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Hydrogen Atoms in Halogen-Atom Transfer

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The generation of carbon radicals by halogen-atom and group transfer chemistry is one the most applied methods in synthetic radical chemistry.[1] The broad availability of organic halides as well as alcohol/thiol derivatives provides a large pool of commercial materials for divergent functionalizations.

These reactions have been generally approached using radicals able to form strong bonds with halogen/O/S atoms and of nucleophilic character to stabilize the transition state by charge-transfer.[2] Tin and silicon species are the most used and versatile reagents to achieve this, despite their cost and toxicity profile.[1,3]

In this presentation, I will discuss some recent work from my group aimed at developing a novel approach for carbon radical generation using H-atoms (H•) as the abstracting species. This H-atom transfer reactivity profiles differs from normal HAT reactions in the way that the H-atom is not abstracted but is the key abstracting species in the process.[4]

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Nickel-Catalyzed Asymmetric Synthesis of α-Arylbenzamides

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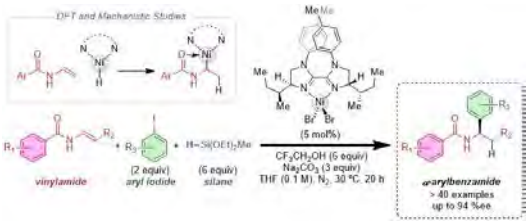
α-Arylbenzamides are pharmacologically relevant and ubiquitous motifs, present in anti-cancer agents,[2a] SARS-CoV PLpro inhibitors[2b] and anti-depressants among many other bioactive molecules.[2c] However, despite their unquestionable importance, straightforward methods to access these enantiomerically enriched motifs are still elusive.

Currently established strategies include the direct enantioenriched arylation of the corresponding C-H bond[3a] or the hydrogenation of α-amidostyrenes[3b] among others. Our methodology relies on an elegant 3-component asymmetric hydroarylation of vinylamides, catalyzed by a chiral Ni-bisimidazoline complex. Control experiments and DFT calculations support a mechanism based on the addition of an *in situ*-formed Ni-hydride complex onto the olefin. The excellent enantiomeric excess (up to 94 %ee) is explained by the coordination of the carbonyl group to the Ni atom.

The broad scope (> 40 examples) demonstrates that the reaction tolerates different functional groups (nitrile, ketone, ester, boronic ester, etc.) and electronic properties in the aryl ring (EWG and EDG), both in the vinylamide as well as in the aryl iodide. Examples using ortho-substituted aryl iodides, vinyl bromides, benzyl bromide and more complex substrates bearing additional stereocenters are also included in this work.



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Amino-oxetanes as amide isosteres by an alternative defluorosulfonylative coupling of sulfonyl fluorides

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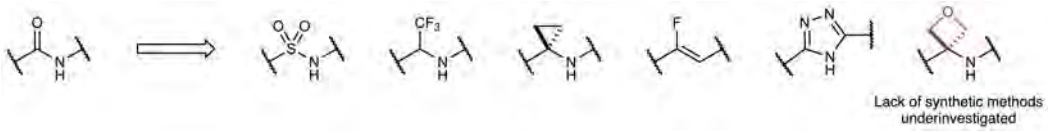
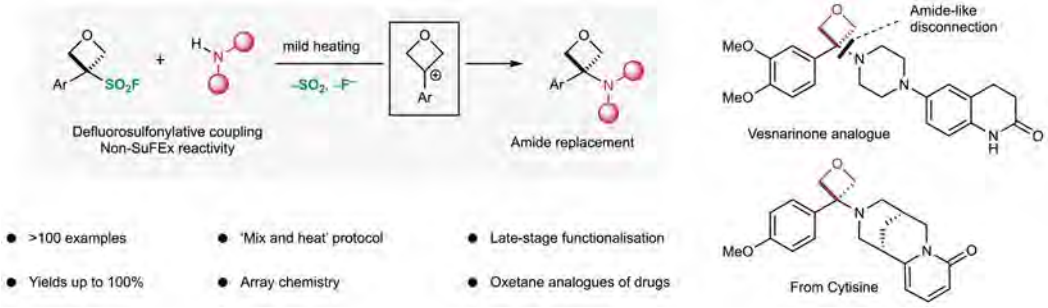
Benzamides are an important medicinal motif present in over 100 approved drugs but often suffer from poor physiochemical properties such as low solubility due to their planar structure. Hence, bioisosteres of benzamides are also common, but are significantly harder to access synthetically (Figure 1).[1] Aryl amino-oxetanes are promising, more 3-dimensional bioisosteric candidates for benzamides but remain uninvestigated due to a dearth of synthetic methods. Sulfonyl fluorides have emerged as popular click reagents that react with nucleophiles in a Sulfur–Fluoride Exchange reaction (SuFEx) to generate S(VI)-derivatives such as sulfonamides and sulfonate esters.[2]



This presentation will describe an alternative *defluorosulfonylation* reaction of oxetane sulfonyl fluorides (OSF) to generate aryl amino-oxetanes as isosteres of benzamides (Figure 2).[3] Instead of reacting in a SuFEx fashion, OSFs liberate SO_2 and fluoride upon warming to generate an oxetane carbocation. This disconnection mimics classic amide couplings and thus, allows the direct use of the vast amine libraries available to pharmaceutical companies. The transformation was showcased through a wide scope, the functionalization of amine-containing drugs, the synthesis of 10 oxetane analogues of benzamide drugs and the generation of a compound library by an array screen. Kinetic and computational experiments support the formation of a planar oxetane carbocation by an S_N1 mechanism.



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Development of New Synthetic Approaches Towards Acridinium Salts and Their Applications

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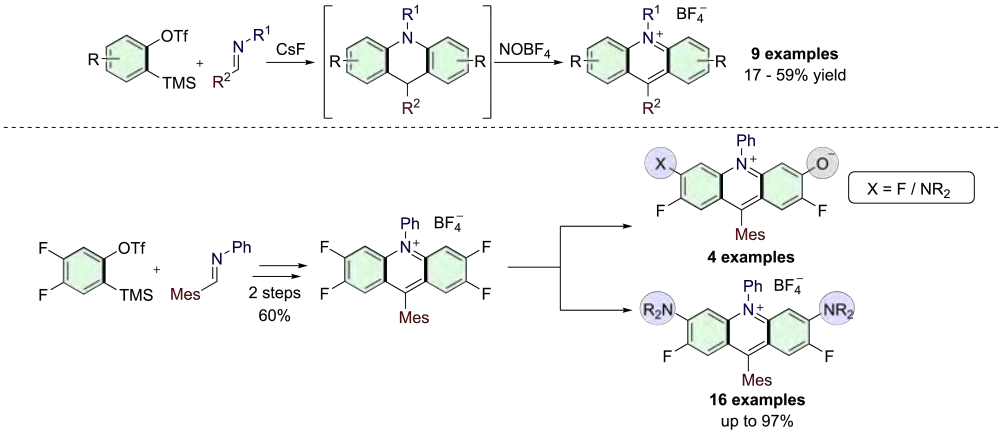
Photoredox catalysis has experienced significant advances over the last decade to become a valuable tool for otherwise intractable transformations under mild conditions.[1] In this context, short and modular synthesis of diverse photocatalysts with different photochemical properties is an important instrument for the further development of the field. As a sustainable replacement for the precious-metal photoredox catalysts, acridinium salts have emerged as valuable organic cationic photocatalysts due to their favorable photophysical features.[2,3] We herein describe a new short two-step route to acridinium dyes comprising aryne-imine-aryne coupling combined with subsequent oxidation.[4, 5] This strategy was also applied for the preparation of a key tetrafluorinated acridinium salt which served as a linchpin intermediate for the late-stage diversification by nucleophilic aromatic substitution. Diverse acridinium derivatives were prepared with high yields using this methodology including aza-rhodols as a novel class of acridinium photocatalysts.[6] The obtained photocatalysts were successfully applied for organocatalytic C-N cross-coupling. Furthermore, the modularity of the developed synthetic strategy allowed the preparation of the acridinium derivatives with efficient intersystem crossing that were suitable for the polyarene reduction and triplet-triplet upconversion.[7]



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(‡ B. F. and V. H. contributed equally)

Benzodiazepinoindoles: Chiral Polycyclic Platforms for Various Applications

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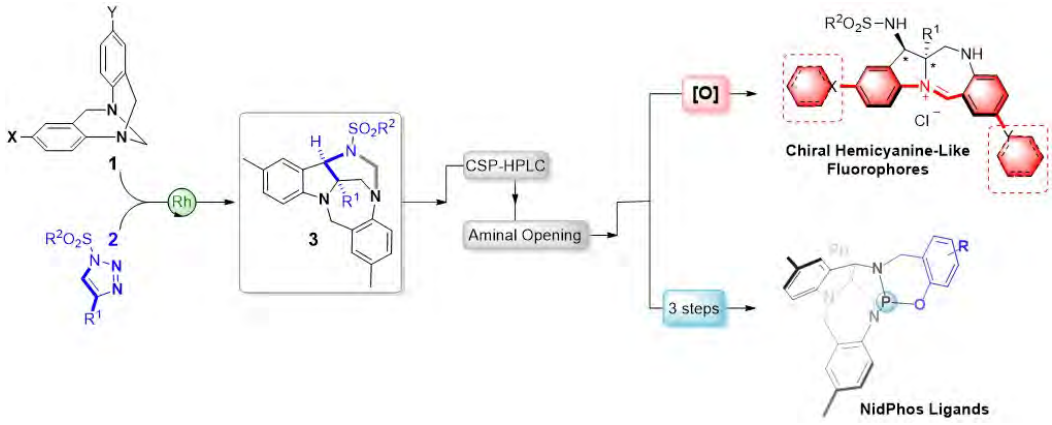
Tröger bases (TB) are chiral bicyclic compounds with stereogenic N-atoms presenting well-defined V-shape geometry. Numerous applications in supramolecular chemistry, molecular recognition, materials, and catalysis have emerged.[1] In our group, routes toward new chiral polycyclic derivatives have been developed using the reactivity of TB **1** with electrophilic carbenes,[2]. In the present context, those generated by Rh(II)-catalyzed decomposition of *N*-sulfonyl-1,2,3-triazoles **2** in particular. In one step, after a cascade of five reactions and rearrangements, novel racemic polycyclic benzodiazepinoindoles **3** were synthesized with high diastereoselectivity (*d.r.*>49:1).[3] The corresponding enantiomers can be easily separated by HPLC over chiral stationary phase. Of interest, the aminal functional group can be enantiospecifically removed under specific acidic conditions while maintaining the cup-like geometry of the scaffold.[4]

Herein, we capitalize on these developments for various applications. For instance, a new class of stable chiral Donor-π-Acceptor **(D-π-A) hemicyanine-like fluorophores** were straightforwardly prepared under oxidative conditions. Their (chir)optical properties can be further fine-tuned by late-stage cross-coupling reactions.[4] On the other hand, a new class of bridged-head stereogenic P-phosphorodiamidite ligands (**NidPhos**) can be synthesized in good yields. These ligands were obtained with full stereoselectivity (b-form) and they show promising results in enantioselective catalysis.[5]



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Harnessing Deep Eutectic Solvents for Polar Organometallic Additions to α,β-unsaturated Ketones in Air

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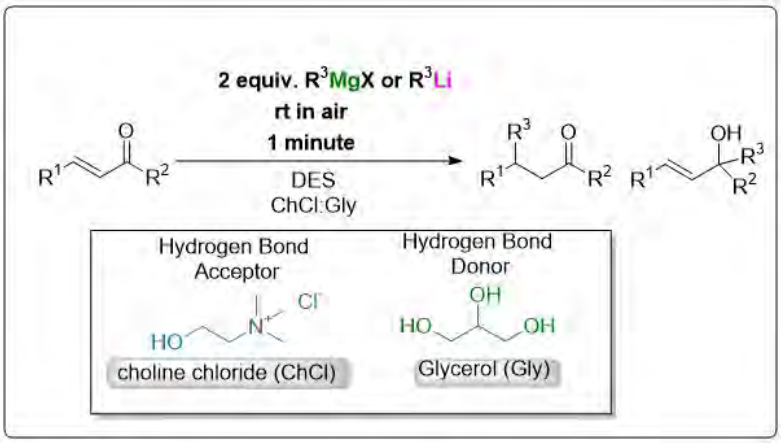
Polar organometallics additions are found widely in modern chemistry, with most syntheses of medicinal and agrochemical products involving one or more steps, utilizing Grignards or organolithiums. Despite their utility, these reactions typically require inert conditions, cryogenic temperatures (-78°C), as well as use of dry polar solvents.[1] To overcome some of these limitations, deep eutectic solvents have emerged as a powerful alternative. Formed by the combination of a hydrogen bond acceptor (Choline chloride) and hydrogen bond donor (glycerol) to form a uniform liquid with low toxicity and volatility.

Recent developments in polar organometallic chemistry have broken the current dogma requiring inert and cryogenic conditions. Our group along with others [3] have shown that polar organometallic reactions can occur rapidly and outcompete the protonolysis side reaction when in non-traditional protic solvents in air. In this work we show that by harnessing deep eutectic solvents, additions to α,β-unsaturated ketones can occur at room temperature in air, with a wealth of different organometallic reagents and substrates.



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The Chemical Development of Adafosbuvir, a Nucleoside Phosphoramidate Prodrug for the Treatment of Hepatitis C Infection

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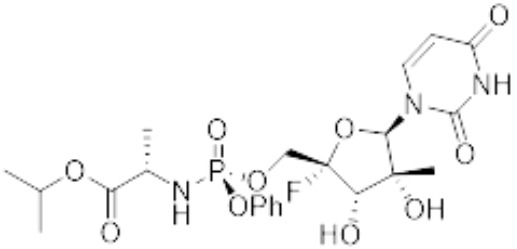
Over the last decades, nucleoside analogues have played significant roles in antiviral therapies and emerged as a well-established platform to treat cancer and viral infections. 4'-fluoro-2'-*C*-methyluridine was discovered as a potent inhibitor of hepatitis C virus RNA-polymerase. Phosphoramidate prodrug strategy was applied, leading to identify a clinical candidate Adafosbuvir (Alios 335). The route definition, the initial scale-up route, and the optimization towards large-scale production of Adafosbuvir will be discussed in this presentation.



Non-innocent electrophiles unlock exogenous base-free coupling reactions

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Being key parts in innumerable catalytic reactions, until this day, electrophiles serve almost exclusively two general purposes through their functional group: first, locating the bond-forming site at the corresponding substrate and second, providing the electronic bias for entering the catalytic cycle. Beyond that, such conventional electrophiles are passive throughout the reaction rendering the functional group and the corresponding prior synthetic efforts to install it highly sacrificial. This work[1] introduces the concept of non-innocent electrophiles. In contrast to conventional electrophiles such as commonly used organic halides or sulfonates, this new class of multifunctional electrophiles actively participates in the reaction beyond the classical paradigm, thus providing extended reactive opportunities. The concept was used as a platform for the development of exogenous base-free coupling reactions and provided a general solution to the 'base problem', a longstanding challenge in cross-coupling chemistry. Considered an inherent requisite for catalytic turnover, the use of (super)stoichiometric amounts of base in transition metal-catalyzed coupling reactions simultaneously limits the accessible chemical space, is suboptimal in terms of resource efficiency, and typically renders reaction conditions heterogeneous which affects reproducibility, scale-up campaigns, and the implementation of emerging technologies, *e.g.* flow chemistry or high-throughput experimentation.[1] Therefore, a general approach that eludes the need for exogenous bases in coupling reactions would be beneficial in various aspects. In summary, the study confirmed the hypothesis and diisopropylcarbamates as well as *tert*-butyl carbonates were found to release a competent base after oxidative addition. Notably, this catalytic release mechanism generates the base on-demand as it is coupled to the oxidative addition of the catalyst, and by that establishes self-sustaining catalytic systems with intrinsic self-regulation and efficiently overrides the deleterious effects caused by the use of an exogenous base. As a result multiple coupling reactions (9 distinct classes of coupling reactions) which traditionally rely on the addition of (super)stoichiometric base could be turned into exogenous base-free, homogeneous processes, that were compatible with base-sensitive functional groups. Importantly, C–H/C–O coupling scenarios proved feasible representing a promising avenue for the development of more sustainable catalytic platforms. Furthermore, the advantageous features of non-innocent electrophiles over conventional electrophiles were demonstrated in multiple relevant applications, *i.e.* miniaturization, reactivity sensing and reaction discovery. For example, a micromole-scale fluorescence-based assay for reaction discovery was developed that reliably and rapidly detects reactivity requiring minimal amounts of materials and in which a common benchtop UV-lamp is sufficient for reactivity detection allowing for naked-eye analysis of the samples. This led to the discovery of a novel Ni-catalyzed exogenous base-free deoxygenation reaction of aryl carbamates using isopropanol as a benign reductant.

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Kinetically controlled stereoselective access to branched 1,3-Dienes by Ru-Catalyzed remote Conjugative Isomerization

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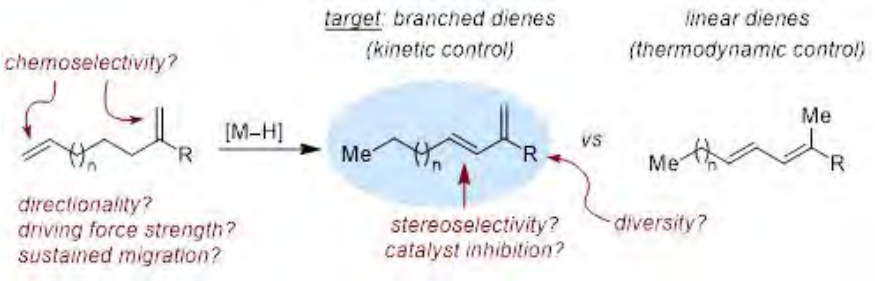
style="text-align: justify;">Dienes are important structural motif in numerous natural products/biologically active molecules and can serve as building blocks for the synthesis of a broad range of compounds.[1] Although a plethora of synthetic processes have been developed their stereoselective synthesis still represents a considerable challenge.[2] Surprisingly examples of conjugated branched 1,3-dienes obtained by alkene isomerization are underdeveloped. Following such a mild redox-economic synthetic methodology could offer great flexibility allowing for their selective synthesis.[3,4]



Herein we describe an operationally simple Ru-catalyzed isomerization reaction that affords stereoselectively branched 1,3-dienes by conjugation of two minimally differentiated remote alkenes.[5] These kinetic products can be obtained in high yield, regio- and stereoselectivity. A variety of functional groups and heterocycles showed to be well tolerated and the isomerization can be sustained over several methylene units. Mechanistic investigations support a metal-hydride mechanism consisting of iterative migratory insertion/β-H elimination, which is initiated preferentially at the terminal olefinic site. The potential of the method has been demonstrated by two sequential multimetallic selective catalytic sequences using [Ru/Cu] and [Ru/Rh] couples.

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Palladium(0)-Catalyzed Enantioselective C(sp^2)–H Arylation of (Hetero)arenes

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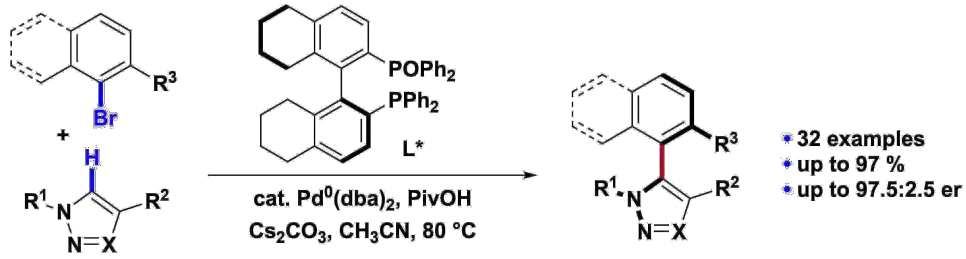
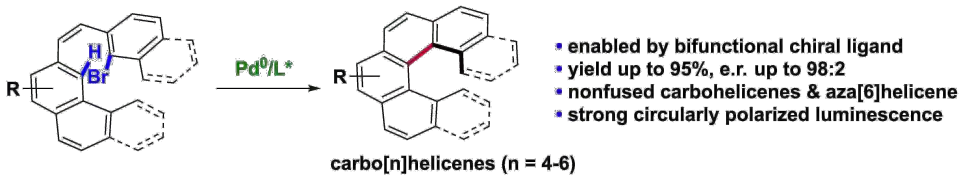
Atropisomeric (hetero)biaryls are motifs with increasing significance in asymmetric catalysis and natural products.[1,2] The straightforward construction of the stereogenic axis by efficient C–H functionalization methods is rare and challenging.[3] An intermolecular and highly enantioselective C–H arylation of relevant heteroarenes providing an efficient access to atropisomeric (hetero)biaryls is reported.[4] The use of a Pd(0) complex equipped with H_8-BINAPO as chiral ligand enables the direct functionalization of a broad range of 1,2,3-triazoles and pyrazoles in excellent yields and selectivities of up to 97.5:2.5 er. The method also allows for an atroposelective double C–H arylation for the construction of two stereogenic axes with >99.5:0.5 er.



