New supramolecular multivalent anti-adhesive agents against SARS-CoV-2

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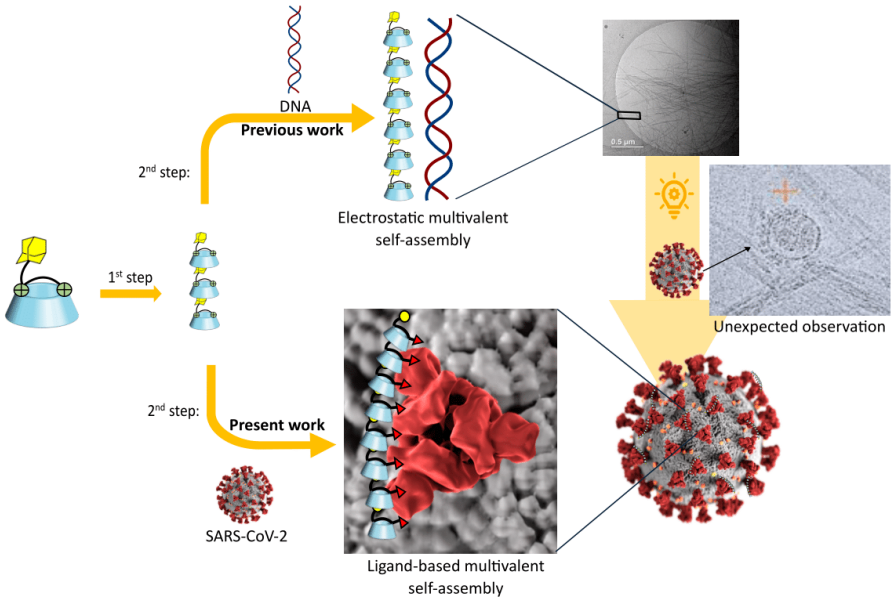
In 2020, during a CRYO-EM experiment, we unexpectedly observed a SARS-CoV-2 particle near self-assembled cyclodextrins fibers. We thus wondered if we could bring specific interactions between them and trigger this assembly on purpose. Indeed, our team previously showed that it was possible to form fibers from small oligomers of DNA and cyclodextrins functionalized by an adamantane and ammonium. The hydrophobic effect between cyclodextrins and adamantanes allows the formation of small supramolecular polymers by self-assembly (1st step). Then, through multivalent electrostatic interactions between the monomers and DNA, the co-assembly becomes a lot bigger (2nd step).[i] The surprising observation encouraged us to explore the ability of cyclodextrins assemblies to cooperatively interact with SARS-CoV-2 particles and use them as anti-adhesive agents to potentially inhibit cell infection by this virus. We therefore changed non-specific electrostatic interactions into more specific ones, using sugar-based ligands allowing multivalent effect. For that, we functionalized cyclodextrins with an adamantane and the targeted ligand on the side. We are now studying their self-assemblies (1st step), their multivalent ability to interact with several receptors at the surface of SARS-CoV-2 and potentially observe cooperative assembly.



Acknowledgments: We acknowledge Pierre Evenou and Léonid Lavnevich, the previous PhD students, Adélie Gothland and Elisa Teyssou, for the biological tests.

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Study of the reactivity of trivalent Phosphorus in a constrained geometry

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T-shaped phosphorus (III) compounds are a particular class of non-trigonal phosphorus compounds with 3 substituents organized around the phosphorus atom with an almost planar[1] environment and angles between two P-X bonds close to 90° - although non-planar compounds have been reported.[2] The first synthesis of these compounds was reported in 1984 by Arduengo and co-workers[1] and since then, various T-shaped P(III) derivatives have been reported by Radosevich,[2] Kinjo,[3] Goicoechea,[4] and Uhl[5] (Figure 1).

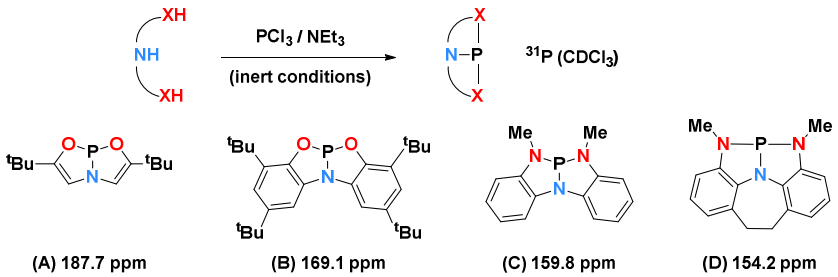

Figure 1: General procedure for the synthesis of the four T-shaped phosphorus

Due to their constrained structure, the LUMO is especially low in energy thus making the P(III) compound electrophilic, which is rather unusual for trivalent phosphorus compounds. They are actually ambiphilic, able to perform formal oxidative addition in polar bonds such as the N-H bond of an amine, [2,3,6,7,8,9,10] the O-H bond of an alcohol[2,10] or water.[4]

