ACS central science

EDITORIAL

ACS Central Science Virtual Issue on Bioinspired Catalysis

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.

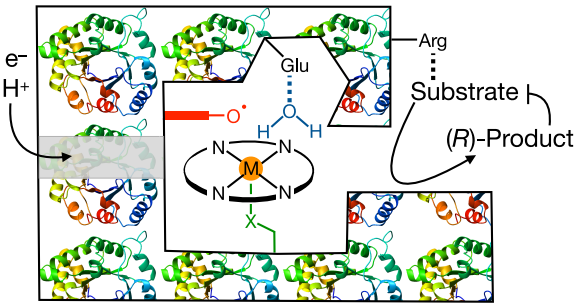
Current challenges in bioinspired catalysis, which relies on both homogeneous catalysts and enzymes, include (i) engineering second coordination sphere interactions to place substrates and solvent in catalytically competent poses; (ii) exploiting selective substrate channels to ensure the timely delivery 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. Some of the essential features of metalloenzymes that are collected in this virtual issue are depicted in Scheme 1.

Brief introductions for each of the 14 articles in this virtual issue are presented below. These sections are arranged according to the grand challenge that they set out to address: the emergence of homochirality, engineering second coordination sphere interactions, C−H activation, substrate engineering, and finally, artificial and repurposed metalloenzymes.

Emergence of homochirality

The prevalence of homochirality observed in the building blocks of life is a fascinating chemical phenomenon. One

Scheme 1. Recapitulating Essential Features of Metalloenzymes



appealing hypothesis to rationalize this observation builds on the amplification of chirality resulting from a catalytic event. Suginome 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−Miayura, 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".[1]

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.[2] 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.[3]

Second coordination sphere interactions

Second coordination sphere interactions play a critical role in biocatalysis. Among others, such weak interactions allow

Published: October 25, 2019

DOI: 10.1021/acscentsci.9b01045
ACS Cent. Sci. 2019, 5, 1732−1735

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_2O.[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_2O_2 vs H_2O, using a homogeneous [Co(porphyrin)] catalyst and a chemical reductant. They demonstrate that the potential for O_2 reduction to H_2O_2 versus H_2O depends on the pK_a of acid, while the Co(II/III) redox potential does not. Accordingly, selective H_2O_2 formation is observed when the catalyst's redox potential lies below the O_2/H_2O_2 potential. When the catalyst's redox potential is higher than the O_2/H_2O_2 potential, H_2O is produced preferentially: a weak acid thus favors the formation of H_2O.[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]

It is striking how an apparently "unsophisticated" catalytic system can incorporate non-trivial, higher-order features reminiscent of metalloenzymes.

Building on Que and Nam's pioneering studies,[12−14] Costas and co-workers report on a [$Mn(N_4)(OTf)_2$]-catalyzed oxidation of monosubstituted cyclohexane to the corresponding enantioenriched ketone, using H_2O_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.[15]

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 nitroxyl 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.[16]

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,[17] 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

DOI: 10.1021/acscentsci.9b01045
ACS Cent. Sci. 2019, 5, 1732−1735

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.[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 positioning group can readily be removed with $[Pd(PPh_3)_4]$ and morpholine.[19]

Artificial and repurposed metalloenzymes

With the aim of expanding the natural enzyme's repertoire, Kaiser[20] and Whitesides[21] independently pioneered the field of artificial metalloenzymes (ArMs). By substituting the native Zn ion by Cu, Kaiser repurposed carboxypeptidase into an oxidase. Whitesides and Wilson pursued another creative approach and anchored a biotinylated $[Rh(diphosphine)]^+$ within avidin. The resulting ArM displayed promising activity and selectivity toward the reduction of acetamidoacrylic acid. Thanks to the development of recombinant protein production, combined with directed evolution tools, the field of ArMs has experienced a revival in the past 20 years.[22] Progress and challenges in this field are highlighted in the Outlook by Davis and Ward.[23]

