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Book of Abstracts

Catalytic Enantioselective 1,2-Rearrangement

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Rearrangement reaction is a broad class of organic transformation involving the migration of an atom or a group from one center (migration origin) to another (migration terminus) within the same molecule.[i] Such bond reorganization process affords a structural isomer of the original substrate allowing, in many cases, the construction of molecular frameworks not easily accessible by other approaches. One particular group of rearrangement proceeds through a carbenium intermediate before the stereocenter-generating C-C/C-X bond forming process.[ii] The involvement of highly reactive carbocation species renders the stereoinduction difficult to realize and indeed in many cases, chiral Lewis acid catalysts is ineffective due to the lack of anchoring points. In this talk we will present our recent work on the development of catalytic enantioselective 1,2-anionotropic rearrangements and their applications in the synthesis of natural products as well as bioactive compounds.[iii]

Acknowledgments: We thank EPFL (Switzerland), Swiss National Science Foundation for financial supports.

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Development of a TRPA1 Antagonist for the Treatment of Asthma

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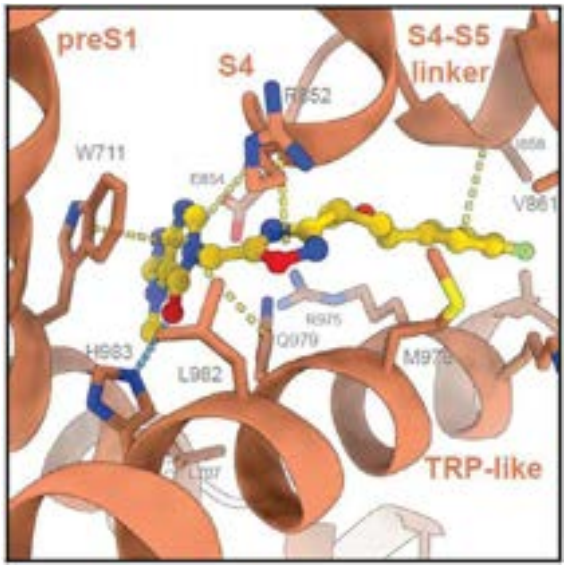

TRPA1 is a calcium-permeable ion channel highly expressed in the primary sensory neurons functioning as a sensor for exogenous and endogenous stimuli that has generated widespread interest as a target for inhibition due to its implication in respiratory disease. Optimization of a chemical series through a ligand-based design approach towards the identification of a potent, selective and orally bioavailable TRPA1 antagonist lead molecule will be presented. Moreover, medicinal chemistry as well as scale-up routes for key compounds will be highlighted. Lastly, in vivo efficacy data as well as CryoEM structure of a lead compound bound to TRPA1 channel will be disclosed, revealing the binding site and mechanism of action for this class of antagonists.

Functional Supramolecular Chemistry

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The integration of principles from supramolecular chemistry into functional systems offers new ways the get into contact on the molecular level. This in turn promises access to new structures and functions which, ultimately, should provide new approaches to central challenges in science and society. This spirit of functional supramolecular chemistry is developed with recent examples from catalysis, fluorescent probes and cellular uptake. For catalysis, the integration of unorthodox interactions, that is anion-π interactions, chalcogen bonds and pnictogen bonds, is shown to afford properties that otherwise do not exist.[1] From the basics to the market, mechanosensitive fluorescent flippers are introduced as planarizable push-pull probes to respond to a central need in current biology, that is the imaging of physical forces in living cells.[2] An understanding of the elusive, most demanding dynamic covalent cascade exchange chemistry, finally, is emerging as the key to penetrate cells generally and reliably, and to combine drug delivery with drug discovery.[3]

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Electronic bistability in iron based metallorganic frameworks: advanced molecular materials for the production of sensors, actuators, and memory devices

