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Site-Selective Direct C–H Arylation

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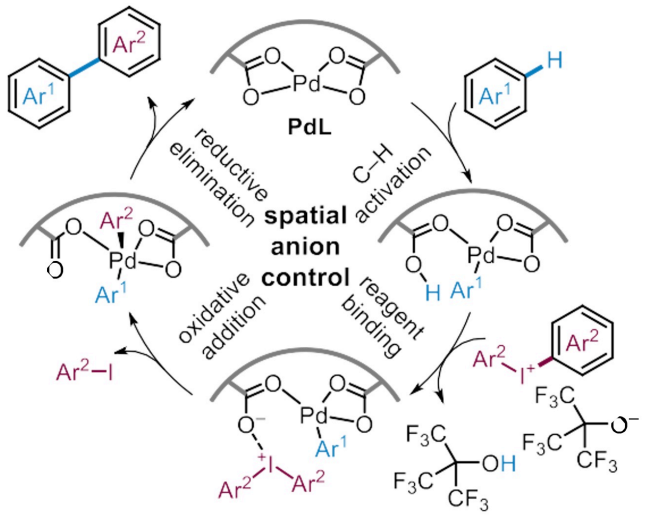
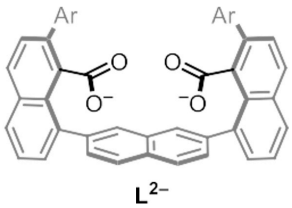
Direct transformations of C−H bonds to C−C bonds using transition metals, such as palladium, show great promise for the synthesis of complex molecules and materials. However, the development of catalytic systems that offer high reactivity and control over site-selectivity is an outstanding challenge.[1],[2] We have recently developed spatial anion control as a concept for the design of catalytic sites for C–H bond activation, thereby enabling nondirected C–H arylation[3] of arenes at ambient temperature.[4] The site- selectivity of the reaction was controlled mainly by theelectronic and steric properties of the substrates, with electronically-rich and sterically-exposed C–H sites displaying higher reactivity. In this presentation, our recent progress on the development of site-selective C–H arylation reactions will be described.[5]





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Radical-mediated azidofunctionalization of alkenes

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The difunctionalization of alkenes is among the most efficient methods for introducing diverse functional groups. Azides, in particular, are recognized as highly versatile and have found broad applications in synthetic chemistry and the pharmaceutical industry.[1] As precursors of various functionalities such as triazoles, they are also widely considered as protected amines and have been used as key intermediates.

In chemical sciences, non-proteinogenic amino acids (NPAAs) show great potential for the optimization of various biological properties (half-life, specificity, potency, membrane permeability and conformation) of peptide drugs.[2] However, the use of α-nitrogen substituted amino acids has been scarce due to their challenging synthesis. In this context, we developed an easy access to α-azido amino acids from dehydroamino acids as alkyl radical acceptors using iron catalysis.[3] Various azidated amino acids, both proteinogenic and non-natural analogues, were successfully synthesized. The obtained compounds appear as versatile building blocks that could be transformed into various unprecedented scaffolds including aminal-type peptides, [7,7]-substituted tetrahydro-triazolopyridine and α-alkyl-α-triazole α-amino acids.

Additionally, we developed a method for the functionalization of other types of C_{sp^2}-C_{sp^2} bonds such as styrenes, enols or enamides enabling the introduction of both an azide moiety and a wide variety of different nucleophiles.[4]

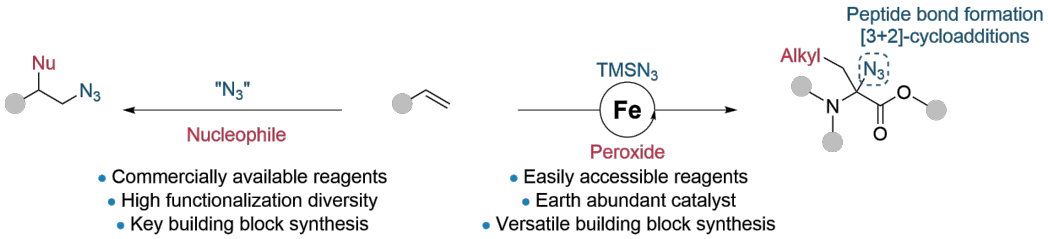

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Photo- and Cobalt-Catalyzed Synthesis of Heterocycles via Cycloisomerization of Unactivated Olefins

W. M. Amberg[1], H. Lindner[1], T. Martini[1], D. M. Fischer[1], E. Moore[1], E. M. Carreira[1]*

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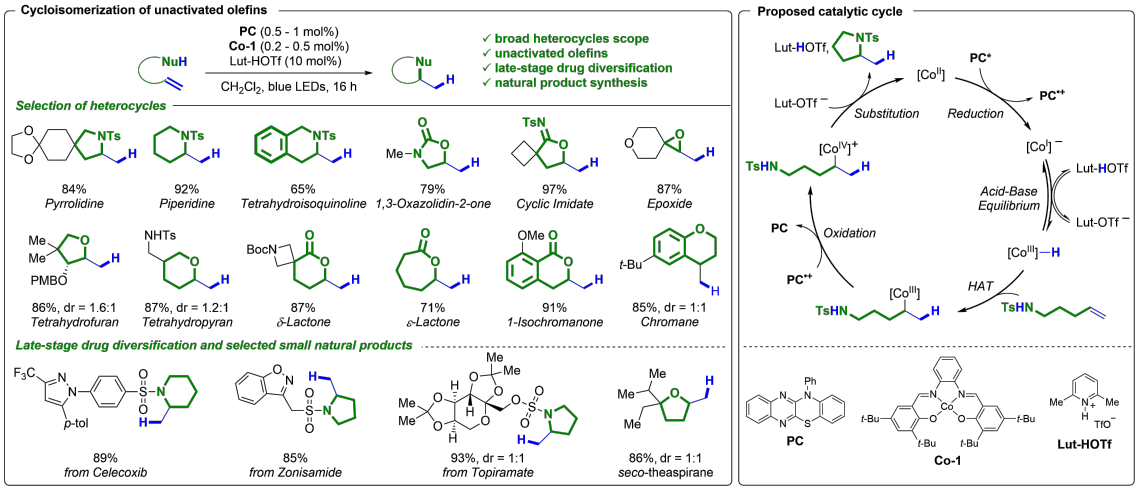
In this work, a general, intramolecular cycloisomerization of unactivated olefins with pendant nucleophiles for the synthesis of heterocycles is reported. The reaction proceeds under mild conditions and tolerates ethers, esters, protected amines, acetals, pyrazoles, carbamates, and arenes. It is amenable to *N*-, *O*-, as well as *C*-nucleophiles, yielding a number of different heterocycles including, but not limited to, pyrrolidines, piperidines, tetrahydroisoquinolines, epoxides, tetrahydrofurans, tetrahydropyrans, lactones, cyclic imidates, oxazolidinones, chromanes, and isochromanones. Use of both a benzothiazinoquinoxaline as organophotocatalyst and a Co-salen catalyst obviates the need for stoichiometric oxidant or reductant. We showcase the utility of the protocol in late-stage drug diversification and synthesis of several heterocycle containing small natural products.[1]



Traditionally, cobalt catalyzed hydrogen-atom transfer (HAT) hydrofunctionalization of olefins prescribed the use of stoichiometric oxidant (e.g. peroxide or *N*-fluoropyridinium salt) and stoichiometric reductant (e.g. silane). However, for new transformations, minimizing the number of stoichiometric reagents is desirable. Consequently, we set out to develop a catalytic system which employs cobalt HAT reactivity but obviates the need for stoichiometric oxidant and reductant. Key to success was the exploitation of a $[Co^{III}]$-H □ $[Co^{I}]^{-}$ acid-base equilibrium and combining a cobalt complex with a reductive photocatalyst under blue light irradiation. To showcase the potential of our catalytic system, we applied it for the synthesis of over ten different types of heterocycles. Our synthetic efforts commenced with nitrogen containing rings. We showed that amines bearing different protecting groups (Ts, Cbz, Boc) can successfully be cyclized to afford pyrrolidines and piperidines amongst other heterocycles. The method was subsequently generalized to include other nucleophiles such as carbamates, sulfonamides, alcohols, and carboxylic acids in the cycloisomerization which successfully afforded 3-, 5-, 6-, and 7- membered heteroatom containing rings in high yield. Finally, we showed that aryls are also competent nucleophiles in the cycloisomerization of unactivated olefins. In summary, we successfully merged organophotoredox- and transition metal-catalysis for the synthesis of valuable building blocks. Our approach is sure to open new horizons for methods development.[1]

[1] Henry Lindner,‡ Willi M. Amberg,‡ Tristano Martini, David M. Fischer, Eléonore Moore, Erick M. Carreira, *Angew. Chem. Int. Ed.*, **2024**, e202319515. (Note: ‡ denotes equal contribution).

Asymmetric, Remote C(sp3)-H Arylation via Sulfinyl-Smiles Rearrangement

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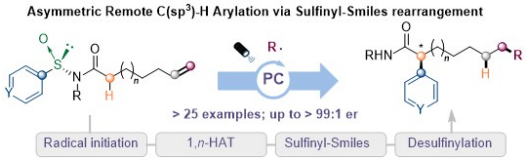
[1]University of Zurich, [2]Universidad de Alcalá, [3]Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS)

An efficient asymmetric remote arylation of C(sp^3)-H bonds under photoredox conditions is described here. The reaction features the addition radicals to a double bond followed by a site-selective radical translocation (1,*n*-hydrogen atom transfer) as well as a stereocontrolled aryl migration via sulfinyl-Smiles rearrangement furnishing a wide range of chiral *α*-arylated amides with up to >99:1 er. Mechanistic studies indicate that the sulfinamido group governs the stereochemistry of the product with the aryl migration being the rate determining step preceded by a kinetically favored 1,*n*-HAT process.



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Flow Chemistry for the Synthesis of the Anesthetic Mepivacaine, a More Sustainable Approach

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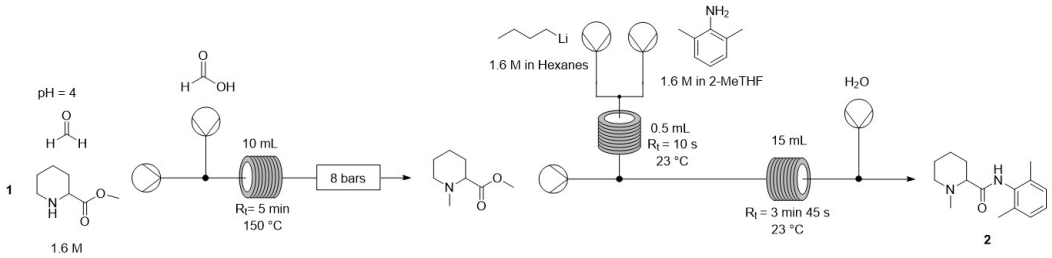
Immediate access to supplies of local anesthetics, such as mepivacaine (2), is important in the field of medicine.[1-3] The swift production of mepivacaine, using readily available reagents, *via* a portable and continuous apparatus, could bring a significant impact to the production of the active pharmaceutical ingredient, especially in underdeveloped countries.[4] In this study, we produced mepivacaine (2), prioritizing sustainability, reaction efficiency, and seamless integration, using *N* -functionalization and amide coupling, and yielding the drug at a gram scale. Initial results showed that the order of the functionalization was a key parameter in the successful synthesis of the final products. *N*-Functionalization of the pipecolic ester (1) was achieved in only five minutes of residence time in up to 99% conversion. The product could be obtained by subsequent pH adjustment and continuous extraction into the green solvent, 2-MeTHF. The amide coupling was performed in continuous-mode, without the need of coupling reagents, using an *in situ* prepared Li-amide[5], and yielding 90% conversion to product (2) in less than four minutes.



The utilization of flow chemistry enabled "forbidden" chemistry to be safely performed at a preparative scale. This continuous platform offers a promising and sustainable approach with the potential to meet the demands of the healthcare industry.

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Total Synthesis of the Diterpenes (+)-*Randainin D* and (+)-*Barekoxide* via Photoredox-Catalyzed Deoxygenative Allylation

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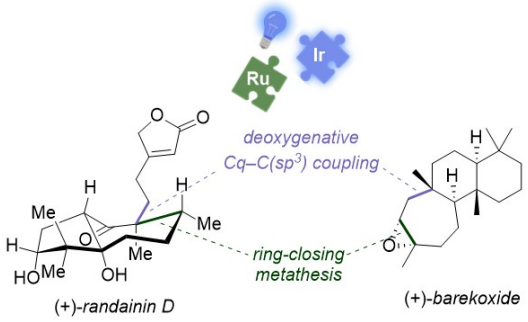
Diterpenes *randainins* A-D, along with *shortolides* B-C, have recently been isolated by research groups of Shen [1] and Williams [2]. These natural products are structurally unique due to the simultaneous presence of *trans*-hydroazulene skeleton and butenolide moiety. *Randainin D* has been found to be a moderate inhibitor of superoxide-anion generation and elastase release. Such biological activity, together with the intriguing structure, including a trans-5/7-ring scaffold and five stereocenters (two tetrasubstituted), makes *randainin D* an attractive and challenging synthetic target.



Herein, we report the first enantioselective total synthesis of (+)-*randainin D*. The *trans*-hydroazulene core was accessed via a highly challenging ring-closing metathesis, leading to a tetrasubstituted enone. The butenolide moiety was installed via a novel deoxygenative allylation under Ir-photoredox catalysis, employing methyl oxalate as a red/ox tag. Our study not only achieved the first asymmetric total synthesis of (+)-*randainin D* but also successfully applied the developed allylation method in the 7-step total synthesis of (+)-*barekoxide*. This underscores the potential of our deoxygenative allylation approach as a promising strategy for the formation of C_q–$C(sp^3)$ bonds (C_q = quaternary center) in the context of natural products synthesis [3].

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Enabling technologies at Syngenta: electrochemistry as a case study

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The challenge of feeding a growing population requires that chemists at Syngenta consistently remain cutting edge. The adoption of multiple enabling technologies in recent years is giving us additional tools to develop new, more efficient, and more sustainable routes to our crop protection products. In this talk, I will introduce the Synthesis Technologies platform within Crop Protection, with a particular emphasis on our journey in developing electrochemistry capabilities. Driven by chemistry needs, we quickly built-up traditional electrochemistry capabilities. As we realized the potential for implementing electrochemical transformations in our research activities, we also developed new technical solution for electrochemistry that would enable generation of industrially relevant data on basic reactivity, as well as scale-up. Case studies on various chemical processes, intertwined with internal capability development will be presented.

Vicinal Nucleophilic Disubstitution Reactions of (Densely Substituted) Arenes via 1,2-Bis-Triazenylarenes

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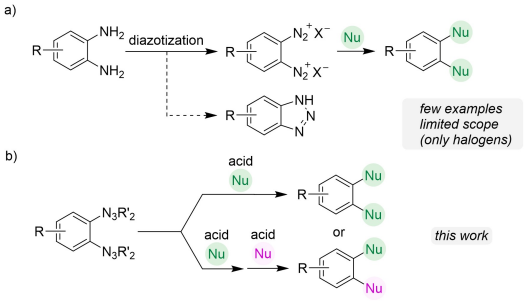
Nucleophilic aromatic substitution reactions of aryl diazonium salts represent a key transformation in synthetic organic chemistry. The Sandmeyer reaction, a method enabling the synthesis of aryl halides or aryl cyanides and the Balz-Schiemann reaction, a convenient method to fluorobenzenes are typical examples.[1] Vicinal nucleophilic disubstitution reactions can be achieved by subjecting *ortho*-diaminobenzenes to Sandmeyer/Balz-Schiemann-type conditions. However, only few examples have been reported in the literature, with limited scope. Challenges arise from the facile generation of benzotriazoles under diazotization conditions, and the precarious stability of the intermediate bis-diazonium salts (scheme 1a).[1] Herein, we show that vicinal nucleophilic disubstitution reactions are facilitated by the use of 1,2-bis-triazenylarenes. The triazene groups can be substituted sequentially by a range of nucleophiles including fluoride, chloride, bromide, iodide, azide, methoxy, and hydroxide (scheme 1b).[2]



Scheme 1. Vicinal Sandmeyer-Type Reactions

The authors greatly appreciate the financial support from EPFL as well as the facility/equipment available within EPFL.