One of the challenges in directed evolution of enzymes toward new reactions is that an initial activity must be detectable in order to evolve it.[24] Thanks to progress in homogeneous aqueous catalysis, combined with deep chemical insight, Arnold and co-workers recently introduced an elegant strategy to expand the natural enzyme's repertoire. They reasoned that the critical [(porphyrin)Fe=O] moiety, responsible for the remarkable X−H insertion and epoxidation activities of cytochrome P450, was isolobal with a [(porphyrin)Fe=CHR] moiety.[25] Since such homogeneous systems were known to catalyze cyclopropanation and X−H insertion reactions,[26] Arnold hypothesized it may be possible to repurpose and evolve hemoproteins to catalyze these new-to-nature reactions. Two remarkable examples are reported by Arnold and co-workers in this virtual issue. Kight et al. report on the directed evolution of heme proteins for the cyclopropanation of various (unactivated) alkenes using *Escherichia coli* whole cells to afford all four cyclopropane diastereomers in high yield and selectivity.[27]

To complement the "cyclopropanase" activity of repurposed hemoproteins, Huang et al. report on their efforts to evolve an enzyme for carbene B−H insertion. For this purpose, they identified and evolved *Rhdothermus marinus cytochrome c* to accept a broad range of trifluorodiazo alkenes, affording α-CF_3 enantiopure organoboron compounds. The solvent exposure of the cofactor allows accommodation of various diazo substrates, thus significantly contributing to expanding the substrate scope of this new-to-nature reaction.[28]

Hu, Ribbe, and co-workers broaden the scope of organic substrates that the isolated M-cluster of nitrogenase can reduce and couple. In addition to its natural substrate, this fascinating cluster had been shown to reduce CO, CN^-, and CO_2, thus highlighting the remarkable versatility of this cluster to catalyze both Haber−Bosch and Fischer−Tropsch-like activities.[29] Here, they show that the M-cluster catalyzes the reductive condensation of aldehydes to afford C_1 to C_4 reduction products in high yields. They further provide convincing evidence that the formation of alkenes proceeds via a β-hydride elimination step.[30]

Building on the metal substitution strategy pioneered by Kaiser,[20] Hartwig and co-workers repurposed hemoproteins by substituting the native Fe ion by an Ir(Me) moiety.[31] The artificially metalated P450 enzymes are optimized by directed evolution to catalyze the cyclopropanation of various alkenes including terminal and (di- and trisubstituted) internal, activated and unactivated, electron-rich and electron-deficient, conjugated, and nonconjugated alkenes. The resulting artificial metalloenzymes display exquisite regio-, diastereo-, and enantioselectivity, combined with excellent turnover numbers.[32]

I hope you enjoy reading this virtual issue and invite you to contemplate the possibility of including some bioinspiration in your research.

Thomas R. Ward
Department of Chemistry, University of Basel, Mattenstrasse 24a BPR 1096, CH-4002 Basel, Switzerland

Author Information
Thomas.ward@unibas.ch.

ORCID
Thomas R. Ward: 0000-0001-8602-5468

Notes
Views expressed in this editorial are those of the author and not necessarily the views of the ACS.

DOI: 10.1021/acscentsci.9b01045
ACS Cent. Sci. 2019, 5, 1732−1735

REFERENCES

(1) Nagata, Y.; Takeda, R.; Suginome, M. Asymmetric Catalysis in Chiral Solvents: Chirality Transfer with Amplification of Homochirality through a Helical Macromolecular Scaffold. *ACS Cent. Sci.* **2019**, *5*, 1235−1240.

(2) Soai, K.; Shibata, T.; Morioka, H.; Choji, K. Asymmetric Autocatalysis and Amplification of Enantiomeric Excess of a Chiral Molecule. *Nature* **1995**, *378*, 767−768.

(3) Hawbaker, N. A.; Blackmond, D. G. Rationalization of Asymmetric Amplification via Autocatalysis Triggered by Isotopically Chiral Molecules. *ACS Cent. Sci.* **2018**, *4*, 776−780.

(4) Jeoung, J. H.; Dobbek, H. Carbon Dioxide Activation at the Ni,Fe-Cluster of Anaerobic Carbon Monoxide Dehydrogenase. *Science* **2007**, *318*, 1461−1464.