Enantiopure carbohelicenes are important target molecules in molecular recognition and material science due to their strong circularly polarized luminescence (CPL) properties.[5,6] However, a general enantioselective process for the construction of lower, nonfused low-order carbo[n]helicenes (n = 4-6) is still lacking.[7] Herein, we report that Pd-catalysed enantioselective C–H arylation provides a simple and general access to these carbo[n]helicenes.[8] Computational studies revealed a complex enantio-induction process. A systematic study of the CPL properties of the synthesised carbo[n]helicenes, showed that carbo[4]helicenes display comparable CPL responses to the higher carbo[6]helicenes. This suggests new avenues for the optimisation of chiroptical properties of helicene systems.



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Chemodivergent Asymmetric Synthesis via Catalytically Formed Chiral Auxiliary

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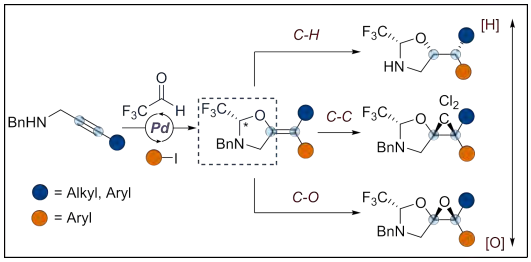
[1]Laboratory of Catalysis and Organic Synthesis (LCSO), Institute of Chemical Sciences and Engineering (ISIC), EPFL

Asymmetric catalysis remains as one of the most efficient ways to obtain enantioenriched products. This approach has culminated in Nobel prizes for asymmetric transition metal catalysis and organocatalysis in 2001 and 2021 respectively. However, catalytic asymmetric reactions are sensitive to the substrate structure and often require specialized reagents or additives [1]. In addition, for each chemically distinct transformation a different fine-tuned catalyst is required, because the catalyst is responsible for both reactivity and stereoselectivity.

We speculated that the reactivity and stereoselectivity could be decoupled by first introducing a chiral auxiliary using asymmetric catalysis, and then performing chemodivergent, robust transformations in a diastereoselective manner. Here we report a Pd-catalyzed enantioselective tethered carboetherification of propargylic amines using a trifluoroacetaldehyde derived molecular tether and aryl iodides as electrophiles (Scheme 1) [2]. The catalytically formed auxiliary was used to control facial selectivity in multiple chemically distinct transformations of the C-C double bond: hydrogenation, cyclopropanation and epoxidation [3]. In all cases challenging asymmetric reaction on tetra-substituted olefin was achieved using very simple conditions – heterogenous hydrogenation, cyclopropanation using free carbene and epoxidation with mCPBA. The obtained products serve as precursors to medicinally relevant amino alcohols or alpha amino ketones.



Scheme 1. Chemodivergent asymmetric synthesis via catalytically formed chiral auxiliary.

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Fluorinated Acyl Anhydrides in Switchable Divergent Photoredox Catalysis

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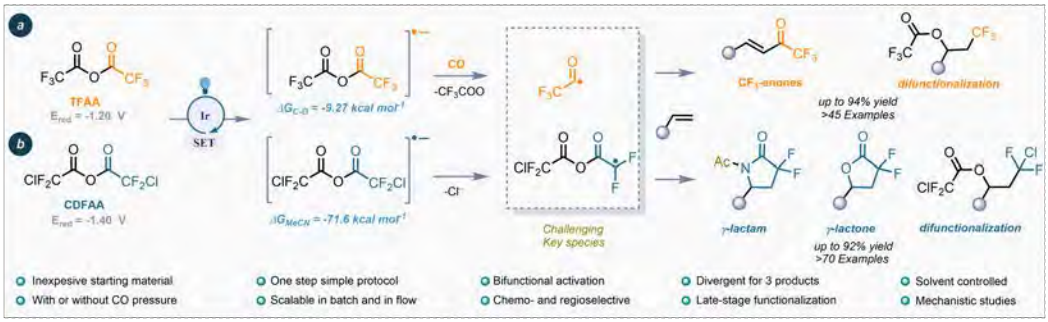
The outstanding impact of the fluorine atoms in drug discovery cannot be overestimated. Substantially, the incorporation of trifluoromethyl acyl (CF_3CO) and *gem*-difluoro (CF_2) moiety into the organic framework are highly sought due to the influence of these units on physicochemical and pharmacological properties of molecules. However, the introduction of these synthons requires the use of prefunctionalized starting materials or a surrogate at the beginning of the synthesis. To address this limitation, perfluoro carboxylic anhydrides can be selected as perfect precursors because they are abundant sources of fluorine building blocks and possess varied reactivity. Herein, we report a visible light-mediated photoredox activation of trifluoroacetic anhydride (*TFAA)* that occurs through a trifluoroacyl radical mechanism. Remarkably, this radical can be stabilized under a CO atmosphere, and in the presence of olefins, delivers the corresponding α,β-unsaturated trifluoromethyl ketone derivatives.[1] This method can also be diversified into a trifluoromethylation protocol by simply changing the reaction parameters. Furthermore, we developed a mild and operationally simple strategy to access *gem*-difluoro compounds using chlorodifloroacetic anhydride (*CDFAA*) as a low-cost and readily available reagent. In this case, photoredox activation selectively triggers pseudo-mesolytic cleavage of a C−Cl bond generating an α,α-difluorinated radical, that acts as an exceptional bifunctional intermediate in reaction with alkenes. The reactivity of this radical is further determined by the solvent effect, detailed mechanistic studies of which have shown to occur by three distinct pathways, delivering in a single chemical step α,α-difluoro-γ-lactams, γ-lactones, or difunctionalized compounds. These methodologies are flow and batch scalable, possess excellent chemo- and regioselectivity, as well as practical for late-stage diversification of biorelevant molecules.[2]



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Benzylic Metalation of Toluenes Using a Hydrocarbon Soluble Sodium Alkyl Reagent

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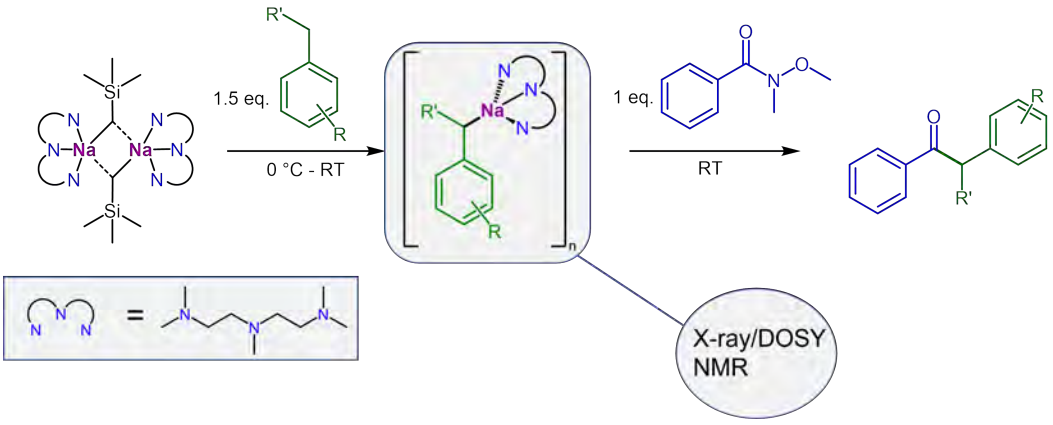
Alkyl sodium reagents have been proposed as an alternative to organolithiums, one of the workhorses of synthetic chemistry.[1] Several factors, however, have hindered their wider synthetic application in organic synthesis. They are plagued by poor solubility in hydrocarbon solvents and low stability in donating ethereal solvents. This combined with their notoriously poor thermal stability has made them inconvenient for use by synthetic chemists, leading to a lower accessibility when compared with their lighter lithium congers.[2] Despite these limitations, recent reports in the field of organosodium chemistry have focused on the development of new reactivity and have demonstrated the potential of these powerful reagents in synthesis, surpassing the reactivity obtained with other organometallic reagents.[3][4] However, the nature of the sodiated intermediates in both the solid state and in solution remains poorly understood, missing an opportunity to improve upon these reagents.

In this communication, we report on the exploitation of the Lewis basicity of PMDETA (N,N,N',N'',N''-pentamethyldiethylenetriamine) to access a hydrocarbon soluble alkyl sodium reagent for use in the development of a facile and selective route towards benzylic metalation of the corresponding toluene derivatives. We demonstrate the reactivity of the formed benzyl sodiums through application in benzylic aroylation with a Weinreb amide to access synthetically useful 2-aryl acetophenones. Reaction intermediates were characterised using a combination of X-ray crystallography and ^{1}H DOSY (Diffusion Ordered SpectroscopY), providing the first reported synthetic and structural insights on the constitution of the intermediates in these reactions, advancing our understanding of how these systems operate in solution.



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Performance boost of a merocyanine photoacid by supramolecular encapsulation

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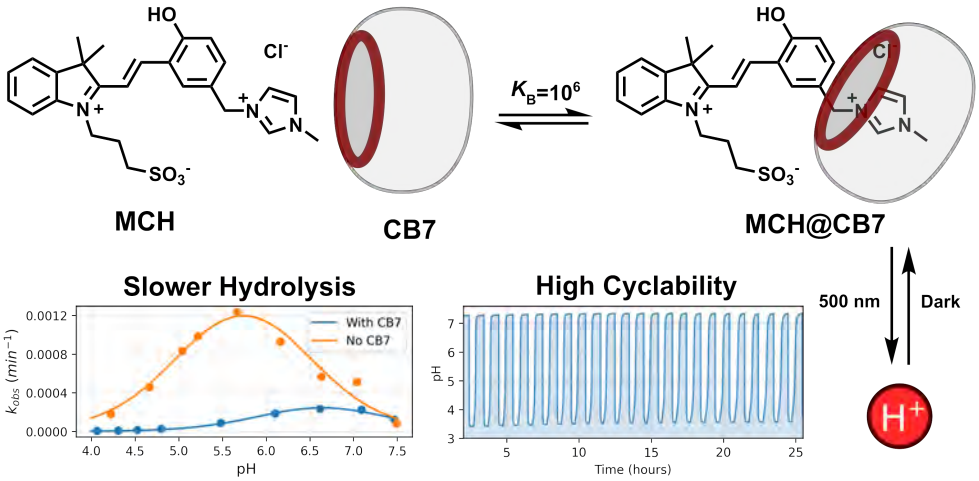
Merocyanine photoacids possess the ability to control the pH of their solutions by means of visible light irradiation. Their applications are remarkable and cover many fields including biochemistry[1], medicinal chemistry[2], material science and engineering[3], analytical chemistry [4], supramolecular chemistry[5] and synthetic organic chemistry[6]. However, the instability of merocyanines towards hydrolysis along with the poor solubility in water are important limiting factors in their application space.



To circumvent these problems, we have synthesized and characterized an imidazolium merocyanine derivative displaying high water solubility and strong affinity towards cucurbit[7]uril. The host-guest complex becomes more stable towards hydrolysis and prolongs the timespan of operation.

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The Bioorthogonal *C,N*-Cyclic Azomethine Imine-Isonitrile Ligation

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[1]ETH Zürich

Bioorthogonal reactions are powerful tools to study and modify a wide range of biomolecules such as proteins, sugars and small metabolites in their native environment.[1-3] In the last decade, bioorthogonal reactions with high reaction rates (k_2 > 1 M^{-1} s^{-1}) and good chemoselectivity have been developed.[4] Most of these reactions utilize large chemical reporters, which limits their utility for labelling a wide array of biomolecules, especially glycans, lipids, and small metabolites.

Here, we introduce a new bioorthogonal reaction between *C,N*-cyclic azomethine imines (AMIs) and isonitriles as the smallest bioorthogonal reporters. AMIs are stable in aqueous media containing biologically relevant nucleophiles. In the presence of functional groups present in biological systems – including often-problematic thiols – AMIs react chemoselectively in aqueous buffer with isonitriles. This AMI-IN ligation is fast (k_2 up to 200 M^{-1} s^{-1}), fully orthogonal to cycloaddition reactions such as the Strain-Promoted Azide-Alkyne Cycloaddition (SPAAC), and provides a stable amide bond as ligation product.

Selective labelling of an isonitrile containing protein *in-vitro* and of a cell surface isonitrile *in-vivo* showcased the compatibility of the ligation with biological systems.

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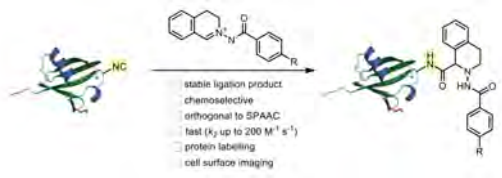

Tosyloxybenziodoxolone: a platform for the umpolung of alkynes

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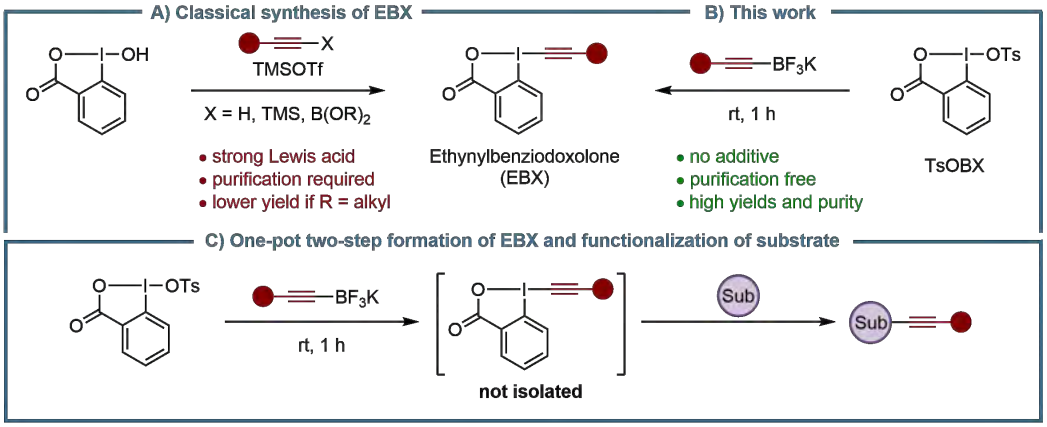
In the last decade, cyclic hypervalent iodine compounds proved to be particularly useful reagents to perform umpolung reactions. Under a variety of conditions, they allow the transfer of the functional group linked to the I(III) center in an electrophilic fashion.[1] One major drawback of those methodologies is the synthesis of the reagents, usually requiring two steps. This is particularly problematic in the case of ethynylbenziodoxolones (EBXs) since different substituents can be present on the alkyne. Currently, each diversification will require the synthesis, isolation and purification of the corresponding reagent, sometimes in poor yields depending on the alkyne substitution. In this context, a method allowing their *in situ* formation and subsequent reaction would allow a straightforward transfer of various alkynes starting from a common intermediate. To the best of our knowledge, this approach has not been explored, potentially due to the strong Lewis acids required to transfer the alkyne to the iodine center (Scheme 1A).[2] We found out that by starting from tosyloxybenziodoxolone (TsOBX),[3] a more activated yet stable precursor, the transfer of an alkynyltrifluoroborate salt can be performed without any activation (Scheme 1B). This reaction proceeds in one hour at room temperature and afford EBXs in high yield and purity upon simple work-up.[4] Using these milder reaction conditions, they could be generated and subsequently used to transfer the alkyne moiety without isolation (Scheme 1C).



Scheme 1: Classical and novel synthesis of EBX reagents and their use for a one-pot two-step process.

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Organocatalyzed Conjugate Addition Reactions of Aldehydes to Nitroolefins with *Anti*-Selectivity

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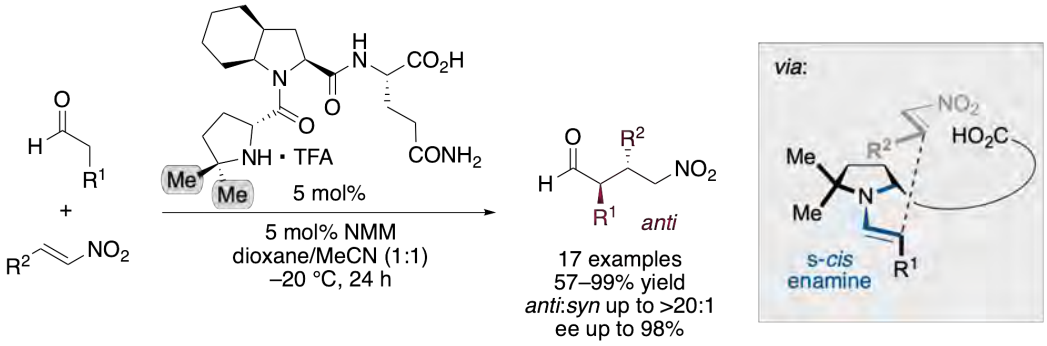
[1]Laboratory of Organic Chemistry, D-CHAB, ETH Zürich

In the past two decades, organocatalyzed stereoselective conjugate addition reactions of aldehydes to nitroolefins have been a subject of intense research.[1] The resulting γ-nitroaldehydes are versatile synthetic intermediates that can be further derivatized into e.g. pyrrolidines and γ-butyrolactams, which are key moieties present in bioactive compounds. While the conjugate addition reaction affording the *syn*-diastereoisomer is well established, broadly applicable, non-substrate specific *anti*-selective methods remain unprecedented.

Our group introduced highly reactive tripeptidic catalysts of the type H-Pro-Pro-Xaa (Xaa = any amino acid), which catalyze conjugate addition reactions of carbonyl compounds to nitroolefins in high yields and with excellent *syn*-diastereoselectivity and enantioselectivity.[2] Detailed mechanistic and conformational studies on these tripeptides showed that the s-*trans* enamine intermediate is involved in the rate- and stereoselectivity-determining step.[3]

Drawing on this knowledge and the ease of structural modification of peptides, we envisioned that a general *anti*-selective catalyst could be developed.[4] The key to the reversal of diastereoselectivity is installing substituents at Cδ of the reactive pyrrolidine. This modification favors the reaction of the s-*cis* enamine with the nitroolefin, forming the *anti*-configured γ-nitroaldehyde. With the optimized peptide catalyst, different aldehydes and nitroolefins were converted to the products in high yields and stereoselectivities, highlighting the generality of our methodology. NMR spectroscopic and computational insights corroborated the preferential formation of the s-*cis* enamine, and showed that the catalytic system operates under a Curtin-Hammett scenario.



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Cyclopentadienone Iron Complex Catalyzed Hydrogenation of Ketones: An *Operando* Spectrometric Study Using Pressurized-Sample-Infusion Electrospray-Ionization Mass-Spectrometry

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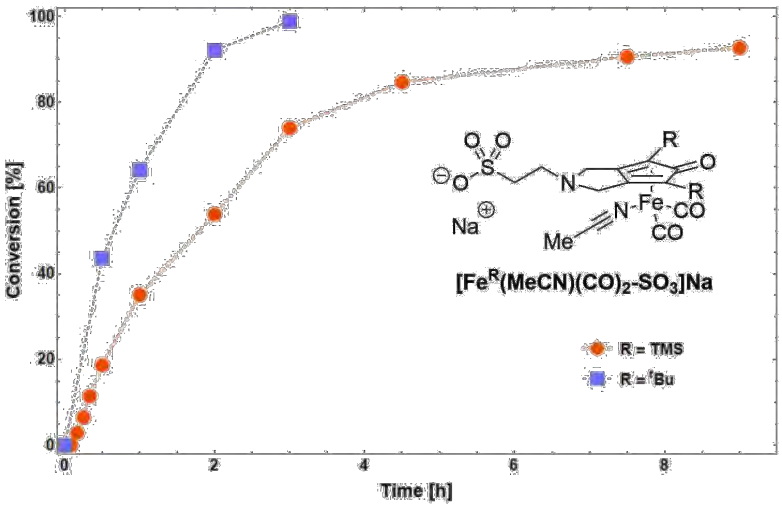
[1]ETH Zurich

In order to gain mechanistic insight into the cyclopentadienone iron complex catalyzed hydrogenation reaction [1,2] conducted in aqueous/alcoholic solvent, we prepared the sulfonate charge-tagged and water soluble complexes **[Fe^{R}(MeCN)(CO)$_2$-SO$_3$]Na** (R = TMS, ^{t}Bu). The introduced charge allows monitoring of hydrogenation reactions by Pressurized-Sample-Infusion Electrospray-Ionization Mass-Spectrometry [3], providing kinetic and mass spectrometric data simultanously. Analysis of the kinetic and mass spectrometric data showed pronounced catalyst decomposition for R = TMS. Based on mass spectrometric and radical inhibition experiments, the decomposition involves solvolysis of the TMS groups followed by dimerization to afford dinuclear Fe(I) complexes, ultimately forming catalytically inactive tricarbonyl species. The identification of the solvolysis decomposition pathway allowed the targeted improvement of the catalytic system by replacing the TMS groups by non-hydrolysable ^{t}Bu groups. The mechanism-guided structural change in the catalyst resulted in an increased rate (full conversion in 3 h instead of 18 h) and a boost in turnover number from ca. 65 to > 1000. The present study suggests that for hydrogenations with cyclopentadienone iron complexes, the use of alkyl groups flanking the C=O double bond in the ligand is beneficial over the use of silyl groups when conducted in aqueous media.



