Geneva chemistry & biochemistry days 2023

TH 12 January 2023, 09:00–18:00
FR 13 January 2023, 09:00–12:00
Sciences II – auditorium A150
No registration required

Dr Loïc Charbonnière
CNRS & Université de Strasbourg

Prof. Olga García Mancheño
Universität Münster

Prof. Albrecht Ott
Universität des Saarlandes

Prof. Markus Seeger
Universität Zürich

Junior Speakers:
• **Meropi Bagka** • **Anne-Laure Boinet** • **Cécile Cadoux** •
• **Maria Fernanda Cifuentes Girard** • **Polyxeni Damala** •
• **Neel Deorukhkar** • **Simao Fernandes Ribeiro Da Silva** •
• **Tara Forrest** • **Mingxue Fu** • **Ina Fureraj** • **Takehiro Kato** •
• **Rebecca Mucci** • **Soroush Naseri** • **Guillaume Pernollet** •
• **Philippe-Alexandre Poisson** • **Elias Polak** • **Simone Scaringi** •
• **Inès Taarit** • **Júlia Viñas Lóbez** • **Victoria Von Glasenapp** •
• **Jiangtao Zhao** •

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FACULTÉ DES SCIENCES
SECTION DE CHIMIE ET BIOCHIMIE

UNIVERSITÉ DE GENÈVE

FOREWORD

The *Section de chimie et biochimie*, University of Geneva, has the pleasure to announce the 13th edition of its “***Geneva Chemistry & Biochemistry Days***”. After so much time spent on Zoom during the two previous editions, the event will be back again on site for the benefit of all participants!

The vocation of the event is to give our students who are close to finishing their PhD studies the opportunity to present their research as attractive speed talks to an audience from academia and industry, and the steering committee is glad to welcome you in this context.

Four distinguished lecturers further enrich the programme. Our four departments have invited them, and they will illustrate the extent and the quality of top-level fundamental research in chemistry and biochemistry today.

Our BSc and MSc students are welcome to smell the very flavour of the research held in our School and abroad, and to learn a bit more about how to present punchy results to a scientific audience.

We expect that the event will catalyse fruitful face-to-face discussions between young and advanced researchers and give our students an opportunity to get ready for their professional career yet offering our guests an overview of the quality of the fundamental research performed in our School.

Looking forward to welcoming you in person at this event, we hope that you will enjoy the lectures and interactions!

Nicolas Winssinger

Prof. Nicolas Winssinger – Prof. Éric Bakker
Président et Vice-président de la Section de chimie et biochimie

Steering and organising committee

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Prof. Karsten Kruse	karsten.kruse@unige.ch *host of the guest speaker for biochemistry*
Prof. Stefan Matile	stefan.matile@unige.ch *host of the guest speaker for organic chemistry*
Dr Didier Perret	didier.perret@unige.ch *Responsable communication – Section de chimie et biochimie*

SESSION 1 – THURSDAY, 12 JANUARY, MORNING

Chair: **Dr Alexandre Fürstenberg** (for Senior Speaker)
Dr Amina Benchohra (for Junior Speakers)

09:00- -09:05	**Prof. Éric Bakker**	Welcome message
09:05- -09:50	**Dr Loïc Charbonnière** CNRS & Université de Strasbourg	Molecular upconversion
09:50- -10:05	**Inès Taarit**	Excited state absorption and energy transfer upconversion in Er^{3+} complexes
10:05- -10:20	**Philippe-Alexandre Poisson**	Nickel catalyzed vinylation of enol phosphates: A comparative mechanistic study
10:20- -10:40	Coffee break	Main hall, Sciences III
10:40- -10:55	**Tara Forrest**	Taking advantage of “click” chemistry for increased stability in potentiometric sensing
10:55- -11:10	**Simone Scaringi**	Assisted tandem Pd catalysis enables regiodivergent Heck arylation of transiently-generated substituted enol ethers
11:10- -11:25	**Simao Fernandes Ribeiro Da Silva**	Exploring the function of microtubule post-translational modifications by semi-synthetic tubulin
11:25- -11:40	**Maria Fernanda Cifuentes Girard**	Liquid Chromatography and vacuum Differential Mobility Spectrometry-Mass Spectrometry for metabolites analysis
11:40- -11:55	**Takehiro Kato**	Cyclic thiosulfonates for thiol-mediated uptake: Cascade exchangers, transporters, inhibitors
11:55- -12:10	**Neel Deorukhkar**	Digging deep: The effect of flipping a ligand on the SCO of octahedral Fe(II) complexes
12:10- -12:20	Group picture	Senior Speakers, Junior Speakers, Chairpersons and School’s authorities
12:20- -13:45	Lunch break	Senior Speakers and Junior Speakers share their lunch at the *Pizzeria Sole Mio*, 43 boulevard Carl-Vogt

SESSION 2 – THURSDAY, 12 JANUARY, AFTERNOON

Chair: **Prof. Enrica Bordignon** (for Senior Speaker #1)
Dr Dimitris Basagiannis (for Junior Speakers)
Prof. Stefan Matile (for Senior Speaker #2)

13:45- -14:30	**Prof. Markus Seeger** Universität Zürich	Exploring the conformational space of membrane proteins using sybodies and nanobodies
14:30- -14:45	**Victoria von Glasenapp**	Controlling the activity of the mitotic kinase Plk1 with light
14:45- -15:00	**Guillaume Pernollet**	Quantifying the impact of mechanical and geometrical stress on epithelial tissue organisation
15:00- -15:15	**Meropi Bagka**	PROTACs as a target deconvolution tool of Hedgehog Pathway Inhibitor 1
15:15- -15:35	Coffee break	Main hall, Sciences III

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15:35- -15:50	**Rebecca Mucci**	Amide-linked cationic [4]helicenes: Synthesis and properties
15:50- -16:05	**Ina Fureraj**	Studying structural changes using ultrafast broadband spectroscopy
16:05- -16:20	**Cécile Cadoux**	Cooperativity in biological nitrogen fixation
16:20- -17:05	**Prof. Olga García Mancheño** Universität Münster	New venues in supramolecular anion-binding catalysis: From the design to synthetic applications
17:05- -18:00	Get-together aperitif	Main hall, Sciences III
19:30-	VIP dinner	Senior Speakers, Chairwomen/men, and School’s authorities at the *Cantine des Commerçants*, 29 boulevard Carl-Vogt

SESSION 3 – FRIDAY, 13 JANUARY, MORNING

Chair: **Prof. Karsten Kruse** (for Senior Speaker)
Dr Nidal Saleh (for Junior Speakers)
Prof. Charlotte Aumeier (for Awards)

09:00- -09:05	**Prof. Éric Bakker**	Welcome message
09:05- -09:20	**Soroush Naseri**	Rigidifying bis(benzimidazole) pyridine scaffolds: The key to improve stability in linear lanthanidopolymers
09:20- -09:35	**Jiangtao Zhao**	Metal complexes-grafted Au_{25} nanoclusters for efficient (photocoupled) electrocatalytic $CO_2 \rightarrow CO$ reduction
09:35- -09:50	**Anne-Laure Boinet**	Using live fluorescent microscopy to elucidate the dynamics of clathrin coat assembly in yeast
09:50- -10:05	**Polyxeni Damala**	Symmetric solid-contact electrodes for potentiometric sensing
10:05- -10:25	Coffee break	Main hall, Sciences III
10:25- -10:40	**Elias Polak**	Tackling the charge leak problem in subsystem Density Functional Theory
10:40- -10:55	**Mingxue Fu**	How to include the excitation-induced polarization from the environment in Frozen Density Embedding Theory
10:55- -11:10	**Júlia Viñas Lóbez**	Synthesis of complex *trans*-fused bicycles *via* photoredox catalyzed cyclization of malonate enol ethers
11:10- -11:55	**Prof. Albrecht Ott** Universität des Saarlandes	Strong role of cooperativity in molecular recognition and epigenetics as revealed in an *E.coli* derived cell free expression system
11:55- -12:00	**Prof. Charlotte Aumeier**	Awards for the best oral Junior presentations
12:00- -12:05	**Prof. Éric Bakker**	Concluding remark

