Introduction

Until recently, both homogeneous and enzymatic catalysis have by-and-large grown independently, ultimately allowing scientists to address complementary synthetic challenges.

Combining computation with detailed structural and mechanistic insights has led to the design and optimization of homogeneous catalysts that bear a well-defined second coordination sphere and proceed via reaction mechanisms that resemble those of highly sophisticated metalloenzymes. The progress in aqueous coordination chemistry has also been beneficial for biocatalysis. This has led to the realization that metalloproteins may be repurposed and ultimately evolved to catalyze new-to-nature reactions, thus greatly expanding the reaction repertoire available to enzymes. This virtual issue of ACS Central Science provides a timely snapshot of the lively field of bioinspired catalysis. Fourteen articles have been selected to highlight the state-of-the-art in this broad field.

Current challenges in bioinspired catalysis, which relies on both homogeneous catalysts and enzymes, include (i) engineering second coordination sphere interactions to place substrates and solvent in catalytically competent poses; (ii) exploiting selective substrate channels to ensure the timely delivery of reagents to a highly reactive catalytic intermediate; (iii) relying on redox mediators to facilitate challenging reactions; (iv) deciphering the subtle catalytic details that lead to chiral amplification and autocatalysis; and (v) combining the versatility of non-natural cofactors with the power of directed evolution.

Emergence of homochirality

The prevalence of homochirality observed in the building blocks of life is a fascinating chemical phenomenon. One appealing hypothesis to rationalize this observation builds on the amplification of chirality resulting from a catalytic event. Sugino and co-workers report on a helical macromolecular polyphosphine ligand whose helical "sense" can be determined by the addition of enantioenriched solvents (e.g., limonene). Addition of various palladium salts affords highly enantioselective catalysts for Suzuki–Miyaura, hydrosilylation, and silaboration reactions. Strikingly, the presence of limonene with only 63% ee leads to a binaphthyl cross-coupled product in 88% ee, thus highlighting the majority-based amplification of homochirality. After the formation of the enantioenriched helix, the enantiopure solvent can be removed, while maintaining the catalyst’s selectivity in the cross-coupling reaction in achiral solvents, illustrating the concept of "chiral memory".

In a related context, the Soai Zn-catalyzed alkylation of ketones offers a unique playground to test various hypotheses in the field of asymmetric amplification via autocatalysis. Hawbaker and Blackmond report on their efforts to rationalize the asymmetric amplification via autocatalysis by isotopically chiral initiators in the Zn-catalyzed alkylation of pyrimidyl aldehydes. Strikingly, they find that the 2:1 product/initiator complex actually inhibits the autocatalytic pathway at the outset of the reaction.

Second coordination sphere interactions

Second coordination sphere interactions play a critical role in biocatalysis. Among others, such weak interactions allow...
synthetic chemists to place solvent molecules with exquisite precision, which plays a critical role in the enzyme’s activity and selectivity. Mimicking such interactions has proven challenging with small molecule catalysts.

Miller III, Marinescu, and co-workers scrutinize the catalytic profile of a bioinspired CO$_2$ reduction catalyst. Sequential introduction of pendant proton donors in the second coordination sphere of the [Co(tetrapyridyl)]-catalyst leads to a 300-fold increase in catalytic activity toward the production of CO. This design bears resemblance with the NiFe cluster of carbon monoxide dehydrogenase whereby the bifunctional CO$_2$ activation relies on the NiFe cluster as well as H-bonding interactions with neighboring amino acid residues.4,5

The study reveals a first-order kinetic rate-dependence on CO$_2$, the number of pendant secondary amines and external acid. They propose a mechanism by which the non-cooperative pendant amines contribute to trifluoroethanol positioning via hydrogen bonding, which, in turn, protonates the HOCOCO-moiety in the rate-determining step, thus releasing CO and H$_2$O.6

Hammes-Schiffer, Stahl, and co-workers provide detailed mechanistic insight into the thermodynamic factors that determine the O$_2$-reduction product, i.e., H$_2$O$_2$ vs H$_2$O using a homogeneous [Co(porphyrin)] catalyst and a chemical reductant. They demonstrate that the potential for O$_2$ reduction to H$_2$O$_2$ versus H$_2$O depends on the pK$_a$ of acid, while the Co(II/III) redox potential does not. Accordingly, selective H$_2$O$_2$ formation is observed when the catalyst’s redox potential lies below the O$_2$/H$_2$O$_2$ potential. When the catalyst’s redox potential is higher than the O$_2$/H$_2$O$_2$ potential, H$_2$O is produced preferentially: a weak acid thus favors the formation of H$_2$O.7