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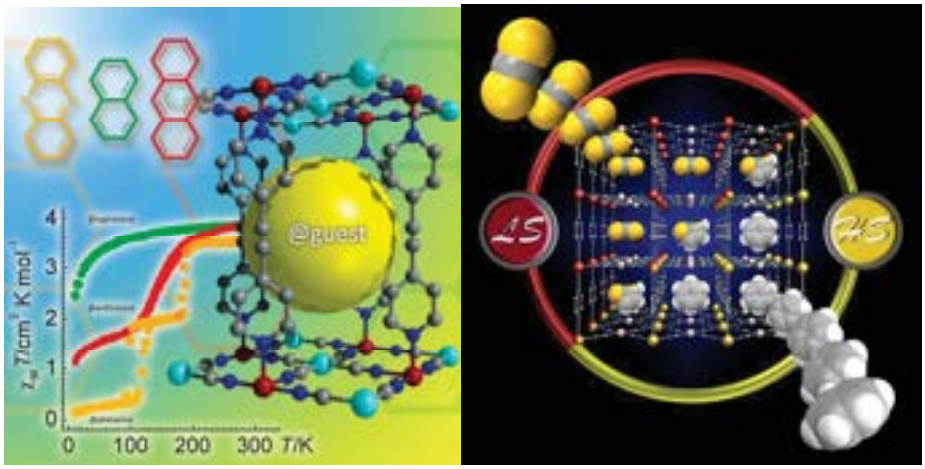
Information storage in the contemporary society relies on an inherent property of the matter, electronic bi-stability. It is the ability of atoms and molecules to switch between different electronic states when interacting with their environment. This language is a binary coding (0-1). In this context, the spin crossover phenomenon exhibited by the iron molecules is one of the best examples of molecular electronic bi-stability.[1] In Fe(Ⅱ) coordination compounds, the orbital occupation of the d shell electron can be converted between $\boxed{t_{2g}^4 e_g^2}$ and $\boxed{t_{2g}^6 e_g^0}$, corresponding to the high-spin state (HS) and the low-spin (LS) states, respectively. In the HS and LS configurations the compounds present distinct metal-donor atom distances (molecular volume), magnetic, dielectric and optical (colour) properties. Switching between the spin states can be induced by an external perturbation such as variation of temperature,[1] application of pressure[2] or light irradiation.[1] The spin crossover properties can be combined with other chemical or physical property in a synergetic fashion, i.e, porosity, liquid crystalline properties, fluorescence, electronic conductivity and magnetic exchange.[1] In this presentation most relevant examples of Fe(II) metallorganic frameworks exhibiting reversible control of the magnetic and optical outputs through the chemical response of the framework will be reviewed.[3]



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Refining Cardiovascular Risk Stratification in Patients using Graphene-based bioFETs

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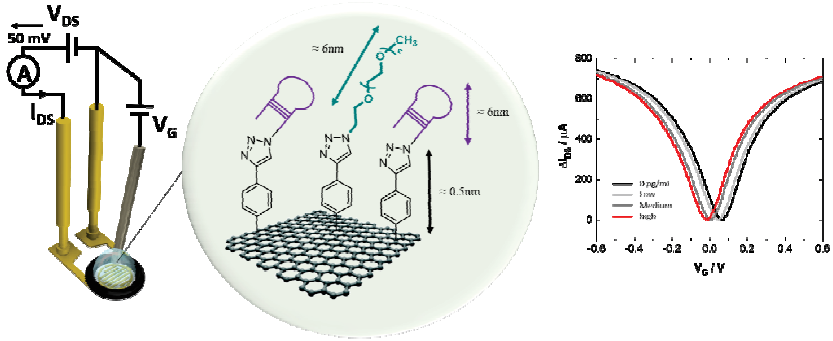

Highly sensitive point-of-care testing (POCT) is the next challenge for the detection of cardiac biomarkers such as troponin (cTnI) and natriuretic peptides. We have recently demonstrated the validity and sensitivity of a graphene-based field-effect transistor (gFET) as a POCT option for the rapid and highly sensitive detection of cTnI, allowing the quantification of cardiac biomarkers in patient blood samples with very low or even undetectable levels with currently used clinical bioassays. The importance of adapted surface chemistry approaches to anchor cardiac specific aptamers on the gFET will be discussed in details The sensor performances within the clinical important window of 10 to 500 pg mL^{-1}, allowing the differentiation between healthy, and people with low and high risk for myocardial infraction (AMI) will be presented. Our goal is to refine cardiovascular risk stratification in patients with cardiovascular risk factors such as smoking, type 2 diabetes, dyslipidemia and obesity, and thus improve the adaptation of preventive measures and medications in a personalized manner

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Selective delivery of radioactive Auger-Emitter Ruthenium complexes to the nucleus of cancer cells

