Book of Abstracts

41st Regiosymposium

Freiburg im Breisgau

August, 2023

EUCOR PRESENTATIONS

Session 1 (Monday)

Rethinking Small Molecule Catalyst Development

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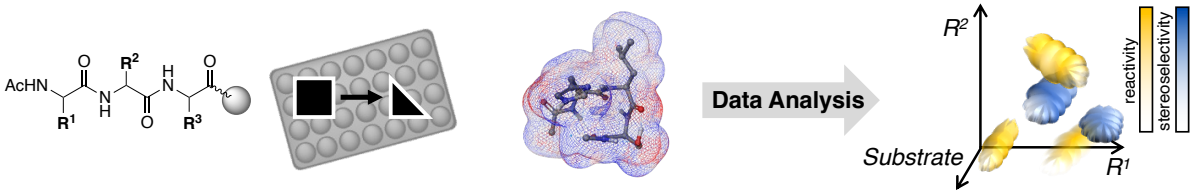
Tailor-made catalysts that exhibit reactivity exclusively towards specific targets – substrates, sites, or sequences – are currently a hallmark of nature. Harnessing this level of precision on-demand and applying it to small molecule catalysts would boost efficacy and sustainability of chemical synthesis. Recent advancements in data-driven workflows have sparked a revolution in catalyst development, offering a departure from traditional "trial-and-error" and rational design approaches.[1]

In our group, we rethink the conventional methods of small molecule catalyst development. We envision that by analyzing vast amounts of data, we can now embark on a more directed path towards identifying catalysts with high specificity for a certain substrate, site or sequence. Towards this goal, our group will harness peptides as powerful organocatalysts.[2] Their modular structure enables rapid, automated and scalable synthesis, making peptides ideal for generating extensive libraries with unparalleled functional and structural diversity.[3] By subjecting this library to a diverse range of reactions and substrates, we will map essential substrate/reaction features and thereby paving the way for the development of a computer-aided workflow that predicts and identifies catalysts with target selectivity.



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From Twofold- to Threefold Stereogenicity: Catalyst-Stereocontrolled synthesis of *o*-Quinodimethane- and C–S Atropisomers

2

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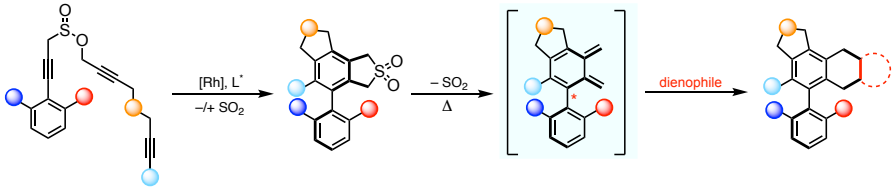
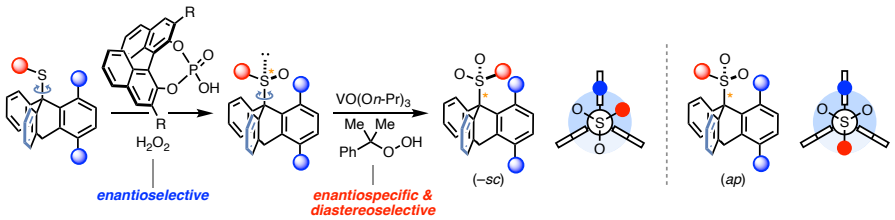


The use of thermally generated *o*-quinodimethanes as reactive intermediates in Diels-Alder reactions is a versatile approach to synthesize complex polycyclic compounds.[1] In this work we describe an intramolecular catalyst-stereocontrolled [2+2+2] cycloaddition of triyne substrates to generate atropisomeric benzocyclobutenes, benzocyclic sulfones and benzosultines which serve as precursors for the rotationally restricted aryl-*o*-quinodimethanes. Owing to their remarkable configurational stability, no racemization of the stereogenic axis occurs during the thermal ring opening. This allows for highly stereospecific Diels-Alder reactions of the in situ formed *o*-quinodimethanes with different dienophiles to form various polycyclic biaryls.



Higher-order stereogenicity arises when more than two isomers emerge from an irreducible stereogenic unit. With only recent methods for catalyst stereocontrol.[3] In this work we report the stereoselective synthesis of threefold stereogenic triptycyl sulfones with atropoisomerism arising from a C(sp^3)–S bond. Enantioselective oxidation of the thioether catalyzed by a chiral phosphoric acid forms the enantioenriched triptycyl sulfoxide which is catalytically oxidized in an enantiospecific and diastereoselective fashion to a threefold stereogenic sulfone. All three stereoisomers were selectively addressed with enantio- and diastereodivergence.

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[3] a) X. Wu, R. M. Witzig, R. Beaud, C. Fischer, D. Häussinger, C. Sparr, *Nat. Catal*. **2021**, *4*, 457. b) T. A. Schmidt, C. Sparr, *Angew. Chem. Int. Ed.* **2021**, *60*, 23911.
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Synthesis of chemical tools to decipher the mode of action of antiparasitic redox-active 3-benzylmenadiones

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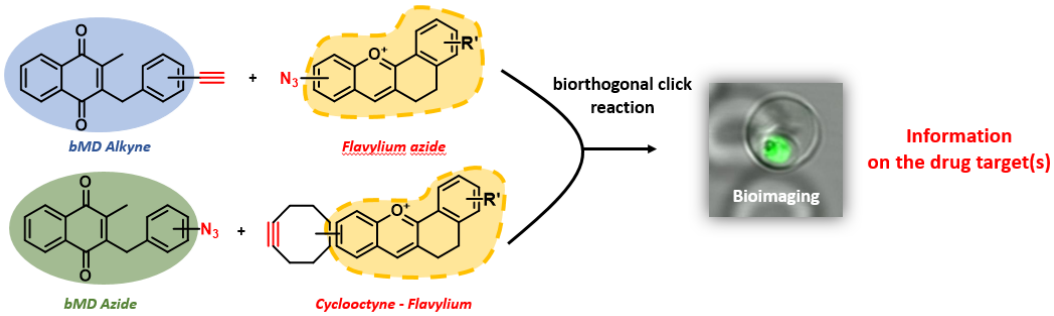
One of the main research topic of the CBM team is focused on the development of redox-active antiparasitic drug-candidates based on the 3-benzylmenadione (bMD) core. Two strategies are currently being developed for the identification/visualisation of the biological targets of bMD, a crucial step to elucidate the modes of action and synthesize more effective drugs in the future through rational drug design.[1] The first strategy is based on a bioorthogonal click reaction between novel bMD-derived alkyne probes and an azide fluorophore using the copper-catalyzed azide-alkyne cycloaddition reaction (CuAAC) to visualize bMD-treated parasitized red blood cells. In addition, azide fluorophores based on a rigid flavylium scaffold are being developed that can react efficiently with these alkyne-bMDs to form bright bMD-flavylium adducts. The latter is justified by the fact that, compared to expensive commercial fluorophores (e.g. rhodamine azide) that are difficult to modify or functionalize, home-made azide fluorophores can be developed with a minimum of synthetic steps (simple and fast synthesis, scale-up, photostable, bright, water-soluble, tuneable emission, post-functionalisation). For example, the length of the spacer that separates the flavylium core from the azide function or the nature of the chromophore substitution offer several interesting perspectives. By taking advantage of the intrinsic redox properties of the bMD moiety, it was possible to achieve an interesting fluorogenic response within the bMD flavylium adducts. These represent redox-sensitive fluorescent probes whose emission is closely related to the redox state of the bMD moiety, thus offering interesting imaging prospects for quantifying the redox status in living parasites. The second strategy still aims to develop other bMD-based probes for parasite imaging, but with the design of the first bMDs functionalised with an azido unit, allowing copper-free cycloadditions (SPAAC) with constrained alkynes (e.g. DBCO functionalised with a flavylium fluorophore) to monitor the transport and localisation of the pharmacophore within the parasite.



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Detection and Quantification of Magic Spot Nucleotides

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Starvation, antibiotics, changes in pH or in temperature stresses bacteria[1] and initiate a stress response, known as stringent response. This signaling cascade is mediated by the magic spot nucleotides guanosine 3'5'-bispyrophosphate (ppGpp) and guanosine 3'-diphosphate 5'-triphosphate (pppGpp). Detection and quantification of (p)ppGpp have, however, have been a challenging task due to low cellular concentrations, fast turnovers and difficult separation possibities.[2]

We examine concentrations of the aforementioned signal molecules via capillary electrophoresis coupled to mass spectrometry (CE-MS). This highly sensitive analytical method is known for the excellently separation of highly charged components at low concentrations and is perfectly suitable for magic spot nucleotides.[3] Here, we describe a method, in which spiking with heavy internal standards before extraction eliminates the losses of specific analytes during extraction. The combination with the sensitive CE-MS analysis provides a powerful tool for the determination of magic spot nucleotides with concentrations below 1 µM. This workflow (see also figure 1) is expected to reveal the bacterial metabolism not only during stress response and could help in the development of more effective antibiotics via the inhibition of the stringent response.

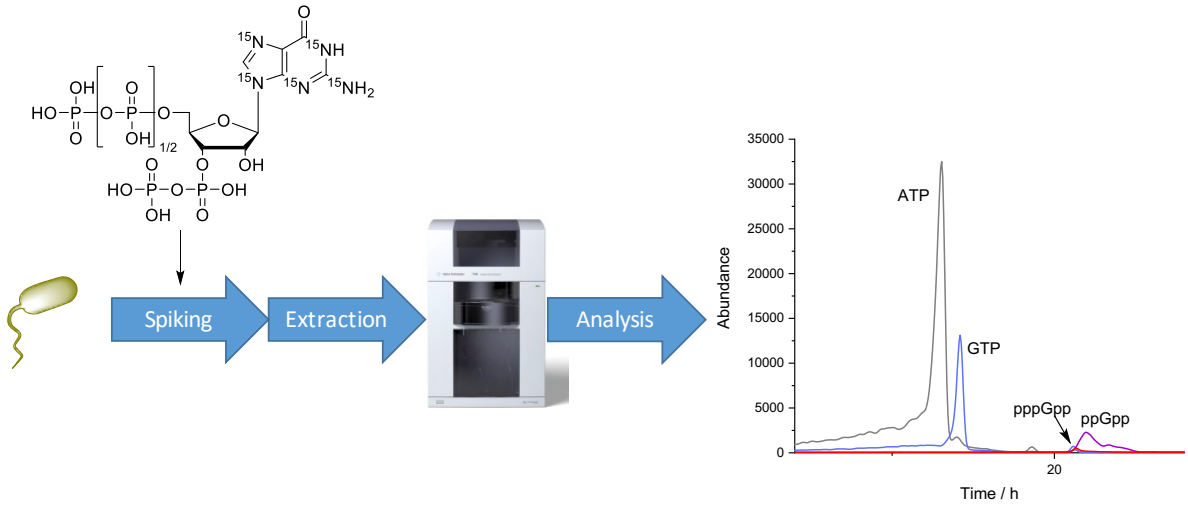

Figure 1. Structural formula of (p)ppGpp and workflow of quantification. Adenosine (ATP) and guanosine (GTP) triphosphates are shown for comparison.

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EUCOR PRESENTATIONS

Session 2 (Tuesday)

Methylene C(sp^3)–H activation enables stereoselective synthesis of Indidene natural products

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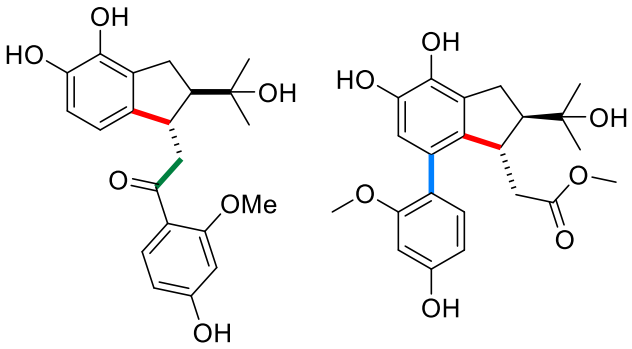
Enantioselective Pd^0-catalyzed arylation

Ni^0-catalyzed oxidative cross coupling

Suzuki coupling



***rac*-indidene A** **(–)-Indidene C**

Recently developed C–H activation methodologies have enabled concise and efficient total syntheses of various bioactive natural products[1]. In this context, Pd^0-catalyzed C–H activation has emerged as a method of choice for construction of cyclopentane rings of various complexity[2]. We report our investigations towards racemic and enantioselective synthesis of Indidenes A and C, polyketides isolated from bark of *S. indicus*, as well as other indidene congeners. The construction of the indane scaffold is enabled by implementation of a Pd0-catalyzed methylene C–H activation[3], which sets the first stereocenter. The installation of the side chain is achieved by a Ni^0-catalyzed oxidative cross-coupling[4] in the case of Indidene A, while Suzuki coupling facilitated formation of a biphenyl system in Indidene C.

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Regio- and Diastereoselective Decarboxylative Allylation of *N*-Aryl α-Amino Acids by Dual Photoredox/Nickel Catalysis

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Homoallylic amines are important building blocks for the synthesis of nitrogen-containing natural products. They are generally synthesized by addition of allyl metal compounds to imines. With the establishment of photoredox catalysis in organic chemistry, research interest in homoallylic amine syntheses via radical reactions has increased. Herein, we present a dual photoredox/nickel catalyzed regio- and diastereoselective allylation reaction of *N*-aryl α-amino acids. Our method yields branched homoallylic amines in high yields and high *syn*-diastereoselectivity under mild and redox-neutral conditions. The synthetic flexibility of our reaction was demonstrated in a broad substrate scope, which is characterized by a high functional group tolerance. Detailed mechanistic studies revealed an imine as the key intermediate in this reaction.[1]

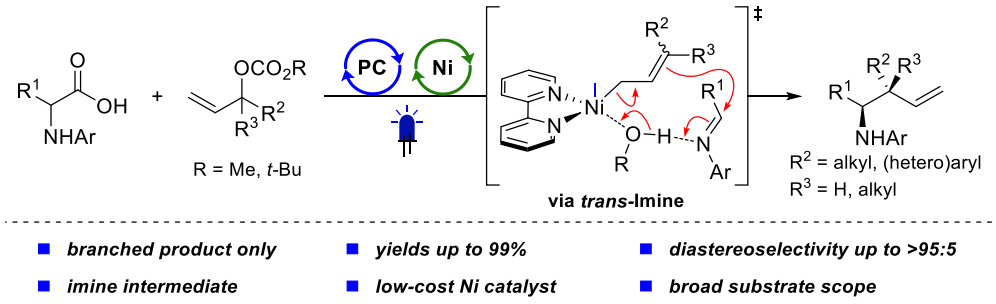

Figure 1. Synthesis of Homoallylic Amines via Dual Photoredox/Nickel Catalysis.

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Geländer Molecules with Orthogonal Joints: Design, Synthesis, and Properties

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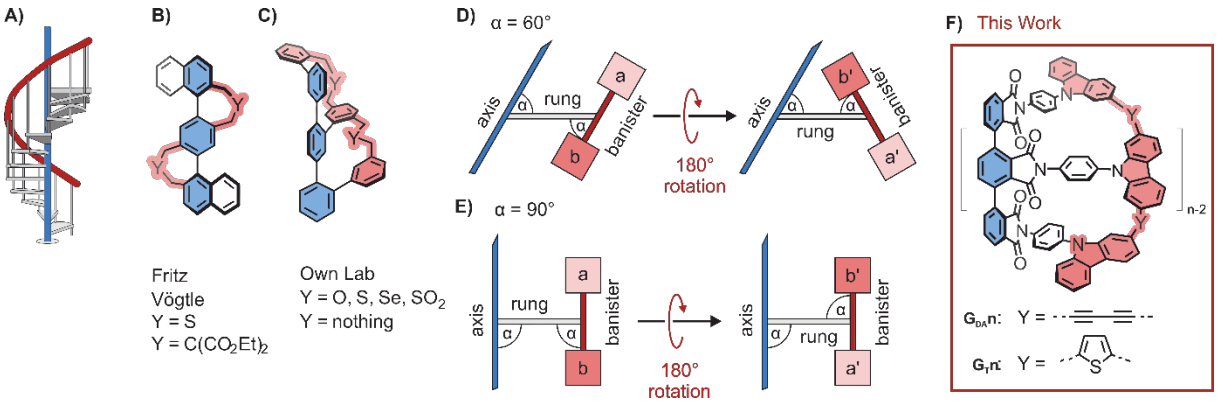
Helical chirality can be induced by forcing long tethers around a central axis. Such molecular architectures are reminiscent of the banister (or "Geländer" in German) of a spiral staircase (Figure **1A**).[1] By extension of a single stringer (banister) in a ladder polymer, exclusively chiroptically active structures are formed with high racemization barriers.[2-4] In initial endeavors, regioisomers were formed in a late divergent synthetic step, owing to the inherent asymmetry of the designed building blocks. These regioisomers are formed due to the free rotation around the rung between the stringers, resulting in acute or obtuse angles to the nearest neighbor (Figure **1D**). This severely limits the feasibility of the synthesis of oligomers with more than three repeating units.[3,4] By symmetrizing the molecular design (Figure **1E**), this divergent step is circumvented.[5] The helical structures (Figure **1F**) are formed in two subsequent robust homo-coupling steps as racemic mixtures, which are resolved to pure enantiomers by chiral stationary phase HPLC.

The design principle and synthesis of Geländer oligomers of varying sizes with orthogonal joints are presented, as well as a chiroptical study thereof.



This work was supported by Swiss National Science Foundation (SNF Grant no. 200020-207744).

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Synthesis and reactivity of F_2HCO-bearing building blocks for accessing valuable difluoromethoxylated scaffolds.

4

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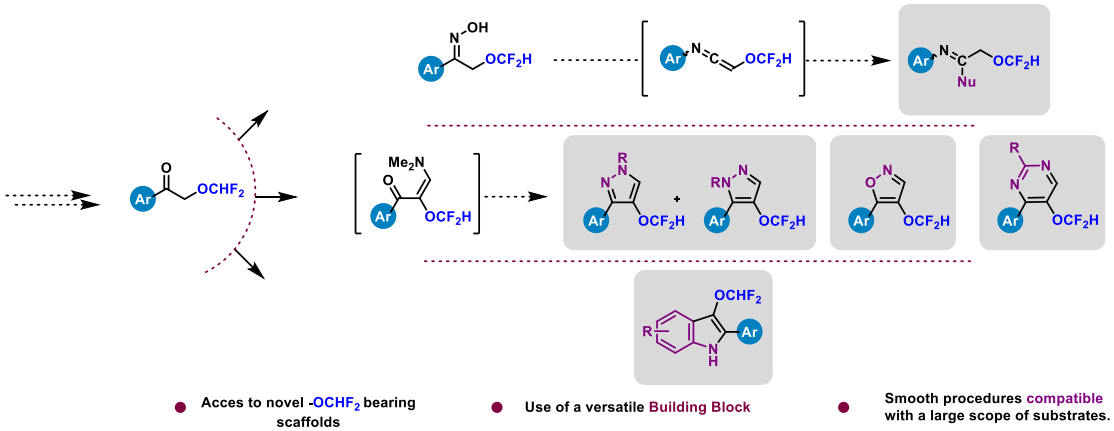
The use of fluorinated groups in medicinal and agrochemistry is constantly increasing. In fact, at least one fluorine atom is present in 18% of pharmaceuticals[1] and 16% of agrochemicals[2]. Fluorine has indeed demonstrated its ability to modify the physico-chemical and biological properties of molecules compared to their hydrogenated analogues, leading for example to an increase in metabolic stability. Nevertheless, most of these compounds are in fact bearing a single fluorine atom, or a trifluoromethyl group, thus explaining the need for more diversity, i.e. Emerging Fluorinated Groups. To this end, our group has developed the synthesis of a versatile building block, namely a ketone, allowing the introduction of the -OCF_2H motif, for which the direct introduction methods, especially on alkyl chains, are still rare[3]. As a matter of fact, the difluoromethoxy moiety appears as particularly interesting, as it combines the classical properties due to the fluorine atoms, with unique properties resulting from its anisotropy and from the presence of a H-bond acidic proton. First the synthesis of the difluoromethoxylated ketone was optimized. Then its synthetic potential was taken advantage of, as it was used for accessing valuable compounds such as amidines, imidates, thioimidates or very rarely encountered difluoromethoxylated heterocycles, which should be particularly relevant structures in Life Sciences. This new method thus allowed us to build a library of high potential molecules bearing the key -OCF_2H motif[4,5].



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EUCOR PRESENTATIONS

Session 3 (Wednesday)

Facile access towards trans-hydroxyoctahydroazulenone core and total synthesis of Randainin D via visible-light-promoted Ir(III)-catalyzed allylation

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Hydroazulene is an abundant framework found in guaiane-type sesquiterpenes. Recently Shen[1] and Williams[2] groups isolated novel natural products (***Randainins A-D*** and ***Shortolides B-C***) possessing simultaneously hydroxyoctahydroazulene skeleton and butenolide moiety. Such framework features make these natural products unique, being structurally related to both, guaiane-type sesquiterpenes and labdane-derived diterpenoids. ***Randainin D*** is a moderate inhibitor of superoxide-anion generation and elastase release. Such biological activity and intriguing structures (trans-5/7-ring scaffold, five stereocenters, four – contiguous, and two – quaternary), make this unusual natural product attractive and challenging synthetic targets.

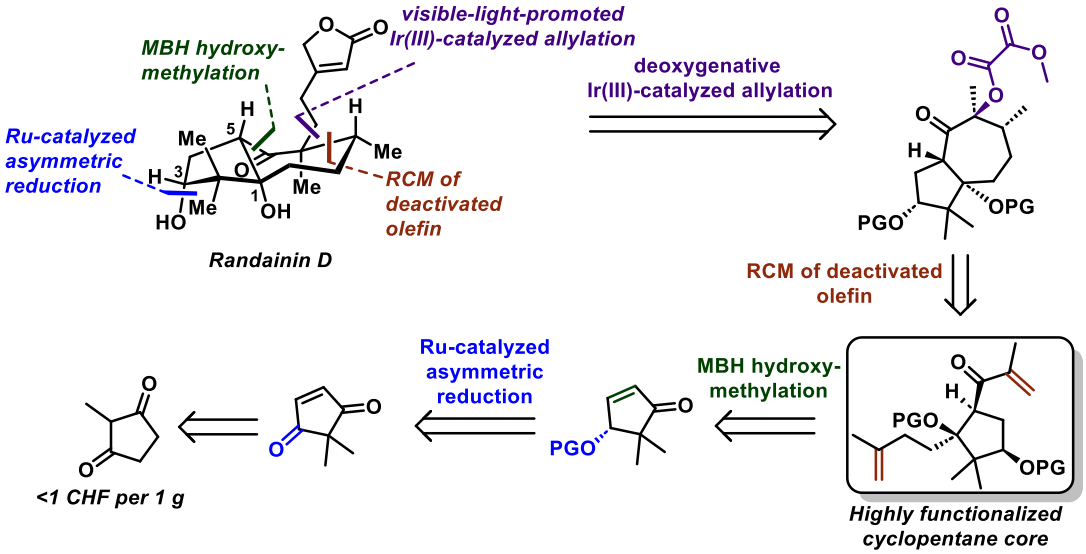

Fig. 1. Retrosynthetic analysis of ***Randainin D***

It was found that Ru-catalyzed asymmetric reduction of 2,2-dimethylcyclopentane-1,3-dione creates the stereocenter at C3, which leads to the desired trans-junction at C1-C5, through the sequence of diastereoselective steps. Assembly of the 7-membered ring was realized via challenging Ru-catalyzed RCM leading to the tetrasubstituted enone. The endgame is a novel visible-light-promoted Ir(III)-catalyzed allylation that allows the direct installation of alkyl substituted butenolide moiety.