With the desire to explore such new reactivity, our team, in collaboration with the Dr Sami Lakhdar group (LHFA, University of Toulouse), is investigating the reactivity of these compounds with protic substrates. In order to correlate the rate of oxidative addition to their unique ambiphilicity, their nucleophilicity and electrophilicity will be ranked on the Mayr scale and their ability of performing oxidative addition at protic compounds will be look at through the lens of their Mayr parameters.

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Design/synthesis of water-soluble and photoactivatable Cu complexes based on modified cyclodextrins for *in cellulo* applications

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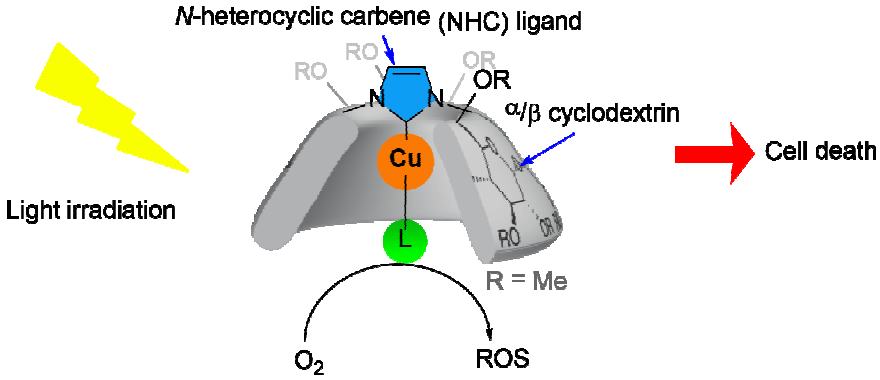
Our team previously has extensively studied the selective modification of the cyclodextrin (CD) structure by different chemical transformations. One of this modification, involving the covalent capping of the CD by a NHC ligand, allowed encapsulation of several metal complexes deep inside the cavity of the cyclodextrin. Although encapsulated, the metal complexes inside the cyclodextrin are still catalytically active and can perform reactions in various solvents (organic or aqueous). Significant cavity effects have been observed in copper and gold-catalyzed reactions (control of regio- and stereoselectivity and stabilization of reactives species).[1] Furthermore, the encapsulation was shown to induce a dramatic decrease of complex cytotoxicity.

The aim of the CataCLiSMS project is to synthetize copper(I) complexes encapsulated inside a cyclodextrin able to perform photocatalysis *in cellulo* to induce cells death. This could be done through generation of reactive oxygen species (ROS) in the cells. For that, we are developing a series of water-soluble permethylated cyclodextrin capped with NHC ligands bearing a photoactivatable copper-ligand unit inside the cavity. We present here preliminary results on the synthesis of such complexes and their photophysical properties. (We will next study their photocatalytic activity in water, their toxicity toward cells and their mode of action *in cellulo*.)



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Syntheses, structures, CO release properties and biological studies of neutral Mn(I) tricarbonyl complexes with 8-hydroxyquinoline and imidazole ligands

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Carbon monoxide (CO) is known in the popular culture as a lethal gas, earning his name of "silent killer". Since the past decade, CO has emerged as a promising therapeutic agent for cancer treatment when administrated at optimal concentrations.[1] However, due to its gaseous form, CO remains difficult to handle. To overcome this issue, Carbon Monoxide Releasing Molecules (CORMs) have been introduced as a more convenient mode of administration.[2] These molecules are mostly organometallic complexes, enabling the release of CO upon a given external stimulus, such as visible light. These complexes, named photoCORMs, remain the most widely developed so far.[3] Despite some recent advances, efforts are still ongoing to synthesize new carbonyl complexes absorbing light in the visible region while having high potency of vectorization for the controlled delivery of CO.[4] In this context, we present a new series of photo-activatable complexes [Mn(8-hydroxyquinoline)$(CO)_3$(Imd)] with Imd = imidazole derivatives. We developed a short step synthesis from the dimeric structure Mn_2(8-HQ)$_2(CO)_6$ and applied a series of imidazole ligands (Fig. 1a). The use of various imidazole-based ancillary ligands allows the synthesis of a wide range of complexes with a high degree of modularity due to the presence of allyl, hydroxyl, or amine groups on the imidazole ring. Moreover, *N,C*-diprotected histidine was successfully applied, opening the way to a further functionalization with peptides (Fig. 1b).

