Scientific program YIW 2021-2022

Friday, September 2

8:30	Opening remarks
9:00	**Kaspars Traskovskis** Carbene-metal-amide complexes: An emerging class of light emitting materials
9:30	**Dorian Didier** Electrocoupling: A catalyst-free alternative for C-C bond formation
10:00	**Dmitry Katayev** Photoredox activation of anhydrides towards divergent synthesis of fluorinated compounds
10:30	Coffee Break
11:00	**Sophie R. Beeren** Enzyme-mediated dynamic cyclodextrin systems
11:30	**Oscar Verho** Building complex molecular architectures through directed C-H functionalization chemistry and amide bond formation
12:00	**Anna Barnard** Mimicking protein-protein interactions in persistent bacteria
12:30	**Anne Nijs** European Journal of Organic Chemistry, Chemistry Europe
12:45	Lunch
13:45	**Juha H. Siitonen** Total synthesis of racemic polyclic alkaloids isatindigotindoline C and setigerumine I
14:15	**Jovana M. Francuz** Natural product protulactone A: synthesis and biological evaluation
14:45	**William P. Unsworth** Ring expansion approaches for the synthesis of functionalised macrocycles
15:15	**Ivana I. Jevtić** Novel class of fentanyl derivatives: Synthesis and in vivo analgesic activity
15:45	**Robert B. P. Elmes** Squaramides: From receptors to antimicrobials
16:15	**Marta da Pian** Reaxys Education: A chemical database designed by chemists
16:30	Coffee Break
17:00	**David Leitch** Chemical cartography - Mapping chemical reaction space using high-throughput experimentation
17:30	**Upendra Sharma** Shedding new light on Boron-centered radical chemistry
18:00	**Xavier Companyó** Novel synthetic methodologies via direct irradiation of aryl ketones under microfluidic conditions
18:30	**Zachary K. Wickens** ***(online)*** Selective synthesis using light and electricity
20:00	Dinner at *Churrasqueira Campo Grande*

Saturday, September 3

8:30	**Alonso Rosas-Hernández** Circumventing scaling relationships in CO2 electroreduction with hybrid catalysts
9:00	**Beatriz Pelaz** Active nanomaterials for bioapplications
9:30	**Michal Kohout** Design, synthesis and application of hybrid chiral organic-inorganic materials
10:00	**Artiom Magomedov** Think small: Phosphonic acid monolayers for record-breaking solar cells
10:30	Coffee Break
11:00	**Julie Broggi** Enamine-based organic reducers: from the tool to the applications
11:30	**Christian Stanetty** Sweet tales from an aldehyde's perspective
12:00	**Philipp Klahn** Inspired by nature´s design – exploiting the chemistry of artificial glucosinolates
12:30	**Kathrin Ulbrich** Thieme
12:45	Lunch
13:45	**Mónica H. Pérez-Temprano** Deciphering mechanisms to design better catalytic reactions
14:15	**Boris Maryasin** Computational chemistry and organic synthesis: Let us build a bridge
14:45	**Etienne Brachet** C-N bond formation via odet strategies
15:15	**Helena Lundberg** Catalytic substitution of alcohols
15:45	**József Kupai** Synthesis and application of a cinchona squaramide organocatalyst immobilized on poly(glycidyl methacrylate)
16:15	Coffee Break
16:45	**Susan Kelleher** TBA
17:15	**Gergely L. Tolnai** Ring opening reactions of [1.1.1]propellane
17:45	**Cátia Teixeira** The amazing world of peptides
18:15	Closing remarks
20:00	Dinner at *Páteo 51*

Carbene-metal-amide complexes: An emerging class of light emitting materials

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Linear two-coordinate metalloorganic complexes composed of coinage metals (Cu, Ag, Au), electron accepting carbene and electron donating amide ligands have recently emerged as a promising emitter class for organic light emitting diode (OLED) applications.[1] Here structural modifications of carbene-metal-amides (CMAs) are explored by introduction of novel thiazoline and imidazole-based carbene ligands (Figure 1). CMAs based on thiazoline ligands exhibit dual emission from monomer and excimer excited states allowing single-emissive-layer white electroluminescence.[2] In the case of imidazole ligands the presence of auxiliary electron acceptors enables through-space charge transfer process, substantially decreasing the singlet-triplet energy gap thus lowering thermal activation barrier for thermally activated delayed emission (TADF) process.

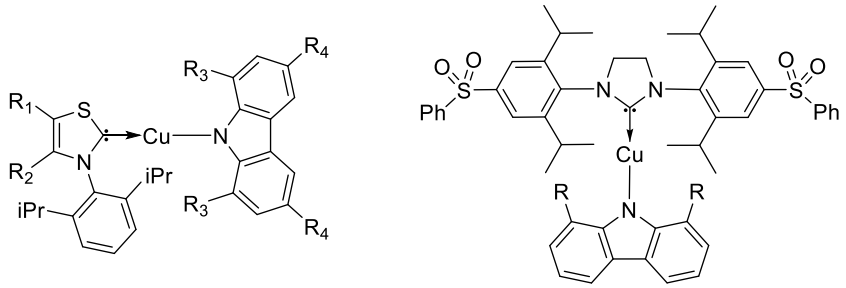

Figure 1. Chemical structures of investigated CMA complexes.

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Electrocoupling: A catalyst-free alternative for C-C bond formation

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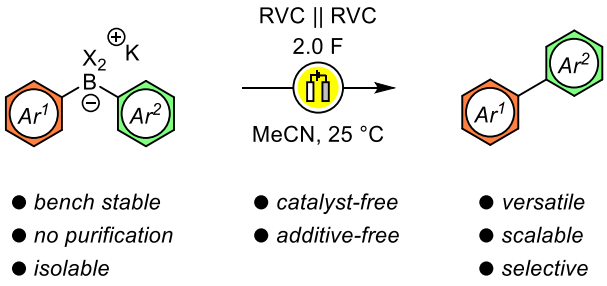
Our efforts toward sustainable C-C bond formation have led us to investigate alternative catalyst-free coupling reactions. Having previously demonstrated that organoboron reagents can serve as templates in Zweifel olefinations[1,2] and strained ring functionalization,[3,4,5] we set out to develop a conceptual approach for hetero-coupling reactions.