(5) Appel, A. M.; Bercaw, J. E.; Bocarsly, A. B.; Dobbek, H.; DuBois, D. L.; Dupuis, M.; Ferry, J. G.; Fujita, E.; Hille, R.; Kenis, P. J. A.; Kerfeld, C. A.; Morris, R. H.; Peden, C. H. F.; Portis, A. R.; Ragsdale, S. W.; Rauchfuss, T. B.; Reek, J. N. H.; Seefeldt, L. C.; Thauer, R. K.; Waldrop, G. L. Frontiers, Opportunities, and Challenges in Biochemical and Chemical Catalysis of CO_2 Fixation. *Chem. Rev.* **2013**, *113*, 6621−6658.

(6) Chapovetsky, A.; Welborn, M.; Luna, J. M.; Haiges, R.; Miller, T. F., III; Marinescu, S. C. Pendant Hydrogen-Bond Donors in Cobalt Catalysts Independently Enhance CO_2 Reduction. *ACS Cent. Sci.* **2018**, *4*, 397−404.

(7) Wang, Y. H.; Schneider, P. E.; Goldsmith, Z. K.; Mondal, B.; Hammes-Schiffer, S.; Stahl, S. S. Bronsted Acid Scaling Relationships Enable Control Over Product Selectivity from O_2 Reduction with a Mononuclear Cobalt Porphyrin Catalyst. *ACS Cent. Sci.* **2019**, *5*, 1024−1034.

(8) Gutekunst, W. R.; Baran, P. S. C-H Functionalization Logic in Total Synthesis. *Chem. Soc. Rev.* **2011**, *40*, 1976−1991.

(9) Olah, G. A. Beyond Oil and Gas: The Methanol Economy. *Angew. Chem., Int. Ed.* **2005**, *44*, 2636−2639.

(10) Collman, J. P. Synthetic Models for the Oxygen-Binding Hemoproteins. *Acc. Chem. Res.* **1977**, *10*, 265−272.

(11) Mukherjee, M.; Dey, A. Electron Transfer Control of Reductase versus Monooxygenase: Catalytic C-H Bond Hydroxylation and Alkene Epoxidation by Molecular Oxygen. *ACS Cent. Sci.* **2019**, *5*, 671−682.

(12) Oloo, W. N.; Que, L. Bioinspired Nonheme Iron Catalysts for C-H and C = C Bond Oxidation: Insights into the Nature of the Metal-Based Oxidants. *Acc. Chem. Res.* **2015**, *48*, 2612−2621.

(13) Nam, W. Synthetic Mononuclear Nonheme Iron-Oxygen Intermediates. *Acc. Chem. Res.* **2015**, *48*, 2415−2423.

(14) White, M. C.; Zhao, J. P. Aliphatic C-H Oxidations for Late-Stage Functionalization. *J. Am. Chem. Soc.* **2018**, *140*, 13988−14009.

(15) Milan, M.; Bietti, M.; Costas, M. Highly Enantioselective Oxidation of Nonactivated Aliphatic C-H Bonds with Hydrogen Peroxide Catalyzed by Manganese Complexes. *ACS Cent. Sci.* **2017**, *3*, 196−204.

(16) McCann, S. D.; Lumb, J. P.; Arndtsen, B. A.; Stahl, S. S. Second-Order Biomimicry: In Situ Oxidative Self-Processing Converts Copper(I)/Diamine Precursor into a Highly Active Aerobic Oxidation Catalyst. *ACS Cent. Sci.* **2017**, *3*, 314−321.

(17) Breslow, R. Biomimetic Control of Chemical Selectivity. *Acc. Chem. Res.* **1980**, *13*, 170−177.

(18) Gilbert, M. M.; DeMars, M. D., II; Yang, S.; Grandner, J. M.; Wang, S.; Wang, H.; Narayan, A. R. H.; Sherman, D. H.; Houk, K. N.; Montgomery, J. Synthesis of Diverse 11- and 12-Membered Macrolactones from a Common Linear Substrate Using a Single Biocatalyst. *ACS Cent. Sci.* **2017**, *3*, 1304−1310.

