Recent Developments in Metalloporphyrin-Catalyzed C-C Bond Formation

Youran Luo Literature Seminar March 29th, 2022

Carbon-carbon (C-C) bonds are found in almost all biomolecules such as lipids, proteins, carbohydrates, and nucleic acids.[1] Many laboratory methods for the catalytic formation of C-C bonds have been devised, which are widely used in the synthesis of pharmaceuticals and other compounds.[2] However, due to the limitations of traditional cross-coupling methods, especially with respect to creating C(sp^3)-C(sp^3) bonds while avoiding β-hydride elimination, there are motivations to explore alternative catalysts.

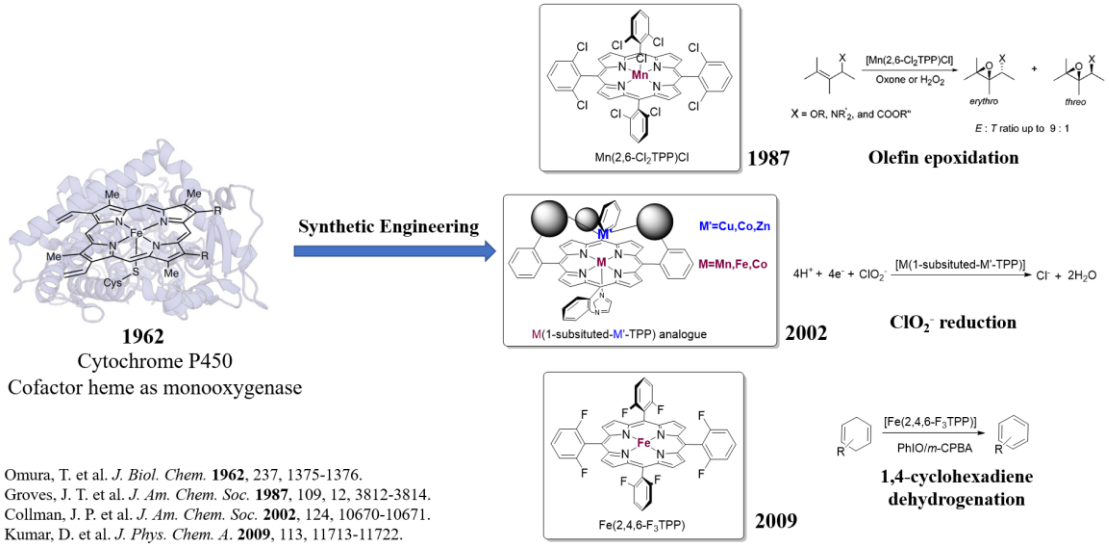

Figure 1. Bioinspired metalloporphyrins for new reactivity.

Since cytochrome P450, a heme-based monooxygenase, was discovered in 1962,[3] metalloporphyrins, which are heme analogs, have been studied extensively and found to promote a variety of reactions, including olefin epoxidation,[4] ClO_2^- reduction,[5] 1,4-cyclohexadiene dehydrogenation,[6] and others (**Figure 1**). Using metalloporphyrins to catalyze C-C bond formation reactions is challenging because the metalloporphyrin platform lacks the potential to satisfy the spatial and orbital requirements for the two-electron oxidative addition step that precedes transmetalation in the traditional cross-coupling mechanism.

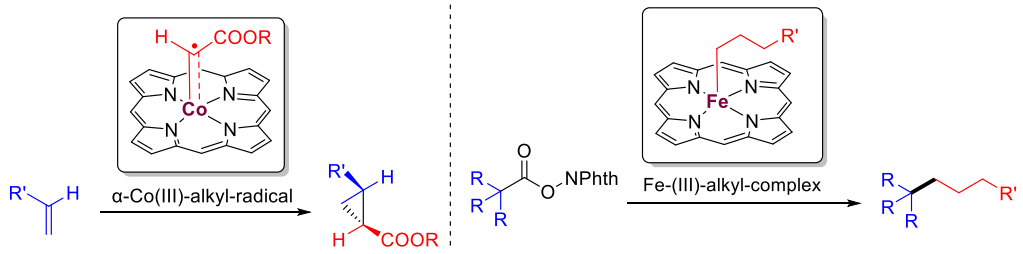

Figure 2. Metalloradical and S_H2 pathway to catalyze C-C bond formation.

Over the years, scientists have proposed various one-electron alternatives to construct C-C bonds to circumvent the oxidative addition step, such as bioinspired cobalt-radical functionalization,[7] and biomimetic radical transfer by S_H2 (bimolecular homolytic substitution) processes (**Figure 2**).[8] These achievements will be discussed in the current presentation.

In 1980, the Rh(TPP)I catalyzed cyclopropanation of activated olefins such as phenanthrene was reported,[9] which demonstrated the capacity of metalloporphyrins to catalyze C-C bond formation *via* carbene transfer. In 2003, the Zhang group further developed this reaction motif to catalyze the cyclopropanation of terminal olefins with Co(TPP).[10] In 2010, a mechanistic investigation revealed that an α-Co(III)-alkyl radical was the precursor to the carbene transfer agent,[11] a Co(Por)-carbene complex. More recently, Cobalt porphyrin complexes have been shown to promote C(sp^3)-H functionalizations,[12] olefin-addition cascade cyclizations,[13] and other transformations **(Figure 3)**.