As many methods for the formation of hetero-biaryls require expensive and/or environmentally challenging transition-metal catalysts as well as inert and dry conditions, we envisioned that bench-stable, hetero-substituted arylborate salts could undergo formation of (hetero)biaryls, triggering the key 1,2-metallate rearrangement step under electrochemical oxidation.[6,7,8]



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Photoredox activation of anhydrides towards divergent synthesis of fluorinated compounds

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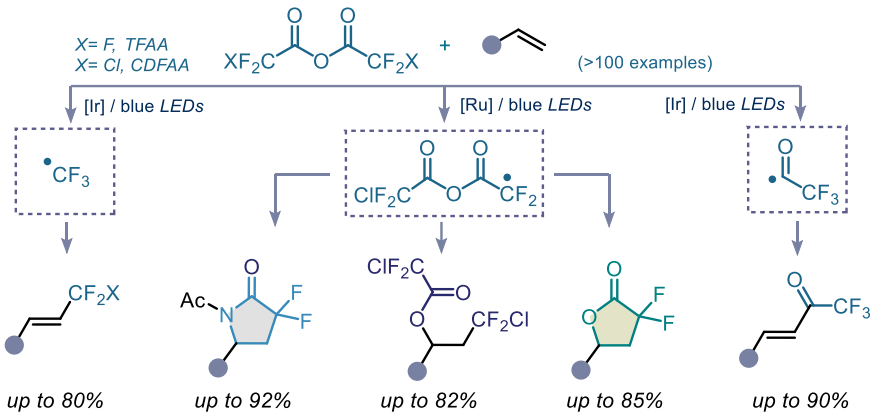
The use of bench-stable and readily available functional group transfer reagents (FGTRs) is a powerful platform for increasing the molecular complexity.[1-2] Herein we report mild, operationally simple, and switchable protocols to access a wide range of fluorinated molecules that employ TFAA and CDFAA as a low cost and versatile fluoroalkylating reagents.[3-4] Detailed mechanistic investigations using combined experimental, spectroscopic and computational tools revealed that electron-transfer photocatalysis triggers a mesolytic cleavage of C–O and C–Cl bonds generating trifluoroacethyl, trifluromethyl, and *gem*-difluoro carboxy radicals, respectively. In the presence of alkene molecule and under carefully controlled reaction conditions, these radical species deliver various fluorinated organic frameworks with a high level of chemo- and regioselectivity.



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Enzyme-mediated dynamic cyclodextrin systems

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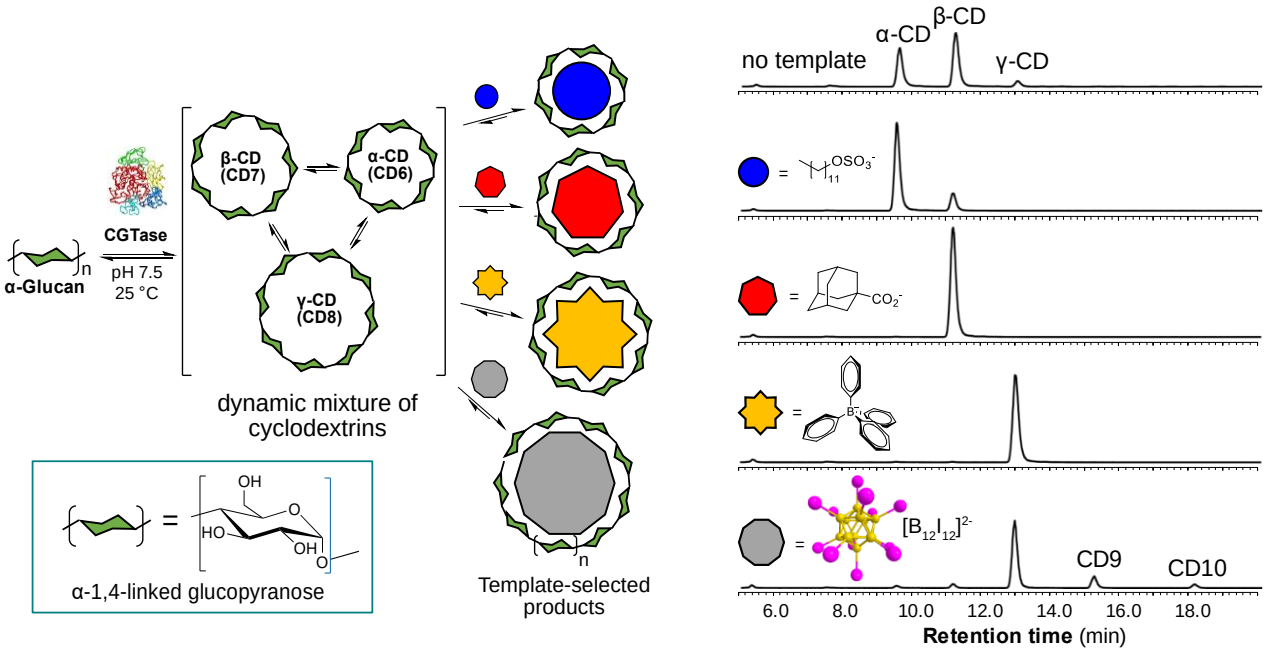
Dynamic combinatorial chemistry (DCC) is a well-established methodology for the templated synthesis of complex molecular architectures, wherein molecular building blocks are linked together using reversible covalent reactions to give dynamic mixtures of oligomers under thermodynamic control. While a range of reversible covalent reactions have been examined for DCC, enzyme-catalysed reactions have been little explored in this context. I will discuss how dynamic mixtures of interconverting cyclodextrins (CDs) can be generated by the action of *cyclodextrin glucanotransferase* (CGTase).[1] Templates can then be used to direct the selective synthesis of specific CDs, including large-ring CDs and modified CDs.[2] By using stimuli-responsive templates, we can control the outcome of this enzymatic reaction by means of light, pH change and redox chemistry.[3]



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Building complex molecular architectures through directed C-H functionalization chemistry and amide bond formation

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Since the seminal study by the group of Daugulis in 2005,[1] the 8-aminoquinoline auxiliary has emerged as one of the most widely used and versatile directing groups for transition metal-catalyzed C-H functionalization chemistry.[2] This directing group has been shown to enable highly selective activation of inert C(sp^2)-H and C(sp^3)-H bonds in a wide range of substrate scaffolds, which can be exploited for the installation of a wide array of functional groups. As a result, 8-aminoquinoline directed C-H functionalization chemistry has found extensive applications in areas where its complexity-generating nature are highly appreciated, as for example in the fields of total synthesis and small molecule library design.[3]

This presentation will describe our group's work related to the applications of different 8-aminoquinoline directed C-H functionalization reactions for the synthesis of complex molecular architectures. Specifically, our efforts to access structurally elaborate benzofuran[4] and cyclobutane[5] derivatives as well as unnatural amino acids will be highlighted.[6] Furthermore, new methods to cleave the 8-aminoquinoline auxiliary will be presented, and it will be demonstrated that this obligatory auxiliary removal step can function as an additional diversification point in the creation of diverse compound collections. In this part, a two-step, one-pot protocol that allows for the overall transamidation of 8-aminoquinoline amides will be presented.[7] Furthermore, our preliminary results from an on-going project featuring tropyllium-assisted amide bond formation will be shown.