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Accessing Asymmetric Nickel-Catalyzed Carbonyl α C-H bond Functionalization

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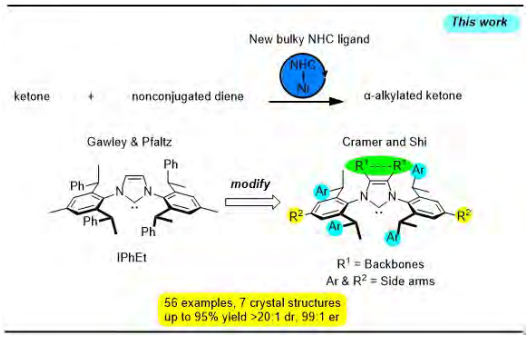
[1]EPFL

Given to the acidity of adjacent C-H bond of carbonyls and the diverse reactivities of the formed enolate, the α-C-H functionalization of ketones becomes one of the most fundamental C-C bond-forming reactions for the access to the carbonyl compounds. Besides them, the metal catalyzed C-H functionalization process provides an alternative strategy to achieve simple ketone α-alkylation with unactivated olefins. However, harsh reaction conditions or additional directing groups are generally required and the reactivity of the di-substituted α-C-H bond is still limited. Herein, we found that a new bulky nickel N-heterocyclic carbene (NHC) system enables the conversion of such acidic α-proton into a reactive nickel hydride species directly, which unlocks an alkylation of various ketones with unconjugated diene, providing γ,δ-unsaturated ketones with vicinal stereocenters in high regio- and diastereo-selectivity. Even excellent enantio-selectivities of this transformation can be achieved when the chiral side-arms are introduced in the NHC ligand. The reaction proceeds under redox neutral and mild condition without any additional base or additive. The mechanistic studies and density functional theory (DFT) calculation support the existence of nickel hydride intermediate and β-hydride elimination chain walking process. The reductive elimination step should be the rate determine step for this C-C bond forming transformation.



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Direct Photoexcitation of Ethynylbenziodoxolones: An Alternative to Photocatalysis for Alkynylation Reactions

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[1]EPFL, Lausanne, Switzerland, [2]Max-Planck-Institut für Kohlenforschung, Mülheim, Germany

Alkynes are important moieties for synthetic and medicinal chemistry, chemical biology and material science.[1] Indeed, they can be used either as inert and rigid linkers as well as reactive moieties.[2] A possible synthetic method for such functional group implies using Ethynylbenziodoxolones (EBXs) as radical traps in photocatalytic alkynylations.[3,4,5]

Here we report the ability of aryl-substituted EBXs to undergo direct photoexcitation. Thus, acting both as photooxidants and radical traps, alleviating the need for a photocatalyst.[6] These properties have been tested on previously reported photocatalyzed EBX-mediated transformations such as decarboxylative[3] and deboronative[4] alkynylations as well as the oxyalkynylation of enamides.[5] In addition, the photoactive properties of Ar-EBXs have been applied to the synthesis of alkynylated quaternary centers from tertiary alcohols, *via* stable cesium oxalate salts, and from tertiary amines, *via* aryl imines.

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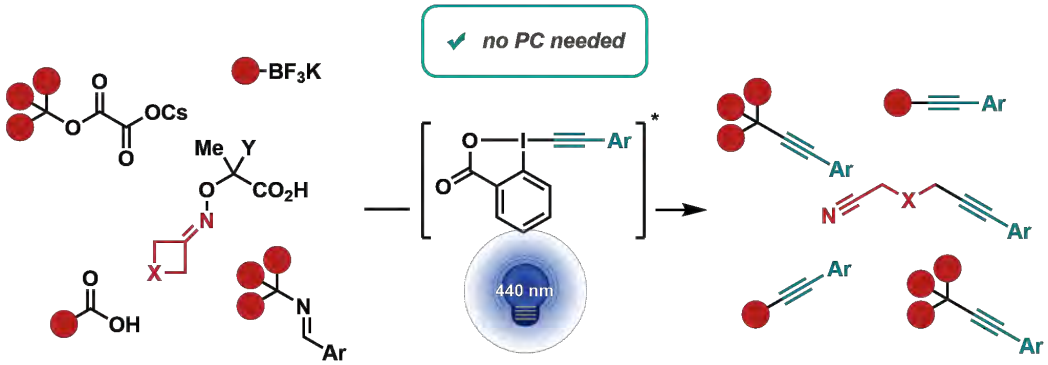

Thiol-Mediated Uptake and Inhibition of Phosphorothioate-Derived Transporters

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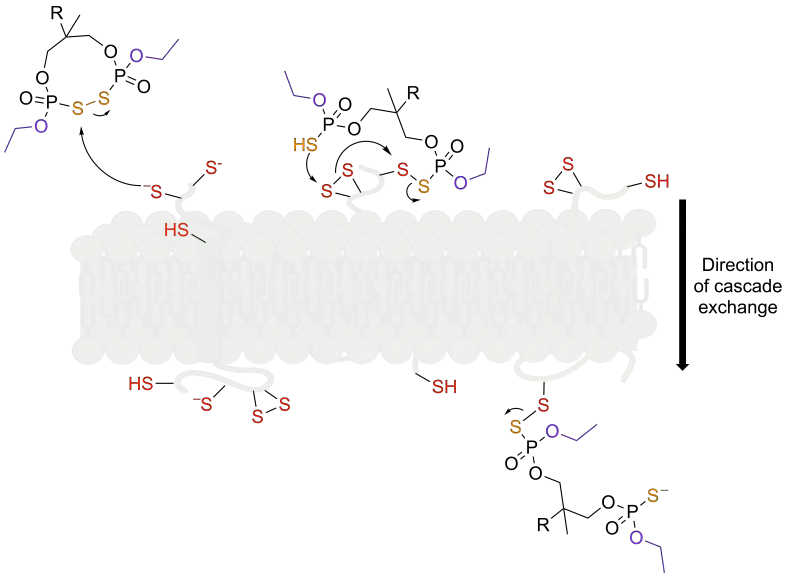
Thiol-mediated uptake (TMU) is a process in which molecules, containing thiol/disulfide reactive moieties, participate in cascade reactions with cell surface thiols/disulfides facilitating the internalization. Some of the most known TMU transporters are cell-penetrating poly(disulfides)[1], cyclic oligochalcogenides[2] and most recently pnictogen-expanded cyclic disulfides[3]. Recently our focus was turned to oligomer phosphorothioates (OPS) since their enhanced uptake as compared to phosphorodiester has been linked to thiol-mediated uptake[4]. The idea is to harvest this enhanced uptake of phosphorothioate group and create new structures that can then be used to deliver other substrates. So, we propose the synthesis and evaluation of a new family of TMU transporters and inhibitors containing two PS groups, linked together by a pseudo-disulfide bond. The studies at the single molecule level will allow better understanding of the internalization process and broader uptake applications.



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Geländer Molecules with orthogonal joints: Design and Synthesis of Macrocyclic Dimers

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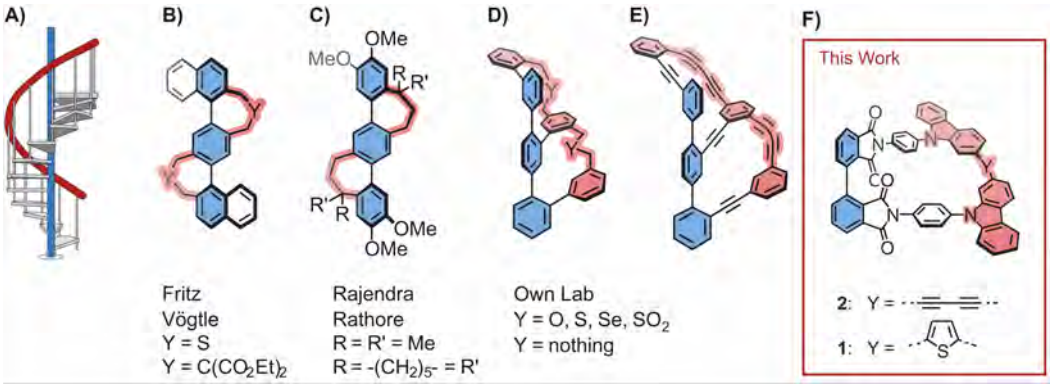
Linking a molecular rod (backbone) with long linkers (banister) forces the latter to wrap around the former, inducing helical chirality (Scheme 1). The wrapping of the linker is reminiscent of the banister of a spiral staircase (Scheme 1A), thus prompting Vögtle and co-workers to coin the German term “Geländer”-oligomers for these architectures (Scheme 1B).[1] In their early investigation, they linked adjacent phenylenes in terphenylene with short linkers yielding beside the chiral (*M,M*) and (*P,P*) isomers the achiral (*M,P*) meso-form in a statistical distribution.[2] Our group introduced the concept of length mismatch in ladder-oligomers, reporting the first “Geländer”-oligomer with the banister wrapping continuously around the backbone in 2014 (Scheme 1D). If a single strand in a ladder-oligomer is elongated, the longer strand (banister) wraps around, the shorter strand (backbone).[3] These structures only contain one helical axis, and therefore, only chiral (*M*) and (*P*) isomers are found. Due to the asymmetry of the junction connecting backbone and banister, regioisomers are eventually formed in a late divergent step by the rotation of the junctions.[4] By symmetrizing the molecular design, the divergent step is circumvented. The helical structure can be formed in two subsequent robust homo-coupling steps and, together with the symmetrical design, eventually allows to synthesize longer oligomers efficiently.



Scheme 1: Figure 1: **A)** Sketch of a spiral staircase as inspiration of “Geländer” molecules with an axle (blue) and a helical banister (red). “Geländer” helices of **B)** Vögtle, **C)** Rathore, and **D)** and **E)** from our own lab. **F)** New “Geländer” macrocycles **1** and **2** with rectangular arrangements between axle and rung, as well as between rung and banister.

The novel “Geländer” structures were obtained in 6 and 7 steps, respectively. Both helical structures were fully characterized and chirally resolved. All enantiomers were assigned by enantiopure synthesis and comparison of experimental and simulated chiroptical properties.

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HTE/Data Science Augmented Investigation of NiZn Nanocrystal Catalyzed Alkyne Semihydrogenation

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Selective hydrogenation of alkynes to alkenes is of broad interest in both industry and academia with processes ranging from purification of ethylene feeds by semihydrogenation of acetylene to synthesis of valuable *Z*-alkenes in vitamins and natural products.[1] Developed in the 1950s, Lindlar catalyst ($Pd/CaCO_3/Pb(OAc)_2$/quinoline) still finds ample use as batch semihydrogenation catalyst, despite several drawbacks *i.e.* scarcity and increasing prices of palladium, inherent toxicity of lead, narrow substrate scope and overhydrogenation to alkanes.[2] Fueled by the continuous search for earth-abundant and non-toxic catalysts, alloyed nickel nanoparticles showed great promise owing to high activity, selectivity and functional group tolerance.[3] However, controlling the size and the composition of nanoparticles, which ultimately influence their reactivity in hydrogenation,[4] remains a difficult challenge.

Herein, we describe the synthesis of highly monodisperse bimetallic Ni-X (X= Zn, Ga, In) nanocrystals, 3-4 nm in size, prepared via a colloidal amalgamation seeded growth procedure that allows for excellent composition control.[5] Using high-throughput experimentation, we show that Ni_3Zn nanocrystals are highly active and selective for the liquid-phase semihydrogenation of alkynes in batch, displaying good functional group tolerance, while operating as non-supported dispersions under mild reaction conditions at low nickel loadings. Through integration of data science techniques encompassing density functional theory featurization, dimensionality reduction and hierarchical clustering, we demonstrate that the studied substrate scope covers the chemical space of commercial alkynes, providing a data set for future studies on alkyne-related reactions.

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Flow Chemistry for the Chemo-Enzymatic Synthesis of Anaesthetics

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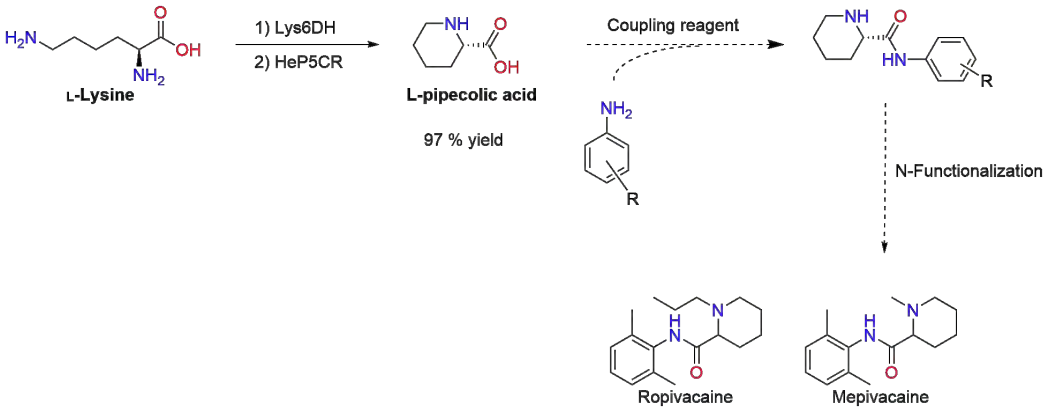
The synthesis of L-pipecolic acid from L-lysine has been proved to be very efficient *via* a continuous biocatalytic cascade.[1] Encouraged by those results, we envisioned the preparation of amide anaesthetics (such as Ropivacaine and Mepivacaine)[2] derived from bulky amines, using a chemo-enzymatic approach.



Initial results showed that the order of the reactions was a key parameter in the successful synthesis of the final products. *N*-Functionalization of pipecolic acid was carried out by reductive amination using $NaBH_3CN$ as the reducing agent, achieving a 92 % yield in batch after 18 h. A significant increase in productivity was observed when performing the reaction under flow conditions, where a 90 % conversion was observed in only 10 minutes. Amide bond formation was performed using a recently published procedure.[5] This strategy, which involves an acyl fluoride intermediate, initially seemed promising since moderate yields were achieved when working in flow at high substrate concentrations (100 mM). However, this was found not to be the case when moving to process concentrations (10 mM), where no product formation under the screened conditions was detected. Work is in progress to replace the aforementioned reducing agent for a safer alternative. Moreover, different coupling reagents and strategies are being screened for amide formation to find a good compromise between synthetic efficiency and low environmental impact. A chemo-enzymatic continuous system affording bulky amides will dramatically decrease the overall environmental impact and cost efficiency of the industrial synthesis of these APIs.[6]

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Arene-Limited Non-directed C–H Arylation of Fluoroarenes

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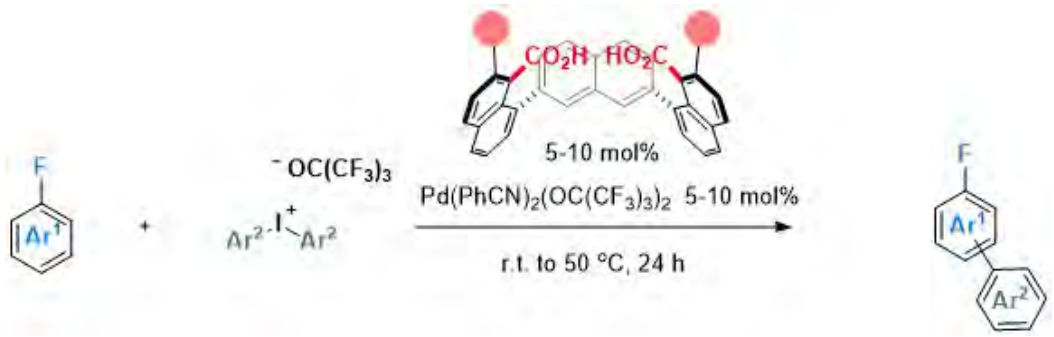
The activation and functionalization of C–H bonds avoids the use of pre-functionalized synthetic equivalents, allows non-traditional disconnections for drug and complex molecules synthesis, and improves synthetic step economy.[1] In the past two decades, numerous research groups contributed to the development of new methods for C–H activation, especially in the area of directed C–H activation, for which pre-installed directing groups are necessary. Many functional groups, transient mediators and templates have been used as directing groups to enable C–H activation at different positions in the molecule.[2] Meanwhile, the non-directed C–H activations are still limited due to the need for excess substrate, which is often used as a (co)solvent.[3]

Recently, our group developed the concept of spatial anion control for non-directed C–H activation using arenes as limiting reactants.[4] Using this strategy, we now demonstrate a Pd-catalysed direct C–H arylation of fluoroarenes[5,6] as limiting reactants. The mild conditions enable functionalization of diverse substrates and site-selectivity complementary to that obtained with other methods of fluoroarene functionalization can be achieved.



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Regioselective Synthesis of (Highly) Substituted Vinyl Ethers through a One-Pot Palladium-Catalyzed Assisted Tandem Olefin Migration/Heck Reaction

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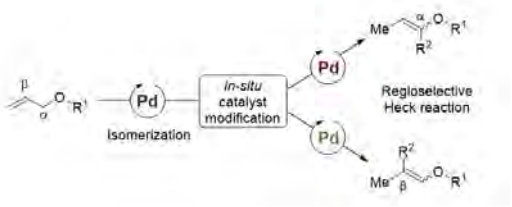
Over the last decades, extensive efforts have focused on accessing substituted vinyl ethers by Heck reactions.[1] In most cases, less hindered and more accessible terminal vinyl ethers were employed. Polysubstituted vinyl ethers were only used sporadically, with limited success.



Part of our research program consists in the design of multicatalytic processes in which transition metal catalysts are engaged in sequential olefin migration/cross coupling reactions.[2] In this context, we aimed at developing a mild assisted tandem catalysis in which sensitive 1,2-disubstituted vinyl ethers formed *in-situ* by olefin migration would be regioselectively cross-coupled with aryl electrophiles. Among the plethora of catalysts already developed in the literature for Pd-catalyzed isomerizations,[3] we selected a palladium(II) hydride catalyst[4] that can be efficiently reduced to a palladium(0) by the addition of an appropriate base. While performing the optimization, we found out that both the supporting phosphine ligands and aryl electrophiles play important roles to achieve high regioselectivities *en route* to tri-substituted vinyl ethers.

