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Bacterial RNA targeting

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RNA is a highly versatile molecule and exhibits many diverse functions. Our lab explores new approaches and chemical tools to target RNA in bacteria. >Our interests lie at the intersection of nucleic acid chemistry and antimicrobial research.

Synthesizing customized affinity-based profiling tools we study RNA structural folding and small molecule ligand binding to bacterial RNAs to explore these as antibacterial targets. We can determine ligand binding sites with single nucleotide resolution. Taking advantage of the unusual nucleophilicity of the 2'-OH position of RNA we are working on a conceptual new approach to covalently target RNA.

We explore new possibilities for antibacterial antisense therapies. Using synthetic versions of endogenous iron-binders known as siderophores, we can effectively transport large antisense oligomers into bacteria and selectively down regulate protein production of essential genes. With this method we can produce potent ‘asobiotics’.

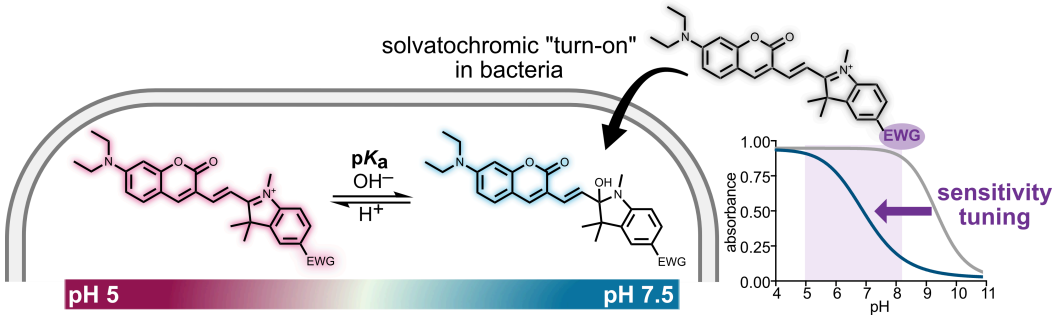
A ratiometric pH sensor for Gram-positive and Gram-negative bacteria.

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Persister cells are phenotypically dormant bacteria that survive antibiotic treatment without genetic resistance. Their formation is modulated by environmental fluctuations, especially exposure to low pH. To understand how individual cells adapt to pH stress, methods are required to analyze single-cell physiology. Yet most pH probes are optimized for mammalian cells and poorly suited for bacterial applications, as bacteria preferentially take up positively charged, polar, or zwitterionic molecules.[1-3]

We report a ratiometric fluorescent probe for sensing cytoplasmic pH in bacteria.[4] Our probes are based on hemicyanine dyes that exhibit good cellular uptake in both Gram-positive and Gram-negative bacteria. Additionally, our probes exhibit improved photophysical properties for bacterial imaging, particularly increased brightness due to the apolar nature of the intracellular space. By tuning the electrophilicity of the molecular scaffold, we obtained a pH-sensing CouCy probe that preferentially reacts with OH^- and exhibits a ratiometric emission change. The response is rapid and reversible, enabling real-time tracking of pH fluctuations around neutrality and biologically relevant acidification. We validated the live-cell imaging using *Escherichia coli*, *Staphylococcus epidermidis*, and a clinically isolated methicillin-resistant *Staphylococcus aureus* strain. Furthermore, the probes enabled monitoring of phagocytosis of clinical strains by immune cells and allowed distinction of virulence phenotypes based on intracellular pH. Our probes are promising tools for detecting phenotypic heterogeneity of clinically relevant bacteria.



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From Supramolecular stacking to Self-assemblies of curved molecules on surfaces

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The Rickhaus group aims to control molecular stacking through shape-governed assembly principles [1]. Because these systems can assemble without relying on covalent bonding, their degree of (non)crystallinity can be finely tuned [2]. This allows to resolve the structure at the molecular level and to increase our understanding over the influence of guests on the supramolecular polymerisation process. While this has been well documented on several systems, our understanding at the molecular level [3,4] remain poor.

Through collaboration with the Auwärter group, we aim to deep our knowledge about self-assemblies. This group focuses on depositing molecules on surfaces to investigate network formation, intermolecular interactions, and self-assembly behaviour. In this contribution, we demonstrate high-quality deposition of curved molecules that, instead of forming supramolecular stacks, give rise to extended supramolecular networks. Additionally, we have carried out H-bonding on this type of assemblies, yielding intriguing results. Understanding how H-bonding incorporation influences supramolecular polymerization is our next challenge, as we work toward deeper control over self-assembly processes and further tuning of these systems.

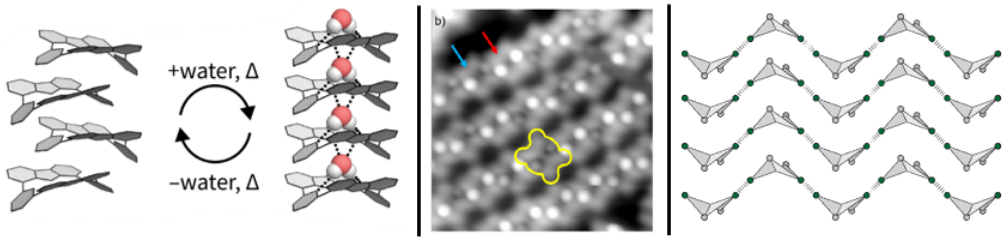


Fig.1: a) Columnar arrangements of carpyridines depending on the presence of water. b) Overview STM image of Cu-Carpyridine /Au (111). c)

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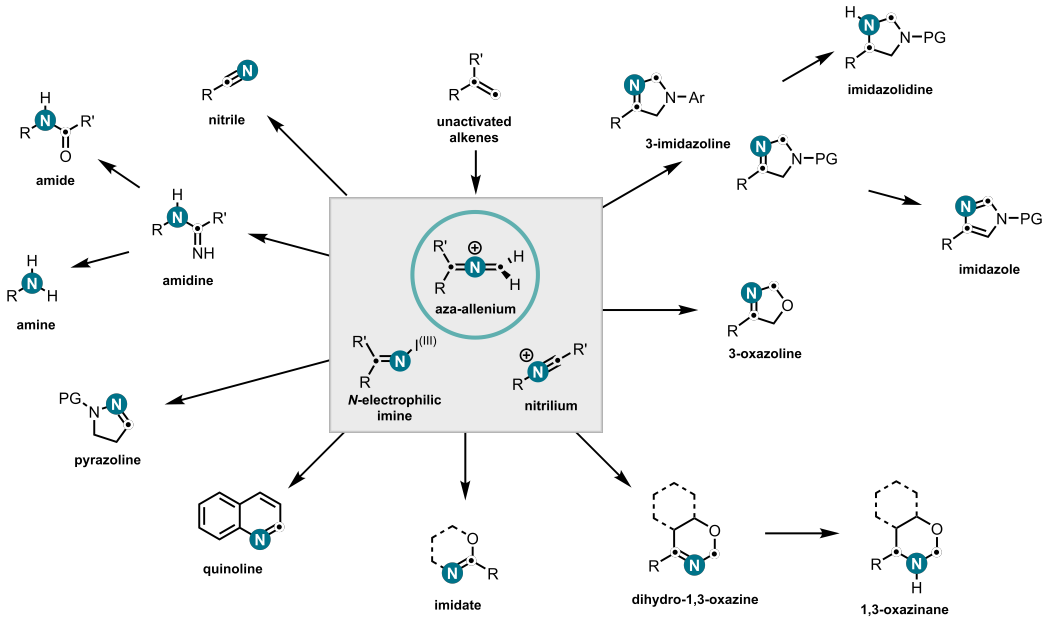
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Oxidative Amination Through Nitrogen Atom Insertion into Unactivated Alkenes

Y. Brägger[1,2], A. K. Paschke[1], E. Tufano[1], B. B. Botlik[1], P. Gärtner[1], N. Nasiri[1], F. Felician[1], M. C. Amberg[1], L. Sorrentino[1], D. T. Egger[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.[1] Herein, we report the direct insertion of a nitrogen atom into unactivated carbon-carbon double bonds to access aza‐allenium intermediates, which can be converted into either nitriles or amidines depending on the initial alkene substitution pattern.[2] This operationally simple and highly functional‐group‐tolerant reaction is effective across a wide range of unactivated alkenes. Mechanistic investigations, including targeted trapping experiments, support the proposed pathway and highlight the synthetic value of these electrophilic intermediates. In particular, allylic nucleophiles engage the aza‐allenium species in efficient *5‐endo‐trig* cyclizations, delivering previously inaccessible semisaturated *N*‐heterocycles with inverse Baldwin selectivity.[3] Together, these findings establish a general blueprint for constructing diverse nitrogen‐containing scaffolds through direct nitrogen insertion and controlled interception of reactive intermediates derived thereof.



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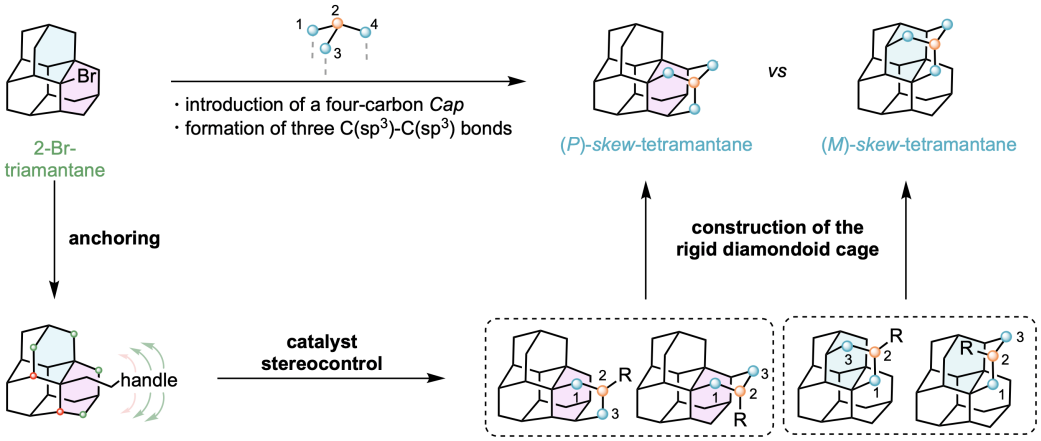
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Stereoselective total synthesis of *skew*-tetramantane, diamond's chiral core

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Diamond's elementary chiral constituent – *skew*-tetramantane – features extreme rigidity, stability and a precisely defined geometry, epitomizing the parent structure of a σ-helicene. While *skew*-tetramantane is naturally occurring in trace fractions in fossil fuels, efforts over several decades for its selective synthesis remained unfruitful. With the recent advances in photo- and transition metal catalysis to tame radical and carbene species, we now devised a targeted total synthesis of *skew* -tetramantane by means of a **stereoselective adamantalogous cage-extension**. A first cap attachment was thereby effected by a **photocatalytic Giese reaction**, while remarkable regio-, diastereo- and enantiocontrol were achieved by an **intramolecular C(sp^3)−H insertion** using Davies' chiral rhodium catalysts. **Density functional theory** (**DFT**) calculations elucidate the origin of this high selectivity, revealing a stereoelectronically biased transition state governed by catalyst–substrate interactions. The fusion to the adamantine *skew*-tetramantane structure was completed after a **Buchner–Curtius–Schlotterbeck ring expansion** and a **stereoselective Mukaiyama hydration** by an **intramolecular C(sp^3)−H insertion of a nonstabilized carbenoid**. Overall, this approach provides access to synthetic *skew*-tetramantane in isomerically pure form with σ-helicity defined by catalyst-control, marking a selective pathway to higher diamondoids.



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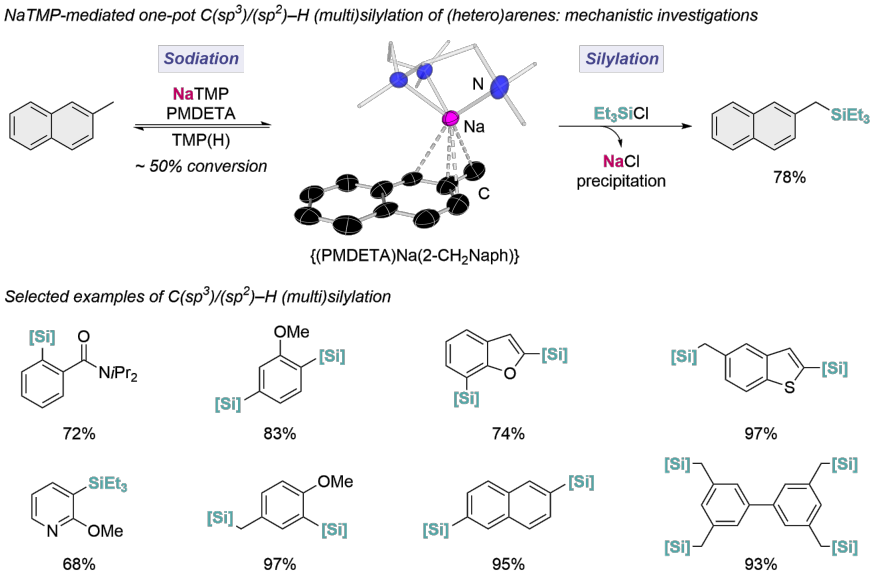
Sodium-Mediated C-H Functionalization: Direct and Selective (Multi)Silylation of (Hetero)Arenes

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[1]Departement für Chemie, Biochemie und Pharmazie, University of Bern

Direct C–H silylation of arenes is a fundamentally important tool to access highly valuable organosilicon compounds, versatile building blocks in organic synthesis, drug discovery and materials science. To date this task has mainly been achieved via precious transition-metal catalysts that can promote C–H bond activation, though reports in main group chemistry have shown some limited potential of alkali-metal species to mediate these processes.[1]

Breaking new ground, here we report a new versatile and efficient approach, using the highly encumbered yet strongly basic sodium amide NaTMP (TMP = 2,2,6,6-tetramethylpiperidide) to achieve selective C–H silylation of an array of arenes and heteroarenes with surprisingly excellent regioselective control. This method relies on the prolific ability of NaTMP to promote metalation of aromatic molecules, providing a mild strategy based on the extraordinary reactivity of sodium organometallics.[2] By pairing this powerful base with bulky electrophilic chlorosilanes, in addition to mono-silylation reactions we can also promote unprecedented regioselective multi-silylation of non-activated arenes such as naphthalene or pyrene. These studies evidence the superior performance of the sodium amide in comparison with other existing metalating reagents. By combining reactivity studies with the trapping of key reaction intermediates, DFT analysis, and NMR reaction monitoring studies, we have gained mechanistic insight into this transformation, where steric and coordination effects possess a key role and reveal the close interplay between sodium and the silicon electrophile required to promote regioselective C–Si bond formation.



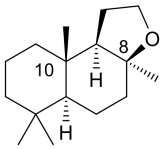
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Decoding the Scent of Ambra: Chemoenzymatic Synthesis of 15 Ambrox Stereoisomers and their GC-Olfactometric Analysis and *in vitro* hOR-Activation

F. Flachsmann[1,2], E. Eichhorn[1], R. Emter[1], A. Natsch[1], L. Hortencio[1], S. Dossenbach[1]

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The iconic ambra odorant (-)-Ambrox ((-)-**1**) features a truncated labdanoid skeleton with 4 chiral centers. Despite the long history and commercial importance of this ingredient, knowledge about structure-odour relationship among the stereoisomers was incomplete. We have now addressed the long-standing challenge of preparation and olfactory assessment of all 16 stereoisomers.[1]



(-)-**1** (Ambrox)

Our strategy comprised the preparation of all geometric isomers of homofarnesol and their cyclization using selected squalene hopene cyclases.[2] This led to the successful preparation of all eight (10*S*) stereoisomers of Ambrox with >99.9% e.e.. The mildness and stereospecificity of the SHC mediated polycyclizations are illustrated by the challenging conversion of the (3*Z*,7*Z*)-isomer **9d** to (-)-**8** and (+)-**6** (Figure 1a).[1] For the enantiomeric (10*R*)-series, we relied on enantiomer separation and isolation by chiral preparative HPLC of racemic samples prepared by semi-synthesis.

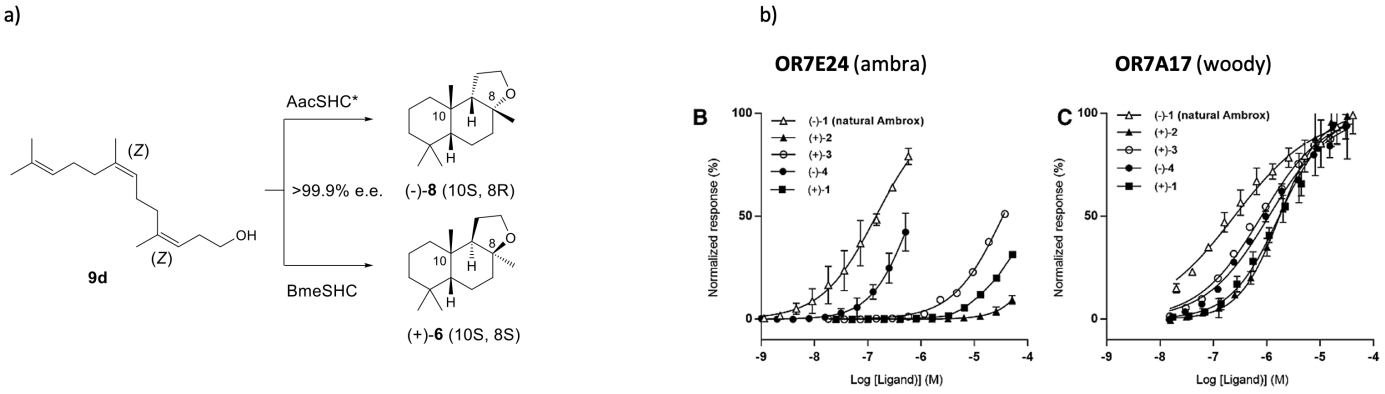


Figure 1. a) SHC mediated cyclization of *Z*,*Z*-homofarnesol. b) Receptor activation results of selected Ambrox stereoisomers.

The final products were evaluated by GC-olfactometry (GCO) with experienced panelists and *in vitro* receptor screening with the human olfactory receptors (hORs) OR7A17 ("woody receptor", broadly tuned to woody smelling odorants) and OR7E24 ("ambra receptor", narrowly tuned to Ambrox-like smelling odorants) (Figure 1b).[3] The results draw a unique picture of dynamic range and odour modulation solely dictated by stereochemistry.

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Rational Design of Photocleavable Tags for Quantum Interferometry of Biomolecules

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Matter-wave interferometry of large biomolecules demands efficient strategies for launching intact neutral particles into high vacuum and detecting them after traversal of the interferometer [1]. A key challenge is generating charged fragments from a neutral beam to enable mass-spectrometric detection.

In our previous work, a series of porphyrin-based photocleavable tags was developed and evaluated for this purpose [2]. These compounds demonstrated clean homolytic cleavage at 411 nm in the gas phase, producing neutral fragments and confirming the viability of laser desorption for neutral beam formation. However, because both fragments are released as neutral species, an additional vacuum ultraviolet postionization step at 157 nm is required for mass-spectrometric detection, adding complexity and further limitations to the overall detection scheme.

To probe an alternative approach to ionization, we present a rationally designed zwitterionic photocleavable tag in which charge separation is already a feature of the molecular architecture. A permanent quaternary ammonium cation and a sulfonate anion are held in fixed spatial relationship across a rigid [2.2]paracyclophane spacer, rendering the intact molecule net-neutral. DFT geometry optimization confirms a charge separation distance of 11.9 Å in the energy-minimized gas-phase conformation (Figure 1), reducing the Coulombic barrier for fragment separation well below the energy of a single 266 nm photon (4.66 eV). The nitrobenzyl ether photocage was selected on the basis of well-established photocleavage reactivity at 266 nm, and the [2.2]paracyclophane spacer was chosen for its rigidity, which enforces a defined charge separation geometry in the gas phase. Upon UV irradiation, intended homolytic cleavage of the nitrobenzyl ether linkage would liberate the pre-existing internal charges as spatially separated ionic fragments, directly detectable by mass spectrometry without any external ionization step.

