New Strategies for Stereoselective Radical Biocatalysis

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Abstract: Radical reactions have enjoyed widespread applications in small molecule and macromolecule synthesis. However, due to the lack of exploitable stereocontrol elements in synthetic systems, steering the absolute and relative stereochemistry of free radical transformations is notoriously difficult in asymmetric catalysis. Combining synthetic chemistry and biocatalysis, our group advanced two new strategies for stereoselective free radical processes. First, by capitalizing on the innate redox properties of first-row transition-metal cofactors in natural metalloproteins, we repurposed natural metalloproteins to catalyze unnatural radical reactions in a stereocontrolled fashion. Through a metalloenzyme-catalyzed atom transfer mechanism, a range of radical-mediated enzymatic C–C, C–Br, and C–F bond formation proceeded with excellent stereocontrol. These evolved metalloenzymes readily function in bacterial cells, displaying excellent total turnover numbers (up to 20,000) and diastereo- and enantioselectivities. Second, by merging visible light photoredox catalysis and biocatalysis, we advanced a new mode of pyridoxal radical biocatalysis which is unprecedented in biochemistry and organic chemistry. This synergistic photoredox–pyridoxal biocatalysis allowed us to repurpose a range of pyridoxal phosphate (PLP)-dependent enzymes as radical enzymes, leading to novel radical PLP enzymology not previously known in either organic chemistry or biochemistry. Pyridoxal radical biocatalysis provides access to a range of non-canonical amino acids, including those bearing a stereochemical dyad or triad or a tetrasubstituted stereocenter, with excellent diastereo- and enantiocontrol. Collectively, new-to-nature radical biocatalysis provides a new solution to discover new modes of catalysis involving transient free radical intermediates, allowing radical transformations to proceed with excellent stereocontrol.

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Biosketch: Dr. Yang obtained his B.S. in Chemistry from Peking University in 2011. He received his Ph.D. degree in Organic Chemistry in 2016 under the guidance of Prof. Steve Buchwald at MIT. 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, Dr. Yang studied biocatalysis and protein engineering and developed biocatalytic asymmetric C–H amination. Dr. Yang started his independent career in the Department of Chemistry and Biochemistry at the University of California Santa Barbara in 2020. By integrating synthetic chemistry, biocatalysis, protein engineering and computational tools, the Yang group is reprograming nature's biosynthetic machineries to address challenging problems in synthesis, catalysis and biomolecular engineering. The Yang group recently coined and implemented two new strategies to advance novel stereoselective biocatalytic reactions, including metalloredox radical biocatalysis and pyridoxal radical biocatalysis. Dr. 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), Thieme Chemistry Journals Award (2023), Army Research Office Young Investigator Award (2023), Packard Fellowship (2023) and Sloan Research Fellowship (2024).