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Accessing Unusual and Large-Ring Cyclodextrins Using Enzyme-Mediated Dynamic Combinatorial Chemistry

S. Beeren¹

¹Technical University of Denmark, Department of Chemistry, Kemitorvet, Building 207, 2800 Kgs. Lyngby, Denmark - sopbee@kemi.dtu.dk

Biomolecular templates define the outcomes of enzymatic reactions in some of the most fundamental of biological processes, such as DNA replication, transcription and translation. In synthetic chemistry, molecular templates have enabled the synthesis of highly complex molecular architectures and interlocked structures. With *Enzyme-Mediated Dynamic Combinatorial Chemistry*, we explore the possibility of using synthetic templates to direct enzymatic reactions and obtain alternative products to those generated in Nature.

α -, β - and γ -cyclodextrin (CD) are industrially important macrocyclic hosts formed from 6, 7, and 8 α -1,4-linked glucopyranose units. While cyclodextrins are usually considered as stable, static molecules, we generate dynamic mixtures of interconverting cyclodextrins by the action of *cyclodextrin glucanotransferase* (CGTase). As the system is dynamic, the product distribution can be manipulated via supramolecular interactions with template molecules.¹ We use templates to direct the selective synthesis of ‘natural’ cyclodextrins as well as modified cyclodextrins, and employ stimuli-responsive templates to control the system using light and redox chemistry.

Large-ring cyclodextrins, formed from more than 8 glucose units have received very little attention due to synthetic inaccessibility. Using the approach of template-directed enzymatic synthesis, we can now obtain δ -CD (formed from 9 glucose units) in unprecedented yields² and on a multi-gram scale.³ Investigations are ongoing to explore the molecular recognition capabilities of this newly accessible macrocyclic host.

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Glucose-derived selective receptors of amino acids in aqueous environments.

B. Lewandowski¹, M. M. Most^{2*}, L. B. Boll^{1*}, P. Gödtel^{2*}, Z. L. Pianowski^{2*}

¹Laboratory of Organic Chemistry ETH Zürich, Vladimir-Prelog-Weg 3, 8093 Zürich, Switzerland, ²Institute of Organic Chemistry, Karlsruhe Institute of Technology (KIT), Kaiserstrasse 12, 76131 Karlsruhe, Germany

Amino acids play key roles in numerous biological processes.^[1] They also found applications in asymmetric synthesis and catalysis,^[2] chemical biology^[3] and materials science.^[4] Selective binding of amino acids, in particular in water, is therefore important for diagnostic, medicinal and technological purposes.^[5] However, it is also challenging since it requires a combination of hydrophobic and polar interactions for binding.^[6] Recently, we reported glucose-derived crown and benzocrown ethers capable of enantioselective binding of amino acid esters with hydrophobic and aromatic side chains in water.^[7,8] Herein, we will present a glucose naphtho crown ether (Fig. 1a) which binds tryptophan selectively over other amino acids in aqueous media.^[9] This receptor is also capable of binding to tryptophan residues within peptides. The naphthalene unit in the receptor allows to monitor the binding process with fluorescence spectroscopy.

Furthermore, we will present glucose-based photoswitchable receptors of amino-acid esters and biogenic amines (Fig. 1b).^[10] The tetrafluoroazobenzene unit in the receptors structure allows to control their binding affinity to dicationic guests, such as lysine, arginine and ornithine esters, in water and PBS buffer, using light. The *Z* isomers of the receptors display 3-4 x higher affinities to the guests than the *E* isomers.

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Electron Donor-Acceptor Complex-Catalyzed Aromatic Nitration: Unveiling the Role of Polymeric Donors

A. J. Fernandes¹, H. Lecomte^{1*}, M. G. Metzger^{1*}, Q. E. Ordan^{1*}, K. N. Houk^{2*}, D. Katayev^{1*}

¹Departement für Chemie, Biochemie und Pharmazie, Universität Bern, Freiestrasse 3, 3012 Bern, Switzerland, ²Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90095-1569, United States

Nitroaromatic compounds are indispensable building blocks in the synthesis of pharmaceuticals, agrochemicals, and functional materials, playing a central role in both academic research and large-scale industrial production.^{1,2} Despite their significance, the development of nitration strategies that are sustainable, highly chemo- and regioselective, and compatible with bench-stable, non-acidic reagents under catalytic and environmentally responsible conditions remains a pressing and unresolved challenge. Recently, light-mediated processes have attracted considerable attention due to their enhanced sustainability, milder conditions, and their ability to take molecules in their excited-states and unlock novel reactivity.

Herein, we report, the first example of an aromatic nitration reaction photocatalyzed by an Electron Donor–Acceptor (EDA) complex. This transformation proceeds under mild, light-mediated conditions and is enabled by a unique combination of two key components: the potent electron acceptor *N*,6-dinitrosaccharin³ and a carbazole-based polymeric donor, which synergistically generate nitryl radicals ($\cdot\text{NO}_2$) through EDA complex^{4,5} activation. The resulting $\cdot\text{NO}_2$ radicals efficiently functionalize a broad range of aromatic substrates, displaying excellent chemoselectivity and tolerance to diverse functional groups. Detailed mechanistic studies combining both experimental and computational evidence support a catalytic cycle initiated by photoinduced EDA complex activation and subsequent $\cdot\text{NO}_2$ radical generation. DFT studies elucidate the intricacies of the *nitryl radical addition* and *radical-pair collapse* pathways that govern the reaction mechanism, while offering key insights into the superior reactivity enabled by the polymeric donor.

Synthesis of phosphorothioates by photocatalytic sulfur transfer from thiosulfate

A. Budeev¹, C. Bon^{1*}, C. Sparr^{1*}

¹University of Basel, Department of Chemistry, St. Johannis-Ring 19

With therapeutic oligonucleotides progressing from the treatment of rare genetic diseases to medications of common disorders, the synthesis of modified oligonucleotides is gaining significant momentum. To improve pharmacokinetic and pharmacodynamic properties, chemical modifications to the nucleotide backbone have thereby been particularly advantageous. Since Eckstein's pioneering discovery in 1966¹, the phosphorothioate linkage has become the most useful oligonucleotide modification. Compared to phosphate, phosphorothioate is more resistant to cleavage by nucleases, resulting in improved elimination half-life of DNA or RNA sequence, extending from minutes to days. Moreover, the introduction of this moiety increases binding to serum proteins, amplifying the time available for uptake into target tissues². This moiety can be found in 9 FDA-approved oligonucleotides³.

However, common reagents used for the sulfuration of phosphorothioate oligonucleotides have several disadvantages, including toxicity, cost- and atom-inefficiency, and compromised stability, underscoring the need for alternative sulfuration protocols. In this work, we therefore developed a more sustainable, mild and general methodology for the photocatalytic sulfuration to prepare phosphorothioates using regular thiosulfate as a benign sulfur source. Furthermore, the method was applied to standard solid-phase phosphoramidite oligonucleotide synthesis in pure water using riboflavin (vitamin B2) as photocatalyst, representing a sustainable alternative to existing sulfuration methods⁴.

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Organocatalyzed Stereoselective Macrocyclizations

J. W. Rackl¹, L. B. Boll^{1*}, H. Wennemers^{1*}

¹Laboratory of Organic Chemistry (LOC), ETH Zurich, Vladimir-Prelog-Weg 1-5/10, 8093 Zurich

Macrocycles are useful scaffolds in drug discovery and common among natural products. The entropic and enthalpic penalties during ring closure render the synthesis of such rings with 12 or more atoms a formidable challenge. Established methods generate planar bonds through e.g. acylation or ring-closing metathesis, moieties that do not contain a stereogenic center.

We have developed the first stereoselective organocatalytic macrocyclization.¹ Key to the controlled macrocyclization with exquisite control over the generated stereogenic centers (>20:1 d.r., 85–99% ee) is the bifunctional catalyst H-DPro- α MePro-Glu-NH₂. This tripeptide is an excellent catalyst for conjugate addition reactions, even tolerating competitive solvents and the presence of enzymes.^{2–4} During the macrocyclization, the unique conformation of the peptide preorganizes the linear substrate for ring closure through synergistic non-covalent and covalent interactions. Our approach uses an intramolecular conjugate addition to form 12–18-membered macrocycles. The method tolerates a broad range of functional groups, including electron-rich and electron-poor aromatic and aliphatic substrates. The reaction proceeds with catalyst control as exemplified by macrocyclizations of enantiomeric starting materials. We highlight the value of our method for the construction of architecturally complex molecules by the synthesis of the Robotnikinin macrocyclic core with stereochemical control.

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Exploring communication between different pi systems through a metal centreO. J. Kanisius^{1,2}¹O. Domecq-Cazaux, L. Sturm, M. Rickhaus, ²Université de Genève, Geneva, Switzerland,
owen.kanisius@unige.ch

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 fibers³, 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 clear redshift of up to 100 nm upon insertion of Cu, Zn and Co, in addition to quenching of fluorescence (Figure 1, left). Appending donor and acceptor groups to, for example, the two opposing pyridine units, allows us to probe direct communication through the metal centre, unlocking potential light harvesting properties. This can also be envisaged between both carbazole units too, or even across a corner, carbazole to pyridine.

Forming both linear and cyclic oligomers of these systems also allows us to probe direct metal-metal communication, due to the absence of local aromaticity within each carpyridine monomer. 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 also could lead to exciting applications in nanotechnology and microelectronics.

Acknowledgements

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Driving Sustainability in API Synthesis at Early-stage DevelopmentT. Cao¹¹Chemical Process R&D, Johnson&Johnson Innovative Medicine, Cilag AG, Hochstrasse 201, 8200 Schaffhausen

In the pharmaceutical industry, the chemical process development function plays a crucial role at the intersection of drug discovery and active pharmaceutical ingredient (API) manufacturing. The primary objective of chemical development is to facilitate rapid, sustainable, safe, and cost-effective access to chemical modalities, whether they are in clinical development or already marketed, as part of life cycle management. Key intrinsic goals of chemical process development include minimizing resource consumption and waste generation, as well as eliminating the use of hazardous chemicals. Achieving these goals not only reduces production costs but also enhances process safety. Today, sustainability has become a “license to operate” topic and additional effort is needed, even at the early-stage development of the portfolio that goes beyond cost reduction. This presentation will emphasize initiatives aimed at advancing sustainability in API synthesis during the early stages of portfolio development.

<https://innovativemedicine.jnj.com/switzerland/de>

Breaking the Resolution Limits: Photouncaging on a Single-Molecule LevelK. Hanc¹, P. Rivera-Fuentes^{1*}, P. Stacko^{1*}¹Department of Chemistry, University of Zurich

The study develops dual-stage photocages (SNAPcages) that can be activated by tissue penetrating near-infrared (NIR) light to release the payload only in the presence of specific biomolecules, offering unprecedented control and precision over the uncaging process.