Molecular upconversion

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Upconversion (UC) is the process by which the energy of two or more photons are stored in a compound and restored in the form of luminescence at a higher energy than the excitation beam. If the process is known for more than 60 years in solid compounds,[1] it is only some ten years ago that the first examples were described in discrete molecules at very low temperature (30K) in organic solvents.[2]

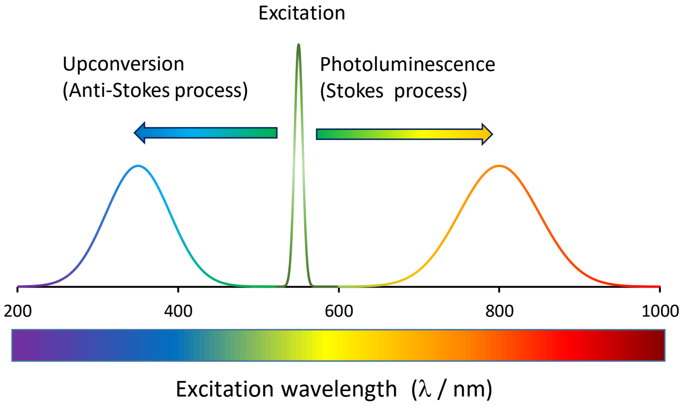

Figure 1. Representation of conventional and non-conventional (Anti-Stokes) luminescence process

Towards the rational design of heteropolynuclear lanthanide complexes, we succeeded to demonstrate that molecular UC can not only be observed at room temperature,[3] but also in aqueous solvents,[4] and even in pure water,[5] opening the space to a brand-new family of luminescent labels.

Additionally, supramolecular architectures enlarged the perspectives of yet unexplored UC mechanism at the molecular level, such as the observation of cooperative sensitization in Yb/Tb nonanuclear clusters,[6] cooperative sensitization of Yb dimers,[7] or Yb to Ru UC energy transfer in hetero-polynuclear d-f complexes.[8]

Since my very first contact with UC at the University of Geneva with Prof. Jørgensen's book,[9] up to the latest advances of our group, I will present you a little journey into molecular UC.

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New venues in supramolecular anion-binding catalysis: From the design to synthetic applications

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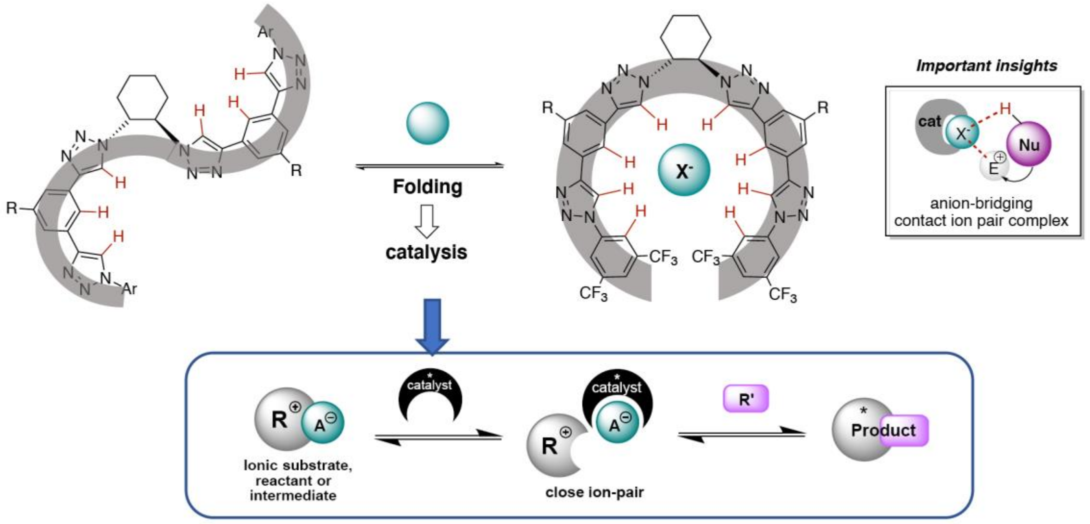
In the past few years, anion-binding organocatalysis have become a promising new catalytic strategy to promote highly enantioselective chemical reactions.[1] In this regard, we have recently introduced helical chiral triazoles as versatile multidentate H-donor structures.[2] Their cooperative multidentate character permits the use of very low loadings (down to 0.05 mol%), while effecting an efficient transfer of chirality from the chiral contact ion-pair formed upon binding of the catalyst to a simple achiral anion to the final product.



Herein, the design and remarkable performance of H-donor chiral triazole foldamers in asymmetric anion-binding catalysis aimed at nucleophilic dearomatization of *N*- and *O*-heteroarenes (up to 99:1 e.r.) are presented.[2,3] Additionally, experimental and computational studies on the anion binding and folding into the key chiral contact ion-pair by combined will be discussed,[4] leading to key mechanistic insights that have already opened new synthetic opportunities for the enrolment of challenging reactants.[5]

References:

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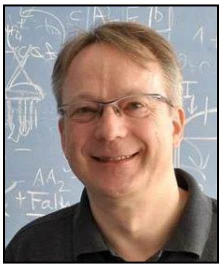
Strong role of cooperativity in molecular recognition epigenetics as revealed in an *E.coli* derived cell free expression system



Albrecht OTT

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The cooperative action of molecules makes biological systems act in interesting, unsuspected ways. At the same time, cooperative effects remain poorly understood. In this talk I will present two phenomena linked to cooperative behavior.

i) We used in vitro expression systems to study the incorporation during protein synthesis of two non-canonical amino acids, the toxic amino acid canavanine as well as hydroxylysine. Following current knowledge, in presence of the canonical amino acid and its non-canonical equivalent, the incorporation should be proportional to the ratio of concentrations adjusted for enzymatic error correction. However, in experiments we achieved 100% replacement of the non-canonical equivalent at all residues – in spite of the presence of residual canonical amino-acid. Our data points towards a non-linear transition to full incorporation of either one or the other of the competing species as a function of concentration. Experiments on DNA molecular recognition showed analog behavior with binding affinities increasing by 10^4 compared to pairwise assessment. Using a mean field model, we quantitatively explained our observations on DNA by a transition to order that arises from two strands competing for the same binding site with, however, different sets of binding micro states. To explain our observations on amino acid incorporation we project that molecular recognition at the level of the synthase follows an equivalent mechanism. Our results cannot be understood from pairwise considerations regarding the participating molecules.

ii) In the second part of the talk I will present experiments that address the bacterial PAP epigenetic gene expression “switch”. This switch contains only two methylation sites. By methylating either one of them, *E.coli* passes the adhesion mode, via pili or not, to the next generation. How just one methylated site can stabilize the PAP gene expression pattern over generations is not fully understood. We realized a simplified *in vitro* construction of the regulatory portion of the PAP1 gene in our cell free expression system and showed that the standard model cannot explain our results. We discovered that the regulating portion of the DNA can form a Holliday junction. We suggest that it is the conformation of the DNA Holliday junction controlled by transcription factors that the stability of the switch relies on. Our work helps to better understand molecular cooperativity that causes unexpected behavior in “lock and key” molecular recognition as well as transcription regulation.

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Exploring the conformational space of membrane proteins using sybodies and nanobodies

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Nanobodies are the variable domains of heavy-chain only antibodies found in camelids such as alpacas and llamas, while sybodies are synthetic nanobodies selected entirely in vitro from large combinatorial libraries. Nanobodies and sybodies have similar features as classical antibodies in terms of specificity and binding affinity. Yet, they are more robust and can be rapidly generated against any protein target.

Membrane transporters are integral transmembrane proteins that undergo large conformational changes to accomplish solute transport across the lipid bilayer. In order to investigate membrane transporters at the structural and biochemical level, they have to be extracted from their native membrane environment using detergents. Therefore, information on the conformational space a membrane transporter assumes in its native environment has thus far been lacking.

In recent pioneering work in collaboration with Enrica Bordignon (UNIGE), we have used spin-labelled nanobodies as highly specific double electron electron resonance (DEER) probes to explore the conformational space of the bacterial Lipid A transporter MsbA in the native context of intact *E. coli* cells.