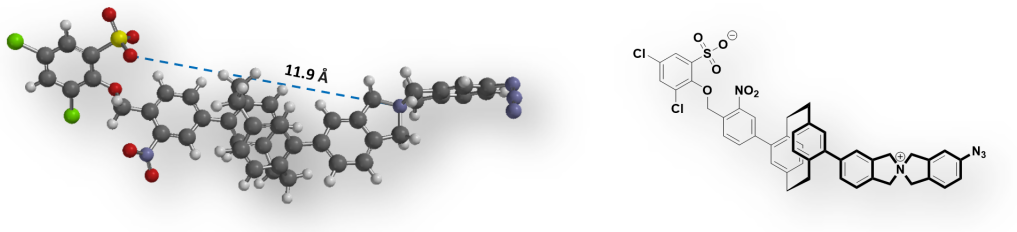


Figure 1. The zwitterionic photocleavable tag: chemical structure (right) and DFT-optimised gas-phase geometry (left), showing a charge separation distance of 11.9 Å between the sulfonate anion and the quaternary ammonium cation across the rigid [2.2] paracyclophane spacer.

The tag incorporates an azide handle for CuAAC bioconjugation, enabling modular conjugation to alkyne-functionalized biomolecules. Gas-phase photocleavage experiments are underway in collaboration with the Arndt group (University of Vienna).

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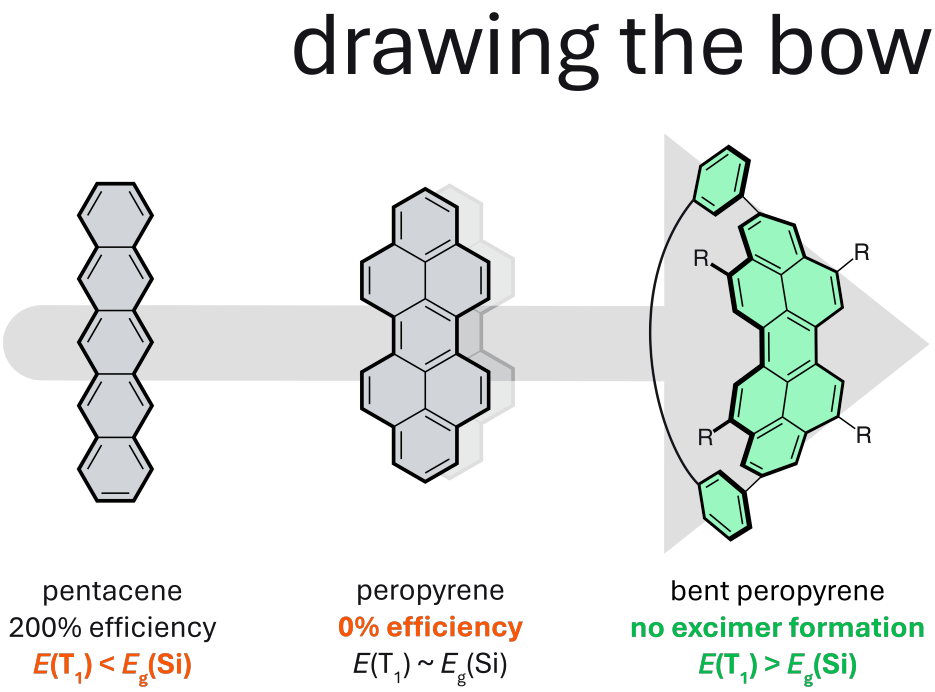
Escaping the excimers: Bending peropyrene for singlet fission

P. L. Widmer[1], D. Čavlović[1], T. Matic[1], O. Blacque[1], M. Juríček[1]*

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Singlet fission can overcome efficiency limits in solar cells by converting one photon into two triplet excitons. But even the most efficient singlet fission organic chromophores like pentacene do not possess triplet energies, $E(T_1)$, compatible with the band gaps, E_g, of commonly used Si- and GaAs-based photovoltaic devices. Peropyrene fulfills these energetic requirements, but unsubstituted peropyrene fails to efficiently undergo singlet fission because of excimer formation. We solve this problem by bending peropyrene to enable favorable packing in the solid-state without perturbing the electronic structure of the chromophore itself.

Bending of shorter and longer homologs of peropyrene has previously been achieved through several strategies. None of these methodologies, however, are transferable to the peropyrene scaffold, leaving the route to progressive bending in peropyrene inaccessible. We address this limitation by employing π-radical cascade reactions[1], a versatile synthetic platform that enables progressive bending of the peropyrene framework, providing a series that allows a systematic evaluation of how molecular curvature suppresses excimer formation in the solid state and ultimately enhances the efficiency of singlet fission.



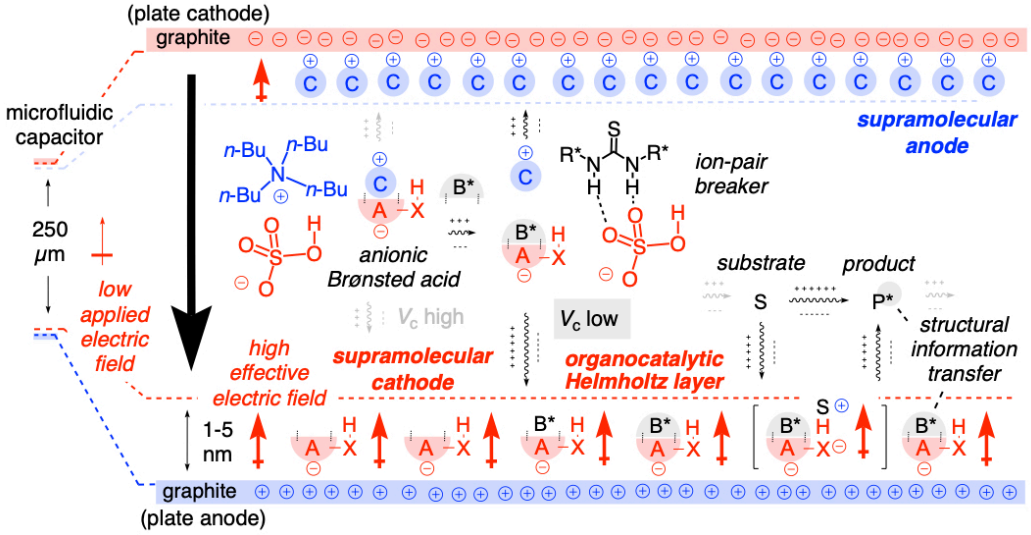
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Electric Field Catalysis

M. Paraja[1], S. Matile[1]*

[1]University of Geneva

Inspired by the intrinsic internal electric field present in enzymes, externally applied electric fields (AEFs) have long been predicted to accelerate and direct electron movement. [1] However, the practical implementation of AEFs under standardized conditions for organic synthesis has yet to be realised. To face this challenge, we implemented catalytic Helmholtz layers in microfluidic capacitors. [2] In response to an AEF, tetrabutylammonium bisulfate in apolar solvents was found to dissociate and assemble into Helmholtz layers, generating strong effective electric fields (EEFs) that enhance the acidity of the bisulfate Bronsted acid anion, thereby catalyzing epoxide-opening polyether cascade cyclizations. To boost catalytic activity and enable unique AEF-driven reactivity, anion-binding ion-pair breakers are introduced. These amplifiers facilitate ion-pair separation and incorporate molecular recognition motifs into the catalytic Helmholtz layers. The insights gained in this study provide a conceptual mechanistic framework for the development of practical AEF catalysis for applications in organic synthesis.



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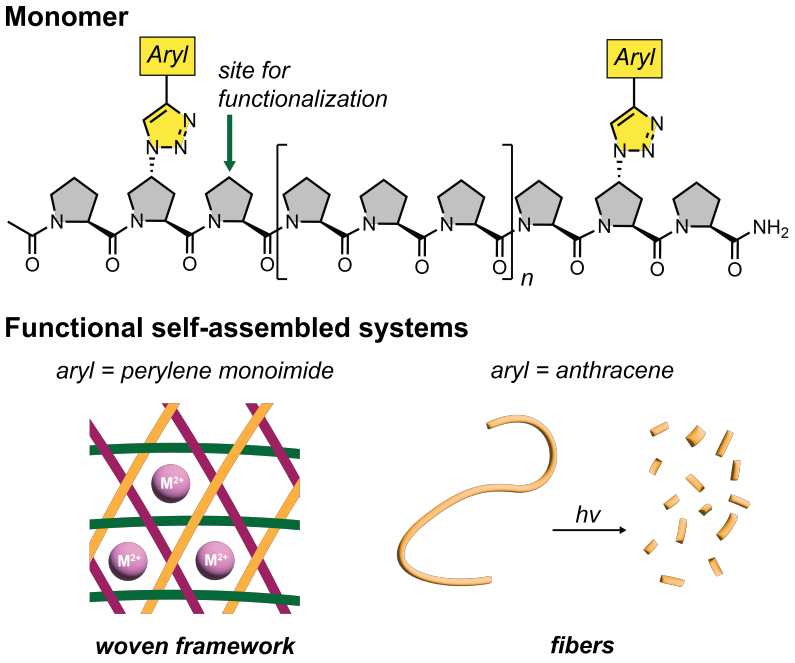
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Functional Self-Assembled Systems from Oligoproline-Chromophore Conjugates

J. F. Woods[1], T. Da Silva-Ferreira[1], A. Herdlitschka[1], H. Wennemers[1]*

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Self-assembly can yield complex molecular architectures from simple molecules yet the formation of such extended supramolecular assemblies can be delicate. Slight alteration of conditions or a seemingly small modification of a molecular building block can lead to drastically different results. Robust assemblies are challenging to create and there is much excitement when they respond to external stimuli.



Our group has reported the self-assembly of oligoproline-chromophore conjugates into several morphologies, including fibers, ribbons, nanosheets and woven frameworks.[1,2] Herein, we will show that the supramolecular weave retains its structure upon addition of functional moieties on the backbone of the oligoproline carrying perylene monoimide chromophores.[3] As an example, we will present a functional weave for binding of toxic metals. Modification of the chromophore to anthracene allows for both fiber and sheet formation, depending on the distance between π-systems. Upon irradiation with blue light, self-assembled morphologies may change, demonstrating the responsiveness to stimulus upon photocyclization.[4]

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Diastereoselective Synthesis of Housanes via the Carbocupration of Cyclopropenes

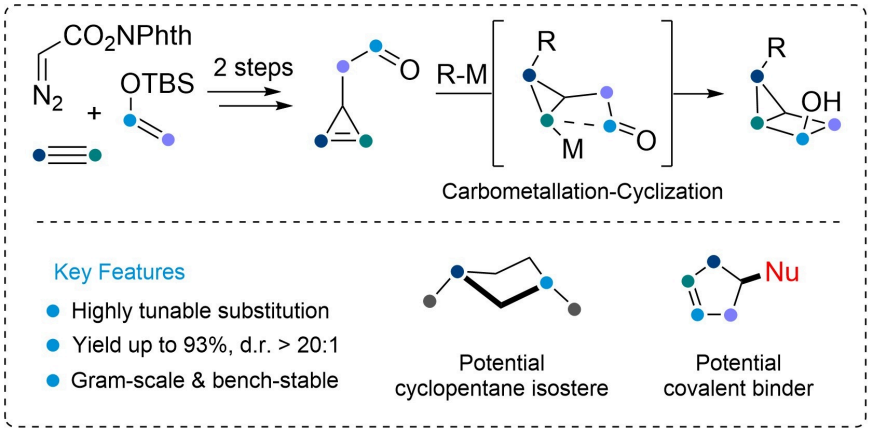
C. Tanguy[1], V. Smyrnov[1], M. Wodrich[2], J. Waser[1]*

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Small-ring containing molecules have recently seen increased interest as building blocks for drug design. Indeed, the movement of "escaping from flatland" has highlighted the usefulness of polycyclic molecules such as bicyclo[1.1.1]pentanes or bicyclo[2.2.2]octanes, to mimic para-substituted benzene rings.[1] While such aromatic replacements have been extensively studied, analogous approaches to rigidify flexible saturated counterparts remain largely underexplored. This led us to investigate whether bicyclo[2.1.0]pentanes, commonly known as housanes, could serve as replacements for cyclopentanes. Here, the isostere aims to rigidify the less stable conformer of the original scaffold, fixing it in the potentially more active geometry.[2]

Current methodologies for housane synthesis are limited either by the accessibility of starting materials (e.g. in diazine homolysis), or by the presence of electron withdrawing groups (e.g. in the transannular alkylation of cyclopentanes).[3] To overcome these limitations, we developed a carbo-metalation-cyclization sequence on carbonyl-substituted cyclopropenes.[4] The carbo-metalation step was rendered regioselective using electronically biased cyclopropenes and diastereoselective through chelation with the carbonyl species. The transient metal complex could then perform 4-exo-trig cyclization to afford the desired bicyclic scaffold.[5]

Key achievements of this work include: (1) high diastereoselectivity (d.r. > 20:1); (2) broad functional group tolerance as substituents (e.g. alcohols, amines, halides, nitriles); (3) gram-scalable applicability. Finally, we calculated geometrical parameters to demonstrate that our housane scaffold closely mimics di-substituted cyclopentanes and performed ring-opening reactions with nucleophiles to highlight their potential as covalent binders.



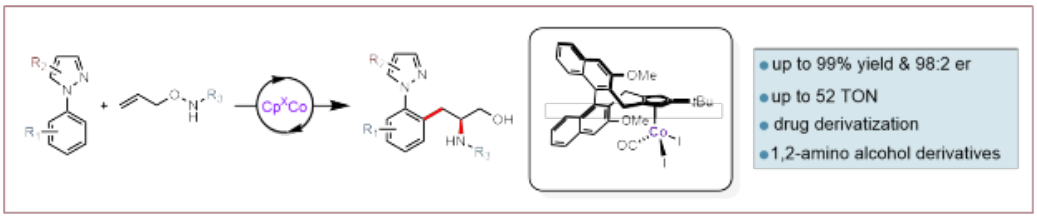
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COBALT(III)-CATALYZED SYNTHESIS OF CHIRAL 1,2-AMINO ALCOHOLS BY C–H CARBOAMIDATION

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Enantioenriched amino alcohols are ubiquitous motifs present in drugs and natural products, as well as precursors to amino acids, ligands and organocatalysts. Thus, efficient, and enantioselective methodologies to synthesize molecules bearing this functionality are sought after. We present a highly enantioselective synthesis of 1,2-amino alcohols under mild conditions using a chiral cyclopentadienyl cobalt(III) catalyst, via C-H activation of a pyrazole-substituted arene and sequential migratory insertion and nitrene insertion of an O -allylhydroxylamine.[1] This methodology delivers yields up to 99%, enantiomeric ratios up to 98:2 and features a turn-over number as high as 52. The work further highlights chiral cyclopentadienyl cobalt(III) complexes as underutilized, complementary, inexpensive, and abundant alternatives to Rh and Ir congeners commonly exploited in C-H functionalization reactions.



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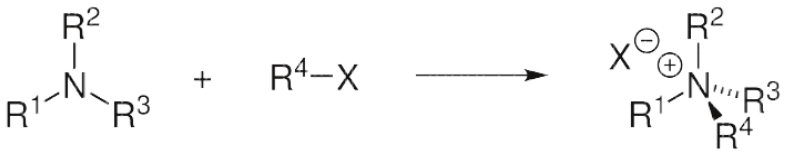
Investigating Solvation Dynamics in Organic Reactions Using Machine Learning

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Understanding solvent reorganization during chemical transformations is fundamental to explaining how local environments, such as enzyme active sites, dramatically accelerate reactions. To probe these complex solvation dynamics, we employ the Menshutkin reaction as a proxy system. Serving as a standard model for both SN_2[1] ion-pair formation and SAM-dependent biological methylation[2], this reaction provides an ideal baseline for mapping the exact relationship between bond modifications and environmental adaptation.

Accurate condensed-phase simulations of this system[3] have historically been limited by classical potential energy surface (PES) models, but machine-learning (ML) potentials[4] now offer a practical workaround. To capture the complex PES of our proxy reaction with *ab initio* accuracy, we trained a PhysNet[5] neural network on the $NH_3 + CH_3X$ (X = halogen) system. We then interfaced this model with pyCHARMM[6] to run simulations in explicit solvent. By calculating the "solvent friction" and observing how the solvent cavity adapts near the transition state, this approach bridges the gap between expensive *ab initio* molecular dynamics and empirical force fields, offering a clearer molecular-level view of how the local environment controls biological methylation.

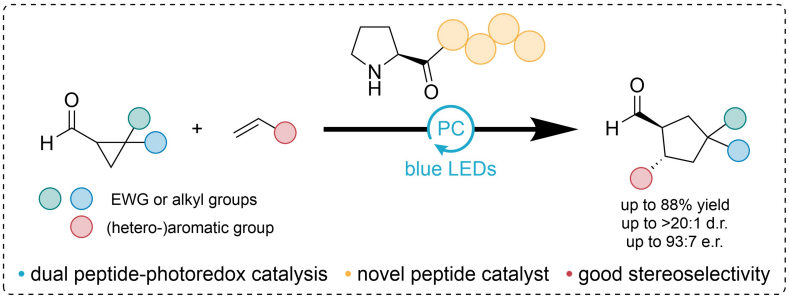


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Asymmetric Ring-Expansion of Cyclopropyl Aldehydes *via* Peptide and Photoredox Catalysis

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Peptide catalysts have emerged as powerful tools in asymmetric synthesis, mimicking the chiral pockets of enzymes while remaining synthetically accessible and structurally tunable.[1] Despite significant advances in peptide-catalyzed stereoselective C–C bond formations,[2] the combination of peptide catalysis with visible-light photoredox systems remains underexplored, with existing examples largely confined to HAT chemistry.[3] Ring-expansion of cyclopropanes offers an attractive route to complex cyclopentane scaffolds of high synthetic relevance, yet asymmetric radical variants have remained limited to substrates bearing specific redox-active functional groups.[4] Cyclopropyl aldehydes are particularly attractive, as the aldehyde handle enables covalent organocatalytic activation, yet their use in stereoselective C–C bond forming reactions remains scarce.[5] We sought to address this gap by developing a fully stereoselective (3+2) radical annulation of cyclopropyl aldehydes with olefins under a dual peptide-photoredox regime, expanding the scope of both peptide catalysis and radical cyclopropane ring-expansion chemistry.

To achieve this, we designed a novel proline-based peptide catalyst, combined with a metal-free organic dye under visible light irradiation. This covalent activation strategy controls stereoselectivity without requiring H-bond donor or acceptor groups on the substrates, enabling broad substrate generality. Styrene derivatives bearing electronically diverse substituents were well tolerated, delivering cyclopentane products in good yields and enantioselectivities. Furthermore, cyclopropyl aldehydes bearing synthetically useful functional groups, including esters, nitriles, sulfones and phosphates, proved competent under our reaction conditions. Importantly, the reaction is also viable for cyclopropanes bearing only alkyl substituents in addition to the aldehyde, demonstrating that additional electron-withdrawing groups are not strictly required for reactivity.

Our study establishes that merging proline-based peptide catalysis with visible-light photoredox catalysis can provide a powerful platform for the asymmetric radical ring-expansion of cyclopropyl aldehydes. This work paves the way for future developments in asymmetric dual peptide-photoredox catalysis.