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Catalyst-stereocontrolled synthesis of alkyne atropisomers

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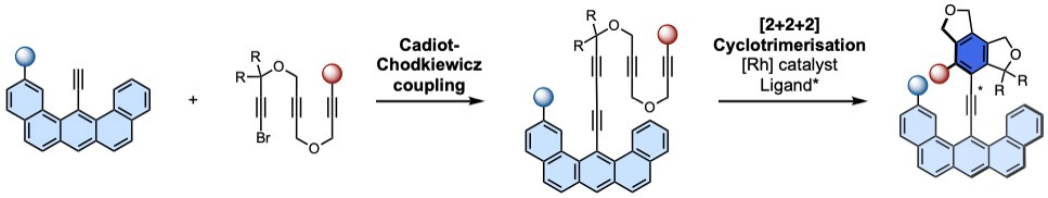
The rotational isomerism about the linear alkyne C-C≡C-C group has been investigated in detail by Toyota [1] and other researchers. However, acyclic systems with sufficient configurational stability at ambient temperature are yet unprecedent. Interestingly, the formal insertion of an alkyne across a stereogenic axis, such as for biaryl atropisomers, represent a 'carbomerization' [2], a concept that can be extended to stereogenic units.

In this work we describe the stereoselective synthesis of atropisomers bearing a rotationally restricted alkyne group using a rhodium-catalyzed [2+2+2]-cyclotrimerisation. Using this strategy, polyaromatic systems that exhibit a restricted rotation about the C-C≡C-C axis were obtained with enantioselectivities up to 91:9 e.r. To the best of our knowledge, this is the first example of a configurationally stable acyclic alkyne atropisomer and catalyst control over an extended stereogenic axis. Notably, the configurational stability allows the isolation and study of these novel chiral rotationally restricted compounds.



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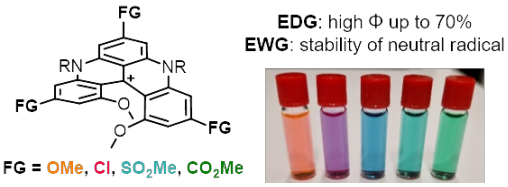
Electronic and Chiroptical Properties of Cations and Neutral Radicals of Enantiopure Diaza[4]helicenes

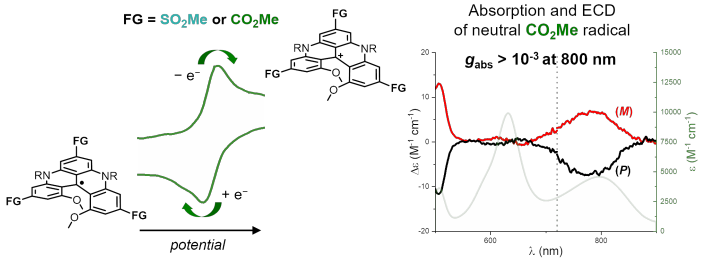
B. Fabri[1], T. Funaioli[2], L. Frédéric[1], C. Elsner[3], E. Bordignon[3], F. Zinna[2], L. Di Bari[2], G. Pescitelli[2], J. Lacour[1]*

[1]University of Geneva, Department of Organic Chemistry, Quai Ernest Ansermet 30, 1211 Genève 4, Switzerland, [2] University of Pisa, Dipartimento di Chimica e Chimica Industriale, Via G. Moruzzi 13, Pisa, Italy, [3]University of Geneva, Department of Physical Chemistry, Quai Ernest Ansermet 30, 1211 Genève 4, Switzerland

Organic chromophores offer the possibility of extensively modulate electronic and optical properties, making them attractive research targets. Furthermore, accessing a series of chiral compounds absorbing and emitting (circularly polarized) light over a wide spectral window is of practical value in chiroptical applications.[1] In this work, thanks to Ir-catalysed direct C-H borylation on derivatives bridging triaryl methyl and helicene domains,[2] we have achieved the regioselective triple introduction of *para* electron-donating or electron-withdrawing substituents.



These newly introduced substituents bring about an extended tuning of electronic (*e.g.*, $E_{1/2}^{red}$ −1.50 V → −0.68 V) and optical (*e.g.*, emission covering from 550 to 850 nm, quantum yields up to 70%) properties of the cations. Persistent neutral radicals were then accessed, with the derivatives bearing electron-withdrawing groups, by mono electron reduction under electrochemical or chemical conditions. Strong Cotton effects are obtained for the radicals at low energies (λ_{abs} □700−900 nm) with g_{abs} values above 10^{-3}. The open-shell electronic nature of these derivatives was further characterized by electron paramagnetic resonance revealing an important spin density delocalization that contributes to their persistence.[3]



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Photochromism in cyclic dipeptides: biocompatible switches and smart materials

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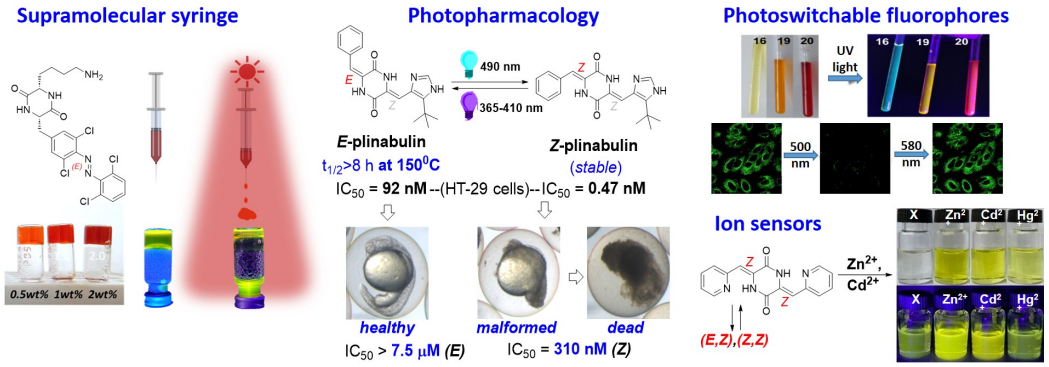
[1]Institute of Biological and Chemical Systems – FMS, KIT Karlsruhe, Kaiserstrasse 12, 76131 Karlsruhe, Germany, [2] Institute of Organic Chemistry, KIT Karlsruhe, Kaiserstrasse 12, 76131 Karlsruhe, Germany

Cyclic dipeptides (CDP) based on 2,5-diketopiperazine core are common structural motifs in biology, potent pharmacophores, and important constituents of numerous supramolecular systems based on hydrogen bonding.[1] Light-triggered photomodulation of their properties opens the way for photopharmacology applications, or producing smart materials. For that, we combined CDPs with molecular photoswitches.[2]

We introduced a series of biocompatilble photochromic hydrogels for light-triggered drug release, including a red-light-triggered "supramolecular syringe".[3] Later, we have discovered a new class of molecular photoswitches - hemipiperazines - acting by *E/Z*-isomerization of arylidene-substituted CDPs.[4] One of them - plinabulin (a low-nM antimitotic agent) - undergoes activity photomodulation *in vitro* by two orders of magnitude,[4] and can be used to photocontrol development of zebrafish embryos.[5] Other hemipiperazines [6] can be used as photochromic metal sensors,[7] and photoswitchable fluorophores *in vitro* [4] or *in vivo*.[8]

We will report the most recent applications of photochromic CDPs in photopharmacology and smart materials developed in our group.



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[8] P. Gödtel, Z. Pianowski *manuscript in preparation*

Synthesis of curved Polycyclic aromatic macrocycles towards shape-assisted self-assembly

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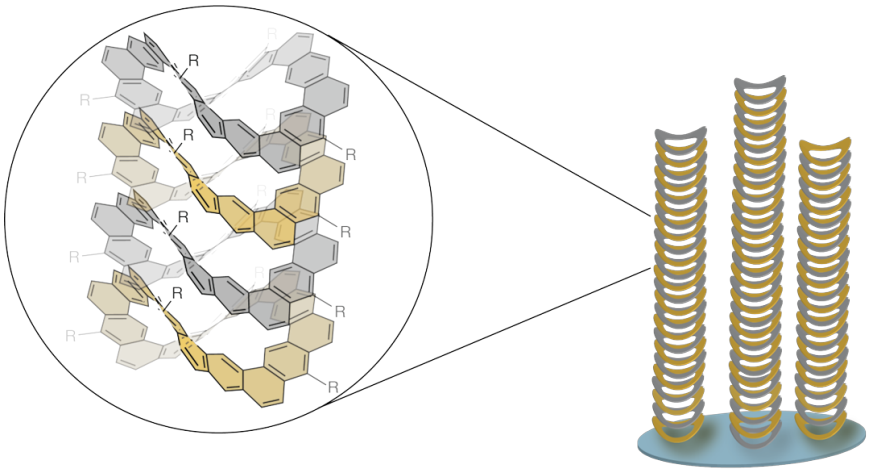
At the Rickhaus lab, we firmly believe that "shape matters." Our research focuses on the self-assembly of nitrogen-rich curved macrocycles. Since our first study on the self-assembly of carpyridine macrocycles in 2022[1],[2], these uniquely shaped structures have become central to several of our research projects. Carpyridine macrocycles, composed of two carbazoles and two pyridines, exhibit a saddle shape that facilitates shape-mediated self-assembly on surfaces.

We are currently exploring new ideas to synthesize carpyridines with various substituents to compare their assembly properties. This work will present innovative synthesis methods for decorating curved macrocycles, including carpyridines, octulene derivatives, and other related structures.



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Enantioselective Total Synthesis of (+)-Aberrarone

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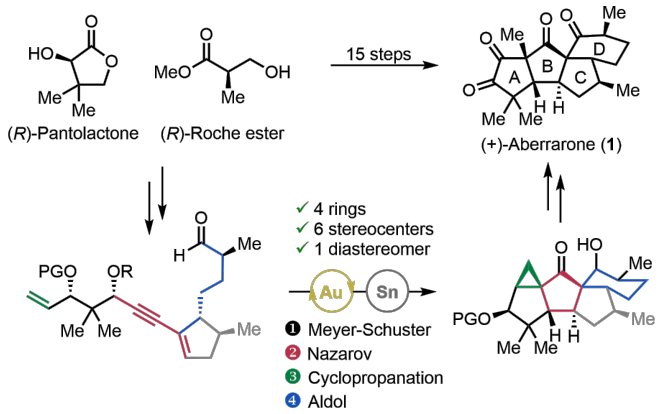
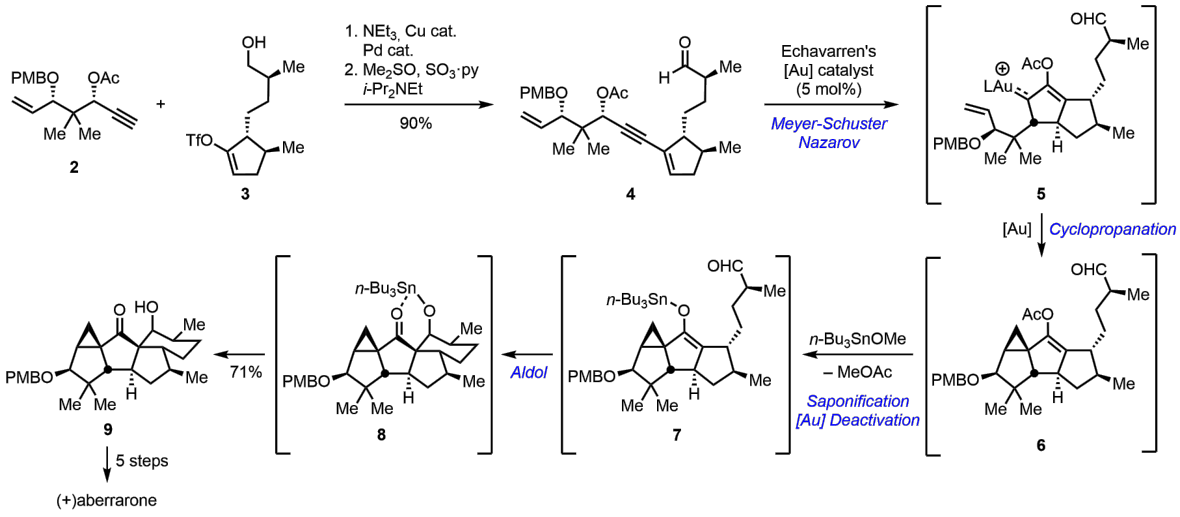
We present the first total synthesis of (+)-aberrarone, a diterpenoid natural product featuring a 5-5-5-6-fused tetracyclic skeleton. The convergent approach furnishes the natural product stereoselectively in 15 steps. Key to success is a Au-catalyzed – Sn-mediated Meyer-Schuster–Nazarov–cyclopropanation–aldol cascade, which closes four rings in one step. This work highlights the benefits of using a Sn-alkoxide to considerably expand the opportunities of Au-catalysis for the synthesis of complex molecules.[1]



The approach to (+)-aberrarone commenced with the synthesis of alkyne **2** from (*R*)-pantolactone and enol triflate **3** from (*R*)-Roche ester. Sonogashira cross-coupling of both fragments followed by Parikh-Doering oxidation gave rapid access to cyclization precursor **4**. The subsequent Au-catalyzed – Sn-mediated step assembled the A, B, and D rings, set six stereogenic centers, and formed two quaternary centers in one step. The successful application of *n*-Bu_3SnOMe in this complex setting to form the six membered ring D has no precedence and has the potential to be used in other complex systems. The quick and highly efficient route to (+)-aberrarone could be applied for the construction of other linear triquinanes with an angular fused cyclohexane.[1]



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Fluorescent Membrane Probes for Increased Partitioning in Membranes

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Fluorescent probes have emerged as a powerful tool for imaging cells, as they are non-invasive, easy to handle and can be used to track live changes in cells. In 2016, the Flipper-TR was introduced to image membrane tension in live cells, by increasing the fluorescent lifetime in higher ordered membranes.[1] The fluorescent contribution of Flipper-TR comes mostly from the plasma membrane and lacks a distinguished partitioning in a certain phase. These phases can either be liquid-ordered (L_o) membranes (containing saturated lipids, with a high concentration of cholesterol) or liquid-disordered (L_d) membranes (with unsaturated lipids). To improve this characteristic, the Flipper was modified with long alkyl chains (H-, L-, and S-Flipper, for L_o) and bulky alkyl chains (G- and O-Flipper, for L_d) to increase the hydrophobic interfacing and therefore the partitioning in artificial or cell plasma membranes. The long alkyl chain Flippers already had an increased partitioning in liquid ordered membranes in mixed (L_o and L_d) giant unilamellar vesicles (GUVs). In contrast the bulky alkyl chain Flippers were staining both L_o and L_d phases in mixed GUVs. Although these hydrophobic probes had an increased partitioning in artificial membranes, they readily internalized in live cells.[2] To overcome the internalization in cells, a more hydrophilic headgroup with four glutamic acids and a 4- formal negative charge (E4P-Flipper) were attached to the probe alongside a palmityl alkyl chain. The lifetime of this new Flipper probe had an increased lifetime of 6.5 ns in L_o and 5.7 ns in mixed GUVs, compared to Flipper-TR with 6.0 ns and 4.8 ns, allowing for higher quality images of membranes.[3]

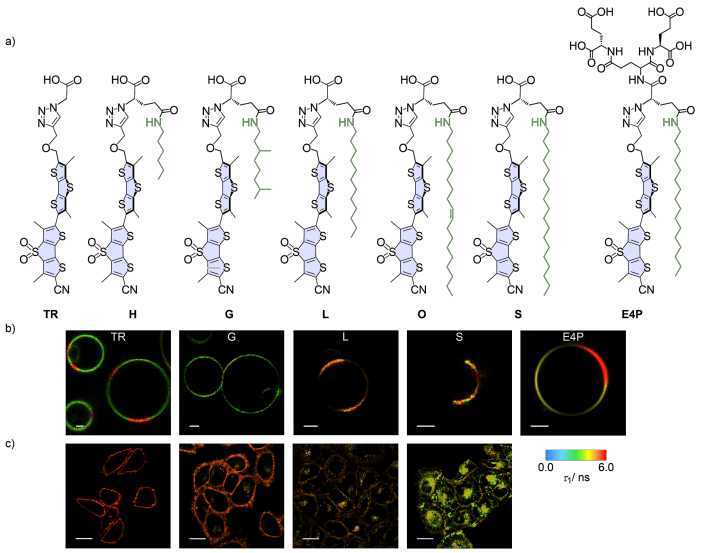

Figure 1. a) Structures of the flipper probes. b) FLIM images of the probes in mixed (DOPC:SM:CL 58:25:17) GUVs. Scale bars = 3 μm. c) FLIM images of the probes in HK cells. Scale bars = 20 μm.