An additional layer of control over photouncaging is incorporated by integrating photocages with site-specific targeting via SNAP-tag proteins in living cells. In strong contrast to conventional photocages that rely solely on light as a stimulus - limiting spatial resolution to the diffraction limit - **SNAPcages** are activated by NIR light only in the presence of specific biomolecular targets. This novel approach enhances spatial precision beyond the current state-of-the-art, enabling targeted uncaging at the subcellular to single-molecule level. The concept is based on a recently introduced fluorogenic system, the utility of which has been shown on a series of polymethine dyes.^[1]

The **SNAPcages** are designed around a Cy7 photocage scaffold containing a drug-like payload attached in the C4' position of the central chain. **Contrary to all the previous photocages pursued in our group,^[2-4] the design herein relies on desymmetrized cyanines that contain two different terminal heterocycles.**

In their native state, the **SNAPcages** are photochemically inactive because of the intramolecular cyclization of the sidechain (red) which disrupts the conjugation of the cyanine chromophore. Upon specific binding of SNAP-ligand (green) to its target (brown), the polarity of the immediate environment surrounding the **SNAPcage** will change, triggering the ring-opening on the heterocycle site and restoring the absorption of Cy7. This will arm the **SNAPcage** for a subsequent activation with light and uncaging of the payload (purple). This arming process induced by specific intracellular targets will provide an additional layer of spatiotemporal control of the uncaging, overcoming the resolution limits imposed by the diffraction limits of light.

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Directed Pd-Catalyzed Carboamination of Conjugated Enynes

H. Solé-Àvila¹, D. K. Brownsey^{1*}, H. Senelle^{1*}, J. Waser^{1*}

¹Laboratory of Catalysis and Organic Synthesis (LCSO) and NCCR Catalysis, École Polytechnique Fédérale de Lausanne (EPFL)

The incorporation of amines into organic scaffolds remains a central goal in synthetic organic chemistry, with broad implications for the construction of pharmaceuticals, agrochemicals, and natural products. In particular, nitrogen heterocycles are abundantly prevalent in bioactive molecules, with 82% of newly approved small-molecule drugs over the past decade containing at least one such moiety.[1] Carboamination reactions, which introduce both carbon and nitrogen units across unsaturated C–C bonds, offer a powerful strategy for assembling complex nitrogen-containing architectures. Established methodologies for alkene carboamination typically rely on tethered nucleophiles to enable intramolecular cyclizations, often under palladium, copper, or nickel catalysis, to afford azaheterocycles. In contrast, intermolecular three-component variants employ directing groups to control regioselectivity, granting access to substituted aliphatic amines in a modular fashion.[2]

We have extended this reactivity paradigm to the carboamination of enynes, providing a new route to multi-substituted nitrogen-containing allenes. Allenes are highly versatile intermediates in organic synthesis, due to their unique axial chirality and electronic properties, and they also feature in a range of natural products and functional materials.[3] Nevertheless, nitrogen-functionalized allenes, particularly complex multisubstituted allenes, remain largely underexplored due to the lack of general and efficient synthetic routes. A streamlined and modular method to access such scaffolds from simple and readily available starting materials is therefore highly desirable.

Recent advances in transition-metal-catalyzed 1,4-functionalization of unactivated enynes highlight the potential of this strategy to access diverse allene frameworks in a concise and regioselective manner.[4] Building on this, we developed an intermolecular, Pd-catalyzed three-component carboamination of conjugated enynes. This transformation enables efficient, modular synthesis of multi-substituted nitrogen-containing allenes, while avoiding common side reactions such as Buchwald–Hartwig amination, double amination, or hydroamination.[5] Notably, the method applies to dihydropyrrole synthesis, highlighting its broader utility in heterocycle construction.

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Catalytic C–N Bond Metathesis of Tertiary Amines

D. T. Egger¹, C. Zachau^{1*}, E. Studer^{1*}, S. Makai^{1,2*}, S. Kotesova^{1*}, H. Park^{3*}, Z. Lian^{2*}, T. Choi^{3*}, B. Morandi^{1,2*}

¹Laboratorium für Organische Chemie, ETH Zurich, Zurich, 8093, Switzerland, ²Max-Planck-Institut für Kohlenforschung, Mülheim an der Ruhr, 45470, Germany, ³Laboratory for Polymer Chemistry, ETH Zurich, Zurich, 8093, Switzerland

Tertiary amines are an important chemical motif due to their ubiquitous presence in many bioactive molecules.^[1] The ability to specifically cleave and re-form the C–N bonds in tertiary amines therefore holds high potential for chemical synthesis. Resulting from our on-going interest in catalytic C–X single bond metathesis reactions,^[2] we herein disclose the development of an iridium-catalyzed metathesis of tertiary alkyl amines.^[3] The synthetic utility and application of a metathesis approach of tertiary amines has been underexplored,^[4] as in the absence of any handles for selectivity such a process will typically result in complicated product mixtures due to a combinatorial explosion.

We have successfully developed strategies to tame this complexity and *inter alia* enable the selective cross-metathesis between selected tertiary amines. Beyond the evident applications in organic synthesis, we have further applied our system for molecular data storage harnessing the combinatorial complexity of statistically distributed product mixtures. Finally, we have also explored the possibility to utilize our amine metathesis methodology for the synthesis of new polyamine polymers.

Figure 1. Iridium-catalyzed metathesis reaction of tertiary alkyl amines and applications towards organic synthesis, molecular data storage and polymer chemistry.

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Designing Electric-Field Catalysis Systems For Monoterpene Cyclizations

A. Jozeliūnaitė¹, S. Guo^{1*}, N. Sakai^{1*}, S. Matile^{1*}

¹Department of Organic Chemistry, University of Geneva, Switzerland

Essentially, all chemical reactions can be viewed as the movement of electrons. In theory, by precisely aligning oriented external electric fields (OEEFs) along the reacting species to direct this movement, it provides control over both the reactivity and selectivity of non-redox reactions. Despite the theoretical promises, the practical application of electric-field catalysis has primarily been restricted to unconventional conditions, such as designed local electric field-based (dLEFs) systems, single molecules on STM tips, or reactions in water droplets. Thus, the transition to scalable organic synthesis poses challenges that must be addressed to develop broadly applicable electric-field catalysis methods.

To contribute to these efforts, we became interested in the development of monoterpene cyclizations initiated by OEEFs.¹ This was accomplished by utilizing an electrochemical microfluidic reactor equipped with a graphite electrode coated with easily polarizable multiwalled carbon nanotubes (MWCNTs).^{1,2} Depending on the orientation of the applied electric field, MWCNTs generated strong local macrodipoles, catalyzing cyclization on the surface through interactions with anionic or cationic parts of reactive intermediates. Going forward, our aim is to broaden the scope of electric-field-controlled transformations by tuning system design to enable catalysis at high electric fields.

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Beyond the Textbook: Is There Still Something to Learn from a Diels–Alder Reaction?

M. D. Salim¹, T. Pastierik^{1*}, P. Ribar^{1*}, T. Šolomek^{2*}, M. Juríček^{1*}

¹Department of Chemistry, University of Zurich, Winterthurerstrasse 190, 8057 Zürich, Switzerland, ²Van 't Hoff Institute for Molecular Sciences, University of Amsterdam, Science Park 904, 1098 XH Amsterdam, The Netherlands.

The Diels–Alder reaction has after its initial description in 1928 quickly evolved to be one of the most frequently used and powerful transformations known to the organic chemist.^[1,2] Despite its widespread use and extensive mechanistic investigations, examples where the diene and the dienophile are part of the same π -conjugated system are scarce in literature.^[3,4] In connection to our ongoing efforts to design an organic, bistable magnetic photoswitch, we coincidentally discovered an example of such an intramolecular Diels–Alder reaction. This reaction additionally stands out because it proceeds with a half-life of 50 min at 293 K, which is exceptionally fast compared to other uncatalyzed Diels–Alder reactions of unactivated systems.^[5] Our findings offer insights that can pave the way for more step-efficient strategies to construct complex polycyclic molecular scaffolds and highlight that, nearly a century after its discovery, the Diels–Alder reaction still raises compelling fundamental questions.

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Selective Recognition of Sucrose by a Synthetic Peptide Receptor in Water

L. K. Beiersdörfer¹, M. Li^{1*}, D. Zetschok^{1*}, N. Wunderling^{1*}, H. Wennemers^{1*}

¹Laboratory of Organic Chemistry, ETH Zürich

The selective recognition of saccharides in aqueous environments is a longstanding challenge due to their structural and functional similarity and the high solvation of carbohydrates in water. The Wennemers group recently developed an oligoproline-based receptor with two boronic acid moieties that binds the disaccharide sucrose with high selectivity and affinity in aqueous media ($K_a \approx 10'000 \text{ M}^{-1}$). The conformationally well-defined proline hexamer allows for precise positioning of the recognition motifs with a distance of $\approx 9 \text{ \AA}$. This spacing reflects the spatial orientation of the 1,3-diol moieties in sucrose. In depth binding studies revealed an unexpected binding mode.

Streamlining the Synthesis of Pyridones through Oxidative Amination of Cyclopentenones

B. B. Botlik¹, M. Weber^{1*}, F. Ruepp^{1*}, K. Kawanaka^{1*}, P. Finkelstein^{1*}, B. Morandi^{1*}

¹ETH Zürich

Pyridones are commonly found among drug molecules and are also widely used in organometallic chemistry as ligands. The traditional methods for the synthesis of 2-pyridones that typically rely on classical condensation processes of acyclic building blocks are often lengthy, require pre-functionalised starting materials, or lack generality. Therefore, an alternative strategy offering more facile access to pyridones would be highly beneficial. We report the development of an oxidative amination process for the streamlined synthesis of pyridones, utilising a nitrogen source and a hypervalent iodine reagent. Cyclopentenone building blocks can undergo *in situ* silyl enol ether formation, followed by the introduction of a nitrogen atom into the carbon skeleton with successive aromatisation to yield 2-pyridones. The reaction sequence is operationally simple, uses commercially available reagents and starting materials, carried out in one-pot, proceeds under mild conditions, exhibits broad functional group tolerance, complete regioselectivity, and scales well. The method also provides access to ¹⁵N-labelled targets and various industrially relevant products.¹

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Modular intramolecular trapping of aza-allenium salts enabled by late-stage nitrogen atom insertionY. Brägger¹, E. Tufano^{1*}, P. Gärtner^{1*}, M. C. Amberg^{1*}, L. Sorrentino^{1*}, B. Morandi^{1*}¹Laboratorium für Organische Chemie, ETH Zürich, Zürich, Switzerland

N-heterocyclic molecules are central to medicinal chemistry, agrochemicals, and material science.¹ While *5-endo-trig* cyclizations would offer a direct route to five-membered heterocyclic skeletons, they are typically disfavored according to the Baldwin Rules due to frontier orbital misalignments in the transition state, rendering them inefficient or requiring harsh conditions. Herein, we report an interrupted oxidative amination of unactivated alkenes that transiently generates aza-allenium salts — reactive intermediates whose alkyne-like orbital configuration enables them to selectively undergo smooth, formally Baldwin-disfavored *5-endo-trig* cyclizations.² This reactivity unlocks access to highly unusual, semi-saturated *N*-heterocycles that are both rare and synthetically challenging to obtain. They serve as versatile synthetic intermediates, undergoing downstream aromatization, reduction, or C–N bond cleavage to afford amines. The reaction is operationally simple, highly functional group tolerant, and amenable to late-stage functionalization. Furthermore, we demonstrate the versatility of this platform through a 'couple-close' protocol enabling the modular synthesis of constitutional isomers, as well as ¹⁵N-labeling conditions to access isotopically labeled analogues.³

