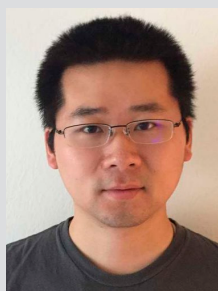


Young Career Focus: Assistant Professor Yang Yang (University of California Santa Barbara, USA)

Background and Purpose. SYNFORM regularly meets young up-and-coming researchers who are performing exceptionally well in the arena of organic chemistry and related fields of research, in order to introduce them to the readership. This Young Career Focus presents Assistant Professor Yang Yang (University of California Santa Barbara, USA).

Biographical Sketch



Asst. Prof. Y. Yang

Yang Yang obtained his B.S. in chemistry from Peking University (P. R. of China) in 2011. He received his Ph.D. in organic chemistry in 2016 under the guidance of Prof. Steve Buchwald at MIT (USA). In the Buchwald lab, he developed CuH-catalyzed methods for the asymmetric hydrofunctionalization of simple olefins. As an NIH Postdoctoral Fellow working with Prof. Frances Arnold at Caltech (USA),

Yang studied biocatalysis and protein engineering and developed biocatalytic asymmetric C–H amination. Yang started his independent career in the Department of Chemistry and Biochemistry at the University of California Santa Barbara (USA) in 2020. By integrating organic chemistry, biocatalysis and protein engineering, the Yang group is reprogramming nature's biosynthetic machineries to address challenging problems in synthesis and catalysis. The Yang group recently coined and implemented two new concepts in biocatalysis, including metalloradical biocatalysis and pyridoxal radical biocatalysis, to enable otherwise challenging asymmetric radical transformations. Yang is a recipient of the Regent's Junior Faculty Fellowship Award (2021), Faculty Career Development Award (2022), NSF CAREER Award (2022), NIH Maximizing Investigators' Research Award (2022), the Thieme Chemistry Journals Award (2023) and the Army Research Office Young Investigator Award (2023).

INTERVIEW

SYNFORM *What is the focus of your current research activity?*

Asst. Prof. Y. Yang By integrating chemistry, biology and artificial intelligence, our group is developing novel enzymatic strategies to tackle daunting challenges in synthesis and catalysis. First, we are addressing long-standing problems in asymmetric catalysis by taking advantage of the intimate enzyme–substrate interaction that can be easily tuned via directed evolution. Second, by synergistically merging small-molecule catalysis and biocatalysis, we are advancing novel biocatalytic processes that are both new-to-biology and new-to-chemistry. Third, we are developing machine learning and laboratory automation methods to accelerate the development of customized biocatalysts with tailored synthetic applications. Collectively, these efforts will provide insight into fundamental synthetic chemistry and enzymology, allowing for the rapid assembly of small molecules and macromolecules of use.

SYNFORM *When did you get interested in synthesis?*

Asst. Prof. Y. Yang When I was in high school, I found an electronic copy of Nicolaou and Sorensen's book *Classics in Total Synthesis*. The beautiful structures and elegant syntheses in this book spurred my early interest in organic synthesis. Throughout my career, I have had the privilege to work with the best mentors who have been incredibly supportive. My experience working with them fostered my passion for organic synthesis. Working with Professor Jianbo Wang at Peking University as an undergraduate student, I developed a good understanding of organic reaction mechanisms. My summer research with Professor Neil Garg at UCLA allowed me to see the synergy between total synthesis and synthetic method-

ology. My graduate research with Professor Steve Buchwald at MIT led me to appreciate the power of impactful fundamental research in solving real-world problems. Working closely with Steve also prompted me to maintain a high standard in my own research. Furthermore, my postdoctoral training with Professor Frances Arnold at Caltech prepared me to tackle difficult problems in organic synthesis using an interdisciplinary approach combining protein engineering and enzymology. Frances' vision for directed evolution and biocatalysis has always been extremely inspiring.

