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Divergent Synthesis of Fluorinated Molecules Using Photoredox Catalysis

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The introduction of fluorine atoms into molecules significantly alters their chemical, physical, and biological properties. Therefore, it is a very attractive method to elaborate innovative materials, agrochemicals, and pharmaceuticals.[1]

Recent progress in the design of redox active reagents, capable to transfer nucleophilic, ambiphilic, and electrophilic type of fluorinated radicals significantly broadened the field of fluorine chemistry. Yet, the synthetic complexity to access such scaffolds is often associated with multi-step processes and hinders the practicability of utilising these reagents for the synthesis of vital molecules.

In this presentation, I will discuss some of the latest works from my group on the strategies of using structurally simple, inexpensive, and readily available fluorinated acetic anhydrides and carboxylic acids as redox active reagents to access various fluoroalkyl radicals.[2] The reactivity of these species can be further adjusted using the principal of switchable divergent synthesis in photocatalysis, allowing to synthesize a wide range of fluorinated molecules.

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Semipinacol Rearrangement of Cyclopropenylcarbinols for the Synthesis of Highly Substituted Cyclopropanes

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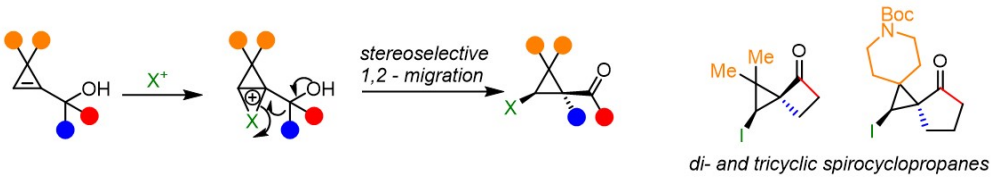
Since their discovery, cyclopropanes have attracted the attention of chemists due to their unique bonding properties, their ring strain, and their rigid conformation. In addition, cyclopropanes are present in numerous bioactive compounds, including both natural products and synthetic molecules. Nevertheless, polysubstituted cyclopropanes are difficult to access. One successful approach relies on the functionalization of cyclopropenes via carbo- or heterometallation of the double bond, which allows the simultaneous introduction of two substituents on the three-membered ring in a stereoselective fashion.[1] In contrast, the electrophilic activation of the cyclopropene double bond is less developed.[2] Herein, we report electrophile-induced semipinacol rearrangement of cyclopropenyl carbinols leading to the stereoselective synthesis of functionalized cyclopropyl ketone products. The transformation is efficient for the generation of di- and tri-spirocyclic compounds, containing cyclopropanes and cyclobutanes. Soft electrophiles, such as I^+, PhS^+, $PhSe^+$, and NCS^+, promoted efficiently the rearrangement. The 1,2-migration was achieved in the case of aryl-substituted alcohols, cyclopropanols, and cyclobutanols. The utility of the obtained products was demonstrated by variety of product modifications. Our work demonstrates the high synthetic potential of the electrophilic activation of cyclopropenes as an underdeveloped strategy for synthesizing complex cyclopropanes.



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Controlling non-enzymatic terpene cyclizations

L. D. Syntrivanis[1,3], T. Klucznik[2,4], W. Beker[2,4], B. A. Grzybowski[2,4], M. D. Burke[3], K. Tiefenbacher[1,5]

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Recent advances in iterative coupling methodologies and reaction automation have paved the way towards the fully automated synthesis of small organic molecules, however the synthesis of topologically complex molecules using such approaches remains a major challenge.[1,2] A potential answer to this challenge for complex terpenes could reside in the Tail-to-Head Terpene (THT) cyclization,[3,4] the reaction that gives rise to the majority of the topologically complex terpene structures encountered in nature. However, controlling the outcome of this reaction in the absence of the precisely structured active site of an enzyme has historically been very difficult. Here I will present a substrate-controlled approach to addressing this problem. Coupled with a predictive computer algorithm, this approach enables the predictable synthesis of a range of complex terpene structures from simple modular precursors, and could provide a pathway for the automated synthesis of terpenes through a linear-to-cyclized approach.

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Iodine atom transfer mediated radical addition - cyclization processes using alpha-boryl radicals

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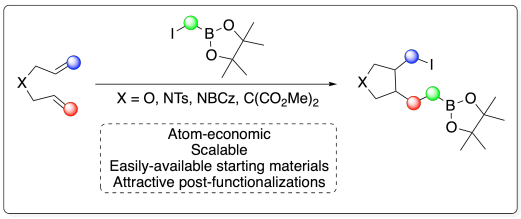
Since the pioneering work of Suzuki[1] and his discovery of cross coupling reactions, boron has emerged as an important element for organic synthesis. Moreover, boron is as well contained in active compounds and, until 2022, 5 of them were approved by the FDA[2]. It is thus important to develop new organic reactions which help synthesizing new boron containing compounds. We exploited the unique features of alpha-boryl radicals and their addition to unsaturated systems[3][4] to develop an easy, scalable and efficient reaction to access 1,5-iodoboronic esters which possess a cyclopentane scaffold via 5-exo-*trig* cyclization. The optimization of the conditions and a scope of the reaction will be presented. The new products can be derivatized using further post-functionalization. Our new methodology could be used for the synthesis of small natural products, such as in the case of iridolactones.



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Frustrated Ion Pair-Enabled Cross-Electrophile Coupling of Unactivated Alkyl Electrophiles

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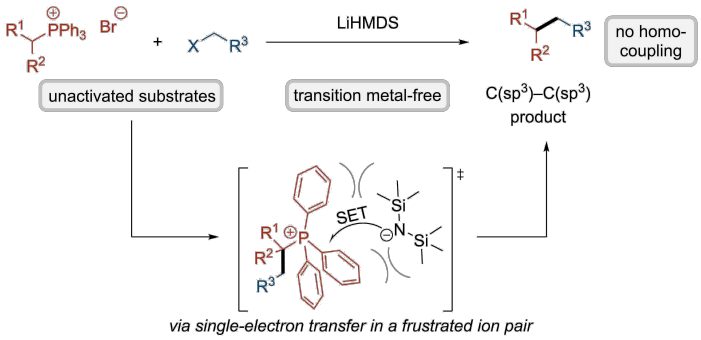
[1]ETH Zürich

Cross-electrophile coupling reactions have emerged as a powerful strategy for C–C bond formation. One of their advantages is that they avoid the need to prefunctionalize one of the coupling partners as a reactive organometallic reagent in contrast to traditional cross-coupling reactions. They are most often catalyzed by transition metals and rely on an external reductant after every turnover. Due to the environmental impact of transition metals and economic considerations, the development of transition metal-free strategies is desirable. Despite progress in this area, the coupling of two unactivated C(sp^3) reaction partners by such means has so far remained elusive.

We report a cross-electrophile coupling between two unactivated C(sp^3) fragments in a transition metal-free protocol. Alkylphosphonium salts are reacted with alkyl halides in the presence of a hindered base as the sole reagent to give rise to the coupled products.[1]



The reaction tolerates several moieties that would be challenging under transition metal-catalyzed conditions, demonstrating the advantages of the metal-free approach. Detailed experimental and computational mechanistic studies indicate that the reaction is enabled by a single-electron transfer event in a frustrated ion pair. This unusual reactivity could be leveraged to extend the reactivity beyond cross-electrophile coupling, highlighting its potential in organic synthesis.

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Organocatalytic Synthesis of Triflones Bearing Two Non-Adjacent Stereogenic Centers

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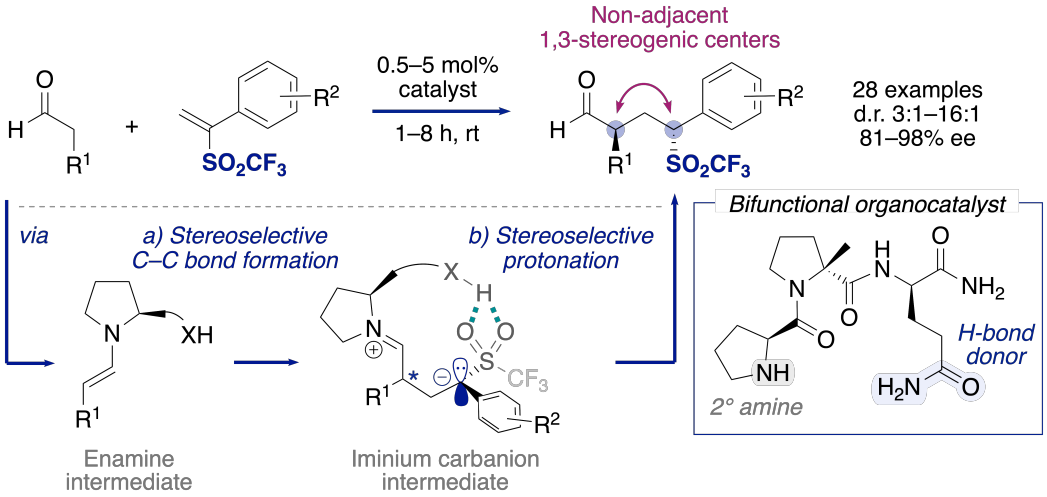
The trifluoromethylsulfonyl (SO_2CF_3, triflyl) group is an intriguing functional group for its properties and unique reactivity since it combines the well-established transformations of alkyl and aryl sulfones with reactivity exclusive to the triflyl group.[1] Methods to access triflones are therefore enabling tools for organic synthesis. However, strategies to obtain chiral triflones are limited.[2]

We developed an efficient organocatalytic synthesis of chiral triflones using α-substituted vinyl triflones, building blocks previously unexplored in asymmetric catalysis.[3] This peptide-catalyzed conjugate addition provides a broad range of γ-triflylaldehydes with two non-adjacent stereogenic centers in high yields and stereoselectivities. The reaction proceeds at a low catalyst loading of 0.5–5 mol% and tolerates a variety of functional groups, including acetal, ester, or ketone moieties. We show that a bifunctional peptide catalyst is crucial for high diastereo- and enantioselectivity through stereocontrol of the conjugate addition and protonation steps. Furthermore, straightforward derivatization of the products into 1,3-disubstituted heterocycles, including δ-sultones, γ-lactones, and pyrrolidines, highlights the versatility of γ-triflylaldehydes. Our results showcase the value of vinyl triflones for organic synthesis and open new possibilities to access chiral compounds with 1,3-stereogenic centers from α-substituted Michael acceptors.



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Radical Dynamic Digital Twin

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[1]Chemspeed Technologies AG, Wölferstrasse 8, 4414 Füllinsdorf, CH

Gamification, Internet of the Lab Tools, Digital Twins, Machine Learning / Artificial Intelligence combined with automation and quality data / data integrity are pivotal tools to move chemical R&D processes and operations into the digital age.

Presented concepts and solutions highlight that digital twins are disruptive for each and every lab and evolutionarily enable the AI / ML pipelines in the future combined with ready-to-apply and quality assured catalysts, reagents, building blocks (SMOLE). The presentation shows Chemspeed’s top-down and bottom-up digitalization approach (ARKSUITE SOFIA) combined with its proprietary globally synchronized protocolling and smallest operational increment based, versatile workflow design that is uniquely and sustainably shaping the R&D sphere in e.g. organic chemistry.

Catalyst Control over Threefold Stereogenicity: C–S Atropisomeric Sulfones

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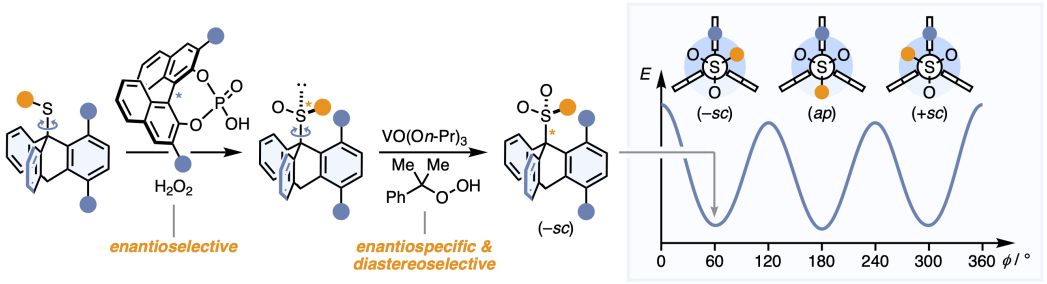
Numerous catalytic methods facilitate the stereoselective synthesis of atropisomers with rotationally restricted C–C, C–N, N–N and C–B single bonds between two planar moieties.[1] In contrast to these systems with two enantiomeric stereochemical states, catalyst control over atropisomers with more than two stereoisomers arising from one stereogenic axis was not accomplished until recently.[2] The Ōki triptycyl sulfones[3] exist in the form of three configurationally stable rotamers, namely the enantiomeric (±*sc*)-isomers and the symmetrical (*ap*)-conformer, which result from a rotationally restricted C–S bond connecting two tetrahedral fragments. We were able to stereoselectively access these systems by the catalyst-controlled oxidation of rotationally dynamic thioethers yielding enantioenriched sulfoxides, which subsequently were oxidized to the respective (*sc*)-sulfones.[4] While a chiral phosphoric acid catalyst defined the configuration of the sulfoxide stereocenter,[5] VO(O*n*-Pr)$_3$ in combination with cumene hydroperoxide rendered the second oxidation to the atropisomeric sulfones with threefold stereogenicity a highly enantiospecific and diastereoselective process. Using this strategy, the (–*sc*)-sulfones were obtained in high degrees of stereoisomeric enrichment with selectivities of up to 94:6:□1 (–*sc*):(+*sc*):(*ap*), representing the to the best of our knowledge first example of catalyst control over C–S atropisomerism. Moreover, by choosing distinct reaction conditions, the diastereoselectivity of the second oxidation step could be directed towards the (*ap*)-sulfone making all three stereoisomeric states selectively accessible under catalyst control.