(19) Dockrey, S. A. B.; Suh, C. E.; Benitez, A. R.; Wymore, T.; Brooks, C. L., III; Narayan, A. R. H. Positioning-Group-Enabled Biocatalytic Oxidative Dearomatization. *ACS Cent. Sci.* **2019**, *5*, 1010−1016.

(20) Yamamura, K.; Kaiser, E. T. Studies on the Oxidase Activity of Copper (II) Carboxypeptidase A. *J. Chem. Soc., Chem. Commun.* **1976**, 830−831.

(21) Wilson, M. E.; Whitesides, G. M. Conversion of a Protein to a Homogeneous Asymmetric Hydrogenation Catalyst by Site Specific Modification with a Diphosphinerhodium(I) Moiety. *J. Am. Chem. Soc.* **1978**, *100*, 306−307.

(22) Schwizer, F.; Okamoto, Y.; Heinisch, T.; Gu, Y.; Pellizzoni, M. M.; Lebrun, V.; Reuter, R.; Kohler, V.; Lewis, J. C.; Ward, T. R. Artificial Metalloenzymes: Reaction Scope and Optimization Strategies. *Chem. Rev.* **2018**, *118*, 142−231.

(23) Davis, H. J.; Ward, T. R. Artificial Metalloenzymes: Challenges and Opportunities. *ACS Cent. Sci.* **2019**, *5*, 1120−1136.

(24) Arnold, F. H. Innovation by Evolution: Bringing New Chemistry to Life. *Angew. Chem., Int. Ed.* **2019**, *58*, 14420−14426.

(25) Brandenberg, O. F.; Fasan, R.; Arnold, F. H. Exploiting and engineering hemoproteins for abiological carbene and nitrene transfer reactions. *Curr. Opin. Biotechnol.* **2017**, *47*, 102−111.

(26) Wolf, J. R.; Hamaker, C. G.; Djukic, J. P.; Kodadek, T.; Woo, L. K. Shape and Stereoselective Cyclopropanation of Alkenes Catalyzed by Iron Porphyrins. *J. Am. Chem. Soc.* **1995**, *117*, 9194−9199.

(27) Knight, A. M.; Kan, S. B. J.; Lewis, R. D.; Brandenberg, O. F.; Chen, K.; Arnold, F. H. Diverse Engineered Heme Proteins Enable Stereodivergent Cyclopropanation of Unactivated Alkenes. *ACS Cent. Sci.* **2018**, *4*, 372−377.

(28) Huang, X.; Garcia-Borras, M.; Miao, K.; Kan, S. B. J.; Zutshi, A.; Houk, K. N.; Arnold, F. H. A Biocatalytic Platform for Synthesis of Chiral alpha-Trifluoromethylated Organoborons. *ACS Cent. Sci.* **2019**, *5*, 270−276.

(29) Hu, Y. L.; Lee, C. C.; Ribbe, M. W. Extending the Carbon Chain: Hydrocarbon Formation Catalyzed by Vanadium/Molybdenum Nitrogenases. *Science* **2011**, *333*, 753−755.

(30) Lee, C. C.; Hu, Y.; Ribbe, M. W. Reduction and Condensation of Aldehydes by the Isolated Cofactor of Nitrogenase. *ACS Cent. Sci.* **2018**, *4* (10), 1430−1435.

(31) Natoli, S. N.; Hartwig, J. F. Noble-Metal Substitution in Hemoproteins: An Emerging Strategy for Abiological Catalysis. *Acc. Chem. Res.* **2019**, *52*, 326−335.

(32) Key, H. M.; Dydio, P.; Liu, Z.; Rha, J. Y.; Nazarenko, A.; Seyedkazemi, V.; Clark, D. S.; Hartwig, J. F. Beyond Iron: Iridium-Containing P450 Enzymes for Selective Cyclopropanations of Structurally Diverse Alkenes. *ACS Cent. Sci.* **2017**, *3*, 302−308.

DOI: 10.1021/acscentsci.9b01045
ACS Cent. Sci. 2019, 5, 1732−1735