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Oxidative amination by nitrogen atom insertion into carbon-carbon double bonds

Y. Brägger¹, A. K. Paschke^{1*}, N. Nasiri^{1*}, B. B. Botlik^{1*}, F. Felician^{1*}, B. Morandi^{1*}

¹Laboratorium für Organische Chemie, ETH Zürich, Zürich, Switzerland

The synthesis of nitrogen-containing molecules through carbon–nitrogen (C–N) bond formation is critical for the discovery and preparation of medicines, agrochemicals, and materials.¹ Traditional synthetic methods using alkenes as ubiquitous substrates leverage the reactivity of the C(*sp*²)–C(*sp*²) π bond for C–N bond formation.² In contrast, methods that can form C–N bonds through complete cleavage of the double bond are scarce, despite the considerable synthetic potential of such a strategy. Here, we report the direct insertion of a nitrogen atom into unactivated carbon-carbon double bonds to access aza-allenium intermediates, which can be converted either into nitriles or amidine products, depending on the initial alkene substitution pattern.³ This operationally simple and highly functionally compatible reaction works on a wide range of unactivated alkenes. Our mechanistic proposal is supported by chemical trapping experiments, which concomitantly demonstrate the utility of our method to access valuable *N*-heterocycles. Additionally, our method can be used as a general strategy for synthesizing amides and amines, as well as ¹⁵N-labeled molecules. Overall, this study demonstrates the possibility to access reactive nitrogen-containing intermediates (i.e. aza-alleniums), which have ample potential for downstream diversification, from unactivated alkenes, opening new avenues for the discovery and preparation of important products.

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Carboetherification of Cyclopropanes via a Stereoselective Tethering Strategy

D. K. Brownsey¹, A. Schöpfer^{1*}, J. Waser^{1*}

¹Laboratory of Catalysis and Organic Synthesis, EPFL

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

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Deoxygenation of Ketones and α -Ketoesters with a Bimetallic Iridium–Molybdenum Catalyst

M. Ciuoli¹, C. Ehinger^{1*}, B. Berger^{1*}, M. Candrian^{1*}, J. De Jesus Silva^{1*}, C. Copéret^{1*}

¹ETH Zürich, Department of Chemistry and Applied Biosciences

The transformation of ketones into hydrocarbons is a key reaction in organic synthesis,¹ with applications ranging from pharmaceutical production to biomass valorization. Conventional methods such as the Wolff–Kishner and Clemmensen reductions often face limitations related to harsh reaction conditions and the use of stoichiometric, toxic reagents, hindering scalability and sustainability.² In this work, we present a bimetallic Ir–Mo catalyst supported on SiO₂ that enables efficient hydrodeoxygenation (HDO) of ketones using molecular dihydrogen, with water as the only benign byproduct. The catalyst is synthesized by grafting Ir(COD)(DIA) (COD = 1,5-cyclooctadiene; DIA = N,N'-diisopropylacetamidinate)^{3,4} onto a Mo-doped silica surface, followed by reduction under H₂ atmosphere (1 atm) to yield alloyed Ir–Mo nanoparticles (2.0 nm).⁵ This alloyed system exhibits very high selectivity toward the deoxygenation of a broad range of substrates, including acetophenone derivatives, aliphatic ketones, and α -ketoesters. Mechanistic insights from ring-opening of cyclopropyl phenyl ketone and carbonyl–carbon coupling in acetophenone derivatives suggest the involvement of carbon-centered radical intermediates. These findings offer a practical and greener alternative to classical reduction protocols, advancing the toolkit for selective ketone reduction.

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Functionalization and Derivatization of di-aza-di-oxa [8]circulenesA. D'Addio¹, J. Rüger^{1,2*}, M. Pittelkow^{1*}¹Department of Chemistry, ²University of Copenhagen

Circulenes, conjugated cyclic compounds composed of *ortho-annulated* aromatic rings, have been a focus of our research. In the Pittelkow group, we have developed a robust and efficient synthesis of di-aza-di-oxa [8]circulenes. These compounds, synthesized from the economical sound starting material carbazole, exhibit excellent optical properties.

While hetero circulenes have not been widely used as building blocks for more elaborate systems, such as porphyrins. Motivated by potential application of circulene-based materials, our endeavors focus on post-synthetic modification and bottom up approaches for chemical addressable circulenes.

First, results and concepts will be presented.

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UPy-based perylene diimide as supramolecular mechanophores

L. Deng^{1,2}, J. Clough^{1,2*}, C. Weder^{1,2*}

¹Adolphe Merkle Institute, ²University of Fribourg

Mechanical forces, such as tension and compression, are widespread in nature and play a role in the growth and development of living organisms. To probe mechanical forces, molecular force sensors known as mechanophores have been developed, which enable the force to be transduced into an optical readout. Perylene diimides have been reported as mechanophores in linear polymer chains or polymer networks, in response to force by changing excimer-to-monomer fluorescence signals. Through connecting two perylene diimides with a short spacer, the motif folds into a looped structure which allows dominated excimer emission. Upon applying force, the looped structure unfolds and results in a monomer emission, transducing force into a ratiometric fluorescence readout. However, the looped perylene diimides can undergo undesired unfolding when exposed to light, which compromises its specificity as a mechanophore. To address this, a supramolecular motif ureidopyrimidinone is introduced to the looped structure, acting as a molecular clamp to stabilize its configuration and prevent the photo-induced unfolding, thereby ensuring that the looped perylene diimides respond selectively to mechanical force.

Enantiospecific Synthesis of Planar Chiral Rhodium and Iridium Indenyl Complexes

J. Denizot¹, N. Cramer^{1*}

¹Ecole Polytechnique Fédérale de Lausanne (EPFL), Laboratory of Asymmetric Catalysis and Synthesis (LCSA),
1015 Lausanne, Switzerland

Transition-metal catalysts have always been crucial in the development of atom-economical transformation. d⁹-metal indenyl complexes have shown a remarkable reactivity and selectivity in asymmetrical synthesis^[1,2]. However, all the reported synthesis of chiral-Indenyl-metal complexes require the separation of complex diastereoisomers^[3] (in case of additional chiral center) or the use of chiral preparatory HPLC^[1,2] to access the enantiopure metal complex. We present here a method to access enantio-enriched planar-chiral-only Indenyl complexes, through an enantiospecific complexation, avoiding any use of chiral preparative HPLC.

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Design and synthesis of shortwave infrared-absorbing squaraine dyes

E. Didier^{1,2}, J. Csuker^{1*}, J. Ferreira Assunção^{1,3*}, R. Hany^{1*}, M. Bauer^{1*}, F. Nüesch^{1,3*}

¹Empa, Laboratory for Functional Polymers, CH-8600 Dübendorf, ²EPFL, Institute of Chemistry and Chemical Engineering, CH-1015 Lausanne, ³EPFL, Institute of Materials Science and Engineering, CH-1015 Lausanne

The availability of organic dyes for optical sensing and imaging in the infrared wavelength range is essential for advanced applications such as deep-tissue imaging, optical communication or industrial and consumer product identification. 1,3-squaraines have been established as an important class of dyes with strong and narrowband absorption in the near-infrared range up to around 900 nm. Here, we report the design and synthesis of a series of new squaraine dyes with peak absorption extending beyond 1100 nm, which is in the shortwave infrared range. The dye absorption can be modulated by tailoring the donor side chains as well as the central acceptor unit. The acceptor strength of the squaric acid core was increased by its functionalization with dicyano- and rhodanine electron accepting groups. For the side chains, we opted for extended aromatic systems such as benz[cd]indoles and dimethoxydiphenylamine-benz[cd]indoles, resulting in dyes with a pronounced donor-acceptor-donor structure. By considering the case of a dicyano-rhodanine substituted squaraine, we discuss possible limits of the "strong donor – strong acceptor" approach to bathochromically shift the absorption. Recently, we demonstrated the use of such dyes in high-performance infrared organic photodetectors.

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Solution NMR investigation of cyclic peptide inhibitors of *S. aureus* phosphoglycerate mutase

L. Glazer¹, E. Yanagi^{2*}, H. Suga^{2*}, S. Riniker^{1*}, M. Ebert^{3*}

¹Department of Chemistry and Applied Biosciences, ETH Zürich, Vladimir-Prelog-Weg 2, Zürich 8093, Switzerland, ²Department of Chemistry, Graduate School of Science, The University of Tokyo, Bunkyo, Tokyo 113-0033, Japan, ³Laboratory of Organic Chemistry, Department of Chemistry and Applied Biosciences, ETH Zürich, Vladimir-Prelog-Weg 3, Zürich 8093, Switzerland

In recent years, peptides have attracted a lot of attention in the field of drug design as an alternative to conventional small-molecule inhibitors [1]. Particularly interesting in this context are cyclic peptides. Their restricted conformational flexibility supports functional group preorganisation and reduces the entropic cost of binding. Furthermore, they show higher activity, proteolytic stability and permeability compared to their linear counterparts [2]. Cyclic peptides also show great potential as new antibiotics against multidrug resistant bacteria. Sa-D3 is a novel macrocyclic inhibitor of *S. aureus* phosphoglycerate mutase (iPGM), found using the random nonstandard peptides integrated discovery (RaPID) system [3]. Even though Sa-D3 is a potent inhibitor for *S. aureus* iPGM, it shows poor passive membrane permeability, which limits its potential as an antibiotic lead compound.

As a first step towards the rational design of a second generation iPGM inhibitor with improved membrane permeability, we have investigated the solution conformation of Sa-D3 and two variants by NMR spectroscopy in methanol and water. We compared the three peptides by analyzing chemical shifts, nuclear Overhauser effect, J-couplings, amide temperature coefficients and exchange rates. NOEs were also converted to distance restraints for structure calculations with the CYANA program package [4].

Figure 1. Structure of Sa-D3 and its key interactions with iPGM (blue). N-methylation of serine circled in pink, repelling interaction marked in red, H-bonding in black dashes, ionic interactions in green dashes and aromatic interaction in blue dashes.

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Engineering Flipper Probes for Enhanced Membrane Anchoring via Peptide and Lipid Modifications

N. Gonzalez Sanchis¹, S. Saidjalolov^{1*}, F. Bayard^{1*}, N. Sakai^{1*}, S. Matile^{1*}

¹Department of Organic Chemistry, University of Geneva, Geneva, Switzerland

Understanding the physicochemical properties of the cell membrane is essential, as it plays a central role in numerous cellular processes. To investigate these dynamics, our group has developed a class of fluorescent probes—termed “Flippers”—that function in live cells to report on membrane mechanical forces. These probes are based on a pushpull chromophore system, formed by coupling electron-rich and electron-deficient aromatic units. Under membrane tension, planarization of the chromophore enhances conjugation, resulting in a fluorescence response. Previous work has demonstrated that modifying the donor and acceptor groups can fine-tune probe properties and broaden their applicability.

