INTRODUCTION

Nature has optimized its biosynthetic machinery over billions of years and can synthesize complex molecules with unmatched efficiency and elegance. Biosynthetic pathways, such as polyketide synthase, implement different combinations of enzymatic transformations in the form of cascade reaction sequences. Most remarkably, these highly selective and processive enzymes successfully catalyze transformations in the presence of other biocatalysts and reactive intermediates. Chemists aim to adopt these fundamental principles of biosynthesis, in particular the concept of cascade reactivity. The synthesis of complex molecules would be streamlined if multiple enzymatic and transition metal catalyzed reactions could be conducted in a single operation under uniform reaction conditions.

CHALLENGES

Combining transition metal catalysts and enzymes presents a considerable challenge. First, transition metal catalysts have been shown to bind to enzymes and cause mutual inactivation. Second, enzymes are typically reactive in aqueous solutions, while transition metal catalysts are reactive in organic solvents and often readily degrade in water. Finally, if the rates of the two catalysts are incompatible, buildup of reactive intermediates could occur. In order to address these challenges, chemists have adopted the concept of compartmentalization. Encapsulation of reactive transition metal catalysts inside macromolecular scaffolds provides protection from the exterior environment, enabling multiple catalytic transformations to take place in a cascade fashion.

BIOTIN-STREPTAVIDIN ENCAPSULATION

In 1978, Whitesides and coworkers reported the enantioselective hydrogenation of an alkene with a biotinylated RhNBD catalyst encapsulated within streptavidin. This report disclosed the first example of an engineered hybrid protein-metal catalyst. The large protein scaffold of streptavidin does not interfere with catalytic activity, serves as a secondary coordination sphere to protect the transition metal species from deleterious pathways and provides a handle for genetic optimization. This field was expanded upon and ultimately pioneered by Ward and coworkers. In 2012, Ward and Rovis et al. reported an enantioselective benzannulation reaction catalyzed by a biotinylated [Cp*RhCl₂]₂ complex encapsulated in a streptavidin mutant. In 2013, Ward demonstrated the first introduction of these hybrid catalysts...
into a synthetic cascade. Combining a monoamine oxidase and a biotinylated iridium transfer hydrogenation catalyst \([\text{Cp}^*\text{Ir(Biot-p-L)Cl}]\) in the presence of a streptavidin mutant, Ward observed double stereoselective deracemization of secondary amines. Without the addition of streptavidin, both catalysts suffered from mutual inactivation. \(^6\) Multiple other enzymes were compatible with this system.

**SUPRAMOLECULAR ENCAPSULATION**

In 1998, Bergman and Raymond reported the formation of a \(\text{M}_4\text{L}_6\) tetrahedral host-guest complex capable of encapsulating cationic metal species. The supramolecular scaffold is formed by the self-assembly of four octahedral metal centers with six bis-catecholamide naphthalene ligands. \(^7\) In 2007, Bergman and Raymond encapsulated a \(\text{Rh(COD)}^+\) complex inside of this nanovessel and demonstrated that it successfully catalyzed the isomerization of terminal allylic alcohols to aldehydes. \(^8\) Additionally, in collaboration with Toste and coworkers, Bergman and Raymond reported that encapsulated \(\text{Me}_3\text{PAuBr}\) catalyzed hydroalkoxylation of allenic alcohols in water. \(^9\) Notably, the assembly protected the transition metal complex from the deleterious aqueous environment and the encapsulated catalytic species demonstrated an eight-fold rate enhancement over the free gold catalyst. Thus, the authors posited that this supramolecular assembly would be ideally suited as an encapsulation strategy for combining transition metal catalysts and enzymes in a reaction cascade. A hydrolysis/cyclization reaction cascade was achieved upon exposure of an allenic acetate to a reaction mixture composed of lipase and encapsulated gold catalyst to afford the desired allylic tetrahydrofuran. The supramolecular assembly prevented mutual inactivation of the two catalytic species and allowed the transformation to be carried out in in water. \(^10\)

**SUMMARY**

Both methods of encapsulation allow for transition metal catalysts to be compatible with enzymes in biomimetic reaction cascades. With further development, these domino reactions could be extremely useful tools in streamlining the synthesis of complex molecules.

**REFERENCES**
