

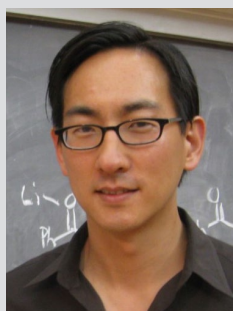
SYNTHESIS Best Paper Award 2018: A General Protocol for Radical Anion [3+2] Cycloaddition Enabled by Tandem Lewis Acid Photoredox Catalysis

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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.

Tehshik Yoon and co-workers, from the University of Wisconsin-Madison in the USA, are the recipients of the SYNTHESIS Best Paper Award 2018. The authors are recognized for their application of tandem Lewis acid photoredox catalysis. According to SYNTHESIS Editor-in-Chief Paul Knochel “It is a paper that is especially appealing since it describes a very general method for performing a radical anion [3+2] cycloaddition leading to highly substituted polyfunctional cyclopentane derivatives starting with readily available styrenes and cyclopropyl phenyl ketones. The tandem Lewis acid/photoredox catalyst is very convenient to prepare and highly effective. It is certainly a very valuable extension of dipolar cycloadditions using photoredox catalysis.” SYNFORM spoke with Prof. Tehshik Yoon, who was happy to share some background information regarding the prize-winning paper as well as current research activities ongoing in his group.

Biographical Sketch



Prof. T. Yoon

Tehshik Yoon is a Professor of Chemistry at the University of Wisconsin-Madison (USA). He received his bachelor's degree in chemistry from Harvard University (USA), where he performed undergraduate research with Prof. David Evans, and his master's degree from Caltech (USA) under the supervision of Prof. Erick Carreira. His Ph.D. thesis with Prof. David MacMillan, first at Berkeley (USA) and then at Caltech, focused

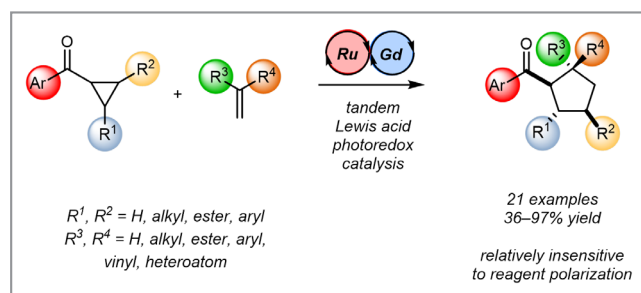
on the development of chiral Lewis acids for enantioselective Claisen rearrangements. After finishing graduate school in 2002, he became an NIH postdoctoral fellow in the laboratory of Prof. Eric Jacobsen at Harvard, where his research involved the development of a hydrogen-bond-donating catalyst for asymmetric nitro-Mannich reactions. Tehshik has been on the faculty at UW-Madison since 2005. His research group has broad interests in organic synthesis and catalysis. In particular, the Yoon group has been pioneering the use of transition-metal

photocatalysts in synthetically useful transformations promoted by visible light. Tehshik's efforts in teaching and research have earned him a variety of prestigious awards, including an NSF CAREER Award (2007), the Research Corporation Cottrell Scholar Award (2008), the Beckman Young Investigator Award (2008), the Amgen Young Investigator Award (2009), an Alfred P. Sloan Research Fellowship (2009), an Eli Lilly Grantee Award (2011), a Friedrich Wilhelm Bessel Award from the Humboldt Foundation (2015), and an ACS Cope Scholar Award (2019).

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. Tehshik Yoon We often hear the Diels–Alder cycloaddition referred to as the “most powerful organic reaction.” Whether or not this assessment is still true in 2019, it is certainly the case that a large variety of six-membered carbocycles can be synthesized in a straightforward manner using Diels–Alder cycloaddition chemistry. Five-membered carbocycles, on the other hand, are comparatively more difficult to assemble. The purpose of the study reported in our paper was to explore the scope of a formal [3+2] cycloaddition that my co-workers had discovered. The reaction involves a novel radical mechanism, which we thought might allow a broad range of reaction partners to participate in the cycloaddition. Our hope was to demonstrate that this new method could start bridging the gap between the capabilities of existing [3+2] cycloaddition methods and reactions as powerful as the Diels–Alder reaction.



Scheme 1 Radical anion [3+2] cycloaddition enabled by tandem Lewis acid photoredox catalysis

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

Prof. Tehshik Yoon This [3+2] reaction was originally inspired by an analogy to the photocatalytic [2+2] cycloaddition that was our first contribution to the field of photoredox catalysis. Our previous work had shown that photoredox reduction of enones afforded reactive radical anions that would react with electron-deficient alkenes to afford cyclobutanes. We imagined that cyclopropyl ketones might behave in an analogous fashion to make cyclopentanes. Interestingly, these two reactions are quite different on a practical and mechanistic level, despite the conceptual analogy that links them. For

instance, we have found that the Lewis acids that are optimal in the [2+2] and [3+2] reactions are not the same. We have also found that the [3+2] reaction engages a very broad range of electronically dissimilar alkene reaction partners, while the [2+2] cycloaddition works only with electron-deficient enone-type structures. This paper's objective was to ascertain how broad the scope of the [3+2] cycloaddition might be.

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

Prof. Tehshik Yoon My laboratory is broadly interested in photochemistry as a tool for organic synthesis. One major thrust of our research is the use of catalysts or other reagents to control the reactivity of photochemically generated reactive intermediates. For instance, we have developed a general strategy for controlling the stereochemistry of photochemical reactions that uses chiral Lewis acids in conjunction with transition-metal photoredox catalysts. Other students in the group are studying how copper salts can divert radical photoredox reactions towards carbocation reactivity.

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

Prof. Tehshik Yoon I think the modern role of organic synthesis remains rooted in its historical role. Synthetic chemistry is indispensable to contemporary science because the structure of a molecular entity dictates its useful physical, electronic, and biological properties. Research at the forefront of the molecular sciences requires access to new molecular compounds, and synthetic organic chemists are unique in their ability to predictably deliver these new structures in practical ways. So the central questions motivating synthetic research remain the same: How do we synthesize new compounds, and how do we synthesize them more efficiently and with better control?

As organic chemistry has matured, it has grown to embrace a much greater variety of technologies and reaction types. For example, one could not be a practicing synthetic organic chemist today without at least a rudimentary grasp of organometallic chemistry, because reactions like cross-coupling and olefin metathesis reactions have become such essential tools in synthesis. So it's gratifying to be a synthetic photochemist during a period when the broader community of synthetic organic chemists are beginning to recognize the capabilities that photochemistry offers; I am optimistic that the tools we are developing will become equally integrated into the arsenal of standard synthetic methods. It's also

exciting to observe the growth of interest in biocatalysis, electrochemistry, and flow chemistry. What makes us synthetic chemists is not any commitment to a specific set of techniques or approaches, but rather the mindset that the construction of complex molecules is an important goal. Any new strategy that makes synthesis more powerful or more efficient, therefore, is a valuable contribution to our field.

This openness to new ideas makes it difficult to offer predictions about the long-term evolution of organic synthesis as a field. Ours is a discipline that has always valued the creativity of its practitioners, and the nature of creativity is to be somewhat unpredictable. But however organic synthesis continues to grow, it will remain a central contributor to the world so long as social problems have molecular solutions.