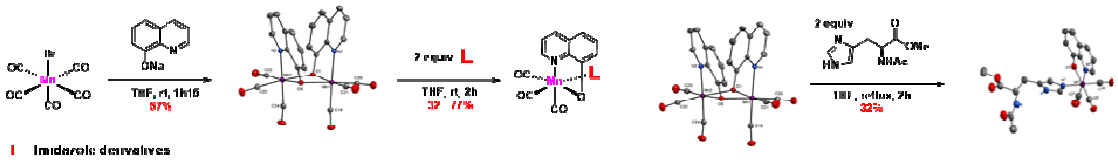

Fig.1 *Synthetic pathway to these new photoCORMs. a) General synthesis pathway b) Synthesis of [Mn(8-HQ)(CO)₃NAc-His-OMe] with corresponding X-ray structures.*

Finally, we successfully developed new glycoconjugated CORM series (GlycoCORMs) to allow targeted delivery of CO and enhanced cytotoxicity against cancer cells (Fig. 2).

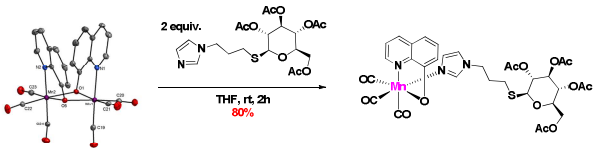

Fig. 2 *Synthesis of [Mn(8-HQ)(CO)₃GluOAcSImd]"GlycoCORM-1"*

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N-Heterocyclic Carbene Coinage Metal Complexes Incorporating Pyrene Chromophore: Synthesis, Structural Motifs, and Luminescent Properties

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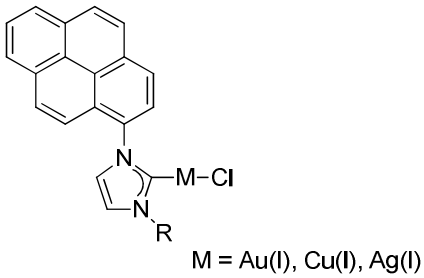
Abstract: N-heterocyclic carbenes (NHCs) are strongly coordinating ligands and have proven themselves as the ligands of choice in a wide-range of the chemistry spectrum spanning from organometallics, catalysis to medicinal chemistry as well.[i-ii] More recently they have been used with success to design stable luminescent organometallic and coordination complexe.[iii-iv] This is because they tend to push the ^{3}dd dark states high in energy and thus avoiding the deactivation processes of the low-lying MC (metal-centered) transition states. In this presentation we describe the design of novel class of luminescent NHC-coinage metal complexes containing a pyrene chromophore (**Figure 1**). All complexes were fully characterized and their molecular structures were ascertained by X-ray diffraction studies. The nature of the coinage metal center and the alkyl substituents on the carbene unit were probed to tune their electronic properties generating blue emitters at room temperature.

Figure 1.



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Novel Chiral Imidazopyridine Au(I)-NHC Complexes for Enantioselective Enyne Cycloisomerizations

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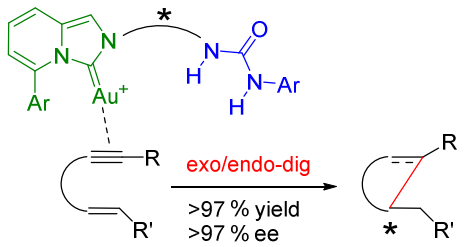
Enyne cycloisomerizations are a powerful tool to create complexity within a molecule from easily accessible starting materials. Metallic Lewis acids such as gold, palladium and platinum have been utilized for this type of reactions in recent years, activating unsaturated hydrocarbon bonds for intramolecular cyclization reactions.[1] Establishing Au(I) complexes as enantioselective catalysts presents a special challenge, which is due to the linear coordination sphere and therefore large distances between a chiral ligand and the reactive center.

Pathfinding works by Echavarren and Toste utilize axial chirality to tackle this issue.[2,3] In their case, binaphthyl-based counterions result in high enantioselectivities. Other approaches employ direct phosphine or N-heterocyclic carbene (NHC)-tethered axial chirality as well as cyclodextrin-based ligands, while examples of ligands featuring a single stereocenter are very rare.[4,5]

In our study we show the first example of a chiral, non-symmetric Au(I)-NHC, which is able to perform various enyne cycloisomerization reactions in up to excellent yields and enantioselectivities. The studied complexes utilize an imidazopyridine-based NHC core in combination with a chiral, urea-containing side-arm. We observe tunable selectivity dependent on the urea-moiety as well as unique reactivity due to urea-substrate interactions.