This study introduces a new generation of Flipper probes functionalized with a glutamic acid-rich peptide and a palmitoyl chain to enhance membrane interaction and localization. The negatively charged glutamic acid moiety serves as a hydrophilic head group, promoting interaction with the membrane interface and influencing the orientation of the probe. The palmitoyl chain acts as a hydrophobic anchor, facilitating stable insertion into the lipid bilayer.

To evaluate the impact of peptide length on membrane behavior, we synthesized and compared Flipper variants bearing glutamic acid-containing sequences of 4, 8, and 16 amino acids. This systematic approach allowed us to investigate how head group size and charge density affect anchoring efficiency, localization, and probe performance in live-cell environments.

Breaking the Resolution Limits: Photouncaging on a Single-Molecule LevelK. Hanc¹, P. Rivera-Fuentes^{1*}, P. Stacko^{1*}¹Department of Chemistry, University of Zurich

The study develops dual-stage photocages (SNAPcages) that can be activated by tissue penetrating near-infrared (NIR) light to release the payload only in the presence of specific biomolecules, offering unprecedented control and precision over the uncaging process.

An additional layer of control over photouncaging is incorporated by integrating photocages with site-specific targeting via SNAP-tag proteins in living cells. In strong contrast to conventional photocages that rely solely on light as a stimulus - limiting spatial resolution to the diffraction limit - **SNAPcages** are activated by NIR light only in the presence of specific biomolecular targets. This novel approach enhances spatial precision beyond the current state-of-the-art, enabling targeted uncaging at the subcellular to single-molecule level. The concept is based on a recently introduced fluorogenic system, the utility of which has been shown on a series of polymethine dyes.^[1]

The **SNAPcages** are designed around a Cy7 photocage scaffold containing a drug-like payload attached in the C4' position of the central chain. **Contrary to all the previous photocages pursued in our group,^[2-4] the design herein relies on desymmetrized cyanines that contain two different terminal heterocycles.**

In their native state, the **SNAPcages** are photochemically inactive because of the intramolecular cyclization of the sidechain (red) which disrupts the conjugation of the cyanine chromophore. Upon specific binding of SNAP-ligand (green) to its target (brown), the polarity of the immediate environment surrounding the **SNAPcage** will change, triggering the ring-opening on the heterocycle site and restoring the absorption of Cy7. This will arm the **SNAPcage** for a subsequent activation with light and uncaging of the payload (purple). This arming process induced by specific intracellular targets will provide an additional layer of spatiotemporal control of the uncaging, overcoming the resolution limits imposed by the diffraction limits of light.

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Mechanochemical functionalization of in situ generated N-aryl and N-acyl pyridinium saltsV. Iaroshenko¹¹Faculty of Natural Sciences, Matej Bel University, Tajovského 40, 97401, Banská Bystrica, Slovakia

The conversion of the primary aromatic amine [C(sp²)-NH₂] and amide [CO(sp²)-NH₂] groups into functional derivatives is a complicated task due to the low heterolytic nucleofugality of the corresponding functional groups (C₆H₅-NH₂, BDE of 102.6 kcal/mol⁻¹; C₆H₅-CO-NH₂, BDE of 96.4 kcal/mol⁻¹).

Continuing our ongoing research on the late-stage functionalization of complex organic molecules under mechanochemical conditions [1,2], herein, we report several practical protocols that permit a straightforward functionalization of in *situ* generated N-aryl and N-acyl pyridinium salts via catalytic and catalyst-free C-N bond cleavage pathways under mechanochemical conditions [3-7]. Namely. We devised sustainable approaches for the mechanochemical synthesis of trifluoromethyl and trifluoromethoxy arenes following two synthetic tactics: (1) Via catalyst-free substitution of a pyridinium moiety; (2) via Ru-catalyzed decarbonylative cross coupling of primary amides, using appropriate nucleophilic sources of CF₃ or OCF₃ moieties. Furthermore, a new method has been introduced that is able to tackle the complexities of N-C(O) bond activation in amide moieties through utilization of pyrylium tetrafluoroborate in a mechanochemical setting, where amide bonds undergo activation and subsequent conversion to biaryl ketones. In several cases the reaction mechanisms were studied by the DFT.

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Shape-assisted assemblies in solution

N. C. Jansen¹, R. Jamange^{1*}, K. Zhang^{1*}, L. Sturm^{1*}, M. Rickhaus^{1*}

¹University of Genève, Genève, Switzerland.

In a typical supramolecular polymer, a flat and rigid core is decorated with suitable tails. While this design has led to fascinating polymers, the core itself is free to rotate and to slip over other cores. To restrict this freedom, shape can be employed. A molecule with a negative curvature is significantly limited in translational and rotational freedom. Our group utilized this shape to generate 1D fibers and 2D sheets on surface while only weak and non-directional interactions were present. The weak interactions are Van der Waals, dipole-dipole and π - π interactions that govern these assemblies. 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.

Figure 1. Left: Shape as design principle to restrict rotational and translational freedom. Right: general structure of carpyrindines.

Therefore, stronger binding units are needed. Yet, it is desired that the assembly process is governed by the shape of the monomers and not the binding units. Thus, different chains were investigated for the monomer, to observe when shape governs the assemblies in solution and on surface.

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Organocatalytic Addition Reactions of Methoxythiomalonates to NitroolefinsF. Kölblin¹, F. Stocker^{1*}, H. Wennemers^{1*}¹ETH Zürich, D-CHAB, LOC

The Wennemers group has developed stereoselective, organocatalytic addition reactions that use malonic acid-derived thioesters. These thioacetate equivalents react in the presence of catalytic amounts of cinchona alkaloid derivatives with different electrophiles, including aldehydes, nitroolefins, and imines. [1]

This type of addition reactions is inspired by the polyketide synthase which utilizes malonyl CoA as activated acetate building block. The polyketide synthase can also accommodate alpha-substituted Malonic acid half-thioesters such as the methoxymalonyl extender unit to introduce methoxy groups into polyketides. [2]

Herein, we present the enantioselective addition of Methoxy thiomalonates to nitroolefins. We screened various organocatalysts and found optimal conditions using a thiourea catalyst. The reaction proceeds in the presence of this chiral hydrogen-bond donor catalysts to yield the addition product with high stereoselectivity (>90% ee) and very good diastereoselectivity (d.r. >15:1).

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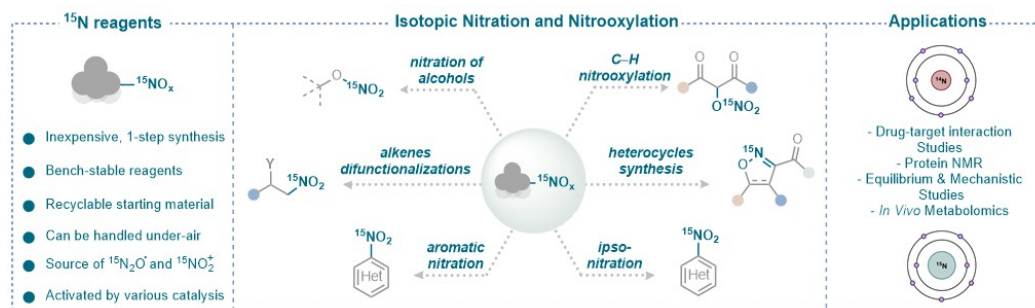
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Nitration and nitrooxylation using ^{15}N labeled reagentsH. Lecomte¹, L. Condrau^{1*}, A. J. Fernandes^{1*}, D. Katayev^{1*}¹University of Bern, Freiestrasse 3, 3012 Bern, Switzerland

The use of stable radioisotopes in organic molecules plays a critical role in advancing a range of scientific fields, from the fundamental understanding of reaction mechanisms to the development of drugs and agrochemicals. These isotopically labeled compounds are indispensable at key stages of the development pipeline, from the determination of molecular structure to the realization of comprehensive pharmacological studies, including absorption, distribution, metabolism, excretion, and toxicology studies (ADMET).^[1] Notably, more than 40% of the new drugs approved by the Food & Drug Administration in 2015 bear amines, while this number was only 20% in 2005.^[2] The nitro group is a key motif in pharmaceuticals and materials, and serves as a valuable functional handle that can be easily converted into amines.

However, ^{15}N -labeled variants remain confined mainly to classical electrophilic nitration, which often suffers from harsh conditions and limited applications. Although the direct addition of nitril radicals has recently emerged as a powerful strategy, the lack of accessible $^{15}\text{N}\text{O}$ radical reagents limits the development of isotopic compounds via radical pathways. Therefore, developing reagents that enable efficient and selective incorporation of $^{15}\text{N}\text{O}$ via radical or electrophilic pathways is highly desirable for synthetic and broader interdisciplinary applications.

Over the years, our group has introduced a novel class of bench-stable nitrating reagents capable of transferring nitro (NO_2) and nitrate (NO_3) groups under mild, sustainable, and catalytic conditions.^[3] Herein, we present the synthesis of ^{15}N -labeled analogues reagents using potassium nitrate (K^{15}NO_3) as a safer and greener alternative to nitric acid. These reagents were successfully applied in diverse transformations, including aromatic nitration, ipso-nitration, alkene difunctionalizations, nitration of alcohols, C–H nitrooxylation, and heterocycle synthesis. The resulting $^{15}\text{NO}_2$, $^{15}\text{NO}_3$, and $^{15}\text{NH}_2$ -containing compounds hold great promise for tracer studies, mechanistic investigations, and the development of labeled pharmaceuticals.



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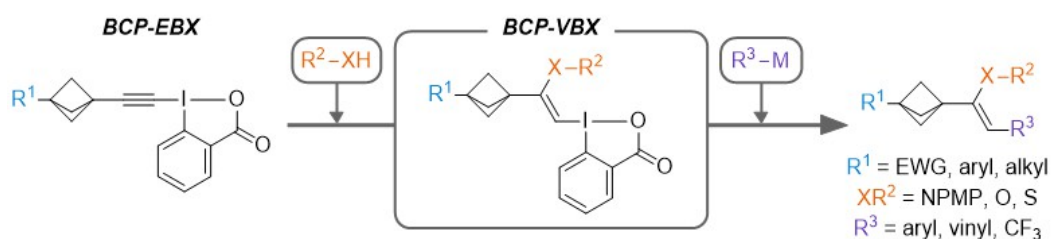
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Synthesis of Bicyclo[1.1.1]pentane Z-Substituted Enamides, Enol Ethers, and Vinyl Sulfides Using Iodine (III) Reagents

N. Lee¹, J. Dechent^{1*}, E. Grinhagena^{1*}, J. Waser^{1*}

¹Laboratory of Catalysis and Organic Synthesis, ISIC, École Polytechnique Fédérale de Lausanne

Bicyclo[1.1.1]pentanes (BCPs) are well-studied bioisosteres for *para*-substituted benzene rings and numerous methods for synthesizing 1,3-difunctionalized BCPs have been developed. However, synthetic approaches to access vinyl BCP motifs remain limited, with only few reports on the synthesis of BCP-olefins bearing heteroatom substituents. Herein, we present the synthesis of BCP-substituted enamides, enol ethers, and vinyl sulfides through the sequential functionalization of ethynylbenziodoxolone (EBX) reagents containing a BCP scaffold.^[1] Stereoselective addition of a nucleophile generates heteroatomic Z-vinylbenziodoxolone (VBX) reagents. The hypervalent iodine substituent of the VBX reagents serves then as a versatile platform for further arylation, vinylation, and trifluoromethylation. This method provides a modular synthesis of previously inaccessible heteroatom-substituted vinyl BCPs.



