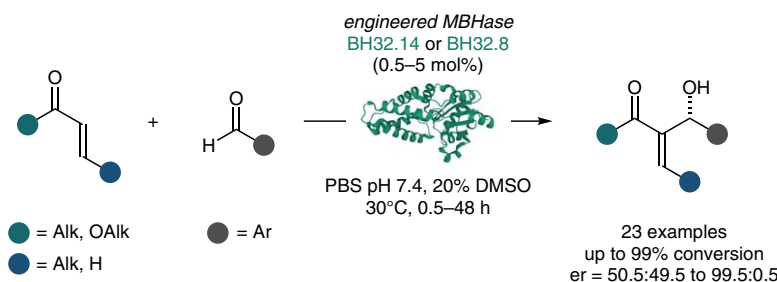
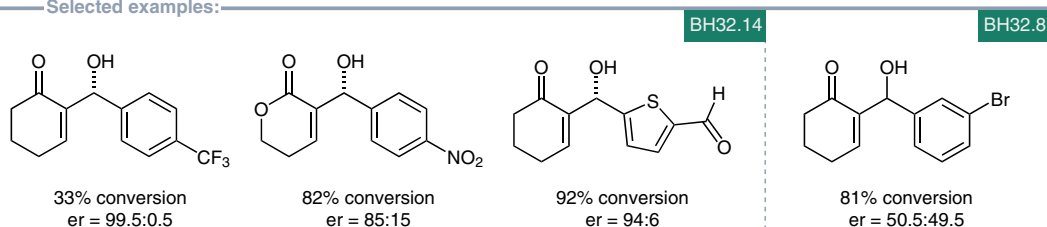


R. CRAWSHAW, A. E. CROSSLEY, L. JOHANNISSEN, A. J. BURKE, S. HAY, C. LEVY, D. BAKER, S. L. LOVELOCK*, A. P. GREEN* (UNIVERSITY OF MANCHESTER, UK)
Engineering an Efficient and Enantioselective Enzyme for the Morita–Baylis–Hillman Reaction
Nat. Chem. **2021**, DOI: 10.1038/s41557-021-00833-9.

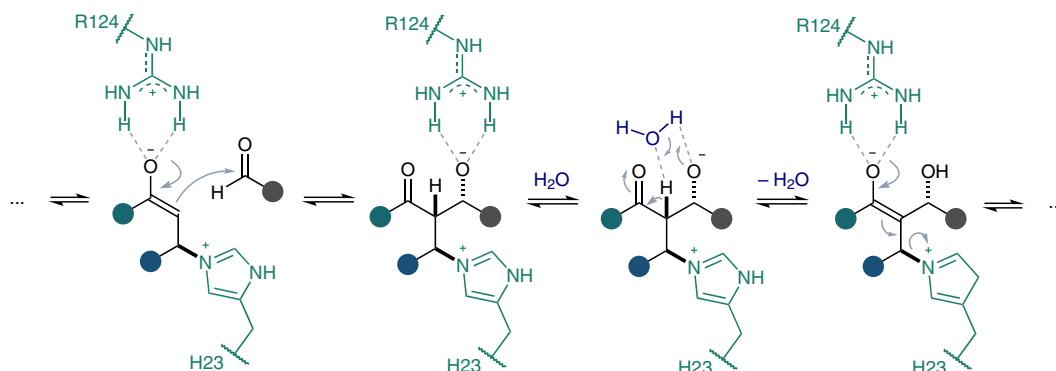
Engineered Biocatalyst Permits Enantioselective Morita–Baylis–Hillman Reaction



Selected examples:



Plausible reaction intermediates:



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).

SYNFACTS Contributors: Benjamin List, Wencke Leinung
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