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Targeted biomimetic microparticles functionalized with tunable fluorescent lipids: FRET-sensing of receptor binding and phagocytosis

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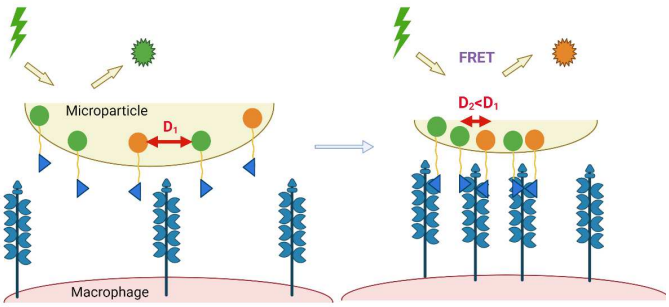
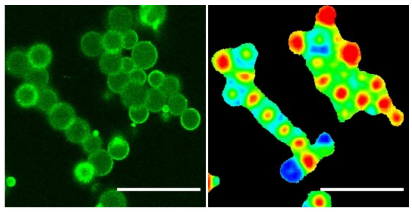
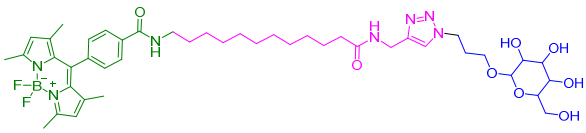
Targeted fluorescent particles are valuable tools to study phagocytosis processes, but they are generally not easily tunable and it can be difficult to conciliate controlled functionalization, shape, size and effective biosensing. In this work we propose a new tunable and versatile platform composed of fluorescent lipids-coated microparticles. Herein, we present the synthesis and characterization of a series of fluorescent lipids and their use in the formulation of emulsion droplets for biosensing application. Glycolipids-coated microparticles are thus used to study the role of C-type lectin membrane receptors involved phagocytosis. Their role in phagocytosis and especially their ability to trigger phagocytosis or to cooperate with other receptors is not determined.[1,2] We have developed micrometer sized oil-in-water emulsion droplets [3,4] functionalized with synthetic fluorescent (bodipy fluorophores) amphiphilic lipids, exposing on their surface sugars or biotin. The functionalization of the droplets with the lipids and the specific interaction of the resulting microparticles with different receptors demonstrating clustering were monitored by fluorescence microscopy. Specific recognition and internalization of this biomimetic platform by macrophages were then tested. Finally, we were able to perform in vitro FRET between fluorescent glycolipids localized at the surface of the microparticle to evidence short-range interactions due to lectin receptor. This work may provide insights into the comprehension of lectin-dependent phagocytosis.







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PHOTOREDOX-CATALYZED PSEUDO-4-COMPONENT ALKYLATIVE AMIDINATION OF ALKENES

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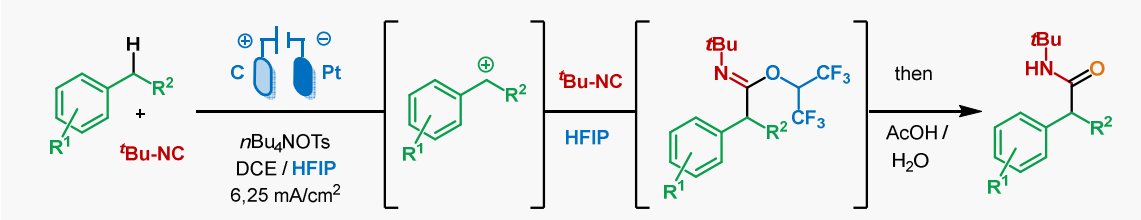
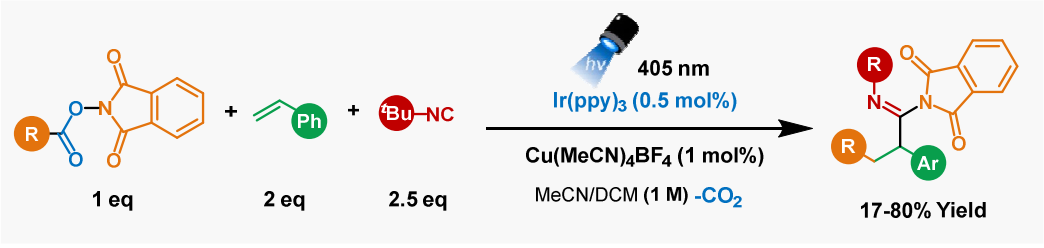
Keywords: *isonitriles, alkenes, photoredox-catalysis, amidination, radical-polar process…*

Isocyanide-based multicomponent reactions (IMCRs) are undoubtedly remarkable tools for generating extensive chemical diversity in in a direct and efficient manner. Ever since 1921, when Passerini reported the first IMCR, this field of research has not ceased to grow.

