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An Enzymatic Alder–Ene Reaction

Nature **2020**, 586, 64–69, DOI: 10.1038/s41586-020-2743-5.

Identification of the First Enzyme-Catalyzed Alder–Ene Reaction

Significance: The groups of Zhou, Houk, and Tang report the discovery of an enzymatic Alder–ene reaction, involved in the biosynthesis of the leporin 2-pyridone alkaloids pyridoxatin and cordy-pyridone. The predicted SAM-independent O-methyltransferase-fold (OMT-fold) enzymes AdxI, Epil, PdxI, ModxI, Upil, and Hpil were identified as pericyclase enzymes that catalyze the stereoselective dehydration of the alcohol substrate to a (Z)-quinone methide and its subsequent pericyclic transformations. The origin of periselectivity was unraveled by a combination of computational studies, crystallography, and site-directed mutagenesis.

Comment: The authors expanded the array of known pericyclase enzymes by identifying two homologous groups of enzymes that catalyze the same stereoselective syn-dehydration of a pyridone alcohol substrate, but with divergent periselectivity. Crystal structure data of PdxI and computations suggest that a lysine residue acts as general acid catalyst to favor the Alder–ene over the hetero-Diels–Alder pathway. In Hpil, a valine residue in the active site is substituted by a methionine residue that prevents this key interaction thus selectively providing the O4-hetero-Diels–Alder product.

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