Artificial Metalloenzymes Based on the Biotin-Avidin Technology : Enantio-selective Catalysis and Beyond

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Artificial metalloenzymes are created by incorporating an organometallic catalyst within a host protein. The resulting hybrid can thus provide access to the best features of two distinct, and often complementary, systems: homogeneous and enzymatic catalysts. The coenzyme may be positioned with covalent, dative, or supramolecular anchoring strategies. Although initial reports date to the late 1970s, artificial metalloenzymes for enantioselective catalysis have gained significant momentum only in the past decade, with the aim of complementing homogeneous, enzymatic, heterogeneous, and organic catalysts. Inspired by a visionary report by Wilson and Whitesides in 1978, we have exploited the potential of biotin−avidin technology in creating artificial metalloenzymes. Owing to the remarkable affinity of biotin for either avidin or streptavidin, covalent linking of a biotin anchor to a catalyst precursor ensures that, upon stoichiometric addition of (strept)avidin, the metal moiety is quantitatively incorporated within the host protein. In this Account, we review our progress in preparing and optimizing these artificial metalloenzymes, beginning with catalytic hydrogenation as a model and expanding from there. These artificial metalloenzymes can be optimized by both chemical (variation of the biotin−spacer−ligand moiety) and genetic (mutation of avidin or streptavidin) means. Such chemogenetic optimization schemes were applied to various enantioselective transformations. The reactions implemented thus far include the following: (i) The rhodium-diphosphine catalyzed hydrogenation of N-protected dehydroaminoacids (ee up to 95%); (ii) the palladium-diphosphine catalyzed allylic alkylation of 1,3-diphenylallylacetate (ee up to 95%); (iii) the ruthenium pianostool-catalyzed transfer hydrogenation of prochiral ketones (ee up to 97% for aryl-alkyl ketones and ee up to 90% for dialkyl ketones); (iv) the vanadyl-catalyzed oxidation of prochiral sulfides (ee up to 93%). A number of noteworthy features are reminiscent of homogeneous catalysis, including straightforward access to both enantiomers of the product, the broad substrate scope, organic solvent tolerance, and an accessible range of reactions that are typical of homogeneous catalysts. Enzyme-like features include access to genetic optimization, an aqueous medium as the preferred solvent, Michaelis−Menten behavior, and single-substrate derivatization. The X-ray characterization of artificial metalloenzymes provides fascinating insight into possible enantioselection mechanisms involving a well-defined second coordination sphere environment. Thus, such artificial metalloenzymes combine attractive features of both homogeneous and enzymatic kingdoms. In the spirit of surface borrowing, that is, modulating ligand affinity by harnessing existing protein surfaces, this strategy can be extended

to selectively binding streptavidin-incorporated biotinylated ruthenium pianostool complexes to telomeric DNA. This application paves the way for chemical biology applications of artificial metalloenzymes.
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