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PROTACs as a target deconvolution tool of Hedgehog Pathway Inhibitor 1

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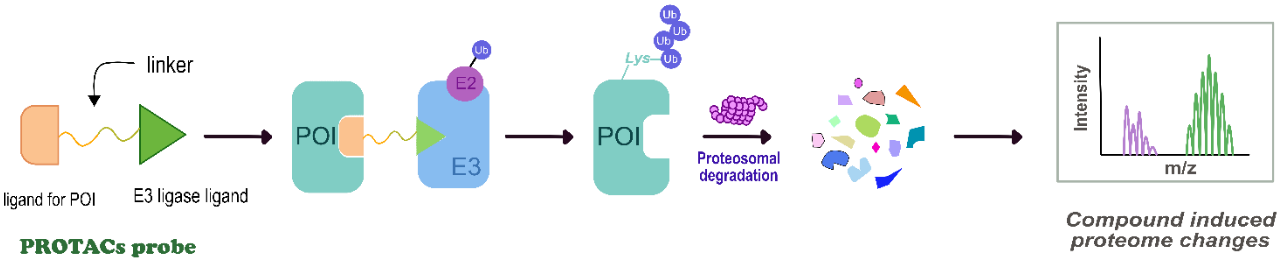
The Hedgehog (Hh) signaling pathway is pivotal for embryonic development of vertebrates, however abnormal activation can lead to tumorigenesis. The current FDA approved drugs targeting the Hh pathway act on the upstream protein Smoothened and suffer from acquired resistance, rendering essential to find new inhibitors with a different target.[1] Hedgehog Pathway Inhibitor 1 (HPI-1) was reported as a downstream inhibitor by Hyman et al. and has subsequently been shown to have anti-cancer activity, but its cellular target has remained elusive for many years.[2]


Target identification by protein degradation and label-free quantitative proteomics

Compound induced proteome changes

To reveal the molecular targets of HPI-1 we designed a proteolysis-targeting chimeras (PROTACs) approach, that involves heterobifunctional molecules consisting of two-headed small ligands which bind to two different proteins; an E3 ligase and a target protein (POI) that is to be degraded through the ubiquitin-proteasome system.[3] The POI can eventually be identified by mass spectrometry-based proteomics. Using this strategy, we discovered the BET bromodomains as the targets of HPI-1, extending the scope of PROTACs as a novel target deconvolution technique.

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Using live fluorescent microscopy to elucidate the dynamics of clathrin coat assembly in yeast

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Endocytosis is a fundamental mechanism in eukaryotic cells, supporting a wide range of vital functions from nutrient uptake to intercellular communication. This internalization process involves various molecular machineries; the best known of which, and probably also the best characterized, being Clathrin-mediated endocytosis (CME). This mechanism happens through the coordinated assembly of a complex mesh of more than 50 different proteins referred to as “coat”. The coat provides both the force necessary for the cell membrane deformation as well as the tight regulation of cargo recruitment and vesicle formation, in a process that is very well conserved across all eukaryotes, yet highly adaptable.[1]

Clathrin itself, while being one of the most highly conserved and best-described proteins of the coat, still finds itself at the centre of numerous debates and studies. Although the protein’s very recognizable triskelion structure has been very well characterized over the years, how it comes into play in the endocytic process is still poorly understood: while it was initially considered only as a scaffolding protein, few studies seem to point towards a regulatory role as well.[2,3] A major hint of this is the ATP-dependent turnover of Clathrin taking place during the whole coat assembly process in vivo,[4,5] reminiscent of a proofreading mechanism.

The aim of the present study is to characterize Clathrin’s assembly properties over time at the molecular scale, using genetically, fluorescently tagged proteins. We use live microscopy techniques in yeast cells to follow in real time the protein’s recruitment at the endocytic site and relate its dynamic behaviour to its various interactors. Our setup not only helps us detail the established structural model of endocytic vesicle building[6] with a more precise time component, but it is also a useful tool in the investigation of Clathrin’s exact function in endocytosis. This protein is a central player of the endocytic process, interacting with numerous other proteins all along its lifetime. Understanding how it assembles at the endocytic site, and how this assembly is regulated could provide an insight on how it can accommodate for the late membrane deformation. It would also shed light on where the interactions with its many partners fall into the regulative network governing the whole endocytic process.

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Cooperativity in biological nitrogen fixation

Cécile CADOUX

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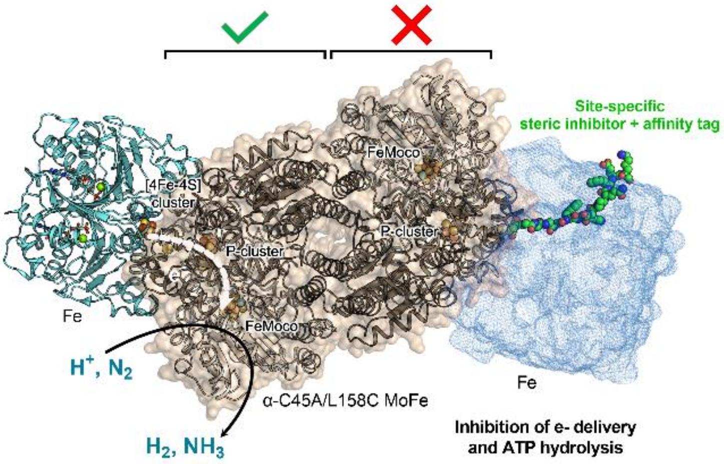
Nitrogenase is a metalloenzyme that catalyzes the reduction of dinitrogen (N_2) to ammonia (NH_3) as a source of N in diazotrophic organisms. It consists of an electron-transferring ATP-hydrolyzing iron protein (Fe protein) and a catalytic molybdenum-containing protein (MoFe protein), enabling catalytic N_2 fixation under ambient conditions according to the following optimal stoichiometry:

$$N_2 + 8H^+ + 8e^- + 16MgATP \rightarrow 2NH_3 + H_2 + 16MgADP + 16P_i$$

The MoFe protein is organized as an $\alpha_2\beta_2$ heterotetramer, where each αß half is considered to be catalytically active.[1] In humans, the organization of myoglobin-like subunits into multimeric hemoglobin introduces subunit cooperativity and enables O_2 transport within our bodies. By extension, the organization of nitrogenase's MoFe protein into a heterotetramer may contribute towards nitrogenase's remarkable selectivity towards N_2. However, there a clear consensus does not yet exist.[2-4]

Here we investigate cooperativity in nitrogenase by selectively inhibiting the Fe/MoFe transient associations that are necessary for catalysis on only one αß half of the MoFe protein. We confirm that half-inhibited nitrogenase is still able to fix N_2; moreover, selectivity towards N_2 is not impacted. Interestingly, we determine that half-inhibited nitrogenase is >50% active (with respect to the uninhibited enzyme), suggesting that negative cooperativity exists between both functional halves. The importance of nitrogenase's cooperativity *in vivo* remains an important unanswered question.



Mo-nitrogenase

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Liquid Chromatography and vacuum Differential Mobility Spectrometry-Mass Spectrometry for metabolites analysis

Maria Fernanda CIFUENTES GIRARD

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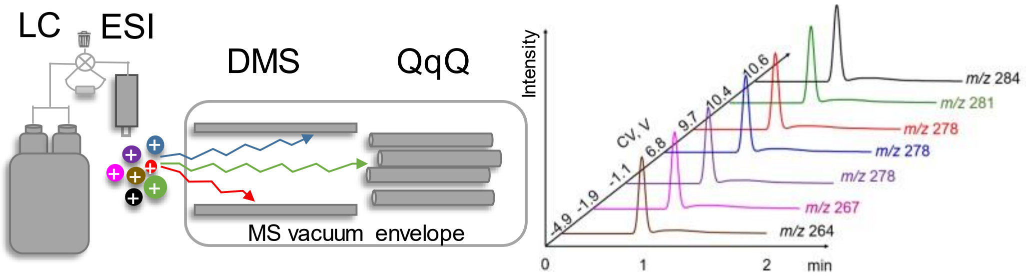
LC-MS analysis in complex biological samples lacks often in selectivity for the qualitative and quantitative analysis of isobaric/isomeric compounds. Ion mobility spectrometry based on the shape of charged particles has gained of interest as an additional separation/filter dimension and has been recently implemented in analytical LC-MS workflows.