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Electrochemically Catalyzed Nitration of Unsaturated Hydrocarbons

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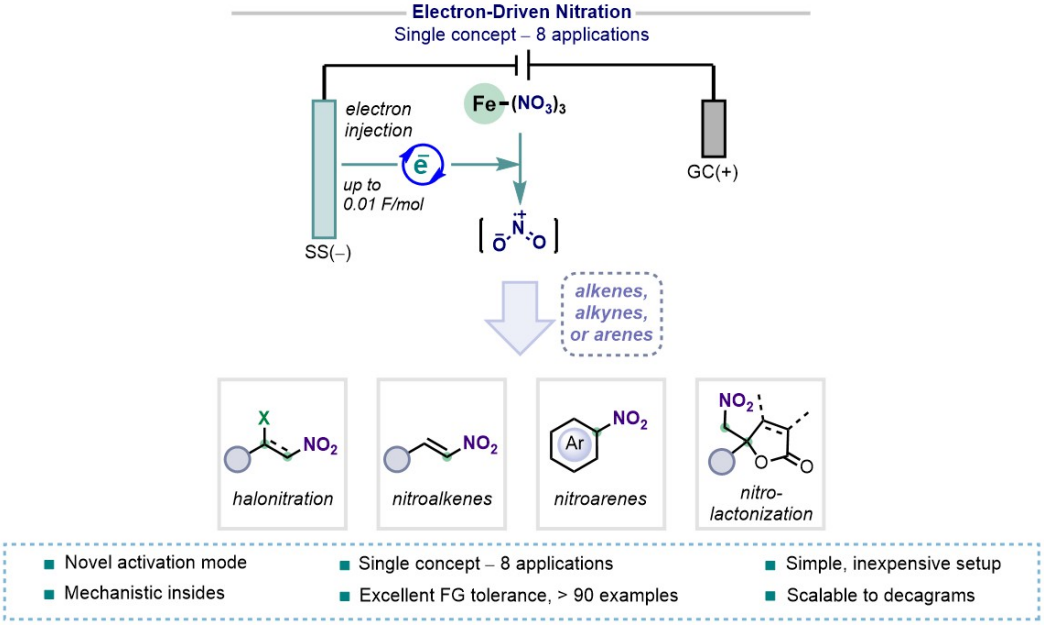
Catalysis is a key feature in organic chemistry and one of the most important and interesting areas of discovery in academic and industry research. Chemical and enzymatic catalysis has been recognized a least 16 times by the Nobel Foundation. Among different catalysts such as transition metals, enzymes, organocatalysts, Lewis base and Brønstead acids, the proton is the smallest, whereas the electron is a tiny element. The field of electron as a catalyst was only recently conceptualized, and is yet lacking practical examples to attract attention of the scientific community. The electron as a catalyst is identified in catalysis as inexpensive, traceless, and green. Moreover, in addition to having the highest mass efficiency among others catalysts, it does not need to be removed from the reaction mixture. In recent years several electrochemical protocols have been reported in which transition metals and electrons in superstoichiometric amounts have been used to promote the catalytic cycle.[1,2] However, in an ideal electrocatalytic reaction, a sub-stoichiometric amount of electrons is required to complete the process.



Herein, we introduce an electrochemically catalyzed paradigm for the generation of nitryl radicals from ferric nitrate under mild and additive-free reaction conditions using a simple setup with inexpensive graphite and stainless steel electrodes. Detailed mechanistic studies and controlled experiments of such a unique activation mode of iron nitrate was examined by combined spectroscopic and detailed experimental studies and revealed that the reaction proceeds via a radical pathway in the presence of nitryl radicals and operates under catalytic electrons. This operationally simple electron-mediated protocol offers straightforward access to a variety of nitro-derived molecules from unsaturated hydrocarbons including alkenes, alkynes, arenes, and also efficiently promotes a series of ipso-nitration reactions and nitrative cyclizations with high levels of chemo- and regioselectivity. In addition to a broad application area, these protocols are easy of scaling to decagrams, while exhibiting exceptional substrate generality and functional group compatibility.[3]

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Surfactant-driven Strategies for Sustainable C–H Activation: Progressing Towards Mild Reaction Conditions

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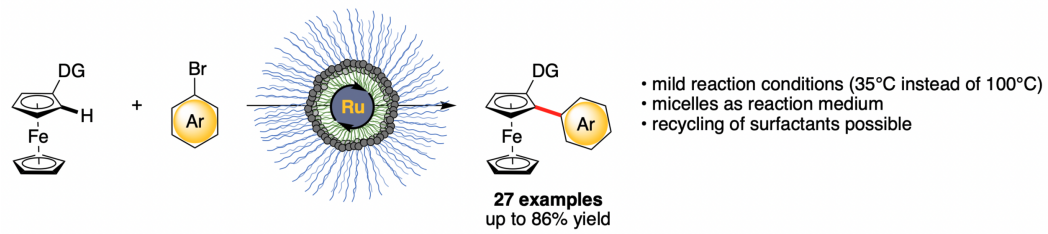
Sustainability has become a top priority for every chemistry practitioner! Considering the development of a new reaction or that of a chemical process, sustainability, waste and energy minimization have become highly significant. The urgency has been further reenforced with the potential for a ban of several reprotoxic polar aprotic solvents such as DMF and NMP through the REACH regulation.[1] Alternatives for such reaction media are indispensable. In the last decade, micellar conditions in bulk water have emerged as promising alternatives for several transformations such as a variety of cross-couplings or amide bond formation. In clear contrast, only a handful of examples emerged for C–H activations under micellar conditions, and the rare examples often require high temperatures.[2]

Our research focuses on the development of new catalytic systems for mild C–H activations occurring under micellar conditions. Two approaches are envisioned: 1) the careful design of additives to commercially available surfactants[3] or 2) the implementation of novel designer surfactants, able to facilitate challenging C–H activations at ambient temperature.[4]

Remarkably, with newly designed surfactant obtained *via* installation of an additional ligand at the core of a commercially available surfactant in hand, we were able to lower the reaction temperature for the ruthenium C–H arylation of ferrocenes from 100°C to 35°C. Our conditions have shown to tolerate a broad spectrum of functional groups with yields up to 86% and a high chemoselectivity, enabling the late-stage functionalization of active pharmaceutical ingredients and natural products.



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A General Strategy to Develop Fluorogenic Polymethine Dyes for Bioimaging

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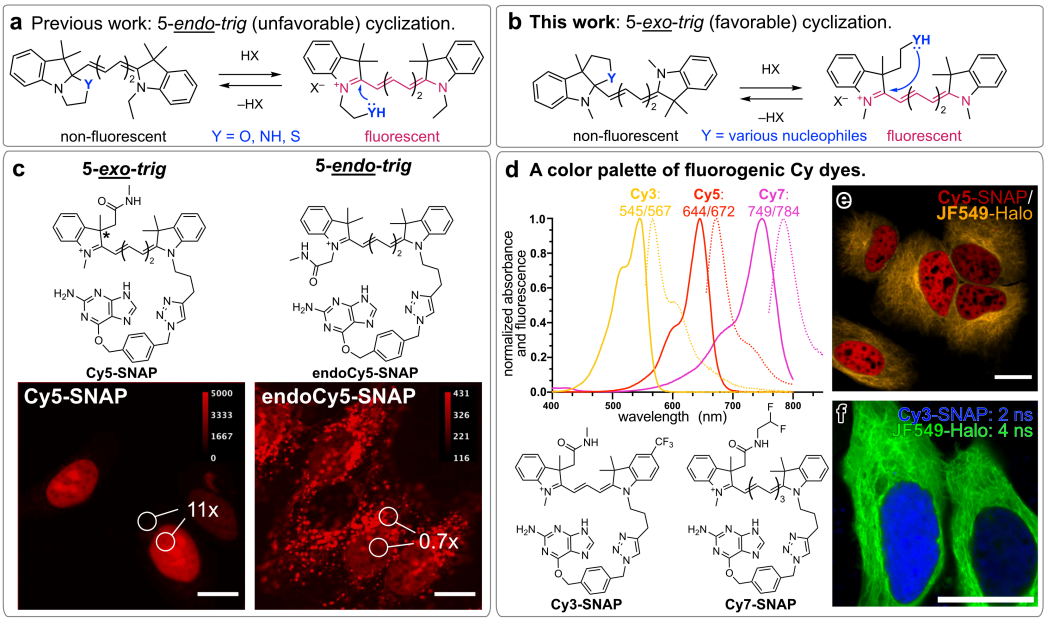
Fluorescence imaging is an invaluable tool to study biological processes and further progress in this research area depends on the development of advanced probes. Fluorogenic dyes are crucial to reach intracellular targets and label them with high specificity. Excellent fluorogenic rhodamine dyes have been reported, but they often require a long and low-yielding synthesis and are spectrally limited to the visible range.

Here, we present a general strategy to transform polymethine compounds into fluorogenic dyes using a 5-exo-*trig* ring closure approach[1], in contrast to previously attempted 5-*endo-trig* ring-closures[2] (Panel a-b). These dyes, regardless of their excitation wavelength, can be readily synthesized in two steps and are easy to derivatize by varying the indoleninium building blocks or the ring-closing moiety. We demonstrate that a 5-*exo-trig* Cy5 probe conjugated to the self-labeling protein tag SNAP-tag shows high fluorogenicity and a bright and specific fluorescence signal in live HeLa cells, whereas the corresponding 5-*endo-trig* probe showed low cell permeability, low fluorogenicity and high unspecific fluorescence signal (Panel c).



We illustrate the generality of this method by creating the first spontaneously blinking Cy5 dye as well as no-wash, turn-on polymethine dyes with emissions across the visible and near-infrared spectrum (Panel d). These probes are not only compatible with self-labeling proteins but also with small-molecule targeting ligands such as jasplakinolide and Hoechst 33342 dye and can be combined with rhodamine-based dyes for multicolor (Panel e) and fluorescence lifetime multiplexing imaging (Panel f). We envision that our simple, yet general, method will be useful to develop improved fluorogenic probes in the future, thus facilitating new bioimaging experiments.

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Directional ionic bonds

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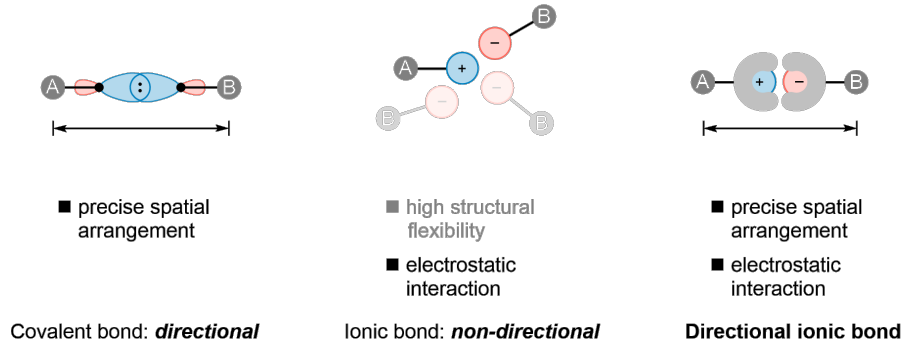
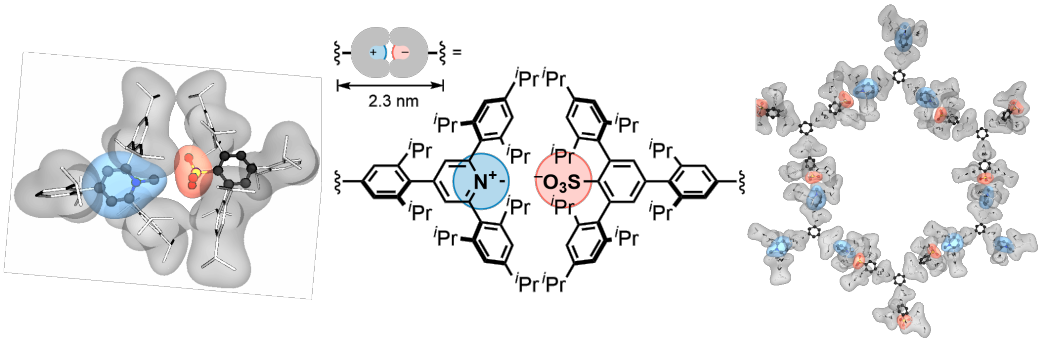
[1]University of Zurich, Department of Chemistry

Ionic bonds are the strongest type of noncovalent interactions and might reach energies comparable to covalent bonds.[1,2] While covalent bonds are inherently highly directional, ionic bonds lack such property due to the spherically-symmetrical nature of the electric field around simple ions.[3] We describe a strategy to impart the directionality to ionic bonds allowing them to acquire a predictable directional orientation.[4] Our design of directional ionic bonds includes the installation of a sterically demanding nonpolar hydrocarbon groups around the ions that leave the charged atoms exposed to one direction only. In this way, we minimize the charge separation and maximize the Coulomb attractive forces, while other relative orientations result in larger charge separations due to the steric repulsion between the shielding backbones.





The generality of our concept is showcased with a series of N-methylpyridinium•••arylsulfonate ion pairs that possess different shielding groups around the charged moieties. Furthermore, multiple directional ionic bonds were utilized to build supramolecular systems at the nanoscale by the formation of a two-dimensional hexagonal lattice composed of six directional ionic bonds. Such ionically bonded framework is an example of a complementary strategy for the directional construction of organic materials by exploiting the otherwise nondirectional Coulomb interactions between two ions.