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Regulation Through Contortion: From Supramolecular Surface-Interaction to Tunable Spin Information Relays

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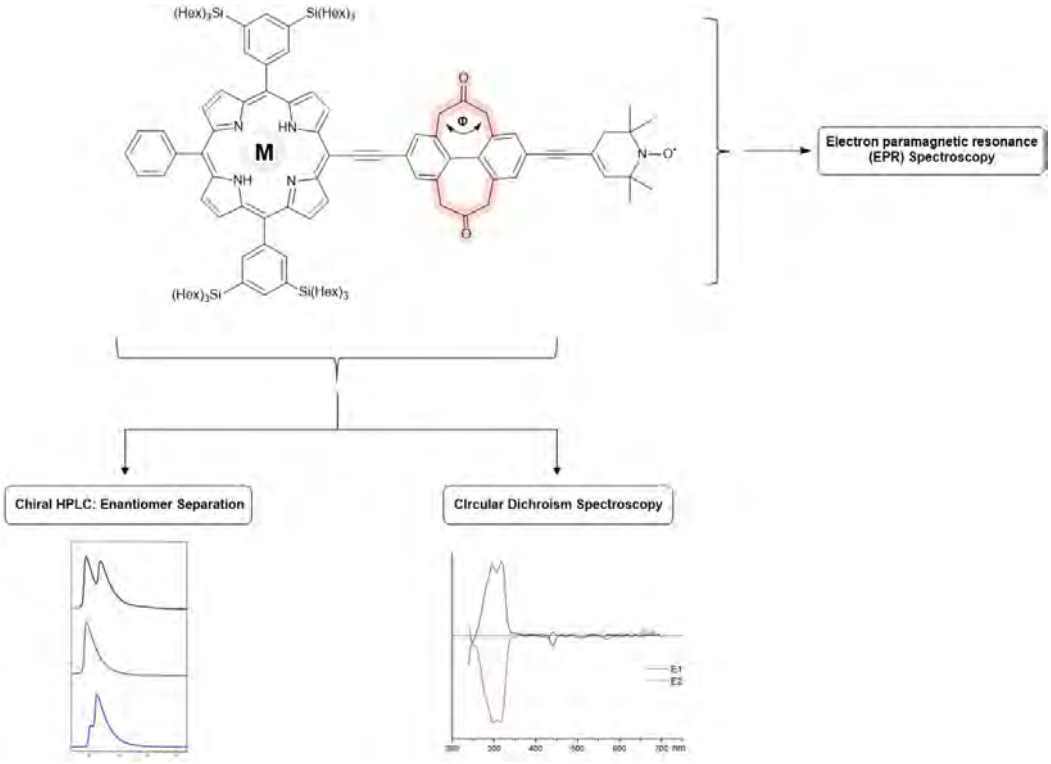
Highly versatile photogenerated multi-spin systems are promising candidates for a wide range of applications such as artificial photosynthesis, molecular spintronics, and spin catalysis.[1] While the radical acts as an efficient sensitizer that improves the intersystem crossing rate, the delicate covalent linkage between chromophore-radical systems serves as a means of controlling the excited state dynamics of the chromophore.[2] The aim of this project is to develop covalent multi-spin systems to study spin-information transfer and storage. This is performed by engineering systems that consist of at least two organic spin centers that we connect by a conjugated framework. The bridge between the two spin centers is then systematically modified in order to trace the changes in the resulting spin communication. By choosing a bridged biphenyl[3] as the linker between the chromophore and the radical, the electronic communication throughout the synthon is expected to vary with the torsion angle Φ between the planes of the two phenyl rings, which in turn modulates the spin-spin interaction.



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New Cationic Helical Dyes through Late-Stage Functionalization and their Electronic and (Chir)Optical Properties

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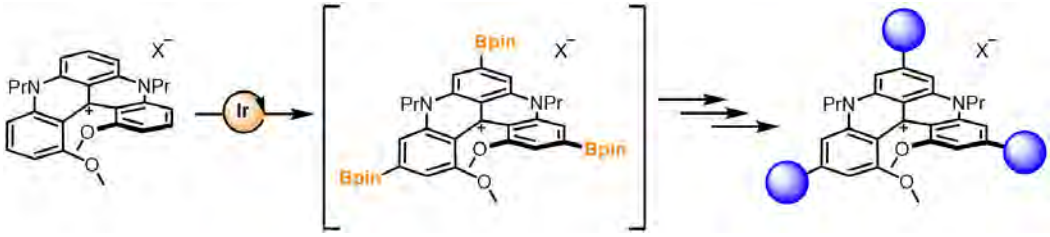
Helicenes are chiral *ortho*-condensed polyaromatic molecules of general scientific interest in view of their application in organic electronics, surface sciences, physics, biochemistry and catalysis.[1] Absorption, fluorescence, electronic circular dichroism (ECD) and circularly polarized luminescence (CPL) are important properties attached to helicenes and, for purely organic derivatives, these features appear usually in the blue range of the visible spectrum.[1,2] However, cationic hetero [4], [5] and [6]helicenes, which beneficiate from the extended delocalization provided by the triarylcarbenium framework, are welcome exceptions and allow the targeting of the red up to the NIR spectral region.[3] To manipulate these helical moieties, chemists often rely on the introduction of substituents at their periphery. In this regard, late-stage functionalization (LSF) of core structures is particularly attractive since it renders the synthesis less time-consuming while favouring a larger scope of products.[4] Herein, a new family of poly-functionalized cationic [4]helicenes and their electronic and chiroptical properties are presented. Thanks to Iridium catalyzed direct C-H borylation, a triple functionalization with regioselectivity *para* to the formal positive charge has been achieved on the classical DiMethoxyQuinAcridinium ($DMQA^+$) scaffold. The tris-borylated derivative is moisture sensitive and therefore impossible to isolate. However, it can be used as a synthetic intermediate to foster tandem derivatizations allowing the introduction of various aromatics, hydroxyl and ester groups. These newly introduced functionalities influence the electronic and optical properties of the helical core (*e.g.,* reduction and oxidation potentials, PLQY and lifetimes) and also impact key features of ECD and CPL spectra. For instance, derivatives presenting additional electron donating groups, show a sign inversion in correspondence to the lowest energy transition band in comparison to $DMQA^+$. Such behavior is unexpected considering that the functional groups are introduced at the periphery of the helical scaffold. Furthermore, thanks to the inclusion of tetraphenylethene (TPE) moieties, water-induced aggregation is observed that provokes a strong increase of g_{abs} and g_{lum} (10^{-3} range).



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Towards Radial Polymers as an Alternative to SWNCTs

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The demand to miniaturize electronics has stimulated researchers in pursue of new classes of nanomaterials such as single-walled carbon nanotubes (SWCNTs). Many properties of SWCNTs are strongly chirality-specific but traditional top-down synthesis of SWCNTs typically provides only mixed samples.[1] Consequently, chirality-specific formation of SWCNTs remains a formidable challenge and only in a few instances the control over the chirality and diameter has been successfully achieved.[2] On the contrary, bottom-up strategies may allow to produce specific SWNCTs by elongation of structurally precise macrocyclic precursors.[3] Although the challenging synthesis of these molecular “seeds” has been achieved, their polymerization has not been properly explored and represents a synthetic challenge.

The limits in the synthesis of SWCNTs motivated us to search for synthetic alternatives to SWCNTs that could (1) allow for both the radial and linear π-electron conjugation analogous to SWCNTs but (2) to use known and well-established chemistry of conducting co-polymers. Therefore, we designed radial polymers with π-electron surface oriented as in SWCNTs that could be assembled by a co-polymerization of easily accessible macrocyclic monomers and linear linkers. Such approach would allow for a high modularity to tailor the properties for specific applications.

Here, we will present the synthesis of functionalized macrocycles based on pyromellitic dianhydride[4] that allows for radial electron conjugation. Subsequently, the initial attempts to co-polymerize the macrocycles (1) covalently by Suzuki–Miyaura or Sonogashira cross-coupling reactions and (2) non-covalently via a supramolecular polymerization based on halogen-bonding into tubular structures will be discussed.

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Regio- and Enantioselective Copper-Catalyzed Protoboration of 1,1-Disubstituted Enecarbamates

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Boron containing molecules are of growing interest in the pharma industry.[1] In this context, the development of catalytic and selective approaches to readily access chiral B-containing compounds has gained important momentum over the last two decades.[2] Specifically, the Cu-catalyzed protoboration of alkenes has established itself as a particularly efficient method. However, while electron-poor and electron-neutral alkenes have been extensively explored, electron-rich substrates remain a fertile ground for investigations (Figure 1-a).[3]

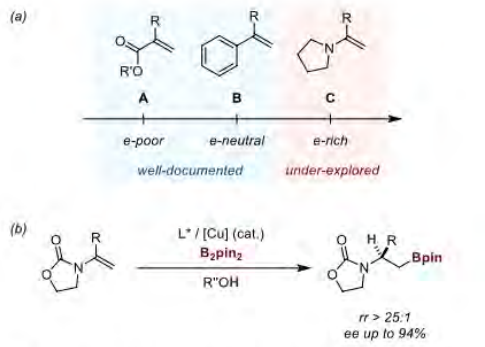

Figure 1. Regio- and enantioselective protoboration of enecarbamates.

Herein, we disclose our first step in this direction with the development of a highly regio- and enantioselective Cu-catalyzed protoboration of 1,1-disubstituted oxazolidinone-derived alkenes (Figure 1-b).

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Pd(II)/(IV)-Redox Cycle Enabled Oxidative [2+2] Annulation between Aryl Boronic Acids and Olefins

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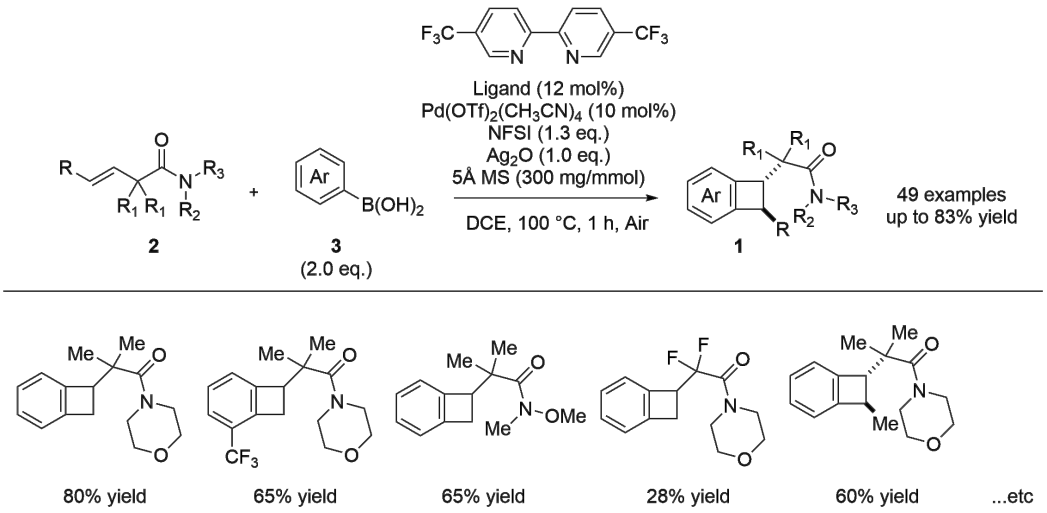
Benzocyclobutenes (BCBs) **1** are highly valuable synthetic targets because of their presence in natural products/drugs and the utility as an intermediate in Diels-Alder reaction. However, limited number of the synthetical strategies are available.[1] We present herein a modular synthesis of BCBs **1** via a Pd(II)-catalyzed oxidative [2+2] annulation of alkenyl amides **2** with arylboronic acids **3**. Mechanistic studies indicate that the C(sp^2)−H bond activation involve the s-alkyl-Pd(IV) intermediate and that the rapid oxidation of s-alkyl-Pd(II) intermediate to its Pd(IV) counterpart is essential to avoid the formation of Heck adduct.[2]



The optimization of reaction conditions, the scope of olefins and boronic acids, the synthetic transformations, and mechanistic studies will be presented in this poster.

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OSCAR: An Extensive Repository of Chemically and Functionally Diverse Organocatalysts

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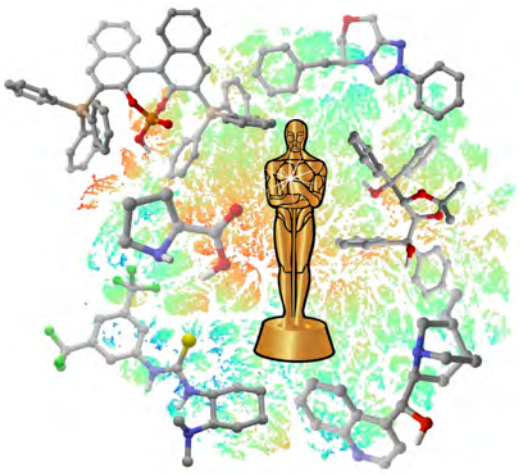
Organocatalysis is a well-recognised pillar of synthetic chemistry. Computational techniques offer invaluable insight into reaction mechanisms and occasionally help perform a fine-tuning of catalyst structure, but have generally failed to become truly predictive, being limited to case-by-case analysis and dominated by trial-and-error.[1] For these reasons, there is a need to develop conceptual and data-driven tools that facilitate both the exploration of a wider range of organocatalyst space and the optimization of reaction properties.[2,3]

In this work, we introduce OSCAR, a repository of organocatalytic species and of the different fragments that are extracted from them. We show how such a dataset is curated and enriched with experimentally obtained structures, and how the fragments are assembled in a combinatorial fashion to generate additional organocatalysts. In this way, the global chemical reactivity (*e.g.*, electro/nucleophilicity) and other electronic and steric properties of larger libraries of *in silico*-generated catalysts are evaluated to gather general trends across diverse classes of organocatalysts. We envision that OSCAR could constitute the starting point to define the combinatorial space for evolutionary experiments, as well as the basis for dataset curation to train statistical models for organocatalysis.



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Shape-Assisted Self-Assembly of Carpyridines into 1D Stacks

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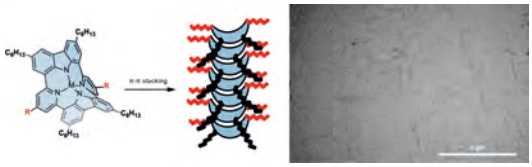
Shape-Assisted Self-Assembly (SASA) is a process in which the shape of a monomeric unit drives its assembly into stacks in the absence of strong non-covalent interactions such as H-bonding[1]. Saddle-shaped molecules stand out for these processes due to the translational and rotational rigidity of the monomers within the stacks. Carpyridines (CPs) are porphyrin-related metal-containing macrocycles bearing two carbazole and two pyridine units alternately connected through ortho aryl-aryl bonds[1,2]. This arrangement results in a saddle-shaped structure, where prefunctionalized building blocks allow the synthesis and tuning of properties of these macrocycles. These units have shown to be effective towards supramolecular assembly purely based on pi-pi interactions, demonstrating the significance of shape in self-assembly processes. Alkyl substitution onto the carbazoles has allowed us to study 2D sheet formation[1], which combined with substitution onto the pyridines with different side chains allows us to study the mechanism of assembly of the monomers into oligomers, and ultimately, into micrometer-long fibers.



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Single-atom heterogeneous catalysts for sustainable organic synthesis

G. Giannakakis[1], S. Mitchell[1], J. Pérez-Ramírez[1]*

[1]ETH Zurich

Organic transformations for the production of fine and specialty chemicals and pharmaceuticals are traditionally facilitated over organometallic precious metal complexes. Despite their widespread use in conventional organic synthesis processes, homogeneous catalysts show poor metal recovery and reuse. Single-atom heterogeneous catalysts (SACs) incorporating isolated metal centers on solid supports demonstrate promise for improving the sustainability of commercial organic transformations by avoiding these issues, while delivering highly selective and stable performance. In recent years, SACs have been employed for a broad range of organic synthesis reactions that include C-C and C-X coupling reactions, direct arylations, hydroborations, hydrosilylations, hydroformylations, and oxidations, among others.[1,2] Herein, we explore the potential for activating specific low-energy pathways through tailoring the chemical and electronic environment of the active metal for chemo-, regio-, and stereoselective applications, while ensuring full accessibility of metal centers. Opportunities and challenges towards their mechanistic understanding and technical implementation, including the influence of the reaction environment, deactivation pathways, and the need for improved sustainability metrics, are discussed.

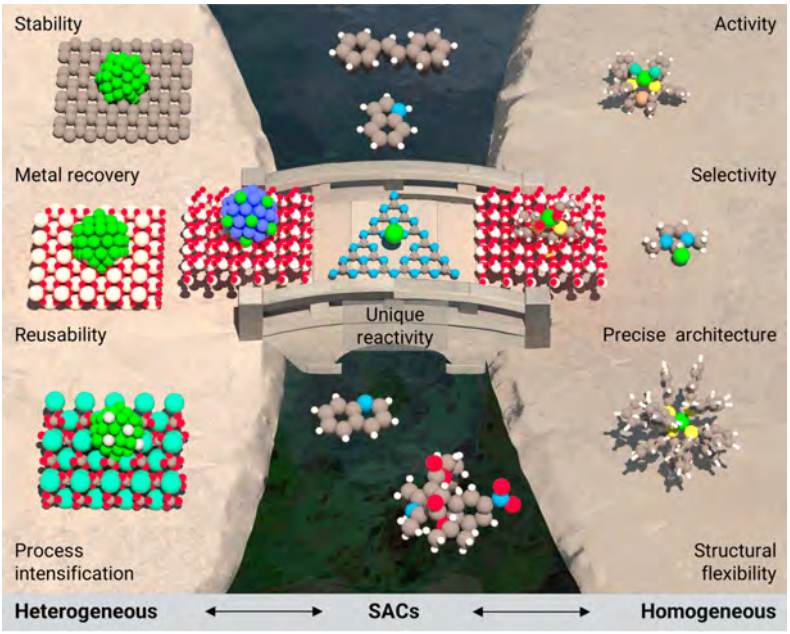

Fig. 1 Design of heterogeneous palladium catalysts based on nanoparticles (left) or single atoms (center) and commonly applied homogeneous systems (right) for sustainable organic synthesis.

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Multi-Photon Excitation with Red Light in Photoredox Catalysis

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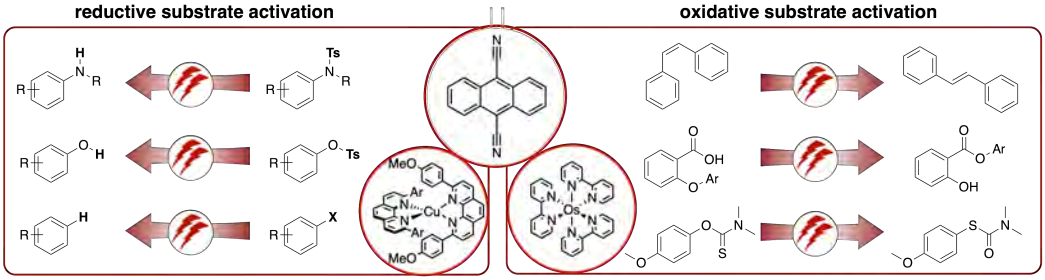
Multi-photonic excitation in photoredox catalysis has received increased attention within the last years as a viable tool for synthetic transformations.[1–3] From a synthetic point of view the main focus has been on reductive transformations while oxidative substrate activation has been rarely investigated.[4] In our proof-of-principle study, we combine 9,10-dicyanoanthracene (DCA) as organic dye with metal-based photocatalysts to achieve reductive as well as oxidative substrate activations with reduction potentials below -2 V *vs* SCE and oxidation potentials up to 2 V *vs* SCE (Figure 1).



The first part follows the concept of the well-known Z-scheme of natural photosynthesis, where two photoactive catalysts are combined to promote a chemical reaction. In our case, a copper-based catalyst serves as primary photoactive chromophore, which enables - in combination with DCA - challenging reductive transformations including dehalogenations of aryl halides as well as detosylations of protected phenols, amines and anilines (Figure 1). This reactivity has been investigated for a scope of over 40 substrates. The second part uses an osmium-based complex to achieve a change in the main reaction mechanism. With this mechanistic pathway, reactions starting with oxidative substrate activation are possible. Different light-driven model reactions including a cis-to-trans isomerisation, an ester-to-ether rearrangement, and a Newman-Kwart rearrangement can be performed with red light irradiation.

The change in reactivity is caused by a change in the reaction mechanism, and a reasonable understanding of the system is crucial. Therefore, both systems were investigated by time-resolved laser spectroscopy to clarify the respective reaction mechanism. Our work provides guidelines for better control of the reactivity in multi-photonic photoredox catalysis.

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Flipper changes in the donor and acceptor

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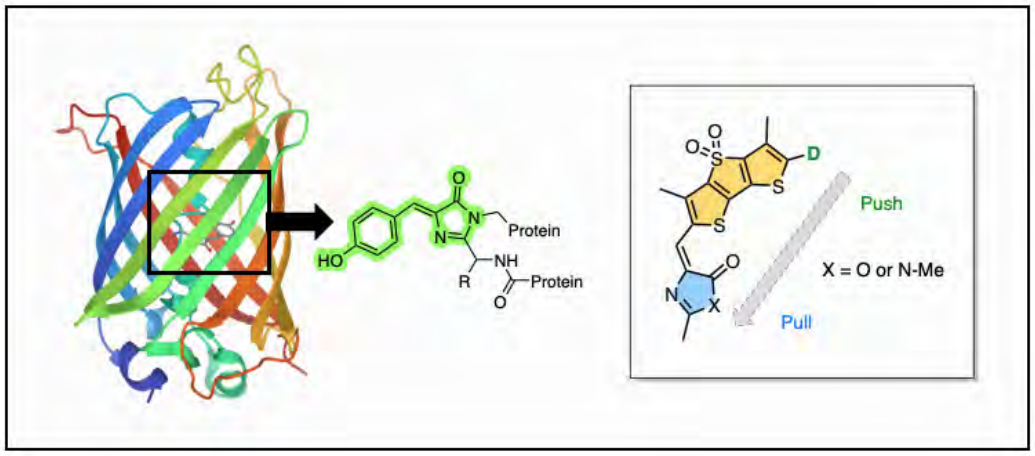
The study of physical-chemical properties in the cell membrane is very important because it is included in many cell processes. In this context to better understand this type of process, during the last decade, our group developed an imaging method based on the planarization of organic probes, such as Flippers, to study the mechanical forces engaged in living cells. Changes in the donor and in the acceptor could directly affect their properties and applications, as can be seen in previous works. Inspired by the naturally occurring fluorophore in GFP, we are now interested in studying the effects of oxazolone and imidazoline as acceptors in the Flipper. Furthermore, we want to study the effect of furan as a donor to improve stability and electronic



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Three- and One-Dimensional Assembly of π-Aromatics for Photo- and Redox-Active Organic Materials

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Aromatic π-assemblies can be observed, monitored and exploited for emergent applications in organic photo- and redox-active materials. Yet it is still a challenge to guide π-interactions in functional aromatic assemblies that have desirable orbital overlap as the orientation of interacting π-surfaces is largely dictated by electrostatic interactions.[1] Supramolecular materials are a popular approach towards guiding π-assembly, however, limitations such as their sensitivity to moisture, temperature, stress and propensity to aggregate into nondesirable orientations hamper their use in a device setting. π-Assembly using macromolecular scaffolds can help to overcome some of these issues by providing access to: i) more robust materials, ii) more reliable assembly processes, iii) materials that have hierarchical ordering, and iv) materials that have advanced functioning. We have utilised various strategies to achieve aromatic assembly using rylene diimides as a canonical π-motif. Capitalising on the recent trends in fullerene hexakis-adduct chemistry (Figure 1a) we have investigated three-dimensional (3D) aromatic assembly.[2] Additionally, the less explored polymer π-assembling[3] (Figure 1b) and shape-assisted[4] self-assembling (Figure 1c) systems that hope to achieve one-dimensional (1D) aromatic assemblies are presented.