Acknowledgements: OV would like to thank the FORMAS, Olle Engkvist, Magnus Bergvall and Wenner-Gren Foundations for funding of the presented research. Furthermore, OV would like to thank all the co-authors that were involved in these studies and the Swedish Chemical Society for a travel grant to attend this workshop.

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Mimicking protein-protein interactions in persistent bacteria

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Bacterial protein-protein interactions (PPIs) are involved in a multitude of cellular functions and are therefore being increasingly explored as potential antibiotic targets.[1] One family of significantly underexplored bacterial PPIs are the type II toxin-antitoxin (TA) modules. These systems consist of toxin and antitoxin proteins that form a tight PPI and act as important stress-responsive elements. In *Salmonella*, the Phd-Doc TA module was suggested to be a major driver of persister formation.[3] Persisters are cells in a growth-arrested state, which can survive antibiotic treatment and hence are recognised as a major cause of recurrent infections.

I will describe the first detailed characterisation of the *S.* Typhimurium Phd-Doc PPI and our initial work towards the development of Phd antitoxin-mimicking peptides to probe the Phd-Doc PPI as potential anti-persistence target. We have developed a novel method for recombinant expression of active Doc toxin and subsequently assessed the role of specific residues of the Phd antitoxin on Doc toxin inhibition. Substitution of some residues in Phd-based peptides led to poor inhibition of Doc, despite the formation of high-affinity complexes, suggesting that toxin neutralisation is achieved by mechanisms beyond high affinity interactions.[2] Phd peptides showing *in vitro* activity were able to counteract Doc toxicity when expressed in *S.* Typhimurium. Finally, we have generated a novel family of Doc-inhibitory, stapled Phd peptides with the aim to evaluate their effect on persister formation in *S.* Typhimurium.

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Total synthesis of racemic polyclic alkaloids isatindigotindoline C and setigerumine I

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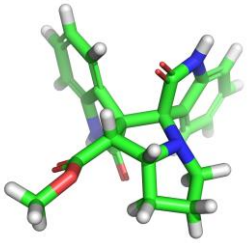
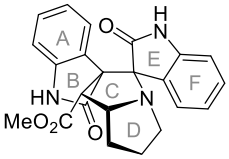
Polyclic alkaloids offer ample opportunities for strategic and mechanistic discoveries. While most chiral alkaloids are isolated as single enantiomers, rare cases of naturally occurring racemic mixtures are also known.[1]

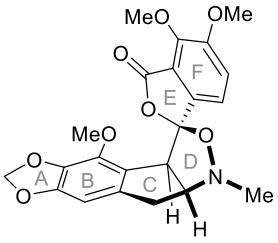
Our group is particularly fascinated by these structurally complex racemic alkaloids, and their underlying mechanistic and biosynthetic implications. Our chemical journeys leading to the syntheses of (±)-Isatindigotindoline C and (±)-Setigerumine I will be discussed.[2,3]



[ScXRD]



Isatindigotindoline C



Setigerumine I

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Natural product protulactone A: synthesis and biological evaluation

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Protulactone A, a naturally occurring bicyclic lactone, has been isolated from EtOAc extract of the marine-derived fungus *Aspergillus* sp. SF-5044.[1] The first total synthesis of this natural product was achieved by the Gracza group.[2] Herein, we report the total synthesis of (+)-protulactone A (PLA, Figure 1.), its C-7 epimer, and new analogues starting from D-galactose, as well as their preliminary antimicrobial and antiproliferative activities. We also report the first crystal structure of protulactone A, which confirms the assumed stereochemistry of this natural product.

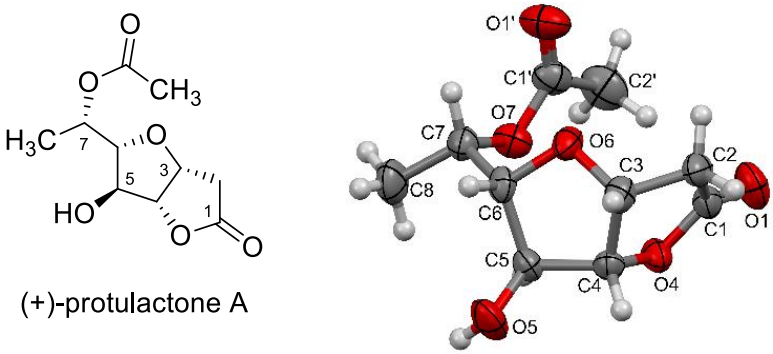

Figure 1. Chemical and crystal structure of protulactone A (PLA).

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Ring expansion approaches for the synthesis of functionalised macrocycles

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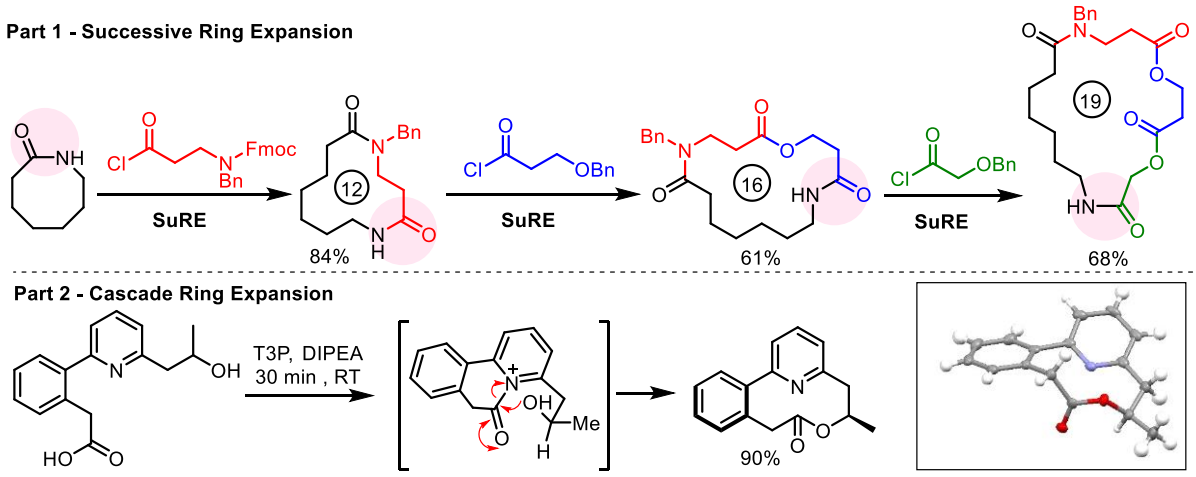
This talk concerns the development of new methods to construct functionalised macrocycles (12+ membered rings) and medium-sized rings (8–11-membered). These ring systems are usually difficult to make, with one of the key challenges being the effective control of intra- and intermolecular reaction during end-to-end cyclisation.[1,2] The approaches I will discuss in this talk are based on strategies by which the difficult end-to-end cyclisation step can be completely avoided. First, I will describe an iterative ring enlargement approach known as 'Successive Ring Expansion' (SuRE).[3-9] SuRE works be enabling the controlled insertion of amino acid and hydroxy acid fragments into ring enlarged products via a telescoped acylation/rearrangement reaction sequence. Background, methods development, substrate scope/limitations, the synthesis of compound libraries for biological evaluation,[4] cascade variants[7,9] and DFT calculations[8] will all be covered. A new ring expansion cascade strategy[10,11] will also be introduced, that enables the atroposelective synthesis of medium sized rings directly from linear precursors.[12]