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Azulene-incorporated 1,3,6,8-Tetraazapyrene derivatives for Optical pH Sensors

X. Liu¹, U. Aschauer^{2*}, S. Decurtins^{1*}, R. Häner^{1*}, S. Liu^{1*}

¹Department of Chemistry, Biochemistry and Pharmaceutical Sciences W. Inäbnit Laboratory for Molecular Quantum Materials and WSS-Research Center for Molecular Quantum Systems, University of Bern, ²Department of Chemistry and Physics of Materials, University of Salzburg

Polycyclic aromatic hydrocarbons (PAHs) are promising materials for controlling charge-transfer pathways within molecular components, rendering them appealing in high-performance organic electronics. Azulene, a non-benzenoid isomer of naphthalene characterized by an electron-rich five-membered ring and an electron-deficient seven-membered ring, exhibits distinctive acid-base responsiveness, making it especially effective in sensor applications.¹ Tetraazapyrene (TAP) can act as a p-electron acceptor in the large conjugated systems.^{2 3} Herein, a series of azulene-TAP conjugates have been synthesized successfully (see Figure 1), showing that their HOMO-LUMO gaps can be tuned by changing the connectivity between these two units. Importantly, all of them exhibit reversible colorimetric pH-response behavior. The electronic properties of the resulting donor-acceptor ensembles are described in detail.

Figure 1: Three Azulene-TAP conjugates showing reversible pH responsiveness.

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Total Synthesis of an Oxidized and Rearranged ent-Kaurenoid

T. Martini¹, J. Muschietti^{1*}, N. Saab^{1*}, E. M. Carreira^{1*}

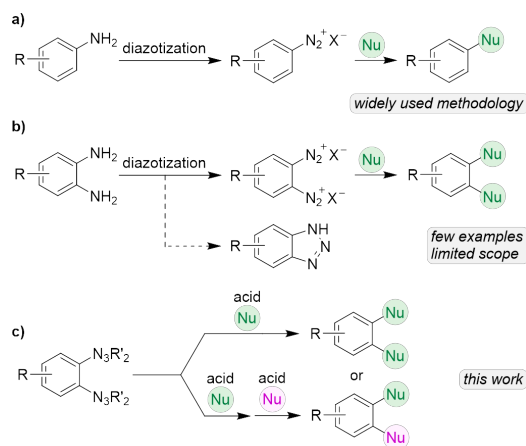
¹Department of Chemistry and Applied Biosciences, Laboratory of Organic Chemistry ETH Zürich Vladimir-Prelog-Weg 3, 8093 Zürich, Switzerland

Ent-kaurene diterpenoids constitute a broad family of bioactive natural products. Fragmentation, rearrangement and oxidation of the parent *ent*-kaurene carboskeleton lead to unique scaffolds that pose considerable synthetic challenges. Herein, we present the total synthesis of a rearranged and highly oxidized member of this family. Notably, this highly functionalized natural product features numerous difficult to access stereocenters and an unprecedented tricyclic ring system. Pivotal for the success of the synthesis were a novel nitrile oxide dipolar cycloaddition to gain rapid entry to an oxidized bicyclo[4.3.1]decane and an unconventional bridgehead propargylation. The latter sets the key quaternary stereocenter concomitant with side-chain installation for a subsequent cycloalkenylation, enabling access to the full carbocyclic framework of the target.

Vicinal Difunctionalization Reactions of Densely Substituted Arenes Via 1,2-Bis-Triazenylarenes

C. Mathew¹, K. Severin^{1*}¹Institut des Sciences et Ingénierie Chimiques, Ecole Polytechnique Fédérale de Lausanne (EPFL) Av. F.-A. Forel 2, 1015 Lausanne, Switzerland

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



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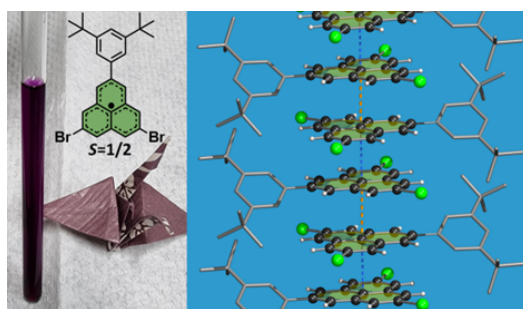
Construction of Multi-Spin Systems with Halogenated Phenalenyl Radicals

M. Metzelaars^{1,2}, T. Kozuma^{2*}, T. Nishiuchi^{2*}, B. Ebel^{3*}, P. Kögerler^{3*}, T. Kubo^{2*}, M. Juriček^{1*}

¹Department of Chemistry, University of Zurich, 8057 Zurich, Switzerland, ²Department of Chemistry, Graduate School of Science, Osaka University, Toyonaka, Osaka 560-0043, Japan, ³Institute of Inorganic Chemistry, RWTH Aachen University, 52074 Aachen, Germany

The precise engineering and manipulation of (electron) 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.^{1,2} The reasonable stability in tandem with its fundamental π -magnetism (spin- $1/2$) 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.^{3,4}

In this contribution, I present the syntheses of functionalized, phenalenyl-based radicals that serve as building blocks for the in-solution and on-surface construction of polyradicals and for the supramolecular design of single-component organic conductors. Special emphasis is put on the characterization of novel halogenated phenalenyl radicals that exhibit decent stability under air in solution and form linear spin- $1/2$ chains in the solid state with a short interplanar distance of 3.024 Å. Furthermore, these halogenated radicals may serve as precursors for on-surface coupling to create spin- $1/2$ chains and rings of varying length.



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Olefination of Activated Alkyl Halides with Phosphonium Salts

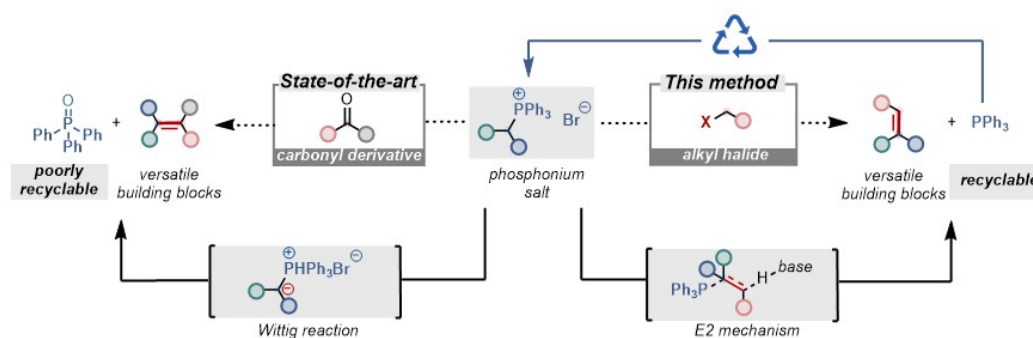
A. Neves Vieira¹, S. Roediger^{1*}, C. L. Brudy^{1*}, M. Trabesinger^{1*}, J. Hübscher^{1*}, B. Morandi^{1*}¹Laboratorium für Organische Chemie, ETH Zürich, 8093 Zürich

Olefins are among the most versatile functional groups in organic synthesis, thanks to their broad potential for functionalization.¹ A key method for olefin construction is the Wittig reaction. However, this classic approach generates triphenylphosphine oxide as a byproduct, which, in catalytic versions, generates a stoichiometric silane waste upon recycling.^{2,3}

To circumvent the production of poorly recyclable oxide, we envisioned a straightforward approach relying on a base to promote the elimination of triphenylphosphine. Our method enables selective *trans*-olefin synthesis from phosphonium salts and activated alkyl halides under mild conditions.

The substrate scope of olefination showed that phosphonium salts with variable cyclic chains, protected amines, as well as linear chains containing aryl bromide or ether, were tolerated. Furthermore, heteroaryl and alkynyl moieties were successfully employed as activated electrophilic partners. This reaction was shown to form *E*-olefin selectively in good to excellent yield and was applicable to large-scale synthesis with a comparable yield to the preparative reaction.

Quantitative ³¹P NMR analysis showed that the overall recycling efficiency of triphenylphosphine could reach up to 76%, offering a good way to avoid triphenylphosphine oxide recycling from the Wittig olefination.



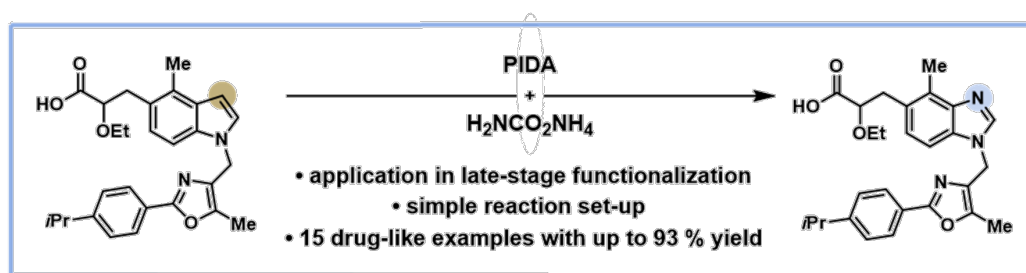
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Carbon-to-Nitrogen Atom Swap Enables Direct Access to Benzimidazoles from Drug-Like IndolesA. K. Paschke¹, Y. Brägger^{1*}, B. B. Botlik^{1*}, E. Staudinger^{1*}, O. Green^{1*}, B. Morandi^{1*}¹ETH Zürich, Vladimir-Prelog-Weg 3, HCI, 8093 Zürich, Switzerland

The ability to selectively edit organic molecules at the atomic level has the potential to streamline lead discovery and optimization in the pharmaceutical and agrochemical industry.^{1,2} While numerous atom insertion and deletion reactions have recently been reported,³ examples of single atom swaps remain scarce due to the challenge of orchestrating the selective cleavage and formation of multiple chemical bonds around the same atom. We report a method for the carbon-to-nitrogen atom swap in N-alkyl indoles, allowing for their direct conversion to the corresponding benzimidazoles.⁴ The reaction leverages the innate reactivity of the indole scaffold to engage in an initial oxidative cleavage step, followed by oxidative amination, Hofmann-type rearrangement and cyclization. This complex sequence of steps is mediated by the simple combination of commercially available PIDA and ammonium carbamate as nitrogen atom source. The reaction tolerates a wide range of functional groups which is demonstrated by the interconversion of 15 drug-like molecules implying its immediate applicability across a wide range of discovery programs. Furthermore, it shows how leveraging the innate reactivity of a common heterocycle can unlock otherwise challenging skeletal editing reactions.



