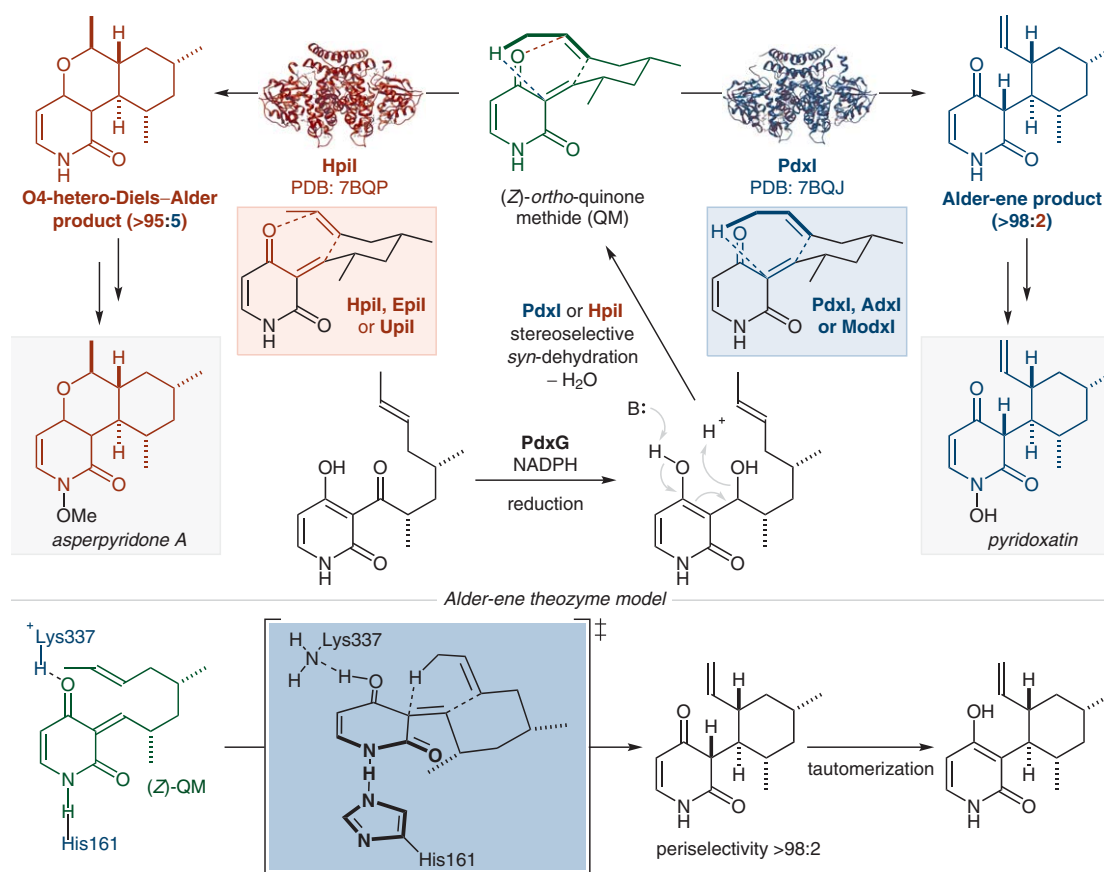


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An Enzymatic Alder–Ene Reaction

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# 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 Adxl, Epil, Pdxl, Modxl, 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 Pdxl 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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