In this work we investigated the potential of a novel prototype vacuum differential ion mobility (vDMS) cell, as an alternative to LC×LC for shortening analysis time, using the LC mobile phase to tune selectivity of the mobility dimension. Isobaric/isomeric compounds such as antidepressant drugs, pyrrolizidine alkaloids and drug of abuse metabolites were used to investigate the performance of the vDMS cell. During the work it was demonstrated that the LC mobile phase at a given flow rate can act as clustering modifier enabling to tune the selectivity of the vDMS separation.[1] In addition to limit ionization suppression effects, short LC trap-elute approaches combined to vDMS-MS were developed for reducing the LC analysis time while maintaining good selectivity for the quantification of the compounds.

Antidepressant drugs amitriptyline, maprotiline, venlafaxine, nortriptyline, imipramine and desipramine were quantified in plasma using a short LC-vDMS-SIM/MS method in less than 2 minutes. Fourteen diastereomeric pyrrolizidine alkaloids were quantified in tea samples using a column switching LC-vDMS-SIM/MS method in less than 7 min.[2] Cocaine and its metabolites (ecgonine methyl ester, cocaethylene, and the isomers norcocaine and benzoylecgonine) and tramadol and its isomeric metabolites (O-desmethyl-cis-tramadol N-desmethyl-cis-tramadol) were quantified in urine samples in less than 1 min. The isomeric cannabinoids THC/CBD and the metabolites (THC-OH, THC-COOH, THC-COOH-GLU) were determined in urine samples using short LC-vDMS-SIM/MS method in 4 min. All methods were compared to classical LC-MRM/MS methods and in all cases inter-assays precision and accuracy were lower than 12% and in the range of 90-105%, respectively but with significantly higher throughput.

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Symmetric solid-contact electrodes for potentiometric sensing

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Potentiometry is one of the most extensively used techniques for the sensing of environmentally and clinically relevant ions. During the last decades there has been a shift to the use of solid-contact electrodes which offer the advantages of robustness and ease of miniaturization compared to traditional designs with an aqueous inner solution containing a Ag/AgCl element. This shift has come with the disadvantage of introducing an asymmetry to the potentiometric cell since the reference and indicating electrodes are no longer of the same nature and result in undesired instabilities of the potentiometric response.

We propose an approach to restore the symmetry by using two identical solid-contact electrodes used as reference and indicating electrodes. By performing differential potential measurements between the two, one can cancel most potential drifts that may arise from changes in the environment (e.g., temperature, light, pressure), the quality of the electrode components or the conditioning of the sensing membranes.[1, 2]

The symmetric setup is successfully used to perform measurements with unconditioned solid-contact ion-selective electrodes (ISEs), allowing for their use “out-of-the-box” without the need for a lengthy conditioning step.[1] The symmetric approach is subsequently also applied for the real-time measurement of nitrate in freshwater with a submersible probe that uses two nitrate-selective electrodes, one measured as reference and the other as indicator electrode. With this setup the direct measurement of concentrations instead of activities is reasonably possible while most fluctuations in the potential caused by environmental factors are cancelled out.[3] As part of this work, existing nitrate ionophores are unfortunately demonstrated to lack selectivity.[4] The development of symmetric systems and selective ionophores in the field of potentiometry and beyond may result in advanced ion sensing applications showing increased stability and overall better performance.

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Digging deep: The effect of flipping a ligand on the SCO of octahedral Fe(II) complexes

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Octahedral complexes of *d*-metals with electronic configurations between d^4 and d^7 exhibit multiple spin-states determined by a balance between the crystal field stabilisation energy (CFSE) and the electron pairing energy. If the energetic separation between these states is in the thermal energy regime, energetic stimuli can allow changing the spin state, i.e., the phenomenon of spin crossover (SCO) occurs.[1] Among these, the spin-states of d^6 Fe(II) with a diamagnetic low-spin state and a paramagnetic high-spin state are especially promising for applications in data storage and sensing.

In octahedral *tris*-homoleptic $[Fe^{II}N_6]$ complexes thermodynamically programmed to exhibit SCO, the use of unsymmetrical didentate ligands results in the formation of configurational *fac* and *mer* isomers, with distinctive properties. In the solid state, these isomers have a fixed configuration around the Fe(II), albeit with the added influence of lattice and solvent interactions on the evolution of magnetic properties. On the contrary, studies in solution allow elucidation of SCO behaviour at a molecular level. Furthermore, an explicit analysis of the isomeric equilibrium involving the *mer* and *fac* isomers offers an unprecedented opportunity for assigning specific thermodynamic spin-crossover parameters to each isomer.[2] This presentation aims to highlight the nuanced modification of complex properties, which results from the apparently negligible flipping of a didentate ligand in going from facial to meridional Fe^{II} spin-crossover complexes.

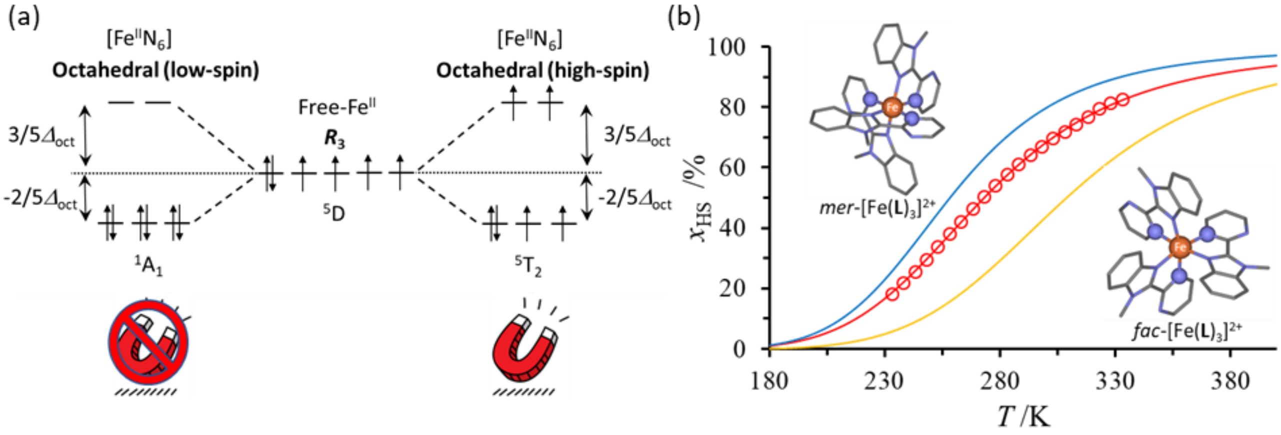

Figure 1. (a) SCO behaviour of d^6-Fe(II) as a function of its electronic distribution, and (b) SCO behaviour of meridional and facial isomers of $[Fe(\mathbf{L})_3]^{2+}$ in solution.

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Exploring the function of microtubule post-translational modifications by semi-synthetic tubulin

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αβ-tubulin isotypes differ mainly in their C-terminal tails (CTT), which are hotspots for post-translational modifications (PTM). These modifications include the attachment of polyglutamate or polyglycine chains and/or the removal of C-terminal amino acids.[1] Together with amino acid sequence of the CTT, these PTMs form a combinatorial code, – the tubulin code.[2] This code affects microtubule stability and regulates the interaction with microtubule associated proteins (MAPs), which is required for diverse cellular processes.[3] However, detailed investigations of the function of combinatorial CTT-PTMs have been hindered due to the lack of methods to purify homogenously modified tubulin dimers.

Here, we address this challenge and present a novel semi-synthetic approach to engineer α- and β-tubulin dimers with precise multiple modifications. To a recombinant tubulin core, we ligate a synthetic tubulin tail, where we can choose the exact position and chain length of our modification. Importantly, this method is not limited to a single type of modification but can be expanded to include all combinations of known PTMs at the tubulin CTT. Moreover, our chemoenzymatic ligation method introduces only a minimal alteration in the protein sequence, allowing the production of practically native tubulin dimers that retain all their dynamic and structural properties. Concluding, our new methodology provides us a chemical control over the CTT-PTM landscape. It will thus allow us to test the detailed effects of defined PTMs in a highly defined system, thereby revealing the molecular intricacies of the tubulin code.