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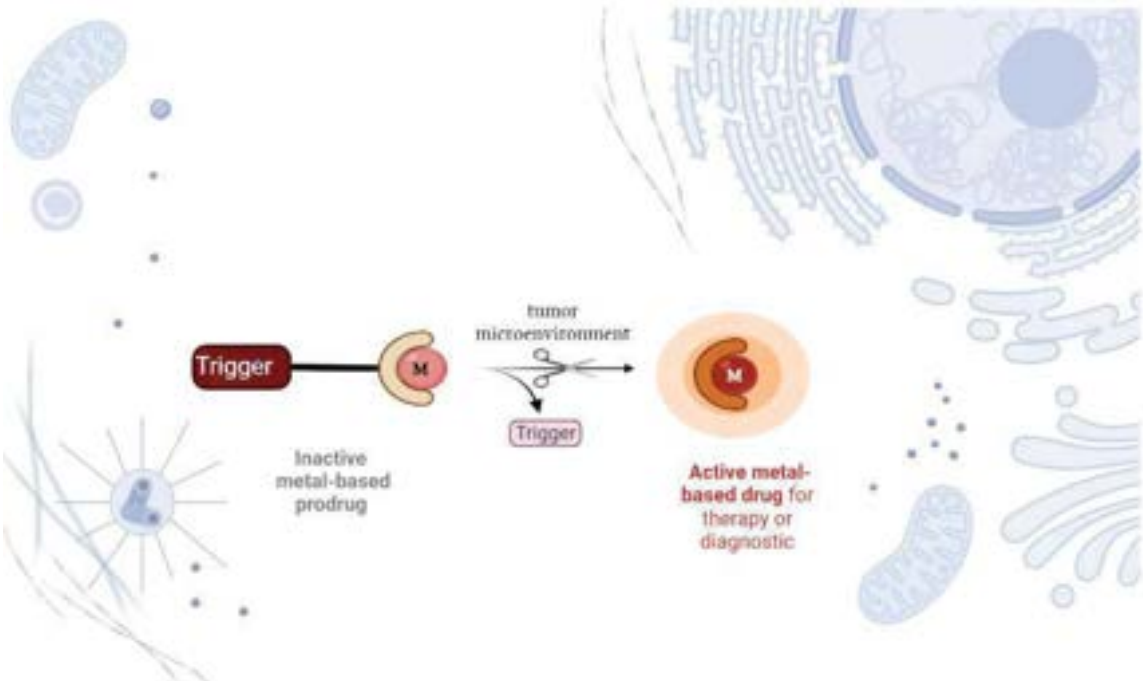
Metal-based compounds have been widely used for biomedical applications. Their unique characteristics make them attractive for both therapeutic and diagnostic purposes. However, numerous issues including toxicity, poor aqueous solubility, and unfavorable biodistribution hamper their widespread use. To overcome these drawbacks, the concept of metal-based prodrugs emerged. This field is particularly developed for applications in oncology. More precisely, tumor-associated stimuli (e.g., pH variation, redox activity, enzyme overexpression, etc.) have been exploited to trigger the selective delivery of active metal-based drugs to the tumor site. The main advances in this area will be discuss during the presentation. [1]



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Selective catalytic C-H functionalization of (+)-limonene

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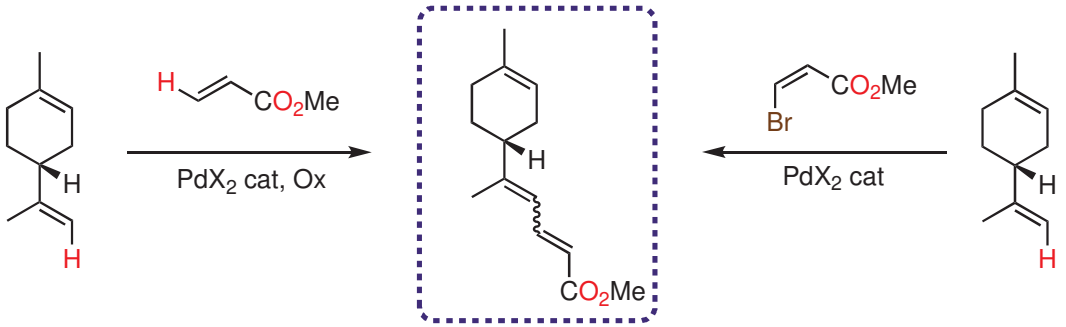
Despite the major progress in C–H functionalization, direct and regioselective C–H activation of terpenes presents a great challenge. Indeed, the existing protocols are far from being satisfactory from the selectivity, yield, as well as the eco-compatibility viewpoint. The C–H coupling of limonene is a virtually unexplored topic, which, if successful, may allow the access to new synthetically useful building blocks belonging to emerging strategies.[1]

The intermolecular direct C–H/C–H alkene coupling represents an ideal atom- and step-economical method to couple two C(sp^2)-H bonds,[2,3] and an alternative attractive strategy is represented by an equally interesting C–H/C–X coupling.[4]

We report here two Pd(II)-catalyzed strategies in which limonene is C–H coupled with electron poor alkenes via either an oxidative C–H/C–H, or a redox-neutral C–H/C–X coupling, to afford the same coupled product. This latter is subsequently used as a key advanced intermediate in the total synthesis of α-bisabolene, a sesquiterpene of relevance in the flagrance industry, and of interest as a possible bio-diesel fuel.



Acknowledgments: This project has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Sklodowska-Curie, Grant Agreement No 860762.

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Further investigation of a self-organized Polyoxometalate-based D-A hybrid material: synthesis, characterization and device

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The control of the molecular organization in semiconducting thin films is a key point for improving their optoelectronic performances. For instance, self-organization of electron donor (D) and acceptor (A) moieties into highly ordered molecular architectures is extremely promising for optoelectronic applications.[i] Polyoxometalates (POMs) are nanosized polyanionic oxocluters with remarkable electron reservoir properties. They can be further functionalized with organic donor moieties providing organic-inorganic hybrids[ii]. The association of POMs with photoactive mesogens should provide a new type of donor-acceptor systems with nanosegregated D and A domains. In this context, a multi-lamellar mesomorph hybrid material composed of a donor-acceptor dyad of a lacunary Keggin-type POM, decorated with four asymmetric benzothiadiazole cores, was synthesized (fig. 1).

In this presentation, we will describe the synthetic strategy to prepare this mesomorph POM-based D-A hybrid material and we will detail its structural characterization as well as its preliminary photophysical properties.

