Engineered Biocatalyst Permits Enantioselective Morita–Baylis–Hillman Reaction

**Significance:** Lovelock, Green, and co-workers disclose a biocatalytic enantioselective Morita–Baylis–Hillman (MBH) reaction between enones and aromatic aldehydes catalyzed by engineered variants of a hydrolase (BH32.14 and BH32.8). Mechanistic studies suggest a histidine residue serving as the nucleophile that covalently binds the activated alkene. Multiple subsequently formed oxyanion intermediates are stabilized by a conformationally flexible arginine. The products of the C–C bond-forming reaction are obtained in moderate to high yields and with poor to excellent enantioselectivities.

**Comment:** By combining computational design with directed evolution, the authors developed an enzyme-engineering protocol that permitted the development of two nonnatural biocatalysts for the MBH reaction. While the less-evolved BH32.8 tolerates a broader range of substrates, the highly specialized BH32.14 operates more efficiently and enantioselectively. Based on DFT calculations, a catalytic mechanism is proposed that exhibits strong similarities to small-molecule systems (see for example: G. W. Amarante et al. Chem. Eur. J. 2009, 15, 12460).