Artificial Chromophoric Metalloenzymes in (Dual) Catalysis

Nature offers a vast diversity of biocatalysts. As a result, enzyme-mediated reactions have become a powerful methodology in asymmetric synthesis. The two main advantages of biocatalysis are the followings: (a) high chemo-, regio- and stereoselectivities and (b) reactions carried out under environmentally friendly conditions (water is used as solvent). The applications of biocatalysts can be further improved owing to the recent progresses in recombinant technologies. However, from a synthetic chemist's point of view, the number of chemical transformations catalyzed by enzymes is limited as compared to the available arsenal of modern organic chemistry. In the past fifty years, homogeneous catalysis has had a major impact on chemistry, as illustrated by four Nobel prizes since 2001. Indeed, very important chemical reactions are catalyzed in a stereoselective manner by transition metals associated to chiral ligands. Thus, metal-mediated homogeneous catalysis and biocatalysis are by many points complementary. Their association (namely Artificial Metalloenzyme) has proven to be very attractive as regards the generation of new catalysts combining the diversity of organometallic catalysts with the selectivity of enzymes. The next frontier in the field strives at implementing efficient homogeneous catalytic transformations with Earth abundant metals and developing new synthetic processes. From the considerations outlined above, the preparation and application of artificial metalloenzymes based on nickel and iron complexes might open new avenue in the targeted enantioselective reactions (intermolecular enantioselective C-C bond formation via dual photoredox/organometallic catalysis, hydrogen (auto-)transfer methodology).

Within this proposal, we plan to develop two important processes as part of eco-efficiency transition, that are:

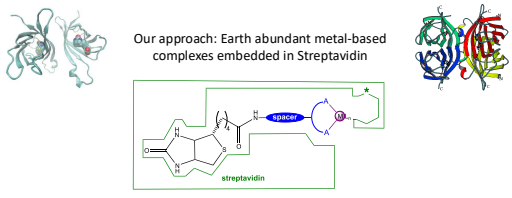
(i) the reduction reactions of carbonyl compounds (hydrogen autotransfer) and alkylation reaction (hydrogen autotransfer methodology) catalyzed by an artificial iron based-metalloenzyme under light irradiation,

(ii) artificial metalloenzymes for dual enantioselective photoredox C-C and C-heteroatom bond forming reactions.

1. State of the Art and scientific objectives

Photoinduced redox processes using visible light offer a great variety of catalytic transformations useful in the realm of organic synthesis, open new retrosynthetic disconnection and is an emerging technology in industry. The recent literature amply demonstrates that this preparative toolbox is expanding substantially, but there are still opportunities to develop new reactions and to introduce new substrates in photoredox reactions. Light, which can be seen as a clean and traceless reagent, can be also exploited to access reactive intermediates in mild conditions, at low temperatures. Moreover, photoredox circumvent the need of stoichiometric amount of oxidant or reductant. Most of these technologies imply the excitation of a photosensitizer catalyst (PS) that promotes the transformation either by hydrogen-atom transfer (HAT), energy transfer or single-electron transfer. The association of photoredox catalysis and transition metal catalysis (namely a dual catalysis strategy) has extended the concept of this light activation. Another complementary approach to photoredox catalysis and dual catalysis is to exploit the inner coordination sphere of a transition metal complex able to harvest the visible light and break/form bonds. Even if platinum complexes (and more specifically ruthenium and rhodium complexes) are at the forefront of this emerging chemistry, few examples with abundant metal-based complexes appeared recently in the literature.

The main objectives of this proposal will focus on the development of artificial metalloenzyme to open new avenue in dual photoredox catalysis and in light-mediated metal-based catalysis. As (strept)avidin is known to be stable under severe chaotropic conditions including 2.2<pH<10.; 5°C<Temp<65°; organic solvent; hydrogen pressure, oxidants and reductants etc., this enzyme will be used in this project. For the incorporation of the catalytic species in the protein, supramolecular anchoring strategies will be pursued.