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Regio- and Stereoselective Hydroelementation of SF_5-Alkynes and Further Functionalizations

2

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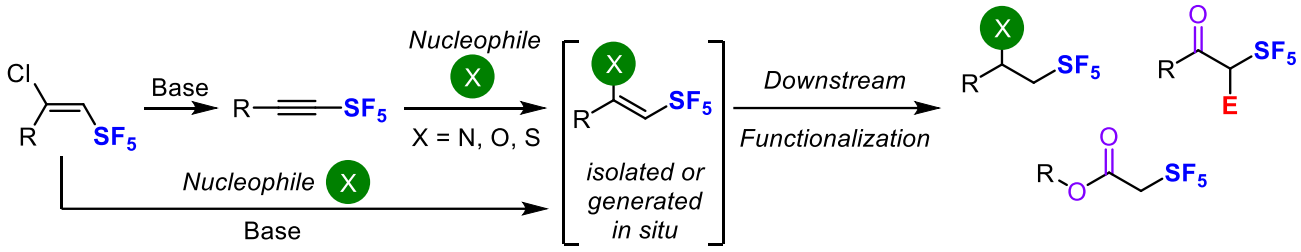
Nowadays, development of novel synthetic routes towards SF_5-containing compounds is on the rise, but the access of structural diversity remains highly challenging. Pentafluorosulfanylated alkynes are easily accessible and versatile SF_5 building blocks, which have been mainly used in cycloaddition, heterocyclic synthesis and few hydrofunctionalization reactions.[1] To our knowledge, the hydrofunctionalization of SF_5-alkynes has been poorly explored and is mainly limited to hydration and hydrofluorination.[2] Noteworthy, two preprints appeared at the same time we developed this study about the hydroamination and hydrotioetherification of SF_5-acetylene generated in situ, showing the actual craze for this motif.[3] In this presentation is disclosed a very efficient method to perform a fully regio- and stereoselective hydroelementation reaction of SF_5 alkynes in mild reaction conditions which does not require the use of any transition metal. This fully atom-economical process gives an easy access to various heterosubstituted vinylic-SF_5 scaffolds (X = N, O, S), as very attractive platforms for downstream functionalization and/or transformation. Experimental and computational comparative studies between SF_5- and CF_3-alkynes have been performed to highlight and explain the difference of reactivity and selectivity observed between these two fluorinated motifs.[4]



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[3] a) J. O. Wenzel, F. Jester, D. Rombach, *ChemRxiv* , **2022**, DOI 10.26434/chemrxiv-2022-brg1w b) H. Kucher, J. O. Wenzel, D. Rombach, *ChemRxiv*, **2022**, DOI 10.26434/chemrxiv-2022-01jhn

[4] L. Popek, J,J. Cabrera-Trujillo, V. Debrauwer, N. Blanchard, K. Miqueu, V. Bizet, *Angew. Chem. Int*.Ed., **2023**, *62*, e202300685

Site-selective hydrogenation/deuteration of benzylic olefins enabled by electroreduction

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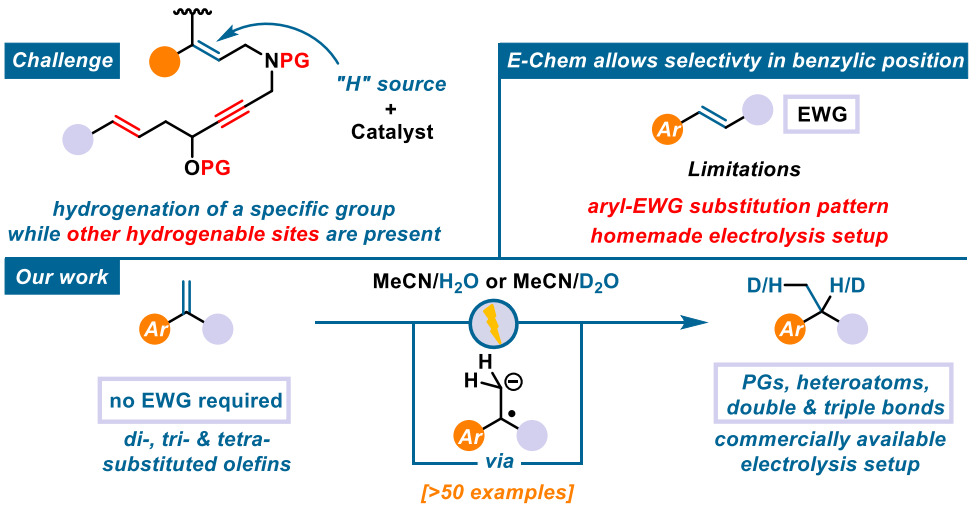
Hydrogenation conveniently allows the construction of C(sp^3)-centers from readily available olefins or alkynes and orthogonality in protecting group strategies. However, the control of site-selectivity when more than one group that is affected by hydrogenation is present, is hard to achieve (Scheme 1). Interested in such a method, we found that electrochemistry was already used to selectively react benzylic olefins by cathodic reduction.[1] While reported methods commonly require an aryl-EWG substituted olefin (cinnamic acid derivatives), we developed a general method that overcomes this limitation and uses a commercially available electrolysis setup.[2] The operationally simple procedure utilizes H_2O or D_2O for the selective hydrogenation and deuteration of benzylic olefins when other C(sp^2)/C(sp)-centers or protecting groups are present. In addition to a broad substrate scope (>50 examples), we performed experiments to support our mechanistic proposal.

Scheme 1. Our protocol allows a challenging site-selective hydrogenation/deuteration of benzylic olefins and overcomes limitations of previously reported electrochemical methods.



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Metal Ions Facilitate Chirality Transfer in Non-Enzymatic Reductions with NADH

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Reduction reactions are essential within biochemical metabolism,[1] but it remains unclear how they emerged before the availability of enzymes at the origins of life. Within early metabolism, NADH is considered to be the most important cofactor, where it takes a central role in reduction reactions.[2] As NADH can be obtained under prebiotic conditions using hydrogen as a reducing agent,[3] NADH takes a central role in theories on the emergence of life by allowing the transition from abiotic to organic reducing agents. However, experimental verification of such models is still missing, as previous studies have shown that NADH is unable to act as a reducing agent in water outside of enzymes.

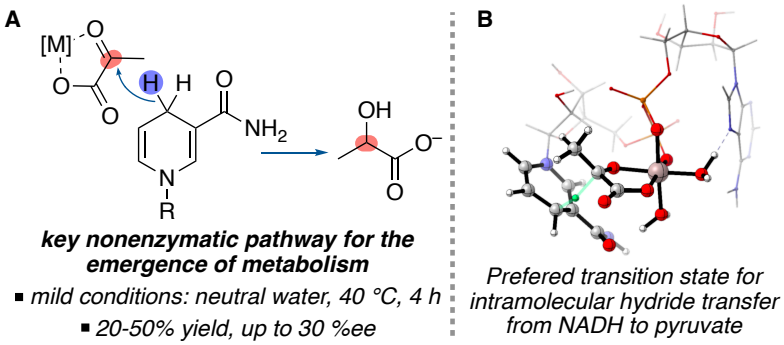

Figure 1. A: Metal-catalyzed nonenzymatic reduction of keto acids by NADH. B. Computational transition state for intramolecular hydride transfer in the reduction of pyruvate.

By combining high-throughput screening and statistical reaction optimization, we have now identified conditions under which catalytic amounts of metal ions drastically enhance the reactivity of keto acids enabling their reduction by NADH and NADH analogs in neutral unbuffered water at 40 °C (Figure 1A).[4] Under the identified reaction conditions, the chirality of the hydride donor NADH is partially translated to the products resulting in a significant preference for the formation of D-hydroxy acids with up to 35 %ee. DFT computations were used to elucidate the detailed reaction mechanism and identified an intramolecular hydride transfer within a highly organized adduct to be responsible for the observed chirality transfer (Figure 1B). The identified reaction conditions constitute the missing link in enabling nonenzymatic reductions in early metabolism and are the first example where a metal ion mimicking enzyme function enables chirality transfer of a biochemical reaction.

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POSTER SESSION

Rhodium-Catalyzed Enantioselective Intramolecular Hydroalkoxylation of Allenes towards Tetrahydropyranes, Tetrahydrofuranes and Morpholines

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Oxygen and nitrogen containing cyclic compounds are widely found in natural and pharmaceutical products[1]. Therefore, procedures for the enantioselective synthesis of these compounds are of utmost importance[2-3].
Herein, we report the development of a Rhodium-catalyzed cyclization of alcohols towards allenes. This methodology provides selective access towards tetrahydropyranes, tetrahydrofuranes and morpholines. High yields, high enantiomeric excess and a good functional group tolerance were achieved.

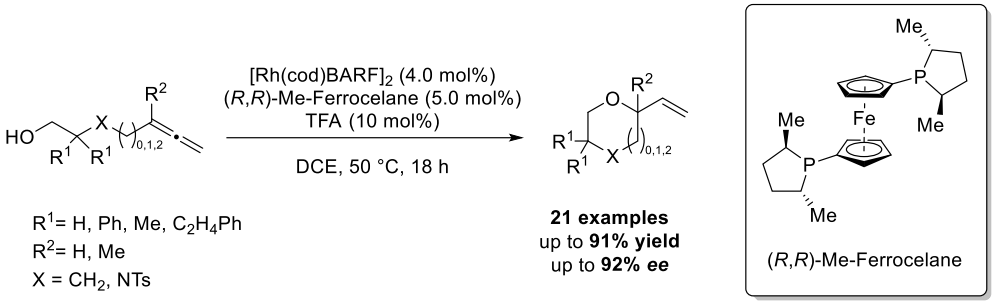

Figure 1. Reaction conditions of the Rhodium-catalyzed cyclization of alcohols towards allenes.

Furthermore, the utility of this method was demonstrated by the asymmetric total synthesis of *α*-Tocopherol.

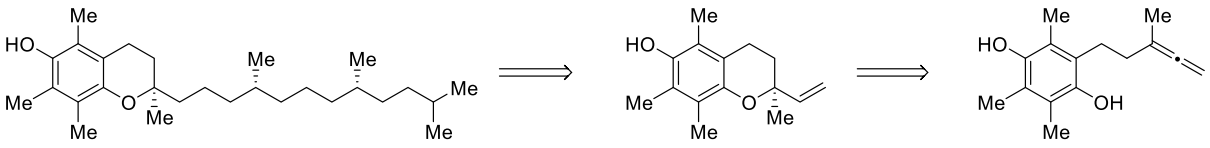

Figure 2. Retrosynthetic analysis of *α*-Tocopherol.

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Oligoamylose from Cyclodextrin: Precursors for Enzymatically Cleavable Polymers **2**

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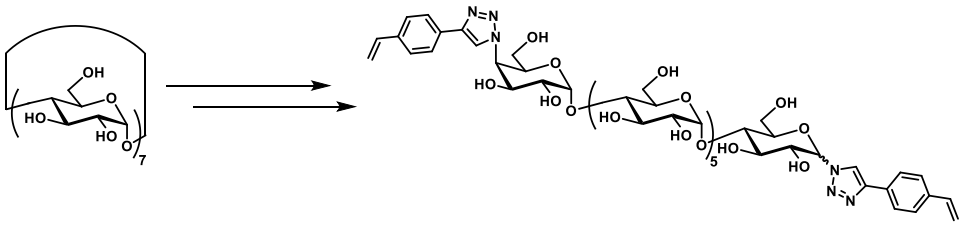
The tailor-made modification of surfaces by adaptive polymers allows a broad spectrum of targeted modification of their surface properties. Cross-linked polymers are commonly employed for such purpose, despite the fact that a later cleavage of those bears difficulties. Therefore, the incorporation of predetermined breaking points is of interest.[1, 2] The enzymatical cleavable glyosidic bond could fit the requirements for such a breaking point. The aim of this project is the synthesis of an oligoamylose bearing terminal polymerizable moieties which allow its incorporation into a cross-linked polymer by copolymerization. This should allow the polymer to be enzymatically cleavable by amylase. To this end, a 1-azido heptaglucopyranose was obtained by the acidic cleavage of perbenzoylated β-cyclodextrin[3]. This was further azidofunctionalized at the 4-position of its other terminus, which set the stage for introduction of terminal styrenes by copper catalyzed azide-alkyne click chemistry. The resulting product could then be globally deprotected under basic conditions to refurbish the native hydroxyl pattern of the carbohydrate.



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New Inositol Pyrophosphate Prometabolites for *in vivo* Release

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Inositol pyrophosphates (PP-InsPs) are highly phosphorylated messenger molecules, which appear as different isomers. Many important biological functions like phosphate homeostasis and insulin sensitivity are associated to this molecules. The metabolic connection between the different isomers with high turnover and low concentrations complicates the investigation of their biological function. We introduced a prometabolite approach to modify the messenger's concentrations *in vivo* (**Figure 1** shows an 1,5-PP_2-$InsP_4$ derivative as an example). The prometabolites has protecting groups (AB) to mask the negative charges, which inhibit the cellular uptake. These modifications are biolabile, as they are cleaved by enzymes after they entered the cell. The activity of the messenger is still blocked by a photo removable protection group (photocage). A short irradiation with UV-light removes the photocage and PP-InsP is set free. New photocages were introduced, as they can be cleaved by higher wavelength (450 nm and higher) to overcome phototoxicity. The alkyne-group of the photocage enables to couple different modifications via click-chemistry, which can improve the cellular uptake or target specific organelles.

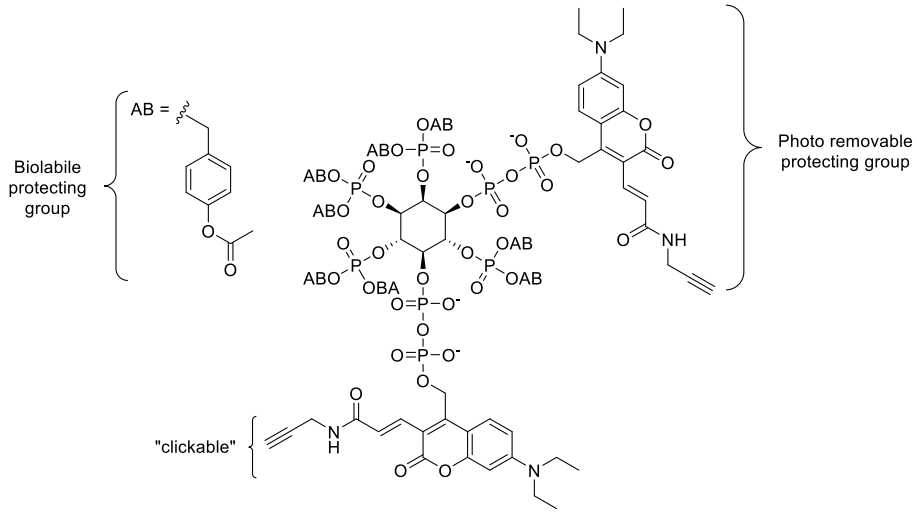

Figure 1. A prometabolite of the isomer 1,5-PP_2-$InsP_4$, with the photocage DEAC450

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Hydrofunctionalization of Propadiene – New Life for a Previously Unwanted Product

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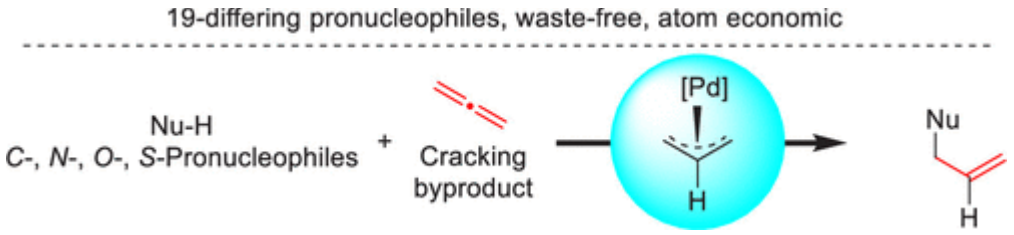
A highly versatile palladium-catalyzed allylation reaction of several pronucleophiles is reported. The use of propadiene in toluene provides an atom economic and waste-free access to allylated nucleophiles, a structural motif with almost unlimited possibilities for further functionalization. In addition to N-, O-, and S-pronucleophiles, the Pd/BINAP system is capable of adding a C-pronuceophile to allene. A plausible mechanism is supported by deuterium labeling experiments.[1]



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Photoinactivation of mycobacteria

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Mycobacteria, belonging to the phylum Actinomycetota, possess a distinct and fascinating cell structure comprising a cytoplasmic membrane and an overlaid peptidoglycan layer. Additionally, they exhibit other structural elements, including an arabinogalactan layer directly attached to the mycomembrane. The inner leaflet of the membrane is composed of long mycolic acids linked to arabinogalactan, while the outer leaflet primarily consists of TMM (trehalose monomycolate) and TDM (trehalose dimycolate). These constituents are synthesized through the extracellular Ag85 enzyme complex. In this project, the potential of this enzyme complex to incorporate not only trehalose but also trehalose analogs is being explored. As previously demonstrated by various research groups, mycobacteria can be specifically modified using trehalose derivatives[1,2].

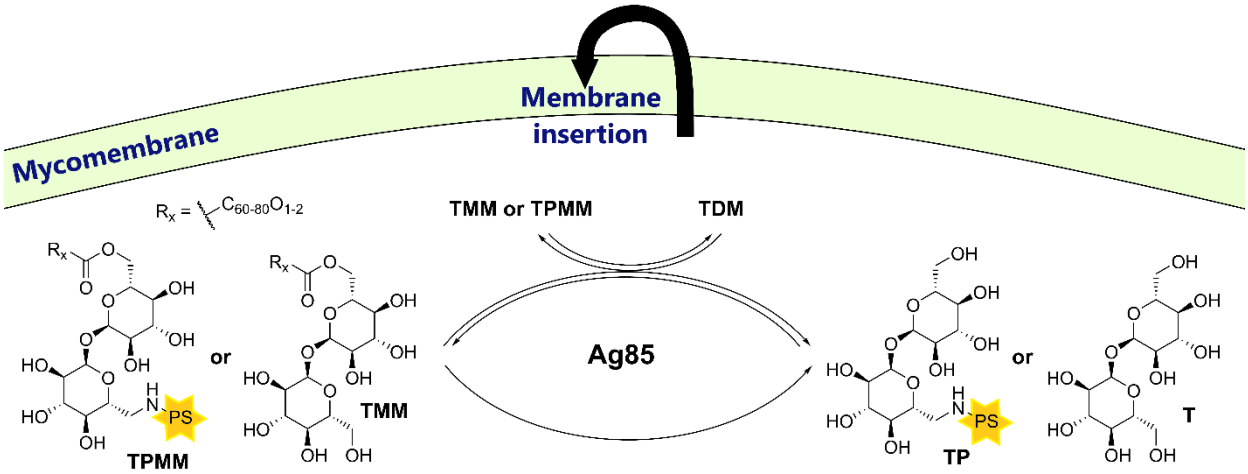

Figure 1: Schematic illustration of the incorporation of trehalose derivatives into the mycomembrane. T is for trehalose, TP for trehalose-photosensitizer derivative, TMM for trehalose monomycolate, TDM for trehalose dimycolate and TPMM for trehalose-photosensitizer monomycolate. (Adapted from Dutta *et al.* (2019)[2])

The work published by our group in 2019, already demonstrated the potential of bacterial functionalization, allowing for photoinduced inactivation of mycobacteria through the generation of reactive oxygen species (ROS) upon exposure to light irradiation[2]. Building upon this foundation, our objective is to develop enhanced photosensitizer-trehalose conjugates specifically tailored for the treatment of skin infections caused by pathogens like *Mycobacterium marinum*. Additionally, we aim to explore the potential of utilizing photosensitizer-modified *Mycobacterium bovis* BCG for the treatment of bladder cancer therapy[3]. Our current synthesis endeavors are primarily centered around BODIPY-photosensitizers and Nile-Blue derivatives. Through our efforts, we have successfully established an enhanced synthesis and purification protocol for known BODIPY-photosensitizers. Presently, our focus is on creating a diverse range of compounds to construct a small library. This library will enable us to evaluate the light-induced killing efficiency against the aforementioned mycobacterial strains, both *in vitro* and within macrophages.

Synthesis of novel Quinoacridane[4]arenes

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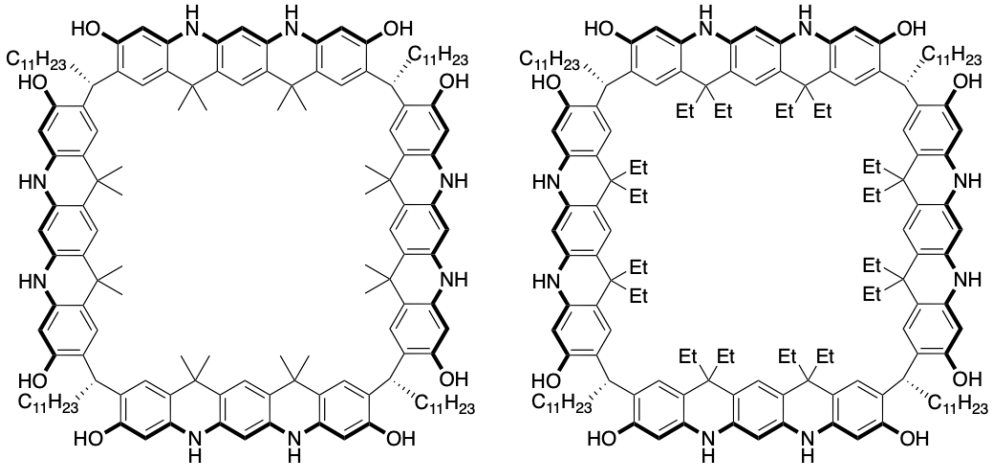
Since the synthesis of the first cavitands, based on resorcinarene much effort has been put in the development of larger cavitands.[1,2] For that reason, larger bowl-shaped macrocycles were synthesised. It has been challenging to derive larger macrocycles, since naphthalenearenes can not be obtained as bowl-shaped macrocycles and xanthene forms only trimeric macrocycles.[3,4,5] By using acridane, it was possible to synthesise the megalo cavitands, with a volume of up to 814 Å^3. So far, the acridane[4]arenes were the largest macrocycles.[6]

Recently, our group developed a new class of macrocycles based on quinoacridane, termed quinoacridane[4]arenes. Macrocycles equipped with methyl and ethyl substituents as inner feet were synthesised.