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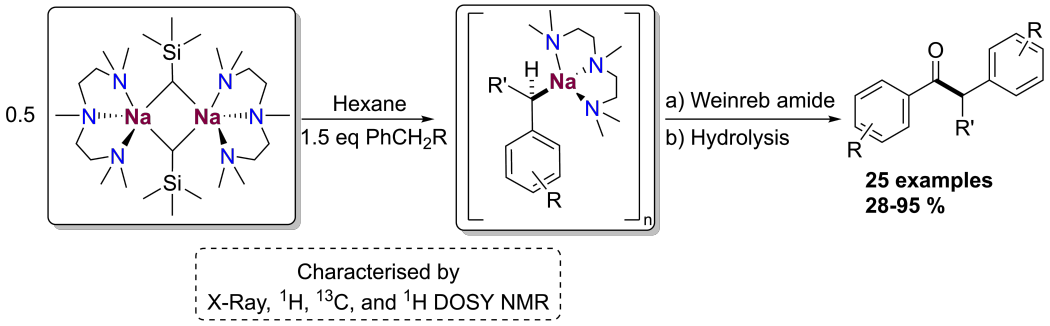
Highly Reactive Hydrocarbon Soluble Alkylsodium Reagents for Benzylic Aroylation of Toluenes using Weinreb Amides

D. Anderson[1], E. Hevia[1]*

[1]University of Bern

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

In this communication, we report on the exploitation of the Lewis basicity of PMDETA (N,N,N',N'',N''-pentamethyldiethylenetriamine) to access and characterise a hydrocarbon soluble alkyl sodium reagent. This astoundingly soluble reagent was subsequently used towards the development of a facile and selective route for benzylic metalation of the corresponding nonactivated toluene derivatives. We demonstrate the reactivity of the formed benzyl sodiums through application in benzylic aroylation with a Weinreb amide to access synthetically useful 2-aryl acetophenones, and in their reactivity towards C=X double bonds (X = C, N or O). Reaction intermediates were characterised using a combination of X-ray crystallography and ^{1}H DOSY (Diffusion Ordered SpectroscopY) NMR, providing the first reported synthetic and structural insights on the constitution of the intermediates in these reactions, advancing our understanding of how these systems operate in solution.[4]



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Studies Towards the Total Synthesis of Griseoviridin

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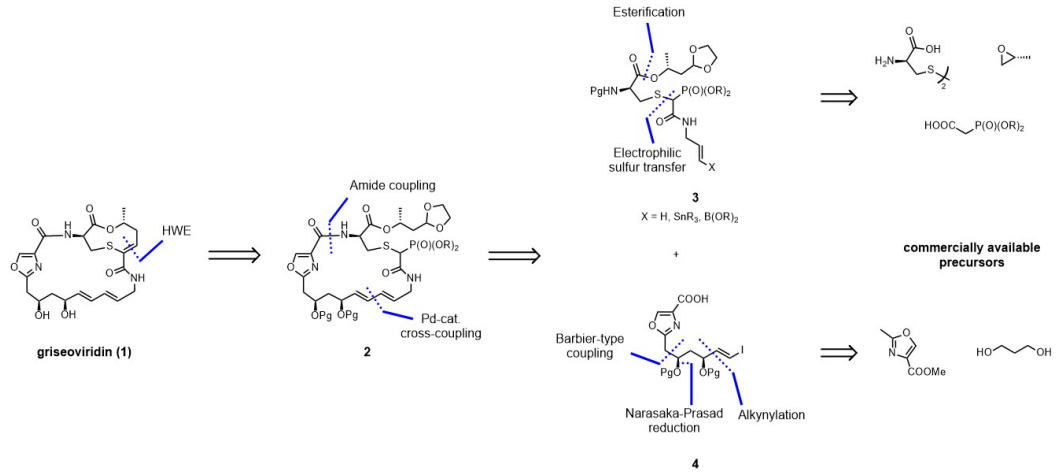
Griseoviridin (**1**) is a natural product of mixed polyketide-non-ribosomal peptide origin, which was first isolated from culture broths of *Streptomyces griseus* in 1955 by Bartz and co-workers. The compound belongs to the streptogramin A class of antibiotics and exerts its antibacterial activity through binding to the ribosome and the inhibition of protein synthesis. Among the various type A streptogramins, griseoviridin (**1**) is the structurally most complex, featuring an additional thio-vinyl ether containing 9-membered lactone ring, and the one whose chemistry and biology has been least studied. Only a single total synthesis has been reported in the literature. Furthermore, no SAR studies on griseoviridin (**1**) have been reported to date. Its challenging chemical structure combined with its antibacterial activity prompted us to embark on the total synthesis of griseoviridin (**1**). We envision to access the natural product via late-stage construction of the macrolactone domain by an intramolecular HWE reaction; we hypothesize that conducting this key step with the macrolactam system already installed could provide a favorable pre-organization effect for the closure of the strained 9-membered ring. The macrocycle **2** is traced back to the two major building blocks **3** and **4** via a Pd-catalyzed cross-coupling / amide coupling sequence. Herein, we present the current state of our efforts towards the total synthesis of griseoviridin (**1**), including the successful synthesis of vinyl iodide **4** and phosphonate **3**, the results of model studies investigating the feasibility of the envisioned intramolecular HWE reaction, and our attempts directed at forging the macrocyclic backbone.



Ethynylbenziodoxolones and Cesium Oxalates under Blue Light: from Deoxyalkynylation to Lactonization

D. Cavalli[1,3], S. G. E. Amos[1,3], F. Le Vaillant[2], J. Waser[1,3]*

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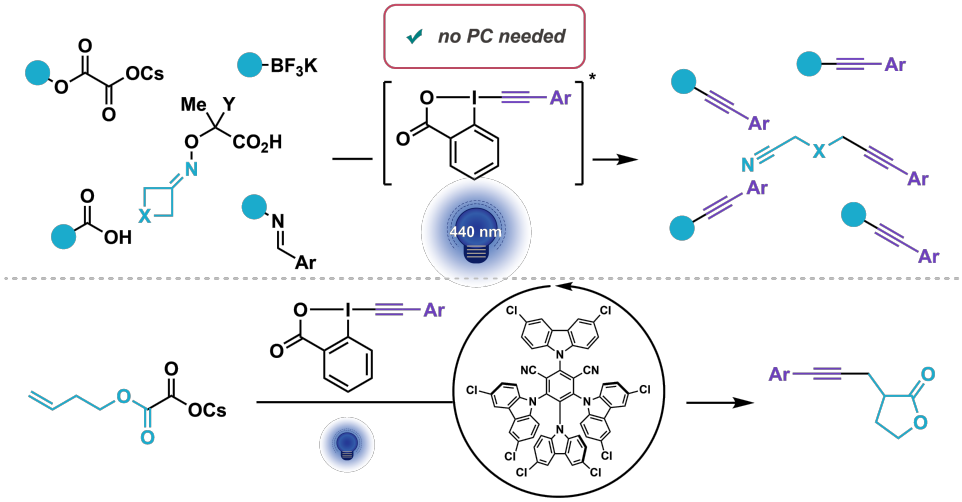
Alkynes are important moieties for synthetic chemists, and have many applications in biochemistry, medicinal chemistry and material science. Developing new alkynylation strategies is therefore of high importance. A possible method is to combine photoredox catalysis with ethynylbenziodoxolones (EBXs), which have been proved to act as efficient SOMOphiles.[1] Because the alcohol functionality is ubiquitous in nature, the development of new strategies for their re-functionalization is highly appealing. In photochemistry, in order to generate a radical via C-O bond cleavage, the alcohol functionality has to be converted into a redox-active group first. One example of active group is the oxalate moiety developed by MacMillan and Overman.[2] Herein, we describe the development of two different strategies that combine radicals generated from cesium oxalates and EBXs. In our first strategy, we demonstrated how aryl-substituted EBXs can undergo direct photoexcitation and act as photooxidant themselves, alleviating the need for a photocatalyst.[3] The developed reaction conditions were further applied to the deoxyalkynylation of tertiary cesium oxalates. The scope was then extended to previously reported photocatalyzed alkynylation reactions to demonstrate the generality. In the second strategy, we combined homoallylic cesium oxalates and EBXs in a photocatalytic lactonization reaction.[4] A weaker irradiation combined with a sustainable organic photocatalyst was necessary to inhibit competing polymerization



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[4] Manuscript in Preparation.

Water-Soluble Cationic Porphyrins for MRI

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Magnetic resonance imaging (MRI) is a non-invasive imaging modality that provides in depth images of tissue with high resolution. In the presence of contrast agents (MRI-CA), MRI images can be greatly enhanced. However, FDA-approved Gd(III)-based contrast agents can occasionally reveal serious side effects, especially in patients with kidney defects. Therefore, safer MRI-CAs are of high demand. Recently, we have reported a water-soluble Gd(III)-porphyrin molecule as a photosensitive MRI-CA[1]. Although we have successfully increased the stability of Gd(III)-porphyrin complexation, it is ideal to have an even more stable chelate for MRI-CAs. Therefore, Mn(III) has been attracting attention as a suitable replacement for Gd(III) in MRI-CAs.

In this study, two types of porphyrins were synthesised as ligands for the MRI-CAs. The synthesised porphyrins are highly soluble in water and show no significant aggregation at physiological pH. By ESR spin-trapping method, efficient reactive oxygen generation was observed under visible light irradiation. Complexation of Mn(III) to the porphyrin centre provided a stable Mn(III)-porphyrin complex—observed by UV-Vis absorption spectra and HR-ESI-MS—presumably due to the smaller ionic radii of Mn(III) which can be placed in the centre of porphyrin without pyramidalisation. Currently, both DNA binding activity and relaxivity of the prepared Mn(III)-porphyrins are under investigation.

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Advancements in *Trypanosoma cruzi* Mucins: Synthesis of a penthasaccharide constituent of core 2 mucins and derivatives

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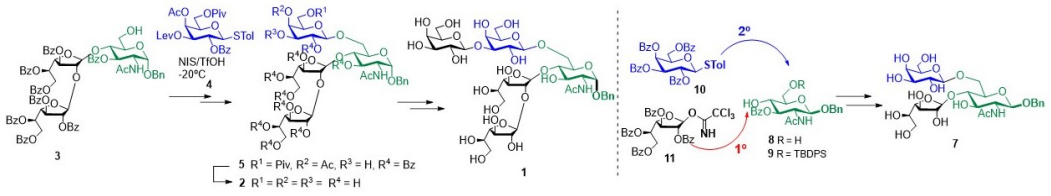
Trypanosoma cruzi, the etiological agent of Chagas disease, is a protozoan parasite with a complex life cycle that alternates between hematophagous triatomine vectors and mammals, including humans. Mucin-like glycoproteins are major components of the *T. cruzi* surface. The oligosaccharides in the mucins are α-*O*-linked to the protein *via* GlcNAc and its composition is characteristic of each differentiation stage and strain.[1] In the internal cuticle of the rectal ampoule of the insect vector, epimastigotes are attached leading its differentiation into highly infectious forms as metacyclic trypomastigotes.

We have been developing synthesis methods for Gal*f*-containing oligosaccharide family (core 2) to explore their structure-activity relationship and biological implications through enzymatic studies and assays. We now present the synthesis of pentasaccharide β-D-Gal*f*-(1→2)-β-D-Gal*f*-(1→4)-[β-D-Gal*p*-(1→3)-β-D-Gal*p*-(1→6)]-α-D-GlcNAc (**1**) and tetrasaccharide **2** as benzyl glycosides. Previously, the synthesis of **1** was performed by a [3+2] convergent strategy with moderate yield. In this case, a sequential strategy was followed using trisaccharide **3** with an internal Gal*f* as acceptor and thiogalactopyranoside **4** as donor to give the corresponding tetrasaccharide with excellent yield. Deprotection of the orthogonal Lev group gave **5**. The differences of both strategies will be discussed.

Ex vivo binding assays in the presence of chemically synthesized oligosaccharides as α-benzyl glycosides by our group allowed the identification of the structure β-D-Gal*p*(1→6)-[β-D-Gal*f*(1→4)]-D-GlcNAcα-OBn (**6**) trisaccharide, as adhesion determinant. [3]

The β-benzyl glycoside of **6** was synthetized with the aim of studying the influence of the anomeric configuration of the GlcNAc unit on the adhesion process. Unlike the synthesis of trisaccharide α-analogue, the β-glycoside **7** was exclusively obtained by the introduction of the Gal*p* unit on secondary OH-4 followed by the Gal*f* unit on primary OH-6. Trisaccharide **7** inhibited the adhesion of epimastigotes to the inner lining hindgut, showing that the anomeric configuration is not relevant in the adhesion process providing more information about the involved receptor.