C–H Activation

Selective C–H activation and functionalization are currently one of the most active fields in catalysis, encompassing heterogeneous, homogeneous, and enzymatic approaches. This research is justified both from the organic methodology perspective (e.g., late-stage functionalization)8 and from a sustainable energy carrier perspective (e.g., the methanol economy).9 Mukherjee and Dey describe a fascinating electrochemical P450-mimic that catalyzes C–H hydroxylation using O$_2$ as oxidant in water. Building on Collman’s pioneering studies,10 they anchor via thiolate coordination an [Fe(picket-fence porphyrin)] on a SAM-decorated electrode. The rate of the electron transfer from the electrode to the catalyst is fine-tuned to favor monooxygenase over reductase activity of the high-valent iron-oxo moiety. Strikingly, the steric bulk provided by the picket-fence environment leads to the preferential hydroxylation of secondary C–H bonds over tertiary C–H bonds. Most importantly, it minimizes overoxidation of the alcohol to the corresponding ketone. The hydroxylation of cyclohexane proceeds with up to $>10^4$ TONs and a rate of 23 s$^{-1}$.11

Costas and co-workers report on a [Mn(N$_2$)(OTf)$_2$]-catalyzed oxidation of monosubstituted cyclohexane to the corresponding enantioenriched ketone, using H$_2$O$_2$ as the oxidant. Introduction of a bulky tert-butyl amide substituent proved essential toward production of the corresponding regio- and enantiopure ketone. This represents the first example of a nonenzymatic highly enantioselective oxidation of a nonactivated methylenic site.12

Lumb, Arndtsen, Stahl, and co-workers scrutinize the mechanism of a [Cu(I)(diamine)] $p$-dimethylaminopyridine catalyst precursor for the oxidation of alcohols using O$_2$ as the oxidant. They show that the system undergoes an in situ oxidative self-processing step to generate a nitroxy radical that serves as a cocatalyst for the oxidation of the alcohol. The mechanism thus bears resemblance to Cu-based oxidases (e.g., galactose oxidase or amine oxidase) that rely on the presence of O-centered radicals as redox mediators. It is striking how an apparently “unsophisticated” catalytic system can incorporate nontrivial higher order features reminiscent of metalloenzymes.13

Substrate engineering

Many synthetic laboratories lack the know-how and the required equipment to carry out protein engineering campaigns to derivatize a non-native substrate for use with commercially available enzymes. To circumvent this challenge, the desired substrate may be linked to a temporary directing group to favor its highly selective derivatization. Although well established in homogeneous catalysis,14 this strategy has received limited attention in biocatalysis.

Sherman, Houk, Montgomery, and co-workers describe an (NHC)Ni-catalyzed regiodivergent macrocyclization combined with a cytochrome P450 PikC-catalyzed site-selective hydroxylation. Thanks to the introduction of a temporary amine-containing directing group, they access a
variety of hydroxylated products with exquisite regio- and diastereoselectivity. Computational analysis provides insight into the influence of the linker on the selectivity of the hydroxylation step. This work offers a generally applicable strategy to access a variety of products via late-stage functionalization of a common intermediate.\(^\text{18}\)

Narayan and co-workers present an elegant study on a computationally guided substrate engineering to expand the synthetic utility of the flavin-dependent monooxygenase SorbC. For this purpose, the authors capitalize on critical interactions between the monooxygenase and its native substrate, which contributes to positioning an engineered substrate in a productive pose. This positioning strategy is beautifully illustrated by an oxidative phenol dearomatization to afford highly enantioenriched quinol products using wild-type SorbC. Importantly, the critical crotyl ester within avidin. The resulting ArM displayed creative approach and anchored a biotinylated [Rh- into an oxidase. Whitesides and Wilson pursued another native Zn ion by Cu, Kaiser repurposed carboxypeptidase of arti- cial metalloenzymes display\(^\text{19}\)...
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