymatic method gives nearly exclusive formation of the cyclized product. This is possible because the enzyme reorganizes the substrate for cyclization prior to radical formation. We think this can be useful to chemists who need to conduct a radical cyclization and want to avoid undesired side product formation.

SYNFORM *Can you explain the origin, motivations and strategy used for conducting the award-winning research?*

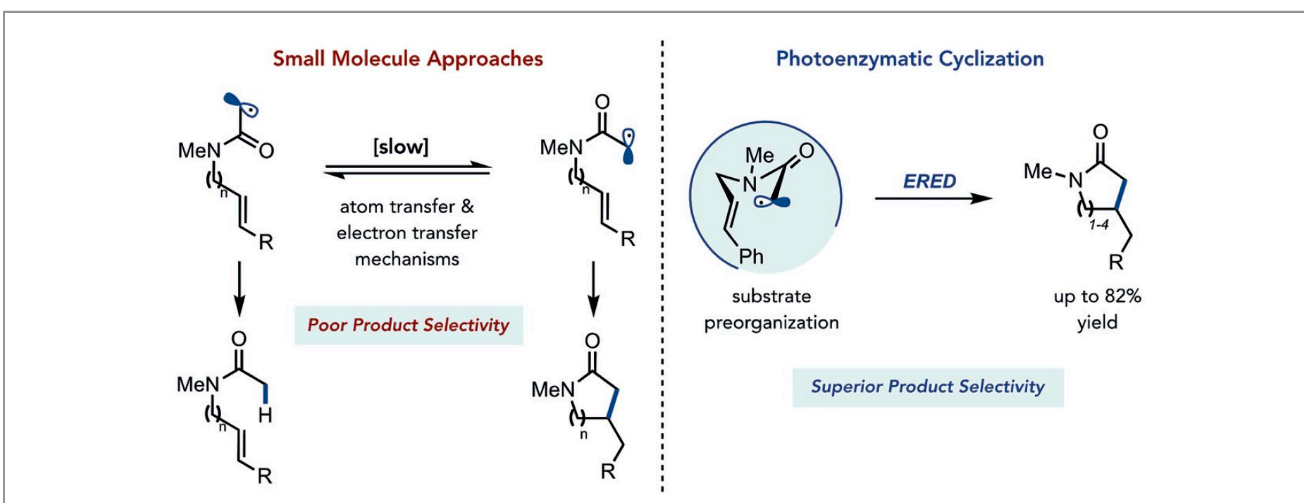
Prof. T. K. Hyster Our group has been focused on developing asymmetric radical cyclizations. When making racemic samples for these reactions, we found that many traditional radical cyclization methods afforded a mixture of cyclized and hydrodehalogenated products. We recognized that our enzymes were better at carrying out these reactions than traditional methods. This work attempted to illustrate the power of biocatalysis not just for asymmetric synthesis but for synthetically challenging bond formations.

SYNFORM *What is the focus of your current research activity, both related to the award paper and in general?*

Prof. T. K. Hyster Our group generally focuses on developing new biocatalytic reactions to solve selectivity challenges in chemical synthesis. We found that when existing enzymes are irradiated with visible light, they gain the ability to carry out electron transfer reactions enabling the formation of organic radicals within their active sites. We are generally interested in how to use this mechanism to facilitate new types of transformations across a broad array of proteins. We recently developed regioselective arene alkylation methods and nontraditional asymmetric cross-electrophile couplings.

SYNFORM *What do you think about the modern role, major challenges and prospects of organic synthesis?*

Prof. T. K. Hyster Small molecule drugs remain an important component of pharmaceutical and agrochemical portfolios. An ongoing challenge is to develop more selective, efficient, and sustainable syntheses. We believe that biocatalysts are an important tool in solving these challenges. It is an incredible time to work in this area because of organic chemists' renewed interest in biocatalysis. Major challenges in this area are to evolve proteins more quickly and to develop enzymes that catalyze reactions that are difficult using traditional



Scheme 1

synthetic approaches. We believe that applying mechanistic insights to unlock new functions can enable the discovery of new bond-forming events currently unknown in the synthetic repertoire. These new disconnections have the potential to significantly accelerate chemical synthesis.

SYNFORM *What does this award mean to you/your group?*

Prof. T. K. Hyster This award is a huge stamp of validation for our group. Working at the interface of many different areas, it can be difficult to know if our work is reaching the desired community. Having synthetic organic chemists at SYNLETT identify our work indicates that we are reaching our desired audience.

Matteo Zanda

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