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Synthesis of Analogs of (−)-Zampanolide and Structure-Activity Relationship Studies

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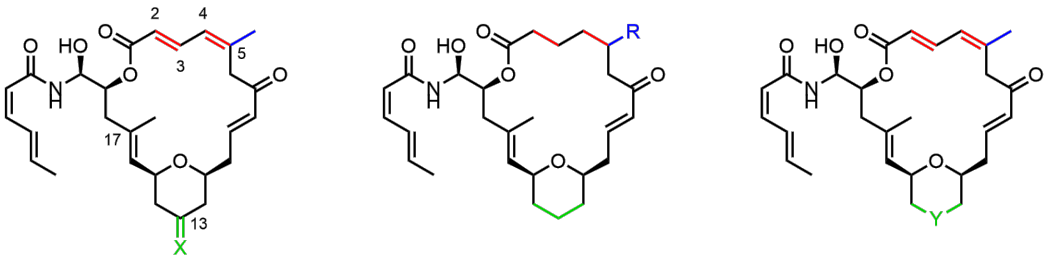
[1]ETH Zurich, [2]CSIC, [3]Dottikon, [4]Syngenta

(−)-Zampanolide (**1**) is a complex marine macrolide that was first isolated from the sponge *Fasciospongia rimosa* in 1996 by *Tanaka* & *Higa* and found to exhibit nanomolar *in vitro* antiproliferative activity against a range of human cancer cell lines.[1]



The compound was subsequently shown to be a microtubule-stabilizing agent which, as the only potent microtubule stabilizer known, binds to β-tubulin in a covalent fashion.[2] (−)-Zampanolide (**1**) has been the target of several total synthesis campaigns,[3-7] including a synthesis developed in our own laboratory that is based on macrocycle formation by intramolecular HWE reaction.[8]

Our group has recently reported the fully stereoselective total synthesis of C(13)-desmethylene-(−)-zampanolide (**2**).[9] C(13)-Desmethylene-(−)-zampanolide (**2**) was found to be at least equipotent with natural **1**. Therefore, it has served as a more readily accessible template for SAR studies that aimed to address the importance of the various double bonds in the macrolactone ring, of the C(5) & C(17) methyl groups[10] and of the atom at position 13. This presentation will describe the synthesis of new analogs of **1**: with a fully saturated C(1) – C(5) domain (**3**), its C(5)-desmethyl variant (**4**)[10] and three analogs where carbon 13 is substituted by either oxygen (**5**) or sulfur (**6**) and its oxidized sulfone analog (**7**). In addition, their binding to microtubules and their cellular activity will be discussed.[10]

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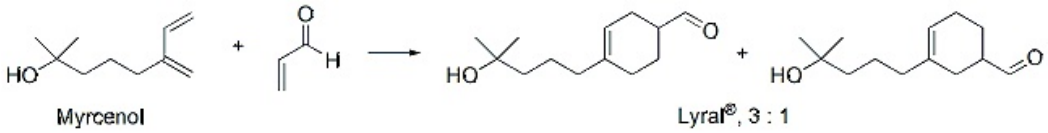
The Lyral Challenge

J. Coulomb[1]

[1]DSM-Firmenich, Science & Research, New Ingredients Discovery Group

Lyral® was patented by IFF in 1958 and has become over the years an increasingly important lily of the valley ingredient with a world annual consumption peaking over 1000 tons a few years ago. It has recently suffered a decrease in usage owing to its proven allergenic properties for a significant percentage of the population. Since 2021, it is notably banned in all products marketed in the European Union, and its replacement by a new, innocuous substance has become one of the leading challenges of perfumery chemistry. Our efforts in this direction have triggered the discovery of several new molecules with olfactory properties faithful to that of the original ingredient. In particular, we have devised aromatic Lyral® analogues able to replicate its smell. We are now equipped with a new set of potential Lyral® replacers.



Myrcenol Lyral®, 3 : 1

Nickel Catalyzed Enantioselective C-H Benzylic Carbamoylation

S. Cuesta-Galisteo[1], C. Hervieu[1], J. Schörgenhumer[1], C. Nevado[1]*

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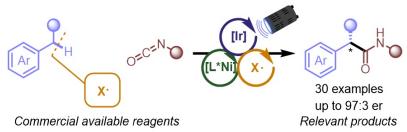
Lignin is a useful and sustainable source of relevant building blocks in organic chemistry. Valuable aromatic compounds can be obtained by reductive depolymerization, including alkylarenes, and thus, new tools to derivatize these products are in high demand. One straightforward approach relies on the functionalization of the benzylic C-H bond because of the relatively low BDE. Recently, halogen-mediated radical abstraction of hydrogen has merged with nickel metallaphotoredox catalysis to forge enantioenriched benzylic derivatives.[1] These protocols represent an attractive alternative to classical functionalization methods and are devoid of highly unstable intermediates.

In the last years, the use of isocyanates as electrophilic coupling partners in nickel catalysis has been well studied, providing elegant alternatives to the classical synthesis of amides.[2] However, asymmetric variants for this reaction are yet to be developed.

Here, we present the combination of the benzylic hydrogen abstraction with isocyanates as coupling partner via nickel metallaphotoredox (See Scheme below).[3] This strategy allows to straightforward generate valuable enantioenriched 2-arylamides, a scaffold found in a plethora of product of interest with bioactive properties or intermediates in total synthesis. In this work we present a scope of 30 examples with enantiomeric ratios up to 97:3. Additionally, several control experiments and DFT calculations allow to propose a plausible mechanism.



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

A. D'Addio[1], M. Mayor[1]*

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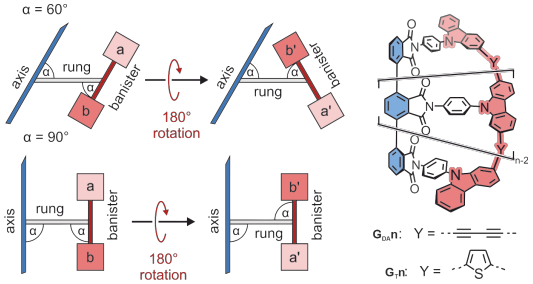
Helical chirality can be induced by forcing long tethers around a central axis. Such molecular architectures are reminiscent of a spiral staircase's banister (or “Geländer” in German).[1] By extension of a single stringer (banister) in a ladder polymer, exclusively chiroptical active structures are formed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



The design principle and synthesis of Geländer oligomers with orthogonal joints and their chiroptical study are presented.

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Iridium-Catalyzed Hydrogenation of Pyridines

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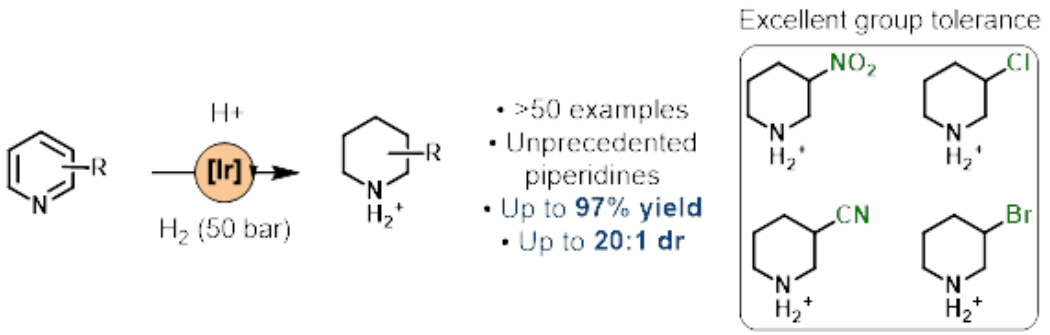
The piperidine core is present in many alkaloids and biologically relevant molecules, shows excellent pharmacological properties and is, as such, the most occurring nitrogen-heterocycle in FDA-approved drugs molecules.(1)

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

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



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Exploring Regio-Selective Spin Interactions: Positional Isomerism and its Influence on Spin Communication in Light-Induced Multi-Spin Systems

M. El Bitar Nehme[1], P. Thielert[2], M. Mayländer[2], T. Quintes[2], M. Franz[2], S. Zimmermann[3], P. Gilch[3], M. Rickhaus[1]*, S. Richert[2]*

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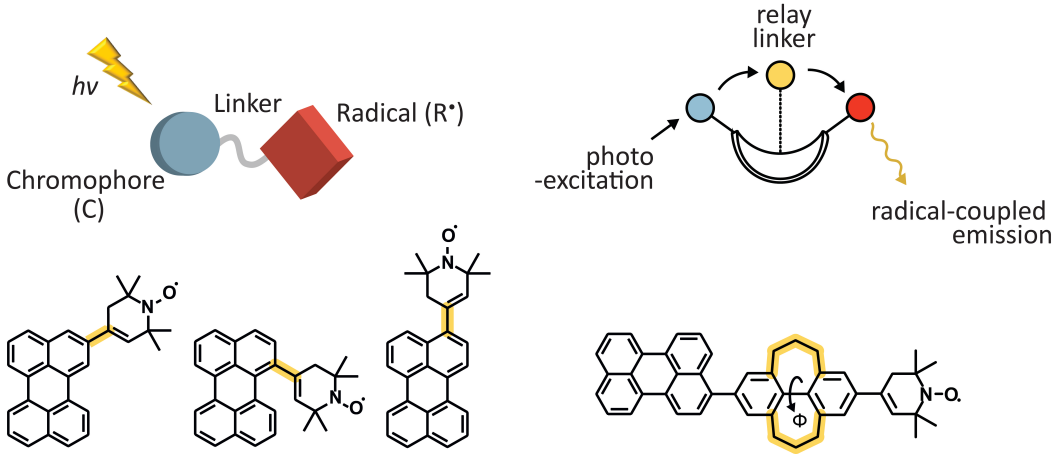
Highly versatile photogenerated multi-spin systems are promising candidates to explore the factors governing spin communication on a molecular level.[1] While the radical acts as a sensitizer that improves the intersystem crossing rate, the delicate covalent linkage between chromophore-radical systems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



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Neutral Radical Chromophores based on Triple-Functionalized [4]Helicene Scaffolds

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

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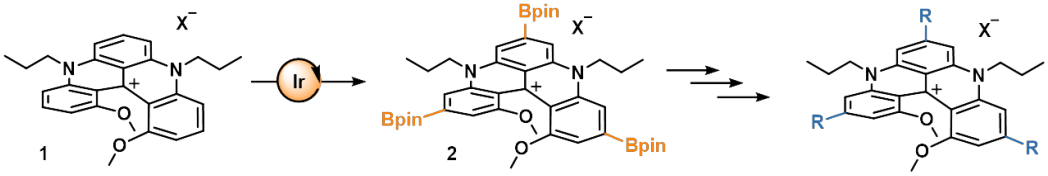
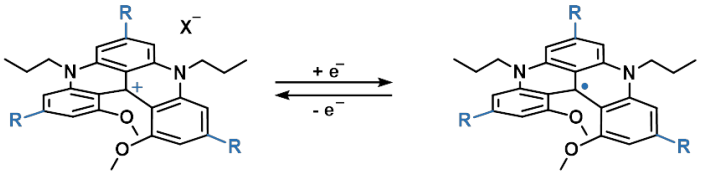
Helicenes are chiral *ortho*-condensed polyaromatics that, for purely organic derivatives, usually display absorption, fluorescence, electronic circular dichroism (ECD) and circularly polarized luminescence (CPL) in the blue range of the visible spectrum.[1,2] Cationic [n]helicenes are, however, welcome exceptions. In fact, the extended delocalization provided by the triarylcarbenium framework allows the targeting of longer visible wavelengths and even of the NIR spectral region.[3] Late-stage functionalization is then a particularly attractive strategy to manipulate the core helical structures, as it renders the synthesis time-efficient while favouring a large scope of products.[3]



In this work, a new family of poly-functionalized cationic [4]helicenes was prepared. Thanks to Ir-catalyzed direct C-H borylations, a triple *para*-functionalization to the formal positive charge has been achieved on the classical scaffold **1**.[4] Tris-borylated **2** is not isolable *per se*, but each BPin moiety is readily transformed through tandem reactions into various functional groups. These newly introduced substituents, depending on their electron-donating (ED) or electron-withdrawing (EW) nature, strongly influence the electronic and optical properties of the helical core (*e.g.*, redox potentials, energy band gap, Φ_f and lifetime). Interestingly, the derivatives bearing EW groups show an enhanced stability upon mono reduction leading to neutral radical species. These radical helicenes present increased ECD at low energies compared to the parent helical cations with g_{abs} values above 10^{-3} (λ ~ 700-900 nm).



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Catalytic *ipso*-Nitration of Organosilanes Enabled by Electrophilic *N*-Nitrosaccharin Reagent

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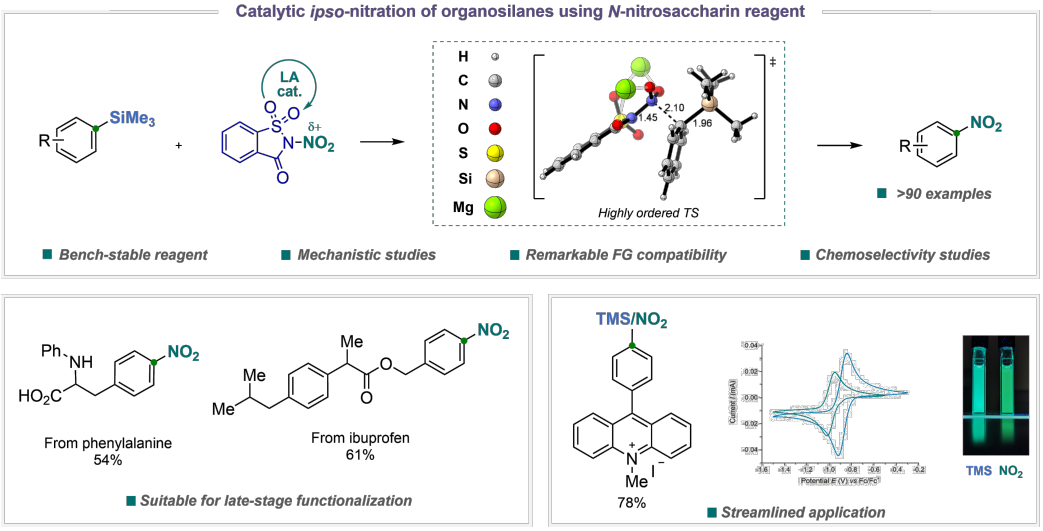
Nitroaromatic compounds represent one of the essential classes of molecules that are widely used not only as feedstock for the synthesis of intermediates on both laboratory and industrial scales, but also for the preparation of nitro-derived pharmaceuticals, agrochemicals, and materials.[1,2] Therefore, the development of sustainable, chemo- and regiospecific nitration processes that utilize bench-stable, easily accessible and non-acidic reagents and operate under catalytic manifold and eco-friendly conditions remain in high demand. We herein disclose the efficient, mild, and catalytic *ipso*-nitration of organotrimethylsilanes, which is enabled by electrophilic *N*-nitrosaccharin reagent[3,4] and allows for the chemoselective nitration under mild reaction conditions, while exhibiting remarkable substrate generality and functional group compatibility. Conversely, the reaction conditions proved to be orthogonal to other common functionalities, allowing to program molecular complexity *via* successive transformations or late-stage nitration. Detailed mechanistic investigation by experimental and computational approaches strongly supported a classical electrophilic aromatic substitution (S_EAr) mechanism, which was found to proceed through a highly ordered transition state.