1 **2**

Figure 1: Synthesised macrocycles **1** and **2** of the Quinoacridane[4]arene family.

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Synthesis of novel bisubstrate analogues of ppGpp containing diphosphate isosteres as potential RSH enzyme inhibitors

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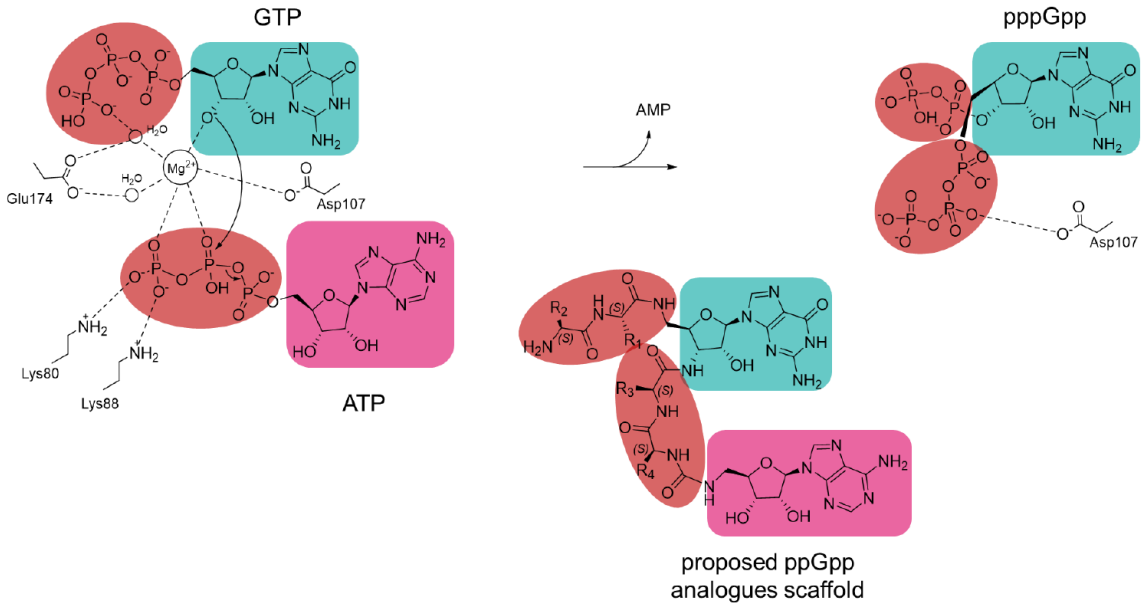
The status quo in antibiotic research is that more and more resistance to established drugs is emerging, while hardly any new antibiotics are being discovered. Therefore, alternative ways to combat antibiotic resistance are being sought. Stringent response is a bacterial survival mechanism that involves the synthesis of highly phosphorylated nucleotides such as (p)ppGpp, known as magic spot nucleotides (MSN). This mechanism is associated with the ability of bacteria to develop resistance and survive under adverse conditions. Thus, its inhibition could provide an opportunity for the development of new antibiotics. In this work, new (p)ppGpp analogs are developed using dipeptides as diphosphate mimics, which are designed to inhibit MSN-synthesizing enzymes in bacteria as transition state analogs.



Concept for novel bisubstrate inhibitors. Inhibition of the RSH proteins (here *Staphylococcus aureus* small alarmone synthetase RelP) is to be achieved by transition state analogues.

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A Modular Approach for the Synthesis of Novel Heterobifunctional Cyanine Dyes

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Heterobifunctional dyes are a versatile tool to link biomolecules of interest and study them. In literature, several approaches towards the synthesis of asymmetric cyanine dyes are described, but they involve high boiling point solvents, RPC and/ or preparative HPLC purification, low yields and small scales or are microwave assisted.[1-4]

The instability of those dyes due to the positive charge makes them rather complicated to handle. Furthermore, formation of the indolium salt through N-alkylation of indolenine requires high temperatures, at which temperature-sensitive functional groups decompose.[2]

Herein, we present a novel synthetic route for the design and synthesis of new asymmetric cyanine 5 dyes. Within this study, we were able to reduce the work up steps by benefitting from the pH- and functional group dependent solubility of the asymmetric cyanine 5 dyes avoiding thereby the necessity of chromatography until the final synthesis step. Furthermore, the synthesis does not require any high boiling point solvents and by using a modular approach, we could circumvent the decomposition of functional groups by adding them in the last step of synthesis. In addition, we could demonstrate that the synthesis is possible in gram-scale with good to excellent yields. All synthesised compounds were analysed using NMR spectroscopy and HR-MS.

The modular approach within this synthesis strategy allows the user to conjugate different blocks together. The synthesised dyes are equipped with a ligand, which can be fused to a self-labelling protein tag and a functional group, which can be coupled or attached via biorthogonal click chemistry to any other molecule, peptide or protein.

Macrocyclic Receptors for Aromatic Amino Acid Recognition

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Phenylketonuria (PKU) is a hereditary disease, caused by partial or total lack of enzymatic function of phenylalanine hydroxylase, which converts the essential amino acid L-phenylalanine (Phe) to L-tyrosine (Tyr). If left untreated in newborns, PKU may cause severe intellectual disability, epilepsy, and behavioral problems.[1] The development of small molecule receptors for effective distinction of the individual aromatic amino acids, especially Phe and Tyr, remains an elusive goal owing to their structural similarity. Such receptors could facilitate monitoring of the disease in patients and accelerate the discovery of drug candidates. By rational design as depicted in *Figure 1*, we realized the synthesis of a macrocyclic receptor comprising a perfluoroarene sandwich-like aryl binding site with micromolar affinity for L-tyrosine methyl ester in $CHCl_3$. Studies regarding selectivity of the binding cavity, shown in *Figure 2*, for individual amino acid methyl esters as well as the synthesis of a water-soluble derivative for stronger, solvophobic π-π-stacking[2] are currently ongoing in our laboratories. Based on the outcome of these studies, the scaffold of the macrocycle will be tuned by functionalization on the nitrogen atom of the carbazole moiety, to give rise to derivatives with a smaller cavity volume for efficient binding of the smaller amino acid Phe.

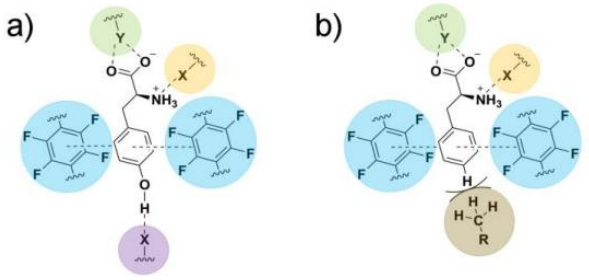

Figure 1. a) Tyr and b) Phe in idealized binding pockets, featuring H-bonding (green/yellow), pi-pi-interactions with perfluoroarenes (blue), and specific interactions to distinguish between their side chains (purple/brown).

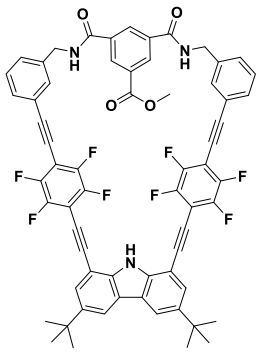

Figure 2. The synthesized macrocyclic scaffold with micromolar affinity for H-Tyr-OMe in $CDCl_3$.

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Rhodium-Catalyzed Diastereo- and Enantioselective Cycloisomerization of 1,5-*Bis*-(allenes) to 1,2-Enyne Cyclic Skeletons

10

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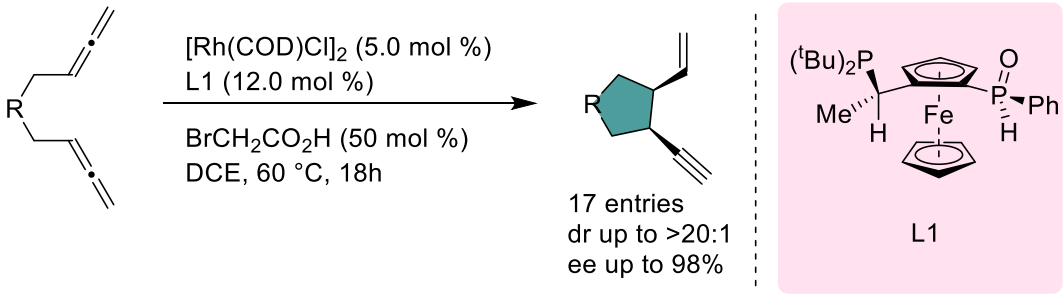
We present here a novel enantioselective Rh-catalyzed cycloisomerization of 1,5-*bis*-(allenes), which provides a versatile route for the synthesis of chiral five-membered ring (hetero)cycles. This method is suitable for the synthesis of spiro carbocyclic compounds, which are valuable chiral building blocks in organic synthesis. The reaction provides high yields of the desired products with excellent diastereoselectivity and high enantioselectivity. The newly formed products possesses both a branched alkene and a terminal alkyne moiety, providing opportunities for further functionalization [1]. This developed scaffold is similar to the structures of drugs such as prostaglandins and natural products such as kainic acid [2]. Furthermore, we demonstrate the scalability of the reaction through a gram-scale synthesis. We also illustrate the synthetic utility of the resulting 1,2-enyne cyclic products through several transformations. Density functional theory (DFT) calculations and deuterium labelling experiments support the proposed reaction mechanism.



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Catalyzing the Enantioselective Tail-to-Head Terpene Cyclization inside Optically Active Hexameric Resorcin[4]arene Capsules: Scope and Limitations

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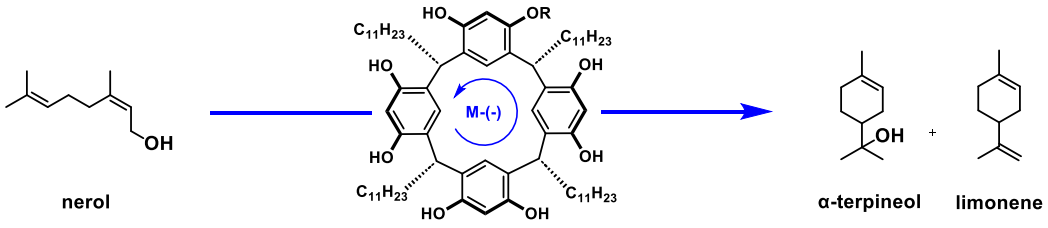
Mimicking the capabilities of terpene cyclases in the tail-to-head terpene cyclizations (THT) represents a great challenge in asymmetric catalysis. Molecular containers, by entrapping guests in a closed cavity, are able to mimic to some extend the enzymatic pockets of natural enzymes. The hydrogen-bond-based resorcin[4]arene capsule, first reported by Atwood in 1997,[1] is able to catalyze the THT cyclization of terpenes by stabilizing the cationic intermediates formed during the reaction cascade.[2] In this context, our group recently reported the first examples of optically active mono-alkylated resorcin[4]arene capsules and their application as supramolecular catalysts in the asymmetric THT cyclization of nerol.[3] Therefore, demonstrating that the chirality transfer from a rather large molecular container (approximately 1400 Å) onto the encapsulated substrate is possible. In this work we enlarged the scope of this supramolecular catalyst reporting 14 novel optically active resorcin[4]arene capsule derivatives, exploring the tolerance of the self-assembling of such systems towards structural modifications. Furthermore, the effects that these modifications have on the enantioselectivity of the THT cyclization studied are presented.



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Developing roles for phosphates in systems chemistry

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Phosphates and phosphate esters underpin biological information transfer, signal transduction, and contribute to the energetics of life. Biochemical fuels that include phosphates (ATP, GTP) drive selective processes, by incorporating chemical information (A vs. G) in their fuel structure. Despite the multifaceted role of phosphates in biology, their use in supramolecular systems chemistry remains largely underexplored. Herein, we aim to develop roles for phosphates outside of biology and capitalize on the idea of providing chemical information within abiotic phosphates to control selectivity and reactivity in the context of fuel-driven structure formation. The information is provided by chemical functionalization of energy-rich phosphates (**Figure 1**), whereby the information encode structural assembly of fuels prior to their consumption, or transfer large chemical groups onto self-assembling species during energy transfer. In particular, we demonstrate that aminoacyl phosphates[1] contain enough chemical information and energy to trigger the selective formation of peptide oligomers and drive orthogonal fueling in dynamic chemical networks. This strategy profoundly contrasts the present non-equilibrium self-assembly research featuring fueling with molecules that lack structural and recognition elements. In the long term, fabricating biocompatible dissipative systems and developing automated platforms that guide fuels to specific functions will be a decisive step toward creating dynamic assemblies in vivo and programming active soft matter.

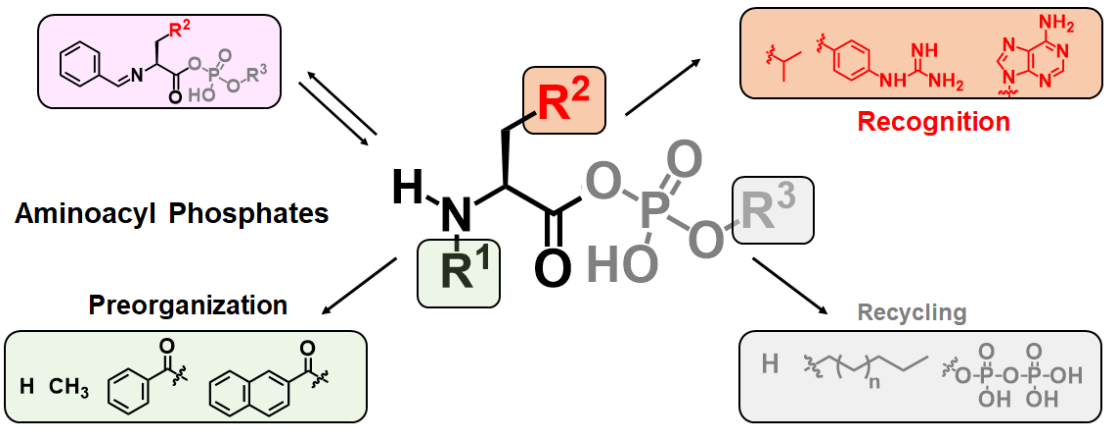

Figure 1: Designer abiotic phosphate fuels

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Identification of inositol phosphates and sugar phosphates isomers

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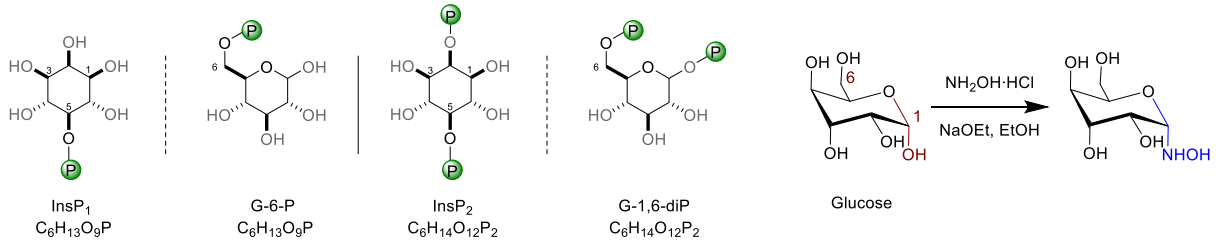
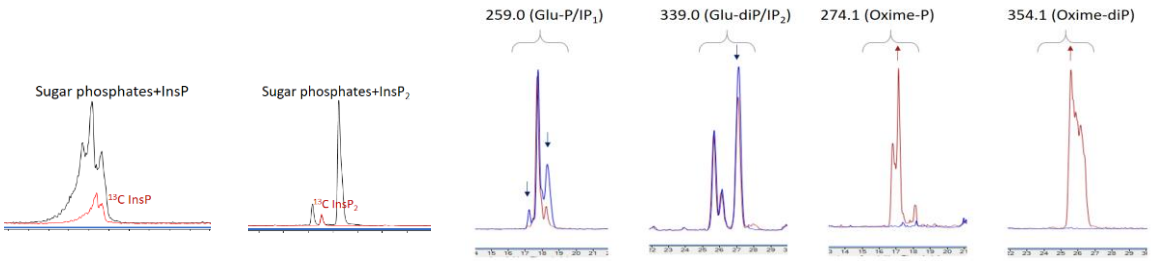
Inositol phosphates play an essential role in the biological world, such as in the regulation of ion channel permeability,[1] transcription and translation.[2] They are a type of molecule with numerous stereoisomers, chromophore-free structures and a high charge density. The nature of these salts results in analytical challenges. Recent deveopment of capillary electrophoresis mass spectrometry (CE-MS) has been shown to be a powerful analysis approach for those salts, especially the myo-inositol phosphates $InsP_3$ to $InsP_8$.[3,4] However, for InsP and $InsP_2$, it is common to find excessive isomers of inositol phosphates, such as sugar phosphates, which share the same mass and complex the assignment by CE-MS. Here we focus on the introducing one possibility for solving the problem: the carbonyl group (hemiacetal) in sugar is specifically transformed into other mass variable functional groups in a synthetic way. Hydroxylamine was introduced in this case to covert carbonyl to oxime, which left the inositol phosphates unchanged and identified in CE-MS.





Biosample: wild-type $HCT116^{UCL}$ after 5 days of incubation with 10 µM of [$^{13}C_6$]-inositol in inositol-free DMEMH. CE-MS: Blue curve: before reaction; red curve: after reaction

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Construction of 4-membered rings through an intramolecular C(sp^3)–H activation

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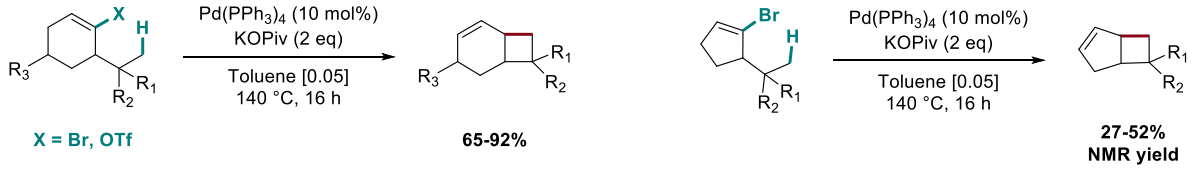
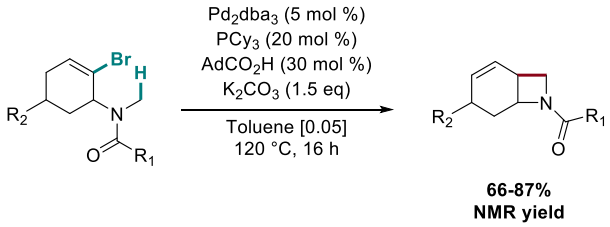
1,4-Palladium shift has been established as an elegant approach towards the functionalization of remote C–H bonds.[1,2] However, its application is restricted to using aryl halides as precursors.[3,4] In this work, we have successfully extended its application to C(sp^2)–X alkenyl precursors. As a result, we report an unprecedented cyclobutanation protocol towards fused cyclobutane derivatives using alkenyl (pseudo)halides through a Pd0-catalyzed C(sp^3)–H activation process. This reaction takes place via 1,4-Pd shift followed by intramolecular Heck coupling. The methodology performs best with cyclohexenyl precursors giving access to a variety of substituted bicyclo[4,2,0]octenes, and also shows a potential for accessing smaller ring systems starting from cyclopentenyl halides. Replacing the alkyl chain with N-methyl amides gives access to fused azetidines via the same mechanism. Early kinetic studies indicate a primary kinetic isotope effect establishing the C–H activation as the rate-limiting step, while deuterium incorporation suggests an irreversible C(sp^3)–H activation process.





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Chemical-Enzymatic Synthesis of Novel (p)ppGpp Derivatives and Their Bio-Functional Study

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Initially identified by Cashal and Gallant 1960s, pppGpp and ppGpp, collectively termed (p)ppGpp (also named by Magic spot nucleotides, MSN) have been unveiled to function as bacterial alarmones, controlling cellular growth under optimal conditions and in response to environmental stress, especially after the prokaryotic organism was deprived of amino acids. Although unique hyperphosphorylated structures of (p)ppGpp produce marked effects on their interaction with the biological target [1], the molecular tools bearing the intact hyperphosphorylated structures, at the same time having functional linkers including photo-crossing tag, biotin, etc., remain less explored.

In this work, we develop a chemical-enzymatic method to prepare the novel 7-substituted pppGpp derivatives (Figure 1). For the first time, we discovered that 7-iodo-substituted deazopurine triphosphate and 7-alkynyl substituted deazopurine triphosphate can be effectively accepted by Relseq protein as the effective substrate to produce pppGpp derivatives with over 85% yields. Interestingly, 7-iodo-pppGpp can bind HflX protein with the almost same binding affinity with pppGpp itself, and the 7-linked photo-crossing biotin-labeled pppGpp probe works well to cross-link pppGpp binding protein in vitro assays. So, 7-substituted pppGpp will offer a new kind of readily accessible and useful molecular tools for exploring the molecular interaction of pppGpp and its binding proteins.