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Selective Recognition of Sucrose in Water by a Synthetic Receptor

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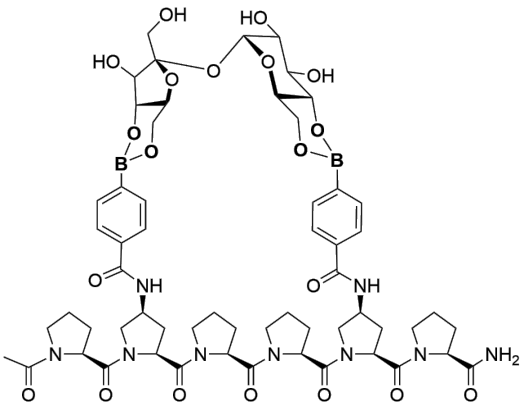
The selective recognition of saccharides in aqueous environments is challenging due to their structural and functional similarity and the high solvation in water. The Wennemers group recently developed an oligoproline-based receptor with two boronic acid moieties that binds the disaccharide sucrose with high selectivity and affinity in aqueous media ($K_a \approx$ 10'000 M^{-1}). The conformationally well-defined peptide scaffold allows for precise positioning of the recognition motifs in a distance of ≈ 9 Å. This spacing reflects the distance of the 1,3-diol moieties in sucrose. Reversible boronic ester formation between the boronic acid residues of the receptor and the diol groups of sucrose leads to a macrocyclic complex.



Oxidative amination of unactivated alkenes *via* nitrogen atom insertion into carbon-carbon double bonds

Y. Brägger[1], A. K. Paschke[1], N. Nasiri[1], B. B. Botlik[1], F. Felician[1], B. Morandi[1]*

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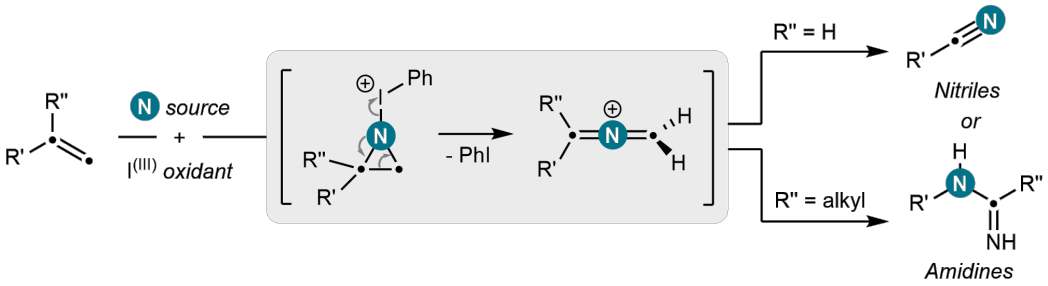
The synthesis of nitrogen-containing molecules through C–N bond formation is critical for the discovery and preparation of medicines, agrochemicals and materials. Traditional synthetic methods using alkenes as ubiquitous substrates leverage the reactivity of the C(sp^2)–C(sp^2) π bond for C–N bond formation. In contrast, methods that can form C–N bonds through complete cleavage of the double bond are scarce, despite the considerable synthetic potential of such a strategy. Here, we report the direct insertion of a nitrogen atom into unactivated carbon-carbon double bonds to access aza-allenium intermediates which can be converted either into nitriles or amidine products, depending on the initial alkene substitution pattern. This operationally simple and highly functional group tolerant reaction works on a wide range of unactivated alkenes. Our mechanistic proposal is supported by chemical trapping experiments, which concomitantly demonstrate the utility of our method to access valuable N-heterocycles. Overall, this study demonstrates the possibility to access reactive nitrogen-containing intermediates (i.e. aza-alleniums), which have ample potential for downstream diversification, from unactivated alkenes, opening new avenues for the discovery and preparation of important products.



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Catalytic Difunctionalization of Cyclopropenes via a Tethering Strategy

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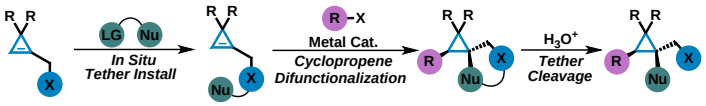
Cyclopropanes are the smallest possible carbocycles and are present in a myriad of biologically active molecules due to their unique structural properties [1]. For example, the rigid cyclic structures of cyclopropanes ensure that their substituents are held within specific conformations, which may enhance their affinity towards a biological target [2]. While highly functionalized cyclopropanes are of interest, preparation of these scaffolds is still limited. One way to rapidly access various complex cyclopropanes is the direct functionalization of their unsaturated analogous cyclopropenes [3]. However, there are several challenges to overcome when controlling the regio- and stereochemical outcomes of this functionalization [3]. The Waser group has previously developed several methods for the difunctionalization of alkenes and alkynes using a palladium-catalyzed tethering strategy [4]. The use of cleavable tethers affords intermolecular products, while benefiting from intramolecular reactivity, allowing for enhanced selectivity of the stereochemical outcomes of the reaction [5]. This work has extended this strategy towards catalytic difunctionalization of cyclopropenes to afford heavily decorated cyclopropanes with good diastereocontrol. Current results and efforts towards reaction development will be discussed during this presentation.



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Catalyst Control Over Pentavalent Stereocenters

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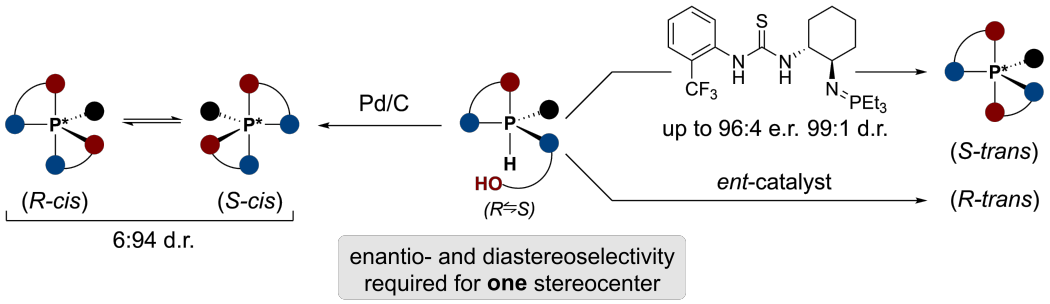
A plethora of catalytic methods have been developed to address one of two configurations of tetravalent stereocenters.[1] Conversely, achieving control over high-valent stereocenters has proven to be a persisting challenge. Pentavalent stereocenters, characterized by a fifth moiety attached to the central atom, encode an extended stereochemical space beyond the classical Le Bel–van 't Hoff stereo-isomerism[2,3] (>2^n), which results in having more than two stereoisomers per one stereocenter. In this work, a catalytic method allowing the selection of configurations in pentavalent stereocenters was developed. A bifunctional iminophosphorane thiourea catalyst[4] enables precise control over enantio- and diastereomers emerging from a single stereocenter of pentavalent phosphoranes, yielding desired dioxophosphoranes with excellent yield and selectivity (up to 99% yield, 96:4 e.r. and 99:1 d.r.). Stereodivergent catalysis allows selective access to each different diastereomeric state of the pentavalent phosphoranes, rendering the expanding stereochemical space of high-valent main group species selectively addressable.[5]



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Reversing the Diastereoselectivity of the Organocatalyzed Conjugate Addition Reactions to Nitroolefins – From Reaction Development to Formal Synthesis of Upadacitinib

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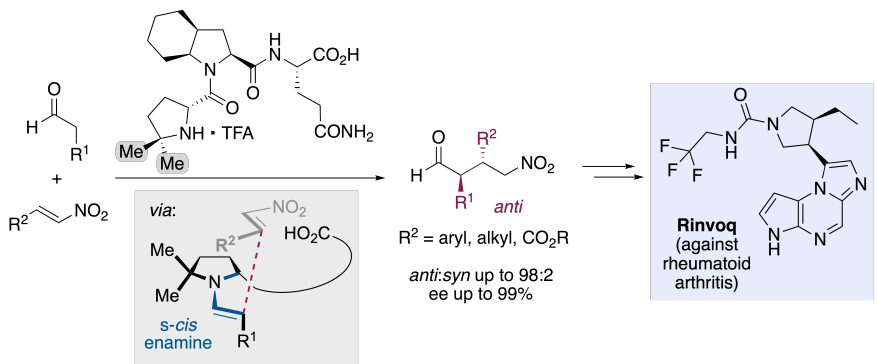
In the past two decades, organocatalyzed stereoselective conjugate addition reactions of aldehydes to nitroolefins have been the subject of intense research. However, essentially all methods afford the *syn*-diastereoisomer of the resulting ?-nitroaldehyde. Broadly applicable, non-substrate specific *anti*-selective methods remain unprecedented.

Our group introduced 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.[1] Detailed mechanistic and conformational studies showed that the s-*trans* enamine intermediate is involved in the rate- and stereoselectivity-determining step.[2]

Drawing on this knowledge, we developed a general *anti*-selective catalyst.[3] The key to the reversal of diastereoselectivity is installing substituents at C? of the reactive pyrrolidine. This modification favors the reaction of the s-*cis* enamine with the nitroolefin, forming the *anti*-configured ?-nitroaldehyde. Different aldehydes and nitroolefins were converted to products in high yields and *anti*-selectivities Recently, we highlighted the generality of our method by expanding the scope to nitroacrylates, which gives access to synthetically versatile *anti*-?-nitroaldehydes.[4] Successful immobilization of the peptide catalyst onto a solid support allowed for recycling and reuse, increasing the efficiency of the process. Lastly, we applied our new approach in a four-step synthesis of the chiral pyrrolidine fragment of the Upadacitinib (®Rinvoq), a top-selling drug against several indications, including rheumatoid arthritis. Our approach is the first organocatalytic and currently the shortest synthesis of this key building block.



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Organic Dye Photocatalyzed Synthesis of Functionalized Lactones and Lactams via a Cyclization-Alkynylation Cascade

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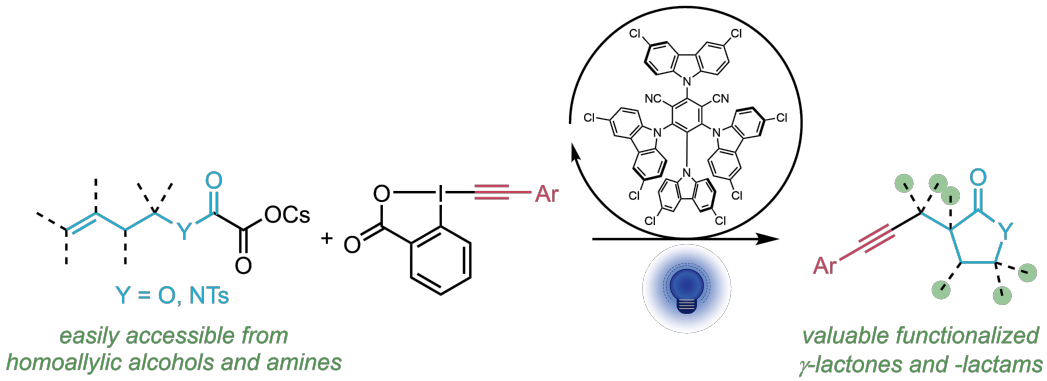
The γ-lactone and -lactam motives are found in many agrochemical and pharmaceutical active compounds. Hence, numerous lactonization methods, mainly focusing on the formation of C–O bonds, have been developed. On the other hand, the synthesis of such heterocycles via C–C bond formation has been less investigated; among these approaches, radical-based approaches are particularly attractive due to their mild reaction conditions, high functional group and steric hinderance tolerance. More precisely, the 5-exo-trig cyclization of an alkoxycarbonyl radical onto an olefin is especially appealing as the radical precursor can be generated from easily accessible homoallylic alcohols and the radical generated after cyclization can be trapped by a SOMOphile, thereby allowing multifunctionalization reactions. In this regard, lactonization reactions were performed under classical radical conditions with only one example of double C–C bond formation,[1] while more recently Overman and co-workers developed the synthesis of arylated spirolactones via a photoredoxcatalyzed cyclization–Ni-catalalyzed cross-coupling cascade using homoallylic cesium oxalates.[2] However, no report has described the formation of alkynylated compounds, nor has there been an application of the methodology to substituted lactams. The alkyne is a versatile functional group, as it can either serve as rigid linker or it can be easily converted into other functionalities such as carboxylic acids.

In this work,[3] we developed an organic dye photocatalyzed cyclization-alkynylation reaction using easily accessible homoallylic cesium oxalates and oxamates and Ethynylbenziodoxolone (EBX) reagents as radical trap. The reaction was carried out using an organic dye as more sustainable alternative to Ir- and Ru-based photocatalysts and provided access to a large variety of functionalized γ-lactones and -lactams.



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Length-Dependant Uptake and Inhibition of Cell-Penetrating Poly(disulfide)s

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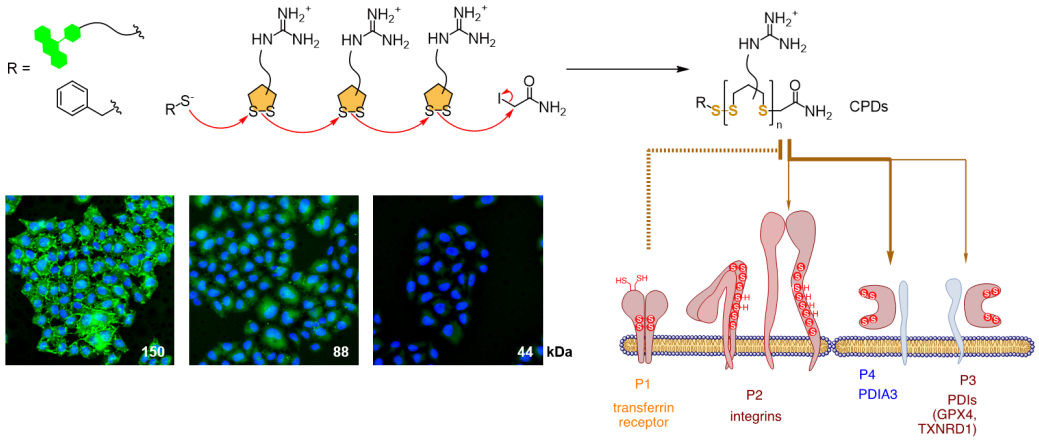
Cell Penetrating Poly(disulfide)s (CPDs) can be internalized through its cascade exchange (CAX) with exofacial thiols and disulfides on transmembrane proteins – Thiol-Mediated Uptake (TMU)[1]. Additionally, the TMU of CPDs can be inhibited by using well known CAXs, hydrophilic surface-thiol-reactive agents that prevent other molecules to participate in any further exchange. Since their inception[2], CPDs were able to perform the intracellular delivery of various relevant cargoes[3], but were never really implemented in the TMU library. This requires a series of tests involving uptake and inhibition profiling, including self-inhibition. A full assay would ultimately allow us to indicate which transmembrane pathway are involved in CPDs' CAX. This work completes the characterisation of CPDs into the library of TMU agents. As polymeric species, the length and dispersity play a huge role in the CPDs' properties, for both uptake and inhibition. To study this effect, CPDs of different molecular weights were prepared, highlighting how increasing the length of CPD transporters not only increases their uptake performance, but also alters their intracellular localisation. Additionally, non-fluorescent CPDs are introduced as potent inhibitors for TMU, with IC_{50} in the nanomolar range, even against the best transporters. Similarly, increasing the length of CPD inhibitors allows for enhanced inhibition performance against TMU agents. These results reveal the involvement of Protein Disulfide Isomerase (PDI) and the thiol/disulfide-rich leg of the β-subunit of Integrins in CPDs' internalization process. This opens new avenues for the development of next generation poly(disulfide)s drugs for TMU.