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Novel class of fentanyl derivatives: Synthesis and in vivo analgesic activity

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As a part of our ongoing research on the preparation and pharmacological evaluation of novel functionalized piperidines, 15 compounds were synthesized as analogues of potent μ-opioid agonist and clinical analgesic, fentanyl.[1,2] Compounds were prepared by the novel and/or optimized synthetic routes and represent the first known fentanyl analogues possessing any nitrogen substituent at C_3 position of the piperidine ring.

The analgesic activity of synthesized compounds was tested *in vivo*.[2] Only four compounds showed analgesic activity. The most potent of them was 1.8 times less potent analgesic than fentanyl, with fast onset and short duration of analgesic effect, which makes this compound potentially suitable for different pharmacological formulation in the pain treatment.

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Squaramides: From receptors to antimicrobials

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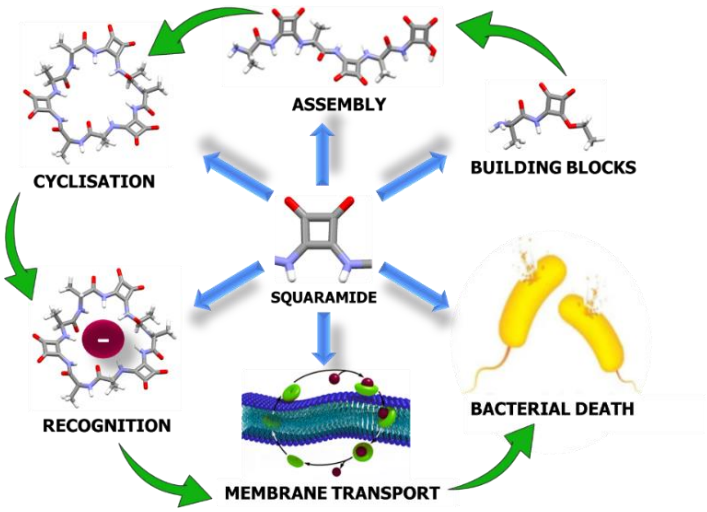
Squaramides, a family of conformationally rigid cyclobutene ring derivatives, are rapidly gaining research interest across diverse areas of the chemical and biological sciences.[1] Composed of two carbonyl hydrogen-bond acceptors in close proximity to two NH hydrogen-bond donors, this small molecular scaffold benefits from unique physical and chemical properties that render it extremely useful as a tool in areas as diverse as catalysis, molecular recognition, bioconjugation, and self-assembly.

Our work has focused on utilising squaramides for the design of anion receptors, sensors and transporters. Squaramides are particularly useful in this regard due to their strong H-bond donating ability, planar structure and the observed increase in aromaticity upon guest binding. Moreover, their synthetic versatility renders squaramides practical for incorporation in a wide range of supramolecular scaffolds.

This lecture will summarise some of our efforts to design easily accessible, and functionally rich squaramides for use as anion receptors and transporters. It will also detail our recent progress towards the application of anions transporters as a new class of anti-microbial agents.



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Chemical cartography - Mapping chemical reaction space using high-throughput experimentation

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Predicting the outcome of chemical reactions is the cornerstone of synthetic chemistry. While every organic chemist learns to make qualitative predictions about the expected reaction products, making quantitative predictions about outcomes – rate, selectivity, yield – is considerably more challenging. To realize advances in computer-assisted synthetic planning/design, accurate quantitative predictions based on reactants/conditions are necessary.

The Leitch lab is taking a bottom-up approach to developing data sets and predictive models for key organic transformations relevant to pharmaceutical and agrochemical synthesis. Our approach is to leverage high-throughput experimentation to rapidly assemble libraries of reaction data, and then combine these data with simple, calculable molecular descriptors. This presentation will cover our recent efforts in this area, including the development of new precatalysts to enable high-throughput experimentation[1] and predictive models for Pd-catalyzed cross coupling[2] and SNAr[3].

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Shedding new light on Boron-centered radical chemistry

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Since its recognition as an enabling tool to form challenging C-C and C-heteroatom bonds under mild and sustainable conditions, photoredox catalysis has been in the spotlight within the synthetic community. As a consequence, the interest in developing novel synthetic strategies has spiked together with the need to define suitable radical sources under ambient conditions with high selectivity, unprecedented functional group tolerance and broad applicability. In the alkyl radical precursor landscape, boron-based species have also begun to play a predominant role.[1] Though the reactivity of trifluoroborates has been deeply investigated, yet, the interest in using other boron species as radical precursors in photocatalyzed reactions has recently been arisen.[1b] This late exploration lies in the fact that the high oxidation potential of boronic acids (BAs) and esters hinders their possible applications. Nevertheless, to circumvent this issue, a diverse array of activation modes has been developed,[2] exploiting in most of the cases the inherent Lewis acidity of boronic acid (derivatives). The aim of this presentation is to highlight our recent contribution in this vibrant field with the focus on broad applicability and selectivity, besides scalability via continuous-flow methodology (Figure 1).[3]

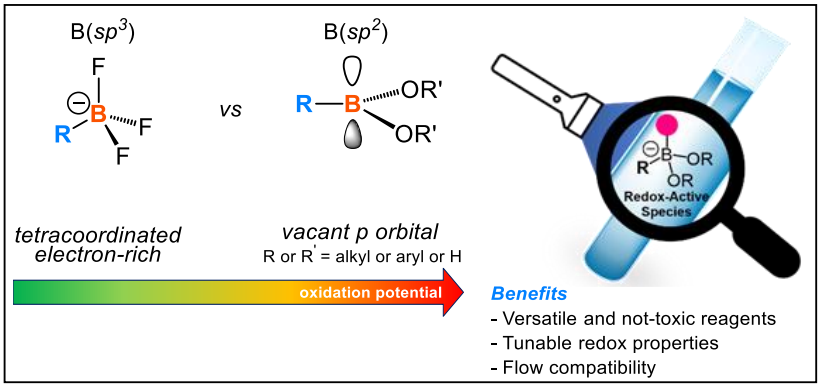

Figure 1: Generation of radicals from boronic acid (derivatives) through photoredox catalysis.