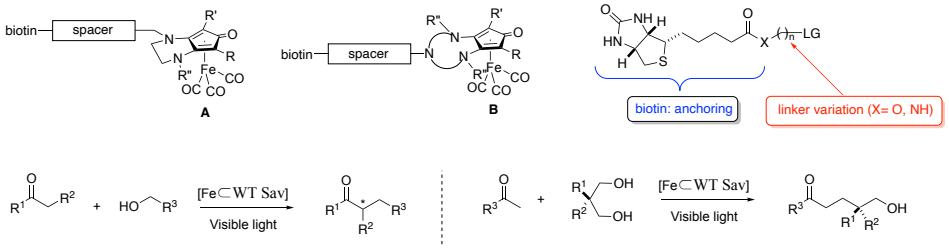
Streptavidin: high affinity with biotin, thermal stability, gram scale preparation

1.1 Hydrogen (auto-) transfer methodology

Hydrogen auto-transfer methodology or borrowing hydrogen reaction is a thrilling area of research. This process is a greener and safer way to create new C-C or C-N bonds from environmentally benign alcohols. Among the reported complexes able to catalyze the borrowing hydrogen reaction, the diaminocyclopentadienone iron tricarbonyl complex has demonstrated its potency in the formation of both C-C and C-N bonds. This complex catalyzed not only the alkylation of ketones, indoles, oxindoles and alcohols, but also the *N*-alkylation of amines and amides. Whilst the hydrogen auto-transfer methodology is a successful technology in fine chemistry, some drawbacks, such as high reaction temperatures (90-150 °C) and stereoselective methodologies, remain. Consequently, there is still room to improve such technology, to introduce new substrates and to develop unprecedented methodologies.

The SU group have recently disclosed a simple and robust visible light-induced iron-catalyzed α-alkylation of a variety of ketones with aliphatic, benzylic, or even more challenging allylic and propargylic alcohols at room temperature. These results not only demonstrate the versatility of the cyclopentadienone iron complexes, as the borrowing hydrogen strategy can now be applied either under thermal or visible light activation, but also open new opportunities. Within this proposal, the objectives will be to anchor cyclopentadienone iron(0) tricarbonyl or triaminocyclopentadienyl iron(II) tricarbonyl complexes within streptavidin site and to develop enantioselective reduction and alkylation reactions using our new "light-induced hydrogen (auto)transfer strategy" at room temperature in order to widen the application of this methodology in organic synthesis (Scheme 1).

Scheme 1: Synthesis of functionalized iron complexes and applications.



1.2 Dual photoredox catalysis

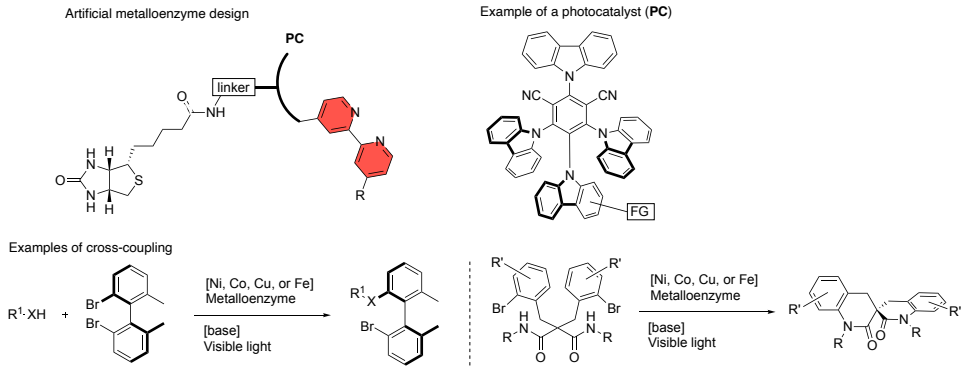
Successful efforts to induce enantioselective catalytic control in photocatalyzed processes have initially required a polarized C=X type bond (aldehydes, ketones, iminium) and have relied mainly on organocatalysis involving chiral amines. Extension of these enantioselective reactions to compounds other than carbonyl derivatives is an attractive challenge and represents a growing research area. Recent work by the UNIMI group has demonstrated that enforcing proximity between the two active sites of metallaphotoredox catalytic systems (i.e., a metal complex and a photocatalyst) may lead to improved catalytic activity and higher reaction rate in C-O cross-coupling compared to the simple dual catalytic system.