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Iridium(III)-catalyzed intermolecular C(sp^3)–H amidation for the synthesis of chiral 1,2-diamines

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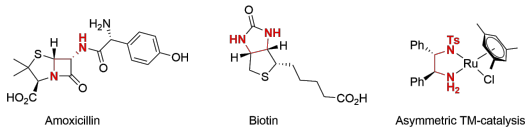
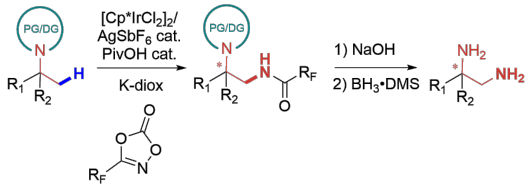
Chiral 1,2-diamines are privileged scaffolds among bioactive natural products, active pharmaceutical ingredients, ligands for transition-metal-based asymmetric catalysis and organocatalysts (Scheme 1)[1]. Although few traditional approaches have facilitated their synthesis[2], the construction of chiral 1,2-diamine motifs remains still a challenge. Lately, transition-metal-catalyzed C(sp^3)–H amination reactions have witnessed impressive advances, providing powerful, straightforward and unconventional strategies to forge new C(sp^3)–N bonds[3].



Motivated by the lack of direct methods to access such a useful scaffold, we developed an iridium(III)-catalyzed intermolecular C(sp^3)–H amidation for the synthesis of chiral 1,2-diamines (Scheme 2). This method takes advantage of the high reactivity of K-Diox[4], a bench-stable 1,4,2-dioxazol-5-one-based nitrene precursor and relies upon the design of a new, cheap and cleavable *exo*-protecting/directing group derived from camphorsulfonic acid, furnishing free enantiopure diamines upon cleavage of both nitrogen substituents[5]. Kinetic and computational studies served as support tools to gain further insights into the reaction mechanism, which proceeds through a sequence of C(sp^3)–H activation (CMD) and inner-sphere nitrene transfer. Moreover, in order to achieve the synthesis of chiral α-tertiary-1,2-diamines, a two-steps protocol involving intermolecular regioselective hydroamination of an unactivated olefin/C(sp^3)–H amidation was developed.



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Efficient C-N cross couplings via heterogeneous single-atom catalysis

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Palladium-catalyzed Buchwald-Hartwig aminations provide a crucial methodology for accessing arylamines in pharmaceuticals manufacture. These reactions currently rely on expensive and unrecoverable soluble metal complexes, which pose challenges for sustainability and product purification.[1] The use of heterogeneous catalysts would enable process intensification, simplify downstream processing, and reduce waste.[2] However, traditional catalytic materials have struggled to match the activity and selectivity of homogeneous systems due to the lack of uniformity and specific properties of active sites. Single-atom heterogeneous catalysts (SACs) present promising new opportunities, where metal atoms anchored on carefully selected host materials, resemble the structural characteristics of metal complexes.[3]

This study explores the reactivity of isolated palladium atoms anchored on a graphitic carbon nitride host (Pd/ECN) in Buchwald-Hartwig amination reactions (**Fig. 1a**) with diverse coupling partners and conditions. Remarkably, the catalyst exhibits high yields for a wide range of aryl halides and amines, highlighting its versatility. Notably, the catalyst can be recycled several times without significant loss of reactivity (**Fig. 1b**). Analysis of the interaction between the individual reaction components (solvent, ligand, base, reactants) and the metal sites by *in situ* X-ray absorption spectroscopy (XAS) studies sheds light on the C-N coupling mechanism over SACs revealing differences from the anticipated mechanisms over organometallic catalysts (**Fig. 1c**). The results highlight the potential of SACs as a complementary tool for exploring a broader chemical space within C-N coupling reactions.

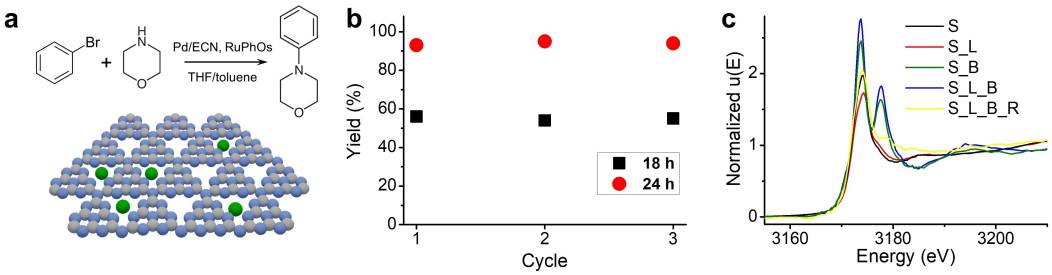

Fig. 1a Schematic of the Buchwald-Hartwig coupling catalyzed by Pd/ECN SAC. **b** Measured yield over 3 reaction cycles after 18 h and 24 h. **c** Pd L_3-edge X-ray absorption near-edge structure analysis under varying environments comprising solvent (S), base (B), ligand (L), and reactants (R).

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Photoredox Activation of Anhydrides and Acids for the Solvent-Controlled Switchable Synthesis of *gem*-Difluoro Compounds

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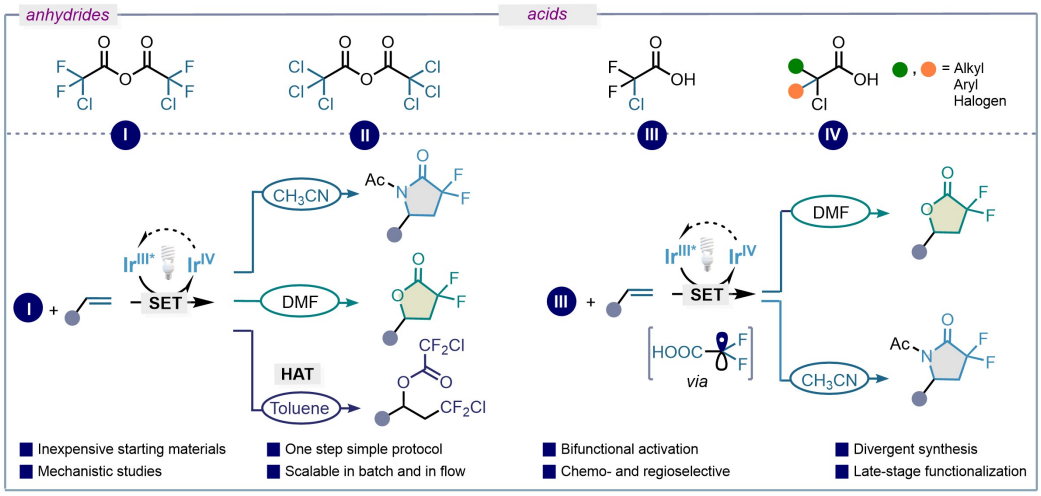
The outstanding impact of fluorine in drug discovery and development cannot be underestimated, since 20–25% of drugs in the pharmaceutical pipeline contain at least one fluorine atom. Substantially, the incorporation of the *gem*-difluoro (CF_2) motif into organic frameworks is highly desired due to the influence of this unit on the physicochemical and pharmacological properties of molecules.[1] However, the introduction of such synthon requires the use of prefunctionalized starting materials or a surrogate at the beginning of the synthesis. To address this limitation chlorodifloroacetic anhydride (CDFAA, I) can be selected as promising precursor because it is an abundant source of fluorine building blocks and it possesses varied reactivity. In the context of the divergency and applicability of such reagents, switchable synthesis can be beneficial to access a wide range of fluorinated compounds. Herein we present our studies to access gem-difluoro compounds that employ CDFAA as a low-cost and versatile fluoroalkylating reagent. Extensive mechanistic studies revealed that electron-transfer photocatalysis triggers mesolytic cleavage of a C−Cl bond generating a *gem*-difluoro carboxy radical. In the presence of olefin, this radical species acts as unique and efficient bifunctional reagent that, under solvent-controlled reaction conditions, delivers a wide range of *gem*-difluorinated γ-lactams, γ-lactones, as well as promotes oxy-perfluoroalkylation.[2] Due to the fact that most anhydrides are prepared from the corresponding acids, developing a mild and operationally simple strategy to access *gem*-difluoro compounds using chlorodifloroacetic acid (CDFA, III) can serve as a beneficial entry for achieving a step-economic and practical synthesis of fluorinated scaffolds. We found, that depending on the polarity of the solvent, CDFA can exhibit varied reactivity under photoredox conditions in the presence of an alkene precursor.[3] These methodologies are flow and batch scalable, possess excellent chemo- and regioselectivity, and are useful for late-stage diversification of complex organic scaffolds.



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Exploring Conductance Phenomena in Single Molecule Break Junctions using Thiophene Macrocycles with Multiple Pathways

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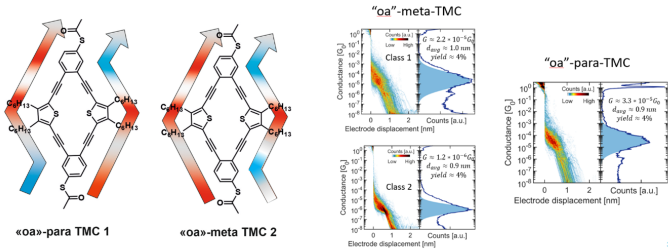
[1]University of Basel, St. Johanns-Ring 19, 4056 Basel, Switzerland, [2]Delft University of Technology, Lorentzweg 1, 2628 CJ Delft, The Netherlands

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



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Visible-light-mediated Enantioselective Arylation of Remote C(sp^3)-H Bonds via Hydrogen Atom Transfer and Sulfinyl-Smiles Rearrangement

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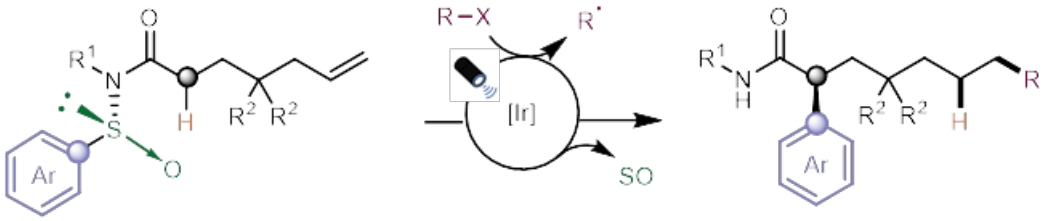
[1]University of Zurich, [2]Universidad de Alcalá

Asymmetric remote C(sp^3)-H functionalization, in particular using 1,*n*-Hydrogen Atom Transfer (HAT) events[1], represents a powerful strategy to forge stereogenic carbon centers in otherwise inaccessible positions. Despite significant progress in combining 1,*n*-HAT with enantioselective transition metal catalysis[2], asymmetric arylation of remote C(sp^3)-H bonds remains a largely unsolved problem. Meanwhile, the radical sulfinyl-Smiles rearrangement has emerged in recent years as a versatile tool for asymmetric (hetero)arylation[3].

Herein, we present a visible-light-mediated remote arylation of sulfinyl heptenamide combining a sequential 1,*n*-HAT and a sulfinyl-Smiles rearrangement. With this protocol, a wide variety of chiral amides are obtained with excellent enantioselectivity. Mechanistic investigations, including deuterium labeling experiments and computational studies, have been conducted to support a comprehensive understanding of this transformation.



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Photouncaging Systems Actuated by Near-Infrared Light

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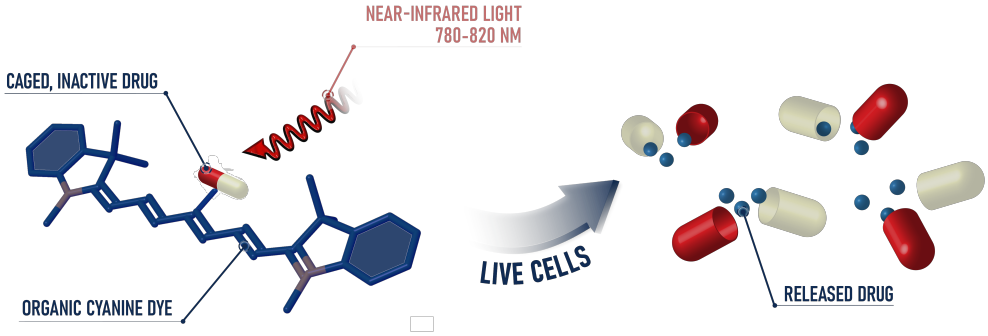
Near-infrared light (NIR; 650–900 nm) offers unparalleled advantages as a biocompatible stimulus. The development of photocages that operate in this region represents a fundamental challenge due to the low energy of the excitation light. Herein, we repurpose cyanine dyes into photocages that are available on a multigram scale in three steps and efficiently release carboxylic acids in aqueous media upon irradiation with NIR light up to 820 nm. The photouncaging process is examined using several techniques (NMR, UV-vis, HPLC), providing evidence that it proceeds *via* photooxidative pathway. We demonstrate the practical utility in live HeLa cells by delivery and release of the carboxylic acid cargo, that was otherwise not up-taken by cells in its free form, using fluorescence microscopy. In combination with modularity of the cyanine scaffold, the realization of these accessible photocages fully unleashes the potential of the emerging field of NIR-photoactivation and can facilitate its widespread adoption outside the photochemistry community.