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Novel synthetic methodologies via direct irradiation of aryl ketones under microfluidic conditions

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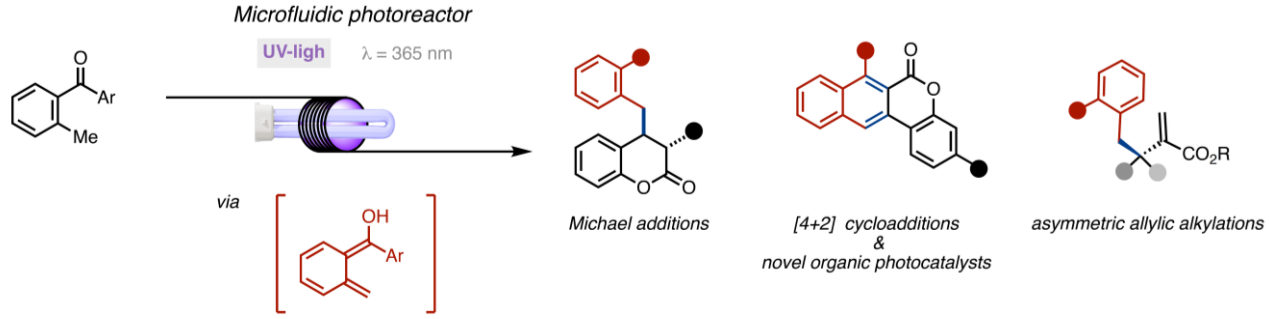
Photochemistry is emerging as a key enabling tool for the construction of molecular architectures using light as a renewable energy source. By exploiting the unprecedented reactivity of excited organic molecules, photochemistry has tremendously increased the toolbox of chemists for the development of novel synthetic transformations. Photochemical methodologies in batch, however, suffer from some common drawbacks, such as irreproducibility, reactivity and selectivity issues related to over-irradiation and light-promoted side-reactions together with difficult reaction up-scaling. Some of these fundamental drawbacks can be address by implementing the photochemical reactions under microfluidic conditions. Microfluidic photoreactors (MFPs) present enhanced surface-to-volume ratio, a uniform irradiation and increased light penetration depth, short diffusion distances for efficient mass and photon transfer, as well as simple synthetic up-scaling in continuous flow for large-scale synthesis.



The ability of 2-methyl benzophenone to generate the reactive photoenol intermediate upon UV-light irradiation is known since the 1960s. However, its potential as a versatile synthetic intermediate has only been recognized recently. In this scenario, we demonstrated how a microfluidic photoreactor setup (MFP) improves both the selectivity and the synthetic performance of several reported transformations of 2-methyl benzophenones, such as cycloadditions, trifluoromethylations and carboxylations.[1] The MFP setup also allowed to develop an unprecedented Michael addition of the photoenol intermediate to 3-substituted coumarins for the synthesis of 4-benzylated cromanones.[1] Furthermore, the microfluidic photoreactor enables the direct assembly of highly functionalized tetracyclic architectures, such as naphthocromene and benzoxanthene scaffolds, through a lightpromoted [4+2] cycloaddition reaction.[2] Using this photochemical cycloaddition, we identify and design a new family of organic photocatalysts based on the naphthochromenone core. These photocatalysts absorb across the UV/Vis region, conferring high-energy excited states and extremely wide redox windows with the use of simple visible light. Hence, the naphthochromenone photocatalysts can engage in both oxidative and reductive quenching processes with strong thermodynamic requirements.[3] Finally, we have also developed an unconventional asymmetric allylic alkylation of Morita-Baylis-Hillman adducts[4] with the photoenol intermediate as non-stabilised, photogenerated carbon-nucleophile. The simultaneous activation of the electrophile via chiral Lewis-base catalysis and the nucleophile under light irradiation enables the stereoselective construction of tertiary and quaternary benzylated stereocenters at allylic positions.[5]

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Circumventing scaling relationships in CO_2 electroreduction with hybrid catalysts

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Developing high-performing catalysts for sustainable and economically viable transformations remains a central goal of the chemical industry.[1] The performance of catalytic materials for the electroconversion of carbon dioxide into value-added products is governed by linear free energy and scaling relationships.[2] Knowledge of these limits offers a shortcut for designing strategies to alter reaction mechanisms for improved performance. With the help of high-throughput experimentation on bulk copper bimetallic alloys, we have identified scaling relationships between the production rates of methane and multicarbon products.[3] This strict dependence represents an intrinsic limit toward the selective production of commercially-relevant products such as ethylene and ethanol. Selectivity analysis highlights the impact of integrating high-throughput experimentation and data science to discover such a power-law scaling relationship that is broken upon coating the electrode surface with an organic additive (*N*,*N*′-ethylene-phenanthrolinium), demonstrating a fundamental limitation of CO_2 electroreduction Cu-based materials and a strategy to overcome it through hybrid inorganic−organic interfaces.

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Active nanomaterials for bioapplications

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Nanotechnology allows the creation of a myriad of materials by producing composite self-assembled architectures, e.g., inorganic and/or organic nanoparticles (NPs), biomolecules, therapeutics, etc. The fine tuning of their properties provides with novel, multifunctional tools for drug-delivery applications.

Between nanotechnology and achieving advanced medicinal products stand entangled challenges such as understanding and controlling the biomolecule–NP (biomolecular corona) in vivo; avoiding intracellular degradation of the nano-formulations due to lysosomal/phagolysosome storage; and highly specific targeting of cells and/or tissues.

When designing a nanomedicine some characteristics should be fulfilled in order to ensure its in vivo success. This includes avoiding sequestration by the mononuclear phagocytic system (MPS); and major accumulation in the liver and spleen; presenting prolonged circulation; targeting abilities to recognize specific cells and tissues; and the ability to perform an action.

This last point can be achieved by developing stimuli-responsive controlled delivery systems triggered by stimuli such as light, ultrasound, magnetic fields, pH, enzymatic catalysis, competitive guests, etc. The interaction of light or alternating magnetic fields with inorganic NPs is orders of magnitude stronger than with organic molecules due to their larger absorption cross-sections. Therefore, inorganic NPs (or hybrid composites) offer a convenient platform to produce remotely controlled colloidal nanosystems. These interactions can be applied to develop nanoheaters, nanoreactors, or to induce a controlled drug release that will offer novel and personalized tools for therapy and imaging.