Enantioselective cross-coupling reactions *via* dual photoredox catalysis is one of these hot topics. Elegant contributions have recently demonstrated that enantioselective photoredox processes could be applied to new substrates, however new complementary approaches have still to be imagined and implemented to broaden the scope. Several groups have recently developed enzyme-catalyzed enantioselective alkylation, reductions or oxidations under visible light activation. All these strategies are constructed by combining photoredox catalysis and biocatalysis but, to the best of our knowledge, there is no report on the use of artificial metalloenzymes for dual enantioselective photoredox C-C and C-heteroatom bond forming reactions.

We foresee that incorporation a photocatalyst and a transition metal complex into a suitably designed enzyme can allow to exploit a **proximity effect** to **attain high activity** and - at the same time - to **impart enantioselectivity**. Indeed, the enzyme pocket is a confined chiral space in which the catalytic groups can act cooperatively. Thus, within this proposal we present an approach to the development of **artificial metalloenzymes** for dual enantioselective photoredox C-C and C-heteroatom cross-coupling reactions. An initial possible type of design will be investigated to introduce a photocatalyst and a bipyridine ligand moiety into the metalloenzyme following a "co-factor approach" with streptavidin, exploiting a

biotinylated version of the bifunctional photocatalyst (Scheme 2). The photocatalysts used for incorporation into metalloenzymes will be functionalized versions of the most effective organic dyes such as, for example, donor-acceptor cyanoarenes (Scheme 2). In terms of catalytic metal, special attention will be devoted to 1st row transition metals ('base metals') such as Mn, Fe, Co, Ni and Cu. The newly synthesized enzyme-supported systems will be tested in several types of base metal-catalyzed cross-coupling (Scheme 2), including both enantioselective and non-enantioselective examples.

Scheme 2: Photoactive artificial metalloenzymes: design strategies and potential applications.



2. Proposed Collaboration

This project will be carried out in collaboration with Prof. Luca Pignataro of the University of Milan (UNIMI). Our two groups are both active in the field of base metal homogeneous catalysis and share a strong expertise in (cyclopentadienone)iron catalysts for hydrogen transfer reactions as well as, more recently, in metallaphotoredox catalysis. Since 2022, the two research groups are collaborating with undergraduate student exchanges and within the frame of the 'Marie Skłodowska-Curie' Doctoral Network NextBase (https://nextbase.network/), whose scientific goal is developing base metal-catalytic methodologies for cross-coupling reactions. Within this sound common background in catalysis, there are also strong **elements of complementarity**:

the Sorbonne Université group has an ongoing collaboration on the synthesis of artificial metalloenzymes with Prof. Agathe Urvoas (I2BC, UMR9198, expertise in recombinant protein production and purification, and molecular biology for directed mutagenesis) and had a collaboration with Prof. Thomas Ward (University of Basel) on the development of artificial hydrogenases based on the anchoring of iron cyclopentadienone tricarbonyl complexes within Streptavidin

the UNIMI group will share its competencies in the field of supramolecular catalysis. the Sorbonne Université group had also previously collaborated.

Overall, this co-supervised thesis project will allow the future doctoral student to acquire strong competencies in organometallic chemistry and catalysis, while working in a stimulating transnational environment exposed to international research/training projects. She/He will have the chance to enjoy the vivid atmosphere of the doctoral network in which the two groups are involved, with the opportunity of scientific exchange with several European research groups from both academia and industry.