Ene-Reductase Permits Cross-Electrophile Coupling of α-Chloro Carbonyls with α-Aryl Nitroalkanes

Significance: Hyster and co-workers describe a cross-electrophile coupling (XEC) between α-aryl nitroalkanes and α-chloro carbonyl compounds catalyzed by a flavin-dependent ene-reductase from Caulobacter segnis (CsER). Unnatural reactivity of the enzyme permits the formation of a new C–C bond through an unprecedented mechanistic pathway. The resulting β-(hetero)aryl carbonyl compounds are obtained in modest to excellent yields with poor to excellent enantioselectivities.

Comment: Mechanistic investigations showed that a charge-transfer complex between flavin hydroquinone and the α-chloro carbonyl substrate favors the reduction of the less oxidizing coupling partner. In contrast, conventional transition-metal-based XEC strategies afford dimerized byproducts due to the inability of organometallic catalysts to differentiate between two C(sp³) electrophiles. The reported approach underlines the potential of exploiting the unique selectivity of enzymes in challenging radical-based C–C bond-forming transformations.