Design, synthesis and application of hybrid chiral organic-inorganic materials

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Chiral compounds are ubiquitous in nature and chirality plays a crucial role in various natural processes because biological properties of individual enantiomers of a chiral compound may differ *in vivo*, despite their almost identical physico-chemical properties. Utilization of chiral compounds in materials chemistry gives rise to smart materials that can serve for various purposes, such as multifunctional dopants to liquid crystal matrixes and chiral sorbents for resolution of racemic mixtures. Recently, we have presented the first example of a multifunctional dopant, which upon mixing with an achiral liquid crystal gives rise to the photosensitive and magnetic nanocomposite exhibiting chiral mesophases (Figure 1 - left).[1] Controlling chirality puts us in front of a challenge to separate the enantiomers prior using them, *e.g.*, as dopants or even pharmaceuticals. To address this need, we have developed several chiral stationary phases (Figure 1 - right) that enable chiral resolution of various racemic mixtures using liquid chromatography.[2,3]

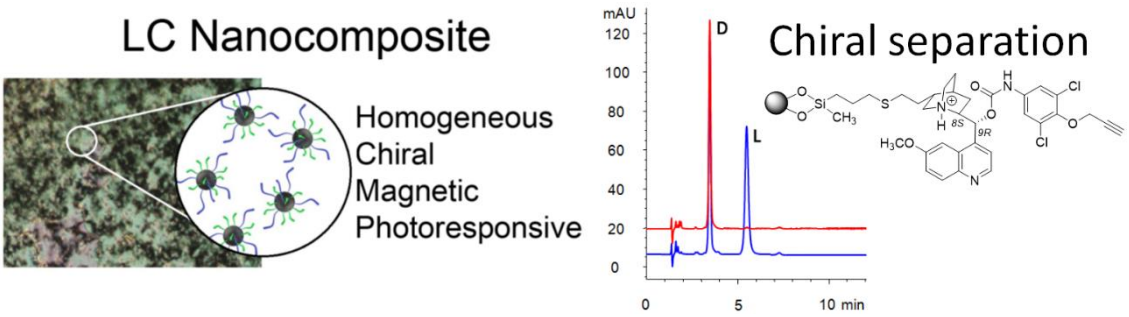

Figure 1. Schematic representation of a nanocomposite (left) and chiral separation (right).

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Think small: Phosphonic acid monolayers for record-breaking solar cells

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In the future, our energy production will more and more rely on Solar light. While the current need is met by conventional, Si-based technologies presented on market, further progress is strongly dependent on new device concepts, such as tandem solar cells. For their successful implementation, new materials need to be developed.

One of the promising technologies is perovskite solar cells (and related tandems). It is a very dynamic and highly competitive field of research, where many developments can be achieved leading to fast publications.

In our work, we have proposed and implemented a new way for the formation of the hole-selective contact layer. One of the best results was achieved for the simple carbazole-based phosphonic acid, called 2PACz, and this and related materials were used in several efficiency record-breaking tandem devices.[1,2]

In my presentation, I will shortly overview the development of the hole-selective monolayers and discuss possible future directions.

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Enamine-based organic reducers: from the tool to the applications

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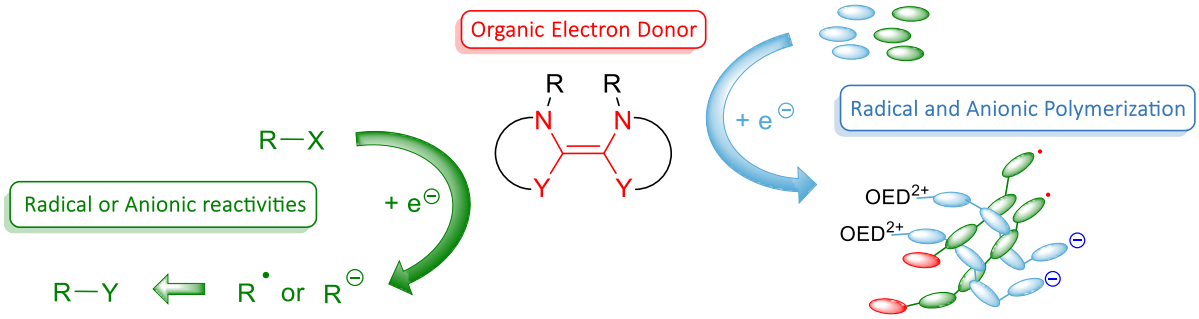
Enamine-based organic electron donors (OEDs) are powerful reducing agents recognized for their potential in the reduction of challenging substrates.[1] They are capable of single- or double-electron transfers to organic substrates under mild and homogeneous conditions, promoting bond formations through the generation of radical or anionic intermediates. They thus emerge as an attractive novel source of reducing electrons in many aspects.

My research focus on synthesizing new organic electron donors and establishing their fields of applications. In this talk, I will give an overview of these achievements, spanning from the development of original reactivities[2] to the preparation of high value-added polymers.[3]



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Sweet tales from an aldehyde's perspective

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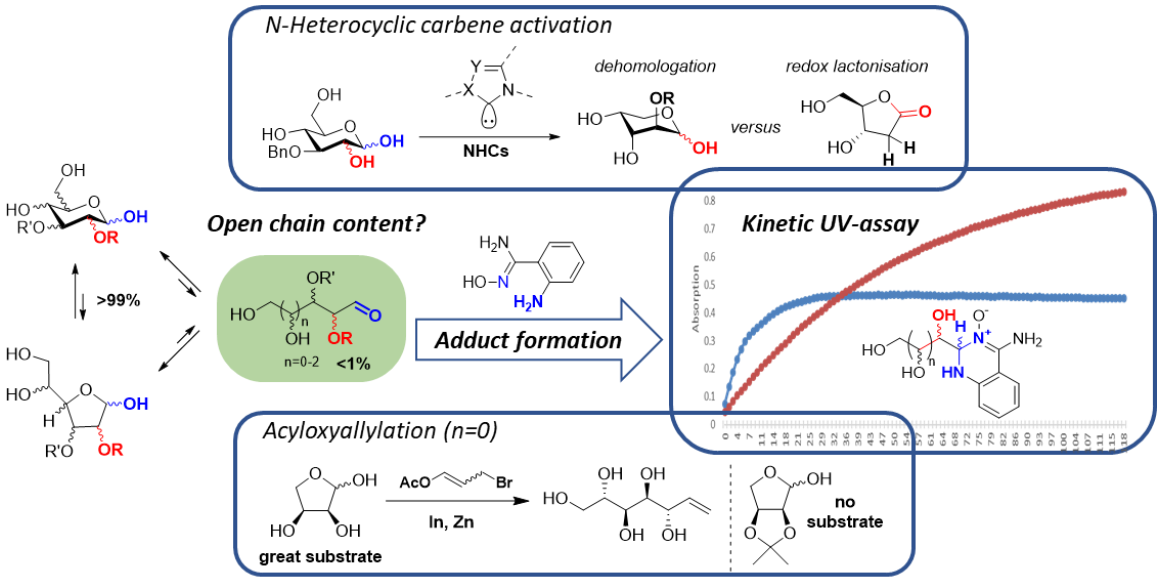
Carbohydrates are a fascinating part of Nature's chiral pool and are provided in renewable fashion in great variety and abundance. It is a burden for extensive use by organic chemists, that only a small fraction of carbohydrates is readily available and consequently studied in great detail. Synthetic glyco-chemistry is challenging due to the structural density of both functional groups and stereochemistry. Adding to this complexity, an equilibrium exists between cyclic hemiacetals and the open chain carbonyl form (minor).