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Illuminating Biology with Molecular Photoswitches

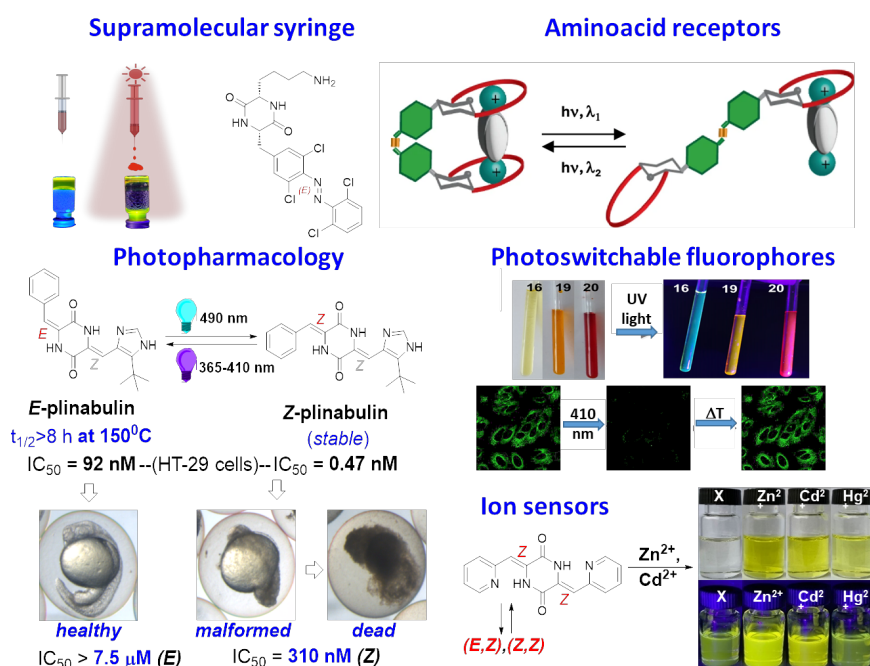
Z. Pianowski¹, P. Gödtel^{2*}, A. Seliwjorstow^{2*}, V. Schäfer^{2*}

¹Institute of Biological and Chemical Systems – FMS, KIT Karlsruhe, ²Institute of Organic Chemistry, KIT Karlsruhe

Molecular photoswitches convert the energy of light into reversible changes of geometry and polarity, which may result in bioactivity changes or macroscopic effects in materials.[1]

We have introduced azobenzene-based biocompatible supramolecular hydrogels triggered with visible light,[2] and aminoacid receptors[3] – all operational in water or aqueous buffers.

We also discovered a novel class of peptide-derived molecular photoswitches – hemipiperazines.[4] One of them – plinabulin (a low-nM antimetabolic agent) – undergoes activity photomodulation *in vitro* by two orders of magnitude,[4] and can be used to photocontrol development of zebrafish embryos.[5] Other hemipiperazines [6] can be used as photochromic metal ion sensors,[7] and photoswitchable fluorophores.[4,8]



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Stem Cell-Compatible PEG Hydrogels Using KAT Ligation

M. Piras¹, S. Ponta^{2*}, P. Fisch^{2*}, K. Maniura^{3*}, J. W. Bode^{1*}

¹Laboratory of Organic Chemistry, Department of Chemistry and Applied Biosciences, ETH Zürich, 8093 Zürich, Switzerland, ²Tissue Engineering and Biofabrication Laboratory, Department of Health Sciences and Technology, ETH Zürich, 8093 Zürich, Switzerland, ³Empa, Swiss Federal Laboratories for Materials Science and Technology, Laboratory for Biointerfaces, Lerchenfeldstrasse 5, St. Gallen, 9014, Switzerland

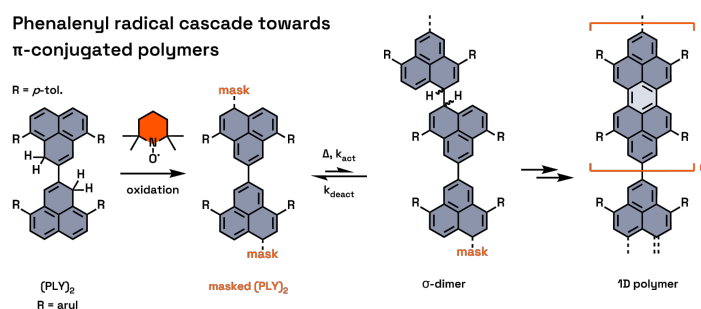
The rapid, self-assembly of covalently crosslinked hydrogels enables cellular behavior to be studied extraneously whilst preserving viability.¹ Amide-bond forming ligations between polyethylene glycol (PEG) chains functionalized with potassium acyltrifluoroborates (KAT) and hydroxylamines deliver biocompatible hydrogels under acidic conditions suitable for the encapsulation of robust cell lines.² Expanding the versatility of this system to the encapsulation of more delicate, stromal cells was impeded by the long gelation times required by the macromers at physiological pH.² Modifying the KAT reaction partner to a recently-discovered, quinolinium acyltrifluoroborate (QAT) functionality overcame this limitation and produced hMSC-compatible PEG hydrogels in under two minutes at pH 7.4. Further, the spontaneous nature of KAT ligation allowed for the facile incorporation of a cyclic RGD cell adhesion peptide functionalized with a QAT moiety. The cytocompatibility of these hydrogels gels was reflected in the high viability after one week (> 70 %), illustrating the benign nature of PEG-derived KAT hydrogels and extrapolating their use to the field of tissue engineering and regenerative medicine.

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Phenalenyl π -Radical Cascade Reactions for the Synthesis of Novel π -Conjugated PolymersN. F. Rychener¹, P. Čmelová^{1*}, M. Juríček^{1*}¹Department of Chemistry, University of Zurich, Winterthurerstrasse 190, Zurich 8057, Switzerland

Graphene-based nanomaterials (GNMs) and π -conjugated polymers are highly sought-after next-generation materials, valued for their electrical and thermal conductivity^[1] with a wide range of applications in molecular electronics,^[2] organic electrochemical transistor (OECTs),^[3] and energy storage.^[4] However, designing and synthesizing these materials remains challenging, as traditional bottom-up and top-down approaches often face significant limitations regarding scale, cost, quality, processability, reproducibility and safety.^[5] Exploring π -radical cascade reactivities of polyaromatic hydrocarbons (PAH) as building blocks offers a promising alternative pathway towards conjugated one-dimensional (1D) polymers. Phenalenyl (PLY) is the smallest polycyclic odd alternant hydrocarbon found in graphene sheets. Utilizing its proneness for self-dimerization to peropyrene (PP) represents an intriguing opportunity to be used as a novel synthetic tool that challenges conventional strategies applied in the synthesis of novel conductive materials. In nitroxide-mediated radical polymerization, thermal regulation of the dormant-active equilibrium ($k_{\text{deact}} \gg k_{\text{act}}$) between alkoxyamine-masked PLY (dormant) and σ -dimer (active) species is central in controlling radical polymerizations.^[6] Preliminary kinetic investigations on the PLY–PP radical cascade with TEMPO have validated the selective formation of PP in a highly selective manner. Nitroxide-mediated PLY–PP radical cascade reactivity, when applied to the phenalenyl homodimer (PLY) $\square$ tetrasubstituted with bulky aryl groups, kinetically suppresses undesired α -position reactivities and promises the controlled growth of 1D oligomers (Scheme 1).



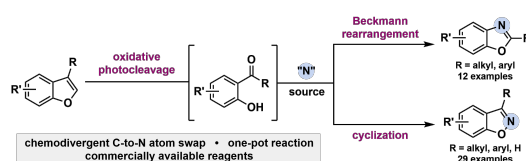
The resulting oligomers will undergo physical characterization. Upon further validation, efforts will shift toward optimizing polymerization conditions to control polymer length and polydispersity. Iterative synthesis using key precursors and variable spacers will enable tuning material properties such as the electronic structure, torsion angle and helicity. Insights gained here may spark future development of extended 2D to 3D GNMs and polymeric networks.

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Chemodivergent C-to-N atom swap from benzofurans to benzisoxazoles and benzoxazoles

S. Schiele¹, A. K. Paschke^{1*}, C. Pinard^{1*}, F. Sandrini^{1*}, B. Morandi^{1*}¹Laboratorium für Organische Chemie, ETH Zürich, Vladimir-Prelog-Weg 3, HCI, 8093 Zürich, Switzerland

Facile derivatization of biologically active compounds without prefunctionalization expands the chemical space and accelerates the discovery of new molecules. Atom swap reactions have recently emerged as powerful molecular editing tools,^[1-3] yet such reactions remain rare. Herein, we describe a convenient, chemodivergent protocol to perform a net C-to-N atom swap in benzofurans, affording benzoxazoles or benzisoxazoles *via* a cascade of oxidative cleavage, oxime formation, and cyclization using commercially available reagents. Given the user-friendly nature and broad range of tolerated functional groups, we believe that this reaction will find immediate utility in both academic and industrial settings.



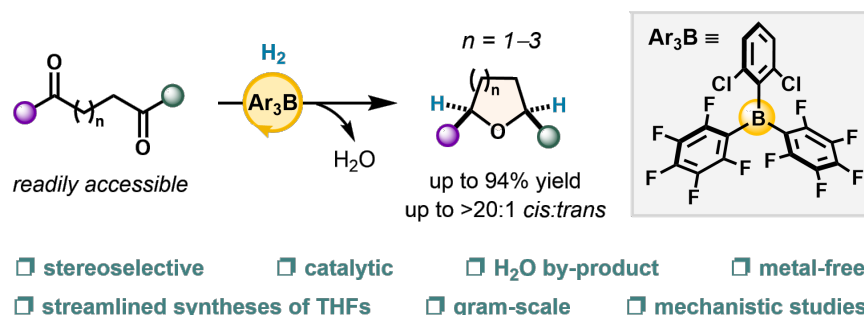
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Borane-catalyzed stereoselective synthesis of cyclic ethers via reductive cycloetherification of diketonesN. V. Shcherbakov¹, N. Potin^{1*}, J. Mas-Roselló^{1*}¹Laboratorium für Organische Chemie, D-CHAB, ETH Zürich, Vladimir-Prelog-Weg 1-5/10, Zürich, 8093, Switzerland

Cyclic ethers, particularly α,α' -disubstituted tetrahydrofurans (THFs) and tetrahydropyrans (THPs), are prevalent motifs in natural products and pharmaceuticals.¹ However, efficient catalytic stereoselective methods for their synthesis are limited, often requiring precious transition-metal catalysts² or pre-functionalized substrates.³ Herein, we report a direct metal-free catalytic approach to *cis*-2,5- and *cis*-2,6-disubstituted THFs and THPs *via* reductive cycloetherification of readily available 1,4- and 1,5-diketones.⁴



This transformation is enabled by a simple triarylborane catalyst and employs molecular hydrogen as the reductant, producing water as the sole byproduct. A broad range of products was obtained in high yields (up to 94%) and with high *cis*-selectivity (up to >20:1 dr). The method was applied to the concise synthesis of pharmaceutically relevant THFs — offering shorter routes with improved yields compared to prior methods — and was scalable to gram quantities. Mechanistic studies support oxocarbenium ion reduction as the stereodetermining step. DFT calculations suggest that favorable non-covalent interactions between the catalyst and the substrate underpin the observed *cis*-diastereoselectivity. This work introduces a new strategy for hydrogenative cyclization and provides a blueprint for the efficient, sustainable synthesis of stereodefined heterocycles.