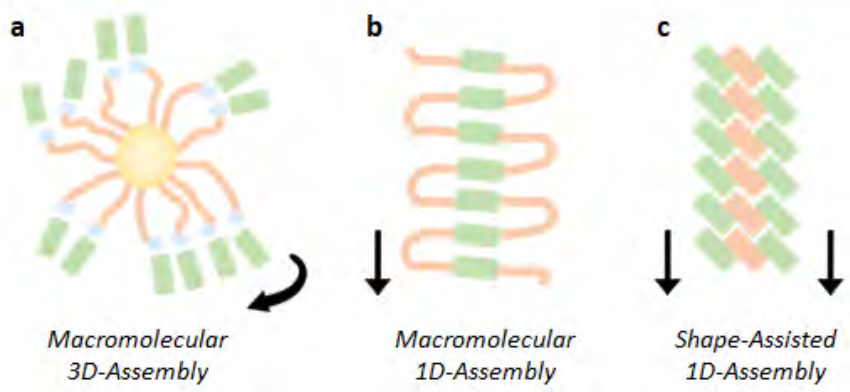

Figure 1. We have explored π-assembly in macromolecular scaffolds such as a) 3D self-assembling fullerenes and b) synthetic polypeptides that have a propensity to form 1D β-sheet assemblies. c) Also in pursuit of 1D assembly, we are currently exploring the shape-assisted self-assembly of photo- and redox-active "saddle" shaped molecules.

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Self-sorting collagen heterotrimers

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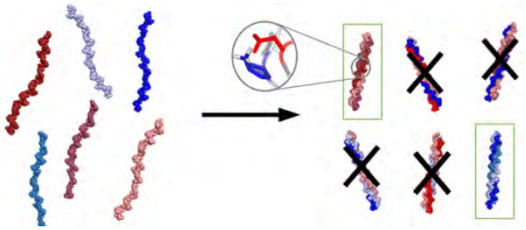
[1]Laboratory of Organic Chemistry, ETH Zurich, D-CHAB

Nature's complex supramolecular structures are an inspiration for the bottom-up design of synthetic biomaterials.[1] Collagen, the most abundant protein in mammals, and its triple helical structure provide strength to connective tissue.[2] The design of materials based on heterotrimeric collagen-like peptides is, however, challenging since a mixture of three different strands can form as many as 27 different combinations. Nature utilizes a disulfide-based code to tackle this problem and allow for the assembly into defined heterotrimeric collagen. Our group developed a method for the selective assembly of collagen model peptides into defined heterotrimeric structures through an interstrand salt bridge between (4*S*)-aminoproline (Amp) and aspartic acid (Asp).[3]



In this work, we studied how the position of the salt bridge influences the selectivity of heterotrimer formation. Heterotrimers with different lengths and distances between the salt bridges were prepared and studied by CD spectroscopy and native ESI-MS. The results enable the design of a self-sorting system in which six different CMPs formed only two triple helices out of 216 possibilities. The work established a code for collagen strand association.

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pH-Dependent Stoppering of Rotaxanes via Electrostatic Attraction

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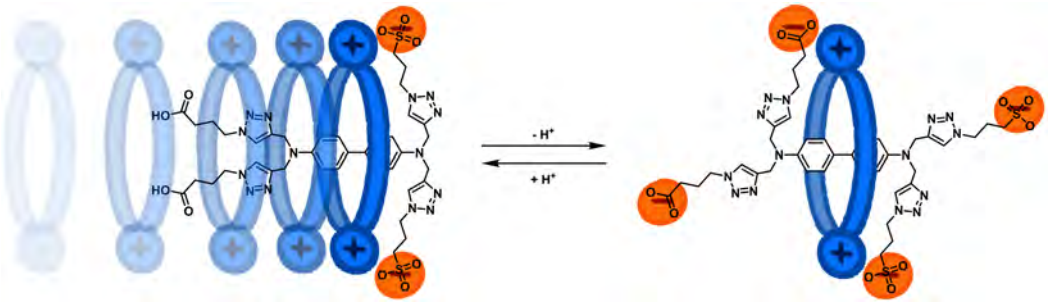
Among mechanically interlocked molecules, the subgroup of rotaxanes has been investigated as molecular machines and switches responding to various stimuli.[1] The macrocycle's linear mobility along the rod has triggered research into controlled, unidirectional translation. This motion is typically confined between two steric barriers ("stoppers") at the ends of the rod, although stimuli-induced slippage and deslippage of the macrocycle has also been achieved.[1] Furthermore, in the slippage assembly of rotaxanes, the stopper is meticulously designed to allow for slippage of the macrocycle onto the rod only at elevated temperature – the formed rotaxane is kinetically stable at room temperature.[2]

The use of electrostatic stoppers has been comparatively limited, with only few examples taking advantage of Coulomb repulsion of the macrocycle and the charged rod to form metastable (pseudo)rotaxanes.[3–5]



We designed a stable rotaxane based on the attractive electrostatic interaction of the dicationic macrocycle with anionic stoppers. The rotaxane comprises carboxylate groups, enabling (dis)assembly at acidic pH while rendering it stable at alkaline pH. Furthermore, the analogous pH-independent sulfonate stopper can be incorporated on one end of the rod to achieve directional slippage of the macrocycle.

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Cyclic Thiosulfonates for Thiol-Mediated Uptake: Cascade Exchangers, Transporters, Inhibitors.

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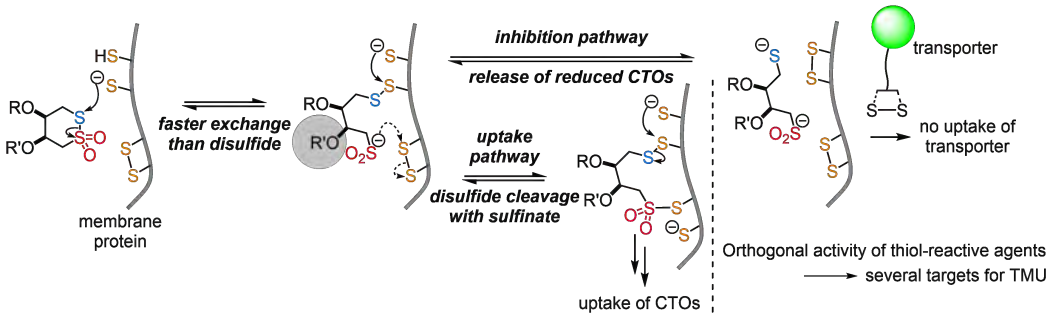
Thiol-mediated uptake (TMU) is one of the pathways of the cellular entry of biomolecules, in which the reversible disulfide exchange between the molecule and a protein on the plasma membrane plays a crucial role. The formation of dynamic covalent disulfide bonds at the cell surface facilitates cellular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

In our exploration of new motifs for efficient transporters and inhibitors, cyclic thiosulfonates (CTOs) have attracted a lot of interest as thiol-reactive agents. However, the use of thiosulfinates and thiosulfonates, oxidized forms of disulfides, has not been much explored so far in the context of cellular uptake, whereas CTOs can serve as anti-HIV agents [2].

Recently, our screening of thiol-reactive compounds over a wide range of chemical space showed that CTOs have good inhibitory activities against TMU [3]. Kinetic experiments revealed the excelled reactivity of CTOs with thiols over disulfides and thiosulfinates, and the ability of the sulfinate products to continue the cascade exchange with another disulfide [4]. As expected from their reactivity, CTOs afforded better fluorescent transporters than a standard disulfide transporter. Further enhancement of the transport activity was achieved with introduction of a hydrophobic group next to the reactive CTO moiety. The uptake of the CTO transporters takes place via TMU, proven by the inhibition with various thiol-reactive agents. An inhibition study with three transporters and more than 50 inhibitor candidates revealed the orthogonality of the inhibition with different TMU-active motifs, which strongly suggests the existence of multi targets for TMU.



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1,3,2-Diazaphospholene-Catalyzed Reductive Cyclizations of Organohalides

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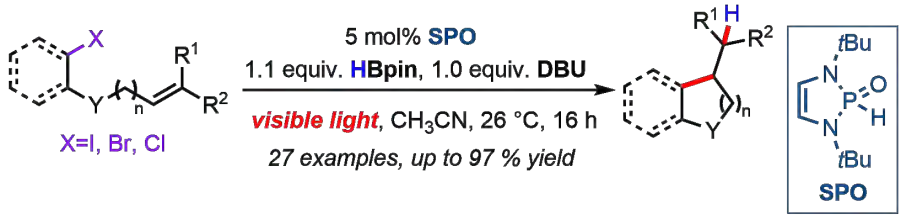
1,3,2-diazaphospholenes hydrides (DAP-Hs) are highly nucleophilic organic hydrides, serving as main-group catalysts for a range of attractive transformations.[1] DAP-Hs can act as stoichiometric hydrogen atom transfer agents in radical reactions.[2] Herein, we report a DAP-catalyzed reductive radical cyclization of a broad range of aryl and alkyl halides under mild conditions. The pivotal DAP catalyst turnover was achieved by a DBU-assisted *σ*-bond metathesis between the formed DAP halide and HBpin rapidly regenerating DAP-H. The transformation is significantly accelerated by irradiation with visible light. Mechanistic investigations indicate that visible light irradiation leads to the formation of DAP dimers $(DAP)_2$ which are in equilibrium with DAP radicals accelerating the cyclization. The direct use of $(DAP)_2$ enabled a catalytic protocol in the absence of light.



♦ ***Stable pre-catalyst*** ♦ ***Aryl and alkyl halides*** ♦ ***Mild conditions*** ♦ ***Mechanistic insights***

J. Klett, Ł. Wozniak, N. Cramer, *Angew. Chem. Int. Ed.* **2022**, DOI: 10.1002/anie.202202306

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Cycloparaphenylene double hoops as circularly polarized light emitters

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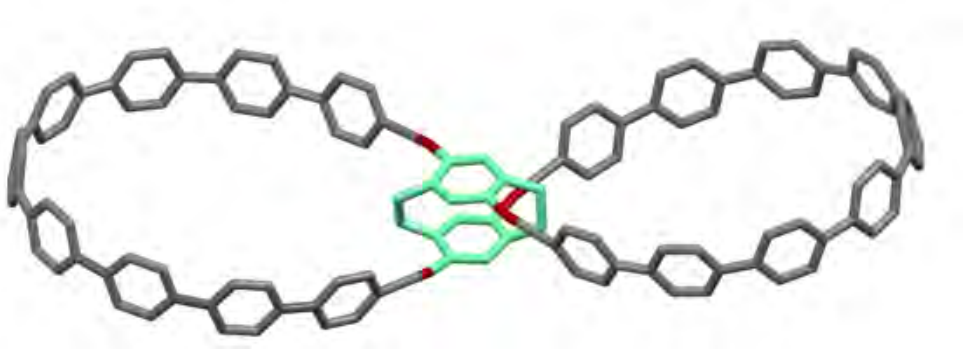
Introducing a curvature to a planar aromatic system affects its optoelectronic properties and may be used to design efficient fluorophores with unusual topologies.[1] In recent years, emission of circularly polarized light (CPL) has received increased attention because it promises to improve performance of optoelectronic devices, such as OLEDs. CPL emission originates from an unequal interaction of a chiral molecule with left- and right-handed polarization of electromagnetic field. The extent of this unequal interaction is expressed by the luminescence dissymmetry factor (g_{lum}), which can range from –2 to +2. Ideal CPL emitters should display large g_{lum} value and high fluorescence quantum yield at the same time.[2]

CPL emitters based on small organic molecules typically exhibit low to moderate g_{lum} ($\sim 10^{-3}$–10^{-2}) values and relatively low quantum yields. On the contrary, cycloparaphenylenes ([n]CPPs) possess excellent luminescence properties, such as visible-light fluorescence with high quantum yields. However, CPPs are not chiral which prevents them from displaying CPL. Interestingly, adapting the topology of CPPs into a figure-eight shape with D_2-symmetry, such as in CPP lemniscates, endows the compounds with inherent chirality and results in promising CPL emission ($g_{lum} = 3.7 \times 10^{-3}$, $\Phi_f = 0.36$).[3] Similarly, D_2-symmetric figure-eight-shaped helicene dimers display high $g_{lum} = 0.015$ albeit low Φ_f.[4]

In this work, we aim to tackle this challenge with the design and synthesis of chiral CPP-based double hoops. These figure-eight-shaped structures combine two highly fluorescent CPP rings and a rigid [2.2]paracyclophane core, which sustains the shape and conjugation and acts as a stereogenic element in the molecule. Such novel molecular topologies with stable chirality could provide CPL response with high overall brightness, *i.e.*, large g_{lum} and Φ_f at the same time.



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Stimuli-responsive molecular nanocarbons

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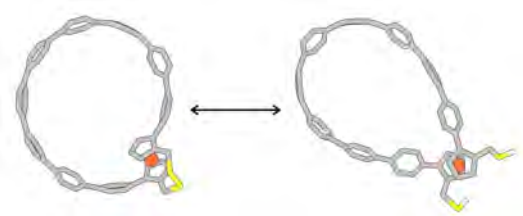
[*n*]Cycloparaphenylenes ([*n*]CPPs) are macrocycles consisting solely of *n* benzene rings connected via their para positions. They represent the shortest armchair carbon nanotubes. Although envisioned decades ago, the first synthesis of these strained molecules was accomplished only in 2008.[1] This achievement opened a new field in the research of polycyclic aromatic hydrocarbons. Small [*n*]CPPs (*n* = 5–12) exhibit unique size-dependent optoelectronic properties and host–guest chemistry giving rise to applications in bioimaging, electronic materials and synthesis of carbon nanomaterials.[2]

Due to their unique architecture, [*n*]CPPs possess a rigid, circular pore. The inward oriented π-orbitals of the benzene rings result in a high electron density inside the cavity, making [*n*]CPPs excellent hosts for electron-poor guests. In particular, [10]CPP was found to encapsulate fullerene C_{60} with a very high binding affinity due to the matching size and curvature of the host and the guest.[3] However, the reversibility of the complexation cannot be currently controlled by applying an external stimulus. The only attempt to control the curvature of a [*n*]CPP was by incorporation of azobenzene photoswitch into its structure. However, no photoswitching could be observed upon irradiation.[4]

In this work, I will present new design strategy that incorporates a ferrocene moiety into the [*n*]CPP backbone. Here, ferrocene represents a molecular hinge that permits to alter the curvature of the macrocycle reversibly. Therefore, the ferrocene molecular hinge should provide the control over the geometry of the cavity of the [*n*]CPP allowing the uptake and release of guests, such as fullerene C_{60}, at will. For this purpose, a synthetic procedure was developed to demonstrate that ferrocene can be successfully incorporated into [*n*]CPP. Furthermore, the structural and electrochemical properties of this new class of macrocycles will be established.



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Enantiospecific Complexation of Planar Chiral Iridium and Rhodium Cyclopentadienyl Complexes and their Application in Catalysis

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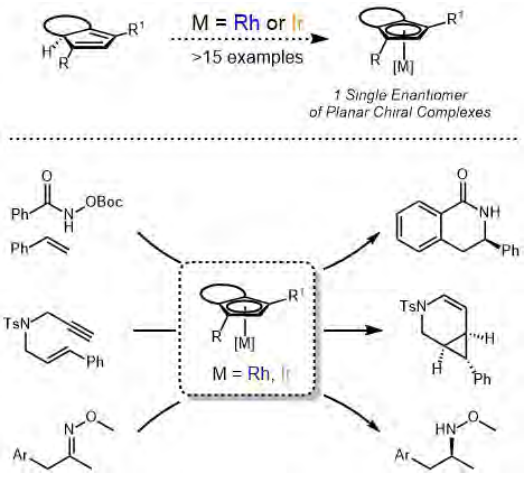
[1]EPFL SB ISIC LCSA

Most of the research on developing new chiral cyclopentadienyl complexes has focused on C_2-symmetrical ligands while C_1-symmetrical ligand remain understudied.[1] This discrepancy can easily be explained by the lack of reliable complexation method for non-symmetrical ligands. Additionally, while more than seven families of planar chiral cyclopentadienyl complexes are known, less than ten applications in asymmetric catalysis are reported: all with rhodium as metal. To tackle the need for a general complexation strategy for such ligands, we describe an enantiospecific complexation from chiral cyclopentadienes. This methodology would enable an easier and more streamlined access to a completely new class of enantiopure planar chiral cyclopentadienyl rhodium and iridium complexes, without the need for preparative HPLC or diastereomeric separations,[2] opening new horizons for future ligand design. To illustrate the catalytic properties of this class of ligand we probed them on various group 9 metal-catalyzed reactions.



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Understanding aggregation formation during peptide synthesis using in-line UV analysis

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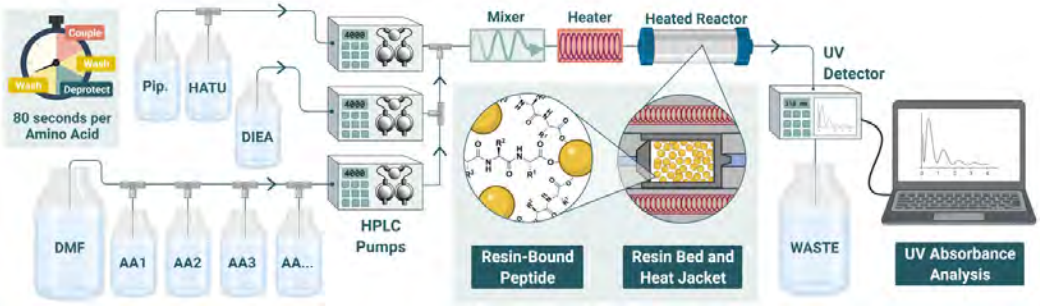
In 2021, 80 peptide drugs were available on the global market, and this number is expected to increase significantly in the incoming years.[1] With more than 150 peptides in clinical development and 500 peptides undergoing preclinical studies, the need for more efficient, reliable, and optimized peptide synthesizers is even more pressing. The use of the first flow-based peptide synthesizers dates back to the early 80s.[2,3] In the recent years, advanced fast-flow peptide synthesizers were developed, allowing for automated and efficient couplings that can be optimized by time-resolved monitoring.[4-6] However, sequence-dependent aggregation is still one of the main reasons for unsuccessful peptide synthesis.



The introduction of time-resolved reaction monitoring, relying on the Fmoc deprotection trace, gives access to valuable data such as the aggregation during synthesis and the efficiency of each coupling. Relying on this in-line data and after postulating that aggregation is dependent on the sequence with an increased effect of the first few amino acids, we investigated the impact of the linker in-between the resin and the peptide itself and tried to determine its role in aggregation formation. The end goal of this study is to give peptide chemists a better understanding of the causes that lead to aggregation. This phenomenon is still one of the biggest challenges for peptide synthesis and tackling it would allow not only for the obtention of better yields and purity, but also for the possibility to understand the origin of the so-called “difficult couplings”.