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Taking advantage of “click” chemistry for increased stability in potentiometric sensing

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Solid-contact ion-selective electrodes have gained significant interest over the last few years and can be used in environmental monitoring to measure a wide range of relevant ions such as nitrate, pH and carbonate. They are also found in the bioanalytical field to measure a range of blood electrolytes. They offer less maintenance and miniaturisation possibilities compared to classical liquid-contact ion-selective electrodes. In this improved design, the inner solution, containing the Ag/AgCl reference element, is often replaced by a redox polymer acting as ion-to-electron transducer. The implementation of this transducing element has been known to improve the stability of the signal and suppress undesired ion transport. Although all conditions seem to be met to have an ideal system, solid-contact electrodes still suffer from a reduced lifetime due to leaching of membrane components, such as plasticisers, ion-exchangers or ionophores.[1]

To minimise components leaching, different strategies were envisioned such as enhancement of lipophilicity[2] or covalent binding[3]. Increasing the lipophilicity only slows down the leaching and can also be detrimental in terms of synthetic modification and solubility in organic media. The second approach was based on a plasticiser-free cross-linked poly(decyl methacrylate) matrix that was functional if a single membrane component (either ion-exchanger or ionophore) was covalently attached, but reports are scarce to attempt the covalent linking of all membrane components.[4]

We present here a novel strategy for creating leak-free ion-selective plasticised membranes. Owing to a simple reaction, chlorine functionalities on polyvinyl chloride (PVC) can be easily replaced by azide groups, thus generating a materials platform to perform an azide alkyne cycloaddition, known as “click” chemistry. Membrane components and the transducing element can in a second step be modified to include an alkyne group that is needed for the final covalent attachment. Taking advantage of the high yield of “click” reactions, all alkyne-modified membrane components can be covalently attached in a quantitative manner by controlling the stoichiometry. These new electrodes will be tested using thin-layer membranes to drastically reduce the development time as done in previous work.[5] It is believed that these electrodes will exhibit a longer lifetime than their counterparts.

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How to include the excitation-induced polarization from the environment in Frozen Density Embedding Theory

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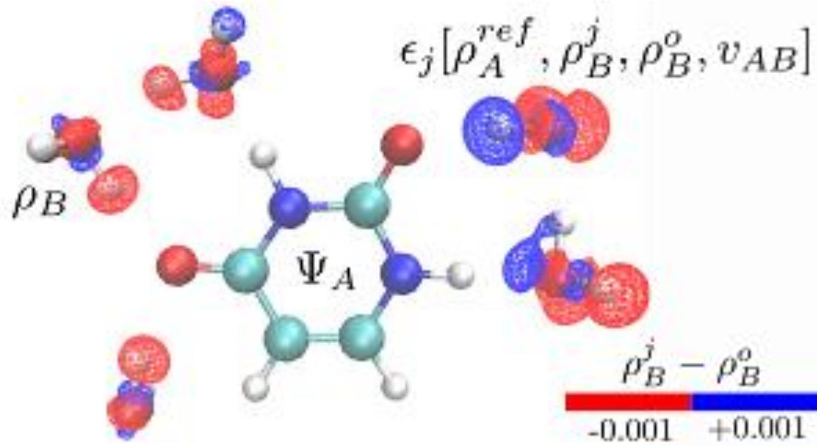
The environment polarization response to the excitation of the chromophore can be critical in many applications. Starting from the Perdew-Levy theorem[1] on extrema of the Hohenberg-Kohn functional, the expression for the vertical excitation energy is derived within the formal framework of Frozen-Density Embedding Theory[2,3] (FDET) that makes it possible to use state-specific electron densities of the environment (ρ_B) of an embedded species.

The derived general expression involves the embedded wave-functions for ground- and excited states that are orthogonal and is exact up to quadratic terms in the appropriate density expansion. It can be applied in practice using various methods differing in the treatment of the electron-electron correlation for embedded electrons, the method to evaluate different contributions to the excitation energy, the method to generate state-specific ρ_B, and the approximation used for the non-electrostatic component of the FDET embedding potential. The derived expression is applied for 47 local excitations in ten embedded organic chromophores. The explicit treatment of the differential polarisation of ρ_B improves indeed the accuracy of the excitation energy as compared to the implicit treatment in which the same ρ_B is used for all states of embedded chromophore.

For 47 local excitations in ten embedded organic chromophores, the average absolute errors in excitation energies drop from 0.04 eV to 0.03 eV and their standard deviations from 0.032 eV to 0.025 eV, respectively. The maximal errors show similar trends.[4]



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Studying structural changes using ultrafast broadband spectroscopy

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To better understand the photochemical processes, we need to first understand what happens directly after photoexcitation. Such processes include vibrational energy relaxations, planarization, isomerization without large amplitude motions, etc. Femtosecond broadband fluorescence up-conversion with a sub 100 fs resolution and tuneable excitation and transient absorption spectroscopy are used to study some of these ultrafast processes.[1]

My work dives into the study of several of these ultrafast processes in different systems. Firstly, 9,10-bisphenylethynyl-anthracene, which undergoes significant structural relaxation involving planarization upon photoexcitation is studied in solvents of varying viscosities and at different excitation energies.[2,3] A photoselection of molecules with different ground-state geometries is achieved. Moving towards more rigid molecules such as perylene and its derivatives which are good candidates for studying the vibrational energy relaxations consisting of IVR (intramolecular vibrational relaxation) and VC (vibrational cooling) and how these are affected by the excess excitation energy and role of substituents. Next, a more complex system , YOYO-1, a DNA tag and its fast dynamics are investigated.[4] Lastly, two multipolar molecules that undergo symmetry breaking in the excited state in polar solvents, have been studied in a series of cosolvents of different polarity.[5] The motivation lies in understanding solvent dynamics, as well as the dielectric enrichment effect on excited state symmetry breaking

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Cyclic thiosulfonates for thiol-mediated uptake: Cascade exchangers, transporters, inhibitors

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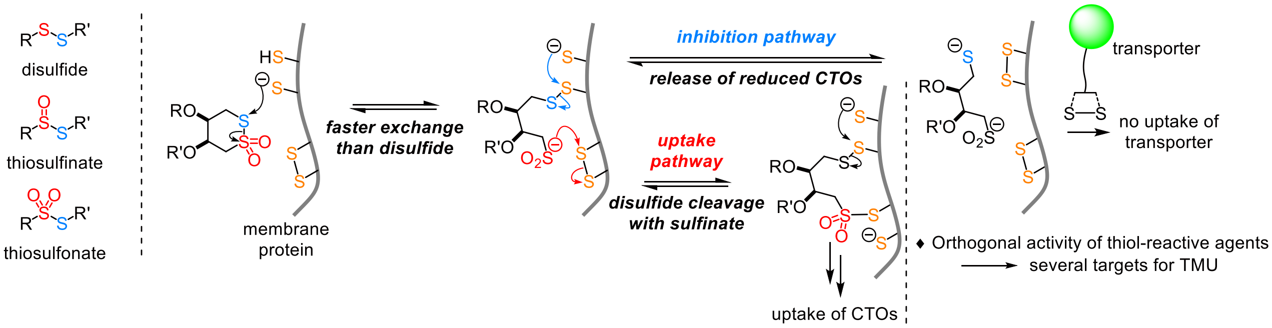
Thiol-mediated uptake (TMU) is one of the pathways of the cellular entry of biomolecules, in which the reversible formation of disulfide bonds between the molecule and a protein on the plasma membrane plays a crucial role. The formation of dynamic covalent bonds at the membrane surface facilitates cellular penetration and ensures internal release by biological thiols, such as glutathione. Similar processes are involved in the uptake of HIV[1] and potentially of SARS-CoV-2,[2] and thus the development of better transporters and inhibitors of this process is of great importance.

In our exploration of new motifs for efficient transporters and inhibitors, cyclic thiosulfonates (CTOs) have attracted a lot of interest as thiol-reactive agents. However, the use of thiosulfinates and thiosulfonates, oxidized forms of disulfides, has not been much explored so far in the context of cellular uptake, whereas CTOs can serve as anti-HIV agents.[3] Our recent screening showed CTOs have good inhibitory activities against TMU.[4]

In our current research,[5] kinetic experiments revealed the excellent reactivity of CTOs with thiols over disulfides and thiosulfinates, and the ability of the sulfinate products to continue the cascade exchange with another disulfide. As expected from their reactivity, CTOs afforded better fluorescent transporters than a standard disulfide counterpart. CTO transporters internalize to the cytosol via TMU, proven by the inhibition with thiol-reactive agents. An inhibition study with three transporters and more than 50 synthetic inhibitor candidates revealed the orthogonality of the inhibition with different thiol-reactive motifs, which strongly suggests the existence of multi targets for TMU.