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Chiral arylsulfinylamides: *all-in-one* reagents for visible light-mediated asymmetric alkene aminoarylations

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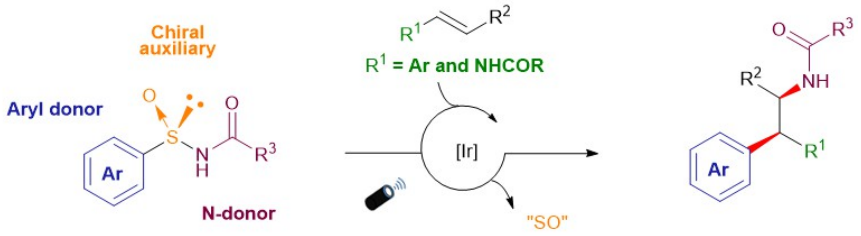
Two- or one-electron mediated difunctionalizations of internal alkenes represent straightforward approaches to assemble molecular complexity by the simultaneous formation of two contiguous Csp^3-stereocenters. While racemic versions have been extensively explored, asymmetric variants, especially those involving open-shell C-centered radical species, are very limited both in number and more importantly, scope.[1,2,3] Recently, our group exploited the ability of chiral N-sulfinyl moieties to impart absolute stereocontrol in the radical mediated transformation to assemble all-C quaternary centers.[4]

Here, we present an asymmetric intermolecular alkene aminoarylation using arylsulfinylamides as multifunctional *all-in-one* reagents featuring a traceless chiral auxiliary.[5] The reaction tolerates a wide variety of N-atom donors and is compatible with both 1,2-disubstituted styrenes, vinyl ethers and vinyl amides thus providing access to valuable *b,b*-diarylethylamines, aryl-*a,b*-ethyleneaminoalcohols, and aryl-*a,b*-ethylenediamines. Excellent levels of both relative and absolute stereocontrol are achieved in the two newly forged stereogenic centers governed by the configuration of the chiral sulfoxide tether. Characterization of the reaction mechanism revealed an interesting dichotomy in the initiation of the photoredox catalytic cycle wherein either electron-rich alkenes or sulfinylamides are preferentially activated at the expense of the Ir photocatalyst.



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Aziridines via 1,3,2-Diazaphospholene-Catalyzed *aza*-MIRC

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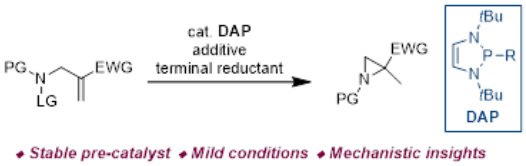
[1]Institute of Chemical Sciences and Engineering (ISIC) EPFL SB ISIC LCSA, BCH 4305

1,3,2-diazaphospholenes hydrides (DAP-Hs) are highly nucleophilic organic hydrides which can act as main-group catalysts for a range of attractive transformations.[1] Herein, we report a DAP-catalyzed *aza*-Michael Induced Ring Closure (MIRC) to access aziridines under mild conditions. A broad range of Michael acceptors were tolerated and preliminary investigations showed even the potential use of chiral DAP catalysts to access enantioenriched aziridines.



◆ *Stable pre-catalyst* ◆ *Mild conditions* ◆ *Mechanistic insights*

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Bioinspired Synthesis of Tetraponerines and Analogues Thereof

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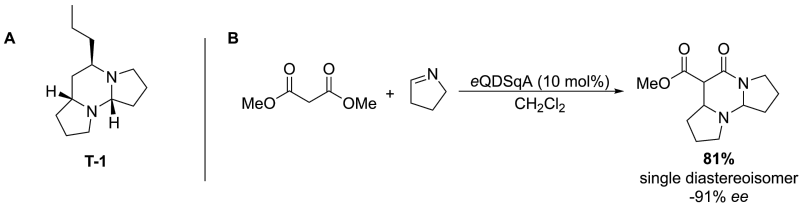
Tetraponerines are natural alkaloids that occur in the smear venom of *Tetraponera* ants. Eight different members (T-1 to T-8) have been identified, with T-8 being the most abundant.[1] All consist of a tricyclic aminal with a linear alkyl substituent (Figure 1). Tetraponerines inhibit non-competitively the nicotinic acetylcholine-receptor and thereby paralyze their enemy.[1]

The Wennemers group has developed stereoselective (thio)acetate and (thio)malonate addition reactions by utilizing malonic acid-derived thioesters. These (thio)acetate equivalents react in the presence of catalytic amounts of cinchona alkaloid derivatives with a variety of different electrophiles, including aldehydes, nitroolefins, and imines.[2]

Herein, we present the stereoselective addition of malonates to cyclic imines that yields the tricyclic core of tetraponerines (Figure 2). This organocatalytic addition reaction proceeds with high stereoselectivity (>90% *ee*). The synthesis of tetraponerines requires only four steps and is, thus, the shortest stereoselective synthesis of tetraponerines known to date. [3],[4]



A: Structure of Tetraponerine T-1; B: Stereoselective addition of dimethyl malonate to Δ1-pyrroline as the key step.

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Functionalization of 1,3,6,8-Tetraazapyrene for fused Donor-Acceptor Ensembles

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Controllable charge-transfer pathways in molecular ensembles are key characteristics for the successful fabrication of organic electronics. To approach this goal, multiple strategies can be followed. For instance, oxidation or reduction can be used to control charge transfer in a chemical way. With this purpose, efficient synthetic approaches to tetrathiafulvalene (TTF)-based electron donor-acceptor (D–A) ensembles were developed.[1] To achieve TTF-annulated D-A systems, tetraazapyrene (TAP) was introduced as a p-conjugated electron acceptor.[2] This work focusses on the synthesis of the TAP building blocks (Figure 1) which are the core compounds of the conjugated ensembles. The construction of the TAP core contains a multi-step reaction starting with nitration of 1,5-dinitronaphthalene followed by reduction to obtain a tin salt.[3] The electronic properties of the resulting D-A ensembles are described in detail.

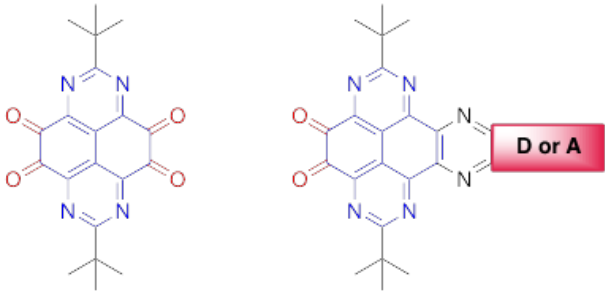

Figure 1: TAP building blocks for Schiff-base reactions

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

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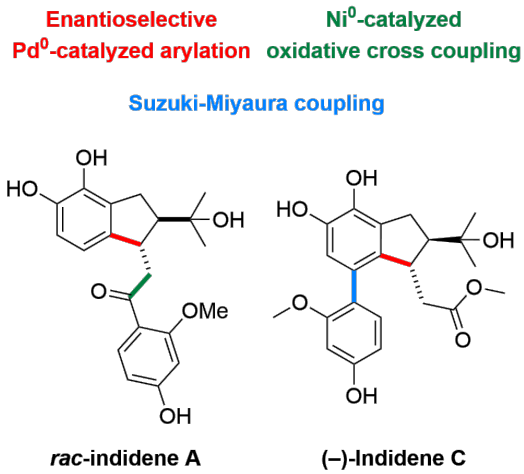
Recently developed C–H activation methodologies have enabled concise and efficient total syntheses of various bioactive natural products[1]. In this context, Pd^0-catalyzed C–H activation has emerged as a method of choice for construction of cyclopentane rings of various complexity[2]. We report our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



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Introducing Cinchona Alkaloid Appended Thiol(s) in Gold Nanocluster Chemistry

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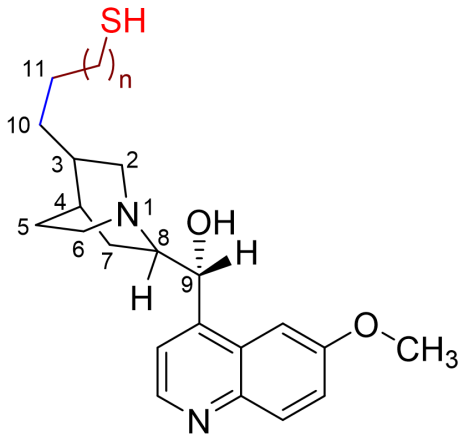
Cinchona alkaloids represent a diverse class of naturally occurring compounds that have been extensively studied and utilized in various fields of chemistry and biochemistry over the past two centuries.[1,2] These versatile molecules have demonstrated a wide range of applications, including their use as chiral organocatalysts, ligands, chromatographic selectors, antimalarial drugs, and NMR discriminating agents.

Our research aims to further explore the potential of cinchona alkaloid-appended thiols with varying chain lengths (n = 0, 2, 4, ...) as chiral ligands in gold nanocluster chemistry, see figure. We plan to synthesize and incorporate these ligands into nanoclusters such as $Au_{25}(PET)_{18}$ through ligand exchange reactions (LER).[3] By introducing these chiral ligands, we aim to investigate their potential applications in enantioselective organocatalysis, NMR discrimination, and other related fields.[4]

In this poster presentation, we will showcase the synthesis of the alkaloid derivative and present its application as chiral ligand on atomically precise gold clusters.



L1 (n = 0, 2, 4, ...)

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Enantioselective beta-arylation of alcohols via a multicatalytic relay

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[1]University of Strasbourg

Alcohols are omnipresent functional groups in many functional fine chemicals, such as pharmaceuticals and agrochemicals. Hence, methods enabling their regio- and stereoselective synthesis and diversification are highly sought after. [1] Inspired by the capacity of multicatalytic systems, [2] our group has recently developed a direct method for the challenging beta-regioselective arylation of alcohols.[3] However, the enantiocontrol of the reaction remained elusive, thereby limiting its utility in the practical synthesis of fine chemicals.

Here, I will present our studies on the development of an efficient protocol allowing for the direct enantioselective beta-arylation of alcohols. Mering the so-called dynamic kinetic resolution (DKR) strategy with the multicatalytic relay system enabled the formation of enantioenriched beta-arylated alcohols. The mild conditions allow for a broad substrate scope, high functional group tolerance, and high enantioselectivity of the transformations, establishing a robust reliable synthetic protocol. In a broader context, this study demonstrates the potential of leveraging multi-catalytic relays to execute the transformations that remain elusive with conventional catalytic strategies.

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Protecting-Group-Free Synthesis of Selenoglycoconjugates in Water

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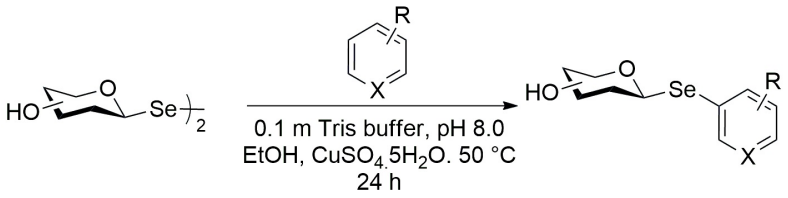
The synthesis of biologically active glycoconjugates is one of the cornerstones of Glycoscience. However, traditional methods typically involve multi-step synthesis, employing complex and protracted protecting group strategies. These methods are generally technically demanding, inefficient, expensive, and logistically difficult to achieve. The development of methodologies which allow direct aqueous conversion of unprotected sugars into glycosides is therefore an ambitious goal.

Herein, we present a broadly applicable method for the synthesis of selenoglycosides in water. We show the ease of direct conjugation of unprotected glycosyl diselenides with various biomolecules, including resorcinol, resveratrol, and the antitumor agent, gimeracil, furnishing the corresponding selenoglycoconjugates in up to 63% yield.



We also demonstrate the oxidatively-triggered release of the bioactive drug from the sugar, priming these molecules for medicinal applications. The generality and broad substrate scope of this novel transformation will provide access to various selenium-containing glycomimetics and glycoconjugates.

Studies Towards the Total Synthesis of Cervinomycin Natural Products

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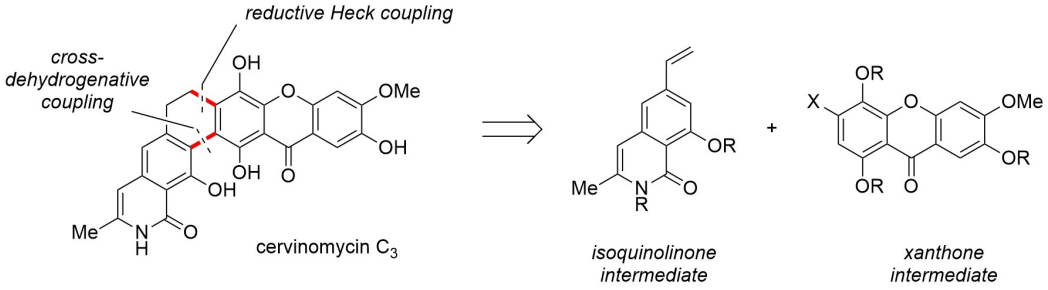
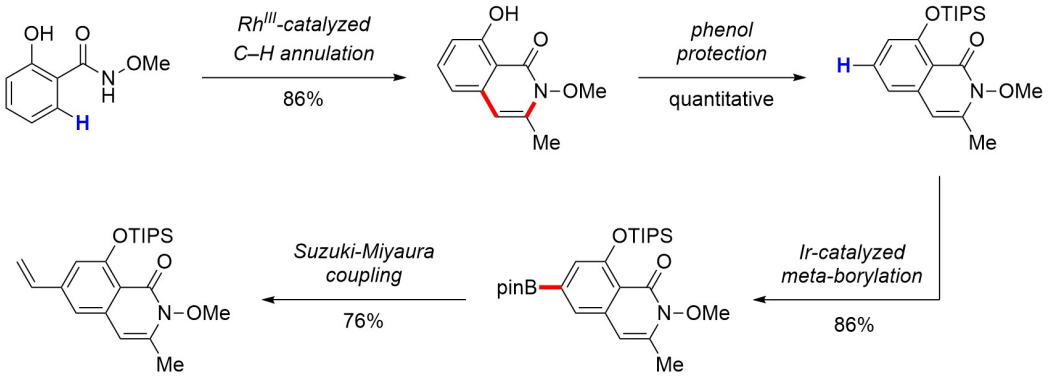
[1]University of Basel, Department of Chemistry