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Iridium-Catalyzed Hydrogenation of Pyridines

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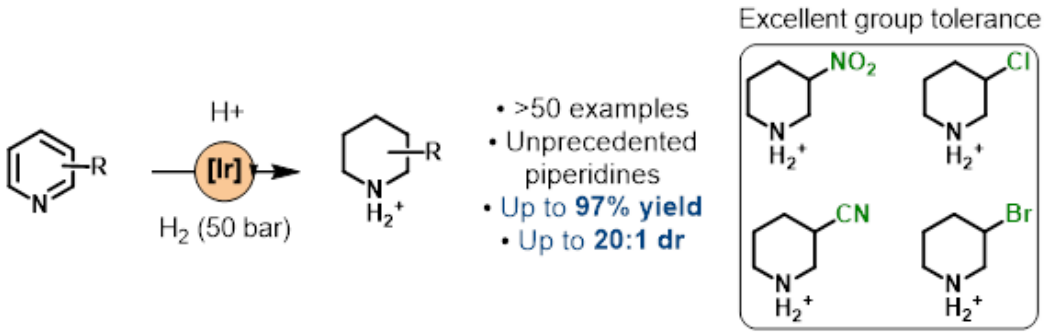
The piperidine core is present in many alkaloids and biologically relevant molecules, shows excellent pharmacological properties and is, as such, the most occurring nitrogen-heterocycle in FDA-approved drugs molecules (1).

Out of the many ways of building complex piperidines: ring construction, ring expansion of pyrrolidines, or modification of existing piperidines (2), hydrogenation or pyridines is an attractive alternative. It takes advantage of a substantial and cheap pyridine feedstock and hydrogen gas as a priceless and harmless reducing agent offering excellent atom economy. Nevertheless, this approach to access piperidines is underdeveloped. Most pyridine reductions so far suffer from harsh reaction conditions, poor functional group tolerance, limited reaction scope, or the need to pre-functionalize the pyridine to break its aromaticity.(3)

Herein, we report a homogeneous Ir-catalyst capable of performing the mild hydrogenation of a wide range of mono- and multi-substituted pyridines. The reaction proceeds with low catalyst loading using an acid co-catalyst to break the aromaticity of the pyridine. Our method gives access to a wide variety of piperidines in excellent yields and good to excellent diastereoselectivities. Virtually any substitution pattern can be accessed with an unprecedently broad functional group tolerance that provides unique substrates, further proving the relevance of this strategy to access the undeniably valuable piperidine core.



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Paracyclophenylenes as functional units and building blocks for SWCNTs

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[1]University of Basel

Carbon nanotubes (CNTs) have emerged as very promising functional materials for semiconductors, photovoltaic cells and chemosensors. One of the drawbacks of CNTs is their production, which is most commonly done via a top-down approach. During the last century, much effort has been put into the investigation of the bottom-up synthesis of CNTs and their subsegments. Cycloparaphenylenes (CPPs) — also referred to as carbon nanohoops — can be thought of as the shortest possible cross section of an armchair carbon nanotube. Although the first attempts to prepare CPPs go back to 1934. It's only in the recent decade that CPPs have moved from theoretical curiosities to synthetically accessible molecules, and with the ready access to the structure of CPPs, several functionalized CPPs have been achieved. The synthesis of CPP structures bearing multiple methoxy groups would provide a suitable platform for subsequent functionalization. Herein, we envisioned a bottom-up approach for synthesis of [16,16]CNTs (Fig. 1), leveraging the uniform methoxy-substituted [16]CPP as a promising avenue for their fabrication.

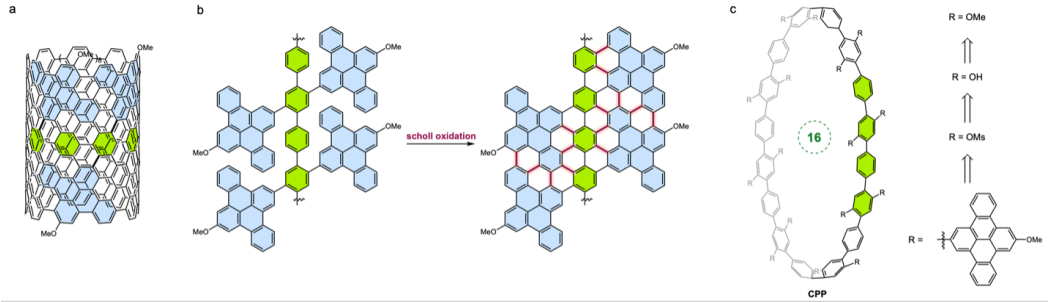

Fig. 1: Displaying our general synthetic strategy towards a [16,16]CNTs.

Traceless photoremovable self-immolative amino acid linker

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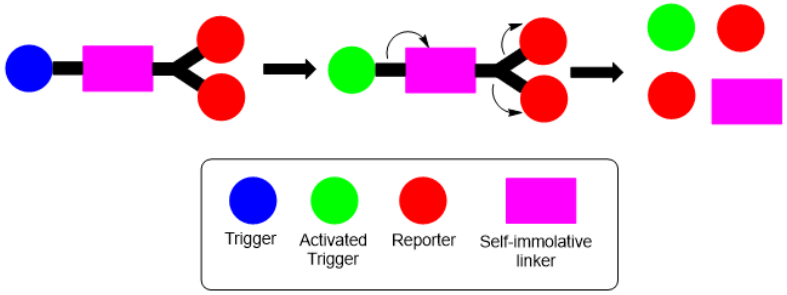
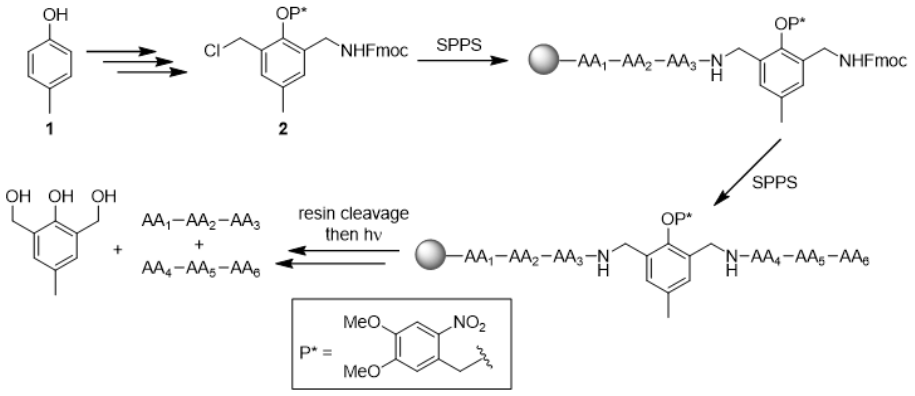
Self-immolative linkers are covalent assemblies (small molecule, polymer, dendrimer) designed to correlate the cleavage of two bonds between a protecting group (trigger) and a compound of interest (reporter) in response to a specific stimulus (pH, temperature, redox, light...) (Scheme 1). They have found plenty of applications especially for drug delivery systems.[1]



Scheme 1: General structure of self-immolative entity with two reporters.

The goal of this project is to design a traceless photoremovable self-immolative linker for amino acids (Scheme 2). The designed linker should be capable to bind two peptide fragments and then release them upon activation with a specific stimulus (although photochemistry will be mainly used this could be, in principle, any reaction able to uncover a phenol). To be useful in real biological applications, the two fragments need to be liberated from complementary termini (N and C) and the introduction of the linker in the full peptide needs to be compatible with automated solid-phase peptide synthesis (SPPS). In order to bind with peptides, the linker **2** should possess an Fmoc or Boc protected amine and an electrophilic site capable to react with the N terminus of the growing chain. Starting from *p*-cresol (**1**), the desired linker **2** bearing a nitroveratrol photolabile protecting group could be synthetically accessed.



Scheme 2: Preparation and release of the fragmentable peptides.

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Nitration Processes Using Bench-Stable Nitrating Reagents

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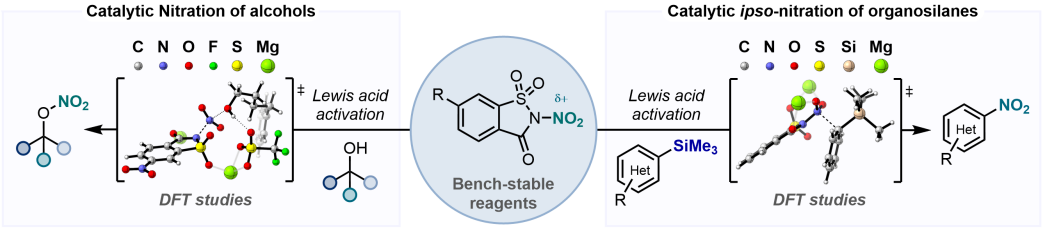
Nitroaromatic compounds represent one of the essential classes of molecules that are widely used as feedstock for the synthesis of intermediates, the preparation of nitro-derived pharmaceuticals, agrochemicals, and materials on both laboratory and industrial scales.[1,2] Therefore, the development of sustainable, chemo- and regiospecific nitration processes that utilize bench-stable, easily accessible and non-acidic reagents and operate under catalytic manifold and eco-friendly conditions remain in high demand. We herein disclose the efficient, mild, and catalytic *ipso*-nitration of organotrimethylsilanes,[3] enabled by an electrophilic *N*-nitrosaccharin reagent[4,5] and allows chemoselective nitration under mild reaction conditions, while exhibiting remarkable substrate generality and functional group compatibility. Additionally, the reaction conditions are orthogonal to other common functionalities, allowing the programming of molecular complexity via successive transformations or late-stage nitration. Detailed mechanistic investigation by experimental and computational approaches strongly supported a classical electrophilic aromatic substitution (SEAr) mechanism. We also report on the deployment of *N*-nitrosaccharin reagents as an advantageous source of nitronium ions, enabling the nitration of alcohols under unprecedentedly mild conditions.[6] This process can be successfully employed for the late-stage synthesis of nitrate derivatives of biologically relevant and complex molecules.



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Bambusurils: Kinetically-Controlled Synthesis of Functionalized Anion-Binding Macrocycles

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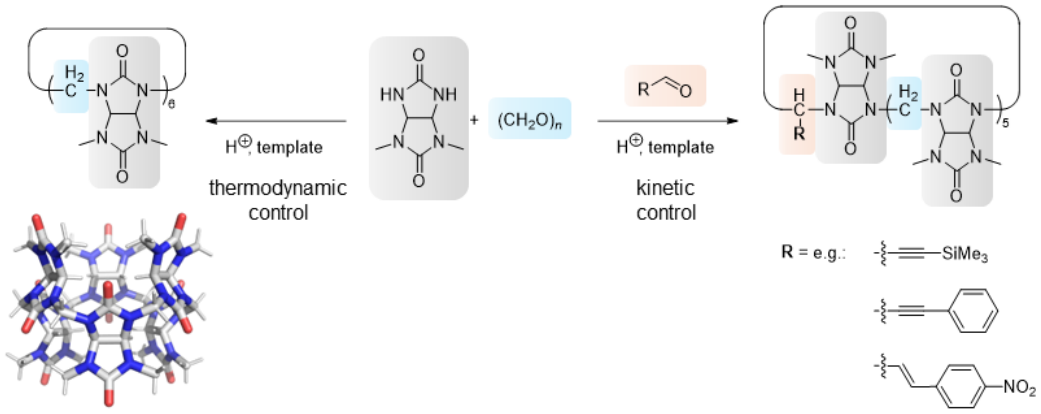
Bambusurils (BUs) are a family of anion-binding macrocycles composed of glycoluril units linked together with a single row of methylene bridges.[1] BUs and the related cucurbiturils (CBs) are conventionally synthesized by an acid-catalyzed Mannich-type reaction between glycoluril and formaldehyde (Figure, left).[2] Substituting formaldehyde with other aldehydes in BU or CB synthesis to access macrocycles functionalized at the methylene bridge has been largely elusive due to the decreased stability of the functionalized condensates.[3] Here we devise a kinetically-controlled synthesis that enables the incorporation of aldehydes other than formaldehyde into the BU structure (Figure, right). Our strategy provides robust access to functionalized BUs and brings new insights into the properties of glycoluril-based macrocycles. We are exploring the functionalized BUs as a platform towards high-affinity supramolecular anion sensors operating in aqueous solutions.



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Fe(II)-catalyzed α C–H amidation of N-heterocycles

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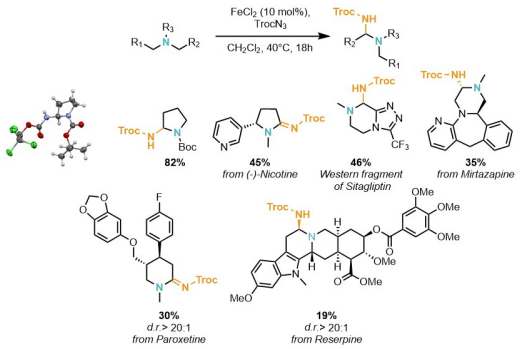
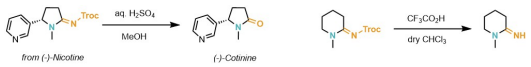
Nitrogen-heterocycles are privileged structures in both marketed drugs and natural products.[1] The development of new powerful C–H functionalization protocols is a major research topic in current organic chemistry, furnishing unconventional and straightforward approaches for the construction of bonds.[2] Yet, most of them are confined to the formation of C–C bonds, whereas the rapid introduction of heteroatom-based functional groups (e.g. C–H aminations) into N-heterocycles remains a synthetic challenge.[3] Precedent protocols have taken advantage of photo-induced radical relay[4] or Ni-catalysis[5], although an unpractical reagent was employed or substrates were used in large excess, respectively. Here we report an intermolecular C–H amidation reaction of N-heterocycles catalyzed by inexpensive $FeCl_2$, which allows the functionalization of complex pharmaceutically relevant amines (Scheme 1).



The C–H amidation occurs regioselectively at the α position to nitrogen. When electron-rich substrates are engaged in the reaction, over-oxidized Troc-amidines are obtained. These valuable compounds can be further elaborated into lactams or deprotected to simple amidines (Scheme 2).



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Solvent-Controlled Switchable Divergent Synthesis

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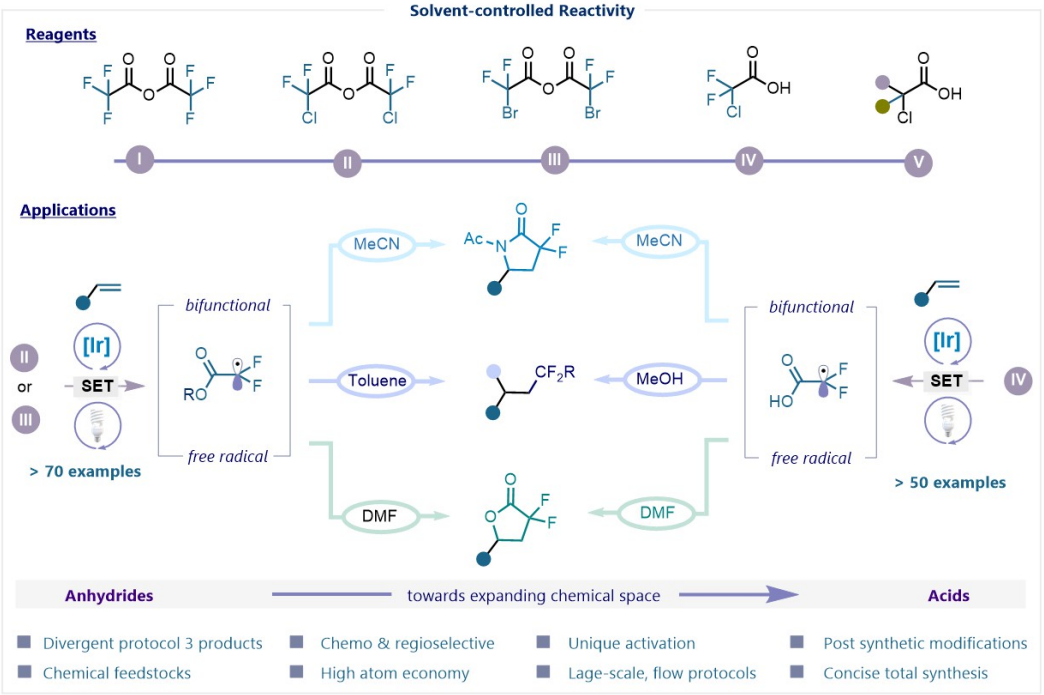
Switchable divergent reactions can be described as chemical processes where the product outcome can be modified by adjusting different reaction parameters, effectively controlling the intermediates and pathways involved in the reaction.[1] Despite its tremendous potential, this concept remains relatively under explored. Most applications have been showcased to obtain two products, whereas achieving divergence into three or more outcomes from the same starting material presents notable challenges. In this context, we have disclosed the utility of fluorinated building blocks such as chlorodifluoroacetic anhydride (II)[2] and chlorodifluoroacetic acid (IV)[3] as bifunctional reagents under photoredox conditions. Through meticulous selection of the solvent system alongside an olefin molecule, these reagents enable the synthesis of a broad spectrum of gem-difluorinated compounds, highlighting their versatility and potential within switchable divergent synthesis.



