Biocatalytic Site- and Enantioselective Oxidative Dearomatization of Phenols

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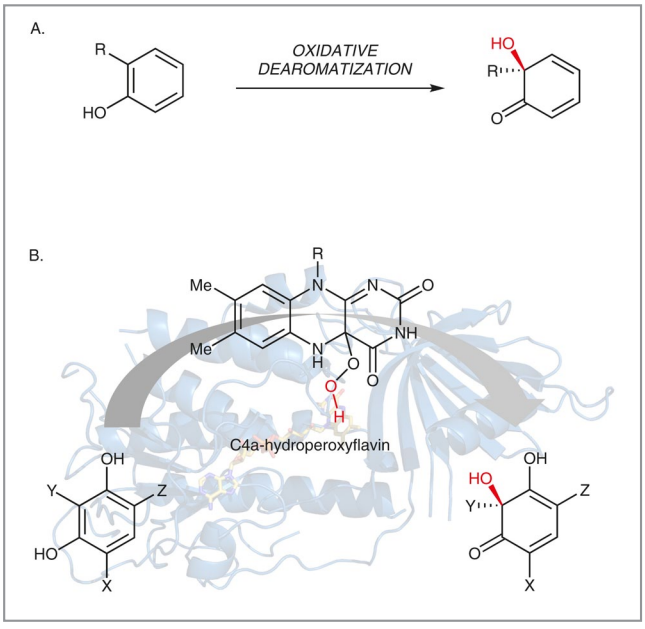
Improving selectivity in the oxidation of complex molecules continues to motivate synthetic chemists to devise innovative new strategies and reagents. The oxidative dearomatization of phenols to afford quinol products is one transformation that presents both site- and stereoselectivity challenges, with the opportunity to hydroxylate at either the *ortho*-position or the *para*-position relative to the phenolic hydroxyl group.

The group of Professor Alison Narayan at the University of Michigan (Ann Arbor, USA) recognized the utility of this transformation and sought to develop a selective catalytic method for the generation of quinol products. Prof. Narayan and her team said: "We were inspired by Nature's mechanism for accomplishing oxidative dearomatization using flavin-dependent monooxygenases, which rely on the generation of a hydroperoxyflavin species which interacts with a phenolic substrate (Scheme 1). In enzymatic oxidative dearomatization, both site- and stereoselectivities in the reaction are controlled by the pose of the substrate within the enzyme's active site relative to the hydroperoxyflavin cofactor."