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Amide-linked cationic [4]helicenes: Synthesis and properties

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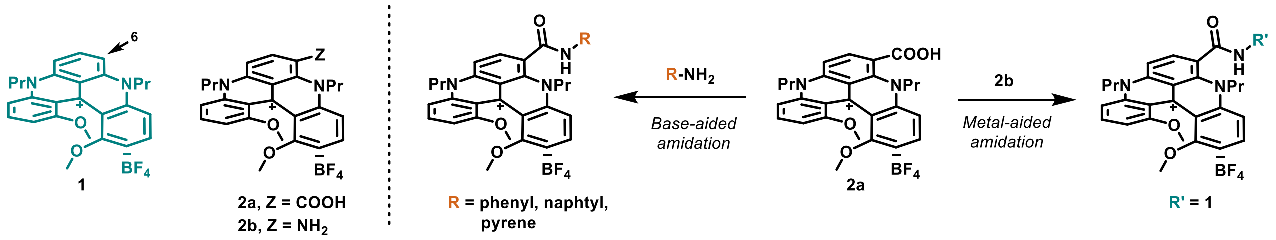
Organic aromatic helicenes commonly feature key properties such as absorption, fluorescence and electronic circular dichroism (ECD), and therefore employed in many research domains and various applications.[1-3] Previously, an efficient tuning of the optical properties of cationic [4]helicene **1** was achieved through late-stage regioselective S_EAr functionalisation, giving access to both carboxylic **2a** and amino **2b**. Electron-withdrawing groups at position 6 generally shift absorption and emission maxima towards higher energies while enhancing the fluorescence quantum yield, compared to unsusbtituted **1**. Conversely, electron-donating groups bathochromically shift the absorption maxima and emission towards the red and even near infrared.[4]



In this work, COOH-functionalised [4]helicene **2a** is reacted with various aliphatic and aromatic amines, leading to a library of amide products with properties similar to that of the helical starting material. Surprisingly difficult, the coupling between **2a** and **2b** had to be achieved under metal reducing conditions. Homo- and heterochiral couplings were performed enantiospecifically to yield a series of four bis-helicene stereoisomers that shows promising (chir)optical properties, ECD and luminescence in particular.

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Rigidifying bis(benzimidazole) pyridine scaffolds: The key to improve stability in linear lanthanidopolymers

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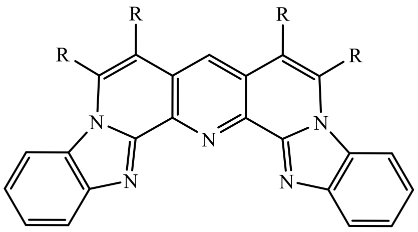
Supramolecular interactions (H-bond, solvation effects, dative bonds, halogen bonds, etc.) have some unique potential for programming the free-energy drift due to the formation of host-guest assemblies.[1] Changes in the free-energy ($\Delta G_{m,n}^{\mathrm{H,G}}$) can be partitioned into two major contributions:[2] (i) a pure entropic contribution provided by the changes in rotational entropy between the reactants and products,[3] and (ii) chemical intercomponent interactions such as host-guest (H-G), guest-guest (G-G) and host-host (H-H).[4]

Adopting these two parameters rationalizes the metal loading in linear metallopolymers, which leads to two highly desired, but opposite strategies. Firstly, the formation of metallic clusters by occupying neighbouring sites finds applications, e.g., in sensing.[5] Secondly, the alternate arrangement of occupied and empty sites is highly desired for light-upconversion.[6]

A rational control of the latter parameters requires improved preorganization and rigidity in the binding sites dispersed along a multi-tridentate receptor. In this regard, we have designed and prepared new neutral and highly preorganized polyaromatic terdentate ligands (**L1**-**L3**) (Figure 1) based on the well-known bis(benzimidazole)-pyridine edifice. Beyond their synthesis via C–H activation and alkyne annulation, the effect of the ligand preorganization on the thermodynamic stability of the 1:1 heteroleptic adducts [**L*k***Ln(hfac)$_3$] with different trivalent lanthanide containers [Ln(hfac)$_3$(diglyme)] will be discussed.



L1: R= phenyl
L2: R= 3,5-dimethylphenyl
L3: R= propyl

Figure 1. Chemical structures of **L1**-**L3**.

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Quantifying the impact of mechanical and geometrical stress on epithelial tissue organisation

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Epithelial tissues are one of the four basic types of tissues in multicellular eukaryotic organisms. These tissues act as barrier and therefore line organs outer surfaces as well as cavities, where they many roles necessary for the proper functioning of organs such as controlling diffusion, transcellular transport, secretion, etc.

Like all tissues, epitheliums need to control their geometrical organisation, both to carry on properly their function, for example with tissue height[1] and connectivity which impact diffusion, and for homeostasis, with apoptosis being controlled by topological defects position in epitheliums.[2] However, we do not yet have a clear understanding of how biochemical signalling, tissue stress and mechanosensing controls tissue geometrical organisation.

My work focuses on how mechanical stress such as substrate rigidity or cell contractility, and geometrical stress such as curvature and confinement, impact epithelial tissues organisation. For this, new image analysis tools were developed to a full 3D characterisation of tissues geometrical parameters, along with state-of-the-art tissue culture technics including hydrogel patterning and tissue encapsulation.

Using this I was able to observe a large range of stress impact on tissue organisation, such as cell volume shrinking due to confinement, cell height tight regulation and homogeneity, curvature impact on cell volume and height, as well as the induction of tilt, cell skew and apical-basal cell junction transition, which could help us better understand the complex mechanisms at play in morphogenesis and tissue homeostasis.

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Nickel catalyzed vinylation of enol phosphates: A comparative mechanistic study

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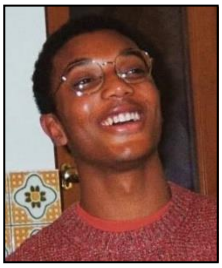
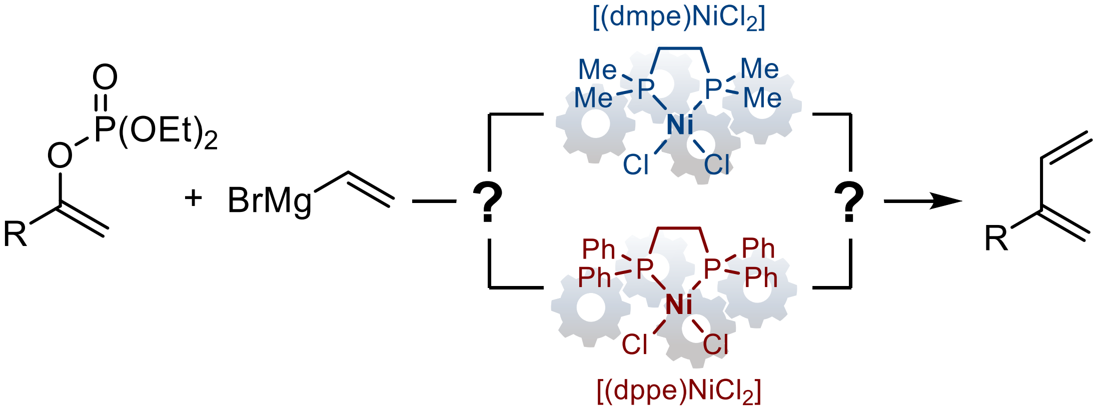


In 2018, our group reported a nickel-catalyzed cross-coupling between vinyl magnesium bromide and a variety of enol phosphates for the synthesis of diversely 2-substituted 1,3-dienes.[1] This methodology relied on the use of two complementary bisphosphine-nickel complexes: [(dmpe)$NiCl_2$] and [(dppe)$NiCl_2$]. In most cases, the cross-coupling products were obtained in excellent yield with either catalyst. Intriguingly, in some case, only one of the two precatalyst proved competent.