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Eco-friendly anaerobic oxidation of aryl diazoesters with heterocyclic N-oxide under ball milling: Synthesis of 1,2-dicarbonyl systems

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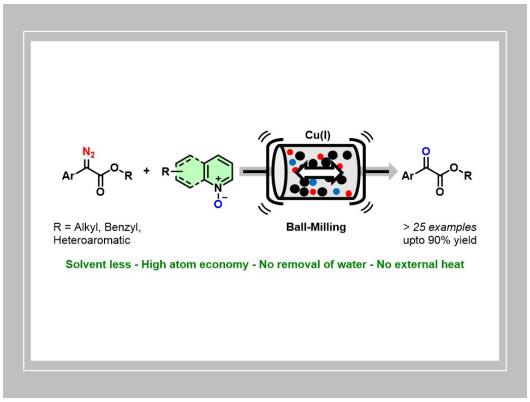
[1]School of Engineering and Architecture of Fribourg Department of Chemistry

The 1, 2-dicarbonyl motif are found extensively in natural products[1-2] and contemporary pharmaceuticals,[3-4] they play a crucial role in modern day drug discovery. Over the past few decades, an increasing number of reports have highlighted various organic transformations achieved through mechanochemical ball milling. These approaches are characterized by their eco-friendliness, as they are either solvent-free or involved microliter volumes of solvents, utilizing liquid-assisted grinding (LAG) auxiliaries represented by η (μL mg^{-1}), typically ranging between 0 and 1.[5-6]

Herein we report anaerobic oxidation of metal carbenoids generated from aryl diazo esters under ball milling, with heterocyclic N-oxide in presence of catalytic copper(I) to afford 1,2-dicarbonyls in excellent yield. Efficiently progressing across a diverse spectrum of substrates, the reaction demonstrates exceptional tolerance to a variety of functional groups, under mild reaction conditions, at low catalyst loading and minimum volume of solvent as a Liquid assisted Grinding (LAG) thereby demonstrating a practical strategy to generate these molecules.



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Electric-Field Induced Asymmetric Enamine Catalysis

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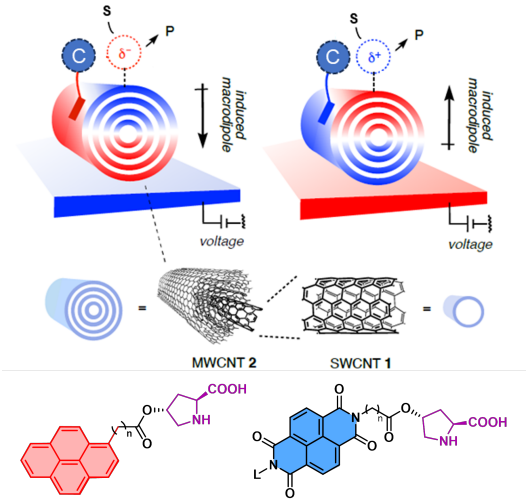
The vision to control the charges migrating during reactions with external electric fields is attractive because of the promise of general catalysis, emergent properties, and programmable devices. Here, we explore this idea with anion-π and cation-π catalysis, which is the stabilization of ionic transition states on aromatic surfaces. Catalyst activation by polarization of the aromatic system is most effective. This polarization is induced by electric fields. The use of electrochemical microfluidic reactors to polarize multiwalled carbon nanotubes as anion-π and cation-π catalysts emerges as essential. These reactors provide access to high fields at low enough voltage to prevent electron transfer, afford meaningful effective catalyst/substrate ratios, and avoid interference from additional electrolytes. Under these conditions, the rates and enantioselectivities of proline-catalysed enamine reactions, such as aldol reactions and Robinson annulations, are enhanced under an external electric field. Proline derivatives substituted with electron-rich pyrene and electron-deficient NDI exhibit different properties. While electromicrofluidics have been conceived for redox chemistry, our results indicate that their use for supramolecular organocatalysis has the potential to noncovalently electrify organic synthesis in the broadest sense.



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Enantioselective access to planar-chiral macrocyclophanes via Pd-catalyzed C−H arylation

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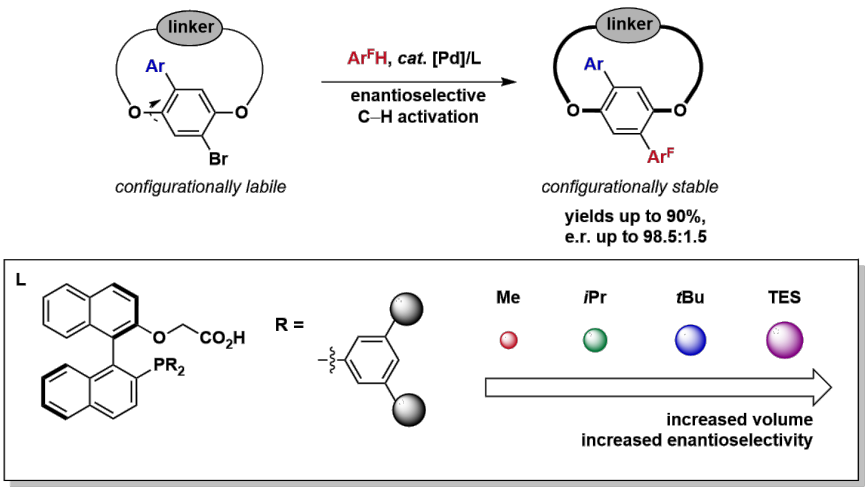
In recent decades, planar chirality has drawn significant research interest from organic chemists due to its occurrence in valuable pharmaceutical intermediates, ligands and material science. As one class of planar chiral molecules, cyclophanes are effective structural scaffolds that contain an aromatic ring with a suitable cross-linked side-chain. Despite their potential, there are only a handful of methods employing asymmetric C−H bond functionalization to access enantioenriched cyclophanes[1]. Herein, we report a Pd-catalyzed method utilizing chiral bifuntional ligands[2] and fluorinated arenes as C−H activation partners. To effectively restrict the configurational flip of the aromatic ring, either the instalment of larger substituents on the aryl ring or the usage of a shorter side-chain was chosen. A key strategy was to install sterically bulky substituent in the ligand to enhance enantioselectivity. This method is applicable for preparing planar-chiral macrocyclophanes in a broad scope containing side-chains with varied length in high yields with excellent enantioselectivities.



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Aromatic Ring-Opening Metathesis

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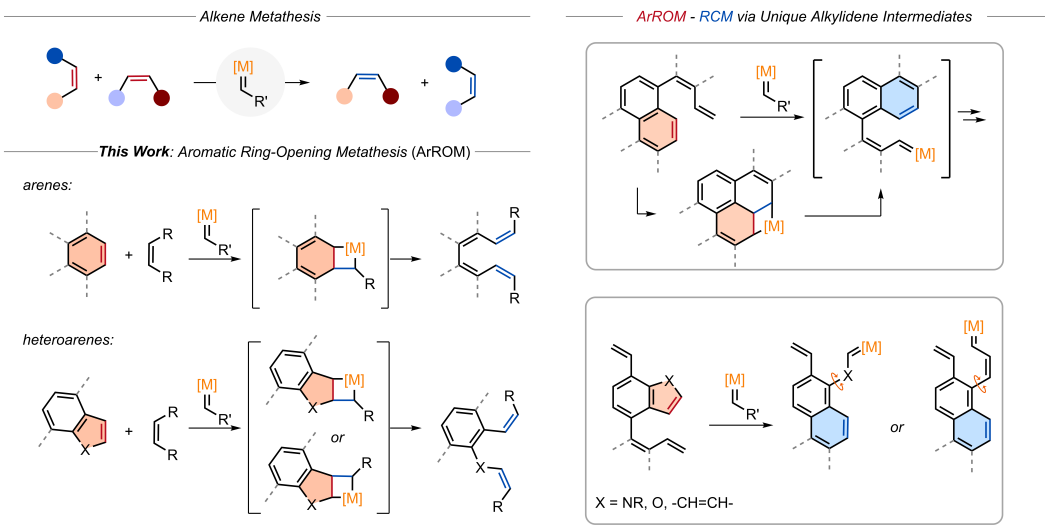
Aromatic compounds are extensively utilized in organic synthesis due to the wide array of methods available for their synthesis and further functionalization of the ring. Contrarily, the transformations involving cleavage of inert aromatic carbon-carbon bonds remained underdeveloped due to the unfavourable energetics of aromaticity disruption.[1] While for non-aromatic structures, alkene metathesis has become an indispensable tool for versatile carbon-carbon bond-forming and breaking reactions both in industry and academia, methods to open aromatic compounds remained challenging and elusive.[2] We herein describe the first examples of aromatic ring-opening metathesis and demonstrate its feasibility and generality by cleaving a diversity of aromatic rings, including tetraphene, naphthalene, indole, benzofuran and phenanthrenes. Proceeding through unique alkylidene intermediates, arene metathesis enables access to a broad range of reaction manifolds and cascades. Furthermore, highly atroposelective transformations (up to > 99 : 1 e.r.) were also achieved with chiral Schrock-Hoveyda molybdenum alkylidene catalysts.[3,4]



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Towards shape-assisted self assemblies in solution

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[1]University of Geneva

In our group, carpyridines have been used to form columnar structures where the only guiding force was shape [1]. These structures were analysed on surfaces and in solid-state, yet their self-assembly mechanism is currently poorly understood. This shortage originates from the absence of self-assembly in solution. To achieve self-assembly in solution, it is planned to incorporate amide bonds into the tails. Yet, the position of the amide group will not be directly attached to the core since it is expected to influence the stacking process depending on the connectivity of the amide group [2]. Therefore, the amide groups will be in the middle of the tails which would design would allow the shape to guide the self-assembly process and not the amide connectivity.

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Mechanistic studies on photochemical reactions: Is the Hammond postulate valid for *meta* effect induced photo-solvolysis of benzylic esters?

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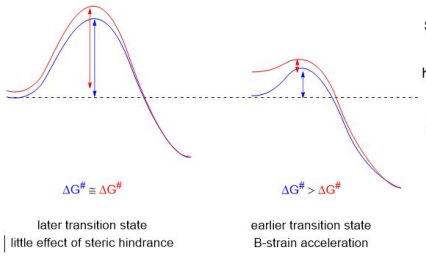
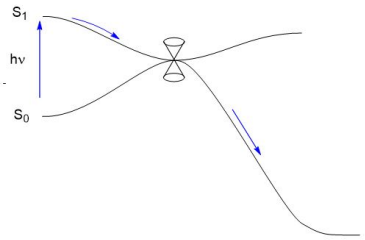
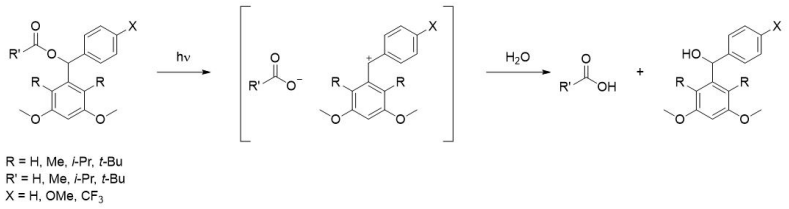
Previous work in our group suggests that Hammond's postulate is valid on some photochemical reactions. In this work, the reactions studied are *meta* effect induced photo-solvolysis of benzylic esters. First described by Zimmerman in 1963,[1] the *meta* effect is a phenomenon in which a benzylic carbocation is stabilized at the excited state by electron donating substituents on the *meta* positions of the aromatic ring. Thus, the bond dissociation must occur on the energy surface of the excited state. If the Hammond postulate is valid in such reactions, one can hypothesise that an early transition state is more sensitive to steric effects than a late transition state. This would result in a change in quantum yields when irradiating hindered and unhindered substrates, the difference being larger for early transition states (**Scheme 1**). A library of compounds with increasing steric hindrance and various electronic effects is being synthesized (**Scheme 3**) and subjected to light irradiation. These reactions are monitored via HPLC or HNMR, and their quantum yields measured in order to determine whether their transition states are early or late.



Scheme 1. Influence of the steric effect on the transition state



Scheme 2. Photochemical reaction in the singlet state



Scheme 3. Photochemical ionization of benzylic esters.

The spin state of these photochemical reactions is to be determined as well since a reaction in the singlet state would go through a conical intersection rather than a transition state (**Scheme 2**). This will be achieved using triplet quenchers and triplet sensitizers.

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Bifunctional Group Transfer

M. Kissling[1], R. Giri[1], E. Zhilin[1], S. Patra[1], A. J. Fernandes[1], D. Katayev[1]*

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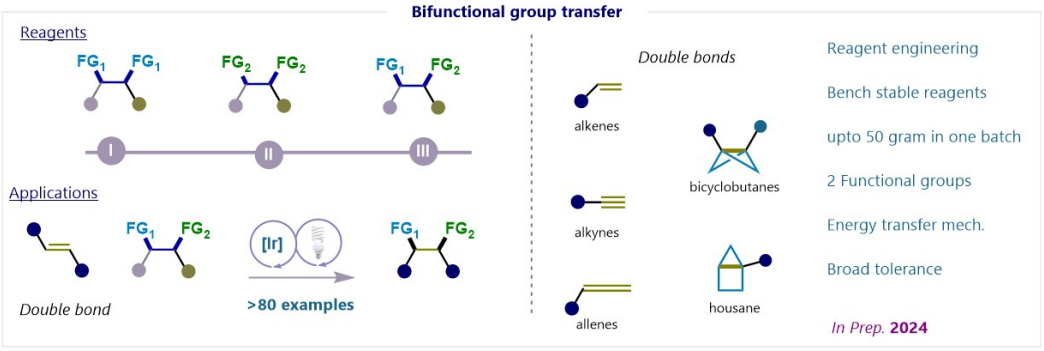
Chemists have extensively explored monofunctional group transfer, Conversely, the examination of dual functional group transfer are limited, yet it holds significant promise in scientific exploration as a novel concept.[1][2] In this study, we delve into a Functional Group Transfer Reaction (FGTR) capable of simultaneously transferring two functional groups.[3]



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Sodium-mediated Nucleophilic Amination of Pyridines

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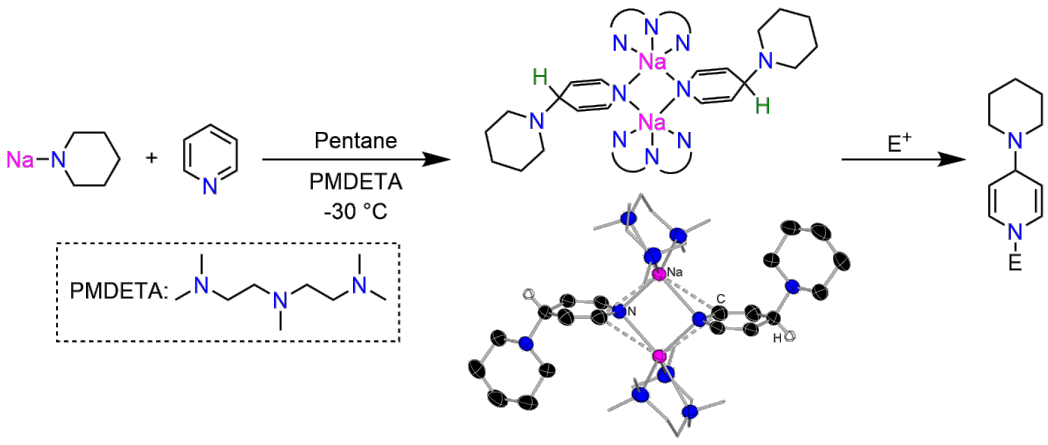
The availability and high reactivity as well as good solubility in hydrocarbon solvents of organolithium compounds has enabled their widespread use in organic synthesis.[1] Looking for more sustainable alternatives, their heavier organosodium congeners have been recently appeared as a powerful alternative.[2] However, the remarkable earth-abundancy and high reactivity of these organosodium compounds are undermined by their low solubility in hydrocarbon solvents and the greater challenge in handling in comparison to organolithium compounds. Previous work in our group has shown how organosodium compounds can be solubilized by using N-donor PMDETA, increasing their reactivity, and opening new avenues in C–B formation and deuteration reactions.[3-5]

Pioneering advancements in this domain, we report the use of organosodium for the formation of C–N bonds via nucleophilic amination of pyridines. These reactions enable the formation of synthetically valuable molecules that can be found in natural alkaloids and potent pharmaceuticals.[6] The reactions can be performed under mild reaction conditions, contrasting with previous studies by Chiba et al, which require the use of a large excess of NaH in combination with LiI and high temperatures. Furthermore, the reactions take place with unique C4-regioselectivity.[6,7] Further advancing the understanding of these reactions, we explore the role of organosodium compounds, including ^{n}BuNa or $NaCH_2SiMe_3$, as well as the nature of the amine scaffold and the pyridine ring. Reaction monitoring and the isolation of intermediates and their characterization via X-ray crystallographic studies have allowed to bring us a step further the use of organosodium compounds, opening new vistas in the use of these organometallic compounds in synthesis.