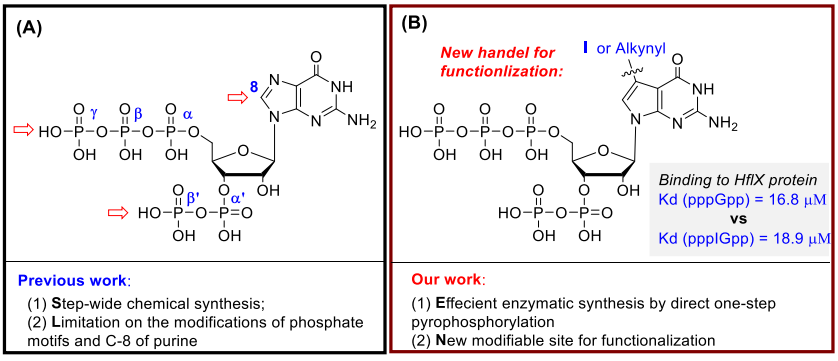

Figure 1 Chemical-Enzymatic method to access 7-substituted pppGpp Derivatives

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Dimethyl Naphthalenes: On the Way to Expanded Arenes

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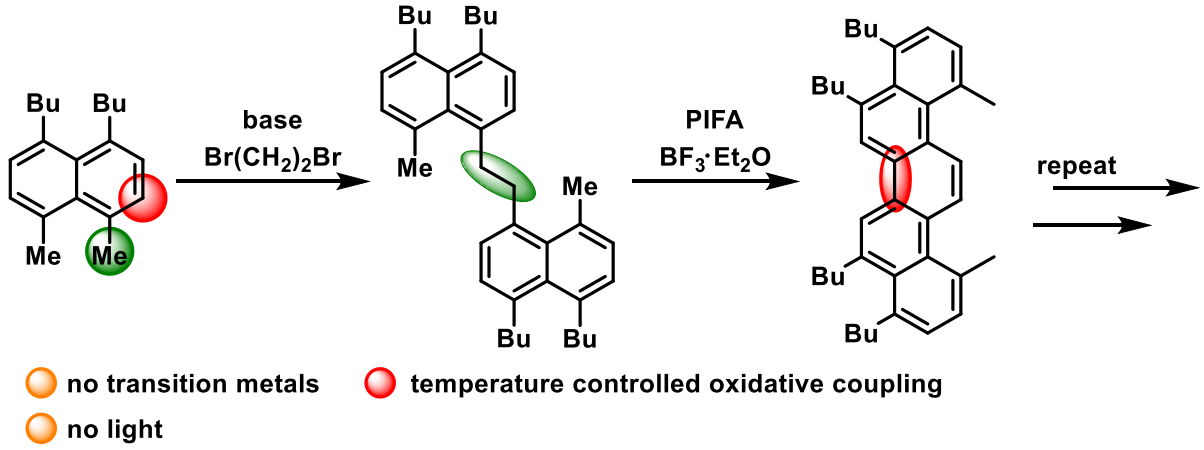
The past decade has witnessed a remarkable growth in the successful synthesis of expanded arenes which include expanded helicenes and kekulenes. These curved polycyclic aromatic compounds have received considerable attention in the fields of supramolecular chemistry and organic functional materials because of their interesting properties and promising applications. But, most of the existing methods for the synthesis of such cycloarenes rely on multistep tedious procedures. In contrast to that, here we use a simple two-step iterative process starting from substituted dimethylnaphthalenes. Depending on the substitution patterns in dimethylnaphthalenes and the way in which they have been fused, various cycloarenes such as expanded helicenes and expanded kekulenes can be produced. Having inspired from the previous works from our group,[1] here we follow a synthetic strategy which relies only on two different oxidative steps. In the first step we will make use of the deprotonatable methyl groups in the naphthalene ring to get ethano-bridged dimers by O' Shea's "LiNK metalation" process.[2] These dimers are then oxidatively coupled with the hypervalent iodine reagent [bis(trifluoroacetoxy)iodo]- benzene (PIFA) in the second step to get benzene-fused dimers.[3] Various expanded cycloarenes can be then accessed via these repetitive oxidative dimerization and dehydrogenation steps.



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Elucidation of the formylglycine generating enzyme/Cd/O_2/substrate intermediate

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The formylglycine generating enzyme (FGE) is a mononuclear copper-dependent oxidase. FGE is found in both prokaryotes and eukaryotes where it catalyses the conversion of specific peptidyl-cysteine residues to formylglycine (fGly, Figure) in the maturation of fGly-dependent sulfatases. [1] Dysfunction of FGE causes a lysosomal storage disorder known as multiple sulfatase deficiency. The ability of FGE to introduce aldehyde functions into recombinant proteins has also been exploited as a tool for bioorthogonal conjugation. [2]

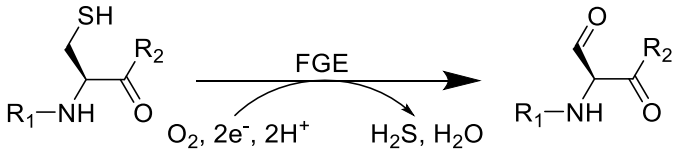

Figure 1. FGE-catalyzed oxidation of peptidyl-cysteine to formylglycine.

FGE is a single-domain protein with a fold that exhibits an unusually low content of secondary structure and a comparatively small hydrophobic core. The holoenzyme contains Cu^{I} in the active site, coordinated by two cysteines in a near-linear geometry. This coordination sphere is more characteristic of copper-trafficking proteins than of redox-active copper-enzyme.

Upon binding, the cysteine residue on the peptidyl substrate ligates to the copper center, giving rise to a tris-thiolate planar Cu^{I} complex. [3] This geometry does not change upon binding of molecular oxygen (O_2) juxtaposed but not coordinated to the copper center. In this presentation I will discuss the experiments we have designed to understand as to how the coordination geometry changes when copper on O_2 combine to form the H-atom abstracting species that is required to convert the peptidyl-cysteine to fGly.

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Synthetic Routes to (Poly-)Phosphorylated Myo-Inositol Derivatives

18

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Abstract

Myo-inositol polyphosphates (InsPs) serve essential tasks in eukaryotic cells like phosphate storage and second messaging. Their most prominent representative - 1,4,5-InsP_3 - is the main factor in controlling the cellular calcium signalling. Furthermore, there are other higher-phosphorylated inositol-derived phosphates - InsP_7 and InsP_8 isomers - that are important factors in cellular signal transduction pathways, although their role could not yet be deciphered precisely in all cases. However, to study the role of these InsPs they need to be synthetically prepared first, which remains quite challenging, requiring several regio- and enantioselective transformations resulting in molecules with a high charge density and labile anhydrides. Here we present the current synthetic routes employed in our laboratory. While symmetric InsPs can be accessed by the proficient use of protecting group chemistry alone, for asymmetric InsPs it is necessary to use chiral phosphorylation reagents to induce a desymmetrisation of myo-inositol beforehand. By introducing ^{18}O-labelled P-amidite precursors, “heavy” InsP derivatives can be created and applied as standards in mass spectrometry analyses or for monitoring cellular InsP uptake and metabolism. We further believe, that the chemistry shown here also bears the potential to be utilised as an elegant method for (poly-)phosphorylation in many other instances beyond the field of inositol phosphates.

Synthesis of Endoperoxides for Reversible Storage of Oxygen

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Oxygen can be reversibly stored in aromatic organic molecules as endoperoxides, emerging as stimulus-responsive materials for the targeted release of oxygen.[1] During this cycloreversion, both the more reactive, electronically excited singlet oxygen ($^1O_2$) and triplet oxygen in its ground state ($^3O_2$) can be formed[2], depending on the structure of the endoperoxide and leading to different applications. However, there are only few examples providing controlled release of oxygen at ambient temperature, which restricts their application possibilities.[1]
Here we show possible endoperoxide structures that could expand the range of applications. Different triggers for the release of oxygen such as acid, light, mechanical stress, or temperature will be investigated. Thereby, the analysis of the released oxygen is particularly interesting to tune the structure as required. In addition to the already known fields of bacterial control[3] or cell survival under anoxic conditions[4], it will also be investigated whether the endoperoxide structures and their released oxygen could be suitable as a driving force in pneumatic systems.

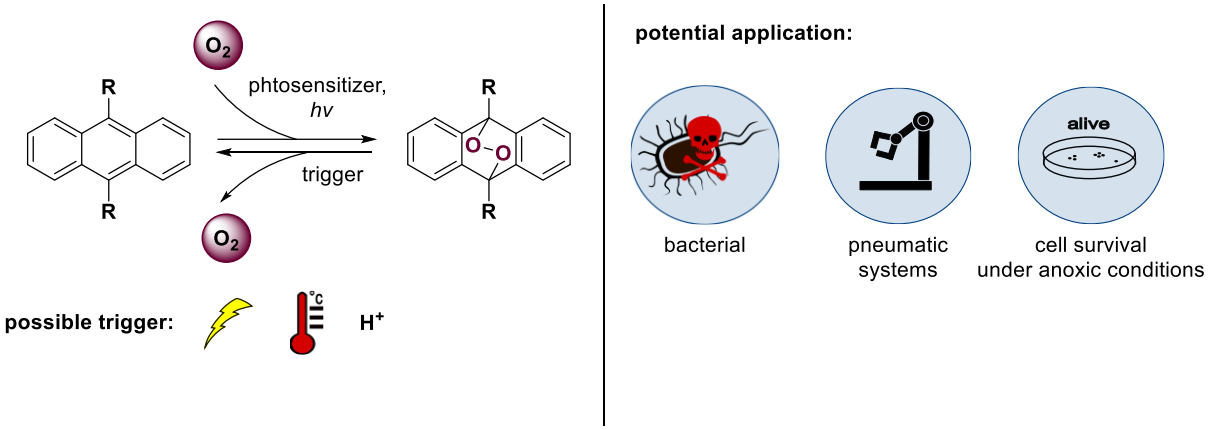

Figure 1: Reversible reaction of anthracene scaffolds with oxygen to form endoperoxides and their potential applications.

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Assemblies and reactivity of preorganized amino acyl phosphates towards selective peptide coupling

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Phosphates and phosphate esters regulate and enable almost all biological functions. In particular, phospholipid diester head groups that are covalently attached to lipid tails are the universal building blocks for biological membranes, serving as barriers. However, outside of biology, coupling of lipids with selective processes remain challenging. Herein, we overcome these challenges, through the design and assembly of amino acyl phosphates. (APs). [1] We have introduced modifications in the amino acid sequence of such building blocks with hydrophobic residues and in the phosphate moiety with long carbon chains. These modifications result in preorganization of APs into micellar and vesicular compartments, driving selective peptide coupling from a pool of amino acids. The assembly protects the activated phosphates from hydrolysis and from other nucleophiles, but selectively recognizes charged amino acid residues (**Figure 1**). In contrast, less hydrophobic APs that remain dissolved give rise to a random mixture of peptide sequences when mixed with different amino acids in aqueous conditions. Moreover, we have followed the reaction pathways with other nucleophiles (thiols and alcohols) to understand the way in which structure and reactivity cross-regulate. In future, we will investigate the effect of preorganization on non-equilibrium processes and how lipids can act as solubilizing agents in chemical reaction networks.

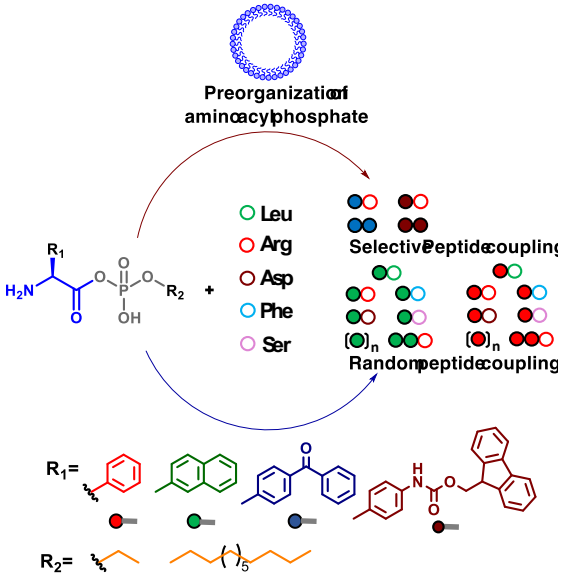

Figure 1. Preorganization of amino acyl phosphates towards selective peptide coupling.

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Synthesis of 2-aminoindenone derivatives through an ynamide carbosilylation / Houben-Hoesch cyclization 2-step sequence

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While the general synthesis of 1-indenone scaffolds has been extensively studied, the selective access to heteroatom-substituted indenones and more especially 3-substituted 2-aminoindenones remains a challenge[1]. With this in mind our group has previously developped a method to form 2-aminoindenone derivatives through a Larock annulation between ynamides and *ortho*-iodobenzaldehydes[2]. Given the moderate regioselectivity observed in some cases, we have recently designed a 2-step sequence to access silylated 2-aminoindenones in a highly regioselective manner. The sequence starts with a silylcyanation of an ynamide[3] followed by a cyclization *via* an intramomecular Houben-Hoesch reaction[4]. The resulting 2-aminoindenones could be valorized through iododesilylation giving access to various cross-coupling reactions. Interestingly some substrates bearing a sulfonamide allowed the obtention of stable 2-aminoindenimines which could be valorized via transformation of the imino group.

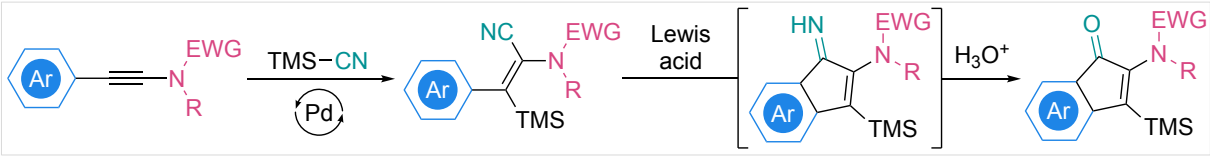

Figure: 2-Step sequence for the selective synthesis of silylated 2-amino-indenones

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Regio- and stereoselective halogenation reactions of SF_5-alkynes

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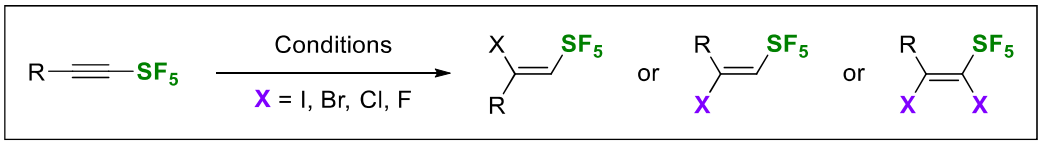
SF_5-Containing haloalkenes are usually obtained by the addition of SF_5X gas (X = Cl, Br) onto the corresponding terminal alkynes but the *E*-stereoselectivity is usually observed under radical condition, [1] or a mixture of *E*/*Z* isomers under thermal conditions. [2] Surprisingly, the hydrohalogenation of SF_5-alkynes is so far limited to a single example of hydrofluorination under gold-catalyzed conditions giving the *Z*-fluoroolefin in low yield.[3] Recently, our group proved that SF_5-alkynes are highly reactive toward the addition of N-, O-, and S-nucleophiles yielding in all cases a single regio- and stereoisomer. [4] We then wondered if the SF_5-alkynes could react both as electrophiles or nucleophiles depending on the reaction conditions, so we selected the hydrohalogenation as benchmark reactions. Herein is presented efficient strategies to perform hydrohalogenation with all the halogens (I, Br, Cl and F) and methods to access both the *E* and the *Z*-SF_5-haloalkenes following two different mechanisms, with relative configuration of all the stereoisomers confirmed by X-ray diffractions. Dihalogenation reactions with I_2, ICl and Br_2 are also discussed. Moreover, preliminary DFT calculations are presented to confirm the reaction mechanisms and to explain the high regio- and stereoselectivity.



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SO_2F_2-mediated *N*-polyfluoroalkylation of weakly nucleophilic nitrogen-containing compounds

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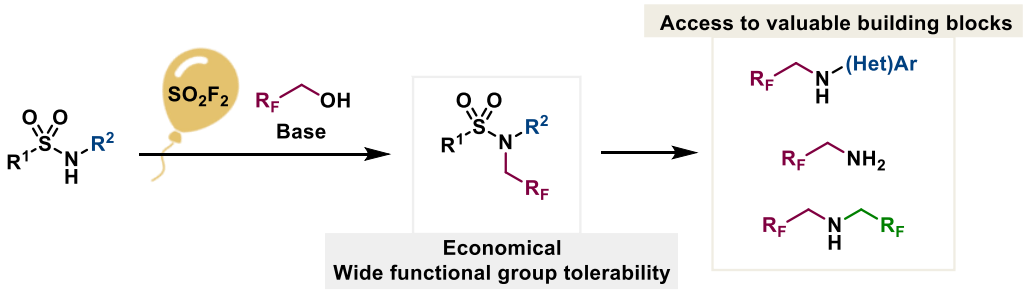
Fluorinated groups are ubiquitous in bioactive compounds as they can greatly improve their physico-chemical properties.[1] For example, one can tune the lipophilicity of a molecule by introducing appropriate fluorinated chains. The metabolic stability and the potency of active ingredients can also be significantly impacted by the introduction of fluorinated groups.

Our work is focused on *N*-polyfluoroalkylation methodologies to access key intermediates with agrochemical and pharmaceutical applications. Based on our expertise in sulfuryl fluoride (SO_2F_2) mediated activation of fluorinated alcohols,[2,3] we took advantage of this reactivity to achieve the *N*-polyfluoroalkylation of weakly nucleophilic nitrogen-containing compounds to access building blocks of high value in Life Sciences.[4,5]



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Dynamic kinetic resolution of racemic amines with stereogenic nitrogen centers by Pd-catalyzed transformations

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Within the last decades, much attention from the chemical community has been directed at the development of asymmetric reactions.[1] Having a tetrahedral configuration, nitrogen with three different substituents is a stereogenic center too. Such tertiary amines, however, usually do not show optical activity due to a low energy of the nitrogen inversion, which results in a rapid racemisation (Fig. 1). This inversion can be stopped by a conformational strain such as the one observed in Tröger's base, or by a quaternization of the nitrogen atom.

Figure 1. Nitrogen (or "umbrella") inversion vs. conformationally stable salt.

Chiral ammonium salts are widely used as phase-transfer catalysts and stereo-controlling cations[2]; they can be found in nature and some exhibit pharmacological activity[3]. Current strategies for the synthesis of such compounds are based on the resolution techniques of diastereoselective adducts or salts.[4] Recently we published the first example of the Pd-catalyzed enantioselective allylation of tertiary amines, where we could realize excellent conversions and significant stereoselectivities. Hence, our research is focused on the dynamic kinetic resolution of racemic amines with a stereogenic nitrogen centers via TM-catalyzed transformations.

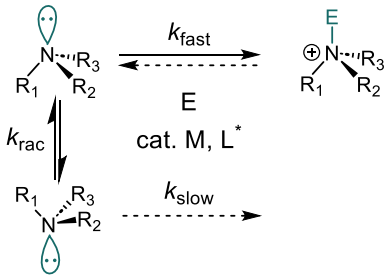

Figure 2. Dynamic kinetic resolution of tertiary amines by asymmetric allylation.

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Synthesis and biological evaluation of inhibitors of the lysine methyltransferase KMT9

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Epigenetic therapy is a promising approach to treat cancer due to the reversible nature of epigenetic modifications. Writer enzymes, such as histone lysine methyltransferases (KMTs) catalyze the methylation of the amino group of lysine on histone tails. A number of KMTs were shown to be overexpressed in different tumor cells and to have a role in cancer development. Targeting these enzymes, several candidates of small-molecule inhibitors have already reached the clinical phase. In addition, the first KMT drug, Tazemetostat was approved by the FDA in 2020.

The Schüle group identified KMT9 as an active histone lysine methyltransferase that monomethylates histone H4 on lysine 12 (H4K12me)[1]. Upon knockdown of KMT9, prostate cancer cells and colon cancer cells[2] were going into apoptosis, furthermore lung cancer cells[3] were going into non-apoptotic cell death. However, healthy cells remained unaffected, making KMT9 a promising drug target. Therefore, we set up a structure-based inhibitor program to target KMT9 in collaboration with the Schüle group. Through hit-to-lead optimization, we successfully synthesized highly potent (low nM) KMT9 inhibitors with great selectivity over 41 other methyltransferases *in vitro*. These synthesized cofactor analogues are bisubstrate inhibitors of KMT9, because they occupy both the cofactor binding pocket and the substrate channel of the enzyme.

Antiproliferative effect of the optimized lead molecules was also detected in prostate cancer cells. However, the performance of the compounds was not satisfactory in order to go to the next stage of the preclinical development. Therefore, further SAR studies and optimization of the physicochemical properties of the molecules are currently ongoing to gain optimal activity in cells.

This work was supported by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) through CRC 992 (Project ID 192904750) and RTG1976 (Project ID 2060043005)

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Oxidative Cyclization of Carbon-Bridged BODIPYs

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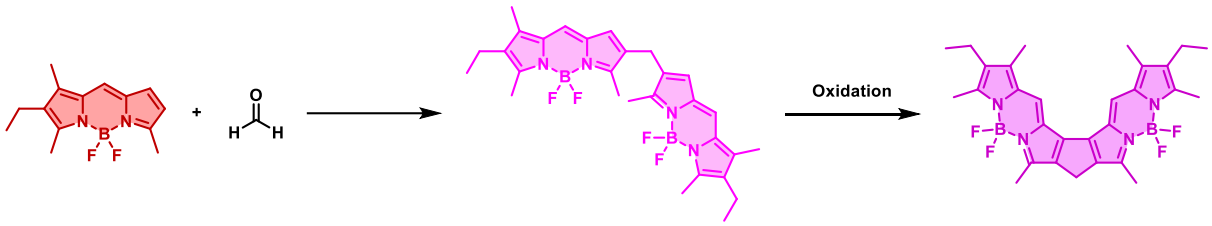
Boron dipyrromethene (BODIPY) structures have been an interest of research for many decades now, because they have promising properties as chromophores. Some of those properties include absorption and emission in the red or near-infrared region,[1] high fluorescence quantum yields[2] and the possibility of modifications[3] and functionalization of the core structure.[4] This renders BODIPYs an object of interest for interdisciplinary sciences, e.g. as fluorescent dyes, biological labels or to be used in OLEDs.[1, 3]

In this work the bridging of two BODIPY-subunits by a single carbon unit followed by an oxidative cyclization was investigated. In contrast to previous studies of carbon-bridged BODIPYs, this work introduces a different synthetic approach starting with the fully formed BODIPY unit. Additionally, the formed five-membered ring connects the BODIPYs in the β and β' position. This forces the molecule into a helical structure once three or more BODIPY units are connected.

Scheme 1. Synthesis of β/β' fused BODIPYs by oxidative cyclization.



