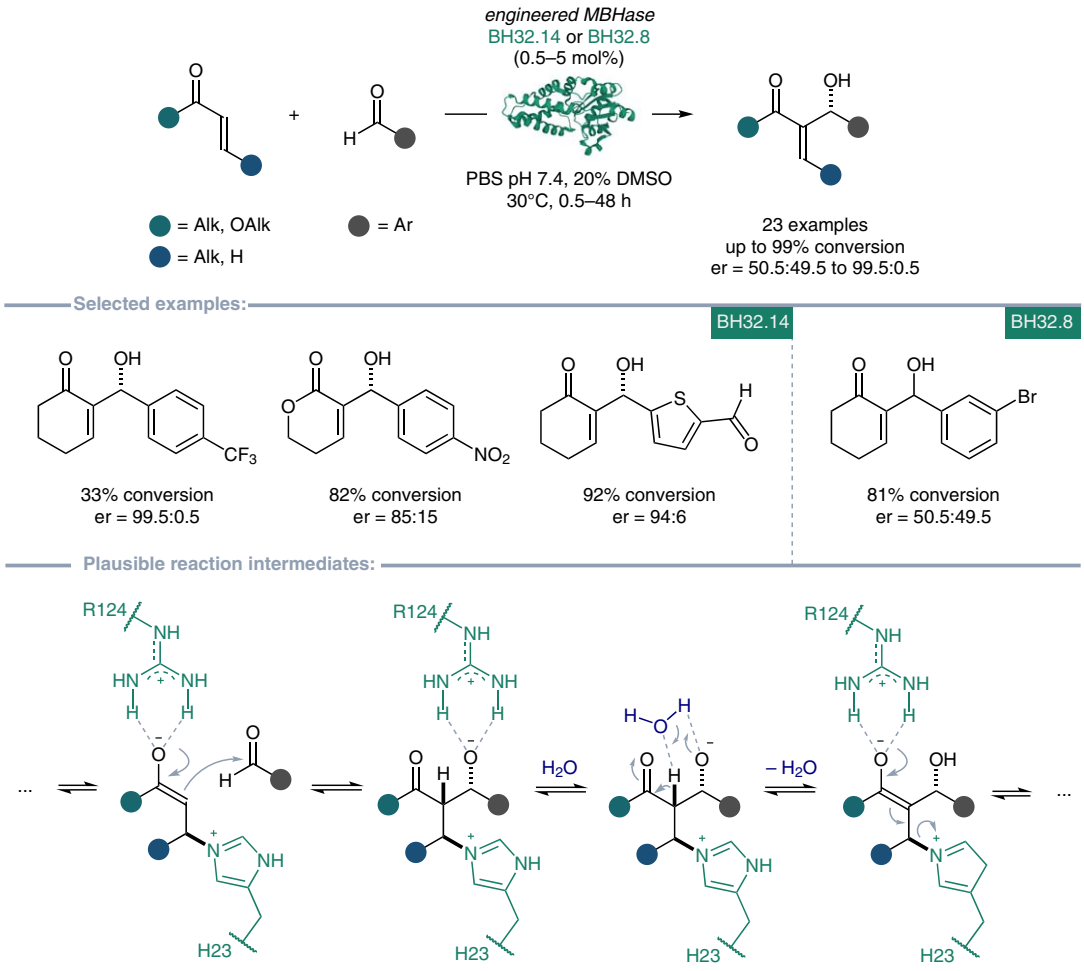
R. CRAWSHAW, A. E. CROSSLEY, L. JOHANNISSEN, A. J. BURKE, S. HAY, C. LEVY, D. BAKER, S. L. LOVELOCK*, A. P. GREEN* (UNIVERSITY OF MANCHESTER, UK)
Engineering an Efficient and Enantioselective Enzyme for the Morita–Baylis–Hillman Reaction
Nat. Chem. **2021**, DOI: 10.1038/s41557-021-00833-9.

Engineered Biocatalyst Permits Enantioselective Morita–Baylis–Hillman Reaction



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
Synfacts 2022, 18(03), 0307 Published online: 16.02.2022
DOI: 10.1055/s-0041-1737540; **Reg-No.:** B00522SF

Category
Organo- and Biocatalysis

Key words
Morita–Baylis–Hillman reaction
MBHase
directed evolution
enzyme engineering
asymmetric catalysis

Synfact of the Month