NEWS AND VIEWS NEWS AND VIEWS NEWS AND VIEWS

A Biocompatible Alkene Hydrogenation Merges Organic Synthesis with Microbial Metabolism

Angew. Chem. Int. Ed. **2014**, *53*, 7785–7788

The metabolism of living organisms, such as microbes, is a powerful tool for producing small molecules directly from fermentations in an efficient and environmentally compatible manner. However, the potential of microbial metabolism would be dramatically boosted if 'traditional' organic synthesis could be efficiently combined with enzymatic methods in living organisms. This remains a challenging endeavor owing to the non-aqueous solvents, extreme temperatures, and reactive intermediates generally used in non-enzymatic synthesis. Recently, a paper published by the research group of Professor Emily Balskus, Harvard University (USA), described a novel approach to this problem and their subsequent successful effort to actually integrate a reaction from synthetic organic chemistry with the chemistry that happens in the biological realm for the purposes of small molecule synthesis. Professor Balskus gave some background on this topic: "I fell in love with chemistry as a high school student and kept pursuing it into my graduate studies, which focused on a mix of asymmetric catalysis and natural product total synthesis. As a postdoc, I became interested in studying the chemistry that happens in biological systems, and for my independent career I wanted to focus on innovative science that can weave these two threads together. My lab's research merges chemical and biological synthesis in multiple ways."

Synthetic chemists have made great strides in bringing biological reactivity (e.g. enzymes and biocatalysis) into the chemical realm, and Professor Balskus hopes this paper shows that the reverse may also be possible, i.e. using reactions and catalysts familiar to synthetic organic chemists in the biological realm. "Over the past century, synthetic chemists have made enormous contributions to both science and society, and we now have an amazing capability to access non-natural small molecules," said Professor Balskus, adding: "Metabolic engineers would like to advance their field to the point where their ability to produce small molecules rivals or surpasses that of synthetic chemists, which is an admirable goal." Professor Balskus continued: "One of the main obstacles I see to achieving that level of synthetic prowess in the biological realm is that there are certain types of chemical reactivity that have not yet been observed in nature." Making certain bond connections is not possible using enzymatic chemistry, explained Professor Balskus, and evolving enzymes to carry out these transformations is still a long way off. "This situation is incredibly common when the small

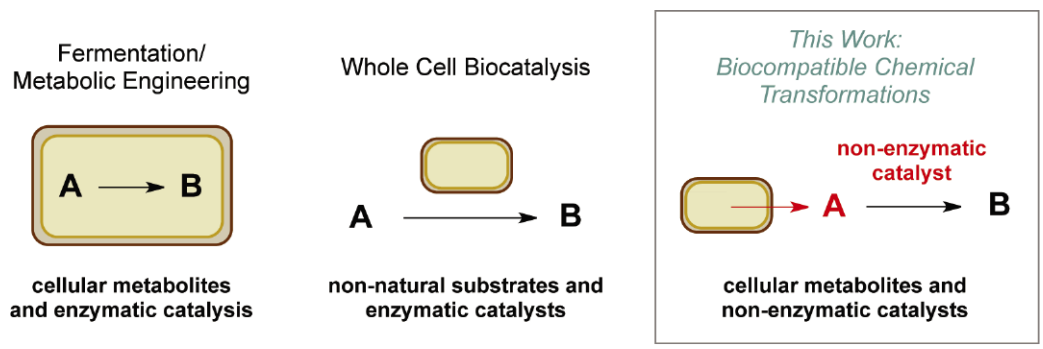

Figure 1 *Overview of biocompatible chemistry*

SYNFORM, 2014/11
Published online: 20.10.2014, **DOI**: 10.1055/s-0034-1379177

molecule target of interest is something like a non-natural pharmaceutical, such as drugs like Lipitor or Januvia," Professor Balskus noted. "So, for metabolic engineers to actually reach their goal, they will need some way to bring the synthetic chemist's repertoire into a biological reaction milieu. That is what we describe in this paper," she explained. "We developed what we have termed 'biocompatible chemistry', the interfacing of a non-enzymatic transformation with the metabolism of a living organism (Figures 1 and 2). This report is a demonstration that such a combination is possible, and we hope that it inspires other scientists, both metabolic engineers and synthetic chemists, to think about how they can bring the power of synthetic organic chemistry to bear on difficult metabolic engineering challenges."

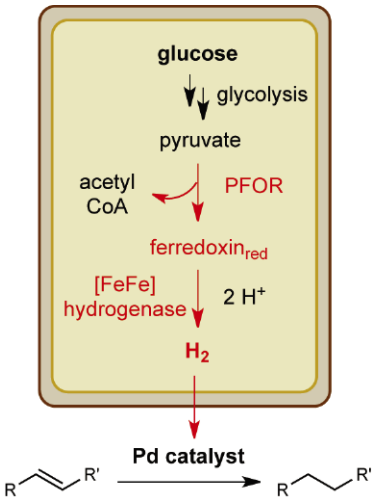

Figure 2 *Bacterially produced hydrogen gas is used in situ for an alkene reduction*

In thinking about the specifics of the paper, one thing that surprised Professor Balskus looking back was how similar the process of developing this reaction was to optimizing any other reaction that she and the co-authors of this work, Dr. Gopal Sirasani and Mr. Liuchuan Tong, have worked on. Professor Balskus said: "Our very early experiments showed that the desired reactivity and compatibility were possible, and from there it was a matter of optimizing the catalyst and reaction conditions. To us, it is very encouraging that many of the reaction conditions we tried did indeed yield product, we didn't just happen upon the one set of conditions that would work in some unique way. The approach we took to reaction development is familiar to all organic chemists, which is why I'm optimistic others will join us in exploring this new frontier in synthesis," she concluded.

Matteo Zanda

About the authors

Prof. E. Balskus

Emily Balskus was born in Cincinnati, Ohio (USA) and became interested in chemistry as a high school student. She graduated from Williams College (USA) in 2002 as valedictorian with highest honors in chemistry. After spending a year at the University of Cambridge (UK) as a Churchill Scholar in the lab of Professor Steven Ley, she pursued graduate studies in the Department of Chemistry and Chemical Biology (CCB) at Harvard University (USA), receiving her PhD in 2008. Her graduate work with Professor Eric Jacobsen focused on the development of asymmetric catalytic transformations and their application in the total synthesis of complex molecules. From 2008–2011 she was an NIH postdoctoral fellow at Harvard Medical School in the lab of Professor Christopher T. Walsh. Her research in the Walsh lab involved elucidating and characterizing biosynthetic pathways for the production of small molecule sunscreens by photosynthetic bacteria. She also received training in microbial ecology and environmental microbiology as a member of the Microbial Diversity Summer Course at the Marine Biology Lab at Woods Hole during the summer of 2009.

Emily joined the CCB faculty in 2011. She is also an Associate Member of the Broad Institute of Harvard and MIT and is a Faculty Associate of the Microbial Sciences Initiative at Harvard. Her independent research has been recognized with multiple awards, including the 2011 Smith Family Award for Excellence in Biomedical Research, the 2012 NIH Director's New Innovator Award, and the 2013 Packard Fellowship for Science and Engineering. She is also a 2012 Searle Scholar.

SYNFORM, 2014/11
Published online: 20.10.2014, **DOI**: 10.1055/s-0034-1379177