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Ground-State Electron Transfer as an Initiation Mechanism for Biocatalytic C–C Bond Forming Reactions
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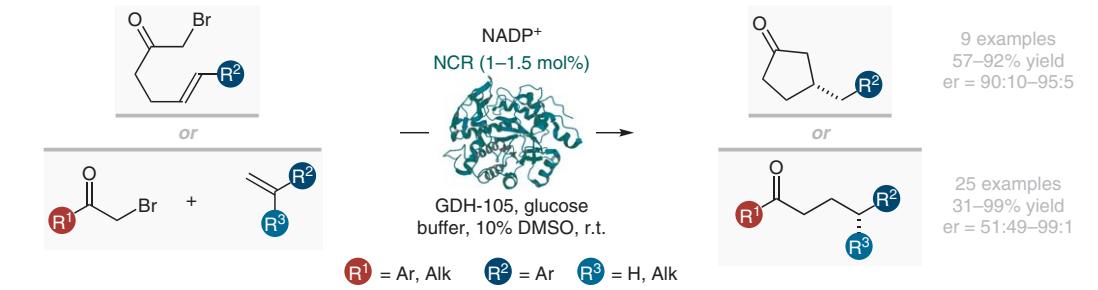
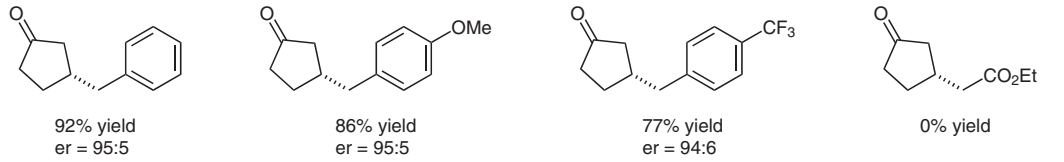
Enzymatic Intra- and Intermolecular Hydroalkylations of Alkenes through Ground-State Electron Transfer

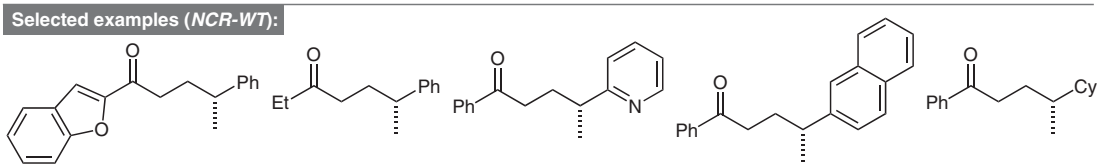


Selected examples (*NCR-C9*):



92% yield, er = 95:5 | 86% yield, er = 95:5 | 77% yield, er = 94:6 | 0% yield

Selected examples (*NCR-WT*):



85% yield, er = 98:2 | 63% yield, er = 95:5 | 61% yield, er = 81:19 | 31% yield, er = 51:49 | 0% yield

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.

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Key words
hydroalkylation
alkenes
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ground-state electron transfer
ketones

Synfact of the Month

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