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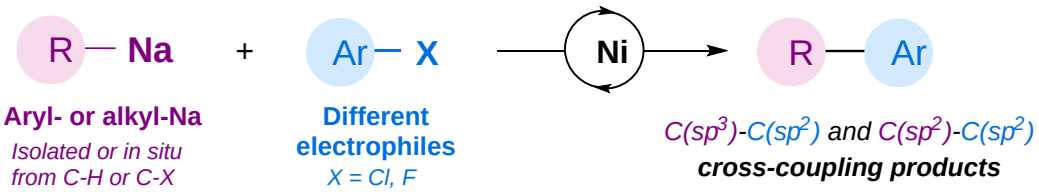
Towards Sustainable Nickel-Catalysed Cross-Couplings Employing Organosodium Reagents

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The development of sustainable carbon–carbon bond-forming methods has driven a paradigm shift toward earth-abundant organometallic reagents. Although organosodium compounds offer a cost-effective and environmentally benign alternative to traditional lithium species,[1] their integration into TM-catalysis has historically been underdeveloped, largely due to the belief that their reactivity is too high to be controlled. Building upon our group's expertise in polar organometallic chemistry, having previously developed Pd-catalyzed methodologies with organopotassium reagents[2] as well as Fe-catalyzed protocols with organosodium species,[3] we envisioned the cross coupling of different organosodium reagents with aryl halides catalyzed by nickel.

The viability of this protocol was initially established by evaluating the reactivity of isolated organosodium compounds towards diverse electrophiles in the presence of Ni precatalysts. To significantly enhance the synthetic utility and practicality of the methodology, one-pot protocols were explored with the *in situ* generation of organosodium species via reductive sodiation processes utilizing sodium dispersion in mineral oil,[4] as well as through metal–halogen exchange and direct C–H metalation employing neopentyl sodium.[5] Furthermore, stoichiometric reactions were conducted to shed light on the underlying reaction mechanism.



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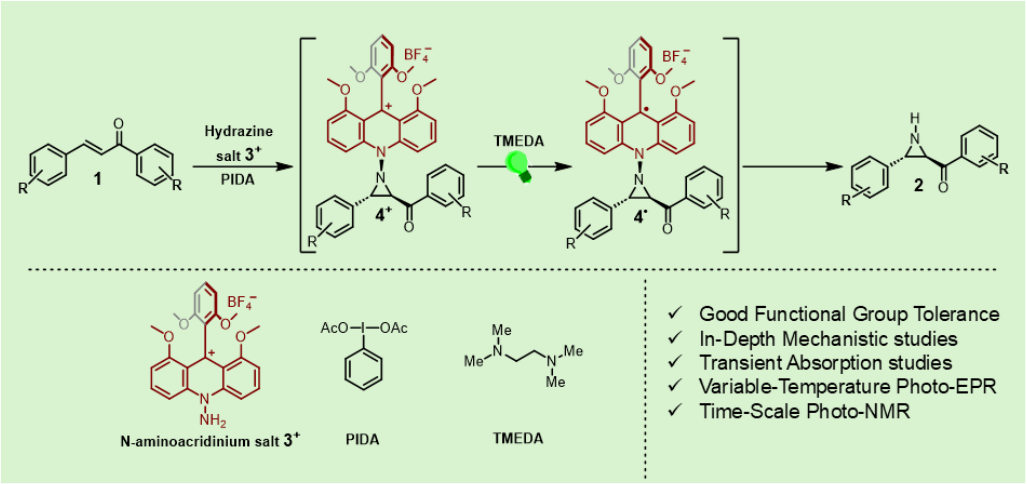
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Photoreductive N-H aziridination of olefins with N-aminoacridinium salt: Synthesis and Mechanistic studies

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Aziridines, *i.e.* saturated three-membered nitrogen heterocycles, are sometimes described as ‘‘epoxide’s ugly cousins’’,[1] due to a certain lack of access routes and often tricky synthetic manipulations. This important scaffold can be found in many active pharmaceutical ingredients and polymer precursors. Yet, direct access to N-H aziridines is still underdeveloped.[2] Herein, stereospecific transformation of olefins **1** [3] into unprotected aziridines **2** [4] are reported using tandem (a) PIDA-mediated [5] addition of N-aminoacridinium salt (**1**+**3**$^{+}$→**4**$^{+}$) [6] and (b) photoreductive cleavage of the aromatic antenna under green light (**4**$^{+}$→**4**$^{\bullet}$→**2**). Stepwise or one-pot sequences are both possible. Good functional group tolerance is noted for chalcone substrates and products alike. While the aziridination step abides by a well-established protocol,[5] the aromatic deprotection follows a multistep mechanistic pathway. In this regard, experimental and theoretical information from detailed transient spectroscopy to photo-EPR and photo-NMR studies will be provided and discussed.



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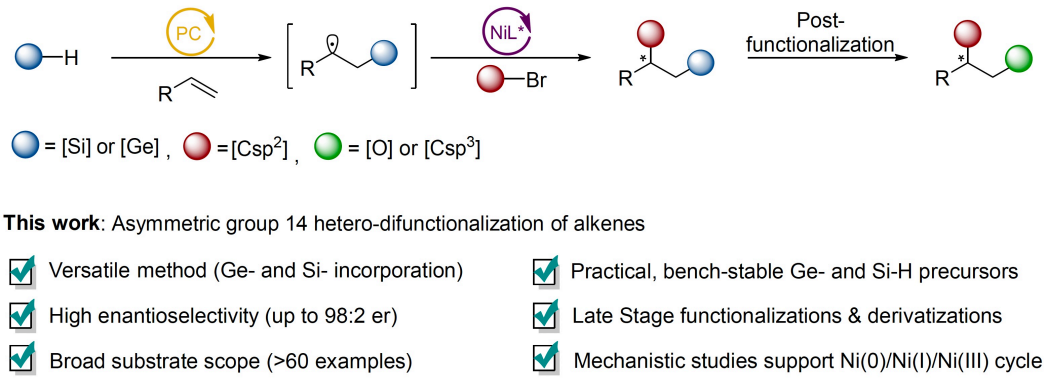
Enantioselective Alkene Difunctionalization with Group 14 Hydrides via Ni/Photoredox Catalysis

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Organic group-14 compounds (Si, Ge, Sn) are important building blocks in materials science, drug discovery, and organic synthesis.[1] While organotin reagents are widely used in cross-coupling reactions, their toxicity has driven the development of safer alternatives. Organosilanes and organogermanes offer high stability, low toxicity, orthogonal reactivity, and serve as effective radical precursors for C–C bond formation under complementary, operationally simple conditions.[2] However, enantioenriched organosilanes and organogermanes remain challenging to access, and asymmetric methods for incorporating heavier group-14 elements lag behind those for carbon analogues.[3]

Here we report a unified Ni/photoredox dual-catalytic platform for the asymmetric heterodifunctionalization of alkenes using readily accessible, bench-stable silanes and germanes. The method affords highly enantioenriched β-aryl germanes, β-aryl silanes, and β-vinyl silanes with broad substrate scope, excellent functional-group tolerance, and compatibility with late-stage modification of complex bioactive scaffolds. The synthetic utility of these products is demonstrated through diverse downstream transformations, including the first C–C bond-forming reaction employing a chiral germane as a radical precursor. Mechanistic studies support a Ni(0)/Ni(I)/Ni(III) catalytic cycle, establishing a general approach to stereodefined organosilicon and organogermanium architectures.



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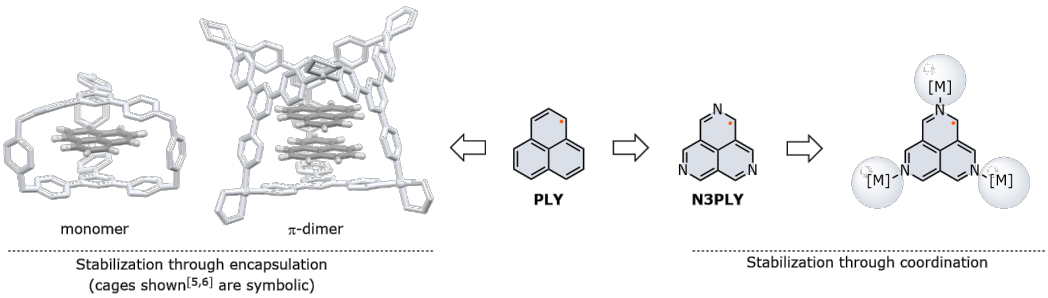
Supramolecular stabilization of π-radicals

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Organic π-radicals are highly interesting candidates for applications in organic electronics and spintronics.[1] Phenalenyl (**PLY**) has an unpaired electron delocalized over six equivalent carbon atoms, resulting in much longer lifetime than simple alkyl or aryl radicals. The non-bonding nature of the singly occupied molecular orbital (SOMO) results in low reorganization energy, which should enable fast electron transfers and high charge-carrier mobility.[2] Unsubstituted phenalenyl, however, quickly degrades in air or even under oxygen-free conditions. Traditional approaches to its stabilization include the introduction of bulky[3] or electron-withdrawing[4] substituents.

In this work, different approaches for the stabilization of phenalenyl are explored. To shield the radical from molecular oxygen, we encapsulate it within suitable supramolecular hosts, and to enable tuning of its steric and electronic properties via coordination to Lewis acids, we incorporate nitrogen atoms into the phenalenyl carbon framework (**N□PLY**) as coordination sites.



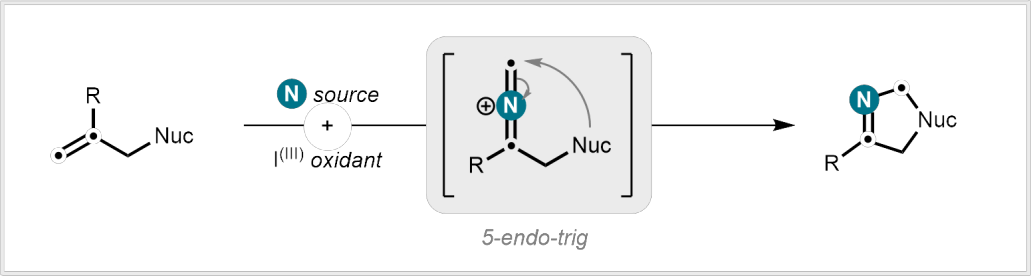
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Modular Synthesis of Rare *N*-Heterocycles by Nitrogen Atom Insertion into Allylic Nucleophiles

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N-Heterocycles are crucial targets in medicinal chemistry, agrochemicals, and materials science.[1] Hence, the modular assembly of heterocyclic scaffolds through cyclization from linear precursors has been a key target for synthetic chemists, yet only few reactions have been developed that utilize ubiquitous, unactivated alkenes for this task.[2,3] Here, we report an interrupted oxidative amination of allylic nucleophiles that transiently generates aza-allenium salts, whose allene-like orbital configuration enables them to selectively undergo facile, formally Baldwin-disfavored 5-endo-trig cyclizations.[4] The reaction is operationally simple, highly functional group-tolerant, and amenable to a range of nucleophiles. This reactivity unlocks access to highly unusual, semi-saturated *N*-heterocycles that are both rare and synthetically challenging to obtain by other methods. As demonstrated in this work, they can serve as versatile synthetic intermediates, undergoing downstream aromatization or reduction to access other heterocycles, or even cleavage to form diamine products. Overall, this study demonstrates that nitrogen insertion into allylic nucleophiles opens new synthetic avenues for the synthesis of rare *N* -heterocycles.



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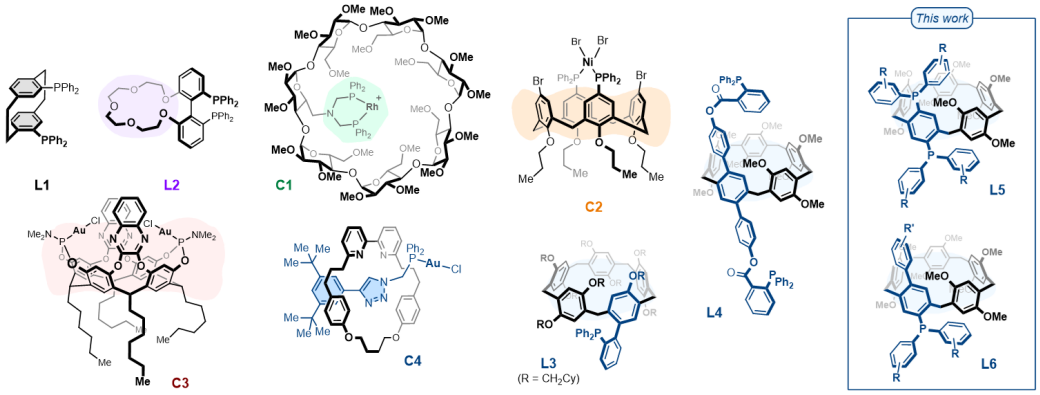
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Pillar[5]arenes as platforms to access macrocycle-based ligands for selective transition-metal catalysis

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In the past decades, macrocycles have played an important role in the fields of material sciences, catalysis and host-guest chemistry.[1] This type of structures has also been used as scaffolds to design ligands (**L1**,**L2**) and related metal complexes (**C1–C4**) for application in transition metal-based selective catalysis; demonstrating that the macrocyclic backbone may exert a direct influence on the selectivity of the reaction.[2] The number of ligands elaborated on pillar[5]arenes is relatively limited to date (**L3**, **L4**).[3,4] The design of ligands based on this scaffold would enable the exploration of uncharted chemical space.



Herein, we report the modular synthesis of mono- and bisphosphine ligands (**L5**, **L6**) based on pillar[5]arenes, the study of their coordination chemistry with various late transition metals and their preliminary application in selective catalysis.

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Harnessing Micellar Stabilization to Access Air-Stable Palladium Hydrides: Unlocking Hydrogen-Driven Reactivity in Aqueous Buchwald–Hartwig Amination

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Palladium hydrides (PdH_x) are central to catalysis[1],[2] and hydrogen-related transformations[3], yet their instability under ambient aqueous conditions has severely limited their practical utility. Herein, we report a robust strategy for accessing air- and moisture-stable, phosphine-free PdH_x nanoparticles via micellar stabilization in water. The resulting PdH_x species remain stable for extended periods (up to one year), representing a significant advance over existing systems. Comprehensive characterization using Pd K-edge X-ray absorption spectroscopy and ^1H NMR confirms the formation and persistence of PdH_x species and highlights the critical role of the nonionic surfactant (PS-750-M) in stabilizing these reactive intermediates. Notably, the resulting hydrides exhibit intrinsic basicity, enabling base-free catalytic transformations under aqueous micellar conditions.[4]

Leveraging these features, we systematically investigate the role of hydrogen atmospheres in modulating catalyst structure, reactivity, and reaction pathways in Buchwald–Hartwig amination. Contrary to conventional inert conditions, hydrogen promotes the in situ generation and stabilization of PdH_x, thereby enhancing catalytic performance for substrates that are otherwise inert or sluggish while suppressing undesired hydrodehalogenation pathways. These findings demonstrate that controlled hydrogen environments and micellar stabilization can synergistically unlock new catalytic regimes, offering a general platform for aqueous cross-coupling. This work provides fundamental insights into PdH_x reactivity while advancing sustainable strategies for transition-metal catalysis in water.

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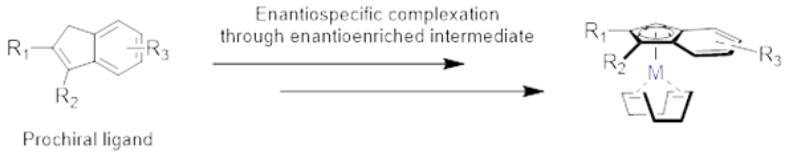
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Enantiospecific Synthesis of Planar Chiral Rhodium and Iridium Indenyl Complexes

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Chiral transition metal complexes are a major class of catalysts for asymmetric transformations. Among them, chiral indenyl d^9 complexes have recently demonstrated remarkable reactivity and selectivity in catalysis.[1,2] Despite interest in these complexes, the straightforward synthesis of enantiopure catalysts remains challenging. Isolation of enantiopure indenyl complexes is mainly achieved by separation of diastereomeric complexes[3] or by resolution using chiral preparative HPLC[1]. Herein, we propose an enantiospecific complexation that provides access to enantioenriched indenyl d^9 metal complexes possessing only planar chirality.



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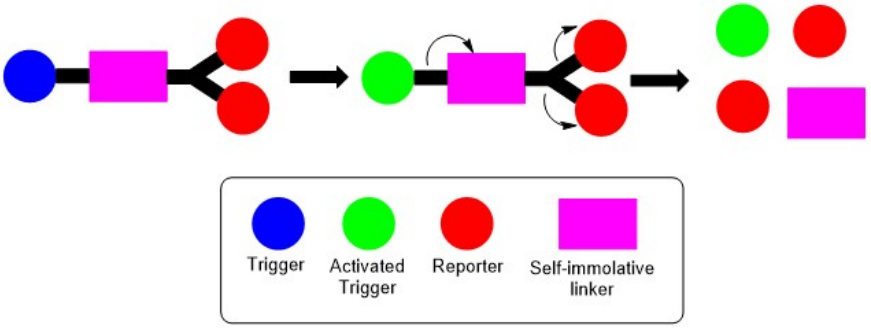
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Self-immolative and traceless linker for amino acids

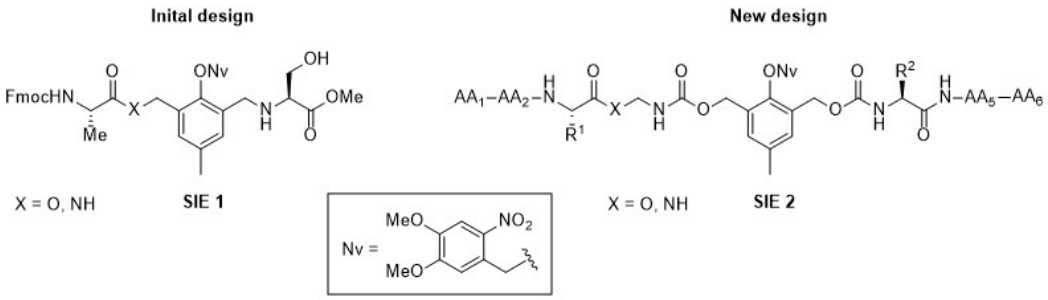
M. Djaïd[1], C. G. Bochet[1]*

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Self-immolative entities (SIE) 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…). They have found plenty of applications especially for drug delivery systems and polymer chemistry.[1]



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 needs to be compatible with automated solid-phase peptide synthesis (SPPS). Starting from *p*-Cresol, the initial target **SIE 1** was synthetized and irradiated at 365 nm. Irradiation was followed by ESI-MS to seek for the expected mass peaks but unfortunately the release of the attached amino acids was inefficient. The most intense peak was the one from unprotected **SIE 1**. The mass peak of serine methyl ester (*N*-terminus) could be observed along with the corresponding moiety suggesting that some release was done but possibly via a side reaction of the photodeprotection of nitroveratryl rather than self-immolation of unprotected phenol. This hypothesis is currently under investigation. A new SIE based on the self-immolation of carbamates and amino/alkoxy methyl carbamate to release amine (*N*-terminus) and carboxylic acid or amide (*C*-terminus) respectively was designed **SIE 2**.