In recent years, numerous mechanistic studies of Ni-catalyzed cross-coupling reactions have been reported.[2,3] However, there are only a handful of mechanistic studies focusing on Ni-catalyzed reactions using C(sp^2)–O electrophiles such as aryl ethers, aryl sulfamates, aryl esters and aryl carbonates.[4-7] Using enol phosphates and vinyl magnesium bromide, we conducted a comparative mechanistic study between the two precatalysts. Our approach, based on supporting stoichiometric organometallic syntheses, structural analyses, reaction monitoring, radical-clock experiments and kinetic investigations demonstrated that the two bisphosphine-nickel complexes operate via distinct catalytic manifolds.[8]

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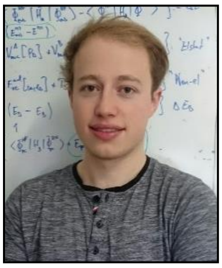
Tackling the charge leak problem in subsystem Density Functional Theory



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In electronic structure theory, based on the Born-Oppenheimer[1] approximation, the electronic Schrödinger equation provides a ground state wavefunction with its energy level that describes the electronic nature of a chemical system. Density Functional Theory[2,3] (DFT) establishes a mathematical sound relation between this ground state energy and the electron density function, which ultimately lead to the Nobel prize in chemistry 1998 by Walter Kohn and John Pople.

Nowadays, subsystem DFT is an efficient framework for performing quantum mechanical computations on large-sized reacting systems such as solutions or proteins. In particular, Frozen-Density Embedding Theory (FDET)[4,5] models the electrostatic and non-electrostatic effects of an environment with the use of a single frozen density function. This pure-state strategy uses orbital-free formulas as approximants for the non-additive kinetic and exchange-correlation bifunctionals.

Common local (LDA) or semilocal (GEA2) models for the corresponding non-additive kinetic potential[4] lack physical exact conditions in the limit[6], which lead to an artificial charge leak[7] when optimizing self-consistently the subsystem densities in Cortona's type of calculations.[8] Thus, a bottom-up approach is needed to impose physical or mathematical exact properties on the potential without specifying an associated "parent" approximation.

We use the exact limit conditions introduced in the work of Lastra et. al.[6] to construct an approximant that covers additionally the complete function space for exponentially decaying densities (NDCS).[9] As a result, the new non-decomposable functional preserves the desired feature of the older approximation, which is the reciprocal singularity if the electron density decays exponentially, and eliminates artificial shallow wells (holes), which are responsible for the charge leak.

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Assisted tandem Pd catalysis enables regiodivergent Heck arylation of transiently-generated substituted enol ethers

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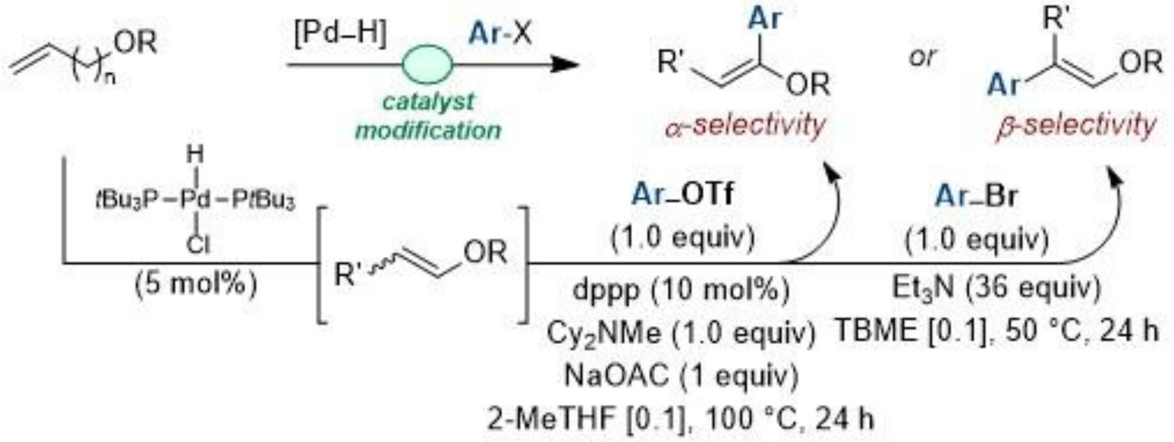
Multi-step syntheses performed in a single reaction vessel ('one-pot') are efficient and environmentally friendly approaches because they prevent purification procedures, reduce the costs, time, and chemical wastes.[1] One such approach consists in combining a metal-catalyzed olefin isomerization reaction with a second transition metal-catalyzed transformation.[2]



• broad scope • high regioselectivity • moderate stereoselectivity

Herein, we describe an operationally-simple assisted tandem catalysis in which sensitive and unexplored 1,2-disubstituted vinyl ethers are formed *in-situ* by olefin migration and then regioselectively cross-coupled with a variety of aryl electrophiles. The isomerization is performed by means of a known [Pd–H] catalyst which is subsequently reduced to [Pd(0)] to initiate a Heck cross-coupling.[3,4] Using aryl triflates as electrophiles, we found that the [Pd–H] catalyst can be modified by addition of a bisphosphine ligand (dppp), to generate preferentially the α-arylation product. Instead, using aryl bromides, the β-arylation product is favored by reducing the catalyst with an excess of an organic base (Et_3N). In all cases, the products are obtained in high yield and regioselectivity. The moderate stereoselectivity reflects the absence of stereocontrol in the isomerization step.

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Excited state absorption and energy transfer upconversion in Er^{3+} complexes

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For a long period, metal-based linear light-upconversion, that is the conversion of near-infrared (NIR) light into emitted visible light by successive linear absorption of NIR photons, was limited to the statistical doping of low phonon bulk solids and garnets. The design of closely related upconversion processes operating in nanoparticles allowed to reach the nanoscale.[1]

The next miniaturizing step aims at reaching molecular level. Achieving this goal requires either the piling up of photons onto a single lanthanide via excited state absorption (ESA) or the alternative energy transfer upconversion (ETU) mechanism combining a lanthanide activator surrounded with long-lived sensitizers.[2] Only a very few of sophisticated multicenter devices which exploit the indirect ETU mechanism could be implemented in molecular complexes.[3]

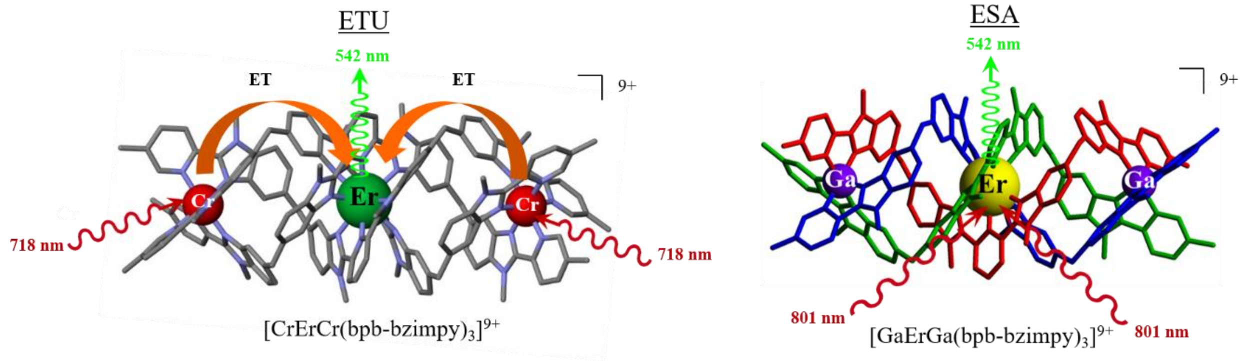

Figure 1. Erbium-based coordination complexes exhibiting linear upconversion processes and associated kinetic model for the single-ion ESA process.