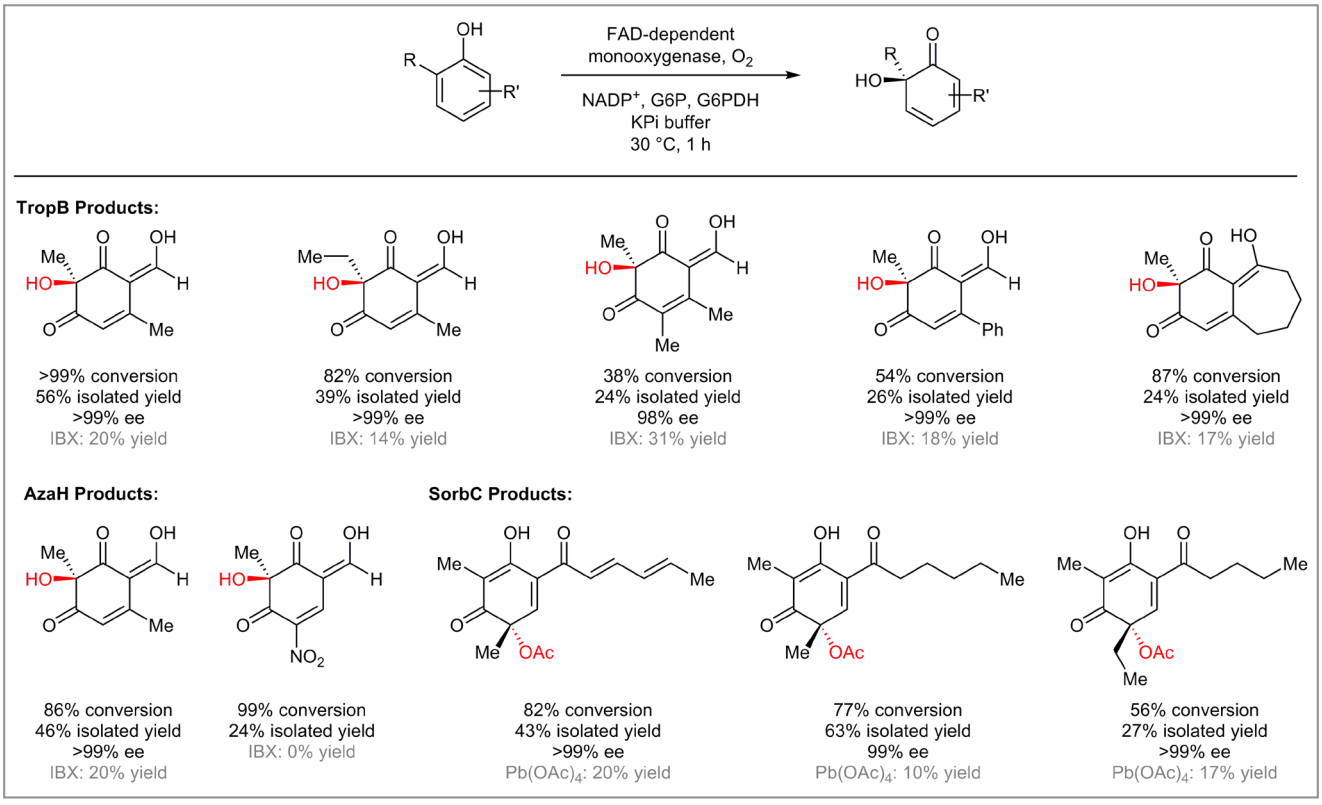
Scheme 1 Site- and stereoselectivities in oxidative dearomatization

April Lukowski, a graduate student in the University of Michigan Program in Chemical Biology, initiated the work in the Narayan lab by expressing and purifying three proteins known to mediate oxidative dearomatization of phenolic intermediates in three unrelated secondary metabolite pathways. Chemistry graduate student Summer Baker Dockrey then evaluated the substrate promiscuity of each enzyme by profiling activity against a panel of sterically and electronically diverse phenolic substrates. "This initial study defined the subset of substrates each enzyme could efficiently oxidize," remarked Professor Narayan. She continued: "While each enzyme demonstrated a substrate scope much broader than the single biosynthetic intermediate it was evolved to process, there was still an outstanding question – were unnatural products being produced with site- and stereoselectivities that matched those of the natural products? Full characterization of products from the enzymatic dearomatization reactions indicated that both the site- and stereoselectivities were preserved across a range of compounds (Scheme 2)."

Initial experiments were carried out using purified protein, which began to constrain the researchers' workflow as the scale of reactions shifted from tens of milligrams to gram scale. "To address this challenge, we explored the use of whole *E. coli* cells used to overexpress each protein directly in reactions, without lysing the cells," explained Professor Narayan. Using this method, the team could store lyophilized cells containing each enzyme in the freezer for months and use these directly in preparative-scale reactions as desired (Figure 1).

"To demonstrate the utility of this biocatalytic oxidative dearomatization, we coupled the generation of reactive quinol products with a second step, either chemical or enzymatic, in the same reaction vessel," said Professor Narayan. She continued: "Using this strategy, Ms. Baker Dockrey, working together with graduate student Marc Becker, completed the one-pot synthesis of three natural products from phenolic starting materials."

Professor Narayan concluded: "We anticipate that the orthogonality and high levels of both site- and stereoselectivities of the method will entice chemists to use these biocatalysts."