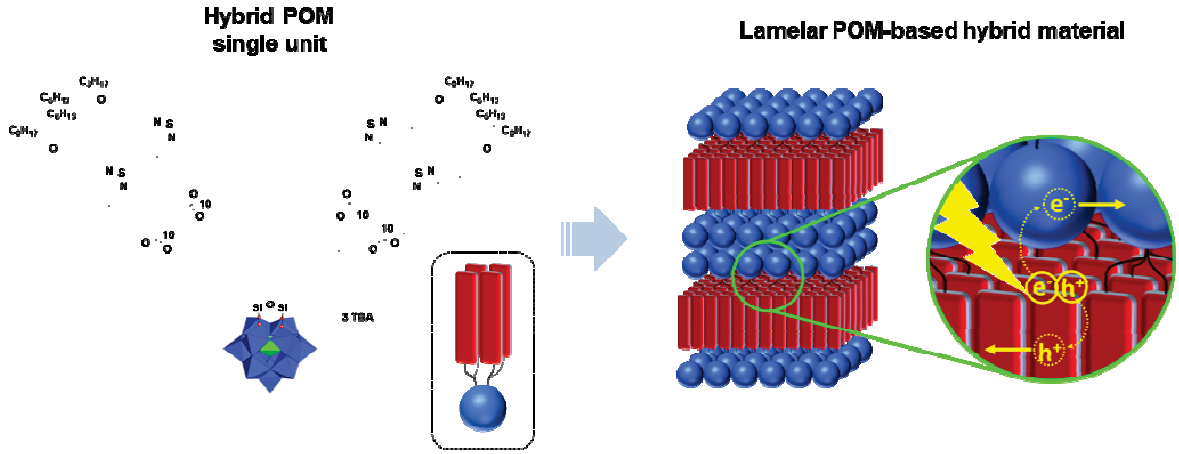

Figure 1: Schematic representation of the target molecular architecture and its self-assembly into multi-lamellar nanostructure intermingling donor and acceptor domains.

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C-H activation by polyoxometalates

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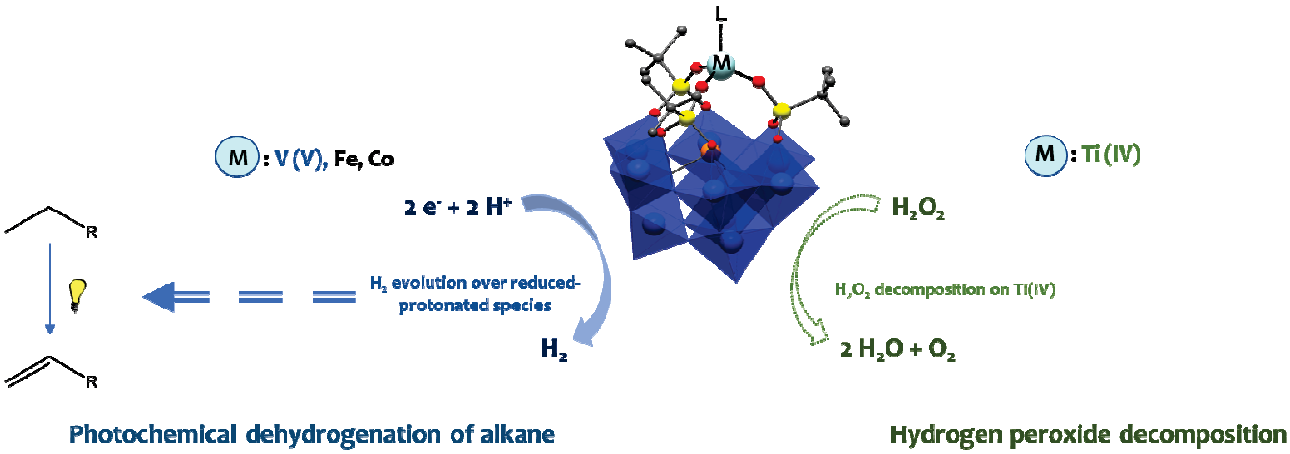
Nowadays, there is a growing interest in the conversion of alkanes to alkenes, to form higher added value synthons with industrial importance and at an economically viable energy cost. This PhD work aims to explore C-H activation through a photochemical dehydrogenation of alkanes.

Since few years, the ability of polyoxometalates to act as multielectron acceptors has been exploited in the context of solar energy conversion. Yet this approach usually requires the association of the POM to a visible photosensitizer.[1] POMs also absorb in the UV part of the spectrum and could act as ideal photocatalysts.[2] In recent years the decatungstate $[W_{10}O_{32}]^{4-}$, used as a tetrabutylammonium salts, has thereof found wide applications in the catalytic photochemical functionalization of alkanes.[3]