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Access to α-Chiral Olefin via Nickel-Catalyzed Enantioconvergent Cross-Coupling between β-Bromostyrenes and Secondary Grignard Reagents

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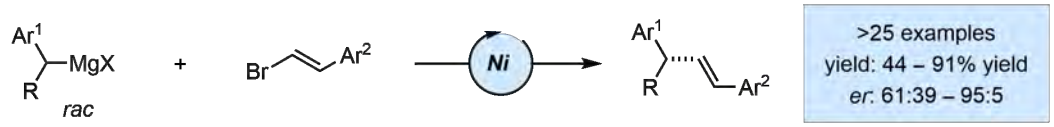
Owing to the prevalence of α-chiral olefins in biologically active compounds, access to this motif has attracted continuous attention.[1] In recent years, significant efforts have been placed on the development of direct methods to forge potentially stereolabile tertiary benzylic/allylic stereocenters via Csp^2–Csp^3 bond-forming strategies.[2] Among other examples, this includes several Ni-catalyzed enantioselective reductive cross-coupling reactions,[3] an enantioselective dual [Cu/Pd]-catalyzed hydroalkenylation of olefins[4] and photo-induced Ni-catalyzed Csp^3–H benzylic alkenylations.[5]



While the Ni-catalyzed cross-coupling between vinyl bromide and rapidly epimerizing benzylic Grignard reagents is well-documented,[2,6] the corresponding reaction using b-bromostyrenes has not reached the same level of achievement.[7] We report herein our efforts in this direction with the identification of a general and highly enantioselective nickel catalyst supported by a chiral (P,N) ligand. The system is operationally simple, and applicable to a broad scope of substrates.

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Protecting-Group-Free Synthesis of 1,2-*cis* Glycosides using a Double Inversion Strategy

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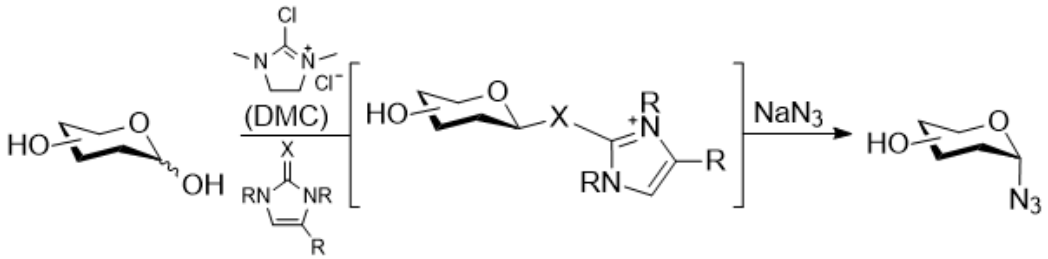
The synthesis of biologically active glycoconjugates is one of the cornerstones of Glycoscience. However, traditional methods typically involve multi-step synthesis, employing complex and protracted protecting group strategies. These methods are generally technically demanding, inefficient, expensive, and logistically difficult to achieve.

Recently, selective reactions of un-protected sugars in water have become a focus of attention. In particular, Shoda and co-workers have reported the use of 1,3-dimethylimidazolinium chloride (DMC), and derivatives thereof, for the selective conversion of un-protected sugars to various target products in water, often furnishing the 1,2-*trans* anomer.[1–3]

Access to the 1,2-*cis* linked glycoside using the DMC chemistry remains elusive. Herein, we report the design and use of a double inversion strategy for the synthesis of 1,2-*cis* glycosides *via* the formation of a 1,2-*trans* chalcoimidazolium intermediate. The synthesis of the chalcoimidazoles will be present, as well as it's reactivity towards various electrophiles. The use of this novel reagent for the stereoselective synthesis of 1,2-*cis* glycosides will allow access to biologically important glycoconjugates possessing this linkage.



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Chiral Cyclic Alkyl Amino Carbene (CAAC) Transition-Metal Complexes: Synthesis, Structural Analysis and Evaluation in Asymmetric Catalysis

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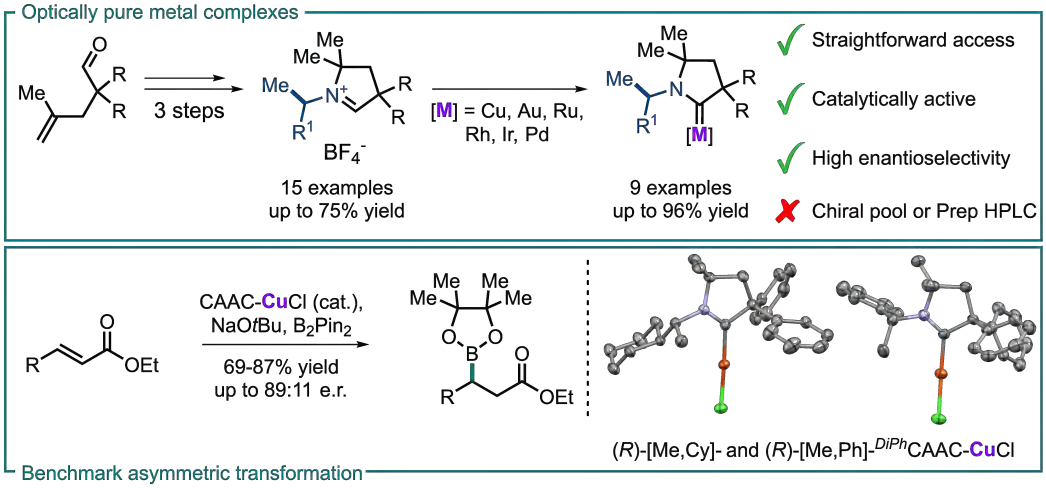
[1]EPFL SB ISIC LCSA

Despite recent advances in the field of cyclic alkyl amino carbenes (CAACs) including few complementary synthetic strategies affording CAACs with various substitution patterns, the application potential of chiral CAACs to efficiently catalyze asymmetric organometallic transformations remains largely underdeveloped. Herein, we describe a convenient and robust route that incorporate common chiral primary amine allowing the access of a broad range of chiral CAACs precursors. The corresponding transition-metal complexes with Cu, Au, Ru, Rh, Ir and Pd were obtained in a straightforward manner. The steric parameters of the complexes were comprehensively collected by X-ray single crystal analysis to serve as a source of information for further ligand design. The preliminary application potential of the copper CAAC complexes was tested in asymmetric conjugate borylation of an α,β-unsatured ester providing 89:11 er, thus illustrating the potential of chiral CAACs in asymmetric catalysis.



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Unprotected 2-azidoamines from alkenes – Facile access to masked diamines by using stable N–O reagents

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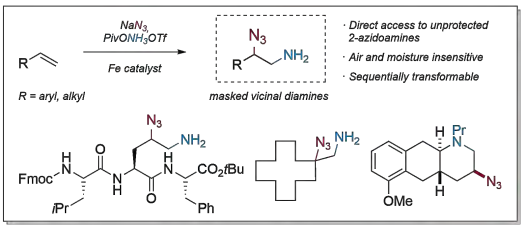
Amines are ubiquitous building blocks in nature encountered throughout all chemical disciplines.[2] Owing to their prevalence and broad applications, robust and versatile methods for their preparation have received significant attention in synthetic chemistry. A popular approach for forging the C–N bond of amines is to employ readily available hydrocarbon feedstocks in metal catalysed reactions.[3] However, for the majority of these reactions, the reagents bearing the nitrogen source are either impractical to handle or introduce the amino motif in a protected form. The latter case usually requires an additional deprotection step which often necessitates harsh reaction conditions before the amino group can be further processed. This shortcoming can be elegantly obviated by introducing the desired amino group in its unprotected form. Reagents which proved to be ideal for this task are *O*-substituted hydroxylammonium salts, especially *O*-pivaloyl hydroxylammonium triflate (= $PivONH_3OTf$, PONT).[4] Making use of this versatile, bench-stable reagent, our group has recently developed several amination reactions which directly yield unprotected anilines, aminoalcohols, beta-chloramines and sulfinamides from unfunctionalised arenes, alkenes and thiols, respectively.[5]

Herein, we present the iron-catalysed synthesis of unprotected 2-azidoamines which feature as ideal precursors for vicinal diamines.[1] Starting from a wide range of unactivated alkenes and vinylarenes, the desired unprotected amines are obtained in high yield and excellent regioselectivity. The mild and robust reaction manifold is tolerant to ambient conditions and applying related aminating reagents allows for the synthesis of isotopic labelled or secondary 2-azidoamines.[6] Down-stream derivatisations included CuAAC Click chemistry as well as synergistic and sequential manipulations of the two differentiable amino functionalities. This chemoselectivity was further showcased in the formal synthesis of several bioactive compounds. Furthermore, initial mechanistic experiments suggest a radical pathway being operative in the transformation.



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Emissive Properties of Helicene Carbon Nanohoops

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Helicenes are polyaromatic hydrocarbons consisting of *ortho*-fused benzene rings which adopt a helical screw-like shape.[1] They display strong chiroptical properties and circularly polarized luminescence although with a low quantum yield. Substantial synthetic modification of the helicene backbone is required in order to improve their emissive properties.[2]

On the other hand, cyclo-paraphenylenes ([*n*]CPPs) have been proven to have favorable luminescence properties, such as visible-light fluorescence with a high quantum yield, which is often preserved even in solid state.[3,4] However, the absence of chirality in CPPs prevent them to display circularly polarized luminescence. This could be circumvented by introducing a chiral unit to the structure of CPPs.[5]

In this contribution, the design and synthesis of helicene carbon nanohoops as chiral emitters that combine helicene scaffolds and [*n*]CPPs will be discussed.[6] The structure of the nanohoops was studied by single crystal X-ray diffraction, 1D and 2D nuclear magnetic resonance, and mass spectrometry and the photophysical properties investigated by absorption and emission spectroscopies. Helicene carbon nanohoops possess emission properties similar to symmetry-broken [*n*]CPPs. We have managed to obtain an enantiomerically pure sample of a helicene carbon nanohoop and study circularly polarized luminescence. Lastly, we discovered that helicene carbon nanohoops adopt Möbius topology in the solid state and in solution.

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Unlocking Aluminum Reagents Towards Deprotonative Metalation Reactions

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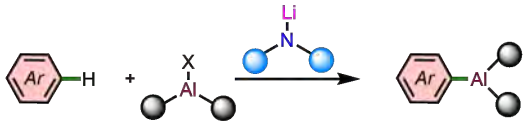
Lithium amides have widely been used for deprotonation reactions, becoming essential reagents in synthetic chemistry due to their high basicity and low nucleophilicity. However, these advantages also come with various limitations as the lack of selectivity, the need for cryogenic temperatures, the formation of unstable intermediates and the sensitivity to air and moisture. Trying to overcome some of these limitations, in 2009 the Knochel group proposed the deprotonative metalation of a broad range of substrates by "$Al(TMP)_3$" (TMP: 2,2,6,6-tetramethylpiperidide), formed by mixing LiTMP and $AlCl_3$.[1] The use of aluminum offers various advantages as it is the third most abundant element on earth, is non-toxic and has a broad functional group tolerance. It has also recently shown to be efficient in organoaluminum-mediated cross-coupling reactions,[2] exhibiting their versatility in synthesis. However, the constitution of these aluminated species has been overlooked and is poorly understood.

Shedding light into the use of aluminum in deprotonative metalations, this work presents a systematic investigation on the alumination of aryl compounds. By combining lithium amide bases and commercially available aluminum reagents, we report a new approach to obtain trivalent Aryl-Al compounds in an easy and general way. The direct access to these compounds from unfunctionalized molecules under mild conditions will pave the way to prepare a wider range of aluminium reagents and their subsequent use in cross-coupling reactions.



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Synthesis of Tetrahydrooxepines *via* Ring Expansion of Medium-Sized Oxacycles

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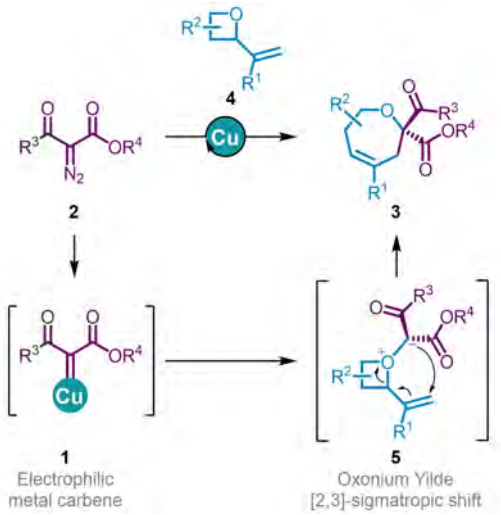
Medium-sized oxacycles are important building blocks present in a large variety of natural and medicinal products.[1] Their synthesis has been investigated over the years and can be achieved *via* cycloaddition, ring-closing metathesis and ring expansion reactions among others.[2] In this context, the propensity of oxonium ylides to undergo ring expansions *via* [1,2]- and/or [2,3]-shifts constitutes an important strategy.[3] To generate the ylide intermediates, decomposition of acceptor diazo reagents under metal-catalyzed conditions is a common synthetic tool; *in-situ* generation of electrophilic metal carbenes **1** and their reactivity with cyclic ethers acting as Lewis bases affording the targeted products.[4]

Herein, with α-diazodiesters and α-diazo-β-ketoesters as reagents **2**, the formation of tetrahydrooxepines **3** was investigated by ring expansion of vinyl oxetanes **4**, using Cu(II) salts as catalysts. The desired 7-membered rings are afforded as major products *via* [2,3]-sigmatropic rearrangements from oxonium ylide intermediates **5**. Further attempts using this strategy to give access to functionalized medium-sized oxacycles will be provided.



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N-Nitrosaccharin: Powerful Organic Reagent for Electrophilic Ipso-Nitration of Silanes

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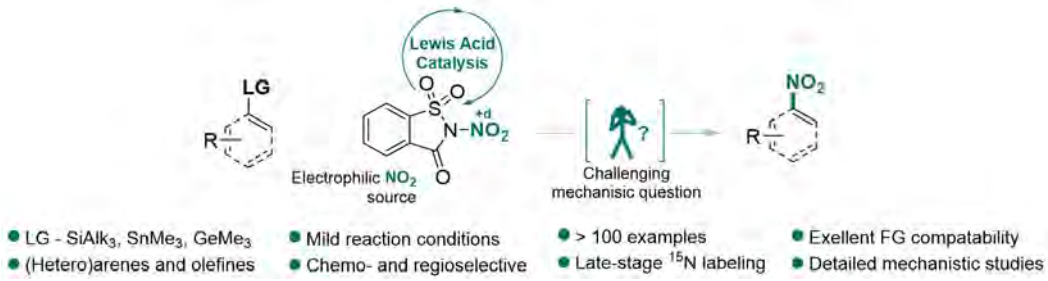
Nitro group does not need an introduction, yet it has to be introduced. Peculiarly, taking into account the novel applications of nitro group, e.g. cross-coupling reactions[1] and a series of recently discovered nitro-derived drugs [2], the traditional direct-electrophilic approach has to be revised, in particular in the context of the late-stage nitration. Indeed, direct nitration of organic frameworks using classical approaches is poorly regioselective, while the use of bulky directing groups detains all the disadvantages of its application. From this perspective, ipso-nitration drugged extensive attention in the last two decades. Thus, the identification of potential functional groups for ipso-nitration is in high demand as it can lead to the development of chemo- and regioselective protocols.

Although, organosilicon compounds are generally believed to be of low reactivity in organic synthesis and homogeneous catalysis, herein we are pleased to showcase the highly efficient and orthogonal responsiveness of aryl silanes with *N*-nitrosaccharin reagent under Lewis Acid catalysis.[3,4] This methodology is characterized by mildness, robustness, and exceptional functional group tolerance, delivering the corresponding nitro-derived adducts with excellent chemical efficiency and regioselectivity.[5] Based on this transformation, an overlooked mechanism of aromatic substitution was revealed. A combination of computational, spectroscopic, and experimental mechanistic studies has strongly supported an unprecedented sequence of transition states and intermediates, which are proposed to be a hidden general mechanism for a broad range of ipso-substitution transformations. We anticipate that our comprehensive mechanistic evidence as well as practical and mild electrophilic ipso-nitration protocol will find application across a broad range of disciplines.



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Direct Light Activation of Hypervalent Iodine Reagents: Substrate-Controlled C-C or C-H Alkynylation of Cyclopropanes.

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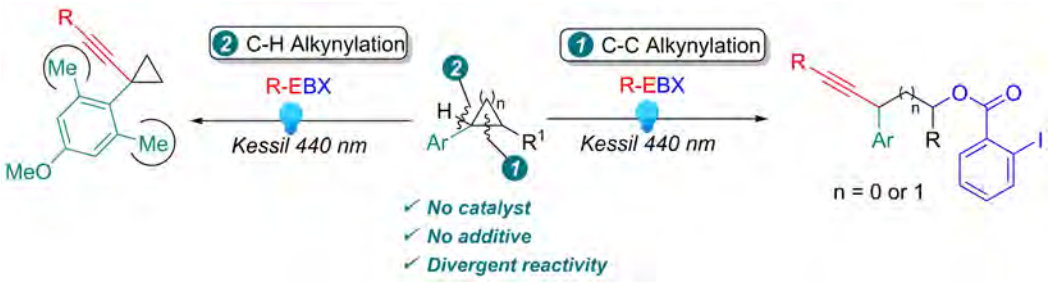
[1]Laboratory of Catalysis and Organic Synthesis, Institute of Chemistry and Chemical Engineering, Ecole Polytechnique Fédérale de Lausanne, [2]Laboratory for Computational Molecular Design, Institute of Chemistry and Chemical Engineering, Ecole Polytechnique Fédérale de Lausanne, [3] Laboratory of Catalysis and Organic Synthesis and NCCR Catalysis, Institute of Chemical Sciences and Engineering, Ecole Poly-technique Fédérale de Lausanne

We report a visible light-mediated alkynylation of cyclopropanes via direct photoactivation of aryl-EBX reagents without the need for a photocatalyst or additive. In addition, we discovered a complete switch of the reaction outcome from C-C to C-H alkynylation when using aryl cyclopropanes bearing two *ortho* substituents on the benzene ring. We tentatively attributed this effect to the conformational constraints induced by the aryl ring. Computational studies indicated that the C-H alkynylation became a favored nearly barrierless process for substrates having two *ortho* methyl groups on the benzene ring



Tin V.T. Nguyen, Jerome Waser, *ChemRxiv,* **2022,** Cambridge: Cambridge Open Engage

Aromatic C−H Insertions of Malonate Metal Carbenes for Late-Stage Functionalization of Diaza [4]Helicenes

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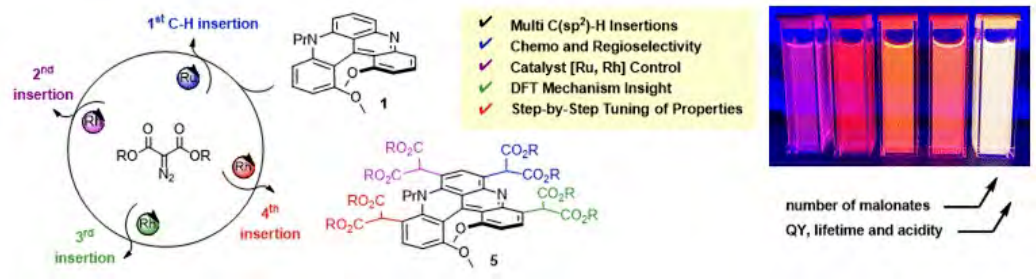
Late-stage functionalization (LSF) strategies are particularly attractive for providing large scope of products or promoting specific reactivities at single site only.[1] Herein, in the context of heterohelicene chemistry, metal-catalyzed decompositions of α-diazomalonates are shown to afford multi-functionalized chiral diaza [4]helicenes – in a controlled stepwise manner. By selecting the catalyst, $[CpRu(CH_3CN)_3][PF_6]$ or $Rh_2(oct)_4$, chemo and regioselective insertions of derived metal carbenes are achieved in favour of mono- or bis-functionalized malonate derivatives, respectively (r.r. > 49:1, up to 77% yield, 12 examples). Mechanism of formation and origin of selectivity are elucidated based on DFT calculations. Controlled formation of products of tris- and tetra-malonate insertions can be further achieved thanks to the higher reactivity of rhodium carbenes. This step-by-step multi-introduction of malonate groups is particularly useful to tune / increase important properties of the [4]helicene core such as absorption (Δλ−44 nm), emission (quantum yield 5-22%, lifetime 3.0-8.4 ns) and Brønsted acidity (pK_a 1•H+ to 5•H+, from 6.63 to −0.42 and lower).