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Copper-Assisted Halo-Chalcogenation of Arynes

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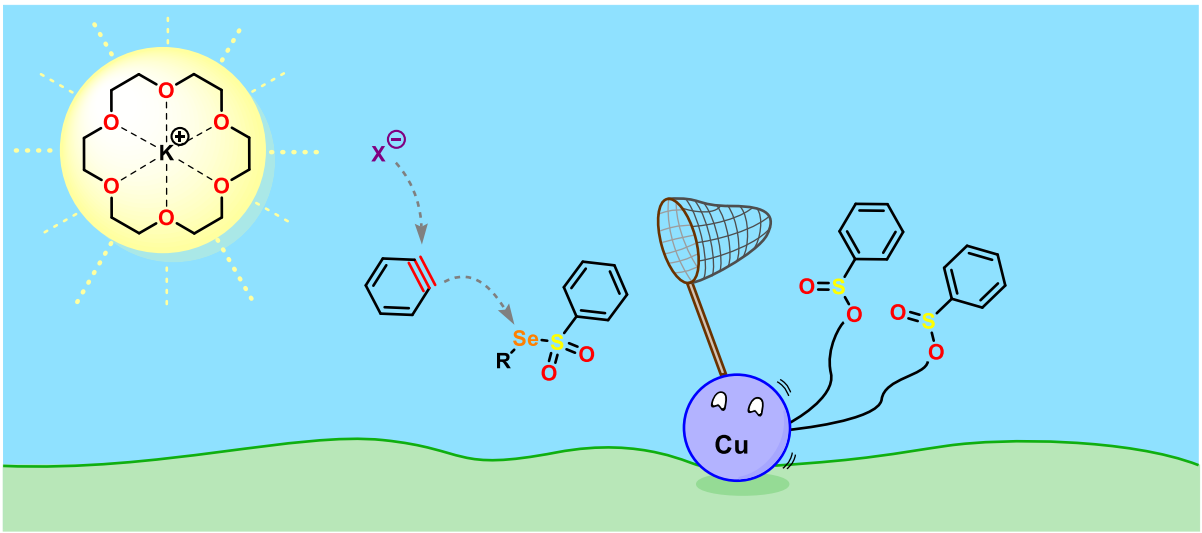
The Kobayashi-aryne precursor has proven valuable for the 1,2-functionalization of arynes, granting access to a multitude of diversely substituted aromatic systems.[1] The addition of (transition)metals can play a key role in these transformations, extending the scope of possible addition partners for the aryne.[2] Copper has been used in the past, mainly for the addition of alkynes[1,2] and also in combination with chalcogen electrophiles.[3] Herein, we report a transformation where sub-stoichiometric amounts of copper-(II) salts enable the halo-chalcogenation of arynes, using potassium halides and seleno- or thiosulfonates as halogen- and electrophilic chalcogen sources respectively. The copper appears to act as a sulfinate scavenger, preventing competition amongst the present nucleophiles and thus enabling a smooth reaction.

Scheme 1. Copper-(II) salts are capable of scavenging sulfinate ions, preventing side reactions.



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Silica Based Heterogeneous Ru-complex Photocatalyst for organic reactions

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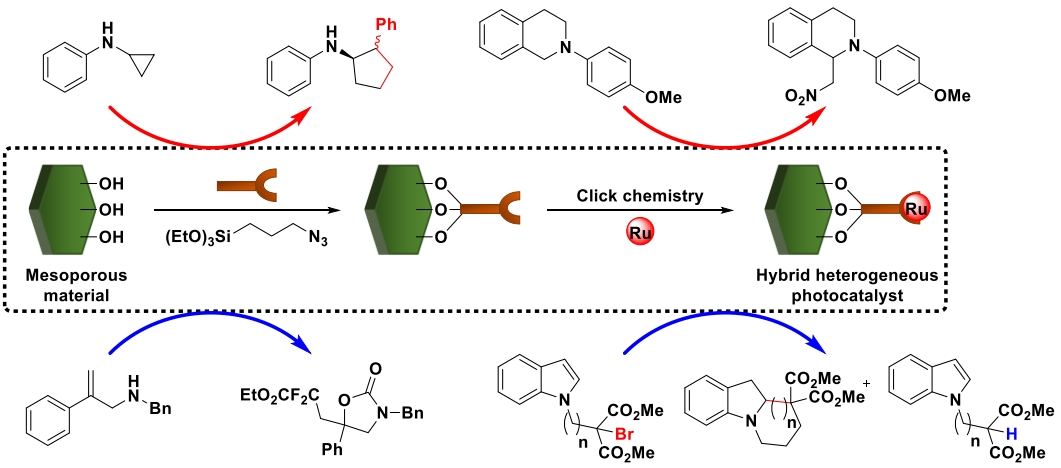
Sustainable and environmentally friendly processes are called chemists to move towards new methods according to green chemistry principles[1] including energy reduction, atom economy, catalysis, less hazardous chemical waste, selective and efficient synthesis. A transition into sustainable processes is required, a photocatalysis branch stands out, the redox photocatalysis. This concept offers reduced environmental impact of chemical processes including energy consumption by lowering temperature and pressure and using a sustainable source of energy such as sunlight[2] and waste production by limiting the use of organic solvents and improving selectivity[3]. Heterogenization of the photocatalyst appears to be a valuable solution to reach sustainable processes. Rapid and efficient synthesis of new supported photocatalyst is still a remaining challenge and the choice of the support material is crucial. Thanks to their stability and versatility, silica-based porous material seems to be an interesting alternative to metal nanoparticles and polymers. The present project aims at preparing a new generation hybrid inorganic/organic photocatalysts and evaluate their performances in challenging organic transformations[4][5].



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Using Aminopalladation Cascades to Access BODIPYs

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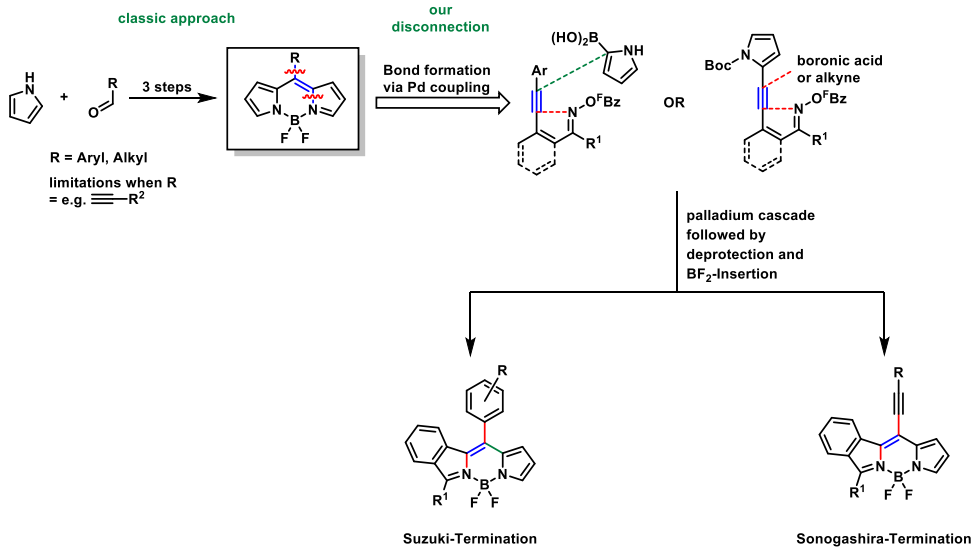
BODIPYs have found wide-ranging applications in interdisciplinary research, e.g. as fluorescence tags, fluorescence imaging, photodynamic therapy, photosensitizers and -catalyst and -cages.[1] While a vast pool of post-functionalization methods has been developed to access the desired compounds, the traditional synthetic route limits the range of groups that can be installed in the *meso*-position of BODIPYs to those which are available as carbonyl precursors. For others, like alkynes, lengthy synthesis routes need to be taken.[2]

Here, we present an alternative retrosynthetic approach which led us via a C-N disconnection to an aminopalladation[3] cascade that gives dipyrromethenes which were then transformed to BODIPYs. Hereby, the residue in the *meso*-position is introduced through the termination step, either with a boronic acid by a Suzuki-Miyaura cross-coupling or with a terminal alkyne through a Sonogashira cross-coupling. In the case of the Suzuki-Miyaura cross-coupling termination it was also possible to install the aryl group already at the triple bond of the precursor and deliver the pyrrole moiety as the boronic acid. We also showed that this method allowed access to hitherto unknown nitrogen-enriched BODIPYs.

Scheme 1. Accessing BODIPYs via a C-N Disconnection Approach by Employing an Aminopalladation Cascade



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Insertion of Aldehydes into Cyclopropanones: An Access to Difunctionalized γ-Butyrolactones

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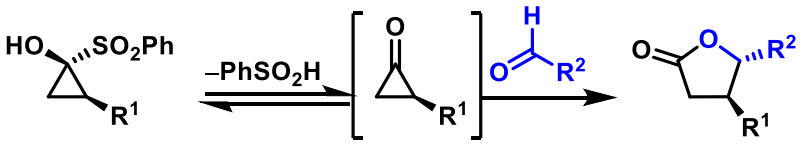
Cyclopropanones, the smallest congeners of cyclic ketones, have been found to be highly reactive intermediates in organic synthesis which is mostly attributed to high ring strain.[1] Although their synthesis and handling have some limitations, cyclopropanone equivalents such as hemiacetals can be readily accessed and used as precursors for the *in situ* formation of cyclopropanones.[2] However, harsh reaction conditions are usually required for the generation of cyclopropanones from their hemiacetals that mostly interfere with the reactivity of cyclopropanones themselves. This major limitation can be circumvented using 1-sulfonylcyclopropanols that allow *in situ* access to cyclopropanones under mild reaction conditions by *α*-elimination of sulfinates.[3] In addition, strategies were developed for the synthesis of enantioenriched 1-sulfonylcyclopropanols that react in an asymmetric fashion once degraded to the corresponding cyclopropanones.[4]



Scheme 1: Insertion of aldehydes in enantioenriched cyclopropanones derived from 1-sulfonylcyclopropanols.

While cyclopropanones show high tendency for ring expansion to cyclobutanones via well studied [1,2]-shifts, the more challenging [1,3]-shifts to five-membered ring systems are only moderately examined.[5] We reasoned that cyclopropanones, due to their high strain, should even be electrophilic enough to be nucleophilically attacked by aldehydes via their carbonyl oxygen atom, setting the stage for [1,3]-ring expansion to *γ*-butyrolactones in a single reaction step. This led our attention to the stereoselective synthesis of difunctionalized *γ*-butyrolactones by the insertion of aldehydes into enantioenriched cyclopropanones derived from 1-sulfonylcyclopropanols (Scheme 1).

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Chemical probes to study the role of the lysine demethylase LSD1 in Leishmania infection

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Epigenetic mechanisms are involved in numerous diseases, including cancer development and immunological microbial infections. In order to promote their own survival, many viral, bacterial, and eukaryotic pathogens that infect mammalian cells have developed co-evolved ways to alter the expression profile of their host cells. The epigenetic mechanisms causing such host cell subversion are still poorly understood, despite the grave repercussions for human health. Parasites of the genus *Leishmania* subverts the function of the macrophage lysine specific demethylase 1 (LSD1) to establish permissive conditions for intracellular parasite survival[1]. LSD1 (aka KDM1A) is a FAD-dependent amine oxidase that removes methyl groups from mono- and demethylated lysine 4 and 9 residues of histone H3 (H3K9/4me1me2)[2]. It was shown that a leishmania infection causes histone H3 demethylation at the activating H3K4 and repressive H3K9 marks which is linked with the suppression of inflammatory gene expression[3]. By developing chemical inhibitors of LSD1, the pathogenic mechanism of *Leishmania* could be reversed and these could then be recognized and destroyed by macrophages without, however, destroying the macrophage itself.

Therefore, chemical degraders (proteolysis targeting chimeras – PROTACs) were synthesized.

PROTACs are heterobifunctional molecules that simultaneously bind a target protein and an E3 ubiquitin ligase. Through such a ternary complex, the target protein and ligase are brought into close distance by the PROTAC. This allows multiple ubiquitinylation of the target protein by the E3 ligase. Modification with polyubiquitin is recognized by the proteasome and leads to proteasomal degradation.

Additionally for cellular target-engagement analysis, biotinylated LSD1 inhibitors scaffold, based on tranylcypromine, was designed, and synthesized.

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Synthesis of all Inositol Pyrophosphate isomers (PP-InsP$_5$'s) starting from Inositol Phosphates (InsP)

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Inositol pyrophosphates (PP-InsP$_5$) are a class of highly phosphorylated molecules, acting as second messengers[1]. Depending on the pyrophosphate position, different roles have been described. While the biological functions of some isomers (*e.g.* 5-PP-InsP$_5$) are well studied (*e.g.* phosphate homeostasis), new fields are still discovered (*e.g.* regulation of glycolysis)[2]. Isomers (4/6-PP-InsP$_5$ and 2-PP-InsP$_5$) with yet unknown functions were identified in biological samples recently by capillary electrophoresis mass-spectrometry (CE-MS)[3]. To unravel their roles, chemical synthesis is still crucial. Even the most recent procedures rely on sophisticated multi-step procedures, *e.g.* leading to 5-PP-InsP$_5$ in an overall yield of 2% starting from *myo*-inositol [4]. Here we report a general one-pot-protocol to access all PP-InsP$_5$-enantiomers in up to 44% yield, starting from the respective InsP$_1$ × tetrabutylammonium (TBA) salts. Selective phosphorylation of the unprotected phosphate of InsP$_1$ was followed by global phosphorylation of the five residual unprotected alcohols. Subsequent *in-situ* de-protection of all phosphates led to unmodified PP-InsP$_5$. All enantiomers were accessible using this procedure. Enzymatic access to specific InP$_1$ derivatives renders this methodology an interesting alternative to established procedures[5,6].

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Synthesis of Fluorescent Inorganic Polyphosphate to Study Lysine Polyphosphorylation

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Inorganic polyphosphate (polyP), an ubiquitous molecule composed of multiple orthophosphates linked by phosphoanhydride bonds, is no longer regarded as a "forgotten polymer".[1] In recent years, the synthesis of defined polyPs was established[2] and many different biological functions of polyP have been discovered.[3] One of them is the covalent attachment to lysine residues, a new nonenzymatic post-translational modification. It is known that lysine polyphosphorylation occurs in polyacidic serine and lysine (PASK) rich clusters, however, the mechanism is not yet understood. The state-of-the-art method for analyzing lysine polyphosphorylation is a band shift-up on NuPAGE, which requires long polyP-chains to be detectable.[4] Here we show the synthesis of fluorescent and FRET labelled short-chain inorganic polyphosphate to study lysine polyphosphorlyation in model proteins. A bidirectional approach, which uses the triphosphorylation reagent cyclic pyrophosphoryl-phosphoramidite (*c*-PyPA) **1**, enables fast access to symmetrical-modified polyPs, while the monodirectional approach allows to install different modifications at the termini (Figure 1). Synthetic fluorescent labelled polyP with a defined chain length facilitates analysis by mass spectrometry and the fluorescence makes the detection on NuPAGE independent on the length of the polyP. Furthermore, FRET labelled polyP will help to monitor lysine polyphosphorylation in living cells. The synthesized modified polyPs will hopefully enable to understand how polyP modifies target proteins non-enzymatically.

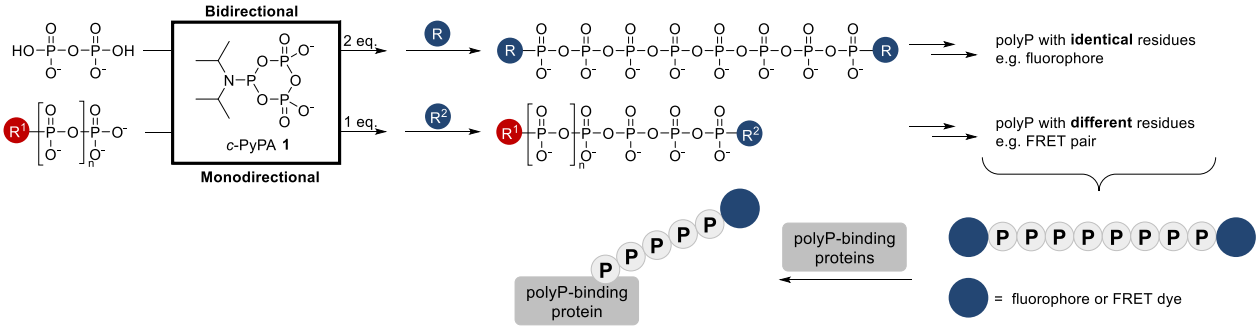

Figure 1: *Overview of the mono- and bidirectional approach using c-PyPA **1** to obtain polyP chains of defined length with modified ends and schematic presentation of lysine polyphosphorylation.*

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Visible-Light Induced Metal-Free Intramolecular Reductive Cyclisations of Ketones with Alkynes and Allenes[1]

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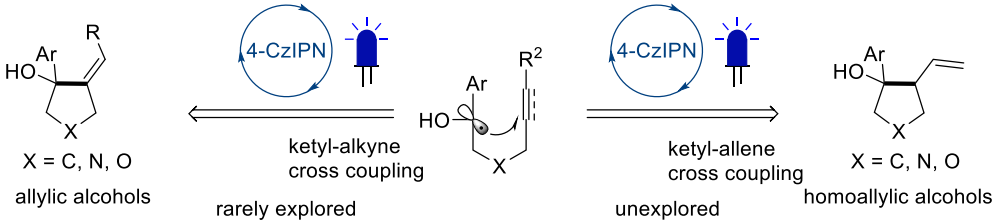

Saturated five-membered rings (e.g. pyrrolidine, tetrahydro-furan and cyclopentane) bearing tertiary alcohols are common structural motifs in various biologically active compounds.[2] Consequentially, numerous methods have been established for the preparation thereof.[3] Among them, formation of the tertiary alcohol via direct cross coupling between the corresponding carbonyl and a π-system is highly desirable.[4] Herein, we report a visible-light-induced, intramolecular, reductive cyclisation of ketones with an unsaturated hydrocarbon moiety. In contrast to conventional protocols requiring resource precious or hazardous metal sources, this method enables facile access to ketyl radicals under metal-free and mild reaction conditions. By polarity-reversed, ketyl radical hydroalkoxylation of alkynes and allenes, a variety of five-membered (hetero-)cyclic products were generated in good yields with good to excellent stereoselectivities. The embedded homoallylic tertiary alcohol could be transformed into other useful functionalities, highlighting the synthetic utility of this reaction. This efficient and sustainable ketyl-alkynes/allenes cross coupling also features broad functional group tolerance and scalability.

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Nitrogen-Bridged BODIPYs

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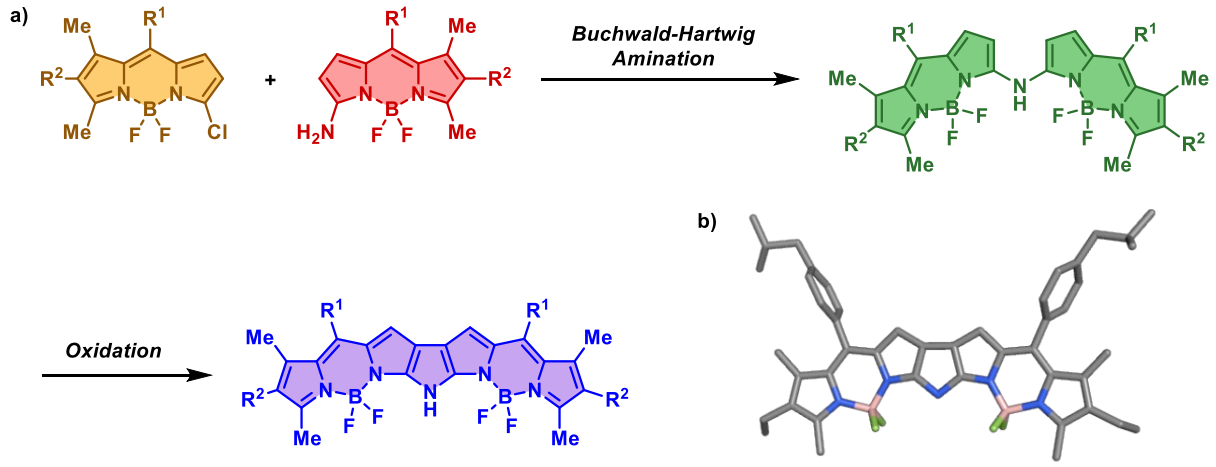
Various types of oligo-BODIPYs have already been shown to exhibit useful properties such as high quantum yields and outstanding attenuation coefficients.[1] Whereas cyclic oligomers have been reported recently, we herein present linear *N*-bridged BODIPYs.[2] The key step of their synthesis is a Buchwald-Hartwig cross-coupling reaction of the respective monomers to provide both symmetric and asymmetric examples. With these *N*-linked BODIPY dimers in hand, we were also able to enlarge the π-system by subsequent oxidation, leading to the formation of a novel tripyrrolic subunit (cf. Scheme 1).



Scheme 1: a) Synthetic route towards nitrogen-bridged BODIPYs; b) Crystal structure of pyrrole-fused BODIPY dimer.

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Development of Mechanochemical reaction conditions for Buchwald-Hartwig amination reaction

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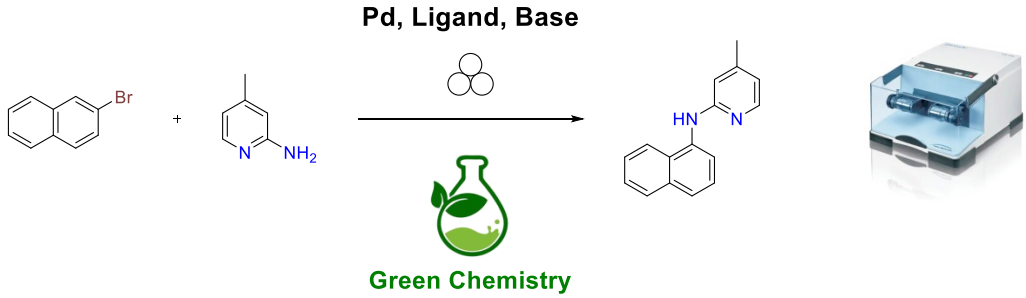
Solvents are acknowledged to hold significant environmental impact, accounting up to 90% of the mass utilization in a given chemical reaction. As one of the largest users of organic solvents, the pharmaceutic industry, have made it a priority these last 20 years to make their production greener by the minimization, replacement, recycling or removal of said solvents[1].
In medicinal chemistry, transition metal catalysed coupling reactions play an important role by facilitating diverse bond formations[2]; such as the formation of an aromatic carbon-nitrogen bond through the Buchwald-Hartwig amination reaction[3]. However effective, these reactions necessitate the use of organic solvents, making them costly to the environment, and making the scale-up pharmaceutical manufacturing disadvantageous.
Mechanochemistry[4], is the discipline based on the use of mechanical energy generated through milling or grinding for chemical transformation. It has experienced a significant comeback thanks to its applicability to green chemistry[5]. Through avoiding the use of bulk solvents, solvent-free mechanochemical reactions provide safer reaction conditions for the environment and profitable conditions for industrial applications.
Although the use of various metal-catalysed reactions under mechanochemical reaction conditions have been investigated[6], few publications can be found for Buchwald-Hartwig aminations [7–9].
In our lab, we developed alternative conditions for the C-N bond formation using $[Pd(allyl)Cl]_2$ and Buchwald monophosphine ligands.