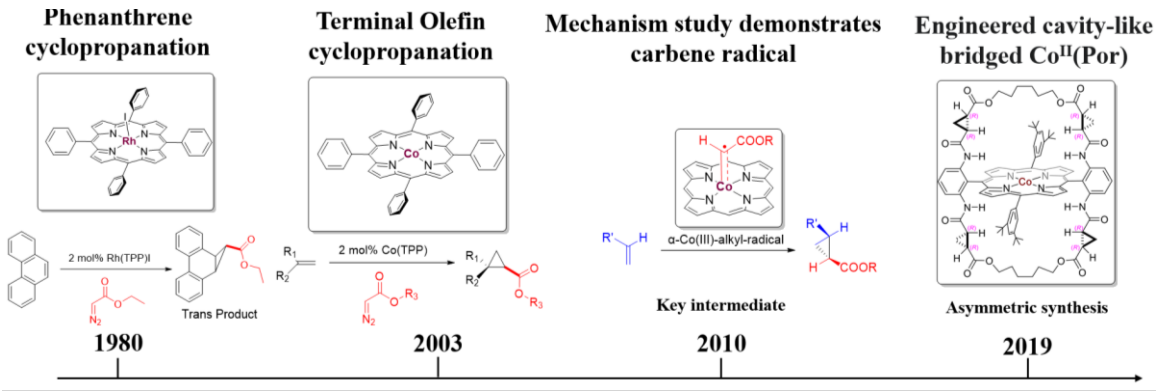

Figure 3. Development of metal-carbene transformations.

To achieve asymmetric synthesis, a symmetric Co(por) platform was further modified with chiral components including (1*R*,2*R*)-cyclopropane-1,2-dicarboxylic acids to create a chiral domain-limited spatial pocket.[14] Interestingly, by controlling the length of the alkyl linker to the end-site carboxylic acids, the restricted space surrounding the porphyrin platform can regulate the e.e. and d.r. of the product **(Figure 3)**.

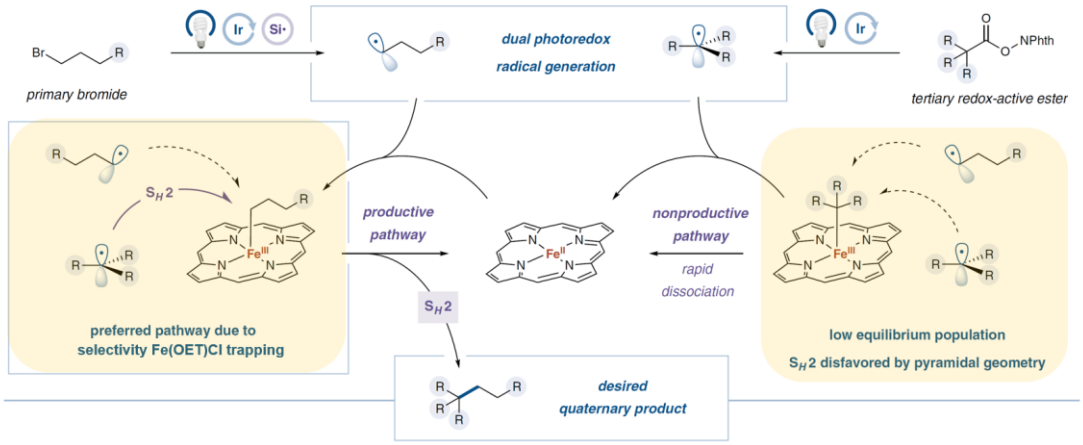

Figure 4. Proposed mechanism to explain radical selectivity.

Inspired by the S_H2 mechanism seen in biochemical alkylation pathways,[15] the Macmillan group developed Fe(OEP)Cl catalytic platform able to construct C(sp^3)-C(*quaternary*) bonds.[8] The reaction mechanism is proposed to initiate by reaction of Fe(II)(OEP)Cl with a 1º radical (formed by photoinitiated oxidation) to generate a Fe(III)-alkyl intermediate, which reacts further with a 3º radical (formed by a photoinitated reduction of an ester) to form sequential products. The photoinitated oxidation and reduction steps involve an iridium photocatalyst. The selectivity of the cross-coupling reaction was attributed to the preferential trapping of the 1º radical by Fe(OET)Cl, which diminishes the concentration of existing 1º radical intermediates and facilitate 3º radical-mediated S_H2 pathway **(Figure 4)**.

In conclusion, the ability of metalloporphyrins to catalyze reactions *in vivo* has been used to inspire the discovery that metalloporphyrins can be used to catalyze C-C bond couplings *in vitro*. Compared with representative enzymes bearing metalloporphyrin cofactors, synthetic organo-metalloporphyrins can be modified to increase the substrate scope, making them potentially suitable for industrial organic synthesis. One remaining challenge is to further increase the enantioselectivity of these systems.

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