In this field, our group and others have implemented electrosynthesis as a means of promoting redox events in mild and sustainable reaction conditions.[1],[2] Notably, we reported the unprecedented benzylic C-H-carbamoylation of aromatic derivatives in which electrosynthesis ensures the transient generation of benzylic carbocations. [1c]



Building on our expertise, our attention turned towards the utilization of photoredox-catalysis to facilitate the formation of benzylic carbocations through a radical-polar pathway.[4] In this study, we present an innovative pseudo 4-component alkylative amidination of alkenes.[5] A crucial aspect of this multicomponent process is the incorporation of Okada's redox active esters, which not only serve as radical sources but also act as nucleophile sources to ensure the completion of the reaction.



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Development, characterization and biological evaluation of a novel theranostic peptide-based nanostructures for cancer therapy

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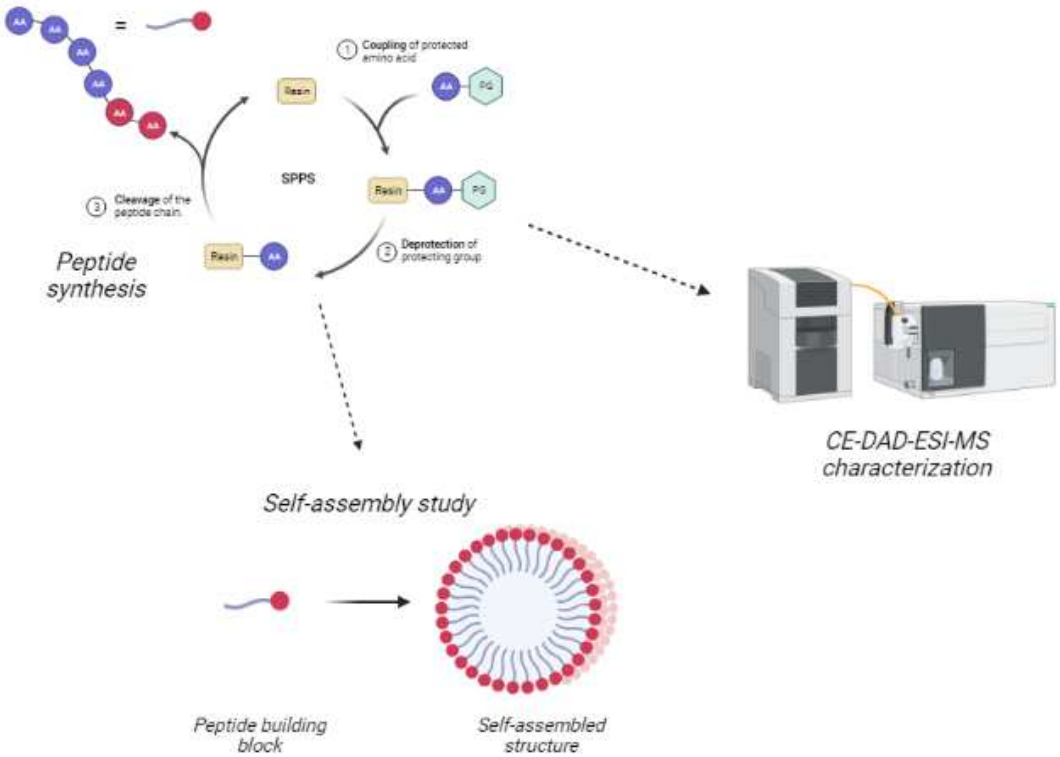
Peptides are attractive building blocks for the design of nanostructures for applications in theranostics. Exploiting the self-assembly property of some peptide sequences, a wide variety of nanoarchitectures with different properties can be achieved due to the versatility of peptides as building blocks.[i]

We report the synthesis of a short amphiphilic peptide in continuous-flow process[ii] and optimization of synthesis conditions, conducted in parallel with the development of a new characterization method for the purity and structural analysis of the resulting synthetic peptides, by coupling capillary electrophoresis and mass spectrometry (CE-MS). The developed method allowed for a fast and simple purity check and identification of impurities. Furthermore, solubilization and self-assembling conditions of the peptide in solution were studied (pH, salt concentration, solubilization process).



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