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Assigning the Absolute Configuration of Inositol Poly- and Pyrophosphates by NMR Using a Single Chiral Solvating Agent

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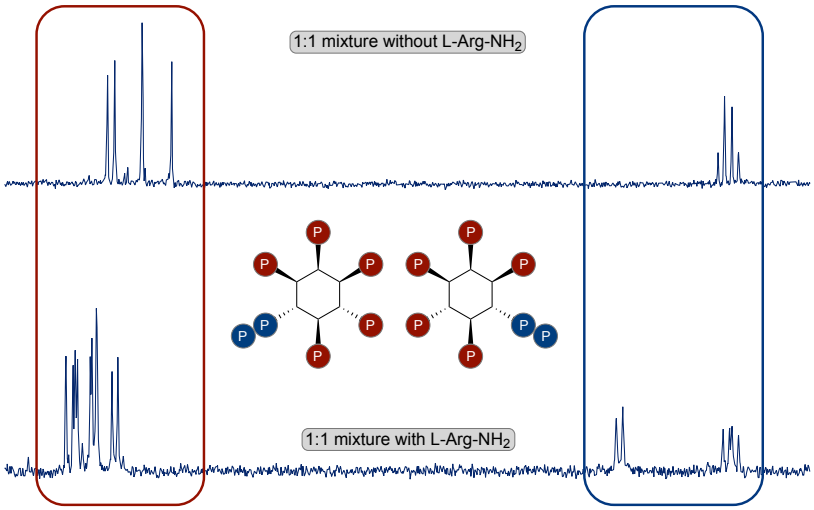

Inositol phosphates constitute a family of highly charged messenger molecules that play diverse roles in cellular processes. The various phosphorylation patterns they exhibit give rise to a vast array of different compounds. To fully comprehend the biological interconnections a precise molecular identification of each compound is crucial. Since the *myo*-inositol scaffold possesses an internal mirror plane, enantiomeric pairs can be formed. Most commonly employed methods for analyzing InsPs have been geared towards resolving regioisomers, but they have not been capable of resolving enantiomers. In this study, we present a general approach for enantiomer assignment using NMR measurements. To achieve this goal, we used ^{31}P-NMR in the presence of L-arginine amide as a chiral solvating agent, which enables differentiation of enantiomers.[1] Using chemically synthesized standard compounds allows for an unambiguous assignment of the enantiomers. This method was applied to highly phosphorylated inositol pyrophosphates, as well as to lower phosphorylated inositol phosphates and bisphosphonate analogs.[2] By isolating naturally occurring compounds from cells, our method will facilitate the assignment of biologically relevant isomers.

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[2] Unpublished Data

TBAF-Promoted Carbanion-Mediated Sulfonamide Cyclization of CF_3-substituted *N*-allenamides: an Access to Fluorinated γ-Sultams

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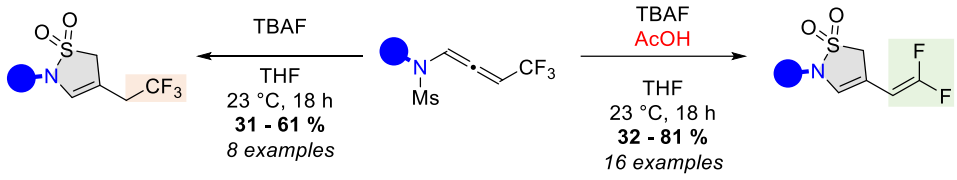
Since the discovery of sulfonamide antibacterials,[1] sulfonamides have played a key role in medicinal chemistry. The cyclic counterparts of sulfonamide compounds (sultams) display enhanced biological activities compared to their acyclic congeners.[2] Although not found in nature, these amide surrogates are considered privileged motifs that have found diverse applications in drug discovery. In view of our previous results on CF_3-substituted *N*-allenamides[3], we anticipated that deprotonation at the α-position of the sulfonyl moiety of *N*-sulfonyl-allenamides might initiate an anionic cyclization to produce cyclic sulfonamides.

N-mesyl based trifluoromethyl-*N*-allenamides were transformed into γ-sultams upon treatment with tetra-*n*-butylammonium fluoride (TBAF). Cyclic sulfonamides bearing an ene-*gem*-difluorinated tether could be obtained by addition of acetic acid to the ammonium salt, whereas TBAF alone provided the corresponding trifluorinated ethyl sultams. A combined experimental and computationnal mechanistic study suggested that this transformation involves a 5-*endo-dig* cyclization on the ene-ynamide generated *in situ*.[4]



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Modular Synthesis of 1,2-Amino Alcohols and 1,2-Diamines Enabled by Photoredox/Palladium Dual Catalysis

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The construction of diverse alkylamines is of importance to drug discovery programmes and nature products synthesis. Herein, we report the efficient photoredox/palladium dual catalytic construction of protected 1,2-amino alcohols and 1,2-diamines *via* enantioselective hydroaminoalkylation of heteroatom-substituted allenes or 1,3-dienes with α-silyl amines. This protocol is characterized by its mild conditions, excellent regio-, enantioselectivities, and wide substrates scope, including aliphatic amines or *N*-heterocyclic substrates as a highlight. Computational and experimental mechanistic studies provided insights into the reaction mechanism and observed regio-, and enantioselectivity.[1]

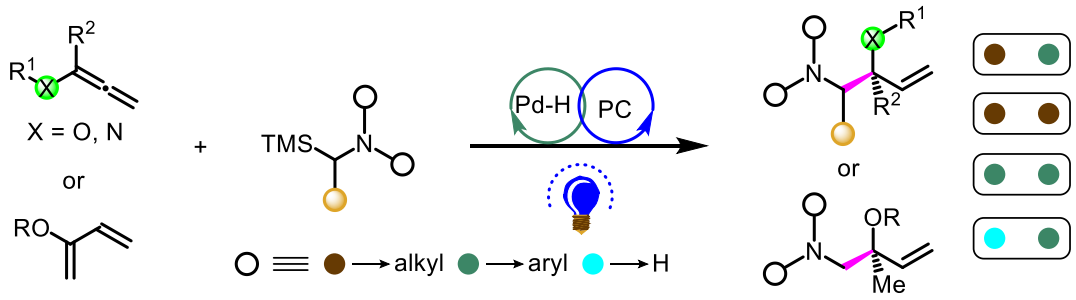

Figure 1. Dual Catalyzed Hydroaminoalkylation of Allenes and 1,3-Dienes

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Synthesis and photochemical properties of fluorescent metabolites generated from fluorinated benzoylmenadiones in living cells

40

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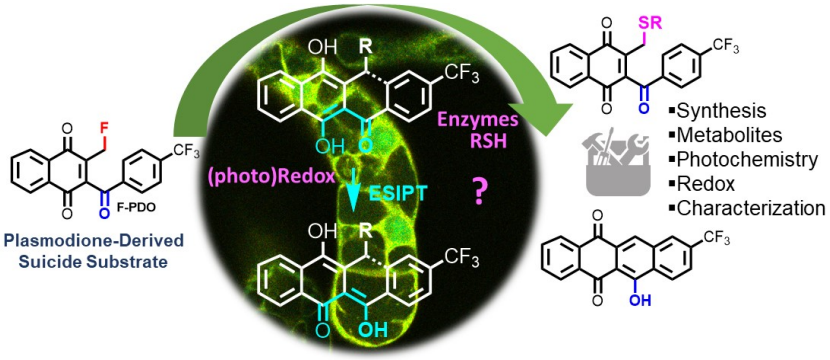
Plasmodione (**PD**) is an early antimalarial lead 3-benzylmenadione displaying valuable redox-activity, which has been demonstrated to act through the generation of a key metabolite, the plasmodione oxide (**PDO**).[1,2] Introduction of a fluorine atom on the 2-methyl group (**F-PD** and **F-PDO**) was shown to markedly increase the oxidant character of the final 2-fluoromethyl-1,4-naphthoquinone derivatives. Interestingly, **F-PDO** generates a bright yellow-green emission in tobacco BY-2 cells, suggesting the formation of fluorescent thiol adducts. A fruitful set of analytical methods has been therefore used to highlight the products resulting from UV-photoreduction in the absence or presence of nucleophiles. Without nucleophile, photoreduction of **F-PDO** generates a highly reactive *ortho*-quinone methide (*o*-QM) capable of leading to the formation of a homodimer. With thiol nucleophiles such as β-mercaptoethanol used as a model, *o*-QMs are continuously regenerated in sequential photoredox reactions generating mono- or disulfanylated products as well as various unreported sulfanyl products. Besides, these photoreduced adducts derived from **F-PDO** are characterized by a bright yellowish emission due to an ESIPT process between the dihydronaphthoquinone and the benzoyl side chain. In order to evidence the possibility of an intramolecular coupling of the *o*-QM intermediate, a synthetic route to two anthrone representatives is described. Tautomerization of the targeted anthrones occurs and affords highly fluorescent and stable hydroxy-anthraquinones that might explain as well the intense visible fluorescence emission observed in tobacco BY-2 cells, but never observed during the photochemical model reactions performed in this study.



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Towards Molecular Textiles: Synthesis and Characterization of Molecular Patches

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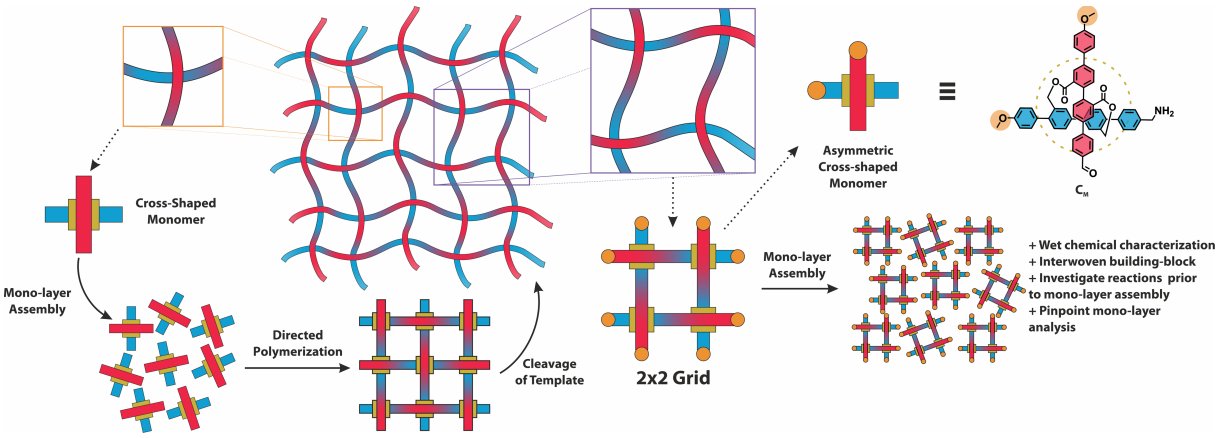
Textiles, material consisting of 2D interwoven yarns and threads, are an exceptional class of materials due to their flexibility, stability and shape adaptability.[1] These extraordinary properties generate a desire to mimic these materials on molecular scale. In the last decade several routes have been explored to interweave 1D linear polymers in order to obtain a molecular 2D textile.[2,3] Recently, we introduced our own innovative approach, where we explore the possibilities of assembling such a highly ordered 2D material on the air-water interface (Fig 1. left)[4]. Here, a cross-shaped monomer is used to ensure the linking via up-down-up-down character to obtain a biaxial woven mono-layer. However, due to the challenging characterization of monolayer materials in terms of chemical transformation and topological features we designed an approach for the synthesis of a molecular patch (Fig. 1, right). The formation of this finite textile cut-out would allow us to investigate the structural properties of a semi interwoven structure, pinpoint mono-layer characterization as XPS shifts and AFM topology, while on the other hand investigate the after mono-layer reactions we want to adopt.

For the formation of our designed 2x2 grid we designed monomer **C_M**, which is an asymmetrical analogue of our previous reported monomer.[4] The central part, two-biphenyls bridged over two esters, gives rise to the cross-shape, while the amine and aldehyde functionality allows for the cyclic oligomerization. The methoxy groups cap the remaining ends of the molecule to ensure the assembly of a finite structure that would be characterizable by conventional techniques as NMR, IR etc.



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Thiophene Containing Macrocycles with Multiple Conductance Pathways for the Investigation in Single Molecule Break Junctions

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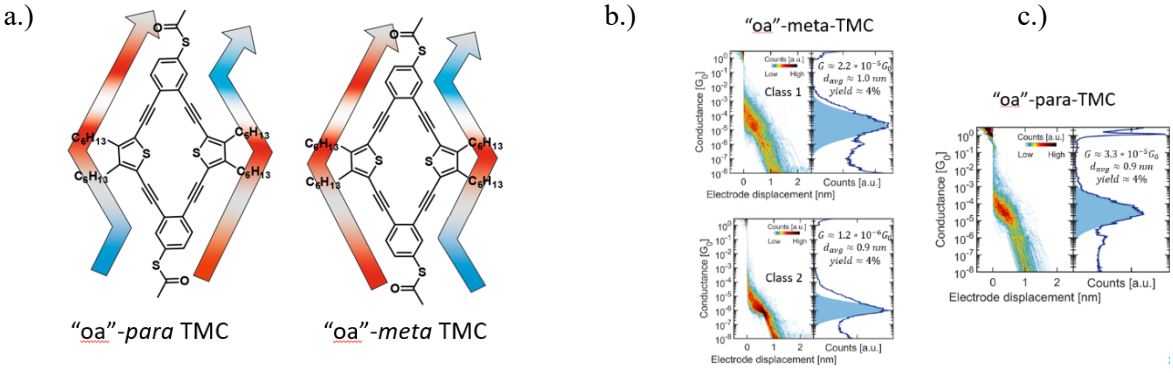
Molecular electronics including the measurement of molecules in single molecule break junctions (SMBJ) is an expanding field of research that leads to an increasing number of new findings[1][2][3]. Recently, the idea of a molecular wire that splits up into two pathways that are equivalent in length sparked our interest since we are interested in interference and phase shift phenomena. For the design of such a system, molecular orbital theory[4], the length of the molecular wire[5], substitutions on connecting units[6] and the kind of anchoring groups[7] must be taken into consideration as these factors all impact the conductance intensity. Thiophene containing macrocycles **1** and **2** (figure 1 a.) with acetylated thiol anchoring groups were therefore synthesized. These planar, strained, conjugated systems are accessible *via* a series of Sonogashira cross couplings and acetylene deprotection reactions. Following the established substitution rules[5] for good (*para* and 2,5-substituted in thiophene, figure 1 in red) and poorly conducting (*meta*, figure 1 in blue) electron transport predictions about conductance of the overall molecule can be made by adding up the sequential substitution patterns of the connecting corner units. In figure 1 the qualitative conductance through the different pathways is depicted. First measurements of both macrocycles **1** and **2** have been performed using the Mechanically Controlled Break-Junction technique. Interestingly, conductance measurements on the "oa"-*meta* TMC show two molecular features, possibly indicating two different pathways for conductance, whilst the "oa"-*para* TMC showed only one in comparison as can be seen in Fig. 1b), c). Further investigations systems are ongoing.



Well conducting para-substitutions or 2,5-substitution on thiophene. Blue: poorly conducting meta-substitutions. b.) Conductance vs. distance histograms accompanied by their respective conductance histograms of the molecular features found for the "oa"-meta TMC c.) same as for b) but for the "oa"-para TMC.

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Playing around the 3-benzylmenadione core through oxetane and heteroaromatic introduction

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In medicinal chemistry, oxetanes have received enormous interest as replacement groups for gem-dimethyl and carbonyl groups with improved physicochemical properties.[1] Introduction of oxetane rings and heteroaromatic cycles can indeed improve both aqueous solubility and metabolic resistance allowing rapid drug improvement through optimized PK properties. Our team has discovered the 3-benzylmenadione skeleton (bMD) as a promising redox-active pharmacophore (Fig. 1).[2] The substituents at the menadione (west part) govern the redox potential of the 1,4-napthoquinone core, while the substituents at the benzyl chain (east part) contribute both at the metabolic fate, fine tuning of the redox behavior and key interactions with numerous biological targets of final molecules.[3,4] In order to prepare more focused libraries of 3-bMDs, synthetic routes were developed to introduce 3-(oxetan-3-yloxy) groups and/or heteroaromatics at the benzyl chain. The benzylation of various menadiones was performed by using the Kochi-Anderson reaction,[2a,2c]or a bioinspired photoredox process[2f] developed in the team. We recently established an effective Suzuki coupling to produce (hetero)aromatic analogues of 3-bMDs. Present chemistry is now aimed at replacing the ether from *O*-oxetanyls by *N*-oxetanyl and *C*-oxetanyl groups. Finally, the library will be of general value in Medicinal Chemistry to evaluate the potential of oxetanes and heteroaromatics as cycles providing opportunities for rapid drug improvement through optimized PK properties.

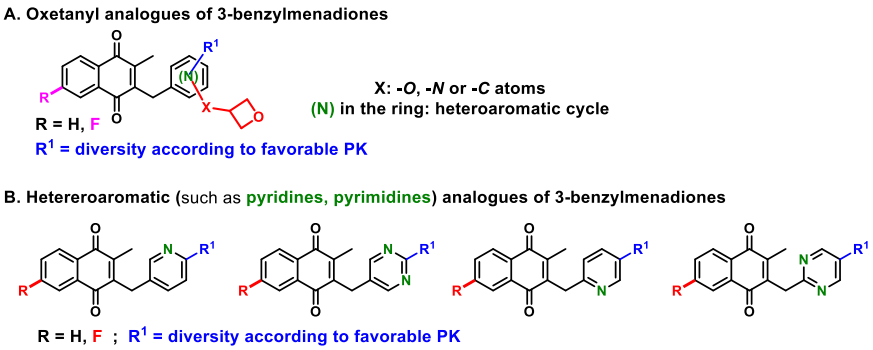

Figure 1. General structures of the oxetanyl (**A**) and heteroaromatic (**B**) analogues of 3-benzylmenadiones prepared in the medicinal chemistry project.

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Design and Synthesis of Original N,S-containing Scaffolds to Access Complex Heterocycles

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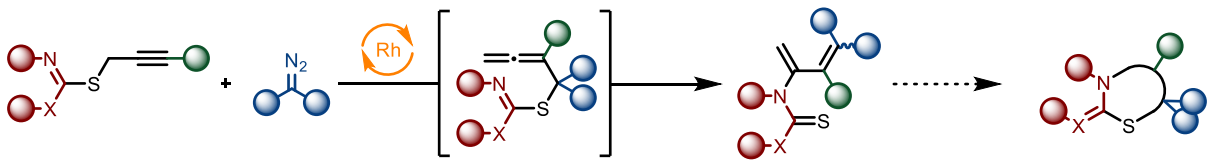
A large majority of bioactive molecules and pharmaceuticals contain at least one heterocycle in their structure.[1] *N,S*-heterocycles are represented in several drugs (i.e. Actos, Claforan, Seroquel),[2] however it is still need to extent the structural diversity of this class of compounds for therapeutic applications.

In this context, our group focus on the development of atom and step economic divergent synthetic strategies,[3] mainly based on metal-catalyzed domino reactions, to access new heterocyclic scaffolds bearing nitrogen and sulfur atoms with large molecular diversity.

Here we report a new domino sequence in which several carbon-carbon, carbon-nitrogen, and carbon-sulfur bonds are formed, leading to complex molecules from simple substrates. Starting from propargyl thioimidates and diazos compounds, the sequence involves a Rh-catalyzed Doyle-Kirmse reaction, followed by an unprecedent type of thio-Claisen rearrangement, and leads to original highly functionalized dienes. This methodology with a high atom economy offers the opportunity to vary more than three positions on the diene structure, giving access to a large molecular diversity. The reactivities of these dienes are under study to synthesize new *N,S*-heterocycles.



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Development of near-infrared photocatalytic systems based on cyanine dyes and applications in organic synthesis

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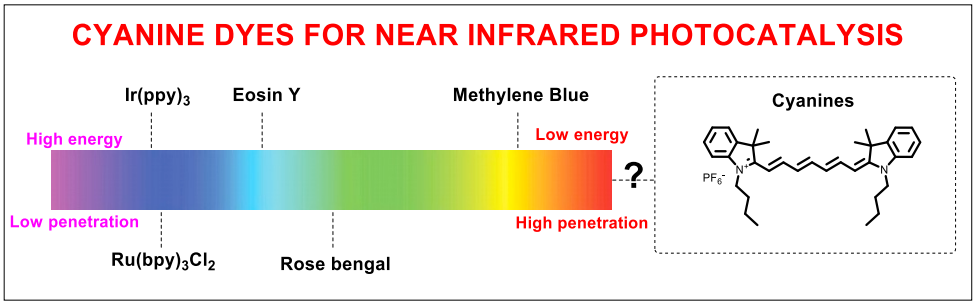
Last decade, photoredox catalysis has been widely investigated [1-3] taking advantage of the mild reaction conditions. The light is used to promote a photocatalyst (PCat) in its excited state (PCat*), which can undergo single electron transfer (SET), and/or energy transfer (EnT) to a substrate. These processes were used under UV or visible light irradiation. Unfortunately, these windows of irradiation lead to several issues: background reactions [4], a low penetration of light in reaction media [5], the opacity of biological tissues toward visible light render its use impossible for some biological or medicinal applications [6]. To circumvent theses drawbacks, near infrared light is promising [7]. In this way, our team has developed photocatalytic systems based on organic dyes [8], that can trigger organic reactions in the near infrared range. To do so, cyanine derivatives have been selected. After a first generation of photocatalytic systems based on cyanine dyes, a second one was developed to improve reaction kinetics and their redox properties. Finally, good yields with better kinetics have been obtained on various transformations using these cyanines dyes as photocatalysts. Whether in oxidation transformation like aza Henry reaction; in reduction transformations also like trifluoromethylation reaction; even in photosensitization of triplet oxygen.



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Formylation as key step for new tandem reactions – Towards BODIPY dyes

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4,4-Difluoro-4-bora-3a,4a-diaza-s-indacene (BODIPY) dyes experience an increasing demand due to their excellent photo- and thermo-, as well as their chemical stability. Therefore, they are utilized in a number of future-oriented applications such as organic lasers, OLEDs, fluorescent sensors, photosensitizers, solar cells etc.[1]
Conventional BODIPY syntheses show low overall yields. Therefore, a one-pot reaction to BODIPY dyes was developed involving literature known hydroformylation[2] or formylation[3] reaction conditions and subsequent substitution reaction with pyrrole nucleophiles under organo-catalytic conditions to obtain dipyrromethanes which are then straight-forward transformed to BODIPYs.

