Catalytic C(sp3)–H Alkylation via an Iron Carbene Intermediate

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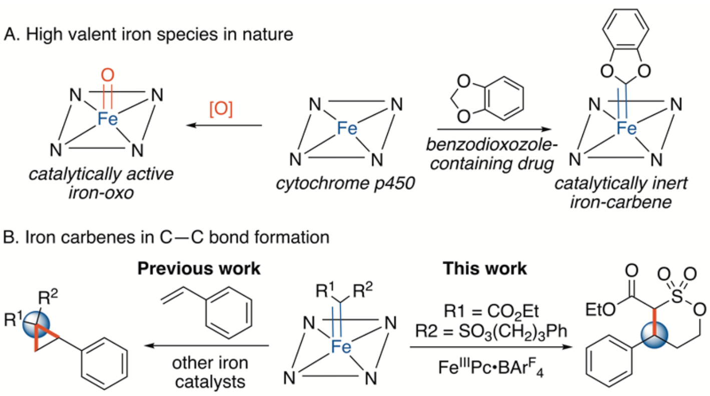

The catalytic transformation of a C(sp3)–H bond to a C(sp3)–C bond via an iron carbene intermediate represents a long-standing challenge. Despite the success of enzymatic and small molecule iron catalysts mediating challenging C(sp3)–H oxidations and aminations via high-valent iron oxos and nitrenes, C(sp3)–H alkylations via isoelectronic iron carbene intermediates have thus far been unsuccessful. Iron carbenes have been shown to favor olefin cyclopropanation and heteroatom-hydrogen insertion. Herein we report an iron phthalocyanine-catalyzed alkylation of allylic and benzylic C(sp3)–H bonds. Mechanistic investigations support that an electrophilic iron carbene mediates homolytic C–H cleavage and rebounds from the resulting organoiron intermediate to form the C–C bond; both steps are tunable via catalyst modifications. These studies suggest that for iron carbenes, distinct from other late metal carbenes, C–H cleavage is partially rate-determining and must be promoted to effect reactivity.

Application of eNTRy Rules for Small Molecule Accumulation in Gram-negative Bacteria to Generate a Broad-spectrum Antibiotic

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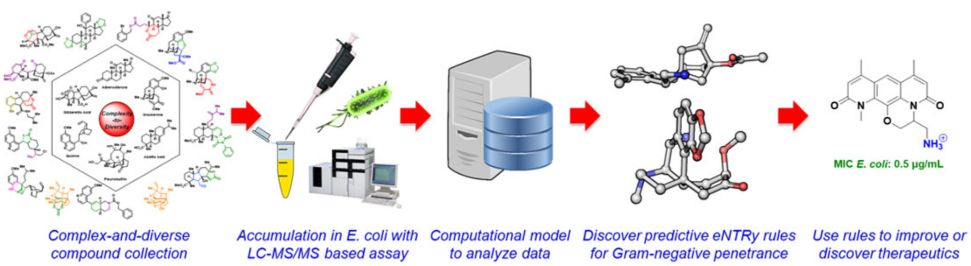
The continuing rise of multi-drug resistant Gram-negative bacteria is a global health concern, and new drug classes are necessary to treat these pathogens. However, no new structural classes of antibiotics for Gram-negative bacteria have been developed since the late 1960s, largely due the impermeable nature of their outer membrane. Until recently there has been a limited understanding of what properties allow small molecule accumulation in *E. coli.* The **eNTRy** rules developed by our lab state that compounds are likely to accumulate if they contain a non-sterically congested ionizable **N**itrogen (primary amine), have low **T**hree-dimensionality (Globularity ≤ 0.25), and are relatively **R**igid (rotatable bonds ≤ 5). These rules are now being used to inform discovery of new classes of antibiotics for Gram-negative bacteria.



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