Our approach is based on the utilization of Silox-POMs and their metallic derivatives as potential photocatalysts.[4,5] The main idea is to couple in a single system the photochemical capacity of POM framework (to promote hydrogen atom transfer) in tandem with single electron transfer chemistry of early transition metal from the first row (V, Fe, Co). In this presentation we will first discuss the capacity of POMs to store electrons and protons and generate H_2, which is important to proceed to an acceptorless dehydrogenation of alkanes under non-oxidative conditions. In a second part, we will discuss the results of an additional theme studied in the team: the mechanism of H_2O_2 activation on titanium (IV)-Silox-POMs. The objective of this study is to determine intermediates and mechanism that lead to the non-productive decomposition of H_2O_2 (undesired reaction in the epoxidation of alkenes).[6,7]



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Importance of two-electron processes in Fe-catalyzed aryl-(hetero)aryl cross-couplings

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Iron-catalyzed cross-coupling reactions have known a revival in the last decades. Thanks to its abundance and low price, this metal led to a significant breakthrough in transition-metal catalysis. However, the mechanistic facets is still a challenging issue, especially due to the short lifetimes[1] of the active species and the large panel of oxidation states formed under catalytically-relevant coupling conditions.

Recently, we have demonstrated that two drastically distinct mechanisms can be involved in aryl-(hetero)aryl Fe-mediated cross-couplings between Grignard reagents and organic halides, depending on the nature of the latter (see **Figure 1**)[2]. (Hetero)aryl electrophiles which easily undergo one-electron reduction can be involved in a Fe^{II} / Fe^{III} coupling sequence featuring an in situ generated organoiron(II) species, akin to their aliphatic analogues[3]. On the other hand, less easily reduced substrates can be activated by transient Fe^0 species formed by reduction of the precatalyst[4-5]. In this case, the coupling mechanism relies on 2-electron elementary steps involving the Fe^0 / Fe^{II} redox couple and proceeds by an oxidative addition / reductive elimination sequence.

Attesting to the feasibility of this bielectronic mechanism, high-spin organoiron(II) intermediates formed by 2-electron oxidative addition onto (hetero)aryl halides in catalytically relevant conditions were characterized for the first time. Those results are sustained by paramagnetic ^{1}H NMR, kinetics monitoring, as well as by DFT calculations.

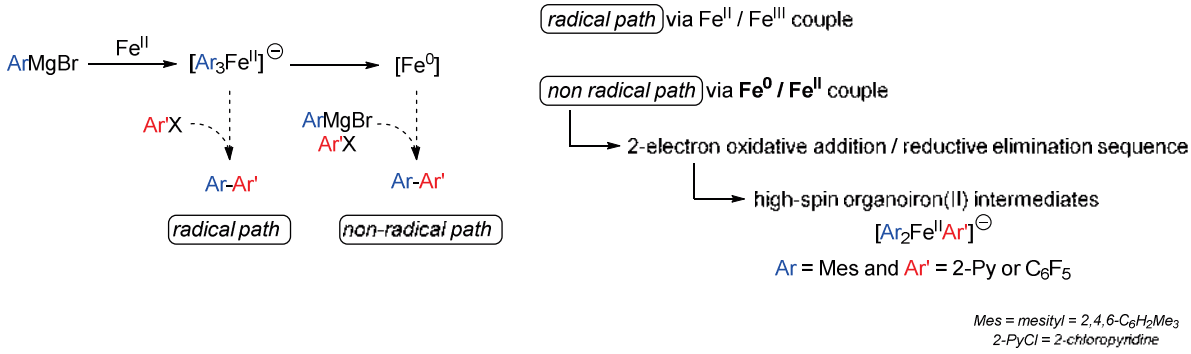

Figure 1: two drastically different routes at work in aryl-(hetero)aryl Fe-mediated cross-couplings

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We thank the ANR (Project JCJC SIROCCO), the ERC (Project DoReMI StG, 852640), and the CNRS (Project IrMaCAR) for their financial support. The NMR shared facilities of Chimie ParisTech (Dr. M.-N. Rager) are thanked for technical support.

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Selective Photo-cleavage of DNA for Gene Therapy

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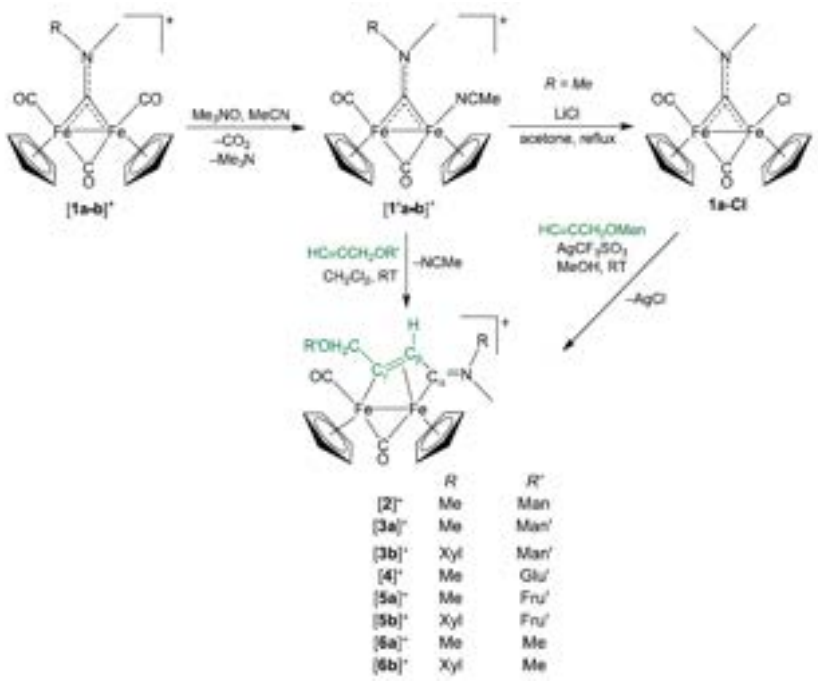