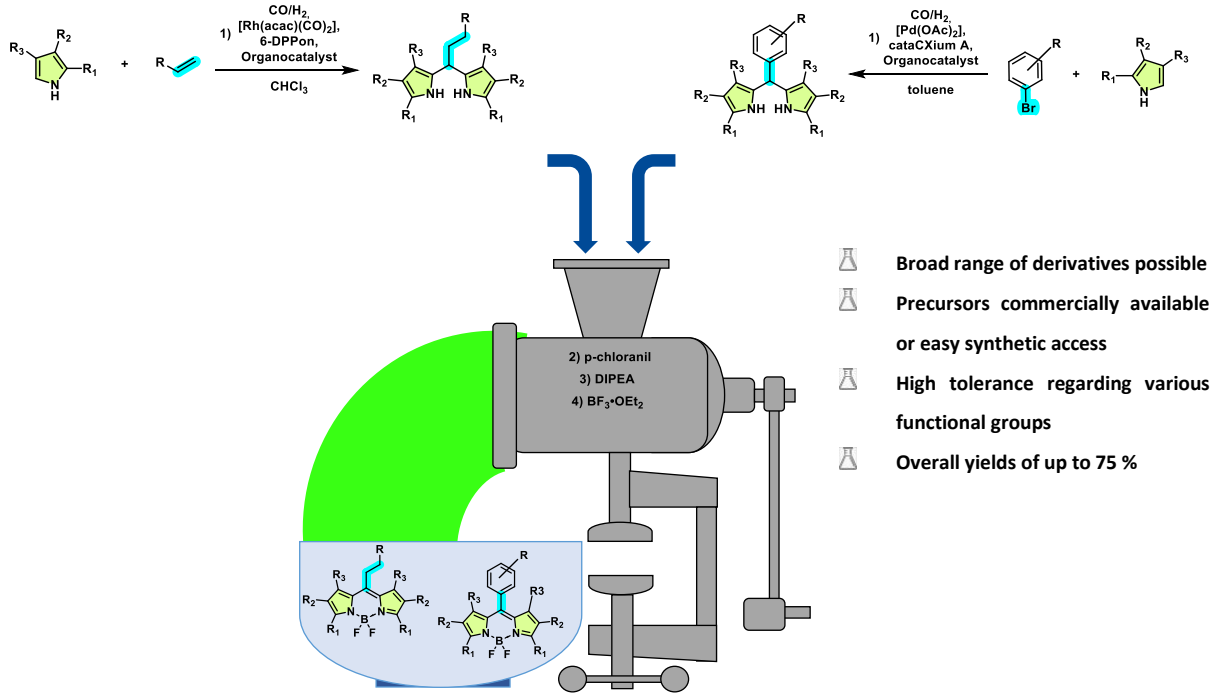

Figure 1: One pot synthesis scheme of BODIPY dyes from available precursors.

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Defined patches of interwoven materials

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The simplest way of producing a textile is by orthogonally interlacing two yarns. The resulting material possesses stability, flexibility, and shape adaptability due to its interwoven structure. The concept of interwoven materials has been adapted to the molecular level in for example tailor-made DNA tiles, coordination polymers and tailor-made organic structures.[1]

A first step towards the bottom-up, self-assembled synthesis of polymer fabrics was done by Wöll *et a*l. by designing textile sheets through pre-orienting the coupling partners to a MOF layer, reacting them, and then removing the metal ions to get the organic textile layer.[2]

We designed a heteroleptic, amphiphilic metal complex to take advantage of its pre-organization to assemble a molecular textile from bottom-up. The octahedral geometry of the metal complex and the rigidity of the tri-dentate ligands ensure angles in between the ligands of close to 90°.[3] By choosing amphiphilic ligands with different functional groups, which can be linked with each other, a moiety that can form an interwoven 2D material by polymerization was designed. Fixing the orientation of the monomer by using an water-air interface to orientate the hydrophilic ligand to the water allows us to have the necessary groups for the polymerization pre-organized in one plane to later form the 2D interlocked material.

In an effort to gain further insight into interwoven materials, we also designed a heteroleptic complex that can only interlink on two sides. To ease the separation of the possible enantiomers, a linker which is chiral itself was chosen. Polymerizing this restricted moiety, a defined patch of an interwoven material is formed. This defined patch would allow a variety of analytical measurements, which are not possible with the polymeric material, to give immense insight into this type of materials.

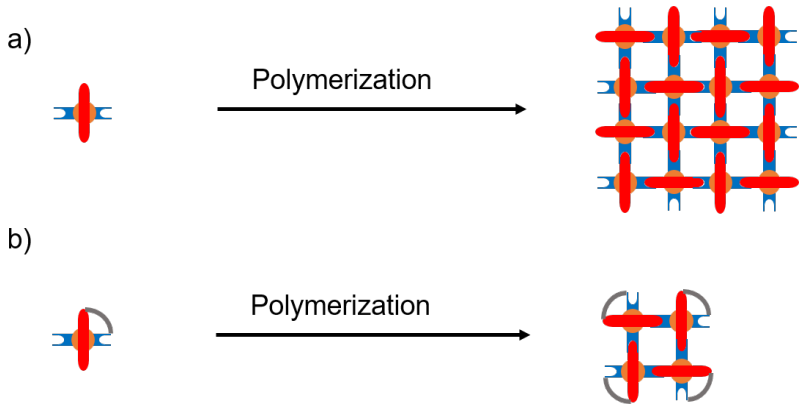

Figure 1: Schematic representation of the heteroleptic complexes on the air-water interface.

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Mechanosensitive Diradical Cyclophanes

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With the first concept of using only a single organic molecule as an electronic device by Aviram and Ratner, the idea of a Single Molecular Junction (SMJ) was born.[1] SMJs are electrical circuits in which two atomically sharp electrodes are bridged by a single molecule. The interest in this research area originates from the idea of benefiting from size reduction using molecules as electronic components. In the beginning simple conjugated Structures such as benzene-1,4-dithiol were investigated using SMJs.[2]

Today the interest in SMJs has shifted towards more elaborate systems which can be manipulated mechanically.[3] Cyclophane systems using Porphyrin as chromophore have been investigated extensively as mechanosensitive dimers in Molecular junction experiments.[4] Radical compounds however are relatively unexplored in SMJs. Lately, a stable radical cation circulene was reported, inspiring this work.[5] To explore the electronic effects of the radical nature of chromophores within close proximity a diradical cyclophane system similar to as shown in Figure 1 is pursued.

In this contribution, the focus will be centered on the discussion of the synthesis and characterization of such a mechanosensitive diradical cyclophane shown in Figure 1.

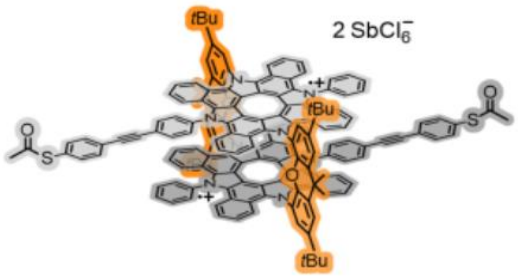

Figure 1: Mechanosensitive Diradical Cyclophane

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Synthesis of Original GlycoBenzoxocin Skeletons *via* Formal Quinone Glycosylation Enabled by Oxidative Radical-Polar Crossover

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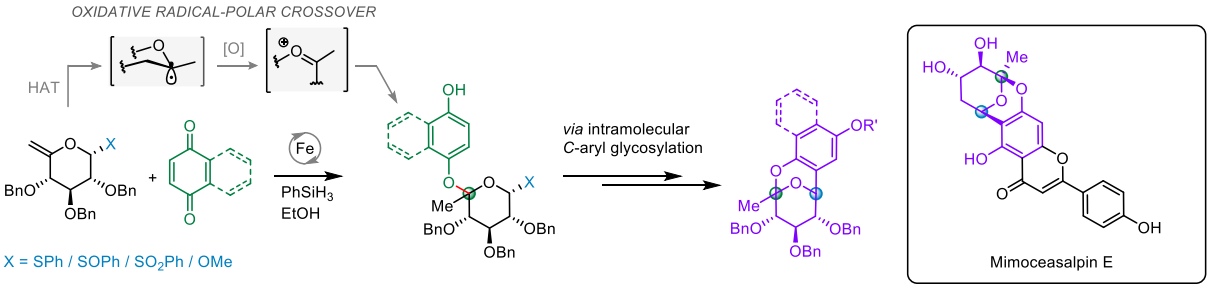
Several natural molecules have been discovered in the last few years, containing original glycobenzoxocin such as Mimocaesalpin E. [1] The rarity of this skeleton coupled with the biological properties of those molecules lead to a high interest in the development of new methodologies allowing to reach such structures. The SYBIO team has recently opened the road to an efficient access to *C,O*-aryl glycoside compounds through the formation of a pseudo tertiary anomeric radical generated *via* iron-mediated hydrogen atom transfer (HAT) subsequently oxidized leading to an oxocarbenium formation.[2]

Due to the lack of methodologies leading to a direct di-functionalization of carbohydrate entities[3] and based on previous results of the lab, a strategy was considered, hinging on several glycosylation methods based on anomeric leaving groups of various reactivity.



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Insight to the C-S bond formation catalyzed by three-domain rhodaneses

50

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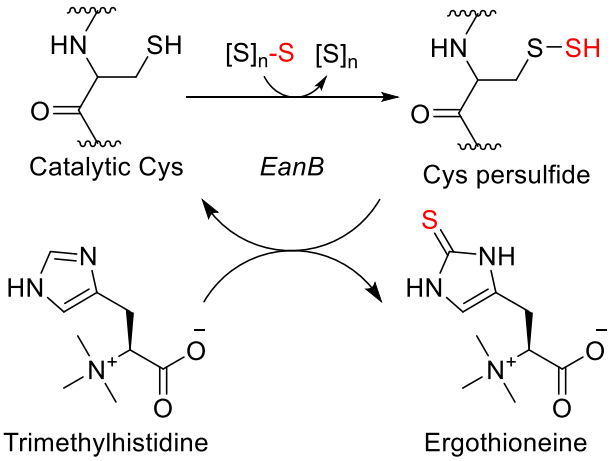

The superfamily of rhodanese-like enzymes is a large class of proteins characterized by a conserved fold comprising a least one rhodanese domain, and the common ability to transfer sulfur atoms from a sulfur donor to an acceptor via ping-pong mechanism. Despite these commonalities, most members of this superfamily are not well characterized with regards to their catalytic activity and specific physiological function.

Our group has described the function and structure of the first representative of the three-domain rhodanese family: the ergothioneine synthase (EanB). This enzyme catalyzes the oxidative sulfurization of N_α-N_α-N_α-trimethylhistidine (TMH) to produce Ergothioneine (Egt).[1] Most members of this enzyme family are found in organisms that do not produce Egt, including *E. coli*, and most likely catalyze different reactions.[2] Nevertheless, as we show in this presentation, many of these enzymes still support ergothioneine biosynthesis in recombinant *E. coli* and are characterized by considerable TMH sulfurization activity *in vitro*. Based on this discovery, we hypothesize that all members of this enzyme family originate from an ancestral ergothioneine synthase but have evolved to sulfurize other imidazole-containing metabolites.

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From Donor-Acceptor Cyclopropanes to Sulfur-Nitrogen Heterocycles and γ-Fluorosulfones

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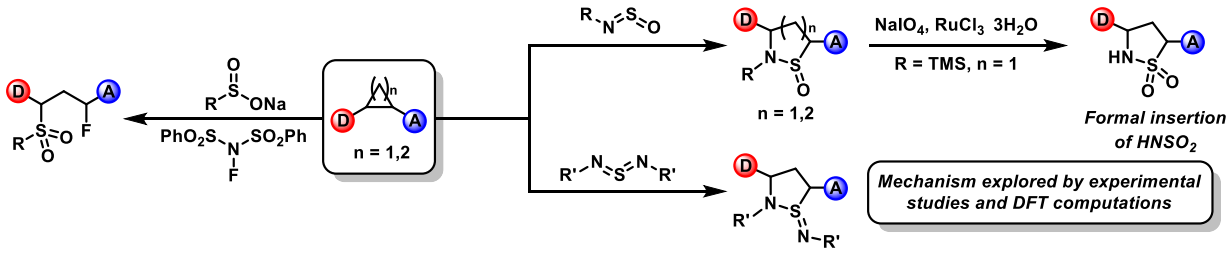
Donor-acceptor (DA) cyclopropanes are valuable C3 synthons. Their ring strain and strongly polarized carbon-carbon bond results in a masked 1,3-zwitterion which can be activated by various catalytic systems allowing a myriad of transformations, most notably a broad range of (3+n)-cycloadditions and 1,3-bisfunctionalizations.[1] Utilizing these compounds as starting materials, we envisioned designing methodologies for the formation of synthetically challenging heterocycles by cycloadditions with S=N-containing reagents, and γ-fluorosulfones by 1,3-bisfunctionalization with sulfinates and electrophilic fluorination reagents. Lewis acid activation allowed for excellent reactivity with sulfinylamine reagents, furnishing a variety of isothiazolidine *S*-oxides. This reactivity was extended to a (4+2)-cycloaddition with DA cyclobutanes, forming 1,2-thiazenanes. TMS substituted sulfinylamine provided one-pot conditions for the (3+2)-cycloaddition followed by oxidation to the γ-sultam with concomitant N-Si bond cleavage, giving formal insertion of $HNSO_2$.[2] Sulfur diimides were also identified as good 2π components for cycloadditions with DA cyclopropanes, leading to the first synthesis of *S*-imino isothiazolidines. Mechanistic understanding was provided by a combination of HPLC experimental investigations, and DFT computation. Ring-opening with sulfinate salts occurred under Lewis acid catalysis, with NFSI found to be a suitable electrophilic fluorine source leading to the desired γ-fluorinated sulfones in excellent yields under mild reaction conditions.[3]

Scheme 1. Synthesis of isothiazolidines, sultams and γ-fluorosulfones from DA cyclopropanes



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Synthesis of acridane[4]arenes with different substituents

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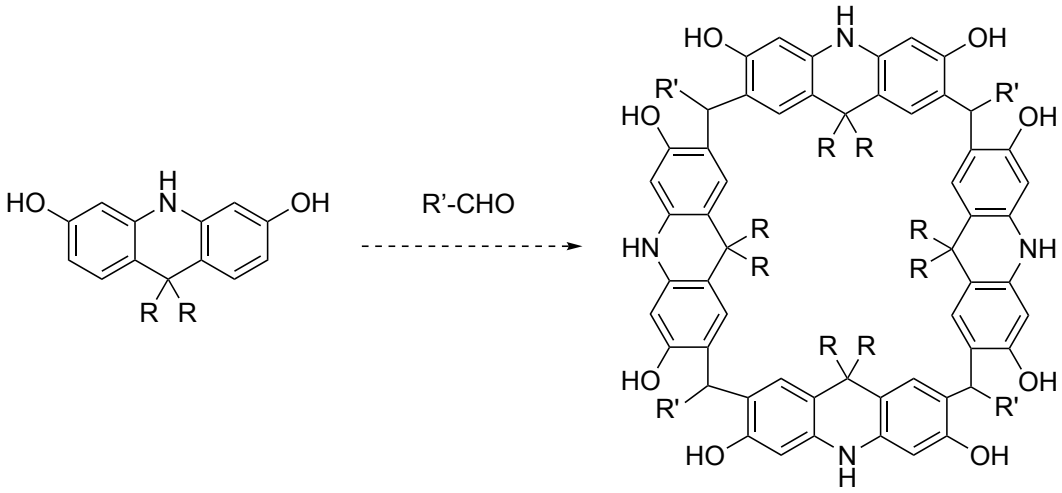
Bowl-shaped phenolic macrocycles, such as resorcinarenes, form a hydrophobic cavity and can be further modified. Therefore, they serve as important structural platforms for larger structures such as capsules[1] and cavitands[2]. The size of the cavitand is limited by the diameter of the macrocycle, and the volume can only be increased by the installation of longer walls. For the synthesis of larger cavitands, a larger structural platform is needed.

This can be achieved by replacement of the benzene-based units with larger ones, such as naphthalene[3] or xanthene units[4]. The xanthene[3]arene exhibits an inner diameter of 9.6 Å, which leads to larger structures upon derivatisation.

Recently our group reported the synthesis of an even larger macrocycle, the arcidane[4]arene[5], which is obtained by the reaction of the 9,9-dimethyl-substituted acridane with different aldehyde. The cavitands build from this macrocycle exhibited a very deep and large cavity. In order to alter the properties of the macrocycle and introduce functional groups, the substituents of the acridine and the residue on the methylene linker can be varied. With that, different acridane derivatives and different macrocycles were obtained.



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Rhodium-Catalyzed Stereoselective Cyclization of 3-Allenylindoles and *N*-Allenyltryptamines.

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Herein we report a highly enantio- and diastereoselective rhodium-catalyzed cyclization of *N*-allenyltryptamines and 3-allenylindoles to 6-membered spirocyclic indolenines.[1] This hydrofunctionalization methodology offers the advantage of using a comparably cheap commercially available ligand with low loadings of an affordable rhodium precursor. It was previously reported that cyclization of 3-allenylindoles with a shorter linker, resulted in the formation of functionalized tetrahydrocarbazoles via a transient 5-membered spirocyclic intermediate.[2] Due to their lower ring strain and thus higher intrinsic stability these 6-membered spirocyclic indolenines don't undergo an acid-catalyzed rearrangement to the corresponding annulated heterocycles. Interestingly, an inverted diastereoselectivity can be observed, compared to the before mentioned 5-membered derivatives.[3] The versatility of the reported methodology was shown by applying malonate tethered substrates as well as tryptamine derivatives with a broad functional group tolerance. Additionally noteworthy is the potential to transform the cyclization products to valuable building blocks for natural product synthesis, such as functionalized spirooxindoles and spiroindolines.

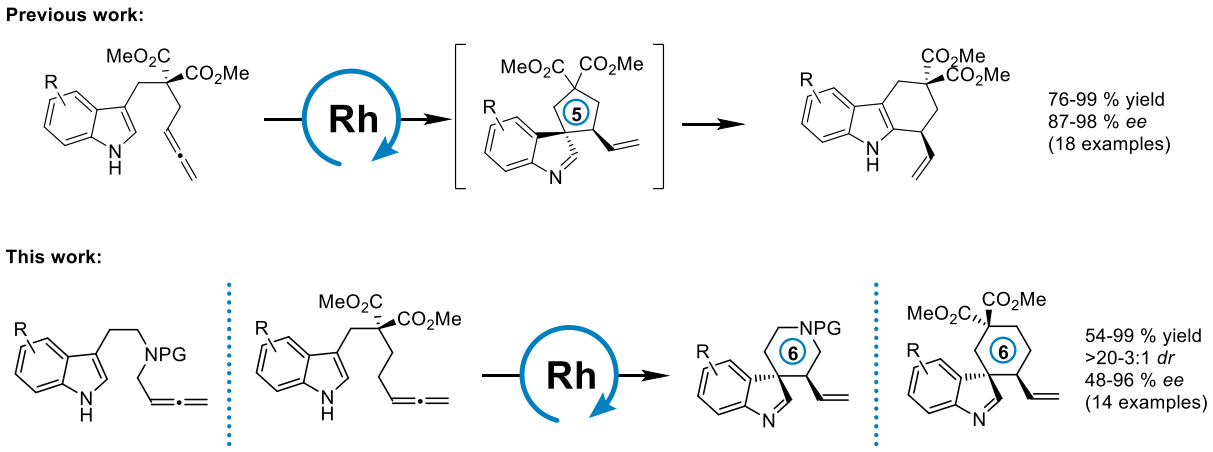

Figure 1. Rhodium-catalyzed cyclization of 3-allenylindoles and *N*-allenyltryptamines.

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Environmentally friendly cyanation reaction using the Design of Experiment (DoE) approach

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Aryl nitrile has a major role in organic synthesis, in particular because nitrile is important for bioactive compounds design. This utility is particularly due to the fact that it allows many interactions with the cellular environment (HBA, polar interactions, etc.)[1]. In addition to its interest in medicinal chemistry, the nitrile moieties are a key intermediate for the synthesis of many functional groups, such as ketones, amines or amide. Typically, the design of this compound uses toxic cyanide sources (KCN, NaCN)[2], polluting organic solvent, noble metal (palladium) and high temperature[3].

In this context, our goal was focused on the development of a more environmentally friendly aryl cyanation using sodium nitroprusside as a non-toxic nitrile source,[4] a copper complex as catalyst, water as green solvent, and a reaction temperature below 80°C (Figure 1).

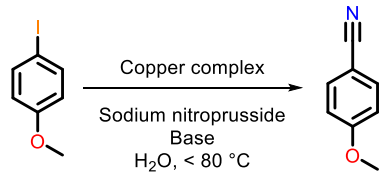

Figure 1 : Environmentally friendly cyanation reaction

The optimization of this methodology was performed through a Design of Experiment (DoE). This statistical approach is commonly practiced in industry, but barely known in academia, where a one-factor-at-time (OFAT) method is often favored. DoE process has the advantage to be generally fastest, and more efficient to find out the potential interactions between the reagents during the reaction (Figure 2). Thanks to this strategy, we were able to establish simple, cost-effective and environmentally friendly conditions to perform aryl cyanation in good yields.

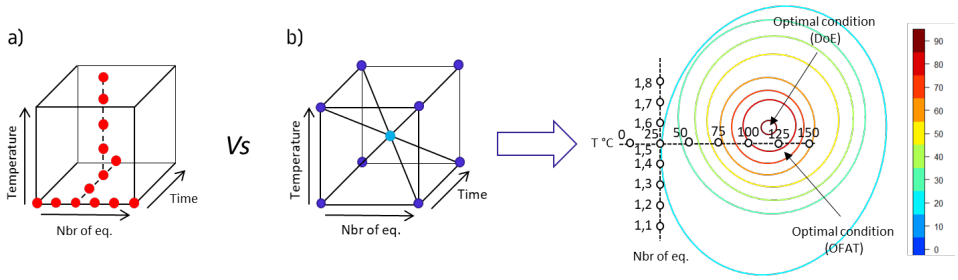

Figure 2 : Comparison between OFAT and DOE study: a) one-factor-at-time approach. b) Design of Experiment approach.