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CpX-Ir^{III}-Enabled Streamlined Access to Highly Efficient Chiral Monophosphorus Ligands Towards Generality-Oriented Asymmetric Catalysis

V. Smal¹, A. Vorobei^{1*}, D. Maye^{1*}, N. Cramer^{1*}

¹Laboratory of Asymmetric Catalysis and Synthesis, Institute of Chemical Sciences and Engineering, Ecole Polytechnique Fédérale de Lausanne (EPFL), 1015 Lausanne, Switzerland

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 state-of-the-art synthetic strategies towards typical privileged chiral monophosphines are often plagued 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 Cp^X-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 (>40 entries) of chiral monophosphines. The new ligand class demonstrated high efficiency in two distinct catalytic applications, namely in a challenging Au-catalyzed 1,6-enyne cyclisation⁴ and Pd-catalyzed arylative phenol dearomatization.^{5,6}

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Ligand-Enabled, Atroposelective Direct C – H Arylation of Thiazole N-OxidesV. Smal¹, N. Cramer^{1*}

¹Laboratory of Asymmetric Catalysis and Synthesis, Institute of Chemical Sciences and Engineering, Ecole Polytechnique Fédérale de Lausanne (EPFL), 1015 Lausanne, Switzerland

Our group has a long-standing interest in enantioselective C – H activation,¹ including atroposelective reactions of the sort. In this context, we more recently published a report on atroposelective arylation with 1,2,3-triazoles and several activated pyrazole derivatives.² However, the enantioselective synthesis of corresponding 1,3-azoles using the same strategy remained elusive, due to the limited thermal stability of the chiral axis of 1,3-azoles combined with a necessary high reaction temperature.³

We then reasoned, by exploiting Fagnou's approach to using the activated N-oxide variants of heterocycle substrates,⁴ our group's heteroaryl cross-coupling protocol could be modified to achieve high efficiency and atroposelectivity for 1,3-azole (N-oxide) substrates. After multiple rounds of screening and optimization, we achieved high yield and enantioselectivity on thiazole N-oxides as model substrates using a ligand from our library that incorporated several elements of chirality. With the best conditions in hand, we prepared a substrate scope (21 entries total), in generally high yield and good enantioselectivities. Moreover, the reaction is proven to be scalable and the corresponding atropoisomeric N-oxides are amenable to downstream derivatization.⁵

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Design and Relaxivity Modulation of Gd³⁺ MRI Probes Responsive to ¹O₂

S. Staudhammer¹, H. Yoshihara^{2*}, A. Bornet^{3*}, Y. Yamakoshi^{1*}

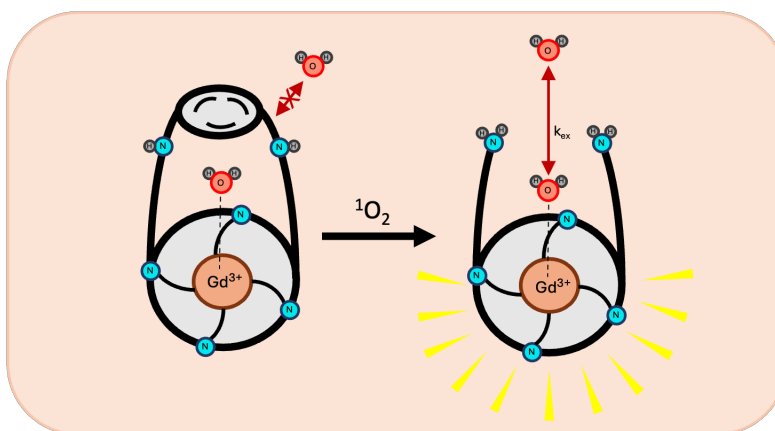
¹Laboratory of Inorganic Chemistry, Department of Chemistry and Applied Biosciences, ETH Zürich, Zürich, Switzerland,

²Institute for Biomedical Engineering, Department of Information Technology and Electrical Engineering, ETH Zurich,

Zurich, Switzerland, ³Institut des Sciences et Ingénierie Chimiques, Ecole Polytechnique Fédérale de Lausanne (EPFL), Lausanne, Switzerland

Photodynamic therapy (PDT), commonly used to treat diseases including cancer and atherosclerosis, involves the injection of a photosensitizer—such as a porphyrin or a fullerene—which ideally distributes throughout the body, including in diseased tissue.[1] After light irradiation, the photosensitizer generates reactive oxygen species (ROSs) most often through a Type II mechanism to produce singlet oxygen (¹O₂), which then destroys malignant cells.[1] Although a variety of techniques—often involving fluorescence sensors—exist for detecting ¹O₂, real-time *in vivo* detection remains limited.

In this study, we report the synthesis of three ¹O₂-responsive MRI contrast agents, ideally designed to monitor the production of ¹O₂ produced by PDT *in vivo*. As previous work in our group has demonstrated the ability of ¹O₂ generated by fullerenes to oxidize secondary benzylamines, we developed and synthesized a series of gadolinium-based contrast agent (GBCA) featuring cleavable aromatic moieties based on this reaction.[2] Upon exposure to ¹O₂, the synthesized probes undergo a transformation that ideally enhances T₁-weighted MRI contrast. To achieve signal amplification with activatable GBCAs, we can modulate key parameters such as the number of water molecules coordinated to the Gd³⁺ ion (*q*-modulation) or the rate of water exchange (*k_{ex}*). Ideally, optimization of the relaxation rate (*r*₁) will be maximized in the open form and minimized in the closed form, improving *in vivo* imaging contrast. By altering the aromatic moiety on our probe, we have demonstrated a 23% increase in *r*₁ in our activated form.



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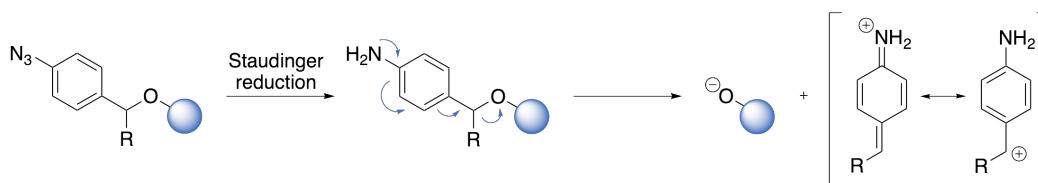
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Substitution Effects on Benzylic Ether Self-immolative Linkers – A General Alcohol Caging Method

M. Stopinšek¹, M. Deen^{1*}, A. Nardelli^{1*}, H. Wennemers^{1*}¹Laboratory of Organic Chemistry, ETH Zürich, Vladimir-Prelog-Weg 3, 8093 Zürich, Switzerland

Self-immolative linkers allow for the controlled and tunable release of functional molecules and are attractive for drug delivery, prodrug design, sensing, and material sciences. For the efficient and fast release of phenols and alcohols, carbonate, ester, acetal, or carbamate linkages are commonly employed. However, these linkages are susceptible to hydrolysis, leading to unwanted background release.^[1] Ethers are hydrolytically stable alternatives, but their use is currently limited to the release of acidic phenols under neutral aqueous conditions. By increasing the electron density on the aromatic core with electron-donating substituents, a shorter immolation half-life has been achieved and the release of poorer leaving groups in both aqueous and organic solutions.^[2]

We investigated how substituents at benzylic ether-based self-immolative linkers influence the release rate of aromatic and aliphatic alcohols. Staudinger reduction of aryl azide-based linkers to anilines triggers the spontaneous 1,6-elimination,^[3] leading to the release of the payload via the azaquinone methide intermediate.^[3] We hypothesized that electron-donating substituents would accelerate the release by stabilizing the partial positive charge of the transition state. We will present the results of kinetic studies that systematically investigated how electron-withdrawing and -donating substituents at the benzylic position affect the stability of the linkers and the release rates of various alcohols in both aqueous and organic solutions. This work offers an alternative for enhancing the release kinetics of alcohol-containing payloads from hydrolytically stable self-immolative systems.



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

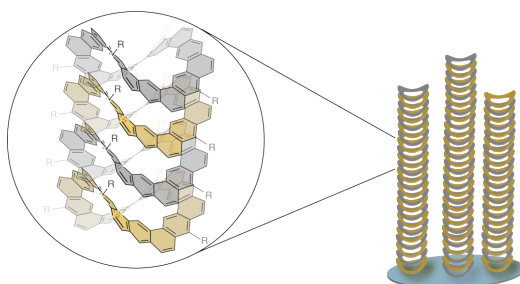
L. Sturm¹, S. F. Vaudano^{1*}, M. Rickhaus^{1*}

¹University of Geveva, Geveva, Switzerland

At the Rickhaus lab, we firmly believe that "shape matters." Our research focuses on the self-assembly of negatively curved macrocycles. Since our first study in 2022 on the self-assembly of carpyridine macrocycles^[1], structures that can self-assemble due to their shape, these uniquely curved molecules have become central to several of our research projects.

We are currently exploring ways to synthesize negatively curved macrocycles with a more extended π -system, such as octulene. We are excited by the possibility that these structures could exhibit enthalpy-driven self-assembly, strengthening their organization into one-dimensional (1D) supramolecular columns.

Additionally, we are investigating how lateral chain decoration around the macrocycles can promote the further assembly of 1D columns into supramolecular materials.



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Fluorescent Probes for Small Molecule Metabolite and Metal Ion SensingE. Su¹, C. Yang^{2*}, J. Gao^{2*}, C. J. Chang^{2*}¹ETH Zürich, ²Princeton University

We developed two sensing strategies exploiting activity- and binding-based mechanisms for live-cell imaging. Both employ modular designs that allow targeted adjustment of recognition chemistry and optical response, forming the basis for ongoing studies toward selective imaging in live-cell systems.

The first project focuses on activity-based sensing of ammonia, a key metabolite in nitrogen homeostasis whose dysregulation is linked to liver disease, cancer metabolism, and gut-brain axis signaling. [1] Small-molecule probes bearing reactive ammonia-sensing warheads are conjugated to bright scaffolds such as BODIPY or rhodol. These undergo reversible covalent transformation with ammonia, producing turn-on responses. Structure- property optimization efforts are aimed at improving brightness and selectivity, with DFT/TD-DFT calculations guiding the design toward favorable emission properties.

The second project applies a binding-based sensing approach to Mn(II) detection. BAPTA-derived scaffolds were systematically re-engineered through heteroaromatic donor substitution, ligand basicity tuning, shifting selectivity from Ca(II) toward Mn(II) and enabling selective fluorescence imaging.