This work is part of a collaboration with Prof. Fabio Marchetti (University of Pisa, Italy).

Metal complexes have been largely evaluated to develop new effective drugs able to overcome the limitations associated with the well-known anticancer platinum compounds. Iron complexes based on the ferrocene scaffold have aroused interest in the recent years. The cytotoxic activity of these compounds is ascribable to the redox chemistry of the ferrocenyl iron(II) center, which is oxidated to Fe^{III} in the tumor cells, triggering the formation of toxic metabolites. Furthermore, "piano-stool" monoiron complexes, containing one cyclopentadienyl moiety and variable co-ligands exert in some cases a strong in vitro cytotoxicity against tumor cell lines. Otherwise, the anticancer properties of di-organoiron complexes have been less explored, despite a diiron carbonyl core constitutes the active unit of impressively efficient enzymes (i.e., hydrogenases). In this work, four propargyl ethers derivatized with mannose, glucose and fructose moieties were synthesized and then incorporated within a diiron structure as part of a vinyliminium ligand. The aim was to increase the cellular uptake of the drugs in cancer cells. Hence, six glycoconjugated diiron complexes, [**2-5**]CF_3SO_3 (see Scheme), and the non-glycosylated analogues [**6a-b**]CF_3SO_3 were obtained in high yields, and unambiguously characterized by several techniques. The cytotoxicity of [**2-6**]CF_3SO_3, as well as that of the previously reported **7** and **8** (non-functionalized with the sugar moiety), was assessed on CT26 (mouse colon carcinoma), U87 (human glioblastoma), MCF-7 (human breast adenocarcinoma) and RPE-1 (human normal retina pigmented epithelium) cell lines. In general, the IC_{50} values correlate with the hydrophobicity of the compounds, and do not show an appreciable level of selectivity against cancer cells. Moreover, the compounds did not display any antimetastatic activity and the cytotoxic effect was not increased in cells grew in no-glucose conditions.

Acknowledgments:
We would like to thank **Prof. Marchetti** and his group at the University of Pisa (Italy) for this collaborative work published in Organometallics: Schoch S, Iacopini D, **Dalla Pozza M**, Di Pietro S, Degano I, **Gasser G**, Di Bussolo V, Marchetti F**.** Organometallics. 2022 Mar 14;41(5):514-526. doi:10.1021/acs.organomet.1c00519.

Plasmonic nanoparticles for biosensing and therapy

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Phenylalanine (Phe) is one of the essential amino acids in human body, but if it exceeds a certain content in human body, it will cause serious neurological diseases- Phenylketonuria (PKU). A rapid assay for the determination of Phe concentration should be very useful.

In this study, we developed a novel colorimetric plasmonic nanoparticle-based sensor for the quantification of Phe on a basis of metal nanoparticle properties.

Herein, the shift of the LSPR band induced by nanoparticle growth (Au) or etching (core-shell Au-Ag) is used to set up colorimetric assays of Phe, as shown in Fig1. The principle of the assay is that oxidation of Phe catalyzed by L-aminoacid oxidase (LAAO) will produce an equimolar quantity of H_2O_2 that, in turn, will reduce $AuCl_4^-$ in the presence of AuNP resulting in NP growth. Alternatively, H_2O_2 will oxidize the silver shell of Au@AgNP. Both reactions will result in a red shift of the LSPR band position whose magnitude will be correlated to the concentration of Phe.

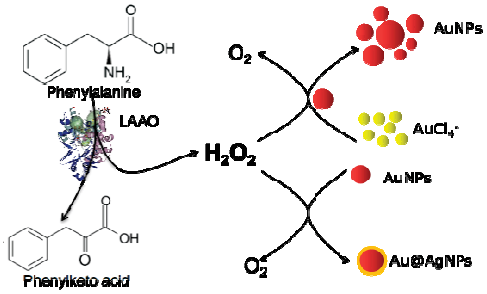

Figure 1: Scheme of Phe assay based on AuNPs growth and Ag etching of Au@AgNPs.