It is this neglected molecular minority, with its intrinsically reactive aldehyde moiety, which is in the focus of our research. An operationally simple UV-based assay was developed to efficiently capture this relevant pre-equilibrium.[1] This tool was utilized in the studied elongation of the carbohydrates *via* indium mediated acyloxyallylation (Fig. bottom)[2] as well as the organocatalytic anomeric activation of reducing sugars by *N*-heterocyclic carbenes towards a controlled dehomologation method (Fig. top).[3]

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Inspired by nature´s design – exploiting the chemistry of artificial glucosinolates

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Natural glucosinolates (GSLs) are glycosidic thiohydroximates produced by plants of the order Brassicales as constituent of the GSL-Myr herbivore defence system. Upon tissue damage of these producer plants, e.g. by herbivore feeding, the thioglycosidic bond of GSLs gets cleaved by the thioglucosidase myrosinase (Myr) and the released thiohydroxiamate aglycone undergoes a thio-Lossen rearrangement to form isothiocyanates (ITCs) displaying feeding deterrent activities and multiple other interesting bioactivities.[1] Here, I report on the synthesis and biochemical evaluation of first fluorescent artificial glucosinolates[2] as well as their recent application as tools compounds to monitor GSL-associated processes in plants.[3] Furthermore, we introduce the concept of totally artificial multi-valent GSLs (mv-GSLs)[4] bearing more than one ITC releasing warhead as well as pseudo-GSLs (psGSLs)[5,6] releasing ITCs in the presence of enzymes different from Myr and demonstrate their potential application as tools in chemical biology.

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Deciphering mechanisms to design better catalytic reactions

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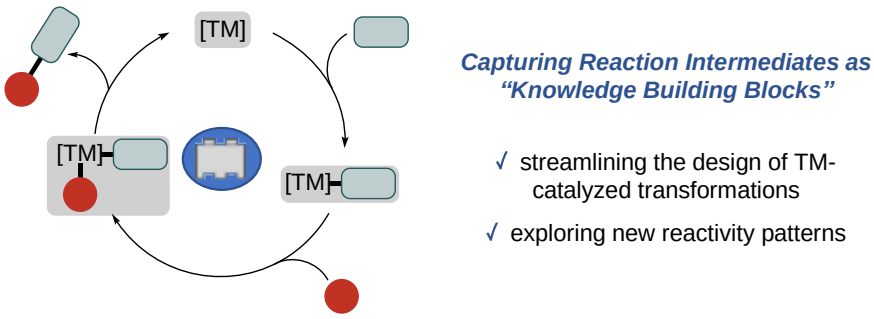
Most reactions set-up in the lab fail.[1] This is one of the biggest problems chemists face when designing transition metal-catalyzed transformations.[2] Moreover, the translation of scientifically well-established reactions to "real-world" applications often does not lead to the desired products.[3] This striking situation prompts two key questions: Why do reactions fail? Can failed reactions be used to trigger a paradigm-shift in reaction design?

Our group aims to answer these questions placing fundamental understanding at the center of process design. We use mechanistic studies as a powerful tool to facilitate the bottom-up design of more efficient chemical processes.[4] Our research program is based on simple, yet usually overlooked, concept: chemical reactions rely on the performance of the reactive intermediates within the catalytic cycles. By capturing these transient species and using them as "knowledge building blocks" (KBBs), we expose the obstacles hindering transition metal-catalyzed transformations efficiency and capitalize on the gathered fundamental knowledge to streamline more resource-efficient transformations.[5]



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Computational chemistry and organic synthesis: Let us build a bridge

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Progress in quantum chemistry allows us to understand and predict the outcome of organic reactions. Hereby we demonstrate the efficiency of combining experiment and theory on some recent examples.

Our joint theoretical-experimental study of novel Claisen-type rearrangements[1] reveals a diversity of possible pathways and products. The calculations investigate the experimental results and predict new reactions.[2–4]

The in-depth theoretical analysis of the reaction mechanism clarifies the vast scope for a recently developed functionalization of amides via *in situ* umpolung.[5] The calculations describe the key intermediates and analyze the main and side pathways.

An unexpected reaction mechanism is discovered purely via calculations for a new synthesis of imidazoles. We show that an atypical sulfonyl migration is responsible for the formation of the final product.[6]

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C-N bond formation via odet strategies

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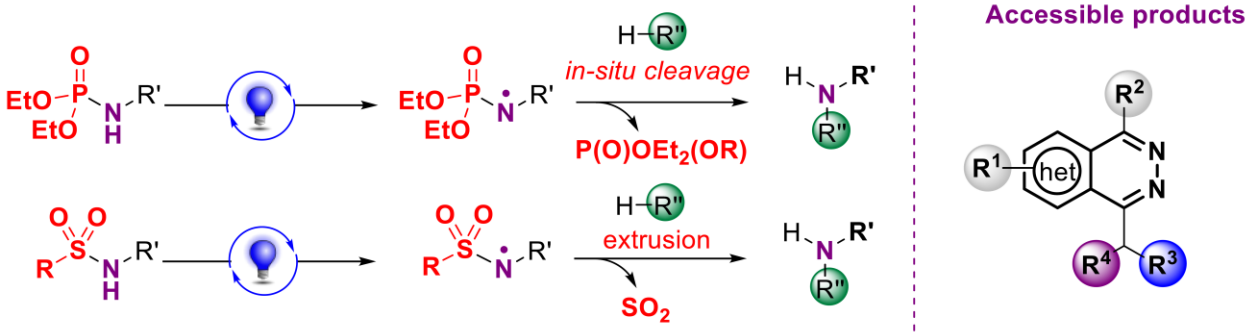
Since the early beginning of organic chemistry, the synthesis of nitrogen-containing heterocycles constantly attracted the interest of the chemistry community. Indeed, their ubiquitous presence in natural products lead to the development of several strategies to build them.[1] Until now, despite many synthetic efforts, many useful structures are still unattainable. For instance, phthalazine structures are one of the less explored scaffolds and therefore development of new synthetic methods is still desirable.