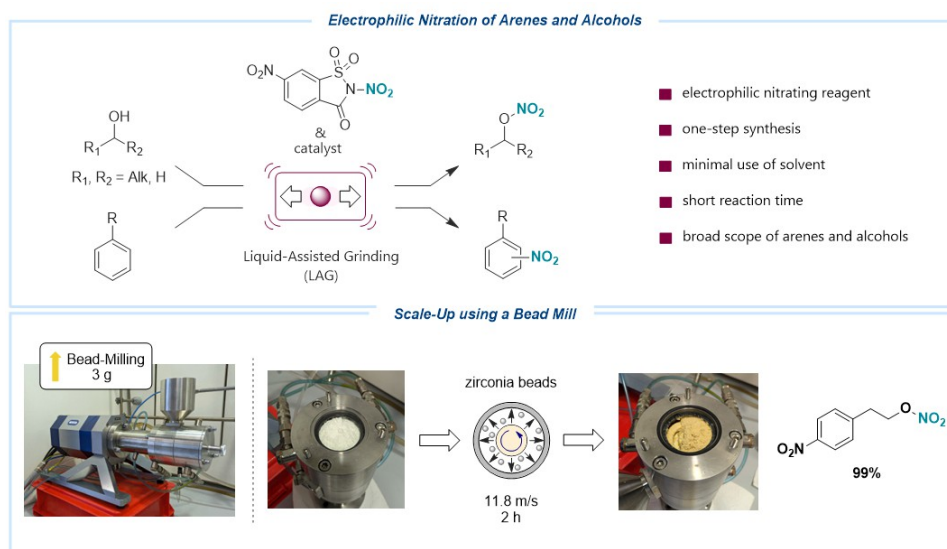
Together, these studies illustrate a unified chemical framework for designing modular, responsive probes to study metabolites and transition metal ions, expanding the molecular imaging toolkit for complex biological systems.

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Mechanochemical Nitration of Arenes and Alcohols Using Bench- Stable Organic Nitrating ReagentV. Valsamidou¹, S. Patra^{1*}, B. Kadriu^{1*}, M. G. Metzger^{1*}, L. Gremaud^{2*}, D. Katayev^{1*}¹University of Bern, ² Haute école d'ingénierie et d'architecture de Fribourg

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

Given our group's long-standing interest in the field of nitration chemistry, we recently implemented ball milling (a form of impact-generating mechanochemistry) into our synthetic approaches toward the nitration of various molecular structures. In 2019, we introduced an easily accessible and recyclable organic nitrating reagent for electrophilic nitration, which tolerates various functional groups and allows for the circumvention of harsh reaction conditions involving mineral acids.^[2] In this work, the reagent was successfully activated using mechanochemical techniques under LAG (Liquid Assisted Grinding) conditions, functionalizing a broad range of arenes and both primary and secondary alcohols.^[3] Compared to solvent-based nitration approaches, the protocol displayed significantly improved green chemistry metrics and shorter reaction times. Additionally, the practical applicability to industrial settings was demonstrated through a scale-up to gram quantities of substrate, resulting in enhanced reaction efficiency and product yields.

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Bending Peropyrene for Enhanced Singlet Fission

P. L. Widmer¹, C. Albrecht^{1*}, M. Juricek^{1*}

¹University of Zurich, Winterthurerstrasse 190, 8057 Zürich

Singlet fission holds the potential to increase the efficiency of single-junction solar cells beyond the traditional theoretical limit. While several efficient singlet fission sensitizers are known, their practical use in silicon-based photovoltaics is limited by factors such as inadequate stability or triplet energy levels that are too low. Carbon-based materials present a promising alternative to address these limitations. However, in these systems, excimer formation frequently outcompetes singlet fission, reducing overall efficiency.¹ Graphene-based radicals emerge as particularly interesting synthetic candidates, though their preparation remains difficult due to the instability of unpaired electrons, which readily polymerize or decompose in solution.

In this study, we explore the phenalenyl radical (PLY) as a model for designing non-planar graphene-derived nanostructures, aiming to circumvent excimer formation. Earlier research demonstrated that PLY follows a decomposition route to yield the planar dimer peropyrene (PP).² Through the precise placement of substituents around the reactive periphery, we managed to suppress reactivity at selected positions, enabling a precise and predictable transformation. When exposed to mild oxidative conditions, PLY engages in a selective π -radical cascade dimerization, producing both σ - and π -bonds in a single, efficient step. This strategy allowed us to isolate multiple isomeric forms of PP. These results highlight the value of π -radical cascades in open-shell graphene systems as a versatile approach for constructing extended carbon architectures.

Ultimately, our goal is to challenge the paradigm that the inherent reactivity of unpaired electrons is a drawback, and instead demonstrate its utility as a powerful tool for synthesis.

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Accessing CF₃-Cyclopropenes via Trifluoromethylation of Cyclopropenyl Benziodoxole (CpBx) Reagents

W. Wu¹, T. M. Milzarek^{1,2*}, J. Waser^{1*}

¹Laboratory of Catalysis and Organic Synthesis (LCSO), École Polytechnique Fédérale de Lausanne (EPFL), 1015 Lausanne (Switzerland), ²Helmholtz Institute for Pharmaceutical Research Saarland (HIPS), Department of Natural Product Biotechnology, Helmholtz Centre for Infection Research (HZI), Saarland University, 66123 Saarbrücken (Germany)

Cyclopropenes are the smallest cyclic alkenes possessing an exceptionally high ring strain, resulting in unique reactivities in C=C bond functionalisations, ring-opening transformations, as well as downstream modifications to highly-substituted, conformationally-rigid cyclopropanes. Our group has recently reported the use of cyclopropenyl benziodoxole (CpBx) reagents as σ -type cyclopropenium cation equivalents, enabling efficient transfer of the cyclopropenyl moiety to alkynes and alkenes,^[1] as well as a cyclopropenyl cross-coupling reaction.^[2] Herein, we present the use of these reagents to access sp²-trifluoromethylated cyclopropenes,^[3] a class of compounds currently with extremely limited methods of access. A general method of preparing these novel products opens a new avenue for accessing poly-substituted, stereo-defined trifluoromethylated cyclopropanes, a medically-relevant scaffold.

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Controlling Supramolecular Stacking in π -Extended Carpyridine Systems Through Water Intercleration.

O. Domecq-Cazaux¹, J. Woods^{1*}, K. Zhang^{1,2*}, M. Rickhaus^{2*}

¹University of Geneva, Switzerland, ²University of Zurich, Switzerland

While supramolecular polymers have gained considerable due to their remarkable properties, like, self-healing and stimulus responsiveness, the precise molecular organisation within an assembly can be hard to deduce. The Rickhaus group aims to stack molecules using shape principles as a governing factor ^[1]. Because these systems can assemble without H-bonding, their (non)crystallinity can be well tuned ^[2].

Figure 1. Different columnar arrangements of carpyridines depending on the presence of water.

The impact of the presence of water on supramolecular polymerisation is well documented but poorly understood on the molecular level ^[3]. On challenge of self-assembly system is notoriously hard to resolve there local, molecular organisation. Here we present the dramatic impact water can have on an assemble stack by resolving the structure of a crystalline analogue by micro-ED. Our findings demonstrate that the local organisation differs significantly between dry and wet solvent environments while nanosheets formed from solutions of varying wetness appear identical under electron microscopy ^[4].

Acknowledgements

We thank funding from the Swiss National Science Foundation, grants PZ00P2_180101 and TMSGI2_218367 and the Sandoz Foundation.

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Extending Scaffold Diversification through Atom Insertion to Previously Unexplored Drug Modalities

E. J. Meeus^{1,2}, A. K. Paschke^{1,2*}, F. Hoffmann^{1*}, B. Morandi^{1*}

¹Laboratorium für Organische Chemie, ETH Zürich, 8093 Zürich, Switzerland, ²These authors contributed equally to this work

Synthetic methods that allow the direct modification of a molecule's core skeleton have recently undergone a renaissance.^{1,2} As an alternative to traditional orthogonal syntheses, these methods offer a straightforward strategy for scaffold diversification with minimal effort, supporting the advancement of drug discovery as novel late-stage diversification tools.³ Although the utility of such methods has been demonstrated for the late-stage diversification of several pharmaceuticals, their full potential remains largely untapped.⁴ Hence, we set out to extend scaffold diversification through atom insertion to previously unexplored drug modalities.

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Polycyclic Aromatic Architectures for Digital Transformation

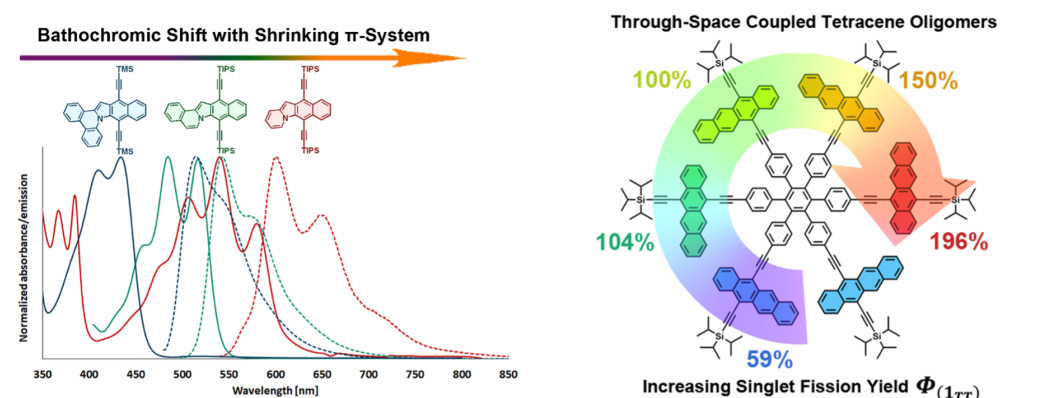
P. Gaweł¹¹Centre of New Technologies, University of Warsaw, Poland

Digital Transformation relies on materials that convert, route, and sense information as photons and electrons, across displays, sensors, modulators, and solar harvesters. Organic optoelectronics are uniquely positioned for this task: they are solution-processable, flexible, and molecularly programmable, enabling property-by-design at scale.

We pursue several complementary research avenues to address key challenges in the field. First, using heteroatom engineering, we merge indole and indolizine within π -expanded indoloindolizines to build robust, tunable π -systems.¹ By selectively enhancing either subunit, we finely adjust HOMO/LUMO levels and band gaps. Computations confirmed by experiments reveal intriguing trends: certain π -expansions increase the gap. These are explained via aromaticity analysis and Clar theory. These semiconductors resist photooxidation far better than acenes and deliver ambipolar transport with balanced hole/electron mobilities in OFETs.

Second, to amplify exciton generation and probe spin physics, we investigate singlet fission (SF). Emulating solid-state coupling in tetracenes, we use a hexaphenylbenzene hub bearing 2–6 tetracene chromophores; steric crowding enforces through-space interactions.² SF yield scales with chromophore count: the hexamer reaches 196% triplet-pair formation (vs. 59% for the dimer) and produces high-spin states with potential in quantum technologies.

Together, stable, heteroatom-tuned indoloindolizines and through-space-coupled tetracene arrays provide a coherent, molecularly precise route to the optoelectronic functions underpinning Digital Transformation.



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