So far, 17 - 19 nm AuNPs and Au@AgNPs coated by silver of about 2 nm thickness have been successfully prepared. These AuNPs and Au@AgNPs are successfully used as both colorimetric and UV-vis spectrophotometer probe for determination of H_2O_2 and Phe. At start, the pure H_2O_2 assay on the growth of AuNPs and Ag etching of Au@AgNPs were investigated to demonstrate the concept. With different concentrations of pure H_2O_2 (0-1mM)and Phe(0-5mM), the solutions gradually turn from pink to purple based on AuNPs growth and from orange to pink based on Ag etching, which can be easily distinguished by the naked eye. For the assay based on AuNPs growth, after the absorbance at 530 nm for each colorful solution was collected, the intensity of the color is in a linear range between 0 and 1 mM (for H_2O_2) and 1-5mM(for Phe).

The corrosion of the silver shell of the Au@AgNPs results in a shift of the LSPR band from 507 to 521nm(the shift value increase with the concentrations of pure H_2O_2 and Phe), and the absorbance at 520 nm and 450 nm of the solution increase and decrease, respectively. And the slope of the increase is in a linear range between 0 and 1 mM (for H_2O_2) and 1-5mM(for Phe). The transmission electron microscopy (TEM) images were obtained to investigate the detailed mechanism of the reactions.

Highly efficient electrochemical CO conversion to ethylene by employing dendritic copper catalyst and alkaline flow cell system

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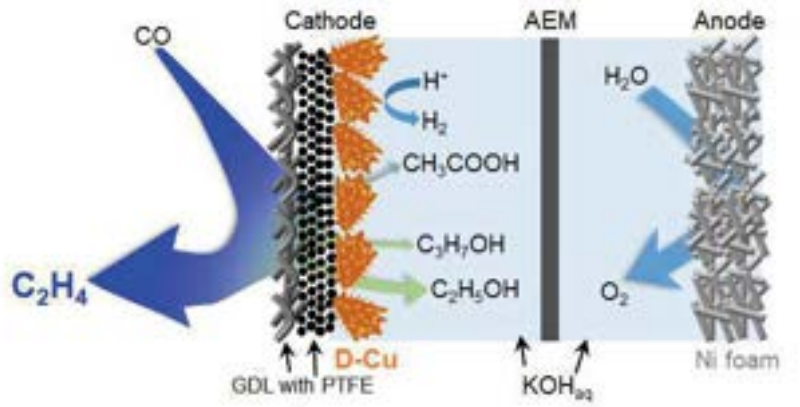
Summary.[i,ii]
Valorization of carbondioxide (CO_2) by electrocatalysis has been considered as a promising method to sustainably produce value added chemicals such as ethylene, ethanol, n-propanol. The major issue of this reaction is the formation of carbonate due to the unwanted reaction between CO_2 and alkaline electrolyte, which significantly decreased the amount of CO_2 supposed to transform to multicarbon products. Therefore, there is a need to find the way to suppress such a loss of reagent. According to the proposed mechanism of electrochemical CO_2 reduction, CO_2 is firstly reduced to carbonmonoxide (CO), then CO species will be further reduced to other value added chemicals, thus CO is the key intermediate of CO_2 reduction and electrochemical CO reduction is thermodynamically easier than CO_2. Besides, CO does not react with alkaline electrolyte. Moreover, the reduction of CO_2 to CO has been intensively studied and nearly ready for practical application. Therefore, many attempts have recently been focused on the research of CO reduction as the carbon feedstock to produce the high value chemicals. In this presentation, I am going to introduce an electrochemical alkaline flow cell reactor combined with our original dendritic copper (D-Cu) catalyst, which showed the highest Faradaic efficiency (FE) reported so far for CO conversion to ethylene of 78% at the applied current densities above 100 $mA.cm^{-2}$. In comparison, electrochemical CO_2 conversion to ethylene gave a FE as only 45% under the similar condition. Optimization of synthetic condition showed that the D-Cu sample synthesize in $CuSO_4$ 0.1 M and H_2SO_4 2 M possessing the highest electrochemical surface active area compared to a bear Cu plate reference showed a high FE for CO conversion to ethylene of more than 70% at 100-200 $mA.cm^{-2}$. Whereas, the D-Cu sample calcined at above 300 °C showed lower FE for ethylene of 40-60% at above 100 $mA.cm^{-2}$. This is likely due to the smaller number of Cu surface active sites, which could produce more hydrogen evolution reaction at high current densities.



Scheme of our electrochemical alkaline flow cell reactor coupled with D-Cu catalyst.

[i] N-H Tran, H.P Duong, G. Rousse, S. Zanna, M.W. Schreiber, M. Fontecave, *ACS Appl. Mater. Interfaces* **2022**, X, XXXX-XXXX.
[ii] Jouny M., Hutchings G.S., Jiao F., *Nat Catal.* **2019**, 2, 1062-1070.

Functional micro and nanoparticles: preparation and biological applications

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In cancer therapies, many effective drugs will have many serious side effects (such as vomiting, aplasia, neurotoxicity) after being taken. These severe side effects are due to the absorption of chemotherapeutic agents by both healthy and cancerous cells [1]. Targeting tumor cells, therefore, appears to be a critical point in reducing the toxicity for surrounding healthy cells. Thus, the challenge is to bring the drug to the right place and to release it locally at a therapeutic concentration [2].

