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

**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 photoenzymatic 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.

**Key words**
hydroalkylation
alkenes
reductase
ground-state electron transfer
ketones