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Pd-Catalyzed Dynamic Kinetic Resolution of Pillar[5]arenes

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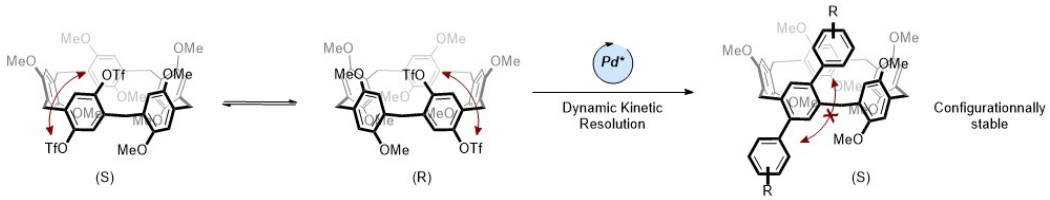
In the past decades, chiral macrocycles have played an important role in the fields of material sciences, catalysis and host-guest chemistry.[1] Among the recently reported macrocyclic compounds, pillar[5]arenes – first described by Ogoshi in 2008 –[2] distinguish themselves by the position of the substituents on the repeating p-units and their inherent planar chirality. Moreover, these macrocycles undergo an unusual enantiomerization process by rotation of the p-units through the *para* -methylene bridges. In the case of pillar[5]arenes, up to 8 stereoisomers (i.e. 4 pairs of enantiomers) exist and interconvert rapidly. However, in the absence of non-covalent interactions, the conformations all-aligned *p*R and *p*S are highly favored because the steric hindrance between each unit is minimized.[3] The introduction of bulky substituents on the rim of pillar[5]arenes has been shown to prevent interconversion and thus grant access to configurationally stable enantiomers.[4] To date, the few reports describing the synthesis of enantiopure pillar[5]arenes rely on either resolution strategies: using HPLC equipped with chiral columns or the temporary introduction of chiral units for diastereomeric separation.[5-6]



Herein, we describe the development of a Pd-catalyzed dynamic kinetic resolution (DKR) based on a Suzuki cross-coupling, which provides access to configurationally stable pillar[5]arenes in high yield and high levels of enantioselectivity. A sequential arylation that affords rim-differentiated pillar[5]arenes is also discussed.

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Sustainable Beckmann Rearrangement using Bead-Milling Technology: The Route to Paracetamol

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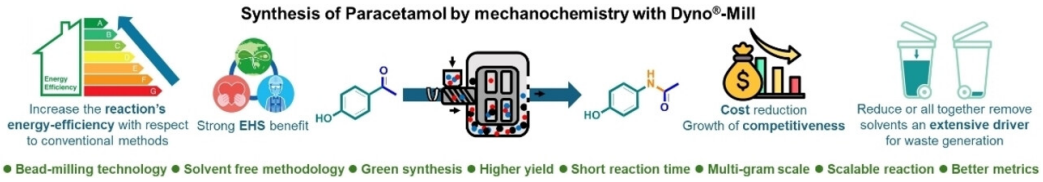
The need for a more sustainable and greener chemistry is becoming more and more important, and implementing mechanochemistry on an industrial scale could help to decrease the ecological impact by considerably reducing the amount of solvents used. To date there is little data highlighting the benefits of these mechanical technologies with regards to process scale-up. Bead-mill technology (Dyno®-Mill) was used for the first time for the sustainable mechanochemical synthesis of Acetaminophen (known as Paracetamol) using Beckmann rearrangement. The optimized solvent-free method was able to deliver around ten grams on a laboratory scale, and gave better yields compared with solvent-based (89 *vs.* 74 %). Implementing such a technology would considerably reduce costs and greatly improve green metrics by eliminating the use of solvents, but would also reduce waste generation.



Geib, R.; Colacino, E.; Gremaud, L. Sustainable Beckmann Rearrangement Using Bead-Milling Technology: The Route to Paracetamol. *ChemSusChem*, **2024**, e202301921. https://doi.org/10.1002/cssc.202301921.

Chemical Surface Modifications

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Due to the growing significance of modified electrodes in various nanotechnology applications, such as molecular electronics, bioelectronics, and sensors, there exists a pressing need to develop methodologies for the chemical attachment of appropriate molecular films onto electrode surfaces. Furthermore, it is imperative to investigate the ensuing behavior of these films. The process of electroreduction of aryl diazonium salts offers a versatile approach for the introduction of a diverse array of functional groups onto electrode surfaces (Figure 1), resulting in high surface coverage by the functional subunit. Remarkably, this electroreduction technique has demonstrated successful application across an extensive range of conducting and semiconducting substrates, underscoring its adaptability to diverse substrate types. Upon successful attachment of the designed molecule onto the electrode surface, our primary objective will involve the comprehensive characterization of the resultant film, coupled with an in-depth study of its inherent properties. The chosen surface for this endeavor is glassy carbon. Furthermore, we intend to execute a controlled deprotection of the ester group, followed by a subsequent decarboxylation of the acid, culminating in the liberation of the triple bond.

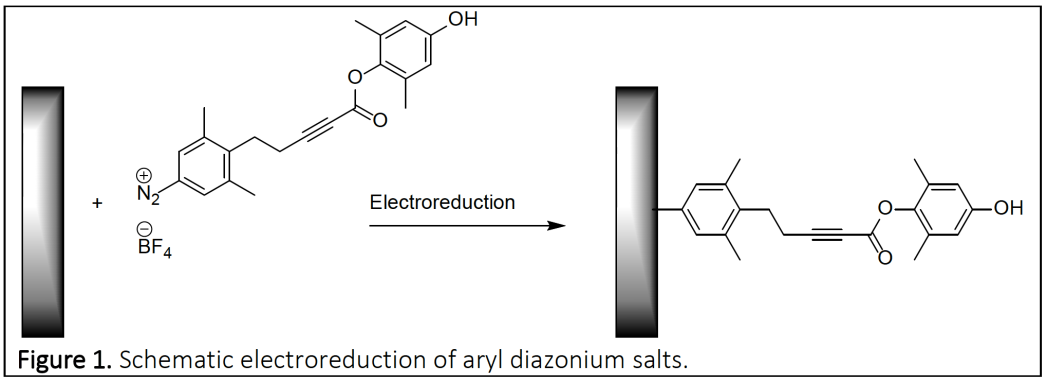

Figure 1. Schematic electroreduction of aryl diazonium salts.

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Mechanochemistry Drives Alkene Difunctionalization via Radical Ligand Transfer and Electron Catalysis

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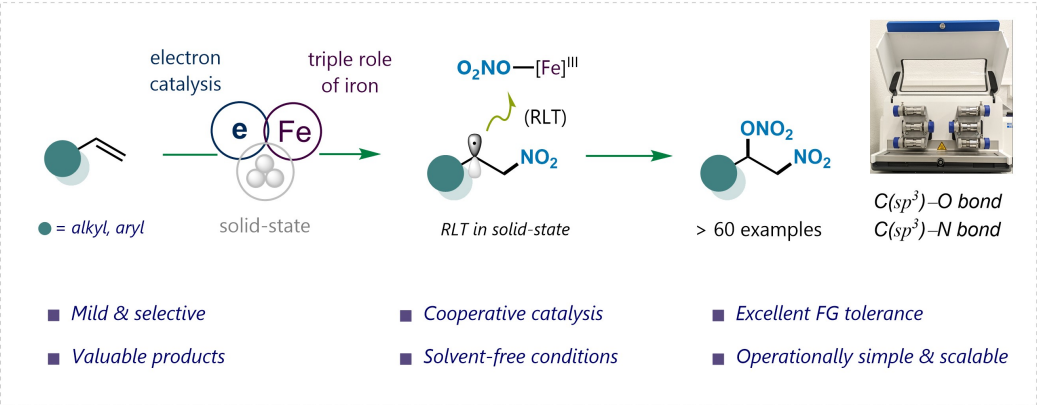
The nitro group (NO_2) plays a pivotal role in organic synthesis and finds extensive application across industry and academia. Despite significant advancements made in the field of nitration chemistry over past decades, nitration reactions of organic frameworks remain challenging from both experimental and practical standpoints.[1] Conventional methods for the direct functionalization of organic molecules involve the formation of the nitronium (NO_2^+) ion species in a highly corrosive acid mixture. However, this approach imposes various limitations, particularly for compounds containing acid-sensitive functional groups. Hence, there is a growing demand for protocols that ensure safety, as well as high level of chemo- and regioselectivity in nitration reactions, while operating under mild conditions.



Herein, we report a general and modular protocol for olefin difunctionalization through mechanochemistry, facilitated by cooperative radical ligand transfer (RLT) and electron catalysis.[2,3] Utilizing mechanochemical force and catalytic amounts of TEMPO, ferric nitrate can leverage nitryl radicals, transfer nitrooxy-functional group via RLT, and mediate an electron catalysis cycle under room temperature. A diverse range of activated and unactivated alkenes exhibited chemo- and regioselective 1,2-nitronitrooxylation under solvent-free or solvent-less conditions, showcasing excellent functional group tolerance. It also demonstrated remarkable substrate compatibility, selectivity, and scalability. Mechanistic studies indicated a significant impact of mechanochemistry and highlighted the radical nature of this nitrative difunctionalization process. Additionally, the versatility of this catalytic concept is further highlighted by its ability to selectively introduce various other functional groups.

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Ficini Reaction with Acrylates for the Stereoselective Synthesis of Aminocyclobutanes

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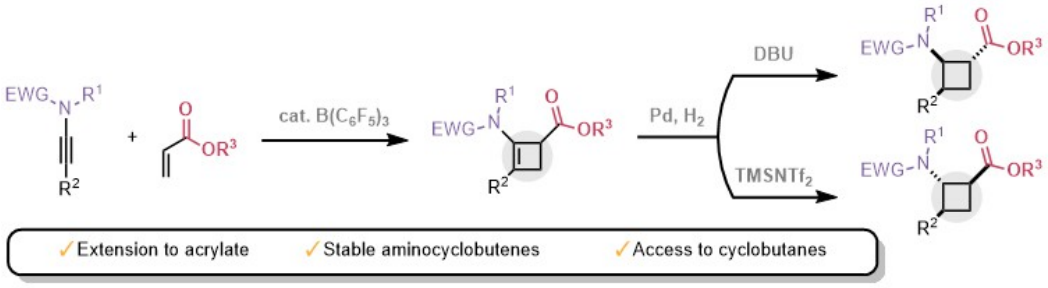
Functionalized cyclobutenes stand out as a versatile platform in synthetic chemistry and can in particular be hydrogenated to form cyclobutanes. However, the range of possible functionalities on the cyclobutene ring remains limited, especially concerning amino and ester groups which are challenging to incorporate. Nevertheless, the presence of these groups is essential and would grant access to cyclobutane amino acids, which are important building blocks in drug discovery.

We report the first Ficini reaction between ynamides and acrylate derivatives to synthetize ester substituted aminocyclobutenes.[1] Previously, only more reactive *α,β*-unsaturated carbonyls such as enones or functionalized enones could be used in the Ficini reaction.[2] We found that acrylate derivatives could be activated under user-friendly Lewis acid catalytic conditions, allowing us to obtain stable *tri*-substituted cyclobutenes in one step. Subsequently, employing a hydrogenation/epimerization sequence on the obtained strained rings enables the selective synthesis of aminocyclobutanes with two distinct stereochemical patterns. Thus, our approach represents a new strategy to access *β*-cyclobutane amino acid derivatives with a complementary substitution pattern and stereochemistry compared to the previously existing methods, thereby expanding the chemical space for medicinal chemistry.



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Further Investigations on Excited State Potential Energy Surfaces: Can the Hammond Postulate be Applied to Photochemical Reactions?

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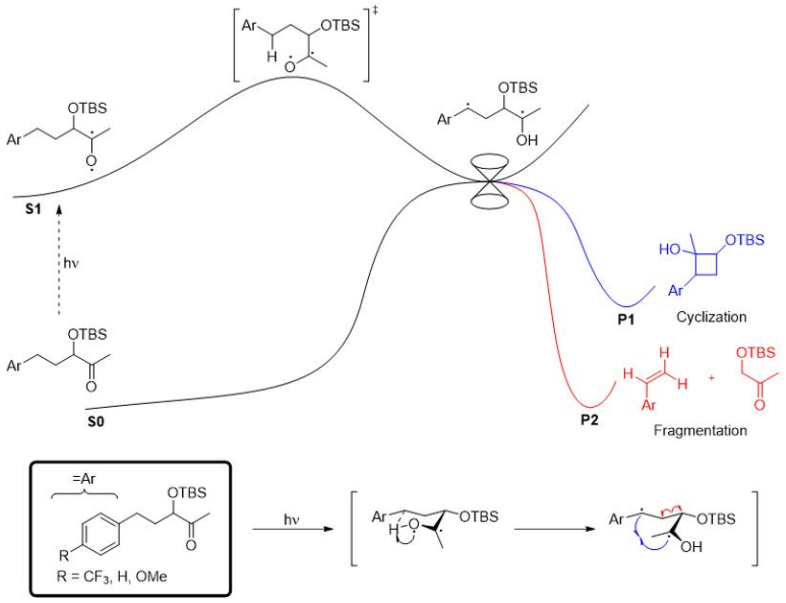
The goal of this project is to investigate the location of the conical intersection between the S_0 and S_1 Potential Energy Surfaces (PES) using a Norrish-Yang type II reaction. A conical intersection (CI) of two or more potential energy surfaces is the set of molecular configurations points where the PES are degenerate. Studies on CIs have become an essential topic for the understanding of reaction mechanisms in photochemistry, paralleling the importance of transition states in thermal chemistry. For this purpose, a series of methylketones were synthesized. As depicted on **Scheme 1**, we hypothesized that CIs are normally close to the products formation in a photochemical reaction and we propose to use the ratio of fragmented *vs* cyclized NYII products to locate it.



Scheme 1 Locating a CI with a NYII reaction.

Upon light excitation the excited carbonyl moiety of our methylketones abstracted one of the two diastereotopic benzylic hydrogen atoms forming a [1,4]-biradical.[1,2] By altering the substituents on the *para* position of the aromating ring, the stability of the benzylic radicals will be altered and this may influence the fragmented *vs* cyclized ratio.[3]

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Investigating the Formation of Iodonitrene from Hypervalent Iodine Oxidants and Ammonia

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In recent years, a multitude of conditions have been developed by our group and others, utilizing hypervalent iodine reagents and ammonia sources to effect oxidative aminative transformations like nitrogen insertion [1] and deletion [2], sulfide oxidation [3,4] or synthesis of diazirines [5] and hydrazinium salts [6]. Common to these is the proposed intermediacy of a highly reactive iodonitrene species, which is suggested to form through *in-situ* oxidation of nitrogen by the hypervalent iodine reagent. This hypothesis is based mainly on the observation of a signal corresponding to the iodonitrene mass in high-resolution mass spectrometry (HRMS) [4], however the intermediate has eluded detection and characterization by other means so far. Therefore, additional investigation into the formation, structure and reactivity of this intermediate is warranted, as this will lead to fundamental insight which may help in the development of new synthetic methods.

In this work, we investigate the speciation and reactivity of the commonly employed combination Phenyl-λ3-iodanediyl bis(trifluoroacetate) (PIFA) and ammonium carbamate using nuclear magnetic resonance (NMR), electrospray ionization mass spectrometry (ESI-MS) and density functional theory (DFT) calculations. We show that in the presence of an ammonia source, the hypervalent iodine reagent undergoes a sequence of ligand substitution and oxidation events that lead to the formation of an iodonitrene. This short-lived intermediate was successfully isolated in the gas-phase after ESI and characterized by infrared-multiphoton dissociation (IRMPD) spectroscopy, confirming its structure by the presence of a characteristic I-N stretching mode at 794cm^{-1}. A flow reactor setup coupled to ESI-MS detection was used to gain insight into the kinetics of formation and depletion of this intermediate.