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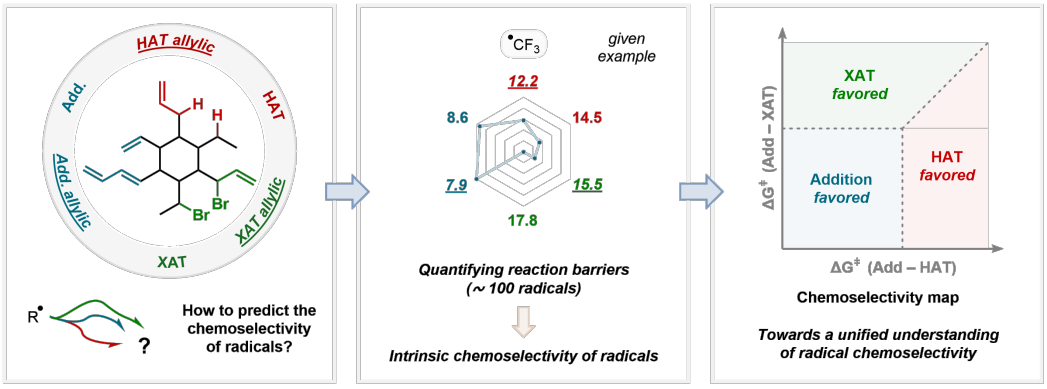
Exploring the Chemoselectivity of Radicals

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Radical chemistry has experienced a renaissance driven by advances in photochemical and electrochemical methods enabling the controlled generation of highly reactive intermediates.[1] In this context, modern radical transformations predominantly rely on three fundamental reaction classes: addition to alkenes (Add), hydrogen atom transfer (HAT), and halogen atom transfer (XAT). Despite these developments, the chemoselectivity of radical reactions (i.e., the intrinsic preference of a radical for competing reaction pathways) remains poorly studied, which can hinder the rational design of selective radical processes. While substantial efforts have been devoted to understanding radical reactivity through reaction barriers or polarity scales,[2-4] most studies have focused on individual reaction classes rather than providing a global description of competing reactivity manifolds.

Herein, we present a systematic computational analysis, benchmarked against experimental data, that quantifies and help rationalizes radical chemoselectivity across the three key reaction manifolds (Add, HAT, XAT), encompassing both well-established and previously unexplored radicals.



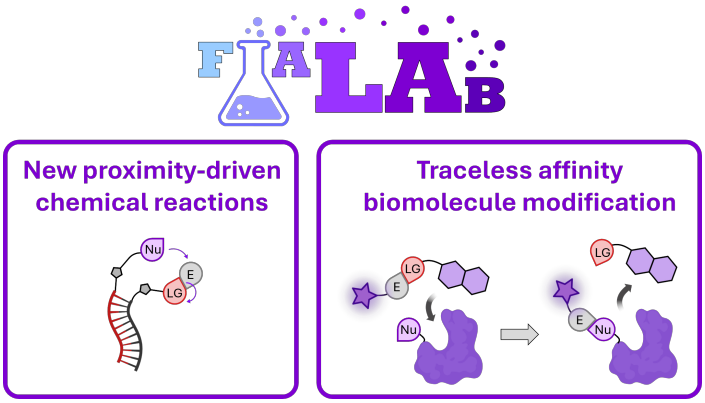
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The Fiala Lab: towards new proximity-driven reactions and self-assembling systems

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The selective chemical editing of biomolecules remains a central challenge at the interface of organic chemistry and chemical biology. In the Fiala Lab at Masaryk University, we develop self-assembling systems as platforms for proximity-driven reactions, enabling precise and programmable modification of proteins and nucleic acids.



This contribution introduces the initial research directions of our newly established group, with a focus on reagents for site-selective manipulation of protein post-translational modifications through non-trivial organic transformations under biologically compatible conditions.

As a case study, we present a series of unexpected findings on SO□–pyridine adducts (pyridinium-*N*-sulfonates), uncovered during efforts to develop proximity-driven protein sulfation reagents. Our results challenge long-standing assumptions about these century-old compounds, providing reliable synthetic access and analytical characterization methods. In doing so, we reveal an underexplored and chemically rich class of reagents with significant potential.

Oxidative Dimerization of Diaza[4]helicenes

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Keywords: *helicenes*, *homochirality*, *chiroptical properties*, *spectroelectrochemistry*

Herein, a straightforward methodology was developed for synthesizing two helicene dimers with strong chiroptical and reversible redox responses.[1] Upon oxidation of diaza[4]helicenes, dimerization proceeds in homochiral, regioselective, stereoretentive and diastereocontrolled manners (**Figure 1A**). Notable Cotton effects and amplification of the dissymmetry factors (g_{abs} & g_{lum}) were observed in both atropisomeric series **TD** and **KI** (**Figure 1B**). In situ spectroelectrochemical studies revealed the formation and stability of neutral diradicals **TD••** upon two-electron reduction (**Figures 1C** & **1D**).[2] For kinetic isomer **KI**, obtained as major component initially, the one-electron oxidation process was found to be reversible. Large property differences are thus demonstrated for **TD** and **KI** atropisomers.

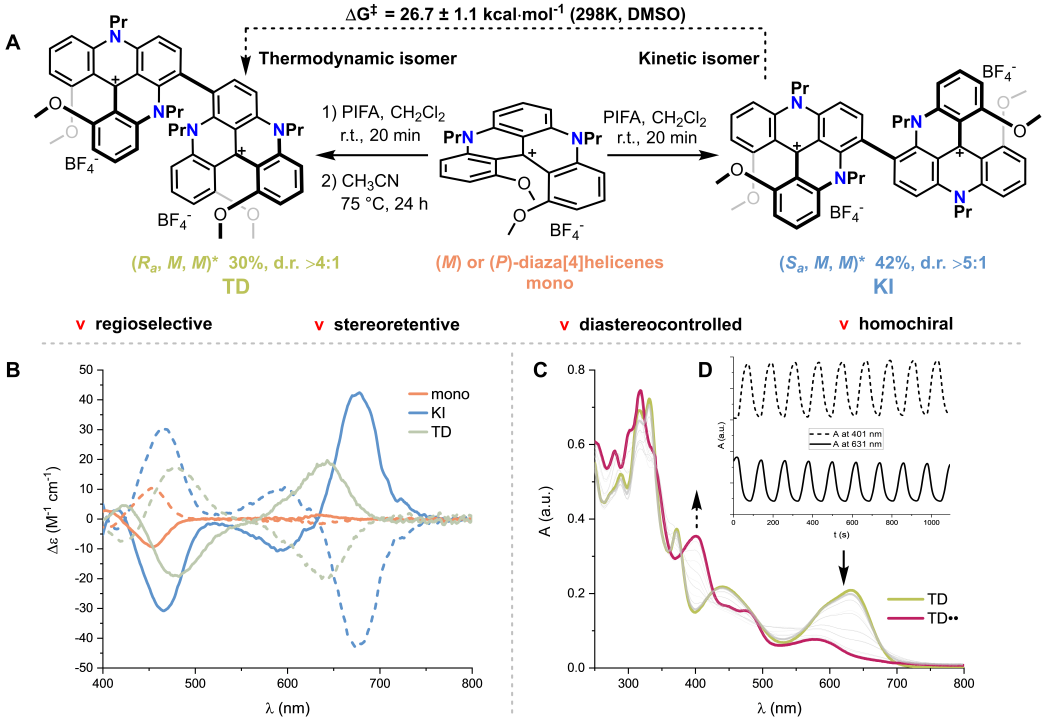


Figure 1. Oxidative syntheses of atropisomeric helicene dimers, their chiroptical properties and spectroelectrochemical responses

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Macrocyclic Polymer Networks for Environmentally Friendly Separation of Lignocellulosic Biomass Derived Chemicals

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[1]University of Fribourg, [2]Bern University of Applied Sciences

Currently, biorefining comes with high energy costs, large amounts of toxic organic solvents needed for extractions, and a reliance on feedstock derived from food crops. Non-edible lignocellulosic material promises to be a more environmentally friendly and ethically less concerning alternative to edible feedstocks. However, the use of lignocellulosic material in biorefining is currently hampered by high recalcitrance and complex product mixtures. One of these products, 5-Hydroxymethylfurfural, is a promising building block for pharmaceuticals, fuel additives, solvents, polymers, and resins. However, different pre-treatments of the lignocellulose biomass result in different product distributions. In this direction, steam pre-treatment of wood has been shown to be a green and efficient method to prepare lignocellulosic biomass for downstream chemical/biochemical conversion. Our collaborators in the Studer group (FHB, Bern) have developed a custom steam-gun reactor for facile steam-pretreatment of wood.

Macrocycle-containing frameworks are promising contenders for many separation applications. This is due to the clearly defined and tunable pore environment given by the macrocycle, combined with the robust structure and insolubility offered by frameworks, such as porous organic polymers (POP). A cyclobenzoin-derived macrocycle, developed by our collaborators, the Miljianic group (UH, Houston), was already successfully utilized by our group to form a robust POP for the separation of organic solvents, showing great promise for the separation of small molecules.

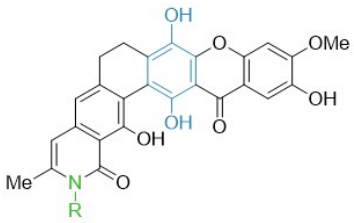
In this project, we, together with our collaborators, aim to develop methods for the green, targeted, non-distillative separation of value-added, lignin-derived chemicals. To this end, cyclobenzoin-derived frameworks will be synthesized and tested in the separation of target molecules obtained from steam pre-treated wood, using a custom steam-gun setup. Additionally, we aim to tackle the challenge presented by recalcitrance by developing reversible carbocation scavengers for use inside the steam gun. Thereby doing our part to deliver value-added chemicals “from forest to flask”.

C–H Functionalization-Enabled Total Synthesis of Cervinomycins C_1–C_4

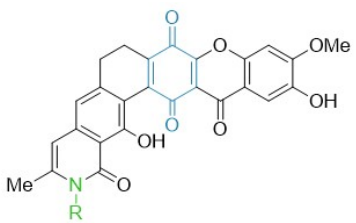
P. Gilbert[1], R. Lombardi[1], O. Baudoin[1]*

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Cervinomycins are a family of complex aromatic polyketides that exhibit potent cytotoxicity and antibacterial activity against Gram-positive bacteria[1]. Herein, we report the first total synthesis of cervinomycins C_1–C_4 from a common late-stage precursor enabled by strategic C–H functionalizations that rapidly increased the complexity of the two key fragments[2,3].

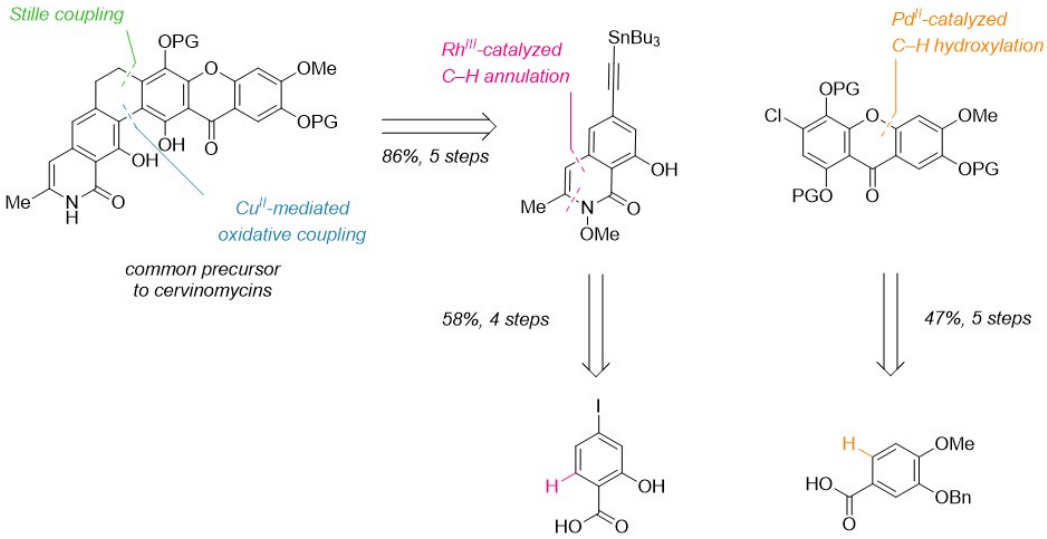


cervinomycin C_1: R= CH_2CH_2OH
cervinomycin C_3: R=H



cervinomycin C_2: R= CH_2CH_2OH
cervinomycin C_4: R=H

In our retrosynthetic analysis, the polycyclic scaffold is assembled by coupling the xanthone and isoquinolone subunits via a Stille reaction, followed by a Cu-mediated oxidative ring closure. Both fragments are derived from readily available benzoic acids through Rh- and Pd-catalyzed C–H activation.



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Amide hydrogen exchange in oxytocin, measured by NMR spectroscopy

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Oxytocin is a well-known natural hormone consisting of nine amino acids. It is produced in the hypothalamus and plays vital roles in human behavior, including social bonding, love, stress regulation, reproduction and childbirth [1].

Amide hydrogen exchange rates in polypeptides have long been used to gain structural insight. Next to solvent composition, pH and temperature, exchange rates depend on amino acid sequence and secondary structure [2]. To assess the solvent accessibility of an amide proton, the ratio between intrinsic and experimentally measured exchange rate is determined, the so-called protection factor. Protection factors greater than one indicate amides in buried regions or involved in intramolecular hydrogen bonds. Experimental rates close to their intrinsic values point to solvent-exposed protons, located in more flexible regions of the peptide [3].

We explored different NMR experiments for the determination of amide hydrogen exchange rates and different methods of analysis. In contrast to previous studies [4], we conducted the experiments at much lower concentration, which is still far, but much closer to the physiological concentration of the hormone. A complementary approach to assess intramolecular hydrogen bond propensities is the determination of amide proton temperature coefficients [5]. We utilized both methods to investigate the solvent accessibility of the amide protons in oxytocin and compared our results to a previously published structure of the peptide in solution [6].

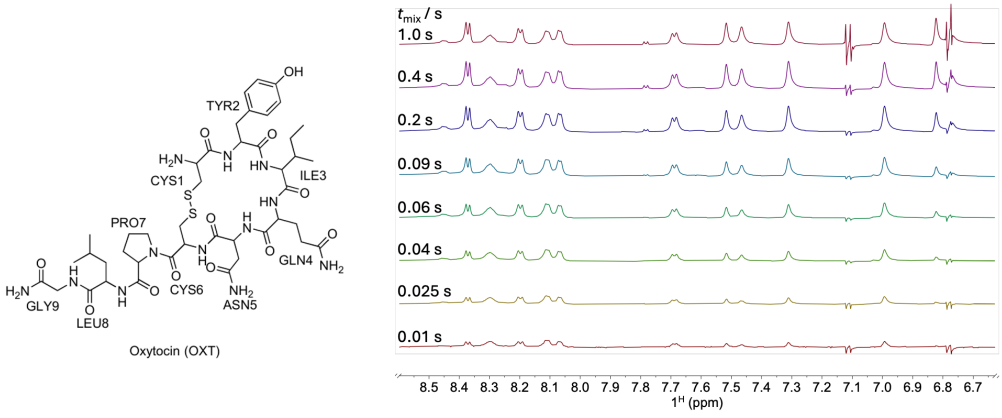


Figure 1. Left: Structure of oxytocin. Right: EXSY spectra of oxytocin (0.56mM in phosphate buffer, pH 6.5) at different mixing times, recorded at 25 °C.

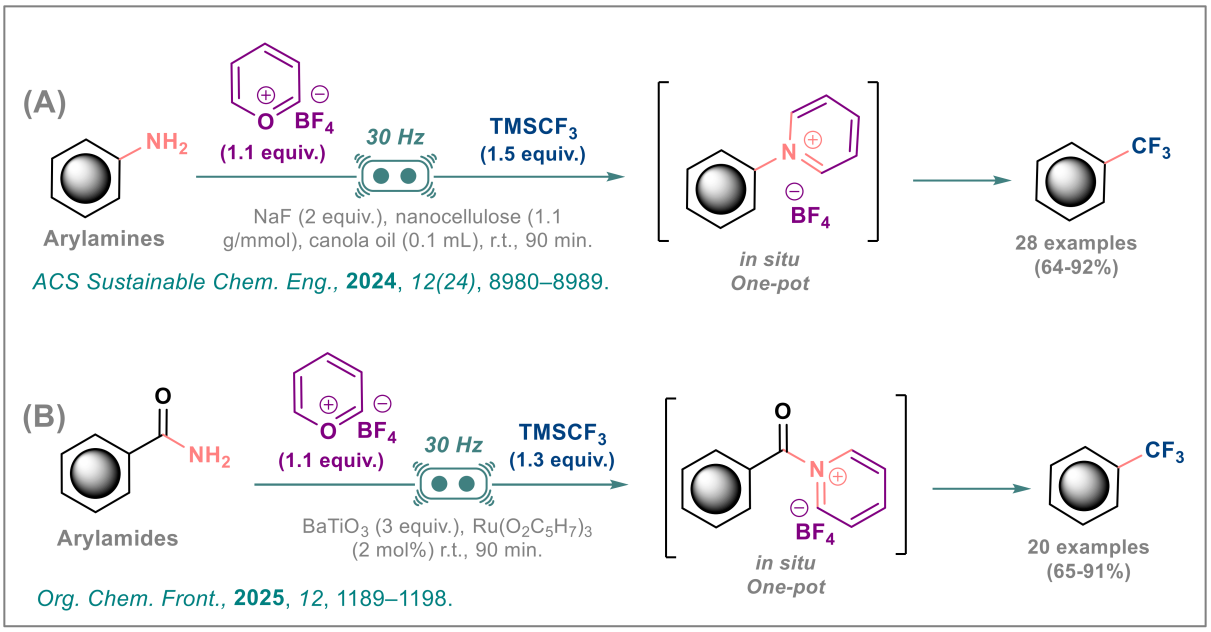
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Mechanochemical Trifluoromethylation of Anilines and Amides: Synthesis of CF_3-Arenes

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A novel synthesis strategy has been introduced for the selective activation of the $C(sp^2)$–NH_2 and $CO(sp^2)$–NH_2 bonds in primary aromatic amines and amides through the utilization of pyrylium tetrafluoroborate under mechanochemical conditions, where the amine and amide groups undergo activation and is selectively substituted with the CF_3 functionality. The transformation of the amide functionalities involves the synergy of a piezoelectric material (barium titanate), as a key-additive for impact-promoted single-electron catalysis, and of ruthenium-catalysis. The ruthenium-catalyzed step in turn is responsible for the elimination of the -C(O)- tether in amides *via* CO- extrusion process promoted by $Ru(O_2C_5H_7)_3$.



Of note, the presented mechanochemical transformations could have significant potential to introduce new chemical spaces in pharmaceutical industry for the development of PASE (pot, atom, and step economy) green mechano-synthesis for the late-stage modification of marketed drugs or other chemical entities.

This work was supported by grant from Vedecká grantová agentúra MŠVVaM SR a SAV (VEGA) (1/0646/26).

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Supramolecular Assembly of Bridged Triarylamine Derivatives

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Organic wires with lightweight, flexible and biocompatible properties are desirable as competitive alternatives to traditional metal-based wires. In order to introduce flexibility to the material while maintaining a well-organized microstructure with minimal defects which are crucial for achieving good electronic properties, soft supramolecular polymers that possess self-healing (self-correcting) properties are highly sort after.[1]

Triphenylamine is selected as the molecule of interest because of its versatility in synthesis and promising conductivity on the resulting supramolecular polymers.[1] Triarylamine-based covalent polymers have been extensively studied for decades because of their excellent electronic and optical properties for material design.[2] However, there are only limited examples of supramolecular polymerization being explored. The reported examples mostly rely on the peripheral modifications to introduce amide H-bond that led to the highly ordered structures. In the current project, we proposed that by introducing carbon chains to constrain the rotation of the aryl groups, the resulting surface (shape) could contribute to a highly ordered supramolecular assembly. In order to systematically investigate how the surface of the monomers contributes to the assembly process, various routes of the synthesis of the bridged triarylamines azatriseptanes have been investigated and optimized.[3,4]Further derivatization and the assembly of the synthesized structures are currently underway.