Cervinomycins are aromatic polyketides which exhibit antibiotic activity against gram-positive bacteria and high cytotoxicity. [1] Herein we report our studies towards the total synthesis of these natural products, in which multiple C–H functionalization steps allow for a convergent route. Retrosynthetically, we aim to construct cervinomycins from functionalized xanthone and isoquinolinone fragments, which will be joined through a reductive Heck coupling and a cross-dehydrogenative coupling. [2]



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



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Mechanistic Investigation of the Rhodium-catalyzed Transfer Hydroarylation between Tertiary Alcohols and Ketones

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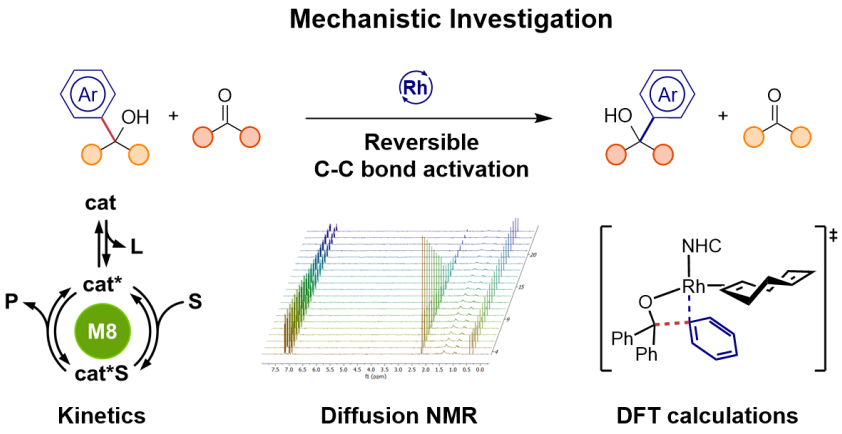
Carbon–carbon bonds are among the most abundant yet least reactive chemical bonds in organic molecules. The targeted activation of these bonds in a general sense remains challenging yet offers great potential to break down and reorganize small molecules without the need for prefunctionalization.

We recently disclosed a catalytic shuttle arylation reaction to interconvert triaryl alcohols and ketones by realizing C–C bond activation via reversible β-carbon elimination.[1] Using this method, unprotected alcohols serve as a benign alternative to stoichiometrically employed organometallic reagents to access value-added alcohol products from ketones. Our method exhibits high chemoselectivity and tolerates functional groups that are vulnerable to traditional nucleophilic and basic reagents encountered in carbonyl addition.

The mechanism of this isofunctional transformation was subsequently investigated by experimental and computational methods including kinetic studies, in situ spectroscopic monitoring, and density functional theory (DFT) calculations, supporting a fully reversible β-carbon elimination/insertion mechanism.[2] The gained insight allowed to develop improved protocols with air-stable precatalysts.

This work highlights the advantages of using alcohols as mild aryl donor reagents in carbonyl addition and sheds light on the mechanism of rhodium-catalyzed C–C bond activation, possibly initiating the development of novel chemical transformations using alcohols as latent carbon-centered nucleophiles.



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Streamlined Synthesis and Catalytic Performance of Chiral Cyclic (Alkyl)(Amino)Carbene Transition Metal Complexes Bearing α-Quaternary Stereogenic Centers

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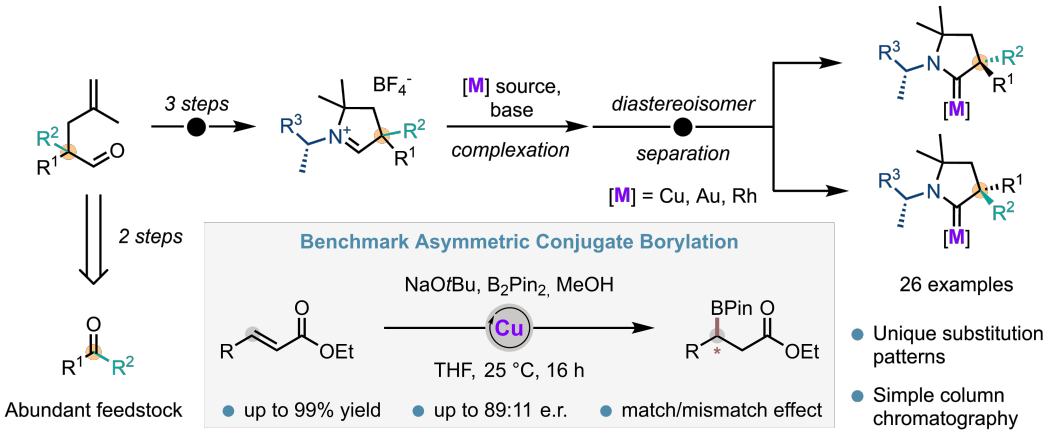
Despite recent advances in the field of chiral Cyclic (Alkyl)(Amino)Carbenes (CAACs), achieving chirality in α-position to the carbene center remains remarkably challenging. CAAC complexes displaying such attributes involved in asymmetric transformations are yet limited to few examples[1,2]. Most efforts were currently targeted at asymmetric ruthenium catalysis (AROCM, ARM, ACM) with optically pure complexes obtained after chiral resolution on preparative HPLC[3]. Herein we describe a complementary approach to access highly modular carbene precursors featuring chiral α-quaternary centers. Chiral amines and readily prepared preallylated racemic aldehydes were merged to prepare diastereoisomeric carbene precursor salts. The two corresponding metal complexes can be obtained separately following the purification step, after complexation with a variety of transition metals (Cu, Au, Rh). A library comprising more than 20 complexes was prepared, showcasing unprecedented α-substitution patterns. The copper complexes unique steric and electronic environments were investigated in benchmark Asymmetric Conjugate Borylation (ACB) reaction, providing excellent yields and high enantioselectivities.



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Interrupted Polonovski strategy for the functionalization of amino acids and peptides

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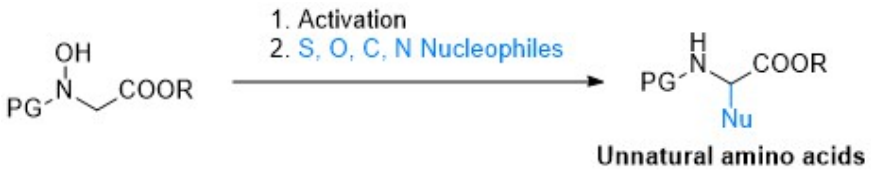
[1]Laboratory of Catalysis and Organic Synthesis, Institute of Chemical Sciences and Engineering, Ecole Polytechnique Fédérale de Lausanne

Unnatural amino acids are an essential class of compounds in peptides and other biologically active products. Many methods have been developed to access them, but they still often require toxic reagents or strongly oxidative or basic conditions. We report here the a functionalization of carbamate-protected hydroxylamine glycine substrates, employed as imine surrogates[1], in an interrupted Polonovski reaction to modify the backbone of the amino acids. The addition of numerous S, N, O and C nucleophiles was achieved in a one-pot procedure under mild basic conditions.



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Synthesis and Reactivity of a Terminal 1-Alkynyl Triazene

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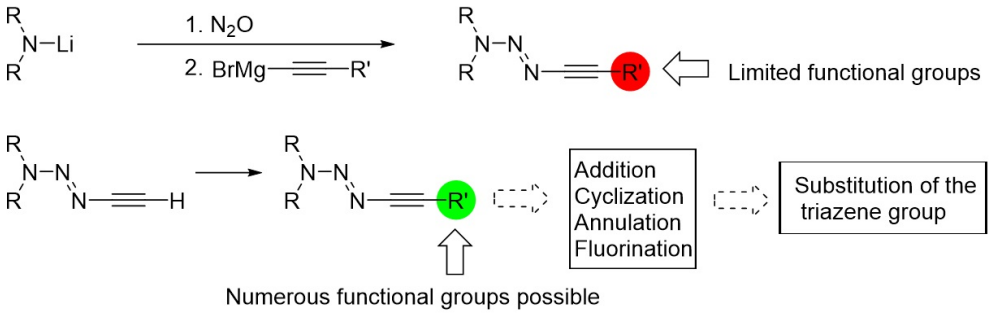
[1]Ecole Polytechnique Fédérale de Lausanne

1-Alkynyl triazenes have emerged as highly versatile reagents in organic synthesis.[1] The electron-donating character of the triazene group activates the triple bond, resulting in ynamide-like reactivity. 1-Alkynyl triazenes can be employed as suitable substrates for a variety of reactions, including cycloadditions, annulations, rearrangements, and 1,2-additions, as well as fluorination reactions. A distinct advantage of using 1-alkynyl triazenes in these transformations is the possibility for further derivatizations of the products. Under acidic conditions, the triazene function can be substituted by a variety of nucleophiles, facilitating divergent product modifications.[1]

Thus far, 1-alkynyl triazenes have been accessible only by one synthetic route, namely, the coupling of lithium amides with first nitrous oxide (N_2O) and then an alkynyl Grignard reagent.[2] The utilization of strongly basic and nucleophilic reagents severely restricts the functional groups, which can be employed. We have now developed a procedure for the synthesis of a terminal 1-alkynyl triazene.[3] The easy-to-access compound enables the preparation of 1-alkynyl triazenes with a range of functional groups including esters, alcohols, cyanides, phosphonates, and amides. The availability of functionalized 1-alkynyl triazenes makes this class of compounds attractive for applications in organic synthesis. The terminal 1-alkynyl triazene can also be used for the synthesis of di- and triynes and for the preparation of (hetero)aromatic triazenes via transition-metal-catalyzed cyclization reactions.[3]



Scheme 1. Versatile reactivity of terminal 1-alkynyl triazene

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CpRu-Catalyzed Multicomponent Synthesis of Polyheterocycles Pyrazolidines Through Cycloadditions and Metal-Carbene Addition

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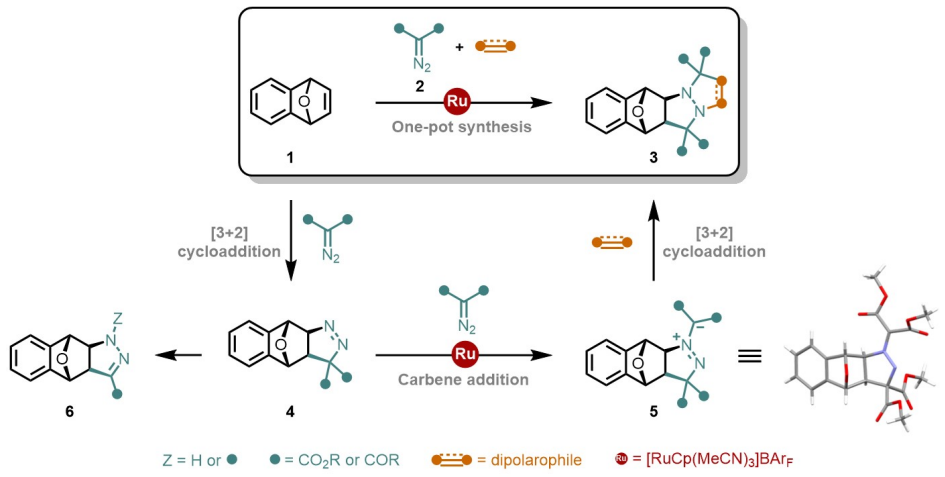
Cyclopentadienyl-Ruthenium (II) complexes are known to efficiently promote the decomposition of diazo malonates and α-diazo-β-ketoesters to generate *Fischer*-type carbenes. These electrophilic intermediates form ylides in presence of various *Lewis* bases, such as cyclic ethers,[1] ketones,[2] and lactams,[3] among others. Subsequently, the reactive zwitterions can undergo different rearrangement or insertion reactions to obtain different classes of functionalized heterocycles.

Based on previous reactivities developed in our lab with oxonium[1] and ammonium[4] ylides, and in divergence with recently reported studies using 2,2,2-trifluorodiazoethane,[5] the reactivity of bicyclic ether **1** and diazomalonate **2** under ruthenium (II) catalysis was investigated. Herein, a fully-diastereoselective one-step synthesis of diaza polycyclic compounds **3** *via a* series of cascade reactions is obtained. More interestingly, this reaction can also be done stepwise, and each intermediate **4** and **5** can be isolated in high yields. Moreover, ylides **5** showed unusual stability, as they can be stored at room temperature under air conditions and can further react with various dipolarophiles to access symmetrical on non-symmetrical polycyclic pyrazolidines. In addition, the cycloadduct **4** can undergo rearrangements such as a 1,3-ester shift or a decarboxylation to afford corresponding pyrazolines scaffolds **6**. We thus report a direct methodology to access valuable N−N bond-containing heterocycles, which are presented in many natural products and bioactive molecules.[6]



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Synthesis of bicyclo[3.1.1]heptanes and cyclopenta(e)nes by photocatalyzed cycloaddition of carbonyl cyclopropanes.