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Functionalization of C_{sp}^2-C_{sp}^2 bonds through earth abundant metal-catalysis

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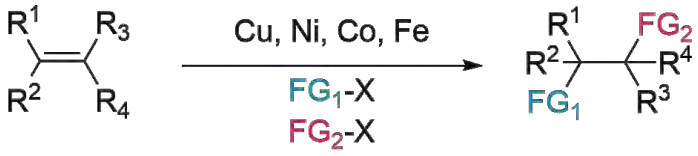
In the last decades, the use of earth abundant metals has emerged as an alternative to the well-established transition-metal catalysts such as rhodium, palladium or iridium. Due to their high availability and reduced cost, they now appear as key catalysts for the development of new synthetic routes.[1] More than replicating known transformations, earth abundant catalysts can surpass traditional metals both in reactivity and selectivity.[2] For instance, difunctionalization of unsaturated carbon-carbon bonds allows access to complex molecules by addition of two new functional groups such as halogens, carbon-based groups or nitrogen-based functionalities.[3] Herein, we report a earth abundant metal catalyzed difunctionalization of unsaturated bonds with a high molecular complexity improvement (Scheme 1).



Scheme 1: Alkenes difunctionalization with earth-abundant metals

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Electrocatalytic Activation of Ferric Nitrate

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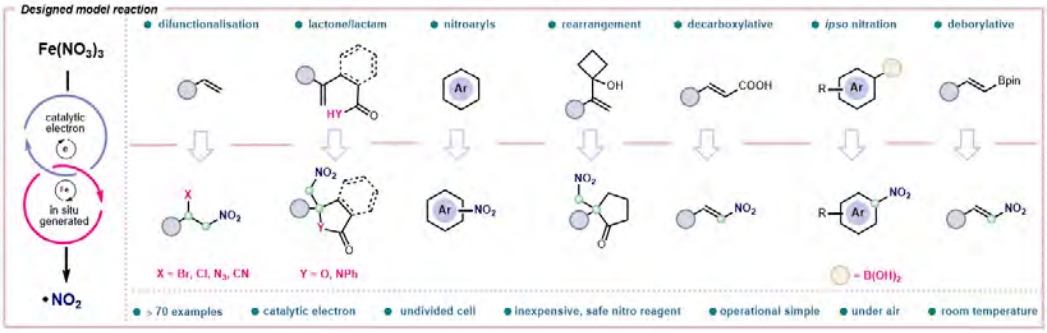
Catalysis, a key technology in organic chemistry, is among the most important and fascinating areas of discovery in both academic and industry research. Chemical and enzymatic catalysis has been recognized at least 16 times by the Nobel Foundation. Among manifold catalysts, which are often based on transition metals and complex ligand systems, the proton is the smallest one, while the electron is just a charged particle. The principle of electron catalysis was introduced almost 60 years ago, however this field is still poorly explored, and today only a handful of reactions that have used electrons in a catalytic or sub-stoichiometric amounts are known.[1] Electrocatalysis is among such rare transformations, where a large excess of toxic reductants/oxidants is replaced by electrons using a controlled potential, making the overall process mild, robust, and sustainable. Hence, the design of concepts of ´the electron as a catalyst´ is challenging, but a very promising field for solving problems with inefficient reactions in modern organic synthesis.



Chemo- and regioselective nitration of carbon-hydrogen bonds is our long-term interest.[2] Iron is the most abundant metal on earth and is also known to form intermediates with diverse valences, which makes this metal an ideal catalyst for designing new directions in catalysis. Ferric nitrate, a potential inorganic nitrating reagent, is inexpensive, safe, bench-stable solids, soluble in various organic solvents, and additionally, can serve as both an electrolyte and a catalyst. Herein, we introduce an electrochemically assisted paradigm for the facile interconversion of organic frameworks to the corresponding nitro-derived molecules. The reaction is demonstrated using iron nitrate to functionalize with a nitro group a wide range of unsaturated and aromatic compounds in a simple setup with inexpensive electrodes. These mild reaction conditions tolerate multiple nitration protocols, as well as vast functionalities, is scalable on decagrams, and delivers the corresponding adducts with high level of chemo- and regioselectivity. The waste, mainly consisting of iron oxide and hydroxides, is generated as only by-product and can be easily separated upon completion of the reaction. Detailed mechanistic studies, including spectroscopic investigations and controlled experiments, highlight the evidence of a fleeting nitryl radical under the concept of electron catalysis.[3]

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A Concise Total Synthesis of the ABO Blood Antigens

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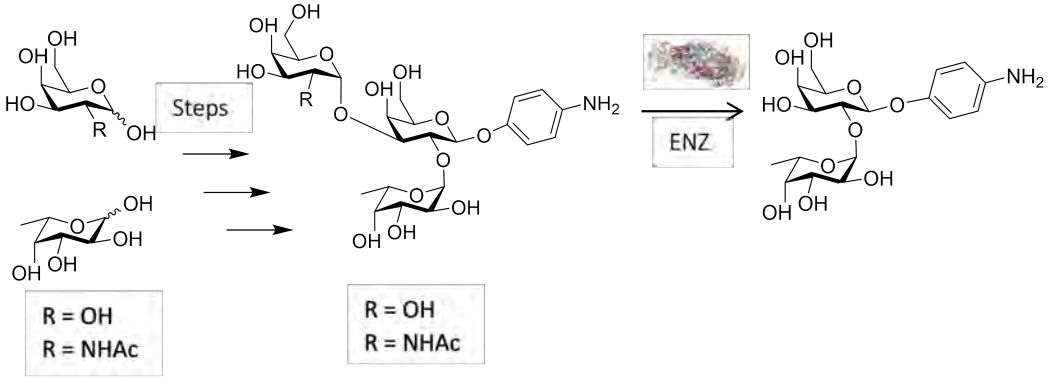
Providing an efficient pathway for the conversion of blood types A and B to the 'universal' donor O would significantly increase the supply for blood transfusions.[1] Although there are several examples on the use of enzymes for this conversion, their specificity or activity is a hurdle for medicinal applications.[2] Furthermore, given the fact that these antigens suffer from extortionate commercial pricing, providing a shorter synthetic route to access these targets is highly desirable.[3]

Currently, a total of three enzymes is required to achieve this goal. [4,5] Therefore, lowering the number of enzymes required for this cascade will enable a more sustainable and easier access to the O blood type, mitigating the need to express an extra enzyme, resulting in a more cost-efficient outcome.

Herein, we report the total synthesis of the A and B trisaccharide's. Starting from cheap and commercially available starting materials, we could access the A and B terminal antigens in 14 and 13 steps, respectively. The availability of a shorter and more concise synthesis will allow access to valuable substrates required for developing a more efficient enzymatic access of the O antigen.



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Nickel-Catalyzed Kumada Vinylation of Enol Phosphates: A Comparative Mechanistic Study

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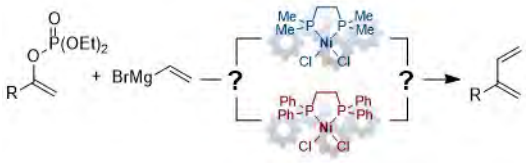
[1]University of Geneva

In 2018, our group reported a catalytic method for the synthesis of diversely 2-substituted 1,3-dienes. This methodology relies on the use of two complementary biphosphine-nickel complexes – [(dppe)NiCl2] and [(dmpe)NiCl2] – for the cross-coupling between vinyl Grignard reagents and enol phosphates.



Based on supporting stoichiometric organometallic syntheses, structural analyses, reaction monitoring, radical-clock experiments and kinetic investigations, a comparative mechanistic study between the two precatalysts has been conducted. We demonstrate that the two bisphosphine-nickel complexes operate via distinct Ni(0)/Ni(II) catalytic manifolds.

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Radical Iodo- and Hydroalkylation Modification of Forskolin

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(–)-Forskolin (7β-acetoxy-1α,6β,9α-trihydroxy-8,13-epoxylabd-14-en-11-one) (*Figure 1*), is a polyfunctionalized labdane diterpene presenting the 8,13-epoxylabd-14-en-11-one diterpenoid skeleton [1] and was isolated in 1977 from *Coleus forskohlii*, an important medicinal plant which grows in tropical and subtropical regions of Asia and Africa [2]. It possess a wide range of biological effects (inhibition of proliferation, motility, and migration in many types of cancer cells, and also the enhancement of the sensitivity to conventional antineoplastic drugs), while the main mechanism of action is based on the direct activation of the adenylate cyclase enzyme regulating many cellular functions [3].

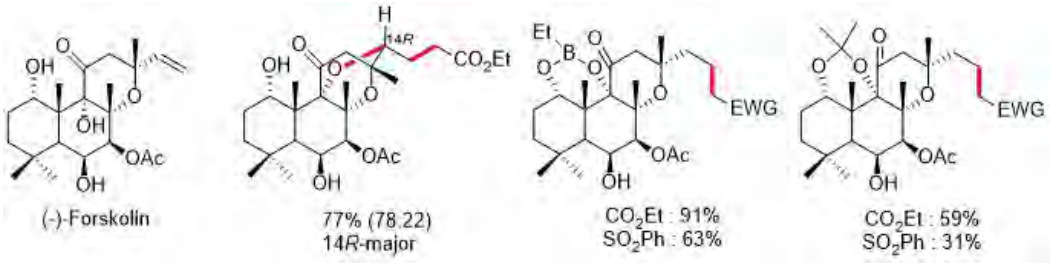

Figure 1. Radical modification of (-)-forskolin

The modification of highly oxygenated forskolin as well as manoyl and *epi*-manoyl oxide (two less functionalized model substrates sharing the same polycyclic skeleton), via intermolecular carbon-centered radical addition to the vinyl moiety, has been investigated [4]. The highly oxygenated skeleton of (–)-forskolin, with its free hydroxyl group at C-9, led to the formation of an interesting cyclic ether resulted formally from an alkoxyalkylation of the vinyl moiety and involving an iodine ATRA followed by an intramolecular nucleophilic substitution process. Deploying Et_3B as a radical initiator circumnavigated the necessity for a protecting group installation prior to ATRA functionalization, thanks to the *in situ* formation of a cyclic boronic ester intermediate which acts as a protecting group for the free hydroxyl groups.

The mild radical chemistry reported here offers many opportunities to prepare elaborated analogues for biological studies that are not accessible by conventional methods.

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Stereoselective Peptide Catalysis in Complex Environments – From River Water to Cell Lysates[1]

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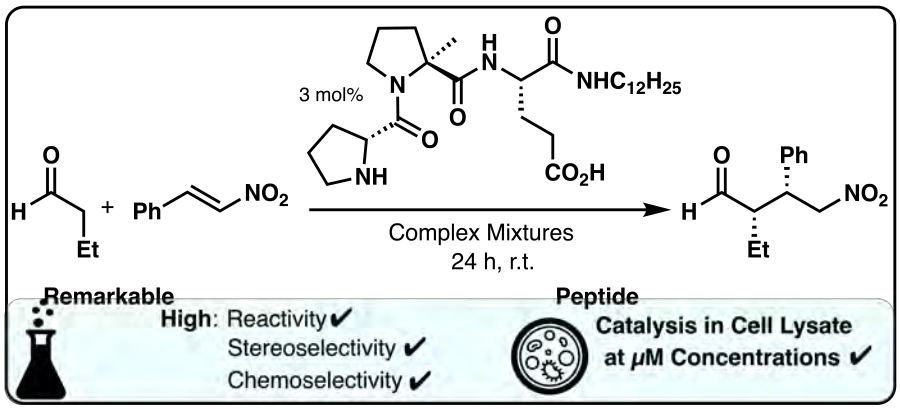
Peptides have been recognized as powerful catalysts for various reactions throughout the last two decades.[2],[3] Of these peptide catalysts, several are characterized by a high degree of stereoselectivity and reactivity. Similar to nature's catalysts, enzymes, they are also composed of amino acids but have a much lower molecular weight and could hence be considered 'mini-enzymes'. Whilst enzymes function splendidly at low concentrations in complex aqueous biological environments, peptide catalysts normally require pure organic solvents and high concentrations.[4a-h]

We were therefore intrigued by the question of whether a peptide catalyst could exhibit chemoselectivity in similar environments reminiscent of enzymes. Consequently, we probed the behavior of tripeptide catalysts in both hydrophobic and aqueous reaction media and further challenged the catalysts with complex reaction media, consisting of aqueous solutions, containing biomolecules, bearing functional groups that can coordinate or react with the catalyst, substrate, or intermediates. Finally, we subjected the peptide catalysts to the ultimate test by investigating their reactivity, chemoselectivity and stereoselectivity in cell lysate in micromolar concentrations, entering a range also typical for enzymes. Despite its relatively short length and small size, H-DPro-αMePro-Glu-$NHC_{12}H_{25}$ proved to be a conformationally well-defined tripeptide, able to catalyze C-C bond formations with high reactivity and stereoselectivity, independent of the solvent and its compound composition. In fact, this peptide yielded our desired product with excellent stereoselectivity (≥ 93% *ee*, *d.r.* 85:15 - 94:6) and yield (80 - 97%), even in cell lysate, a highly complex mixture with numerous compounds that could either react or coordinate to the catalyst, the substrates, or the reaction intermediates. These findings provoke the question of the potential role of peptide catalysis in nature and during the evolution of enzymes.



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Insights into the Molecular Mechanism of Cobalt(II) Catalyzed C-O cross-Coupling Reaction: A DFT study

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O-arylation reactions represent a synthetically important class of reactions that are widely employed for the preparation of diaryl ethers [1]. Cobalt catalyzed cross-coupling reactions are gaining importance owing to the low cost, mild reaction conditions, and high chemoselectivity [2,3]. In the present work, a detailed computational investigation into the mechanism of the Co(II) catalyzed C-O cross-coupling of phenols with aryl iodides, is carried out for the first -time, using Density Functional Theory employing B3LYP-D3 functional [3] augmented with CPCM solvation model using acetonitrile as the solvent. The Co and I atoms are described using (LANL2DZ) for the inner electrons and its associated double-ζ basis set for the outer electrons. The C, H, N, O, and Cl atoms were described by a 6-31+G(d) basis set. L-valine is the ancillary ligand used in this study. The active catalyst species is tetrahedral, L-valine ligated cobalt (II) phenoxide complex. The investigated O-arylation reaction proceeds through a **σ** – bond metathesis mechanism involving the concerted breaking of the Csp^2 – I bond and the formation of the Csp^2 – O bond proceeding through a four-centered transition state. Frontier Molecular Orbital (FMO) analysis was performed to investigate the effect of functional groups at the *para* position of the substrates. The substitution by electron-withdrawing groups (EWG) considerably decreases the energy of FMO's involved. The presence of EWG on aryl iodides tends to favor the reaction by reducing the energy of its LUMO. However, for the phenolic substrates, a decrease in the energy of the HOMO by the electron-withdrawing groups leads to an increased HOMO-LUMO gap [5].

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Enantioselective 3-Component Reaction between Hypervalent Iodine Reagents, Fluorinated Diazo Compounds and Nucleophiles

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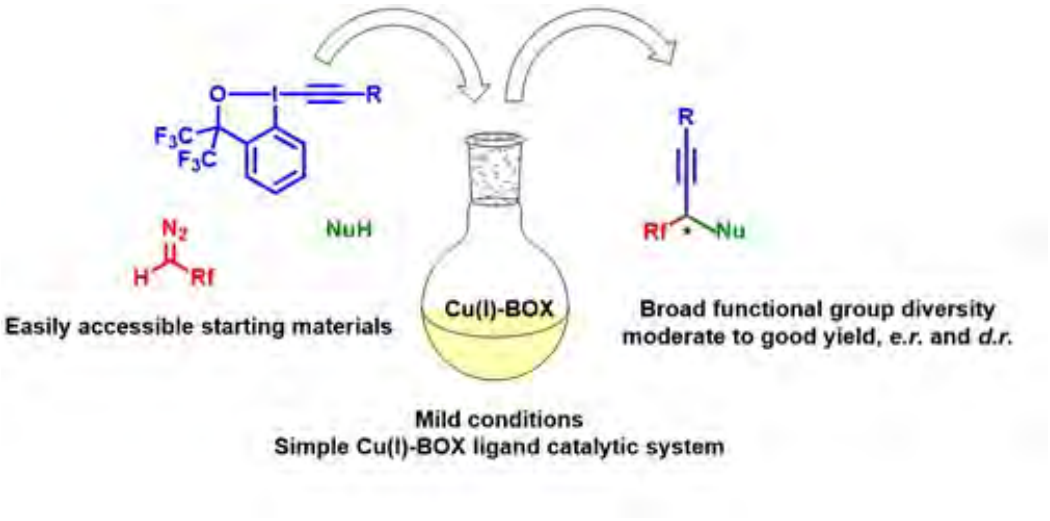
[1]EPFL-Laboratory of Catalysis and Organic Synthesis, [2]NCCR Catalysis

Multi-Component Reactions (MCRs) are very useful in medicinal and organic synthesis, as they convert simple and small molecules into compounds with higher structure and functional complexity. Similarly, the development of MCRs in an asymmetric manner is very important due to the relevance of chiral compounds in medicinal chemistry. However, this is still a challenge for organic chemists, and more efforts are necessary to do in this field.

During the last years, diazo compounds have become in very good starting materials in MCRs. In this context, fluorinated diazo compounds deserve a special attention since the fluorine atom is very important in medicinal chemistry, agrochemistry or material science.[1]

Hypervalent Iodine Reagents (HIRs) present an Umpolung reactivity making them very interesting precursors in organic synthesis. The combination of HIR and diazo compounds is therefore a very attractive strategy to develop new MCRs. Remarkably, this type of reaction has been only barely investigated and the first example was reported by our group in 2017.[3] More recently, we reported the racemic version of the 3-component reaction employing HIR, diazo compounds and easily accessible nucleophiles, such as alcohols and anilines, allowing the formation of propargylic alcohols and amines.[4] Nevertheless, the asymmetric reaction for these protocols has not been reported so far. Herein, we present our results on the enantioselective version of these transformations.[5]



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Activation of amino monoester strained rings with silylium catalysis.