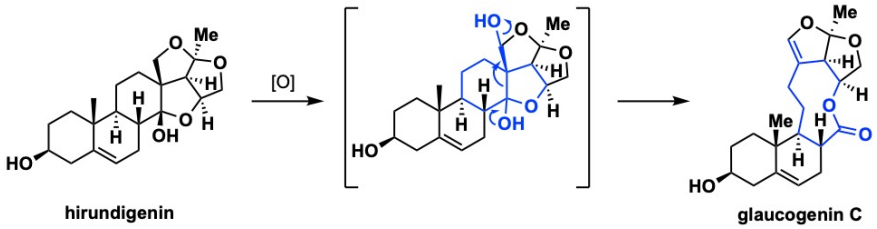
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Towards the Total Synthesis of Diseco Pregnane Steroids

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Diseco pregnane steroids, primarily isolated from plants of the genus *Cynanchum*, exhibit widespread biological activities. Members like glaucogenin C share a characteristic central nine-membered lactone, as well as a *cis*-fused bis-furan system. Biosynthetically, the nine-membered lactone has been proposed to originate from a hirundigenin derivate, including a Grob-type fragmentation of a 6,5-hemiacetal system.[1] Hirundigenin itself was isolated from the local plant *Cynanchum vincetoxicum* by Reichstein and co-workers in the 1960s.[2] Due to their intriguing structures and promising biological activity, we decided to embark on the first total synthesis of these molecules.



hirundigenin glaucogenin C

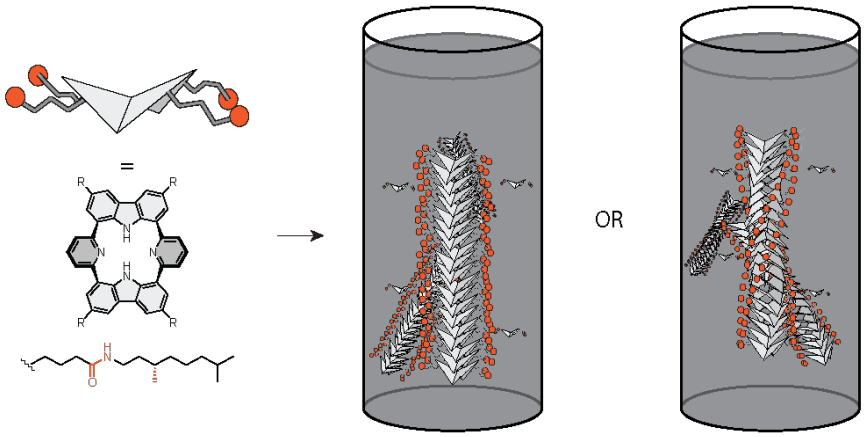
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Chirality in Shape-assisted Self-Assemblies

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In a typical supramolecular architectures, a flat and rigid core is decorated with suitable tails. While this design has led to fascinating polymers and structures, the core itself is free to rotate and to slip over other cores. To restrict this freedom, shape can be employed. For example, a molecule with a negative curvature is significantly limited in translational and rotational freedom. Our group utilized this principle to generate 1D fibers and 2D sheets on surface while only weak and non-directional interactions were present.



However, in dilute solution, these interactions are insufficient, causing the assemblies to dissociate. This disassembly hinders us to investigate the polymerization mechanism of the assemblies. Therefore, stronger binding units are needed. Yet, this addition results in a competition between the core and the binding units to determine which one governs the assembly process. To fully investigate this clash different spacers will be used to observe which interaction governs the assembly in solution and on surface.

For these polymers, a bias (chirality) was used and we wondered if this interaction would disrupt or help the non-amide containing assemblies on surfaces. Therefore, a libary of chiral Carpys was made to investigate this struggle.

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Exploring pi-pi communication through a metal centre in different organic systems

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In the Rickhaus lab, there is a strong focus on curved aromatic systems. In particular, saddle shaped molecules, such as carpyridines. We have recently shown that these self-assemble into 2D sheets[1,2], or fibers[3], through shape assisted self-assembly. Their intrinsic curvature results in the formation of four disconnected π systems – two pyridine and two carbazole units. This disconnection can be bridged by the insertion of a metal into the carpyridine centre, enabling communication between all four. This has been detected using UV/vis spectroscopy, showing a marked redshift upon insertion of Zn, Cu and Ni (Figure 1, left).

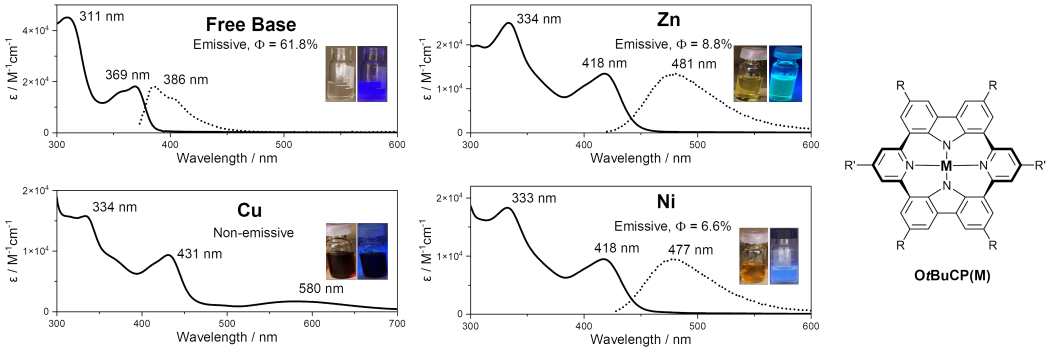


Figure 1 UV/vis absorption spectra of different carpyridine metal complexes (R=*t*Bu, R'=O*t*Bu).

Appending different groups to the carbazole and pyridine units allows us to probe direct communication through the metal centre. This can also be envisaged between different carpyridine monomers, by forming either linear or cyclic carpyridine oligomers. This presents the unique opportunity to investigate electric currents on the molecular level that are forced to pass directly through one or more metal centres. This is of fundamental interest and could lead to exciting applications in nanotechnology and microelectronics.

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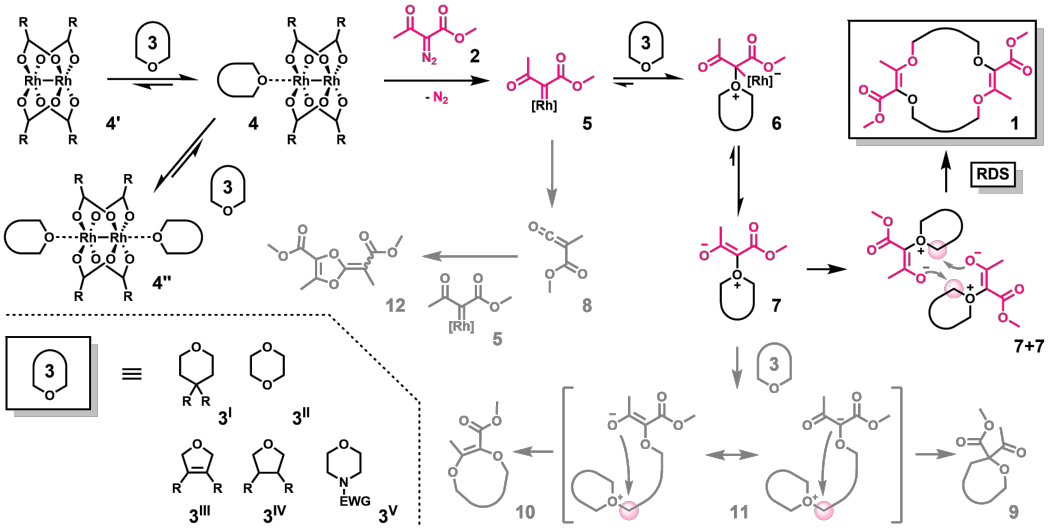
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The Control of Effective Concentration of Oxonium Ylide and Regioselectivity in [3+n+3+n] Macrocyclizations

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Previously, the synthesis of unsaturated polyether macrocycles **1** by [3+n+3+n] condensations of α-diazo-β-ketoesters **2** and cyclic ethers **3** was reported under dirhodium catalysis **4** (0.05 mol%). [1,2] Usually, this reaction yields macrocycles with isolated yields up to 78%, starting from common heterocycles **3** (e.g., 1,4-dioxane, THF). Productivity requires *6 equivalents* of cyclic ethers **3**, and this excess is a drawback with non-volatile and elaborated substrates. Herein, a new method is developed to lower the amount of starting heterocycle down to *1.5 equiv*. In effect, slow addition of diazo reagent **2** [3] can significantly increase the yield of targeted macrocycles **1**, for instance providing a two-fold yield increase with EWG-substituted morpholines $\mathbf{3}^{V}$. Such a result is rationalized mechanistically considering the ratio between metalcarbene **5** and cyclic ethers **3**; the higher the value of **3**/**5**, the easier the formation of ylides **6** or **7** and the lower the occurrence of ketenes **8** by Wolf rearrangement. Then, the abundance of **7** favors the rate-determining 2nd-order dimerization. Moreover, for certain (unshown) substrates, C- vs. O-enolate reactivity can be managed to provide compounds of type **9** over **10** and **1**.



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Generative machine learning for catalyst design

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[1]Laboratory of Artificial Chemical Intelligence (LIAC), ISIC, EPFL, [2]Department of Chemistry, University of Zurich, [3] ISIC, EPFL, [4]National Centre of Competence in Research (NCCR) Catalysis, EPFL

Conventional catalyst design is rooted in detailed knowledge of the existing literature and chemical intuition. Because catalyst synthesis and evaluation are costly, structurally novel catalysts are routinely passed over in favor of incremental tweaks to known scaffolds. Here, we use generative machine learning (ML) for the de novo design of organocatalysts for our test transformation, the Morita–Baylis–Hillman (MBH) reaction. Our framework freely explores chemical space to discover a structurally novel class of azetidine-based tertiary-amine catalysts featuring a "winged" 1,4-diaryl motif, which we term the TACOCAT family.

Generative models learn to propose high-scoring molecules according to a scoring criterion; steer with a flawed judge and the model will confidently chase nonsense. Robust prediction is particularly challenging as models venture into diverse regions of chemical space, where predictors validated only on familiar scaffolds break down [1]. Indeed, an existing predictor for the MBH reaction failed catastrophically, predicting high rate constants for catalysts where experiments showed no transformation [2]. To build a scoring function that generalizes across chemical space, we ran a generate–validate–redesign loop: the ML model proposed catalysts, we synthesized them and measured their kinetics, and we used each gap between prediction and experiment to drive the predictor's redesign. After three rounds, we identified catalyst flexibility as the factor previous pipelines neglected and developed a new scoring function that captures the entire conformational ensemble through the Winstein–Holness equation [3]. On a 19-catalyst benchmark synthesized in-house, it substantially outperforms earlier predictors.

Guided by this robust predictor, the TACOCAT family shows a clear mechanistic basis for its predicted activity: intramolecular π-stacking between the aryl rings folds them away from the catalytic amine, leaving it exposed for conjugate addition, while electronically stabilizing the cationic ammonium of the zwitterionic intermediate at the rate-determining proton-transfer step [4]. Synthesis and kinetic characterization are underway, and we will present experimental rate constants benchmarked against 1,4-diazabicyclo[2.2.2]octane (DABCO), the standard catalyst for the reaction. Our results showcase the promise of hybrid experimental–ML methods for catalyst design.

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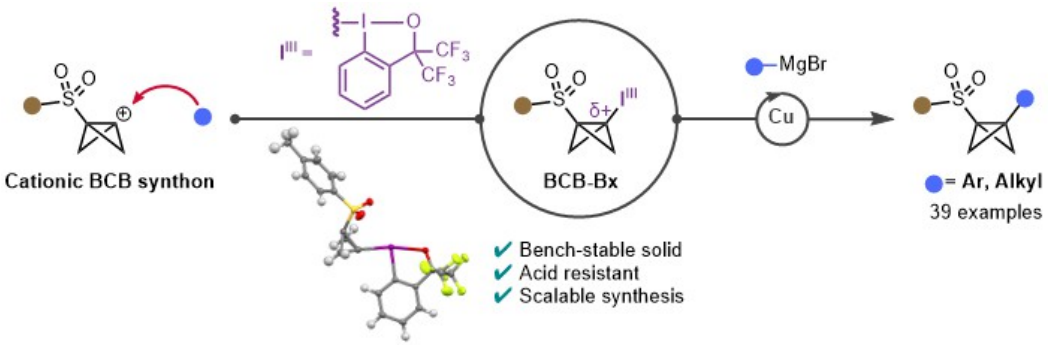
Electrophilic Bicyclo[1.1.0]butane Transfer

N. Lee[1], W. Wu[1], P. Schoch[1], D. K. Brownsey[1], J. Kristek[1], M. D. Wodrich[2], J. Waser[1]*

[1]Laboratory of Catalysis and Organic Synthesis (LCSO), Institute of Chemical Sciences and Engineering (ISIC), École Polytechnique Fédérale de Lausanne, CH-1015 Lausanne, Switzerland, [2]Laboratory for Computational Molecular Design (LCMD), Institute of Chemical Sciences and Engineering (ISIC), École Polytechnique Fédérale de Lausanne, CH-1015 Lausanne, Switzerland

Bicyclo[1.1.0]butane (BCB) is an emerging scaffold that gained substantial attention in the field of strained ring chemistry. Over the past decade, numerous transformations exploiting the strained central bond of BCBs have been developed, including cycloadditions, strain-release nucleophilic additions, carbene additions, and rearrangement reactions [1,2]. Therefore, BCBs have become important synthetic building blocks to access multifunctionalized cyclobutanes and complex polycyclic systems [3]. The vast majority of the transformations rely on 1,3-disubstituted BCBs, typically with an electron-withdrawing group and an (hetero)aryl substituent. The synthesis of these precursors often requires multiple low-yielding steps, and they frequently suffer from thermal and chemical instability. Consequently, it would be of a great synthetic interest to develop BCB-containing reagent that would serve as a universal intermediate for further functionalization into disubstituted BCB motifs.

Herein, we report the synthesis and application of novel hypervalent iodine (III) reagents bearing a BCB motif as a powerful platform for electrophilic bicyclobutylation [4]. These BCB-benziodoxole (BCB-Bx) reagents are bench-stable, crystalline solids that exhibit remarkable tolerance to a variety of conditions, including Brønsted acids like trifluoroacetic acid. The synthesis of these reagents is highly efficient, tolerating both aryl- and heteroaryl sulfones and sulfonamides. With the unique umpolung reactivity of the hypervalent iodine center, we achieved the previously unreported addition of carbon-based nucleophiles to the BCB core. The copper-catalyzed reaction with various aryl and alkyl Grignard reagents enabled installation of carbon centre. These novel BCB-Bx reagents provide rapid access to the modular synthesis of 1,3-disubstituted BCB scaffolds. We anticipate this general method will enable the discovery of new strained-ring chemistry and give access to valuable cyclic building blocks.



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Non-oxidant photochemical fusion of Azulene-incorporated 1,3,6,8-Tetraazapyrene derivatives

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Nitrogen-doped polycyclic aromatic hydrocarbons provide versatile platforms for tuning frontier orbital energies, redox properties, and visible-light absorption. In this work, 4,10-(azulenyl)phenyl-2,7-di-tert-buty-tetraazapyrene (compound **4**) derivatives are investigated as conformationally twisted precursors to extended fused chromophores. The target structures combine an electron-deficient tetraazapyrene (TAP) core with peripheral non-benzenoid aromatic units, offering a modular route to π-systems in which topology and fusion pattern can be systematically varied.

The synthetic route starts from borylated azulene building blocks and proceeds through Suzuki-Miyaura coupling with ortho-haloaryl partners, followed by borylation and coupling to the TAP core. A representative 4,9-bis-substituted precursor, compound **4**, was isolated as a green solid and characterized by NMR spectroscopy and high-resolution mass spectrometry. The key transformation is a non-oxidant photochemical fusion: under natural light in dichloromethane, and without an external oxidant, the twisted precursor undergoes stepwise intramolecular cyclization. Dichloromethane acts as an electron acceptor in this formal non-oxidant oxidation process, enabling C-C bond formation and rearomatization to give mono-fused intermediate **4a** after two days and, upon prolonged irradiation, the fully-fused product **4b**.

UV-vis absorption spectroscopy reveals clear structure-property changes across the series **4**, **4a** and **4b**. Progressive fusion modifies the high-energy absorption profile and extends weak low-energy absorption into the visible region, consistent with increased conjugation and altered electronic coupling between the TAP core and peripheral aromatic fragments. These results establish photochemical ring fusion as a useful strategy for accessing topology-controlled nitrogen-doped nanographene-like molecules.

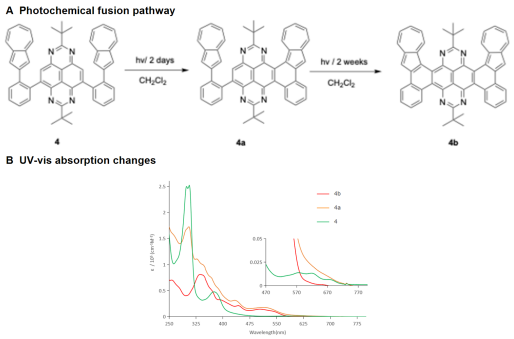


Figure 1: UV-vis absorption spectra of **4** , **4a** and **4b** in DCM.

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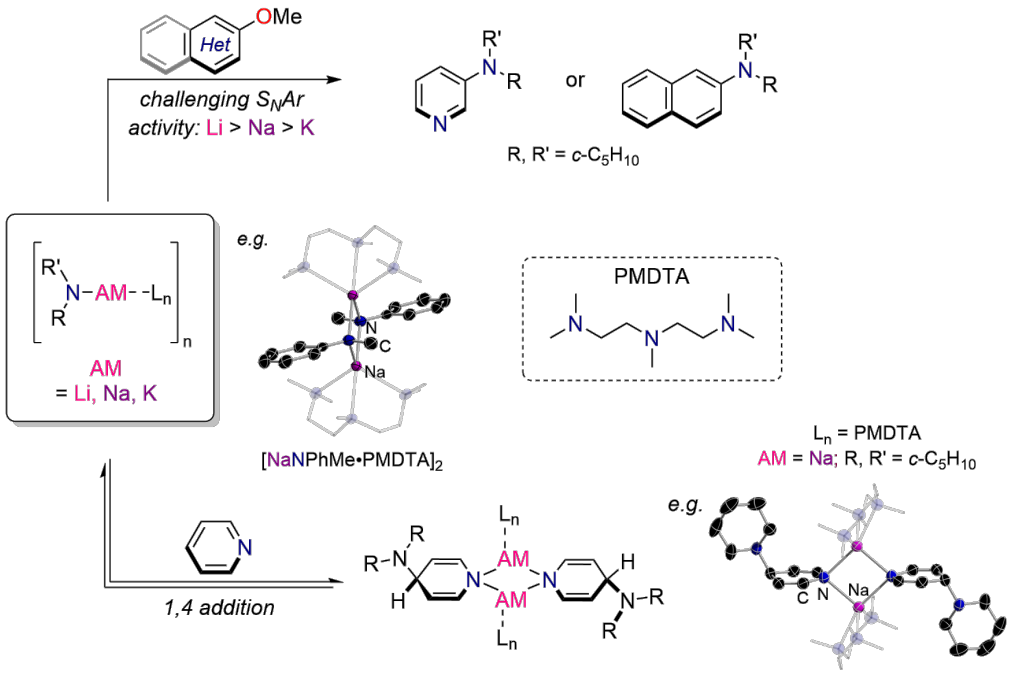
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Alkali Metal Amides for Pyridine Amination

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Pyridine scaffolds are ubiquitous in pharmaceuticals and agrochemicals. Commonly, amination of pyridines is achieved through nucleophilic aromatic substitution or electrophilic amination reagents, often requiring activated substrates or the use of transition-metal catalysts.[1] Recently, the Chiba group reported that NaH-LiI composites in combination with amines allow for nucleophilic aromatic substitutions to occur on 3-methoxypyridines, however the exact structure of the active species remains unclear.[2]



Building on these findings, isolated lithium, sodium and potassium amides were employed in this model reaction in order to systematically investigate alkali-metal effects. A progressive increase of activity was found going from potassium to sodium to lithium amides. In the absence of leaving groups, reversible nucleophilic addition to pyridine was observed as second mode of action. This might serve as an entry point for further diversification strategies of pyridines without the need for prefunctionalization.