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

Asst. Prof. Y. Yang I think that organic synthesis remains a central discipline to discover fundamentally new reactivity that can both satisfy our curiosity and find utility in the real world. In my opinion, new concepts of catalysis and new catalyst development remain the central innovation engine in modern organic synthesis. It is new concepts of catalysis and new forms of catalysts that differentiate us from organic chemistry pioneers, when it comes to what types of new reactions that could not be imagined a few decades ago. To push organic chemistry to the next level of sophistication and practicality, it is imperative for us to innovate, and not just to revisit what was discovered a few decades ago. As researchers and educators, it is our responsibility to convey the excitement of fundamental organic chemistry research to the new generation of students. Organic chemistry is fun, not only because it is useful in the pharmaceutical and agrochemical industries, but also because it can be rationalized and there remain new exciting reactivities to be discovered.

SYNFORM *Could you tell us more about your group's areas of research and your aims?*

Asst. Prof. Y. Yang Since we started at the University of California Santa Barbara in 2020, my group has made contributions to two areas of stereoselective radical biocatalysis, including metalloradical biocatalysis and pyridoxal radical biocatalysis.

In the first area, by leveraging the unique redox property of first-row transition-metal cofactors spanning a wide potential window, we repurpose and evolve natural metalloenzymes to catalyze unnatural free-radical reactions in a stereocontrolled fashion. Our group is the first to coin and implement the general concept of "metalloradical biocatalysis" to impose stereocontrol over fleeting radical intermediates.¹⁻³ Using metalloradical biocatalysis, we developed atom-

transfer radical reactions, whose asymmetric catalysis has long eluded synthetic organic chemists.

In the second area, by converting natural two-electron pyridoxal enzymes to catalyze single-electron processes, we develop pyridoxal radical biocatalysis to enable the stereoselective synthesis of valuable non-canonical amino acids (ncAAs), including those possessing multiple contiguous stereocenters that are difficult to prepare by other means (Scheme 1). Our group is the first to design and implement "synergistic photoredox-pyridoxal radical biocatalysis" as a general strategy for convergent ncAA synthesis without protecting groups through a radical mechanism.⁴

