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An Enzymatic Alder–Ene Reaction

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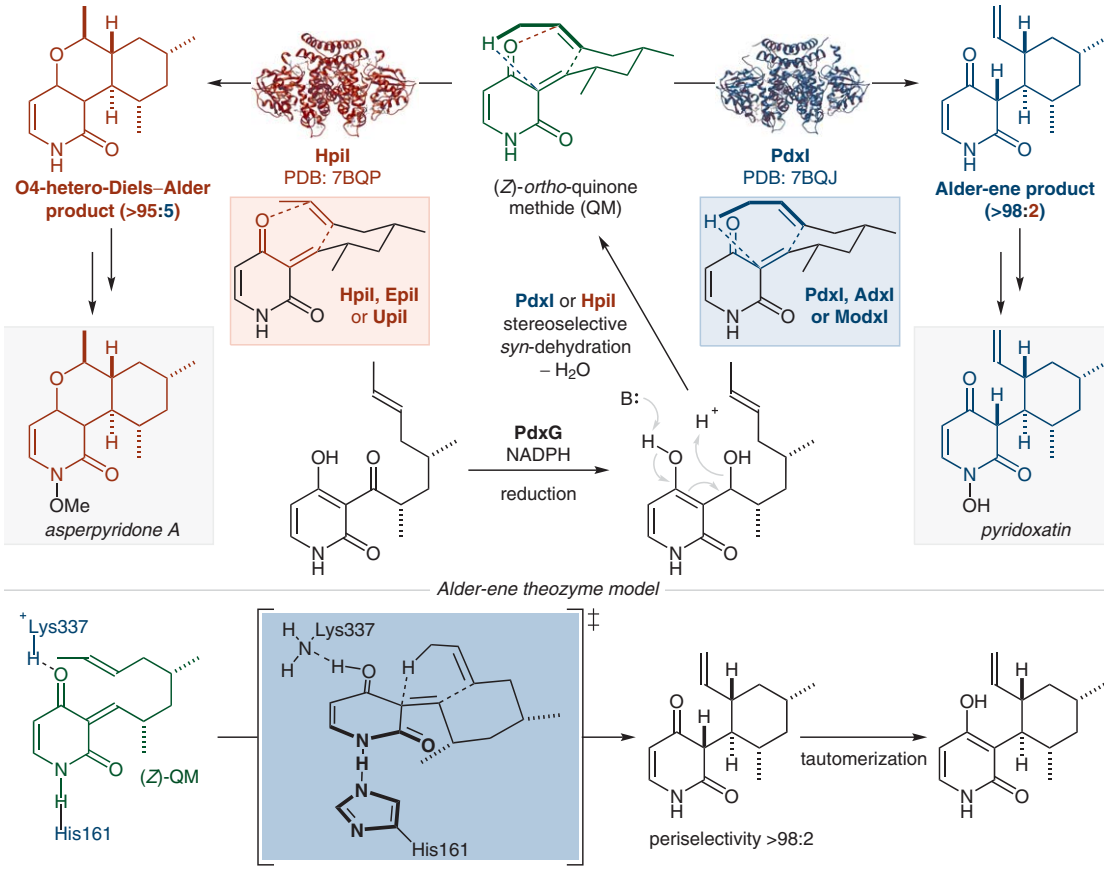
Identification of the First Enzyme-Catalyzed Alder–Ene Reaction



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 cordypyridone. The predicted SAM-independent *O*-methyltransferase-fold (OMT-fold) enzymes AdxI, EpiI, PdxI, ModxI, UpiI, and HpiI 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 HpiI, 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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Category

Organo- and Biocatalysis

Key words

Alder–ene reaction

hetero Diels–Alder reaction

periselective pericyclase

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