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A Convergent Synthesis of Azabicyclo[4.1.1]octanes through the Formal Cycloaddition of Bicyclobutanes with 2-Azadienes.

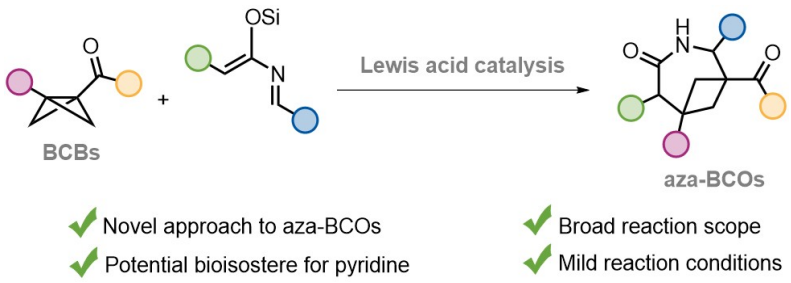
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[1]Institute of Chemical Sciences and Engineering (ISIC), École Polytechnique Fédérale de Lausanne (EPFL)

The increasing demand for three-dimensional molecular structures in medicinal chemistry has driven the development of saturated carbocyclic frameworks as alternatives to planar aromatic motifs.[1] In line with this "escape from flatland" approach, strained bicyclic carbocycles with high Csp^3 character have become attractive synthetic targets due to their potential to improve pharmacodynamic and pharmacokinetic properties, including solubility, membrane permeability and metabolic stability.[2] Among these scaffolds, bicyclobutanes (BCBs) are particularly valuable building blocks, representing the smallest bicyclic carbocycles and possessing significant ring strain energy (ca. 64 kcal/mol). This high strain enables diverse transformations[3], including bridge functionalization[4a], addition reactions[4b], insertions[4c] and cycloadditions[4d].

Cycloaddition reactions of BCBs with two- or three-atom partners have been extensively explored, providing access to bicyclopentanes (BCPs) and bicyclohexanes (BCHs) respectively. In contrast, the synthesis of medium-sized bridged carbocycles remains considerably more challenging, resulting in comparatively few reports on these frameworks. Bicyclooctanes (BCOs), including their oxa- and thia-analogues, have previously been synthesized.[5] However, access to aza-bicyclooctanes (aza-BCOs) has remained limited. Existing approaches rely either on harsh ring expansion strategies, such as Beckmann transpositions[6], or on BCB-based methods restricted primarily to benzofused systems.[7]

Herein, we report a formal [4+3] annulation of BCB ketones with 2-azadienes to afford azabicyclo[4.1.1]octanes in the presence of a Lewis acid catalyst. The method exhibits a broad substrate scope, tolerating diverse substitution patterns on both the BCB ketone and azadiene coupling partners.



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From Rigid Molecular Crosses to “Molecular Chains”: Synthetic Strategy Towards Mechanically Interlocked [n]Catenane Polymers

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Strategies towards poly[n]catenanes are very rare and remain a significant challenge in polymer chemistry. This project explores the rigid molecular cross 1, a scaffold consisting of a rigid π- conjugated para-quarterphenyl beam and a phenanthrene strand, preorganized by cleavable ester joints. Through mild Pd-catalyzed C-C coupling, a diverse library of functionalized monomers is accessible. We propose a bottom-up strategy to transition from this discrete cross to complex interlocked networks. The phenanthrene synthons provide precise control over the directionality of functional groups, enabling the assembly of mechanically fixed pseudo-rotaxanes 2 and 3. The core synthetic objective is a sequence of selective acetylene liberation and oxidative coupling to yield linear, covalently fixed catenane oligomers. Subsequent cleavage of the ester joints via reduction or hydrolysis releases the mechanical constraints, resulting in poly[n]catenanes that resemble "molecular chains". This approach explores the feasibility of generating topologically interlocked polymers with potential for adaptive and stimuli-responsive behavior.

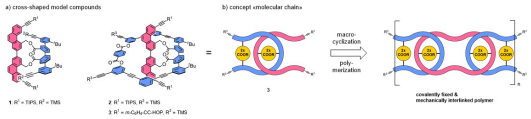


Figure 1: a) cross-shaped organic model compounds: molecular cross 1 controlling the spatial orientation of the exposed acetylenes, and covalently fixed pseudo-rotaxanes 2 and 3 with cleavable macrocyclic unit; b) concept developing a mechanically interlocked “molecular chain”.

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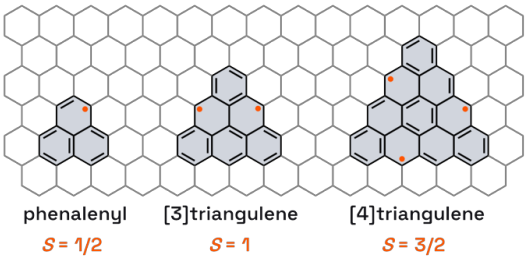
Engineering Spin Systems with Fluorescent Phenalenyl Radicals

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The precise engineering and manipulation of spins within molecule-based materials is at the heart of molecular spintronics, quantum information processing, and the exceptional physics of novel quantum materials. In this context, open-shell polycyclic aromatic hydrocarbons provide great potential for the chemical bottom-up fabrication of molecular magnetic materials with (delocalized) unpaired electrons and weak spin-orbit coupling.[1] The reasonable stability in tandem with its fundamental π-magnetism (spin-½) renders the triangular graphene fragment phenalenyl (or [2]triangulene) an ideal basic unit of synthetic spin chemistry that permits the systematic formation of structures with multiple interacting spins.[2] Recently it was discovered that tribrominated phenalenyl exhibits long-lived fluorescence,[3] which is rare feature for radicals, and provides a promising materials platform for the development of efficient OLEDs, fluorescence sensing, phototheranostics and optically addressable molecular Qubits.[4]

In this contribution, I present the systematic synthesis and characterization of a range of functionalized phenalenyl-based radicals and highlight their spin-related and optical properties. It will be demonstrated how these novel radicals can serve as building blocks for the in-solution and on-surface construction of polyradicals, and the supramolecular design of spin networks.



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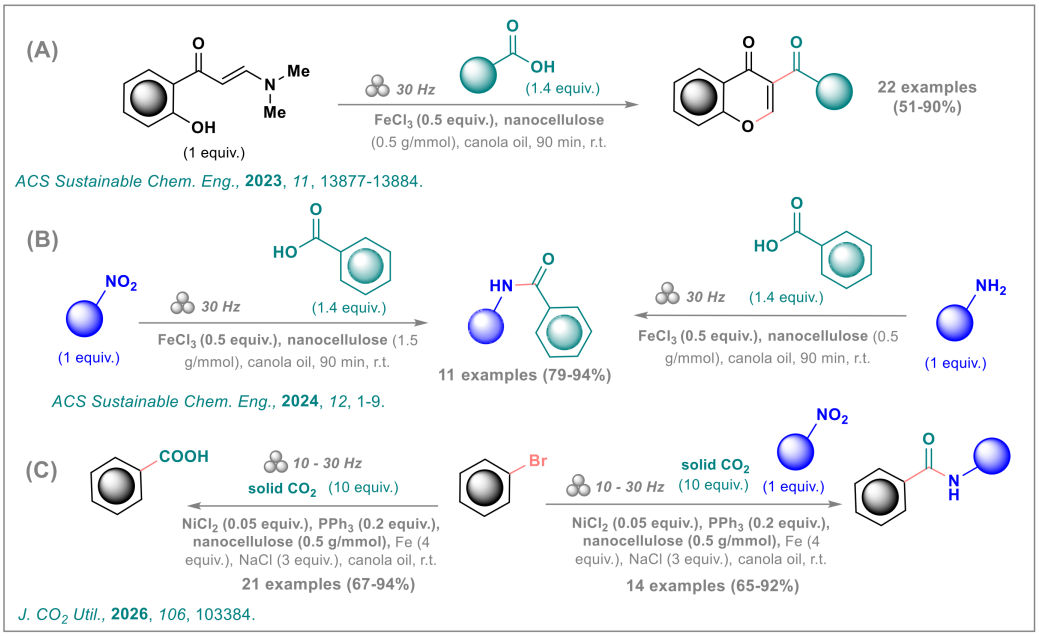
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Utilization of nanocellulose as a green reaction media for organic mechano-synthesis

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Derived from renewable bioresources, nanocellulose has received considerable attention in synthetic chemistry due to its unique physical and chemical properties including high specific surface area, high crystallinity and mechanical strength, and controllable surface phenomena. [1]



Continuing our ongoing research on the late-stage functionalization of complex organic molecules under mechanochemical conditions [2,3], herein, we report three synthetic protocols that utilises nanocellulose as a green auxiliary for a straightforward synthesis of 3-ayclchromones, amides and Ni-catalysed CO_2-fixation utilising mechanochemical ball milling as a green tool (Scheme 1, **A-C**). [4-6] This work was supported by a grant from Vedecká Grantová Agentúra MŠVVaM SR a SAV (VEGA) (1/0646/26).

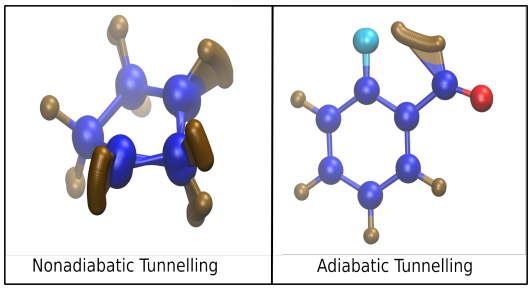
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Multidimensional Tunneling in Organic Synthesis at Room Temperatures

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Quantum mechanical tunnelling enables molecules to react through energy barriers even with low energies and is particularly relevant at low temperatures. We present a number of cases of H-atom tunnelling as well as heavy-atom tunnelling where traditional theories based on one-dimensional reaction pathways lead not just to an incorrect description of the tunnelling mechanism but also orders of magnitude deviation from experiment. Using instanton theory we highlight how multidimensional tunnelling can significantly change the reaction pathway via “corner-cutting” and is crucial for correctly predicting experimentally observed rates in ketene synthesis (e.g. Tunnelling involving Nitrenes and Carbenes formed via photo-excitation in Argon matrices). Further, we also showcase pronounced effects of heavy-atom tunnelling for spin-forbidden reactions in strained molecules when the widely used Born-Oppenheimer approximation breaks down. Remarkably, we find that heavy-atom tunnelling continues to play an important role at room temperature, in contrast to what one would expect from traditional one-dimensional estimates.



In recent years, there has been significant interest in the synthesis of strained molecules in the field of organic chemistry as part of the “escape from flatland" strategy, where cubanes and other strained systems serve as biologically active isosteres of “flat" aromatic systems. Our findings open up possibilities for tunnelling control in organic synthesis not just at cryogenic temperatures, but under ordinary laboratory conditions.

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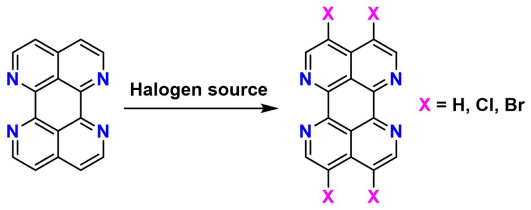
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Tailoring the Electronic Properties of 1,6,7,12-Tetraazaperylene Through Cascade Halogenation

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Polycyclic aromatic hydrocarbons (PAHs) are key molecular building blocks for the bottom-up synthesis of graphene nanostructures due to their structural planarity, thermal stability, and tunable electronic properties. In particular, nitrogen-containing PAHs have attracted considerable attention because incorporation of nitrogen atoms into the π-conjugated framework lowers the LUMO energy and enhances electron-accepting and charge-transport properties[1]. Among these, 1,6,7,12-tetraazaperylene (TAPE) represents a highly electron-deficient azaacene scaffold with promising potential for organic electronics and topological quantum materials[2,3]. Precise functionalization of the TAPE core is essential for tuning its electronic properties and intermolecular interactions; however, selective halogenation of azaacenes remains synthetically challenging. Herein, we report an efficient cascade C-H halogenation strategy for the synthesis of chlorinated and brominated TAPE derivatives using different halogenating sources in acidic media, including ICl, IBr, and Br_2. This straightforward protocol enables systematic modulation of the degree of halogenation, providing access to a series of electron-deficient TAPE derivatives with tunable frontier molecular orbital energies. These compounds constitute promising building blocks for the development of advanced optoelectronic and on-surface self-assembled nanostructures.



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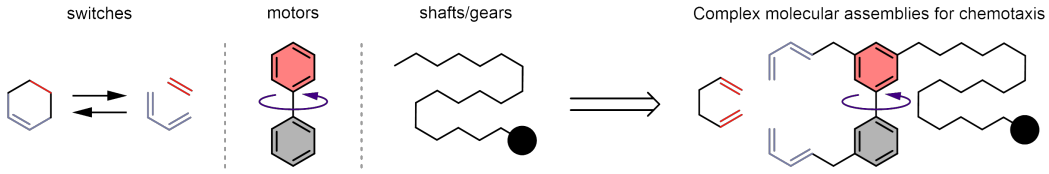
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From Small Machines to Complex Assemblies

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The design and synthesis of molecular machines, and notably chemically fuelled motors, has evolved considerably in recent years [1–4]. One fundamental challenge is now to assemble these discrete units into higher-order architectures capable of performing collective work, as exemplified in biology by ATP synthase. Our small team is currently developing elementary machine units—switches and motors—with the aim of integrating them into complex assemblies and devices with applications in endergonic synthesis [5], artificial muscles, and smart materials, where nanoscale mechanical motion translates into programmable material behaviour.



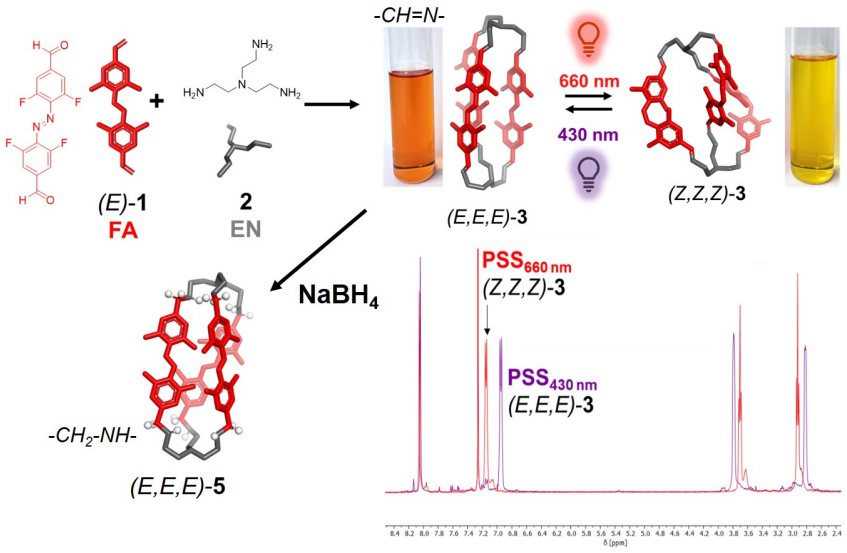
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Photochromic molecular cages switchable with red light in water

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Molecular photoswitches convert light energy into reversible changes of molecular properties (shape, polarity, stiffness).[1] Our group uses them in numerous applications - smart materials, bioactive compounds, photopharmacology. We used well-established azobenzenes to produce biocompatible supramolecular hydrogels. We also discovered a new class of peptide-based photoswitches - hemipiperazines. We used them in photopharmacology,[2] and as photoswitchable fluorophores.[3] In 2021, we introduced a fluorinated azobenzene motif switchable with red light (which deeply penetrates soft human tissues).[4] In 2026, we demonstrated fluorinated-azobenzene-based molecular cages assembled via dynamic covalent chemistry.[5]



The cages photoisomerize almost quantitatively with red light, undergo dynamic exchange with other aldehyde building blocks, and can be reduced to non-dynamic covalent cages. The latter upon protonation can be extracted into water, and undergo photoisomerization in both organic and aqueous phases. The formation, dynamics, and possible applications of that system will be demonstrated.

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Electrochemical synthesis of isoxazole derivatives

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Isoxazoles represent an important class of heterocyclic compounds with broad applications in medicinal chemistry, agrochemicals, and synthetic organic chemistry (e.g., Valdecoxib, Parecoxib, Sulfamethoxazole, etc.). (1-3) Their synthetic utility arises from the unique combination of an aromatic-like heterocyclic framework and a relatively weak N–O bond, which can be selectively cleaved to access diverse value-added molecular architectures.

Given the growing demand for sustainable synthetic methodologies, the development of efficient and environmentally benign routes to isoxazoles remains highly desirable. Herein, we report an electrochemical strategy for the synthesis of isoxazoles through the cyclization of alkynes using readily available $Fe(NO_3)_3$ as the nitrating source. In contrast to conventional approaches that often require high temperatures, additives, or pre-functionalized substrates (4), the present method directly employs simple alkyne feedstocks under mild electrochemical conditions.

Notably, this study demonstrates, for the first time, an electrochemical alkyne nitration followed by an in situ [3 + 2] cycloaddition sequence for the synthesis of isoxazole derivatives. The reaction conditions were systematically optimized, and a broad range of alkynes was investigated to establish the scope and functional group tolerance of the protocol. Overall, the method offers a sustainable and scalable approach to isoxazole synthesis with improved operational simplicity and mild reaction conditions.

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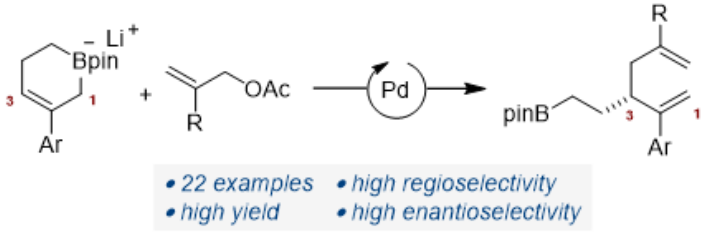
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Access to 1,5-dienes through Pd-catalyzed regio- and enantioselective allylation of cyclic allylboronates

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Chiral 1,5-dienes are common motifs that are found in numerous natural products (*e.g.* terpenes) and bioactive compounds, and which often serve as pivotal building blocks in organic synthesis.[1-3] The catalytic enantioselective allyl-allyl cross-coupling between prochiral allyl metal reagents and allyl electrophiles offers a direct route to chiral 1,5-dienes.[4-6]



Herein, we report a protocol for the Pd-catalyzed regio- and enantioselective allylic substitution of 6-membered cyclic boronate salts[7] to afford products featuring two distinct alkenes, an allylic tertiary stereocenter and a synthetically modular boron functionality. High levels of regio- and enantioselectivity have been obtained with a wide range of electrophile/nucleophile combinations. The synthetic utility of the products has been demonstrated through a series of metal-catalyzed post-catalytic derivatizations.