Scheme 2 Substrate scope of enzymatic dearomatization

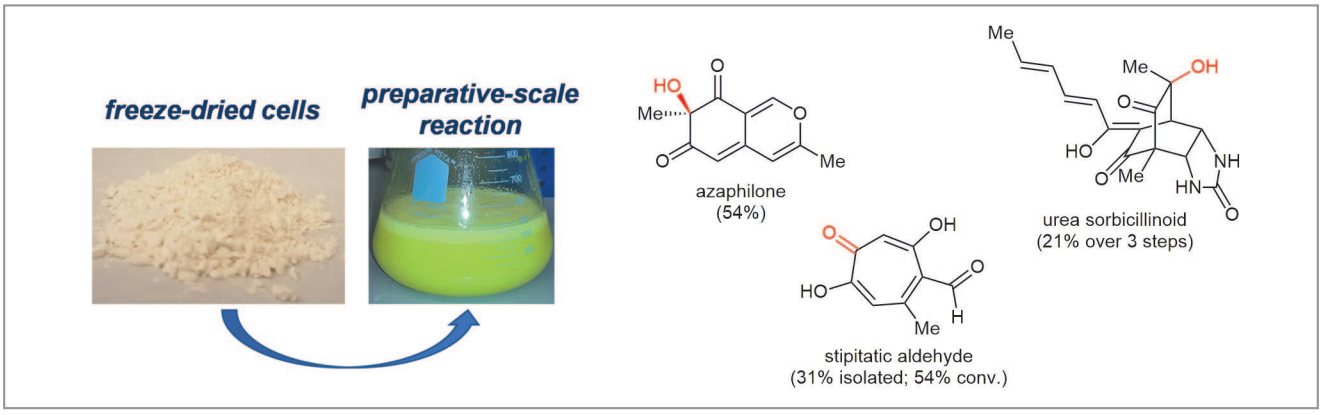


Figure 1 Preparative-scale enzymatic dearomatization using lyophilized *E. coli* cells

About the authors

S. Baker Dockrey

Summer Baker Dockrey obtained an A.B. in Chemistry from Bryn Mawr College (USA) in 2015, where she worked under Professor Jason Schmink on the development of Corey-Seebach umpolung reagents as nucleophiles in palladium-catalyzed cross-coupling reactions. She joined the Narayan Lab in 2016 where she has focused on identifying enzymes from secondary metabolite pathways with potential synthetic utility and developing methods based on these biocatalysts to enable access to biologically active target molecules.

A. Lukowski

April Lukowski graduated from Saginaw Valley State University (USA) in 2015 with a B.S. in biochemistry where she studied plant enzymology and analytical biochemistry. She worked on projects pertaining to the identification of isoprene synthases in conifers and the quantification of bacterial contamination in local waterways. Inspired by enzymes nature and their abilities to perform complex reactions, she began her doctoral studies in the Program in Chemical Biology and the University of Michigan (USA) in 2015, joining the Narayan lab. Her favorite part of her research is expressing and purifying new proteins and uncovering their activities.

M. Becker

Marc Becker was born in Germany and received his B.S. and M.S. degree in chemistry at the University of Muenster, Germany. In 2016, he started his graduate studies at the University of Michigan (USA), where he is currently pursuing his Ph.D. under the supervision of Prof. Corinna S. Schindler. His research interests are method development and their application in natural product synthesis.

Prof. A. Narayan

Alison Narayan earned a B.S. in Chemistry from the University of Michigan (USA). She completed her Ph.D. at the University of California, Berkeley (USA), where she developed novel methods for the synthesis of nitrogen heterocycles and the total synthesis of complex natural products in the group of Prof. Richmond Sarpong. As a Life Sciences Research Foundation Postdoctoral Fellow, Alison studied natural product biosynthesis and biocatalysis with Prof. David Sherman. In 2015, Alison began her independent career as an assistant professor in the Department of Chemistry and the Life Sciences Institute at the University of Michigan. The Narayan lab is focused on elucidating the function of enzymes involved in natural product biosynthesis and the development of biocatalytic synthetic methods.

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