In this contribution, the erbium-centered downshifted emission and NIR to visible upconversion and their quantifying in molecular complexes will be discussed as well as their mechanisms. The associated quantum yields measured for ESA and ETU appear to be larger than those predicted with theoretical models. An unexpected, boosted ESA process is proposed for reconciling predictions and measurements.[4]

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Synthesis of complex *trans*-fused bicycles *via* photoredox catalyzed cyclization of malonate enol ethers

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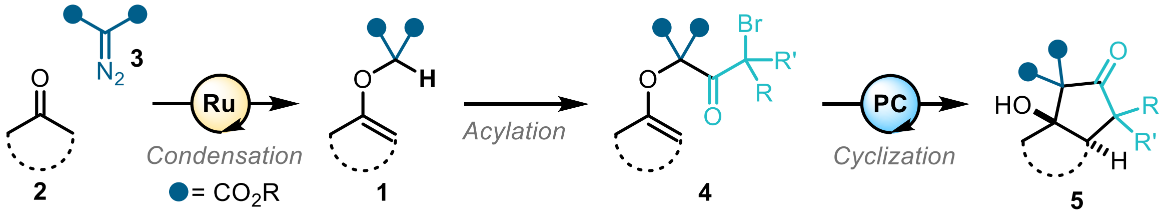
Diazo reagents substituted with two electron-withdrawing groups are among the most stable diazo derivatives.[1] Yet, under metal catalysis, they readily decompose to form highly reactive electrophilic carbenes[2] which, upon trapping of various Lewis bases, generate subsequent ylide intermediates that afford original reactivities.[3]

In this context, with α-diazodiesters as reagents, we reported the effective formation of malonate enol ethers **1** by condensations of ketones **2** with metal carbenes derived from α-diazomalonates **3** and $[CpRu(CH_3CN)_3][BAr_F]$[4] as catalyst. Malonate enol ethers **1** of different ring sizes and geometries are obtained in good to excellent yields, often as single regioisomers.[5]

Moreover, they are interesting building blocks due to the presence of two different nucleophilic active sites, the enol and malonate groups. They can be exploited separately but also in synergy to promote diverse annulation processes,[5] considerably expanding the classical scope of cyclizations derived from carbonyl ylide intermediates.[6]

Capitalizing on the dual reactivity of **1**, we demonstrate herein that its late stage functionalization into **4** paves the way towards the synthesis of complex *trans*-fused bicycles **5**, under visible-light photoredox catalysis.



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Controlling the activity of the mitotic kinase Plk1 with light

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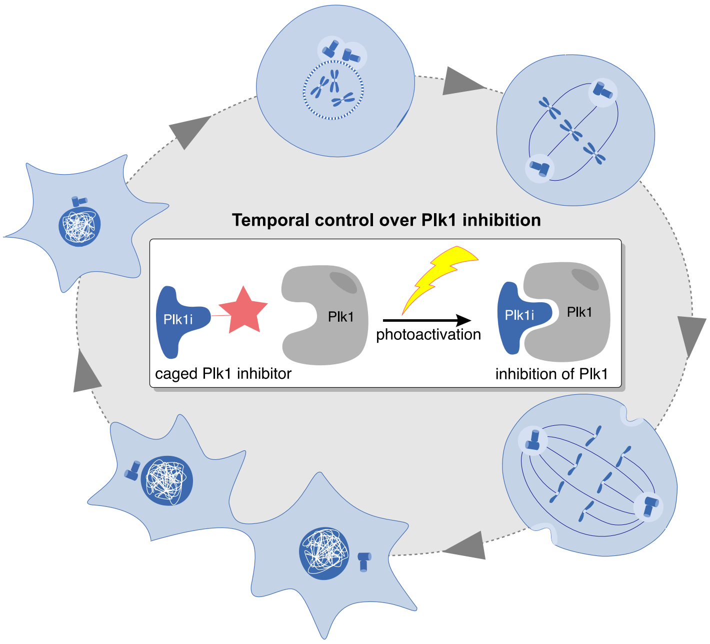
Cell division is a tightly regulated process that requires the activity of different proteins at precise locations in the cell at specific time points during the cell cycle.

One of these proteins is Polo-like kinase 1 (Plk1), a conserved mitotic kinase, that is important for several processes during cell division, such as mitotic entry, bipolar spindle assembly and cytokinesis. The activity of the kinase is regulated during the course of mitosis to be active at specific time points. The small molecule inhibitor BI2536 has been widely used to study the functions of Plk1.

We have developed a Plk1 inhibitor based on BI2536 that can be controlled with light to have precise temporal control. We have attached a coumarin based photoremovable protecting group to the inhibitor at a position important for interaction with the kinase. In HeLa and hTERT-RPE cells the caged inhibitor is stable and does not interfere with the cell cycle even at high concentrations. It can be rapidly uncaged and activated under the confocal microscope as well as wide field microscopes equipped with a laser or a lamp of a wavelength of 488 nm. Once uncaged, the inhibitor efficiently interferes with Plk1 activity. We have successfully used the caged inhibitor in high-content microscopy and achieved precise temporal control of Plk1 inhibition. We are now functionalizing the inhibitor to introduce spatial control. This tool will allow us to dissect the roles of Plk1 at different locations and in individual cells of developing organisms and organoids.



Metal complexes-grafted Au_{25} nanoclusters for efficient (photocoupled) electrocatalytic CO_2 → CO reduction

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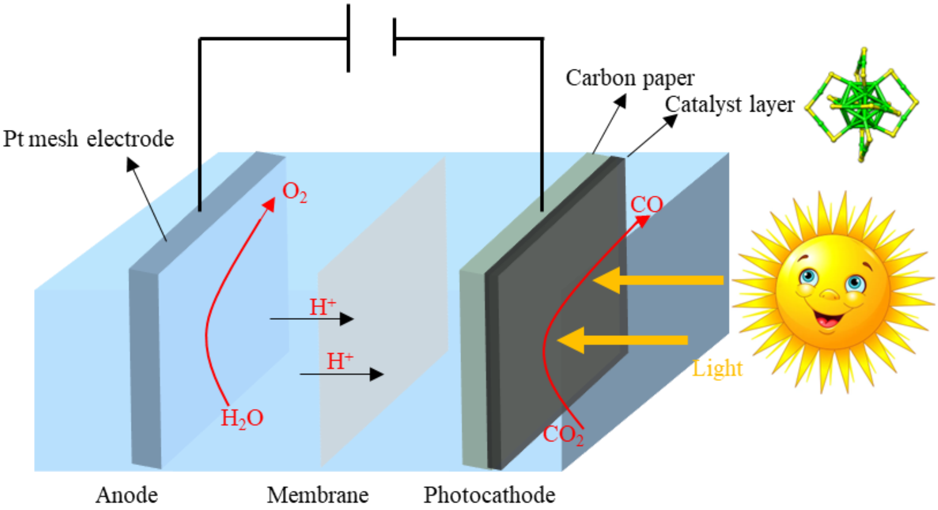
Atomically precise Au nanoclusters (NCs) with discrete energy levels exhibit visible light absorption properties as photosensitizers. Here, a series of metal-terpyridine complexes (metal complex, metal = Ru, Ni, Fe, Co) are rationally designed and grafted on Au_{25} NCs by ligand exchange reactions (LERs), in addition to electrochemical reduction (ECR), photocoupled electrocatalytic CO_2 reduction (PECR) of these novel catalysts (abbreviated as Au_{25}-M, M = Fe, Ni, Ru, Co) is also investigated.



For ECR, Au_{25}-Ni and Au_{25}-Ru exhibit high turnover frequencies (TOFs) of 56138 h^{-1} at -1.07 V and 53044 h^{-1} at -0.97 V (vs. RHE), respectively. CO Faraday efficiency (FE_{CO}) exceeds 90% in a potential range from -0.47 to -0.77 V (vs. RHE) for Au_{25}-Ru, and Au_{25}-Ni shows the maximum FE_{CO} = 94.4% at -0.57 V. Moreover, when coupled with light, partial current density of CO (j_{CO}) is further improved across the potential range (from -0.47 to -1.07 V) for Au_{25}-Ru (increases from 27.7 to 32.9 mA/cm^2 at -0.97 V) and Au_{25}-Ni (from 26.1 to 32.4 mA/cm^2 at -0.97V) compared with that under dark conditions. Furthermore, TOFs are also dramatically enhanced to 69989 h^{-1} (Au_{25}-Ni) at -1.07 V and 63012 h^{-1} (Au_{25}-Ru) at -0.97V. This work opens up a potential application for Au NCs to act as photosensitizer and perform the photocoupled electrocatalytic reactions.

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