MULTISTEP SYNTHESIS

Cycloalkenes from plant oil in one pot

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Chemical and biological catalysts can provide complementary tools to valorize renewable chemicals. In principle, operating them in concurrent cascade reactions could reduce work steps, operation time and waste, while potentially enhancing overall selectivity and yield. However, the combination of homogeneous and biological catalysts in one pot usually faces compatibility challenges.

Now, Shuke Wu, Thomas R. Ward and colleagues report complex chemo-enzymatic cascade reactions for the production of cycloalkenes — traditionally sourced from petroleum and used as bulk chemicals in various industrial processes — from renewable starting materials. Compatibility issues between the homogeneous metathesis catalyst and the enzymes were circumvented by compartmentalization of the biocatalysts within *E. coli* whole-cells — rather than relying on isolated enzymes.

Specifically, the combination of the whole-cell biocatalysts with the chemical metathesis catalyst allowed the production of cyclopentene, cyclohexene and cycloheptene in one pot from bio-based resources. One synthetic route included an enzymatic oxidative decarboxylation of oleic acid (which is usually derived from plant oils such as olive oil) affording 1,8-heptadecadiene that underwent ring-closing metathesis in the reaction mixture in the presence of the chemical catalyst to yield cycloheptene. Integration of a

lipase enzyme even facilitated the one-pot synthesis of cycloheptene using olive oil as a starting material via initial hydrolysis to oleic acid. Another chemo-enzymatic cascade — involving hydration, oxidation, hydrolysis, decarboxylation and metathesis — led to the production of cyclopentene and cyclohexene from olive oil. Hereby *E. coli* strains expressing up to nine recombinant enzymes were used to produce either 1,6-heptadiene or 1,7-octadiene, which ultimately underwent ruthenium-catalysed ring-closing metathesis.

In general, this work demonstrates the feasibility of synergizing enzymes with homogeneous chemical catalysts in highly complex cascade reactions for the production of value-added chemicals from renewable resources. Interfacing a biocompatible organometallic catalyst with multi-enzymatic cascade reactions allowed one-pot transformations that appear inaccessible with enzymes or small-molecule catalysts alone. In the future, unlocking synthetic routes by following this approach and subsequent optimization might provide sustainable processes based on renewable resources that could replace the industrial manufacturing of certain chemicals from fossil-fuels.

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