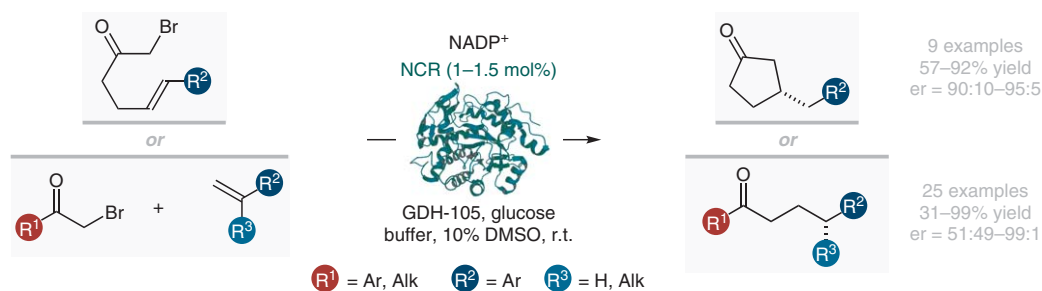
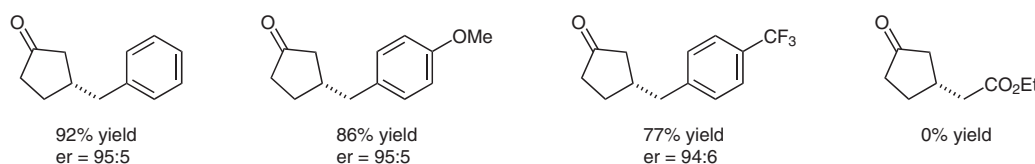


H. FU, H. LAM, M. A. EMMANUEL, J. H. KIM, B. A. SANDOVAL, T. K. HYSTER*
(PRINCETON UNIVERSITY AND CORNELL UNIVERSITY, ITHACA, USA)
Ground-State Electron Transfer as an Initiation Mechanism for Biocatalytic C–C Bond Forming Reactions
J. Am. Chem. Soc. **2021**, *143*, 9622–9629, DOI: 10.1021/jacs.1c04334.

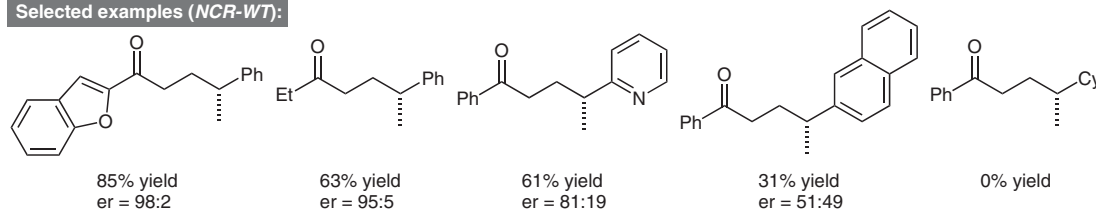
Enzymatic Intra- and Intermolecular Hydroalkylations of Alkenes through Ground-State Electron Transfer



Selected examples (NCR-C9):



Selected examples (NCR-WT):



Significance: Hyster and co-workers report intra- and intermolecular reductive hydroalkylations of aromatic olefins to form cyclopentanones or linear ketones in excellent yields and enantioselectivities. Quadruply mutated or wild-type nicotinamide-dependent cyclohexanone reductase (NCR), respectively, serve as efficient biocatalysts. Starting from α -bromo ketones, ground-state electron transfer from a flavinmononucleotide generates a ketyl radical that, through mesolytic C–Br bond cleavage, generates the reactive α -ketonyl radical. Notably, whereas the stereocenter in the cyclization reaction is set in the C–C bond-forming step, the enantiocontrol in intermolecular reactions originates from a stereoselective radical-terminating hydrogen-atom transfer.

Comment: Flavin-dependent ene-reductases (EREDs) have been previously applied in photo-enzymatic settings (see, for example: K. F. Biegasiewicz et al. *Science* **2019**, *364*, 1166). Whereas those reactions rely on the photoexcitation of a charge-transfer complex between enzyme, cofactor, and substrates, the analogous ground-state electron transfer had not previously been utilized as an initiation mechanism in C–C bond-forming reactions. The authors therefore selected α -bromo ketones as substrates due to their relatively high reduction potential, rendering ground-state reactivity kinetically feasible. Although the present method is an impressive example of enantiocontrol over real radical intermediates, the extension to less-stabilized nonaromatic substrates represents a considerable challenge for future research.

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