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A Traceless Tag for proteins delivery through TMU

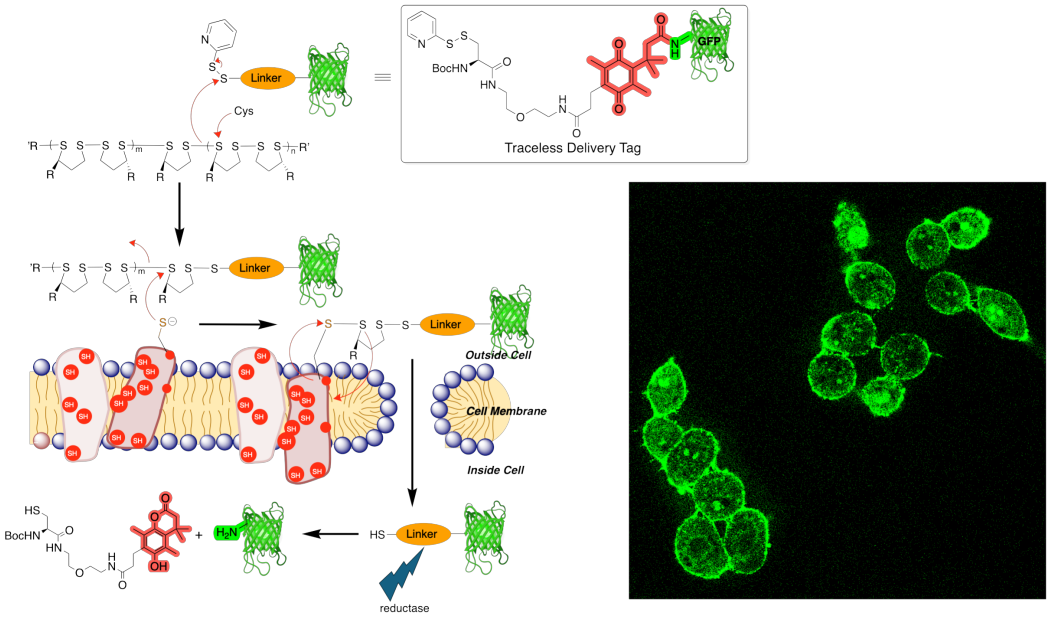
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[1]Department of Organic Chemistry, University of Geneva

The delivery of proteins through cell membranes without modifying their structure (traceless delivery) is of vital importance but remains challenging. Among all the pathways for achieving the delivery, thiol-mediated uptake (TMU) has attracted growing attention as an unorthodox yet powerful approach[1], involving dynamic covalent exchange networks (Figure left). Recently, the Matile group developed a new cell-penetrating polydisulfides (CPDs) method[2], enabling the traceless delivery of cysteine-modified GFP at nanomolar concentrations via grafting-to bioconjugation.

Compared to thiols, amines are among the most abundant reactive groups on native proteins, being present on lysine side chains and at peptide *N*-termini. For generalising the aforementioned CPDs method to amine-based bioconjugation, as well as preserve the traceless property, we designed a delivery tag (Structure in box) in which the target proteins (GFP as an example) are linked to a trimethyl lock (red) though an amide bond which is cleavable by cellular reductase. Meanwhile, the structure incorporates an active disulfide moiety enabling rapid disulfide exchanges with the CPDs and facilitating cellular uptake via TMU.

Preliminary studies on GFP have shown promising results (Figure right), demonstrating the delivery efficiency and the tracelessness. Ongoing work is extending this approach to more complex cargos, such as antibodies and streptavidin.



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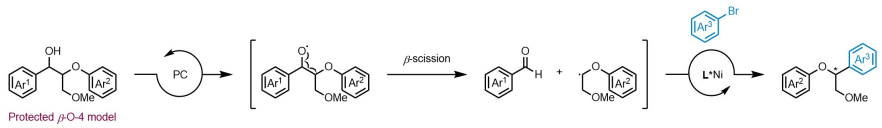
Photocatalytic Cleavage and Enantioselective Arylation of Lignin β-O-4 models via Ni/Photoredox Catalysis

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Lignin is the second most abundant biomass resource and the most abundant aromatic polymer in nature. As such, it represents a promising renewable source for the sustainable production of aromatic chemicals. However, selective lignin depolymerization remains challenging due to its highly heterogeneous structure, consisting of three phenylpropanoid subunits linked through a broad variety of C–O and C–C bonds.[1] To date, numerous strategies have targeted the β-O-4 linkage, the most prevalent interunit bond in lignin, enabling the production of valuable aromatic compounds such as benzaldehydes, benzoic acids, ketones, and phenols.[2]
To expand the range of accessible functional groups, photocatalytic approaches have attracted significant interest. These methods generate carbon-centered radicals that can be intercepted by external coupling partners, providing access to functionalized lignin-derived fragments. However, the scope of radical-trapping reagents has thus far remained largely limited to azodicarboxylates and a small number of electron-deficient alkenes.[3]

Herein, we report the first asymmetric functionalization of protected lignin β-O-4 model compounds with aryl bromides. This transformation is achieved using a dual Ni/photoredox catalytic platform. We propose that photoinduced oxidation of the lignin model is followed by a proton-coupled electron transfer (PCET) process, generating an oxygen-centered radical. Subsequent β-scission affords an aldehyde fragment together with a carbon-centered radical, which is intercepted by a Ni(0) species. Following oxidative addition of an aryl bromide and reductive elimination, the desired arylated product is formed.



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Phenalenyl π-Radical Cascades for Oligomerization

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Graphene-based nanomaterials (GNMs) and π-conjugated polymers are desirable, cutting-edge materials investigated for their electronic structure and conductive properties.[1] Potential applications range from fields in molecular electronics,[1] organic electrochemical transistor (OECTs),[2] to energy storage.[3] However, designing and synthesizing these materials remains troublesome since traditional synthetic approaches often face limitations regarding scale, cost, quality, and processability.[4]

Our approach leverages the self-dimerization of phenalenyl radicals forming several new bonds in a controlled π-radical cascade. Utilizing the cascade through purpose-built precursors enables the formation of peropyrene-containing PAHs with varied topologies.[5,6] Pursuing π-radical cascade mediated oligomerizations as a proof-of-concept pushes the methodology to its limits (Figure 1) and challenges conventional strategies applied in the synthesis of conductive materials.

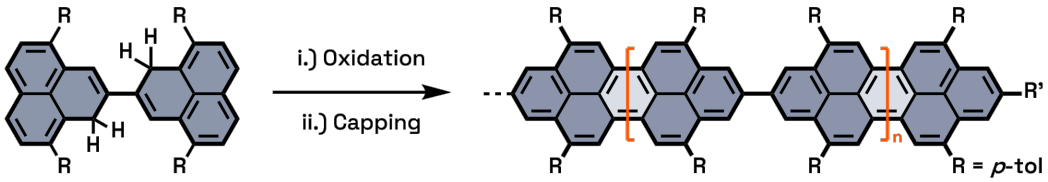


Figure 1. π-Radical Cascade applied in the synthesis of peropyrene oligomers.

This approach is being developed to demonstrate access to low n-oligomers. These are attractive targets for their in-solution processability and the characterisation of physical properties. Mixtures of higher n-oligomers will be studied at later stages for their bulk properties.

Iterative synthesis enables tuning material properties using key precursors, spacers and variable terminal capping units, such as the optoelectronic structure, torsion angles and helicity. Insights gained here may spark future development of novel macrocycles, 2D and 3D materials.

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Tunable water-soluble TADF probes for oxygen sensing

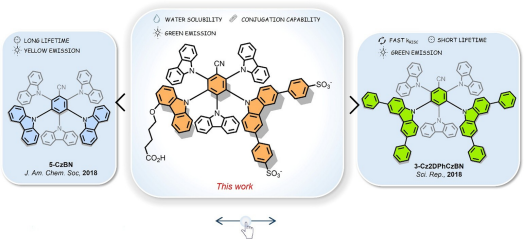
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Oxygen sensing in aqueous environments is critical for applications in biomedical diagnostics and environmental monitoring. Luminescent oxygen sensors are predominantly based on noble-metal (Ru, Pt) complexes, which suffer from limited performance in aqueous media, high cost, potential toxicity, and reduced photostability.[1]

Thermally activated delayed fluorescence (TADF) emitters represent a promising alternative to metal-based oxygen sensors. These dyes enable the harvesting of both singlet and triplet excitons via reverse intersystem crossing (RISC), thus giving long-lived excited states which can be efficiently quenched by molecular oxygen.[2]

Herein, we report the development of water-soluble TADF oxygen probes based on 5-CzBN motif (Figure 1).[3] This platform allows systematic tuning of photophysical and sensing properties through variation of donor units.[4] In particular, suitable substituents at the *meta* position of the CN group enable to introduce properties like water solubility and conjugation capability with a minimal alteration of the optical properties of the pristine compound. This design strategy provides a versatile platform for the realization of robust, adaptable, and high-performance oxygen sensors for complex aqueous environments, including biologically relevant and environmental systems.



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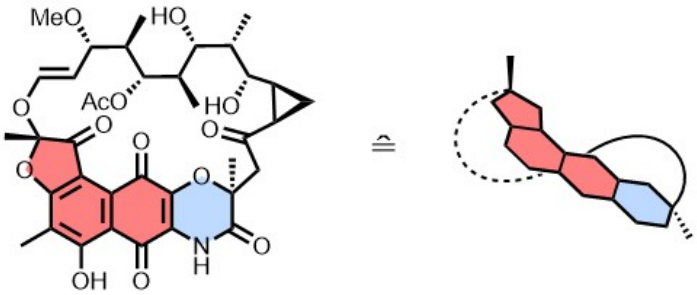
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Towards the Total Synthesis of Sporalactam B

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The rise of antimicrobial resistance in human pathogens combined with the lessening of newly approved antibiotics poses a major health threat for mankind.[1] On our mission to drive forward antibiotic discovery, the ansamycin antibiotic sporalactam B captured our attention. It is a biogenetic relative of the rifamycins and was isolated in 2017 from *Micromonospora* sp. with a unique *helicoid* architecture.[2] Thanks to *anti*-arrangement of the bridgehead stereocenters, the densely functionalized *ansa* chain wraps around the unprecedented tetracyclic core.



Fascinated by this structure, we embarked on a total synthesis campaign focusing on convergence and stereocontrol. Herein, we wish to report our efforts to construct the *ansa* chain of Sporalactam B and its union with the naphtalenoid core. With these findings we hope to advance ansamycin synthesis and eventually the fight against antimicrobial resistance.

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Electric-Field Catalysis of Diels-Alder Reactions

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[1]University of Geneva

The dream to catalyze reactions with externally applied electric fields is so obvious and so promising, it has attracted immense scientific attention. The Diels-Alder (DA) reaction has become the primary reaction to elaborate on this dream. However, despite much effort and supportive results from elegant single-molecule break junction experiments, electric-field catalysis (EFC) of this primary reaction has not been possible so far under practical organic synthesis conditions. The objective of this study was to challenge the emerging principles of scalable EFC in microfluidic capacitors with this holy grail in the field. Functional Helmholtz layers are assembled in microfluidic capacitors to translate the applied electric fields into effective electric fields that are, according to chronoamperometry, with 4.5 V/nm more than sufficient to catalyze the cycloaddition of maleimides to anthrones by direct transition-state stabilization. The absence of oxidation products and the negligible steady-state currents exclude faradaic processes to account for the reaction. Yields increase in a gated, non-linear manner from around 0% up to 90% with applied voltage. In chiral cationic Helmholtz layers assembled from polyarginines, benzylated quinines or ammonium binaphthyls, enantioselectivity up to 31% *ee* is obtained. These results demonstrate that the emerging principles of scalable EFC in microfluidic capacitors pass the ultimate test in the field with distinction: Besides realizing scalable DA-EFC with externally applied electric fields under scalable bulk conditions, this study also introduces chiral Helmholtz layers as i) the primary catalysts, with an impressive efficiency of EC_{50} = 0.2 mol%, and as ii) the unique source of chirality for asymmetric EFC.

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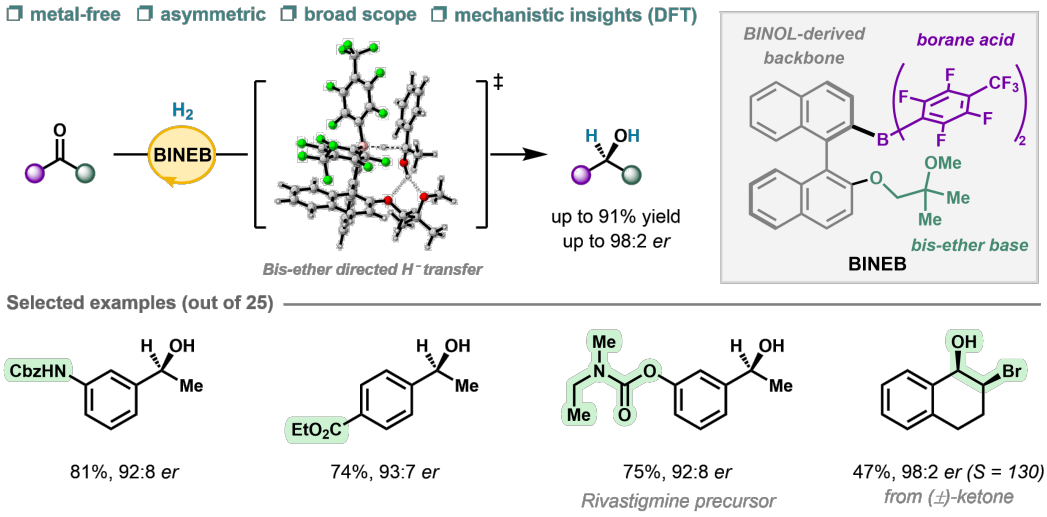
Design of Chiral Frustrated Lewis Pair Catalysts for Metal-Free Asymmetric Hydrogenation of Ketones

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Homogeneous asymmetric hydrogenation (AH) is a cornerstone of modern organic synthesis, providing efficient access to valuable chiral molecules from simple unsaturated precursors using H_2 as a clean reductant.[1] While AH remains dominated by precious transition-metal catalysts, more sustainable metal-free alternatives are highly desirable. Frustrated Lewis pairs (FLPs) have emerged as promising metal-free hydrogenation platforms,[2] but their application to AH has largely been limited to aza-substrates, such as imines. In contrast, less basic carbonyl substrates remain more challenging and underdeveloped.[3]

To tackle this challenge, we have developed BINEBs, chiral intramolecular FLPs in which a borane Lewis acid and a bis-ether Lewis base are linked through a BINOL-derived scaffold.[4] BINEBs catalyze the AH of ketones to alcohols with high enantioselectivity, reaching up to 97:3 er, and show proof-of-concept activity of up to 10 TON. This metal-free method tolerates diverse functional groups, including hydrogenation-sensitive Cbz and ester groups, and provides access to chiral alcohol intermediates of bioactive compounds. Moreover, BINEB catalysts enable the first kinetic resolution of racemic α-bromoketones by AH, affording versatile *cis*-β-bromoalcohols with excellent diastereo- and enantioselectivity.



Experimental SAR and computational studies provided insight into catalyst performance. Strong Lewis acidity is crucial for efficient heterolytic H_2 activation, while the intramolecular bis-ether unit governs enantioinduction by facilitating selective hydride transfer to the substrate. Overall, this work establishes intramolecular borane-ether FLPs as a promising platform for metal-free AH and provides design principles for expanding FLP catalysis to weakly basic substrates.

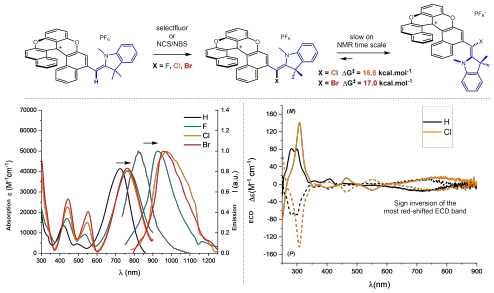
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Dynamic Atropisomerism and chiroptical properties of halogenated hemicyanines made of dioxa[6]helicene enamine conjugates

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Helicenes are an important class of chiral *ortho*-fused polyaromatic derivatives characterized by and dissymmetry originating from the steric repulsion between terminal substituents or rings.[1] Previously, direct oxidative cross-coupling between dioxa[6]helicene and methyl indoline fragments was realized.[2] X-ray structural analysis revealed an out-of-plane twist of the cyclic enamine moiety, giving rise to two atropisomers in rapid conversion on the NMR time scale, even at –90 °C. Herein, direct enamine functionalization is reported by electrophilic halogenation (**H** → **F**, **Cl**, **Br**). As a consequence, barriers of epimerization increase up to 17 kcal.mol^{-1} (VT-NMR monitoring) and further structural analyses reveal unexpected geometrical changes towards new preferred conformations allied with chiroptical changes. Furthermore, the halogen atoms promote strong bathochromic shifts extending even further absorptions and emissions into the near infrared region (NIR), a domain of light particularly advantageous for biological applications.[3]



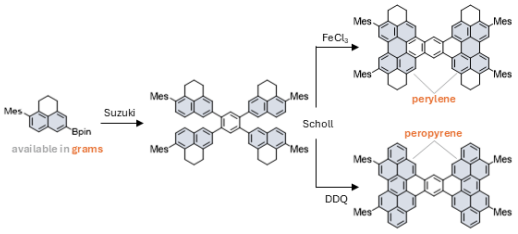
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Facile Synthesis of Peropyrene and Perylene Architectures

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Polycyclic aromatic hydrocarbons (PAHs) are an intriguing class of compounds with fascinating optoelectronic properties used in a multitude of technological applications. Owing to their effectively delocalized π electrons, PAHs offer solutions to many current global issues, including energy conversion, energy storage and climate change. Peropyrene is of particular interest because it has been theoretically predicted to undergo singlet fission upon photoexcitation, a process that could help surpass the Shockley–Queisser limit in photovoltaic devices.[1] However, unsubstituted parent peropyrene undergoes rapid deexcitation in the solid state due to self-quenching.[2] Thus, a reliable synthetic route to access new peropyrene architectures with novel properties and increased singlet fission efficacy is highly desirable.[3]



To address this challenge, we have developed a facile synthetic route toward various compounds embedding (multiple) peropyrene units within the molecular scaffold. The route involves a borylated semi-saturated phenalene unit that is available in grams and can be used to create many desired molecules within two subsequent reaction steps. The figure above shows one example scaffold synthesized within this study. Notably, modulation of the final Scholl oxidation conditions enables selective access to either the peropyrene or perylene framework from the same starting materials. The obtained structures display high fluorescence quantum yields and strongly redshifted emission wavelengths. The developed synthetic route demonstrates that complex PAHs incorporating multiple peropyrene or perylene units can be obtained in high yields and only a few reaction steps.