The objective of the thesis is to prepare and evaluate bioactive and biodegradable nanoparticles to deliver drugs to a specific type of cell. This shuttle will have a reservoir that will contain the active drug, a decorated surface targeting the right type of cell (using specific peptides or carbohydrates), and an optimized delayed or controlled release mechanism. The biological activity will be evaluated in cell culture using different cell lines (for the treatment of cancer) and with various bacteria (for the antibiotic effect). The optimized construction will be evaluated in an in vivo model, in the topical treatment of cutaneous and mucous pathologies.

For this topic, nanoparticles and polymers used to modify their surfaces have been successfully synthesized and basic characterizations has been completed. The results show that the surface-modified polymers can effectively improve the chemical and colloidal stability of nanoparticles in different environments.

For the next stage, the selection of effective anti-cancer drugs, testing the drug loading and release rate in nanoparticles becomes the focus. Finally, modify the target-recognized proteins onto the surface of nanoparticles and successfully achieve targeted release become a big challenge.

[1] Barber N A, Afzal W, Akhtari M. Hematologic toxicities of small molecule tyrosine kinase inhibitors[J]. Targeted Oncology, 2011, 6(4):203-215.
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Bioengineering of metabolic pathways of pyrrocidines for the generation of chemical diversity in this family of compounds.

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The maize endophytic fungus, *Sarocladium zeae*, is known to have a protective effect on its host plant against microbial pathogens. This bioactivity is likely due to the production of secondary metabolites, the pyrrocidines. Indeed, these compounds exhibit antifungal and antibiotic activities,[1] as well as cytotoxicity.[2]

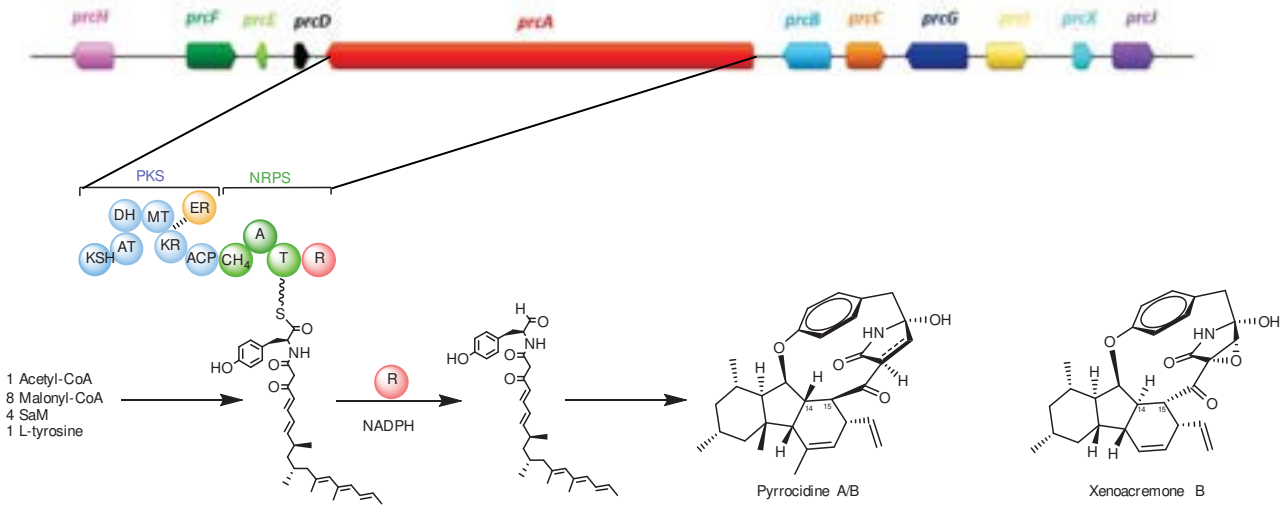

Figure: biosynthetic gene cluster at the origin of pyrrocidines and biosynthetic pathway involving a PKS-NRPS and Xenoacremone B, Pyrrocidines analogues.

The biosynthetic pathway of pyrrocidines has been identify in the fungus:[3] a megasynthase hybrid PKS-NRPS build a linear backbone which is then cyclized by auxiliary enzymes to give the final polycyclic compounds. The study of these enzymes was first conducted by *in silico* analysis to determine amino-acids involved in enzymatic mechanism and then verify by genetic mutation. We focused on the enzyme catalyzing cyclophane formation, and proposed a mechanism with the involvement of a cysteine pair and a lysine. In a second approach, a *S. zeae* mutant was obtained by substitution of this enzyme by a homologue involved in the formation of xenoacremones, analogues of pyrrocidines that differ in the configurations of C14 and C15 carbons. This combinatorial biosynthesis should generate a molecular diversity.

(1) Wicklow, D. T.; Poling, S. M. *Phytopathology* **2009**, *99* (1).
(2) Uesugi, S.; Fujisawa, N.; Yoshida, J.; Watanabe, M.; Dan, S.; Yamori, T.; Shiono, Y.; Kimura, K. *J Antibiot* **2016**, *69* (3)
(3) Chen Youwei, Thesis 2022