In this aim, we focused our research projects on the development of new photoredox strategies to build the carbon-nitrogen bond.[2] The search of new precursors able to generate efficiently a nitrogen centered radical intermediate is thus highly needed. This kind of intermediate is indeed attractive because it can be then added on unsaturated derivatives for instance and thus lead to the CN bond formation.

In our laboratory we tried to develop phosphono- and sulfono-hydrazone precursors in order to build interesting heterocyclic scaffolds. Starting from simple ortho-alkynylbenzaldehyde patterns, already well-mastered in our group towards silver catalysis,[3] we thought to develop a new photoredox cyclization reactions leading in one step to phthalazine derivatives.[4] Thanks to this new reaction, many useful phthalazine derivatives are now accessible. Mechanistic studies, scope and limitations of these methods will be presented.



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Synthesis and application of a cinchona squaramide organocatalyst immobilized on poly(glycidyl methacrylate)

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Very recently, organocatalysis has received a great deal of attention due to the award of the Nobel Prize[1] to *David MacMillan* and *Benjamin List* for their pioneering work in this research area.[2,3] Nowadays, organocatalysts have wide application in asymmetric reactions, and their recovery is essential for their economical application. The immobilization on a polymer support can mean a promising solution.

During this work, a cinchona squaramide enantioselective organocatalyst was synthesized from quinine (**1**, Figure 1.) using published synthetic methods. Poly(glycidyl methacrylate) (PGMA) was chosen for the part of the polymer support in the light of its modifiable reactive epoxide functional groups. The cinchona squaramide catalyst was successfully immobilized on this polymer. The activity of the immobilized organocatalyst (**2**, Figure 1.) was examined in different solvents (ethyl acetate, dichloromethane) in enantioselective Michael addition of 1,3-dioxo compounds to β-nitrostyrene. The immobilized catalyst was recovered from the reaction mixture 4 times by centrifugation, and successfully reused.

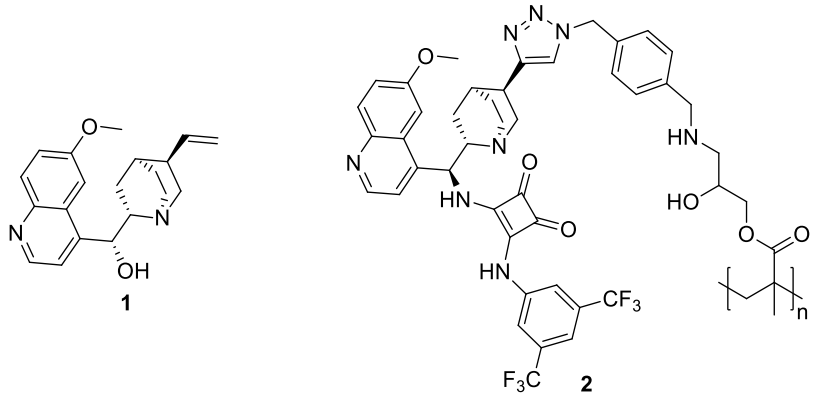

Figure 1. Quinine (**1**) and the immobilized organocatalyst (**2**)

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Ring opening reactions of [1.1.1]propellane

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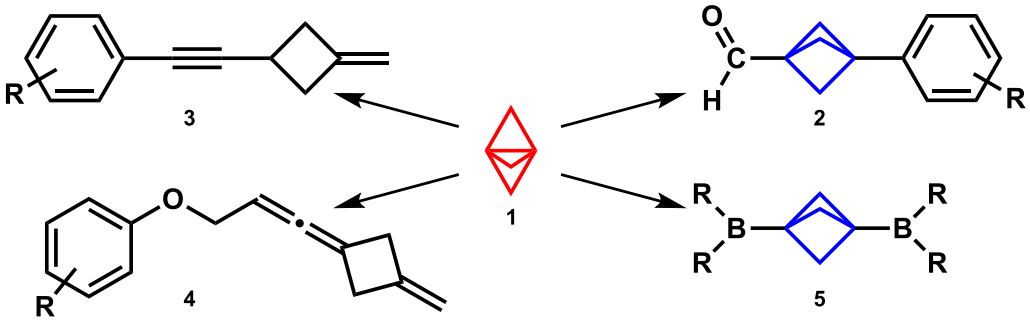
[1.1.1]Propellane (**1**) is an obscure molecule that was shortly investigated for its interesting structure in the end of the last century. Its utility is to produce bicyclo[1.1.1]pentanes(BCP), that gained popularity due to the bioisosteric properties to some often-utilized linear pharmaceutical building blocks.[1] We are aiming to provide easy access to BCPs and new insights to the chemistry of these classes of compounds.



BCP aldehydes (**2**) are versatile intermediates. In contrast to earlier 4-6 step multiday procedures, we have developed a fast one pot procedure.[2] During our attempts a new reactivity of **1** through cyclobutylcarbene was discovered. This resulted is a novel synthesis of cyclobutanes (**3**, **4**).[3]

We are also aiming to produce shelf-stable reagents (**5**) to introduce this interesting scaffold via simple reactions such as Suzuki coupling. Some interesting technicalities on this latter reaction will also be discussed.[5]

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The amazing world of peptides

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In 1963, solid-phase peptide synthesis (SPPS), a "simple and ingenious" technique invented by Merrifield, Merrifield revolutionized organic chemistry. As it was said for Merrifield's 1984 Nobel Prize in Chemistry, SPPS created a paradigm shift in synthetic chemistry and profoundly affected biomedical research.[1] Indeed, the easy availability of synthetic peptides in high purity, in parallel and on a large scale has transformed research in biology, biochemistry, microbiology, medicinal chemistry, and new drug development.[2]

A brief overview of different applications of peptides developed by our group will be presented. A special focus will be given to peptide/ionic liquid conjugates as potential active pharmaceutical ingredients for topical formulations to tackle complicated skin and soft tissue infections.[3,4] Promising results were obtained with chimeric peptides combining a host-defense sequence[5] with a collagenesis-inducing peptide widely used in cosmetics.[6] The best constructs exhibited: (i) antibacterial and anti-biofilm activity against Gram-positive and Gram-negative bacteria, including MDR clinical isolates; (iii) improved action against *S. aureus* (prevalent pathogen in chronically-infected DFU) in simulated wound fluid; and (v) antifungal activity.[4]

Relevantly, their ionic liquid-modified conjugates were proven to display equally potent antimicrobial and anti-biofilm activities, and retain or enhance the collagenesis-inducing action of the cosmeceutical parent peptide.[4,7] Given the foreseen benefits of IL for diverse pharmaceutical applications, including skin permeation enhancers, these promising results will be highlighted.

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