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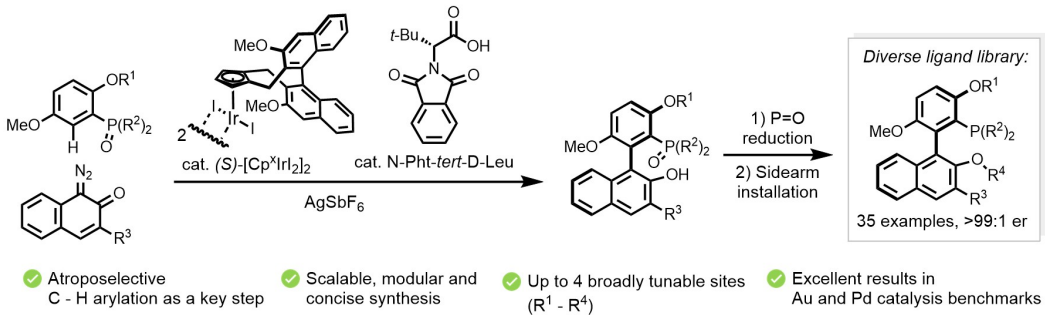
Diverse Library of Chiral Buchwald-Type Biaryl Monophosphine Ligands, Accessed via Ir-catalysed Atroposelective C – H Arylation: Synthesis and Applications in Asymmetric Catalysis

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The utilization of chiral monodentate phosphines is fundamental to modern asymmetric catalysis, both as ancillary ligands for transition metal complexes and as standalone organocatalysts.[1] However, the commonly used synthetic strategies towards typical privileged chiral monophosphines are often constrained by lack of efficiency, tunability and modularity stemming from multistep procedures and usage of chiral pool precursors or racemate resolution.[2]

Our group previously reported an intermolecular CpX-Ir^{III}-catalyzed asymmetric phosphine oxide arylation, with excellent yields and enantioselectivities under ambient conditions.[3] On the outset of this project, we envisioned that this reaction could therefore enable rapid access to a broad scope of phosphine oxides with axial chirality and subsequently, upon further reduction, a library of novel chiral monophosphines with previously unexplored functional and structural motifs. Following such a blueprint, we assembled a large combinatorial library (35 entries) of chiral monophosphines. The new ligand class demonstrated high efficiency in two distinct catalytic applications, namely in Au-catalyzed 1,6-enyne cyclisation[4] and Pd-catalyzed arylative phenol dearomatization.[5,6]



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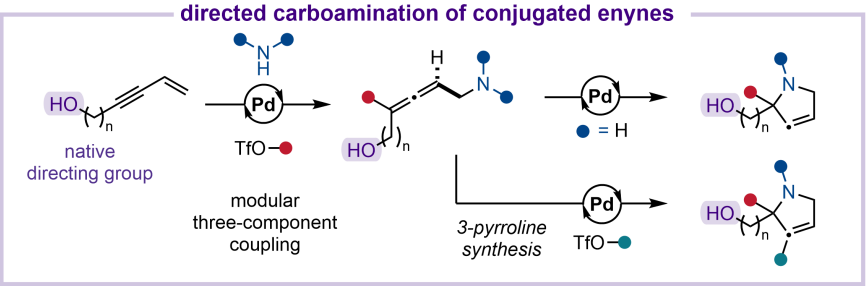
Alcohol-Directed Carboamination of Conjugated Enynes

H. Solé-Àvila[1,2], D. K. Brownsey[1,2], H. Senelle[1], J. Waser[1,2]*

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Nitrogen heterocycles are found in 82% of small-molecule drugs approved over the past decade, making efficient routes to nitrogen-containing scaffolds a central goal in synthetic chemistry.[1] Carboamination reactions, which form carbon and nitrogen bonds simultaneously across unsaturated C–C bonds, provide a direct and efficient approach to these targets. Established alkene carboamination methods rely on tethered nucleophiles for intramolecular cyclization under palladium, copper, or nickel catalysis, while three-component intermolecular variants use directing groups to control regioselectivity and access substituted aliphatic amines.[2]

We extended this reactivity to conjugated enynes, providing a new route to multi-substituted nitrogen-containing allenes. These scaffolds are valuable in synthesis for their axial chirality and electronic properties,[3] yet efficient routes to nitrogen-functionalized allenes remain scarce. Our Pd-catalyzed three-component carboamination addresses this gap in a modular and concise manner. A native alcohol in the substrate acts as a directing group, organizing reactivity without requiring a dedicated handle to be installed or removed. The reaction cleanly avoids competing pathways such as C–O coupling, Buchwald–Hartwig amination and hydroamination, and also enables dihydropyrrole synthesis, pointing to broader utility in heterocycle construction.[4][5]



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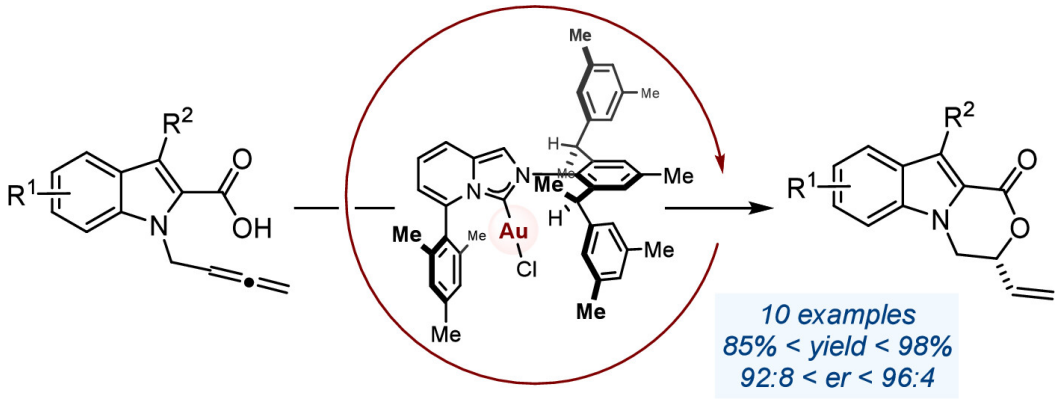
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Chiral Imidazo[1,5-*a*]pyridine-Based Ligands for the Au-Catalyzed Enantioselective Intramolecular Hydrocarboxylation of Allenes

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As part of our program aimed at designing chiral ligands for use in selective catalysis,[1-3] we report herein the synthesis of gold(I) complexes supported by imidazo[1,5-*a*]pyridine-based ligands[4,5] featuring chiral aniline moieties at N(2). The synthesis is short, efficient, and modular, allowing for precise control over the steric and electronic properties of the coordination sphere of the metal.



The design of these atypical chiral ligands was validated in the Au(I)-catalyzed enantioselective intramolecular hydrocarboxylation of allenes,[6] which furnished tricyclic N(1)−C(2)-fused oxazino-indolones in high yield and unprecedented levels of enantiocontrol.[7]

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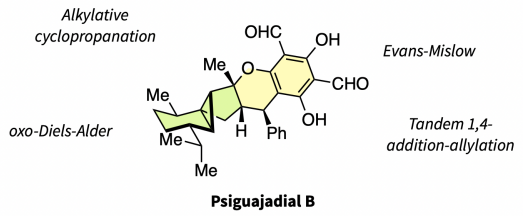
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Towards the Total Synthesis of Psiguajadial B

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[1]University of Zurich

Psiguajadial B is a structurally complex meroterpenoid isolated from *Psidium guajava*.[1] The structure features a highly oxygenated benzodihydropyran moiety fused to a strained tricyclo[4.4.0.0^{1,5}]decane skeleton. The latter 6/3/5 ring system is common to the cubebane sesquiterpenoids.[2] Herein, we report our efforts towards a concise total synthesis of psiguajadial B, centered around a transannular cyclopropanation strategy recently developed in our group. Moreover, our strategy aims to convergently assemble the central dihydropyran via an *oxo-Diels-Alder* reaction guided by the putative biogenesis.[3] This work demonstrates an efficient synthetic approach towards psiguajadial B and highlights several challenges associated with strained polycyclic natural products. The developed strategy provides a versatile platform for the synthesis of related natural products and may facilitate future biological evaluation.



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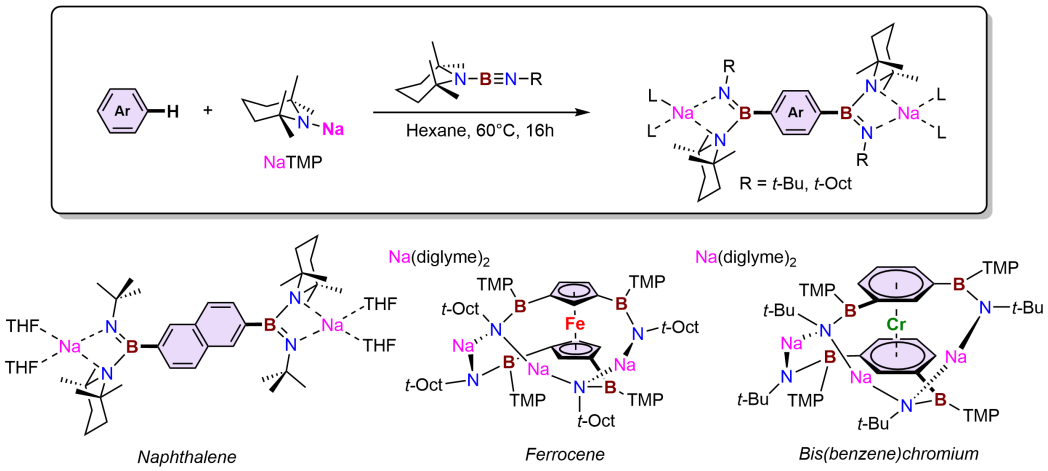
Sodium-mediated C-H polyborylation of non-activated arenes and metallocenes

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Organoboron compounds have found widespread use in the synthesis of pharmaceuticals and functional materials in recent years. However, current methods of installing boryl groups on non-activated arenes require unsustainable transition metals,[1] while transition-metal free methods require extremely harsh conditions.[2] Stoichiometric deprotonative protocols offer a complementary method to borylate non-activated arenes but are currently limited to mono-borylations.[3] Recently, we have shown that combining NaTMP with sterically demanding iminoboranes promotes the C-H borylation of relatively acidic heteroarenes when using catalytic amounts of the Na base.[4] However, this approach proved challenging when applied to non-activated systems such as anisole and benzene.

In this contribution, we demonstrate the regioselective deprotonative polyborylation of polycyclic aromatic hydrocarbons and metallocenes using stoichiometric amounts of superbasic sodium amides and trapping with an iminoborane reagent. Control of reaction temperature and stoichiometry allows for the selective synthesis of the relevant polyborylated products. Stoichiometric experiments and characterisation of organometallic intermediates provide key insights into the challenges of deprotonative polyfunctionalisation of non-activated arenes and metallocenes such as anthracene, perylene and ferrocene.



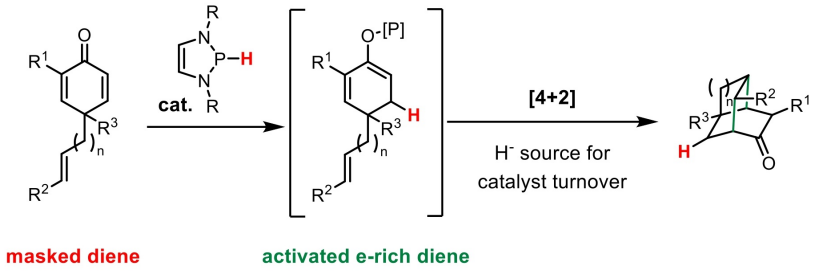
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Reductively Triggered Diels-Alder Reaction Catalyzed by 1,3,2-Diazaphospholenes

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1,3,2-Diazaphospholenes (DAPs) have demonstrated their ability to catalytically transfer a non-basic hydride to α,β-unsaturated carbonyl compounds.[1] The resulting phosphorous-enolate species are proven to be competent in [3,3]- and [2,3]-sigmatropic rearrangements.[2] Herein, we use DAPs to convert dienones into [4+2]-cycloaddition substrates. The 1,4-hydride addition generates P-enolate diene species, which subsequently undergo Diels-Alder reaction with suitable dienophiles. First reactivity proof of principle is shown.



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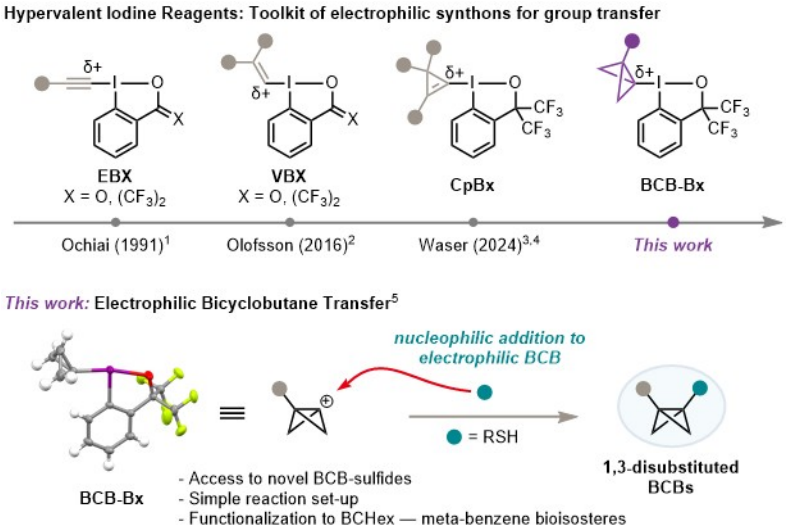
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Electrophilic Bicyclobutane Transfer

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Cyclic hypervalent iodine reagents have been widely applied in the transfer of functional groups such as alkynes,[1] alkenes,[2] and more recently, cyclopropenes.[3,4] In this work,[5] we present a novel hypervalent iodine reagent, BCB-Bx, for the electrophilic transfer of bicyclo[1.1.0]butanes (BCBs), the smallest bicyclic carbocycles. First synthesized in 1959 as a mere structural curiosity,[6] BCBs have seen a substantial resurgence in the past decade, owing to their broad utility in accessing synthetically and medicinally relevant motifs.



We report a robust and scalable synthesis of BCB-Bx reagents, and their utilization as electrophilic synthons of bicyclobutanes (BCBs). First, we developed a practical and general methodology to access BCB-sulfides, a previously elusive class of compounds. The BCB products synthesized are then functionalized via their central bond to access medicinally-relevant scaffolds, such as bicyclo[1.1.1]pentanes (BCPs), bicyclo[2.1.1]hexanes (BCHexs) and bicyclo[3.1.1]heptanes (BCHeps). These scaffolds have garnered significant interest in recent decades as key building blocks within the “Escape from Flatland” concept, serving as saturated bioisosteric replacements for substituted benzene rings. The addition of further carbon-based nucleophiles to our novel electrophilic BCB synthon will also be presented.

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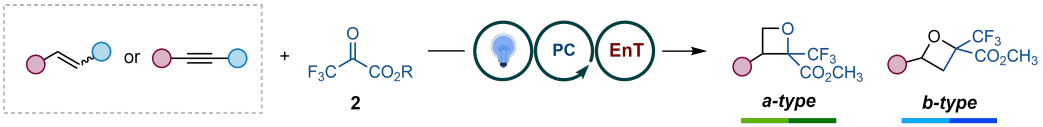
Triplet Energy Transfer-Mediated Intermolecular Paternò–Büchi Reaction for the Synthesis of Trifluoromethylated Oxetanes

Y. Zhu[1], A. J. Fernandes[1], E. Zhilin[1], D. Katayev[1]*

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Oxetanes have emerged as valuable, compact, and polar bioisosteres in medicinal chemistry, while the incorporation of a trifluoromethyl group provides an additional handle for fine-tuning molecular properties. However, direct and general access to trifluoromethylated oxetanes remains synthetically challenging. Herein, we report a visible-light-mediated intermolecular Paternò–Büchi reaction for the synthesis of CF_3-substituted oxetanes via triplet energy transfer catalysis. Using readily available alkenes and methyl trifluoropyruvate as the carbonyl coupling partner, this method provides broad access to trifluoromethylated oxetanes under mild conditions with excellent regio- and diastereoselectivity.

The reaction tolerates diverse alkene classes, including terminal styrenes, β-substituted styrenes, functionalized cinnamyl derivatives, cyclic alkenes, dienes, and alkynes. The operational simplicity and synthetic utility of the protocol were demonstrated by a 10 mmol-scale reaction followed by ester reduction and Suzuki–Miyaura cross-coupling. Mechanistic studies, including Stern–Volmer quenching, alkene isomerization experiments, and DFT calculations, support a stepwise triplet-energy-transfer-mediated cycloaddition pathway. Although both alkene and carbonyl sensitization can occur, the productive cycloaddition proceeds preferentially from the triplet excited state of the CF_3-substituted carbonyl partner.
This work expands the synthetic toolbox for accessing fluorinated oxetane building blocks and provides a practical platform for constructing three-dimensional motifs relevant to drug discovery.



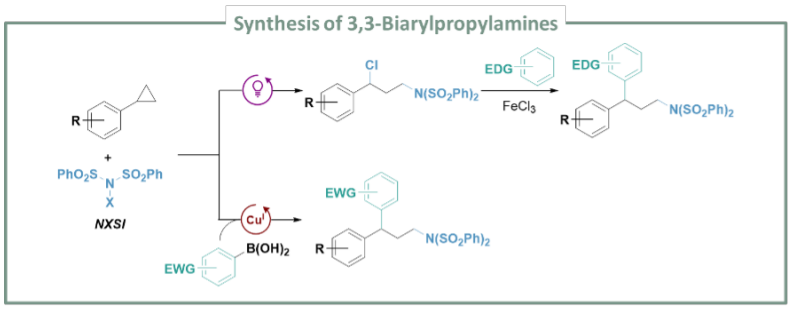
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3,3-Biarylpropylamines: A Strain-Release Strategy for Direct Synthesis from Aryl cyclopropanes

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Amines are among the most prevalent functional groups in drug molecules, frequently contributing to molecular recognition, target binding, and favorable physicochemical and pharmacokinetic properties. In this context, 3,3-biarylpropylamines represent an important class of bioactive compounds in medicinal chemistry and are present in numerous pharmacologically relevant molecules, including Tolterodine, Fendiline, and Desfesoterodine.[1–3] The synthesis of this scaffold can be achieved using cyclopropanes as synthons, which represent versatile C3 building blocks in organic synthesis. As the smallest members of the cycloalkane family, cyclopropanes possess substantial ring strain resulting from a combination of angular and torsional strain, that renders them susceptible to σ Csp^3-Csp^3 bond cleavage, enabling their use as precursors for the formation of n-propyl chains.[4] Building on several reports that exploit arylcyclopropanes in aminofunctionalization reactions,[5–7] we report a concise and efficient synthetic approach to the 3,3-biarylpropylamine scaffold via C–C bond cleavage of arylcyclopropanes through two complementary strategies. A photocatalyzed 1,3-aminochlorination of arylcyclopropanes, which can be combined with a Friedel–Crafts-type benzylation of arenes in a two-step, one-pot sequence and a copper-catalysed 1,3-aminoarylation were developed to access diverse 3,3-biarylpropylamine derivatives.



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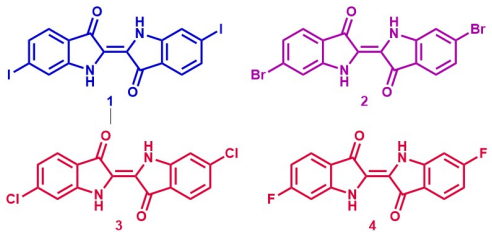
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6,6'-Dihalogenoindigos - A Maturarbeit growing bigger and bigger

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Tyrian Purple **2** has a rich history dating back to ancient Phoenicia. It was extracted from the glands of certain sea snails and valued for its vibrant, long-lasting hue. Reserved for royality and church, this rare and extremely expensive dye became a powerful symbol of wealth and status throughout the ancient mediterranean world.[1] The presented work started out as a Maturarbeit in synthetic organic chemistry intended to prepare Tyrian Purple (6,6'-Dibromoindigo, **2**) as well as its chlorinated analogon **3** to test if the higher electronegativity of Cl will lead to the expected shift of the absorption maxima. Since then, a year has passed, the lab has shifted from school to university and the remaining Iodo **1** and Fluoro **4** analogons have been prepared via improved preparative strategies. As scientific interest in halogenated indigo derivatives has seen a revival over the past few years[2,3] due to their potential applications as natural product-based, non-toxic material for organic electronics like bio-sensing platforms, our lab currently focuses on investigations into phosphorescent and other photophysical charachteristics of compounds **1-4**. Newest results are presented.



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