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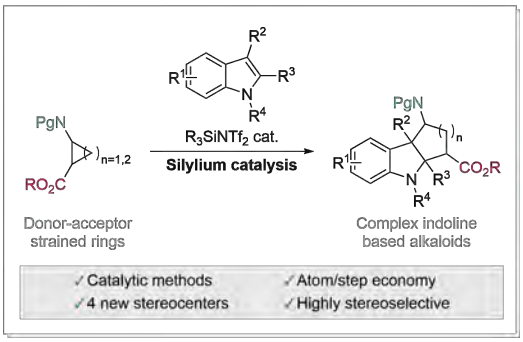
[1] EPFL, Laboratory of Catalysis and Organic Synthesis, EPFL SB ISIC LCSO, BCH 4306, 1015 Lausanne, CH, Switzerland

Cyclopropanes and cyclobutanes vicinally substituted with electron-donating and electron-accepting groups, called donor-acceptor cyclopropanes and cyclobutanes respectively, are among the most studied strained ring motifs.[1] Upon activation, the polarisation of the bond induced by the donor and acceptor substituents can result in heterolytic bond cleavage, providing 1,3 or 1,4 formal dipoles. These zwitterionic intermediates can further react *via* cyclisation or annulation, providing an alternative to classical bond-disconnection strategies.[2] In most reports, donor-acceptor strained ring systems bearing two geminal carbonyl groups as acceptors are used.[3] In contrast, mono carbonyl acceptor systems have been much less studied despite their synthetic relevance. Indeed, an extra stereocenter is obtained and no additional decarboxylation step is required after product formation. Nitrogen substituted cyclic structures are omnipresent in natural products and bioactive molecules. By taking advantage of the unique reactivity profile of donor-acceptor aminocyclopropanes and cyclobutanes, complex nitrogen substituted molecules can be prepared.[4] In 2021, our group published a highly selective [3+2] annulation between aminocyclopropanes monoester and indoles through silylium catalysis.[5] In this poster, recent advances on the synthesis and the reactivity of less activated donor-acceptor systems toward [4+2] annulation will be presented.[6]



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Pd(II)-Catalyzed Aminoacetoxylation of Alkenes via Tether Formation

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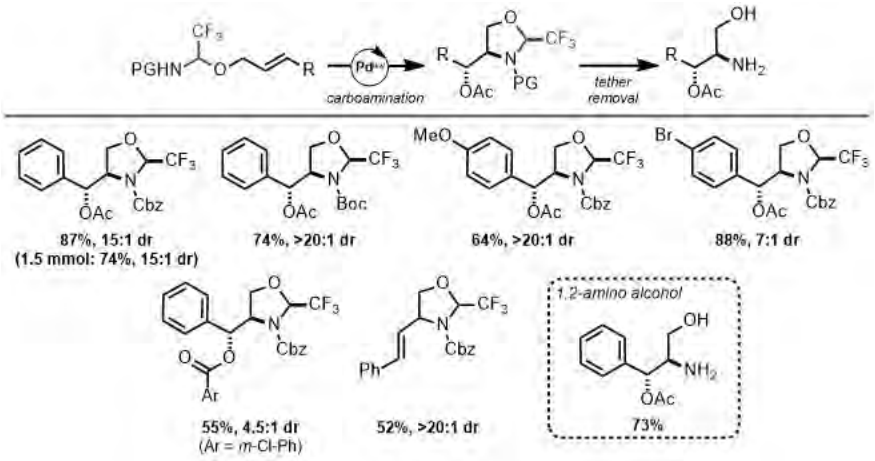
Owing to their broad accessibility and unparalleled reactivity, olefin components play a key role in the synthesis of valuable building blocks, generating molecular complexity from simple precursors.[1] Palladium-catalyzed processes constitute a major synthetic approach in the field of alkene derivatization strategies,[2] ranging from standard intermolecular cross-coupling reactions to cascade cyclization in natural product synthesis.[3,4] Despite significant advances in palladium catalysis towards alkene multifunctionalization, reactivity and selectivity challenges commonly encountered in intermolecular transition-metal catalyzed reactions limit broad application of these transformations.[5] To this end, a novel catalytic tethering approach involving a high-valent palladium center for olefin difunctionalization is reported. Pivoting on an easily introduced trifluoroacetaldehyde-derived tether, simultaneous introduction of oxygen and nitrogen heteroatoms across an unsaturated carbon-carbon bond under oxidative conditions is accomplished. While good reaction efficiency and high diastereoselectivity is demonstrated with a range of unactivated alkenes, non-terminal aliphatic-derived olefin substrates give access to aza-Heck cyclization products. Tether cleavage under mild conditions gives access to functionalized β-amino alcohols, which represent important building blocks frequently found in ligands and bioactive molecules.[6,7]



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Overcoming Catalyst Deactivation: Access to Fluorinated γ-Nitroaldehydes by Peptide Catalysis

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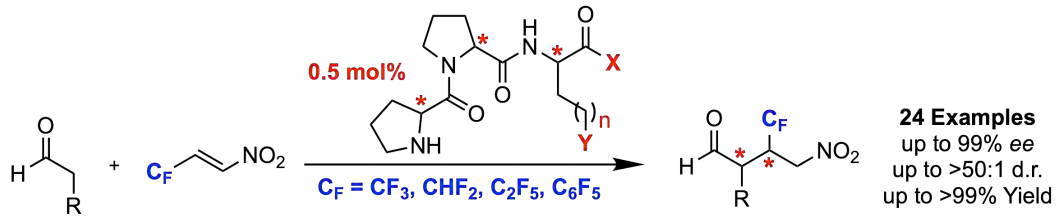
Tripeptides of the H-Pro-Pro-Xaa type are highly reactive and stereoselective catalysts for asymmetric aldol reactions and conjugate addition reactions of carbonyl compounds to nitroolefins[1-4], dicyanoolefins[5] and maleimide.[6] For example, as little as 0.05 mol% H-DPro-Pro-Glu-NH_2 suffices to catalyze conjugate addition reactions of aldehydes to nitroolefins in high yields and excellent stereoselectivities.[7]

Herein we present the stereoselective conjugate addition of aldehydes to β-fluorinated nitroolefins, a highly reactive class of electrophiles which usually deactivate secondary amine based organocatalysts by *N*-alkylation. By using peptide catalysts, we were able to overcome this deactivation and perform the reaction with only 0.5 mol% catalyst, while maintaining high yield and stereoselectivity.



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Digitalization and optimization of enantioselective multicomponent reactions

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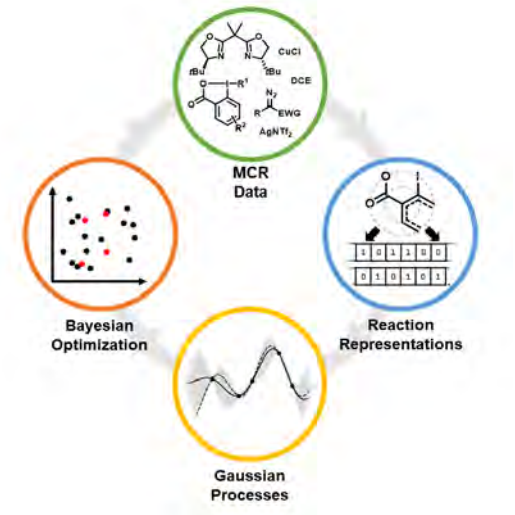
Multicomponent reactions (MCRs) are an atom-economic and efficient way to obtain organic compounds with high complexity and diversity from simple molecular building blocks. Additionally, enantioselective versions of MCRs also enable direct access to biologically active constructs. A recent example includes the asymmetric oxy-alkynylation of diazo compounds through the formation of metal carbenes, using hypervalent iodine reagents (HIRs).[1] While these reactions exhibit high yields and enantioselectivity, the substrate scope remains narrow and the underlying mechanism largely unknown. Similar selectivities have yet to be reported for the related oxy-vinylation and three-component reactions.

In this work, we develop and exploit (un)supervised learning approaches and Bayesian optimization to accelerate the optimization of the enantioselective transformations of these diazo compounds.[2] Efforts are placed into the extraction of data from electronic laboratory notebooks with the aim of creating and curating standardized datasets of HIR/Diazo reactions. We then design reaction representations that capture varying degrees of chemical specificity and combine them with machine-learning algorithms. Bayesian optimization workflows are finally exploited such as to efficiently explore predefined reaction spaces and reduce the number of experiments required to achieve high yields and enantioselectivity for these types of reactions.



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Radical Mediated Hydroperfluoroalkylation of Unactivated Alkenes

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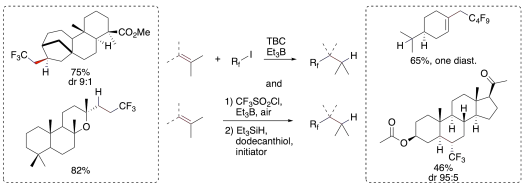
Recent advances in fluorination methods bring a huge impact on research areas such as medicinal chemistry, agrochemistry and material science.[1] Trifluoromethyl groups are known for their ability to increase the lipophilicity of the molecules while retaining their biological activity.[2,3] Classical strategies to access fluorinated substrates include iodoperfluoroalkylation, utilization of fluorinated sulfones and sulfonyl chlorides.[4] The hydroalkylation method developed in our group[5] has been extended to perfluoroalkylation of unactivated alkenes.



Scheme 1. Radical mediated hydroperfluoroalkylations and structures of some modified natural products.

The introduction of perfluorinated alkyl chains into a wide range of substrates was achieved with iodoperfluoroalkanes. The trifluoromethylation was conveniently achieved in two steps using trifluoromethanesulfonyl chloride as the source of CF_3 radical, followed by the dechlorination step adopted from polarity-reversal catalysis (PRC) method by Roberts et. al.[6,7] Under the applied reaction conditions, a diversity of functional groups can be tolerated and olefin-containing natural products can be readily derivatised.

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Synthesis and applications of novel chiral monophosphine ligands

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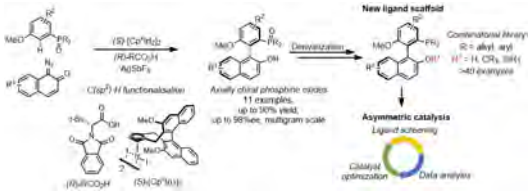
Chiral phosphines are privileged ligand class in asymmetric transition metal catalysis.[1] Compared to the more established chelating bidentate phosphines, monodentate ligands provide greater flexibility of coordination environment around the metal center, which allows for development of the new transformations.[2] Convenient access to structurally diverse libraries of these ligands represents one of the major bottlenecks in terms of reaction development.

Recently, our group reported efficient Cp^XIr-catalyzed asymmetric C – H arylation of phosphine oxides.[3] Using this transformation as a key stereochemistry-generating step, we extended the original reaction scope to include compounds resembling substitution patterns of privileged phosphorus ligands, in particular dialkyl biarylphosphines.[4] We have prepared a group of axially chiral phosphine oxides on multigram scale and subsequently derivatized them to the corresponding phosphines in two steps via P=O reduction and sidearm installation, which was accomplished by alkylation or silylation of the phenol moiety. In order to facilitate the discovery of the promising scaffolds, we have built a combinatorial library comprising more than 40 chiral phosphines with various substitution patterns. We are currently studying the potential of the novel ligands for applications in various asymmetric palladium-catalyzed cross-coupling reactions.[5]



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Radical azidation of cyclopropenes towards synthesis of quinolines

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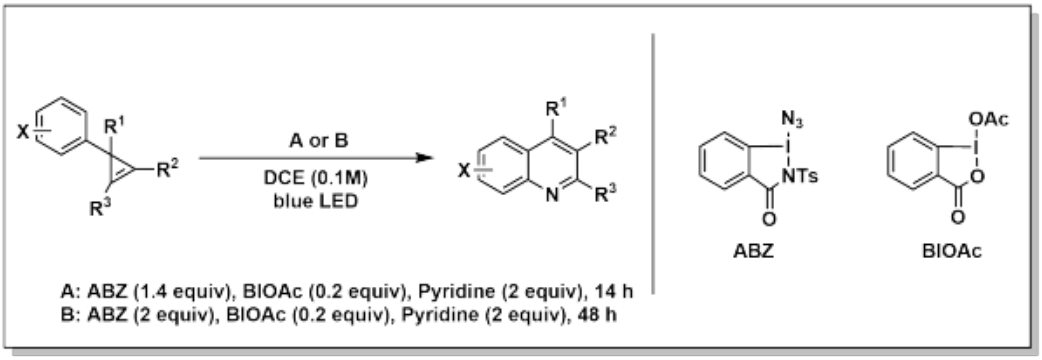
Cyclopropenes represent the smallest cyclic alkenes. Due to the simultaneous presence of ring strain and the double bond cyclopropenes are unique 3-carbon synthons in organic synthesis. Starting from the 1950s, many synthetic methods that involve cyclopropenes have appeared.[1] Nevertheless, reactions relying on the addition of radicals to cyclopropenes remain scarce. Therefore, our group became interested in these transformations.[2] Herein, we report a radical azidation of cyclopropenes leading to the formation of quinoline products. The transformation is enabled by the use of the safe hypervalent iodine(III) azidating reagent (ABZ) under blue LED irradiation. The utility of the transformation was demonstrated by the synthesis of diversely substituted quinoline products (Scheme 1). Moreover, other investigations of underexplored reactivities of cyclopropenes are ongoing in our lab.



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Defined “patches“ of interwoven materials

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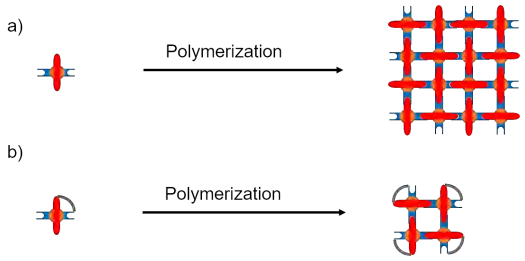
Textiles, consisting of only two orthogonally interlaced yarns, have intriguing physical features. They possess stability, flexibility and shape adaptability due to their interwoven structure. The concept of interwoven materials has been adapted to the molecular level for example tailor-made DNA tiles, forming 2D interwoven frameworks, 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 by pre-orienting the coupling partners to a MOF layer, reacting them, and then removing the metal ions to get the organic textile layer.[2]

Using the pre-organization approach to build a molecular textile from bottom-up, we designed a heteroleptic, amphiphilic metal complex. By having one hydrophilic and one hydrophobic ligand with different functional groups, that can be linked with each other, a moiety that can form an interwoven 2D material by polymerization was designed. The octahedral geometry of the metal complex and the rigidity of the three-dentate ligands ensure angles in between the ligands of close to 90°.[3] Through the amphiphilic nature of the complex, it can be put onto a water-air interface and always have the hydrophilic ligand face downwards and the hydrophobic ligand face upwards. Fixing the orientation of the monomer makes it possible to have the reacting groups in one plane and so to form the 2D material.

In an effort to further gain insight into interwoven materials we also designed a heteroleptic complex, that can only interlink twice. Polymerizing this blocked 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 material.



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Anion-π Catalyzed Ether Cascade Cyclization in Vesicles

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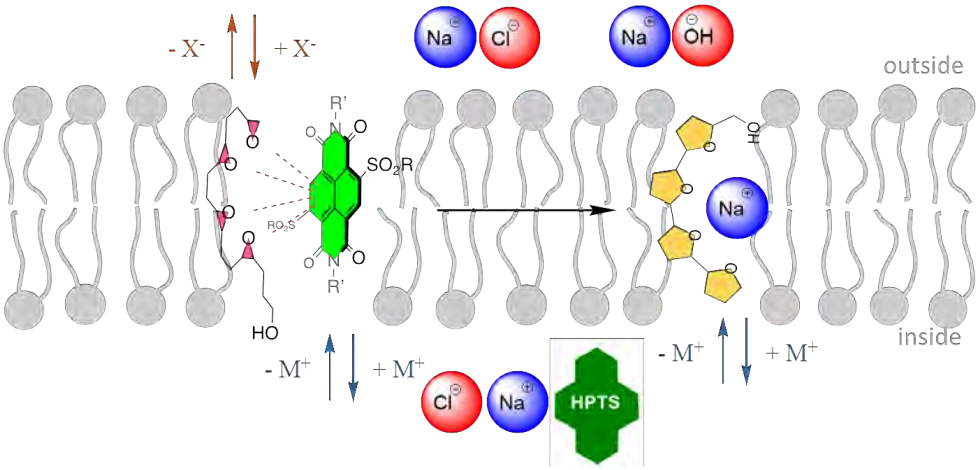
Anion-π interaction is a novel type of non-covalent force between electron deficient aromatic system and anion. The π-acidic surfaces could stabilize anionic intermediates and transition-states, and delocalized over large aromatic planes. The combination of catalysis and transport across lipid bilayer membranes promises directional access to a solvent free and structured nano-space that could accelerate, modulate, and, at best, enable new chemical reactions. To elaborate on these expectations, anion transport and catalysis with anion-π interaction are combined with polyether cascade cyclizations into bioinspired cation transporters. Characterized separately, synergistic anion and cation transporters of very high activity are identified. Combined for catalysis in membranes, cascade cyclization is found to occur and product formation is detected in situ as an increase in transport activity by employing HPTS as intravesicular *p*H meter.



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Tailoring Sodium Organometallic Reagents for Arene Functionalization

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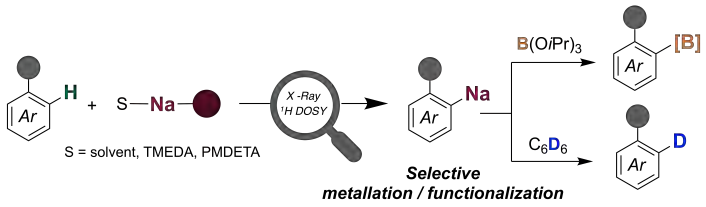
Organosodium compounds have attracted the attention of the scientific community in recent years as an alternative to widely used organolithium reagents.[1] Lithium alkyls and amides reside at the front of organometallic synthesis as key players in countless transformations, owing to their availability, substantial stability and solubility in hydrocarbon solvents.[2][3] However, these desirable traits are often pitfalls of heavier alkali-metal organometallics, meaning that their applications have remained underexplored. While recent reports have hinted at the untapped potential of these reagents,[3] the constitution of the organometallic intermediates that operate in these reactions has been overlooked, missing an opportunity to tackle their high reactivity and improve their poor solubility.

Filling this gap in the knowledge, in this communication we present the results obtained in the study of the reactivity of sodium alkyl and amide reagents in the presence donor molecules such as TMEDA (*N*,*N*,*N*′,*N*′-tetramethylethylenediamine) or PMDETA (*N*,*N*,*N*′,*N*′′,*N*′′-pentamethyldiethylenetriamine). The preparation of organosodium compounds soluble in hydrocarbon solvents and the isolation and characterization of reactive sodium organometallic intermediates in the solid state and in solution by X-Ray crystallography and ^{1}H DOSY (Diffusion Ordered SpectroscopY) have allowed the development of new protocols for the functionalization of organic molecules. Our efforts have been focused on selective deprotonative metallation reactions of synthetically attractive arenes, providing access to the selective functionalization of these scaffolds, including the borylation and the deuteration of the aromatic substrates. The reactivity and/or selectivity obtained with organosodium compounds was different to the one with its lithium analogues, opening new vistas in the use of polar organometallic reagents for the functionalization of organic molecules.



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Carpyridine sheets: shape (and size) matters!

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Questioning how molecular topography can govern supramolecular ordering is a relatively unexplored avenue of thought and one which poses great synthetic challenge that could lead towards new functional materials. “Carpyridines” (Figure 1a) — macrocycles fused from carbazoles and pyridines — are an underdeveloped example of a simple system with the shape of a saddle that could hold such promise[1]. Derivatisation of these non-planar systems through peripheral alkylation of the aromatic core and varying the chain length has yielded unusual supramolecular assemblies (Figure 1b, c) in the form of 2D sheets with the thickness of a single molecule[2]. The size, aspect ratio and definition of these sheets details the effect shape can have to nurture order in the absence of other, stronger directional interactions.

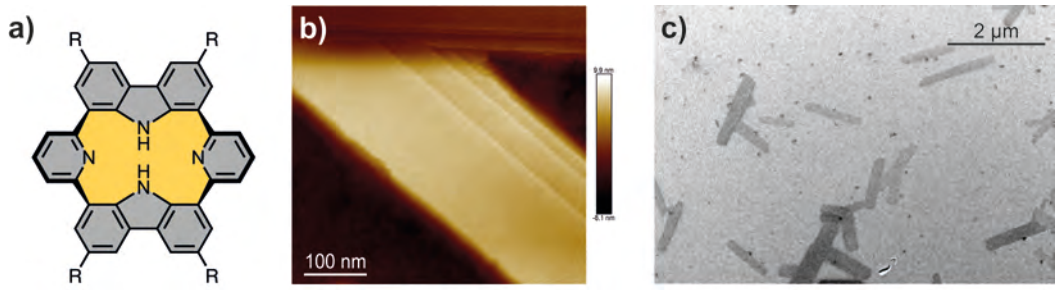

Figure 1. (a) Structure of Carpyridine free base (2H-Car-R) functionalised with R groups, and when R = *n*-C_6H_{13}, assemblies were visualized under b) AFM and c) TEM as 2D sheets either stacked on top of each other or isolated.

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At the Core of Dynamic Polymers: The Self-Assembly of Twisted Aryl Amines

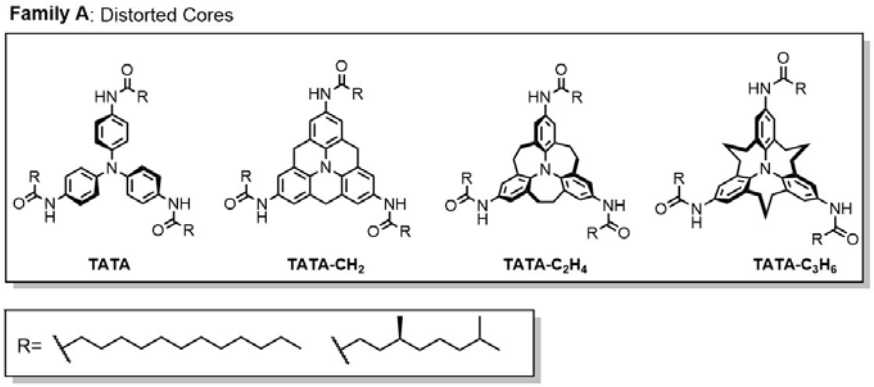
K. Zhang[1], M. Nehme[1], M. Rickhaus[1]*

[1]University of Zurich, Department of Chemistry

Triphenylamines (TPAs) and its derivatives have received considerable attention over the past years[1] thanks to their attractive properties that enable their electroactive and photoactive applications[2-3]. Their molecular configurations and electronic properties greatly influence their aggregation states as well as their charge carrier-transporting properties[4]. Previous studies reported that substituting the TPA with at least one amide group[5] could induce supramolecular polymerization that can form helical structures via intermolecular H-bonds. To date, there is no reliable method to predict how exactly a given building block will organize itself in solution or the solid state, consequently allowing us to formulate the following questions:

1. What rules govern supramolecular order? And how do we encode these rules into molecular building blocks?
2. Can we predict new properties that emerge as a result of an assembly of subunits?

To address these seminal goals, we aim to study the influence of systematic variations of the core of a triarylamine trisamide core unit, while keeping the outer layer constant. This ensures that the main driving force for the assembly (the hydrogen bonds) located at the periphery remain in place, leading to columnar stacking. For this purpose, we have devised Family A, which aims at highlighting different parameters such as geometry, steric hindrance, size, and flexibility. The length of the bridge is anticipated to induce different degrees of twist to the core, distorting the available π-surface.



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