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Chemoselective Approaches for the Discovery of Natural Products

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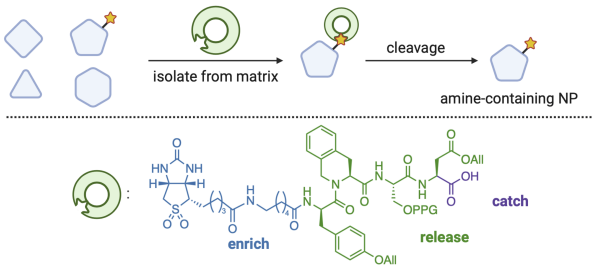
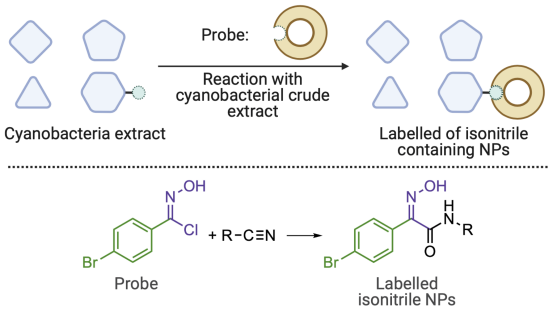
[1]Department of Chemistry, University of Zurich, 8057 Zurich,

The discovery of novel bioactive natural products (NPs) has been crucial for developing the human health system.[1] However, the field suffers from the high cost of the isolation and extraction process and the rediscovery of known compounds.[2] To overcome those issues, several technologies have emerged, such as using well-designed derivatization agents to target a specific class of NPs.[3] Those strategies can be combined with an enrichment system composed of a chemoselective probe to catch, enrich, and release a particular class of NPs. Herein, we present a novel strategy for the enrichment of amine-containing NPs[4] and a methodology to profile isonitrile NPs in a complex mixture.[5]

Catch, enrich, and release underivatized amine-containing natural products



Profiling of isonitrile-containing natural products



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Photocatalytic Generation of Cyclopropenium Cations

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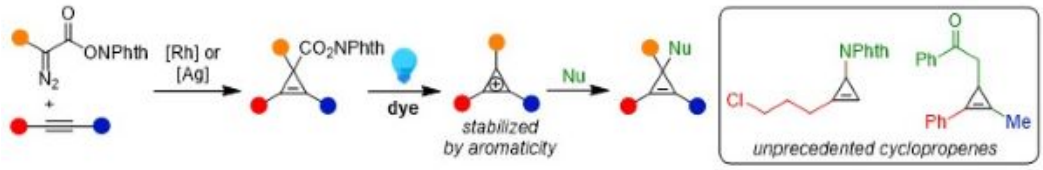
[1]Laboratory of Catalysis and Organic Synthesis (LCSO), Institute of Chemical Sciences and Engineering (ISIC), EPFL

We report photocatalytic decarboxylative functionalization of cyclopropenes. Cyclopropenylphthalimides are obtained starting from a broad range of redox-active ester-substituted cyclopropenes in the absence of a nucleophile. Moreover, different carbon and heteroatom nucleophiles can be introduced when the acidic additive is present in the mixture. The mechanistic studies provide support for the radical-polar crossover mechanism proceeding through the formation of an aromatic cyclopropenium cation, followed by trapping with the nucleophiles.



Enamine Synthesis via Regiocontrolled 6-endo-dig and 5-exo-dig Tethered Carboamination of Propargylic Alcohols

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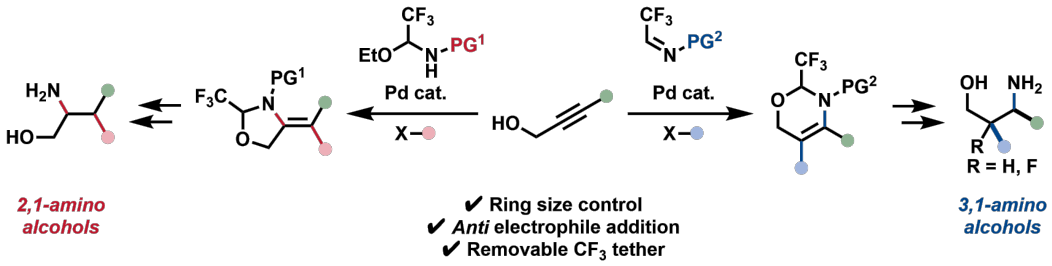
Unsaturated compounds, including alkynes, are highly versatile functional groups for accessing highly substituted alkenes through difunctionalization reactions. The introduction of nitrogen substituents, particularly to prepare enamines, is of significant interest due to their utility in synthesizing biologically active compounds. However, regio- and stereoselective strategies for highly substituted enamine synthesis are limited.

We present a method for regiocontrolled 6-*endo-dig* and 5-*exo-dig* tethered carboamination of propargylic alcohols for the synthesis of trisubstituted enamines. This approach integrates molecular tethers to direct the Pd-catalyzed difunctionalization reaction, achieving selective cyclization by fine-tuning the amine protecting group. The trifluoromethylated tethers not only facilitate the regioselective formation of enamines but also enable further stereoselective transformations such as hydrogenation and fluorination. The resulting trisubstituted enamines can be further transformed into 2,1-amino alcohols and 3,1-amino alcohols, important structures present in therapeutics and natural products.



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Sodium catalysed borylation of arenes with Iminoboranes

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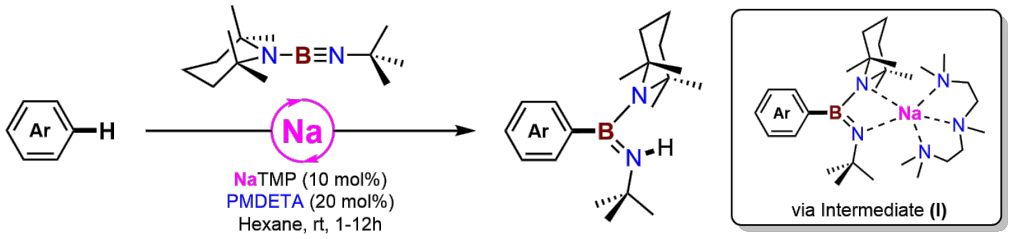
Organoboron compounds have found widespread use in the synthesis of pharmaceuticals and materials, owing to the high functional group tolerance and mild conditions of the Suzuki-Miyaura Coupling reaction. Catalytic C-H borylation stands out as an atom-efficient strategy to prepare these compounds. However, state-of-the-art protocols require transition metals that are expensive, toxic or require sophisticated ligand architecture,[1,2] while transition-metal free methods generally proceed via electrophilic C-H activation.[3,4] Alternatively, deprotonative borylation can give access to the desired borylated compounds, but it requires stoichiometric amounts of organometallic reagents.[5-7]

Charting new territory in the field, we have now demonstrated the borylation of arenes and heteroarenes using catalytic amounts of the sodium amide NaTMP (TMP = 2,2,6,6-tetramethylpiperidide) and Lewis donor PMDETA in combination with the low-coordinate iminoborane which acts as a trapping agent. As a proof of concept, catalytic deprotonative borylation shows improved functional group tolerance, milder reaction conditions and allows for the stepwise installation of C–B bonds on polyfluorinated arenes. Characterisation of a range of catalytic intermediates using NMR spectroscopic and X-Ray crystallographic studies has advanced the mechanistic understanding of this new catalytic system, showing the key use of bulky iminoboranes to stabilise the fragile metalated arenes, but also generating a highly basic intermediate (**I**) (see Scheme) that can further turn the catalytic cycle by metalating the substrate.



Scheme 1: Borylation of Arenes catalysed by Sodium Amides

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Tailoring sodium organometallic reagents for catalytic deuteration and isomerization reactions

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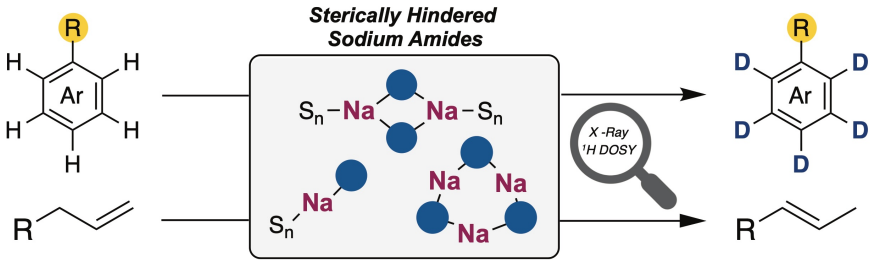
Organosodium compounds have attracted the attention of the scientific community in recent years as an alternative to widely used organolithium reagents.[1] Lithium alkyls and amides reside at the front of organometallic synthesis as key players in countless transformations, owing to their availability, substantial stability and solubility in hydrocarbon solvents.[2] However, these desirable traits are often pitfalls of heavier alkali-metal organometallics, meaning that their applications have remained underexplored.

Filling this gap in the knowledge, 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 metalation reactions of synthetically attractive arenes, providing access to the selective functionalization of these scaffolds, including the borylation[3] and the catalytic deuteration of aromatic substrates.[4] Expanding the applications of sodium amides in synthesis, we have uncovered their use for the catalytic isomerization of terminal alkenes into more synthetically useful internal olefins. Moving away from transition metals, we have studied the mechanism of this reaction with stoichiometric experiments and DFT calculations, revealing the formation of the organometallic sodium intermediates via deprotonation and showing the key role of the in-situ generated amine for an effective transformation.



Scheme 1. Deuteration and Alkene Isomerization Catalyzed by Sodium Amides.

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Photoswitching neutral homoaromatic hydrocarbons

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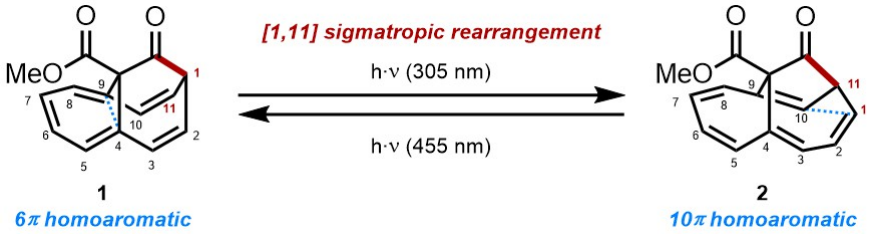
Homoaromatic structures possess characteristics of aromatic stabilization even though the cyclic conjugated π-system is interrupted. The concept of homoaromaticity is based on the interaction between the interrupted π-system via through-bond or through-space homoconjugation. This has been highly controversial in the past due to the difficulty of establishing clear criteria for the classification of molecules as homoaromatic. Homoconjugation and homoaromatics have mainly been observed and studied in charged molecules, whereas examples of neutral homoaromatics are extremely rare.[1]

We have reported the synthesis and characterization of a new class of neutral and stable homoaromatic compounds, the so-called homoannulenes,[2,3] in which through-space homoconjugation was experimentally supported by the observation of a ring current effect by NMR spectroscopy and bond length equalization by X-ray crystallographic analysis. Additionally, computational analysis of *the Anisotropy of Current (Induced) Density* (ACID) and *Nuclear Independent Chemical Shift* (NICS) supports the homoaromatic character of homoannulenes **1**.[2,3] This was realized by the precise tailoring of strain imposed by the exoskeleton utilizing the concept of geometry control.[3]

Furthermore, we show that local 6π-homoaromatic compound **1** is photoswitchable to a 10π-homoaromatic **2** by a reversible photochemical [1,11] sigmatropic rearrangement, providing a novel structural scaffold for molecular switches.[2,4]



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1,4-Pd Shift-Enabled Synthesis of Fused 4-Membered Rings

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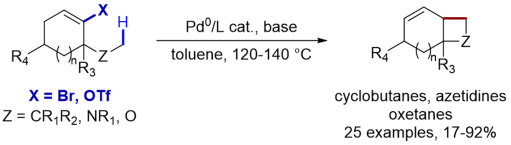
1,4-Palladium shift has been established as an elegant approach towards the functionalization of remote C–H bonds.[1,2] However, its application has been restricted to aryl halide precursors.[3] In this work, we are expanding the application of 1,4-Pd shift to alkenyl (pseudo)halides and we report an unprecedented Pd^0-catalysed cyclobutanation protocol towards fused cyclobutanes. This reaction takes place via alkenyl-to-alkyl 1,4-Pd shift, followed by intramolecular Heck coupling. The method performs best with cyclohexenyl precursors giving access to a variety of substituted bicyclo[4,2,0]octenes, and also shows a potential for accessing smaller ring systems starting from cyclopentenyl halides. Precursors containing an *N* -methyl or methoxy group lead to fused azetidines or oxetanes, respectively, via the same mechanism. Determination of orders for the reaction using variable time normalization analysis (VTNA)[4] and deuterium-labelling studies (k_H/k_D 3.1) point towards a rate-limiting C(sp^3)–H activation step.



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Mechanochemical Nitration of Arenes and Alcohols Using Bench-Stable Organic Nitrating Reagent

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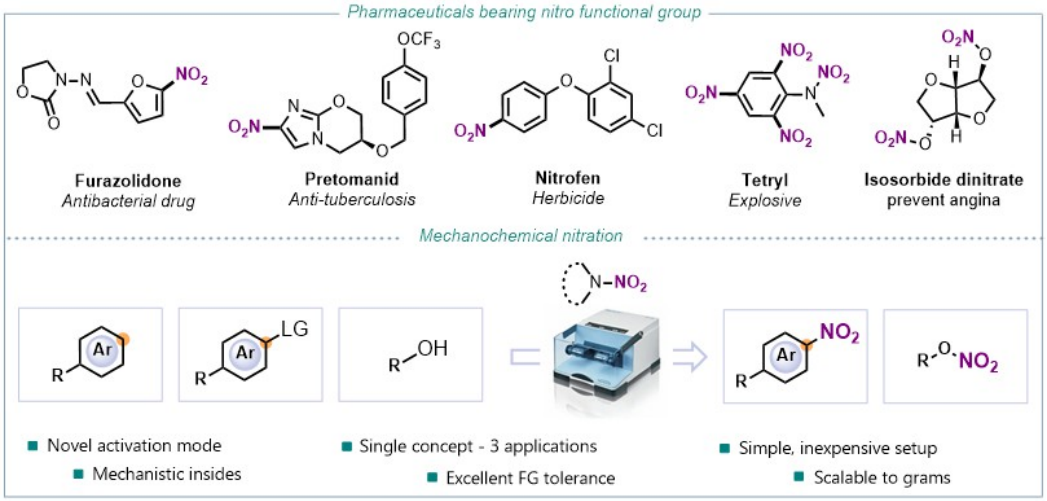
Driven by the search for greener and more sustainable synthetic methodologies, mechanochemistry has received increasing interest in the past years, also being acknowledged as one of the top ten emerging sustainable chemistry technologies by IUPAC in 2019.[1]

Given our group's long-standing interest in the field of nitration chemistry, we recently implemented ball milling (a form of impact-generating mechanochemistry) into our synthetic approaches toward the nitration of various molecular structures. In 2019, we introduced an easily accessible and recyclable organic nitrating reagent for electrophilic nitration, which tolerates various functional groups and allows for the circumvention of harsh reaction conditions involving mineral acids.[2] Our initial experimental results showed the successful nitration of various aromatic molecules, the *ipso*-nitration of prefunctionalized compounds, and the nitration of alcohols while using no or minimal amounts of solvent (≤ 2 µL/mg of reagent), thus minimizing environmental and health hazards. Further comprehensive results and mechanistic insights of into this intriguing process will be provided.[3]



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Under Control: π-Radical Cascades of Triangulene

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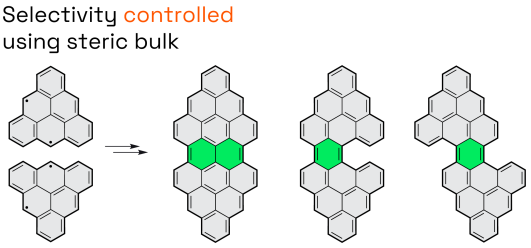
The synthesis of persistent triangulene, the most iconic member of the open-shell nanographene family, represented a challenge for over half a century,[1,2] due to the high reactivity of this diradical and therefore high likeliness to polymerize. Radical reactions are among the fastest and most efficient, but it is difficult to control and direct their selectivity. To demonstrate that such control is possible in π-radicals, we investigated the dimerization of triangulene, which can lead up to three different products, fused over one or two benzenoid rings.