SYNFORM *What is your most important scientific achievement to date and why?*

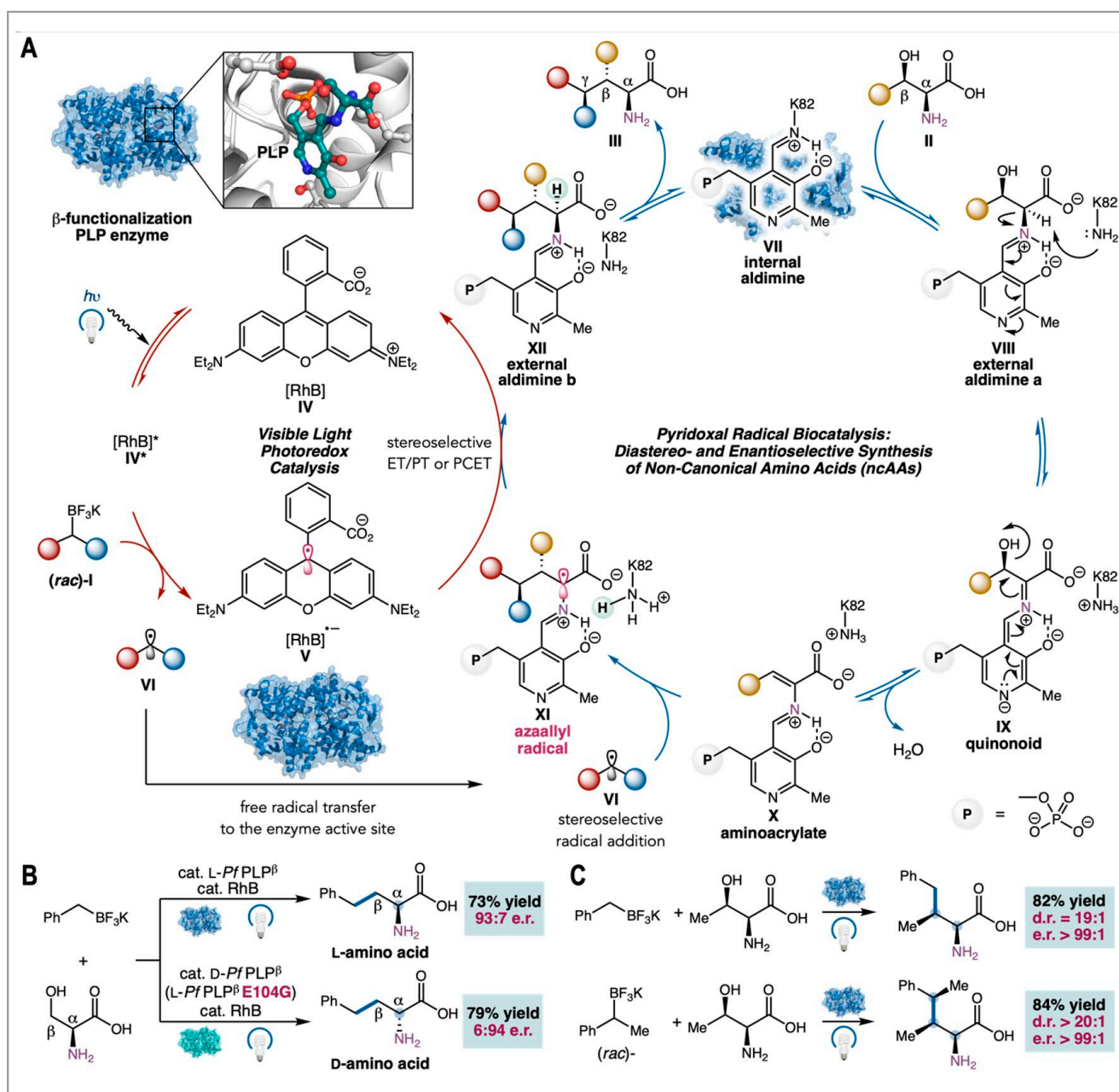
Asst. Prof. Y. Yang In my mentored research with Professor Steve Buchwald at MIT, I made contributions to copper(I) hydride catalyzed asymmetric hydrofunctionalization of olefins. Working closely with other labmates, I developed a CuH-catalyzed asymmetric hydroamination of unactivated internal olefins.^{5,6} Working with my long-term computational collaborator Prof. Peng Liu at the University of Pittsburgh, I rationalized the unusual ligand effect involving DTBM-SEGPHOS by attractive dispersion interactions.⁶ I also developed a set of Cu-catalyzed methods for the asymmetric addition of olefin-derived nucleophiles to carbonyls and imines.⁷⁻¹² These methods allow abundant olefins to be used as latent organometallic reagents in carbonyl and imine addition chemistry. Together, these methods allowed for a range of amines and alcohols, including those possessing multiple contiguous stereogenic centers, to be prepared with excellent stereocontrol.

In my independent research, my group developed two new modes of stereoselective radical biocatalysis. Our metalloenzyme work allowed atom-transfer reactions that were not previously known in the biological world to be developed with evolved metalloproteins.¹⁻³ These stereocontrolled biotransformations provided a new means to impose stereocontrol over free-radical intermediates. By synergistically merging photoredox catalysis and pyridoxal radical biocatalysis, we advanced a new mode of catalysis which is not known in either synthetic organic chemistry or biochemistry.⁴ Pyridoxal radical biocatalysis has the potential to furnish a wide range of non-canonical amino acids with excellent diastereo- and enantiocontrol.

SYNFORM *What is the most exciting aspect of your job, the one you like the most?*

Asst. Prof. Y. Yang The most exciting aspect of my job as a researcher is to work with talented young students and post-docs. They contribute key ideas to our ongoing program and get challenging projects to work. None of my published work at UCSB would be possible without

Mattias Fomale



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