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Quantification of Magic Spot Nucleotides Produced by Rel_{Mtb} from *Mycobacterium tuberculosis*

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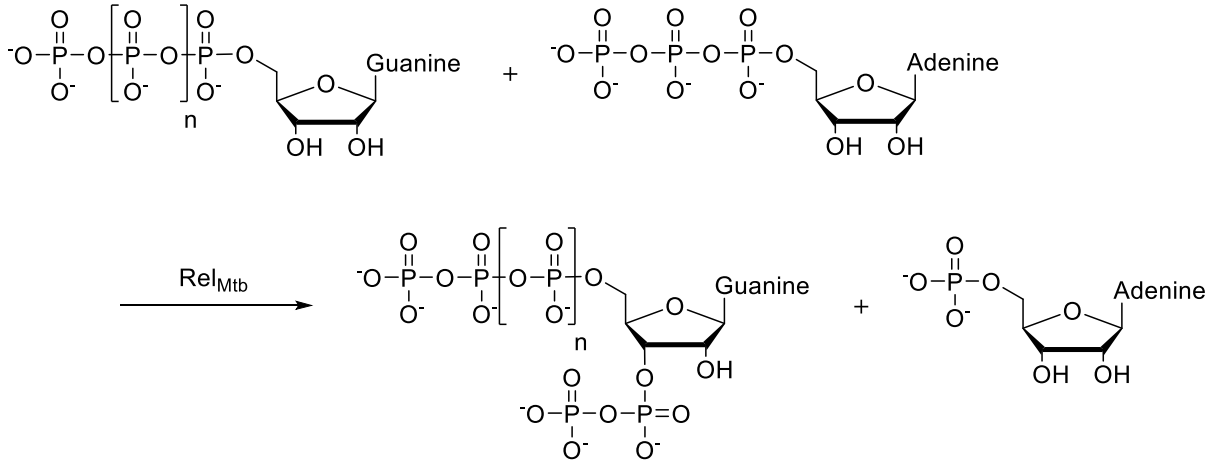
Bacteria can resist diverse stress like nutritional deficiency, heat or antibiotics by using the stringent response (SR). During SR, a protein of the RelA/SpoT Homolog (RSH) Superfamily synthesizes magic spot nucleotides (MSN) like pppGpp or ppGpp. MSN are able to regulate gene expression, whereby the metabolism is shut down, until the stress factor is not affecting the bacteria anymore[1]. Since antibiotics do not work as intended during SR, the synthesis of MSN is a good target to prevent bacteria from bypassing the antibiotic effects[2]. In this project, we show a possibility to seperate all known Nucleotides taking part in SR with HPLC. With fitting calibration curves all reactants can be quantified.



***In vitro* synthesis of (p)ppGpp**. Rel_{Mtb} from *M. tuberculosis* transfers a pyrophosphate from ATP to either GDP (n=0) or GTP (n=1) to form AMP and either ppGpp (n=0) or pppGpp (n=1).

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Magnetic Metallocarbon Membranes – Towards a new semiconductor class

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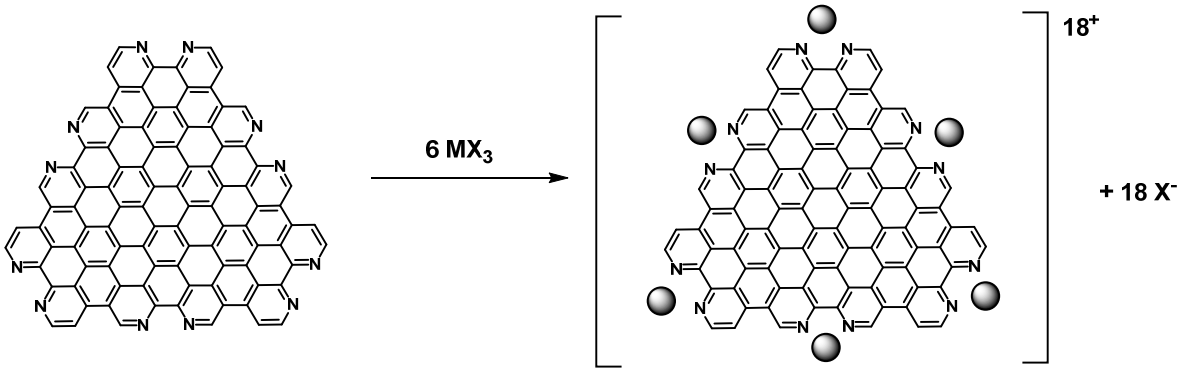
Magnetic Metallocarbon Membranes (MMCMs) are a new semiconductor class based on nanographene and transition metals. The concept offers the option of tuning competing magnetic interactions in solid materials, specifically the exchange interaction between electrons and the spin-orbit interaction[1]. The resulting large dipole opens up the possibility of using nanoconfined water as dopant, thus opening up the possibility to study artificial biological systems and proton-electron interactions in ultraconfinement.

The membrane topology was chosen due to the inherent wave nature of matter which was proposed in 1924 by Louis de Broglie[2]. Quantum objects like photons, electrons and protons thus obey to a large degree superposition logics which are intrinsically anisotropic.



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Phase behavior of activated amino acids

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Compartmentalisation and non-equilibrium pathways are considered as two of the most important ingredients on constructing life-like assemblies. Liquid-Liquid Phase Separation (LLPS) and transient self-assemblies have been demonstrated with a variety of chemical fuels like carbodiimides[1] or methylation agents.[2] However, in these systems, the fuel is either not incorporated in the self-assembly (carbodiimides) or has not been modified (methylating agent). Herein, we report on a new class of modified high energy molecules that bind covalently to a precursor. Inspired by nature's ability to use the properties of 20 amino acid side chains to build complex structures, we apply a biomimetic approach using aminoacyl phosphates – the synthetic analogues of aminoacyl adenylates. In our chemical reaction networks, the structure and properties of the newly formed phases result from modifications on the structure of the fuels and the precursors. In particular, we demonstrate that the reaction of amino acyl phosphates with phenols gives rise to LLPS and self-assembly. The phase transitions affect oligomer distribution, lifetime and allow for selectivity in mixtures of amino acids according to hydrophobicity (**Figure 1**). Our strategy establishes non-biological phosphates for compartmentalisation and could be extended towards microfluidics materials discovery.

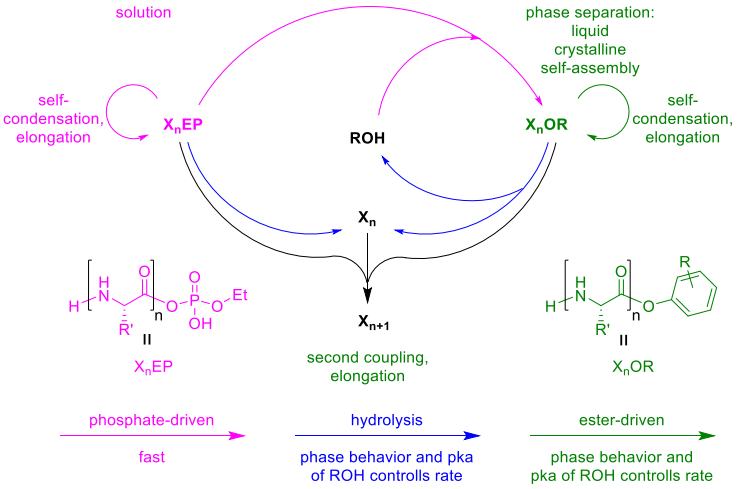

Figure 1: Schematic reaction network of aminoacyl phosphates (X_nEP) with a phenolic precursor (ROH).

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Cycloparaphenylenes

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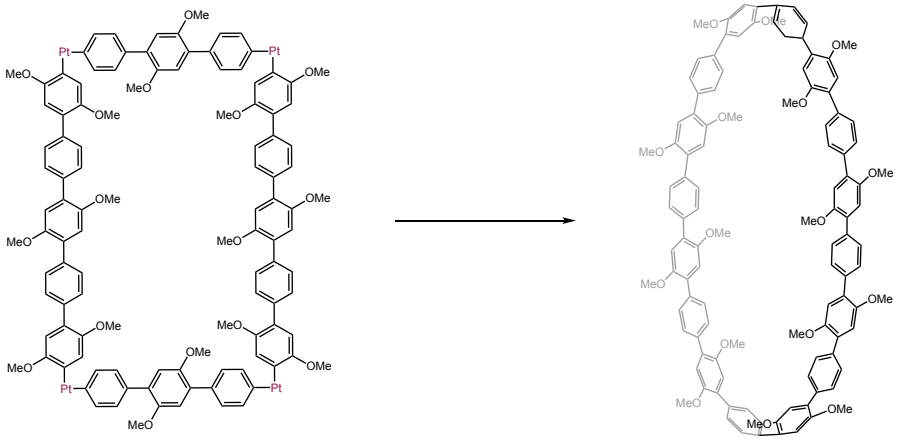
Cycloparaphenylenes — also referred to as carbon nanohoops— can be thought of as the shortest possible cross section of an armchair carbon nanotube. These molecules have been envisioned for many years but their synthesis has been challenging due to the requirement for precise control over ring size and connectivity, as well as the high strain they can possess. Over the past decade, significant progress has been made in developing methods to synthesize carbon nanohoops with different sizes and compositions. While most of these studies deal with small nanohoops, larger nanohoops such as those derived from [16]CPP remain barely studied.[1]

Yamago's group utilized a square-shaped tetranuclear platinum complex with aromatic biphenyl units as a precursor, which introduced curvature to the structure through sp^3-hybridized carbon atoms. By performing reductive elimination of platinum, [8]CPP was successfully synthesized.[2] Based on this work, we expect to selective synthesis of methoxy-substituted [16]CPP and study their unique properties, such as size-dependent photophysical, electronic properties. Furthermore, we intend to examine the effects induced by the substituents on the properties.



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Access to Thiazepanes and Bicyclic Derivatives via Gold-Catalyzed Cyclizations

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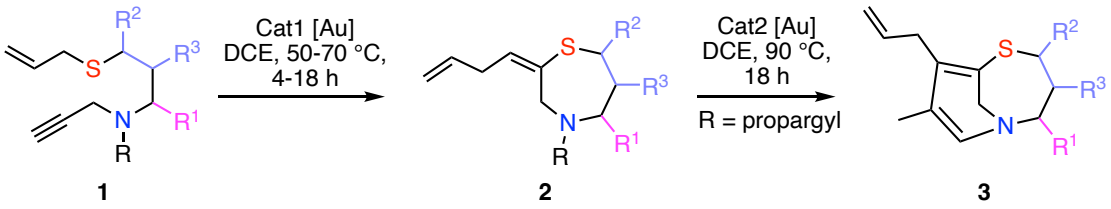
Gold-catalyzed cyclizations represent a powerful method for the preparation of various heterocycles, which are valuable compounds in the fields of pharmaceutical, agrochemical and materials chemistry. Recent reviews showed the interest in accessing 7-membered rings and medium-sized rings (8 to 11 atoms) by gold-mediated cyclizations.[1] Indeed, these molecular structures are interesting due to their presence in bioactive natural products and pharmaceuticals, however they are renowned for their challenging accessibility. Thus, the intramolecular carbon-heteroatom bond formation involving the attack of a heteronucleophile on the gold-activated triple bond is a common method to synthesize 5- and 6-membered heterocycles, while it is rarely used for the direct construction of larger rings.

In this context, our recent work dealt with the synthesis of new structural family of 1,4-thiazepanes from 1,3-aminothioethers **1** having two or three carbon stereocenters using gold-catalysis. The process consisted in an unprecedented 7-*exo*-dig cyclization with C-S bond formation and concomitant allyl S-to-C migration. Finally, the obtained *N*-propargyl 1,4-thiazepanes **2** underwent a new sulfur-assisted 1,6-enyne cycloisomerization, which led to original *N,S*-heterobicyclo[4.3.1] systems **3** with a bridgehead double bond.[2]



1 **2** **3**

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In Situ Formation of Cationic π-Allylpalladium Precatalysts in Alcoholic Solvents: Application to C–N Bond Formation

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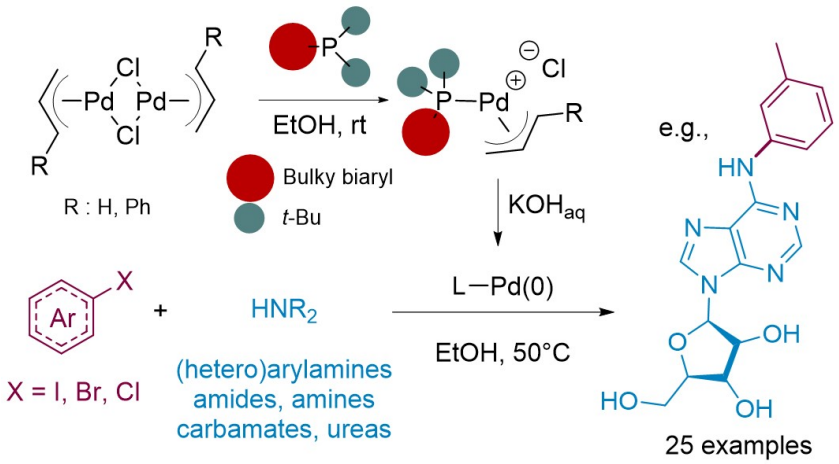
In the context of our researches of greener conditions for metal-catalyzed reactions, we developed an efficient Buchwald–Hartwig cross-coupling reaction in alcoholic solvent, in which a low catalyst loading showed excellent performance for coupling aryl halides (I, Br, and Cl) with a broad set of amines, amides, ureas, and carbamates under mild conditions. Mechanistically speaking, in a protic and polar medium, extremely bulky biarylphosphine ligands interact with the dimeric precatalyst [Pd(π-(R)-allyl)Cl]$_2$ to form *in situ* and spontaneously a cationic complexe [Pd(π-(R)-allyl)(L)]Cl, which cannot be obtained in classical organic solvents such as toluene or THF. The resulting precatalyst further evolves under basic conditions into the corresponding L-Pd(0) catalyst, which is commonly employed for cross-coupling reactions. This mechanistic study highlights the prominent role of alcoholic solvents for the formation of the active catalyst.[1]



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Rh-catalyzed Hydroamination of Allenes: Asymmetric Functionalization of Amino Acids and Peptides

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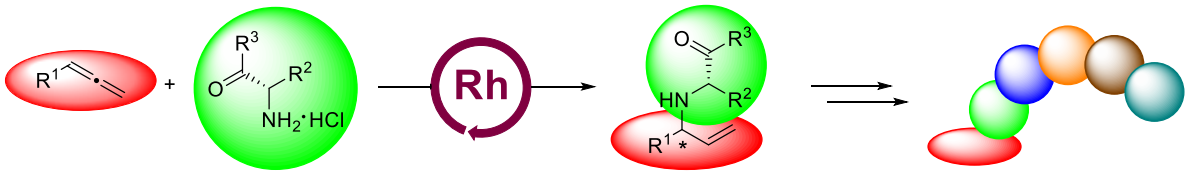
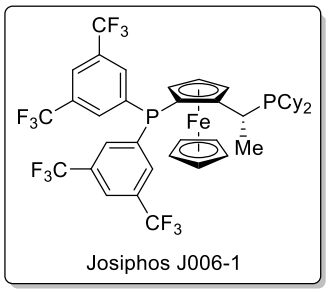
Since the synthesis of insulin in 1921 and its use as first commercial therapeutic peptide in 1923, development of peptide drugs has become an important field in pharmaceutical research.[1] To further improve pharmaceutical properties like metabolic stability, bioavailability, receptor activity and selectivity, the use of peptidomimetics has become a growing field in drug discovery likewise. The strategy of the peptidomimetic approach is to perform focused modifications to the peptidic backbone or side chains.[2] In our group, numerous methods to hydrofunctionalize allenes with C-, N-, O-, and S-nucleophiles to obtain branched allylic compounds stereoselectively have been developed.[3] However the use of aliphatic amines as nucleophiles remained an unsolved problem due to basicity of the amine moiety and possible overalkylation.

In this work a catalytic method is described, which enables stereoselective and atom-economic allylation of aliphatic amines focusing on amino acids and small peptides. As possible application the syntheses of two peptidomimetic compounds utilizing solid phase peptide synthesis (SPPS) were performed.



- 32 examples
- yields up to 98%
- *d.r.* up to >95:5
- catalyst-controlled stereoselectivity
- gram-scale reactions
- workup without column chromatography
- pentapeptides as suitable substrates



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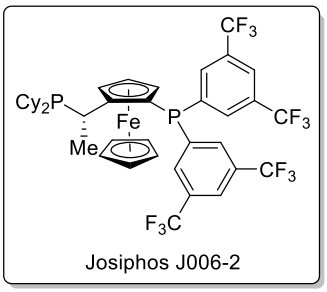

Josiphos J006-2

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Elaboration of porous hybrid catalysts for heterogeneous photoredox catalysis

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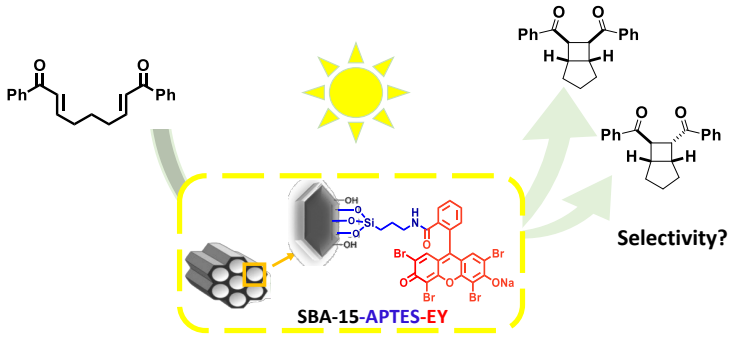
The current global trend to follow the concept of green chemistry favors the development of photochemical pathways using sunlight[1]. The direct visible light irradiation of the substrate is not always possible, since few organic molecules absorb in this wavelengths range[2]. To circumvent this problem, the photocatalysis appeared as a pertinent solution. This concept used a photocatalyst (PC) which absorbs the visible light to activate the organic substrate. The organic dyes are considered as interesting PCs. Indeed, they are neither expensive nor toxic[3]. Thus, to strengthen the green aspects of these organic transformations, the heterogeneization of PC on organized mesoporous silica has been carried out[4]. These materials can play a dual role in organic synthesis, first by supporting the PCs and then by providing a confined environment that can impact the reactivity and the selectivity of the reactions. In this context, eosin Y has been covalently linked to different organized mesoporous silicas to obtain a heterogeneous photocatalytic system whose performance in organic reactions such as radical cyclization has been evaluated[5].



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Studies Towards the Total Synthesis of Cervinomycin Natural Product

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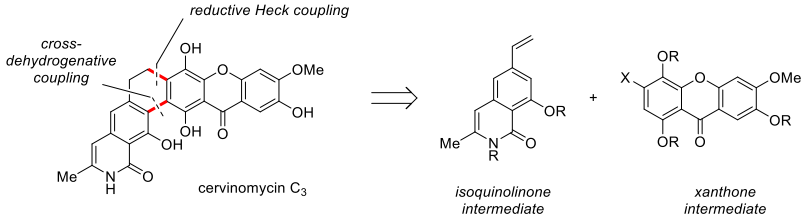
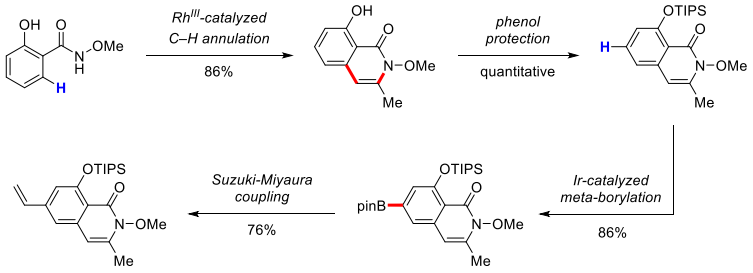
Cervinomycins are aromatic polyketides which exhibit antibiotic activity against gram-positive bacteria and high cytotoxicity.[1] Herein we report our studies towards the total synthesis of these natural products, in which multiple C–H functionalization steps allow for a convergent route.



Retrosynthetically, we aim to construct cervinomycins from functionalized xanthone and isoquinolinone fragments, which will be joined through a reductive Heck coupling and a cross-dehydrogenative coupling.[2]



The isoquinolinone fragment was accessed in 5 steps from salicylic acid, using two strategic C–H activation reactions. A rhodium-catalyzed C–H annulation of 2-hydroxy-N-methoxybenzamide with chloroacetone gave the corresponding isoquinolinone product.[3] After protection of the phenol, an iridium-catalyzed C–H borylation furnished the meta-borylated isoquinolinone as a single isomer.[4] Suzuki-Miyaura coupling with vinyl tosylate gave the corresponding 6-vinylisoquinolinone intermediate. Currently, we are examining different C–H activation-based routes towards the xanthone fragment.

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Delivery of Caged Magic Spot Nucleotides into *Escherichia coli*

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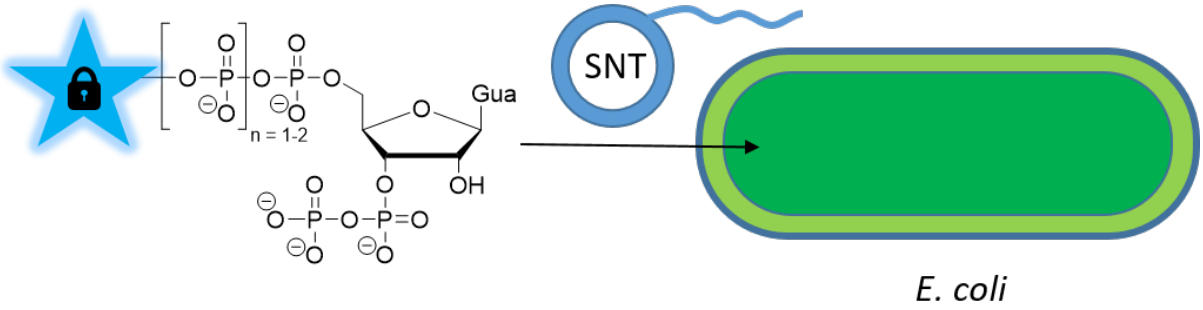
Magic spot nucleotides (MSN) are bacterial alarmones involved in the highly conserved stringent response, a bacterial stress response mechanism enabling survival in challenging environments. [1] New chemical tools such as photocaged MSN-analogues are important to better understand the cellular implications of these signalling molecules. Here we describe the synthesis of caged and clickable MSN analogues and their delivery into E. coli cells. These highly phosphorylated nucleotides contain multiple negative charges and cannot permeate bacterial cell membranes spontaneously. Cellular transport was facilitated by conjugation to a cell-penetrating peptide and through a cyclodextrin based synthetic nucleotide transporter. [2] The novel probes will enable studies of MSN involvement in the stringent response with spatial and temporal control.



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