In the recent work of Wu and co-workers, the intramolecular dimerization was successfully demonstrated.[3] Herein, we found that by strategic placement of substituents, we can block certain positions from reacting, and thus control the selectivity and the reaction outcome intermolecularly. This new synthetic approach opens up opportunities to access new tailor-made materials and shifts the paradigm that π-radical reactivity is undesired.



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Towards the polymerization of Centrohexaindane

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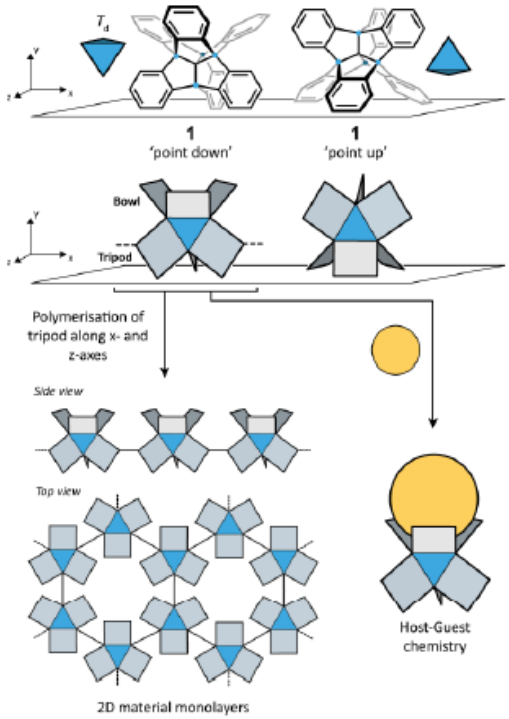
[1]Science 2, Quai Ernest-Ansermet 30, 1205 Genève

Following the discovery of graphene in 2004, interest in two-dimensional molecular sheets increased enormously because of their unique physicochemical properties giving very special surfaces for interactions compared to their three-dimensional analogues.[1] In most cases, 2D surfaces are produced via a complicated top-down approach, whereby layer after layer of the 3D material is removed.[2] A bottom-up approach, in which individual building blocks are covalently bonded to each other, could simplify the generation of 2D covalent organic frameworks (COVs).[3] Centrohexaindane is a polycyclic building block whose central carbon atom is surrounded by six cyclopentane rings which are attached to six phenylene groups, giving ($Cq(Cq)_4$) tetrahedral coordination.[4] Functionalisation of centrohexaindane in the lower molecular part creates monomeric building blocks that could be covalently bound together forming a two-dimensional surface in a bottom-up approach. With its bowl-shaped surface, centrohexaindane could act as a receptor for curved molecules like fullerene or corranulene and, as a two-dimensional polymer, could be an interesting area for future research.



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Site-Selective Deuteration of (hetero)arenes Catalyzed by Supported Ir Nanoparticles

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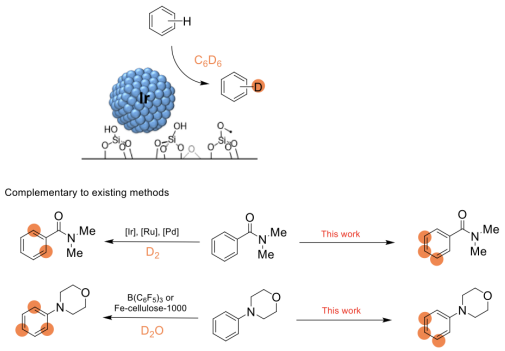
The substitution of C-H with C-D bonds in drug molecules presents a simple way of modifying drug's absorption, distribution, metabolism, and excretion (ADME) properties, while maintaining the interaction with target and selectivity.[1] Direct deuteration of C-H bonds prevents multistep de novo synthesis and offers an efficient method for late-stage isotopic labelling. In this study, we report the development of a silica-supported iridium nanoparticle catalyst for the selective deuteration of arenes and heteroarenes using C_6D_6 as the deuterium source. This catalytic system demonstrates high functional group tolerance and regioselectivity, favoring para and meta positions without affecting ortho and sp^3 C-H bonds, which complements well with existing methods.[2] The catalyst exhibits excellent chemo- and regioselectivity, overcoming the limitations of previous methods that used D_2, and thus often suffered from unwanted hydrogenation.[3] Our findings highlight the broad applicability of this method to various pharmaceuticals, showcasing its potential for enhancing drug development through deuterium incorporation.



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Repurposing Myoglobin into an Abiological Asymmetric Ketoreductase

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Thanks to recent advances in enzyme repurposing, hemoproteins have gained significant attention as versatile biocatalysts that catalyze a variety of transformations, ranging from oxidation to redox-neutral reactions. To complement these achievements, we report herein on our efforts to repurpose myoglobin (Mb) into an asymmetric ketoreductase using $PhSiH_3$ as reductant. Two rounds of mutagenesis afforded a double mutant capable of reducing with high enantioselectivity a broad range of prochiral aliphatic and aromatic ketones in the presence of whole-cells. Additional rounds of directed evolution afforded a quintuple mutant with opposite enantioselectivity. Mechanistic investigations suggest that a fleeting Fe-H species undergoes heterolytic hydride-transfer to afford enantiopure alcohols from the corresponding ketones. The excellent saturation kinetics profile, combined with the practicality of whole-cell biocatalysis under aerobic conditions, highlight the potential of repurposed Mb as an asymmetric ketoreductase with a broad substrate scope, thus expanding the reaction repertoire catalyzed by hemoproteins.

Synthesis and Self-Assembly of Contorted Aryl Amines

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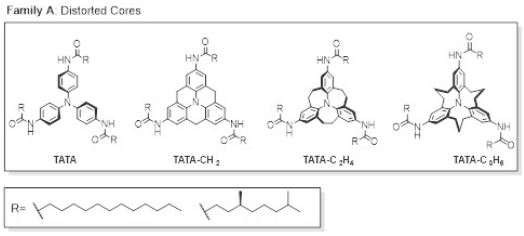
Triphenylamines (TPAs) and its derivatives have received considerable attention over the past years[1] thanks to their attractive properties that enable their electroactive and photoactive applications[2-3]. Their molecular configurations and electronic properties greatly influence their aggregation 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 research that reveal how the shape of the core affects the supramolecular polymerization.

To address these seminal goals, we aim to study the influence of systematic variations of the core of a triarylamine trisamide (TATA) core unit, while keeping the outer layer (i.e. sidechains) 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 (Figure 1), 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. The main objective in this family is thus to investigate if it is possible to find a direct relationship between the distortion of the flat surface and the observed degrees of supramolecular order.



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Access to Cyclic Borates by Cu-Catalyzed Borylation of Unactivated Vinylcyclopropanes

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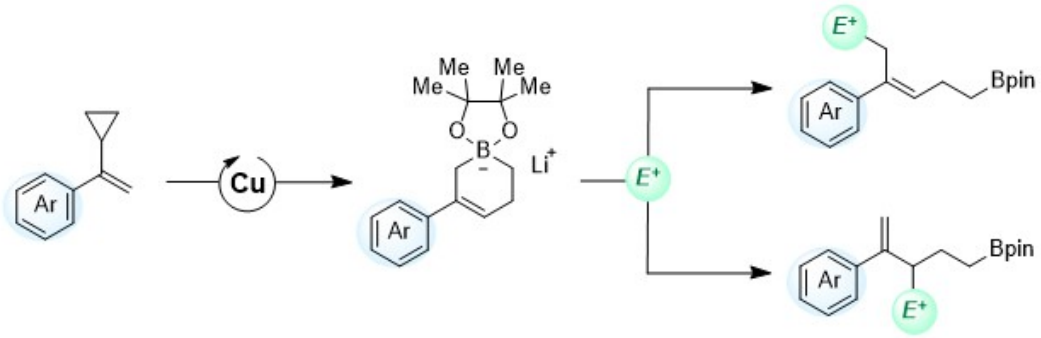
Because vinyl cyclopropanes (VCPs) can undergo a variety of transformations such as cycloadditions, rearrangements, or ring-openings, they are often perceived as pivotal building blocks for organic synthesis.[1-2]Moreover, selective catalysis using VCPs provides access to valuable, highly functionalized five-carbon synthons. However, while excellent levels of chemo-, regio and sometimes enantioselectivity have been obtained for a number of activated VCPs (i.e. VCP bearing electron-withdrawing substituents), examples of selective catalytic methods using less reactive non-activated VCPs (i.e. substrates devoid of activating functions) are scarce.[3-4]



Herein, we report the development of a general Cu-catalyzed borylation of non-activated VCPs, which provides access to uncommon cyclic allylboronates. The reactivity of these derivatives toward a broad range of electrophiles will be presented. This includes, *inter alia*, an unusual ligand-controlled Pd-catalyzed regiodivergent arylation reaction.

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Pnictogen-Bonding Catalyzed Hydrogenation Reaction and Ion Transports in Vesicles

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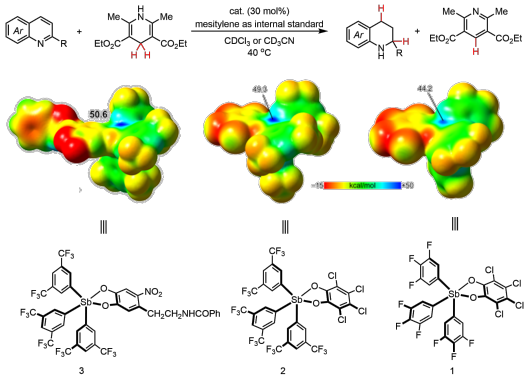
[1]Department of Organic Chemistry, University of Geneva, Geneva (Switzerland)

Our ongoing research interest lies in the design of pnictogen-bonding and its application in anion transport and catalysis of new reactions. It is well-known that Sb(V), with its higher oxidation state, exhibits greater catalytic activity compared to Sb(III). Thus, by modulating the electronic properties of the substituents on the catalyst, a series of new Sb(V) catalysts have been synthesized. In organic solvents, based on the hydrogenation rate of quinoline, the catalytic activity of Sb(V) is significantly higher than that of Sb(III). Additionally, we aim to investigate the UV-Vis spectra of the catalyst, substrate, and their mixtures to verify the presence of interactions within the reaction system. A red shift observed in the mixture of the substrate and catalyst indicates the interaction between Sb(V) and the substrate. Subsequently, we applied antimony catalysts to ion transport of hydroxide ions across the phospholipid bilayers. The ion transport results of EYPC vesicles containing HPTS channels show that the ion transport activity of Sb(V) is significantly stronger than that of Sb(III). As we all know, vesicles can enhance the reaction concentration in the microenvironment, thereby increasing the reaction rate. Therefore, we hope to combine Sb-catalyzed hydrogenation reactions with vesicles to enhance the reaction rate. This part of the work is currently in progress.



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Unlocking Molecular Design via Dihalogenation of Unsaturated Hydrocarbons

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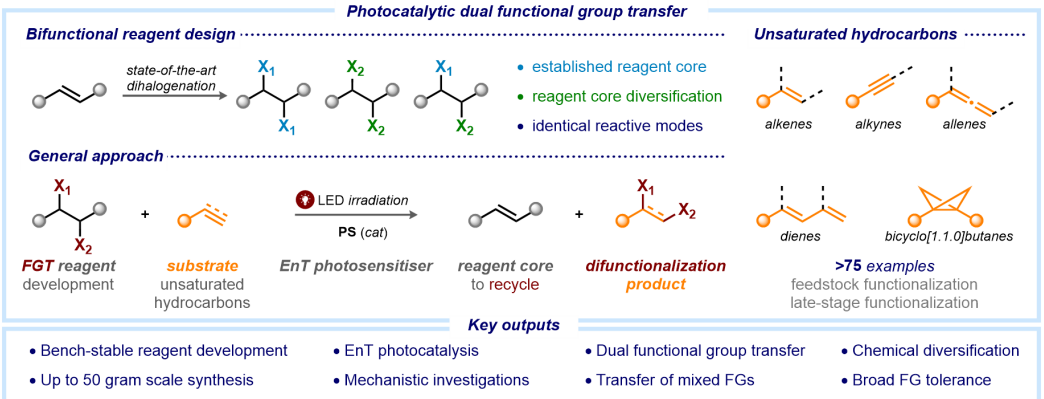
Functional group transfer (FGT) in organic chemistry is a fascinating research field of scientific discovery that provides opportunities for innovation in the area of advanced organic synthesis. These processes enable the creation of a wide range of complex molecules with diverse structures and functionalities in a straightforward and atom-economic fashion, which greatly facilitates the development of new chemical entities and materials. To date, the concept of monofunctional group transfer for installing singular transferrable functionality has been actively investigated by chemists and has already found widespread application in molecular design[1]. In contrast, dual functional group transfer is poorly examined and, as a relatively new concept in scientific exploration, has very promising applicability and significant fundamental advances. Given the strengths of photocatalytic methodologies that possess inexpensive, effective and wasteless protocols for efficient organization of chemical synthesis[2], we wish to report the unique fusion of energy transfer photocatalysis and dual functional group transfer that exhibits unprecedented atomic efficiency and overall low-cost of manipulation for dihalogenation of unsaturated compounds.

Initially, extensive research on reagent design was carried out to find key chemical frameworks suitable for sequential transfer of two halogens to unactivated olefins in a mild and selective manner and further reinstallation of desired functionalities to the reagent core for recycling purposes. Following investigations were conducted on optimization of the conditions for photocatalytic energy transfer, specifically targeting powerful photosensitizer possessing tolerance towards highly derivatized starting materials. Additionally, performed comprehensive mechanistic studies revealed the fundamentals of precisely controlled stepwise dihalogenations. Finally, the broad scope of unsaturated hydrocarbons was successively employed in the developed protocol of EnT-mediated dihalogen transfer, empowering methodology application and chemical diversification to advance late-stage functionalization in the fields of drug design and fine organic synthesis.



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An Evolved Artificial Radical Cyclase Enables the Construction of Bicyclic Terpenoid Scaffolds via an H-Atom Transfer Pathway

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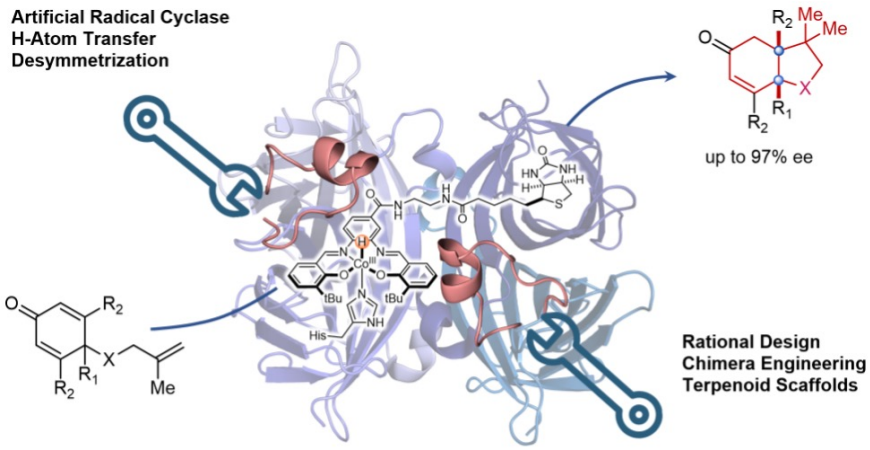
While natural terpenoid cyclases generate complex terpenoid structures via cationic mechanisms, alternative radical cyclization pathways are underexplored. The metal-catalyzed hydrogen-atom-transfer (M-HAT) reaction offers an attractive means for hydrofunctionalizing olefins, providing access to terpenoid-like structures. Artificial metalloenzymes offer a promising strategy for introducing M-HAT reactivity into a protein scaffold. Herein, we report our efforts towards engineering an artificial radical cyclase (ARCase)[1], resulting from anchoring a biotinylated [Co(Schiff-base)] cofactor within an engineered chimeric streptavidin. After two rounds of directed evolution, a double mutant catalyzes a radical cyclization to afford bicyclic products with a cis-5-6-fused ring structure and up to 97% enantiomeric excess. The involvement of a histidine ligation to the Co-cofactor is confirmed by crystallography. A time-course experiment reveals a cascade reaction catalyzed by the ARCase, combining a radical cyclization with a conjugate reduction. The ARCase exhibits tolerance towards variations in the dienone substrate, highlighting its potential to access terpenoid scaffolds.



[1] D. Chen, X. Zhang, A. A. Vorobieva, R. Tachibana, Z. Zou, P. R. Jakob, D. A. Graf, T. Maier, A. Li; B. Correia*; T. R. Ward, *Nat. Chem*. In press.