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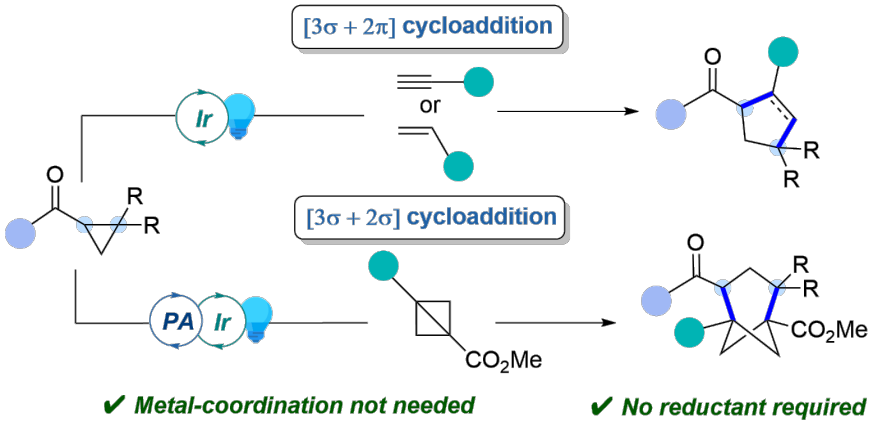
Cyclopropanes play a key role in synthetic chemistry, both as structural elements and reactive building blocks.[1] The studies of donor-acceptor cyclopropanes are well-established in synthetic chemistry to enable C-C bond cleavage and generate 1,3 dipole intermediate for further transformation.[1] However, it is usually required a diester group as an acceptor. Cyclopropanes bearing a single carbonyl group are usually not sufficient to promote ring opening under mild condition.



In this study, we report a photocatalyzed homolytic ring-opening of carbonyl cyclopropanes under mild conditions without the need for a metal co-catalyst or a strong reductant. The resulting intermediate can be used for cycloaddition with alkynes, alkenes, and bicyclo[1.1.0]butanes, yielding cyclopentenes, cyclopentanes, and bicyclo[3.1.1]heptanes (BCH) respectively.[2] In addition, bicyclo[3.1.1]heptanes have been recently studied as bioisosteres for *meta*-substituted aromatic rings.[3] Therefore, our protocol enables a convergent way to approach BCH scaffolds under mild and operationally simple conditions.

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o-Quinodimethane Atropisomers: Enantioselective Synthesis and Stereospecific Transformation

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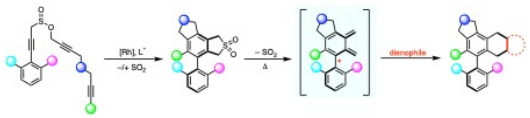
The use of *o*-quinodimethanes as reactive intermediates in Diels-Alder reactions is a versatile approach to synthesize complex polycyclic compounds.[1] There are different precursors to thermally generate *o*-quinodimethanes,[2] but due to the required high temperatures and the high reactivity of *o*-quinodimethanes, stereoselectivity to afford isomerically defined products constitutes a major challenge. Since our group is interested in developing methodologies for the synthesis of axially chiral biaryls by *de novo* ring construction,[3] we aimed to identify atropisomeric *o*-quinodimethanes. In this work we describe an intramolecular catalyst-stereocontrolled [2+2+2] cycloaddition of triyne substrates to generate atropisomeric benzocyclobutenes, benzocyclic sulfones and benzosultines which serve as precursors for the rotationally restricted aryl-o-quinodimethanes. Owing to their remarkable configurational stability, no racemization of the stereogenic axis occurs during the thermal ring opening. This allows for highly stereospecific Diels-Alder reactions of the *in situ* formed *o*-quinodimethanes with various dienophiles to form various polycyclic biaryls.



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([+] denotes equal contribution)

From Naked-Eye Detection of H-Bond Donors to Chiroptical Sensing of Enantiopure Reagents

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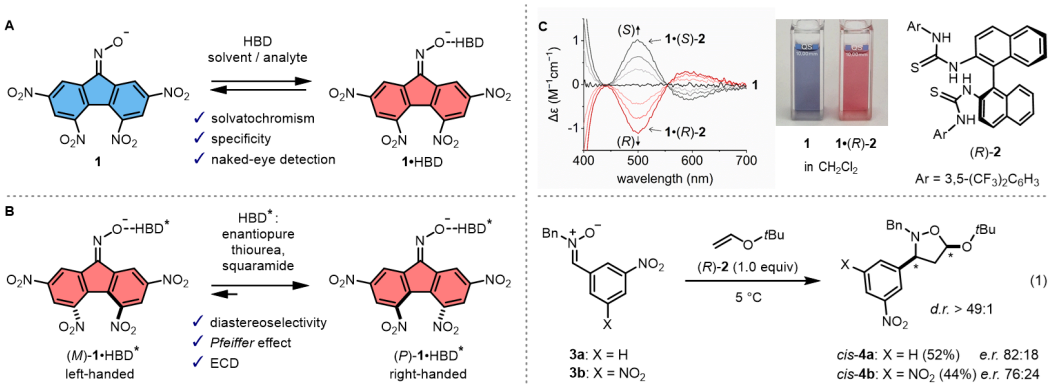
2,4,5,7-Tetranitro-9*H*-fluoren-9-one and its derivatives are classical examples of strong *π*-acceptor molecules used in applications from chemistry to industrial and material sciences. Examples include supramolecular nanostructures and removal of aromatic sulfur and nitrogen compounds from diesel fuel based on the formation of charge-transfer complexes. With derivatives containing grafted enantiopure side chains, chiral resolution procedures have been reported, and that of [6]helicene in particular.[1] Herein, in a new development for this class of molecules, we report that readily-accessible oximate **1** presents solvatochromic properties specific to H-bond donors (HBDs), either used as solvents or as individual moieties (Fig. A). In fact, dissolution of dye [Bu_4N][**1**] or [Na][**1**] gives a blue solution ($\lambda_{max} \approx 600$ nm) in aprotic solvents independently of polarity, on the other hand, solvents possessing H-bond donating capabilities are clearly distinguished upon strong hypsochromic shifts ($\Delta\lambda_{max}$ up to −137 nm, blue to red-turning solutions). Notably, an excellent linear correlation was found between λ_{max} of **1** and *Kamlet–Taft* parameter *α* for water and alcohols,[2] linked to their ability to donate a proton in a solvent-to-solute hydrogen bond. As such, water, alcohols, amines, amides, squaramides, thioureas and their different H-bond donating ability can be effectively detected using oximate **1**.



We also demonstrate the existence of helical deformations (twists) within the 2,4,5,7-tetranitro-9*H*-fluorenylidene skeleton and exploit the occurrence of configurationally labile *M* and *P* geometries for the chiroptical sensing (electronic circular dichroism: ECD) of enantiopure reagents: addition of enantiopure thioureas and squaramides to the solution of **1** in aprotic solvents led to remarkable, 50–85 nm hypsochromic shifts in the absorption spectra, accompanied by emerging ECD bands (*Pfeiffer* effect,[3] Fig. B and C) in several instances.

Finally, in an attempt to link ECD chiral recognition and reaction enantioselectivity, the stereoinductions of bis-thioureas onto (i) configurationally labile oximate **1** and (ii) the 1,3-dipolar cycloaddition of structurally related nitrones **3a** and **3b** (eq 1) were compared. The asymmetric induction between bis-thioureas and (*M*)- / (*P*)-**1** served as a direct probing method to select the most effective HBD for asymmetric synthesis.

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Iron-catalyzed synthesis of alpha-azido amino acids: an easy access to versatile building blocks

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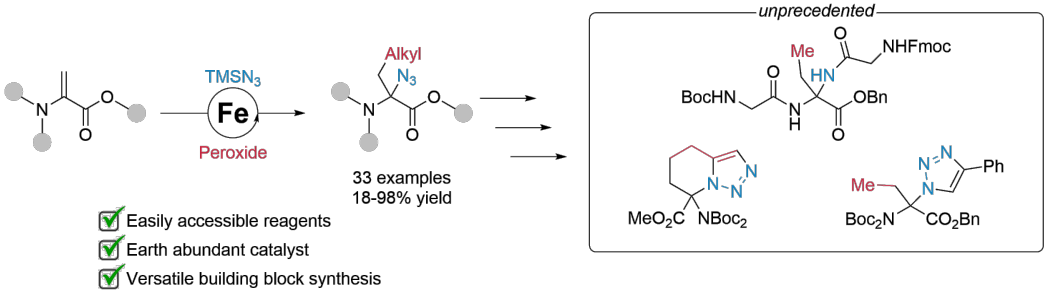
The pharmaceutical industry is interested in the development of new transformations to access diversified amino acids and peptides.[1] Non-proteinogenic amino acids (NPAAs) show great potential for the optimization of various biological properties (half-life, specificity, potency, membrane permeability and conformation) of peptide drugs.[2] However, the use of *α*-nitrogen substituted amino acids has been scarce due to their challenging synthesis.[3,4] To access these underdeveloped scaffolds, we turned ourselves to earth abundant metal catalysis. In the last decades, the use of first-row transition metals such as iron has emerged as an alternative to the well-established transition-metal catalysts such as rhodium, palladium or iridium. In addition to their high availability and reduced cost, they now appear as key catalysts for the development of new radical-mediated synthetic routes.[5] In this context, we developed an easy access to *α*-azido amino acids from dehydroamino acids as alkyl radical acceptors using iron catalysis. Various azidated amino acids, both proteinogenic and non-natural analogues, were successfully synthesized. The obtained compounds appear as versatile building blocks that could be transformed into various unprecedented scaffolds including aminal-type peptides, [7,7]-substituted tetrahydro-triazolopyridine and *α*-alkyl-α-triazole α-amino acids.[6]



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[6] Manuscript submitted

Core Alkynylated FLIPPER for Fluorescence Membrane Tension Probes

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The plasma membrane is a key interface that mediates cell mechanobiological responses to external mechanical stimuli. For example, a high stiffness environment induced the metastatic phenotype of integrin that is related to cancer.[1] To understand the mechanobiological response of the cell, a number of techniques focusing on the plasma membrane tension have been introduced**.** The most common methods are micropipette aspiration and atomic force microscope cantilevers. These methods can provide quantitative measurements but are considered invasive to the plasma membrane.

Fluorescence bioimaging allows researchers to monitor biomolecular processes in living cells using a noninvasive optical method. Recently, our group introduced a small organic molecule based on the dithienothiophene skeleton (FLIPPER) for a fluorescence membrane tension probe.[2] The working principle of FLIPPER probes is based on the twisted conformation of electron donor-acceptor dithienothiophene dimers. Planarization upon mechanical stimuli shifts excitation to the red along with the increase in fluorescence intensity. Therefore, the modification around the mechanosensitive bond greatly influences the performance of the probe in membranes.[3]

Organic compounds with aromatic groups that are conjugated through triple bond linkages show efficient electronic communication along their conjugated structures. This effect can be attributed to the cylindrical symmetry of the triple bond which is able to maintain conjugation between adjacent phenyl groups regardless of the relative orientation of the aromatic planes.[4] Herein, we report a series of novel FLIPPER probes having mono- and double-alkyne bonds at the central mechanosensitive bond between dithienothiophene dimers. The different dihedral angles between two dithienothiophene dimers could be due to several possibilities of p-orbital overlap, which can lead to a difference in photophysical properties upon planarization in different environments. The findings demonstrated the mechanosensitivity properties of the novel FLIPPER probes. Additionally, an examination of their characteristics in vesicles and cells as well as an analysis of their structural details are disclosed.

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Nonacethrene as a magnetic photoswitch: can one methyl group change the game?

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In this project we aim to design a new all organic chiral magnetic photoswitch. The target compound is called nonacethrene and is the bigger homolog of cethrene, a chiroptical diradicaloid photoswitch. Pristine cethrene is too reactive but functionalization with two methyl groups in the fjord region leads to dimethylcethrene, which can be switched between an open and a closed form via light but does not possess an electron paramagnetic resonance (EPR) signal at room temperature. By expanding the π-backbone and therefore lowering the singlet-triplet gap, nonacethrene is EPR active. Nonacethrene undergoes an unwanted cascade reaction and dimethylnonacethrene is not reactive enough to act as a photoswitch. The adjustment of the steric bulk in the fjord region with only one methyl group represents an opportunity for further optimization to achieve bistability and is a viable strategy to realize a magnetic photoswitch operating at ambient temperature.

Utilizing Sodium Amides in Deep Eutectic Solvents

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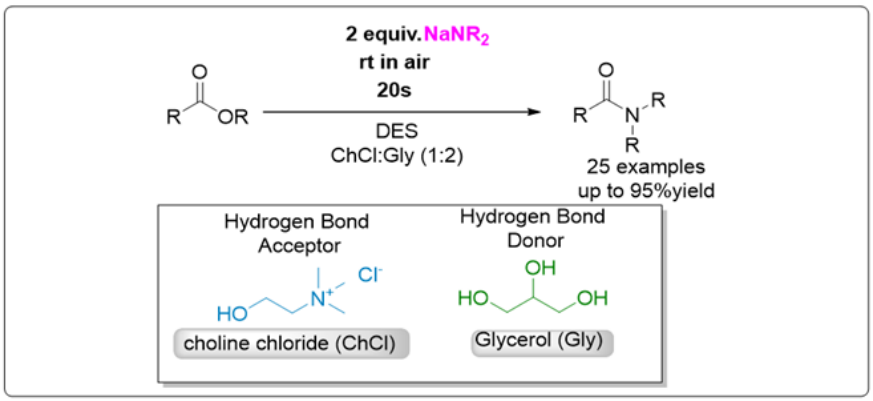
Sodium chemistry has received a recent renaissance due in part to its greater abundancy compared to lithium along with its ability to offer unique reactivity. Despite this renewed interest, organosodium reagents are highly reactive requiring strictly inert conditions as well as cryogenic temperatures (-78 °C) to prevent unwanted side reactions. Recent work from our group and others has shown that organolithium reagents and even organosodium reagents can be utilized in air by using Deep Eutectic Solvents (DES) [1]. Formed by the combination of a hydrogen bond acceptor (e.g. choline chloride) and hydrogen bond donor (e.g. glycerol), DES are recognized as inexpensive, environmentally friendly, and tunable solvents with growing applications [2].

This work will showcase how sodium amides can be used in DES for nucleophilic substitution reactions to esters and fluoroarenes. Building off recent work, we will also demonstrate how batch conditions can be upgraded to flow.[3]



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New neo-clerodane diterpenes from *Teucrium polium* subsp. *capitatum*

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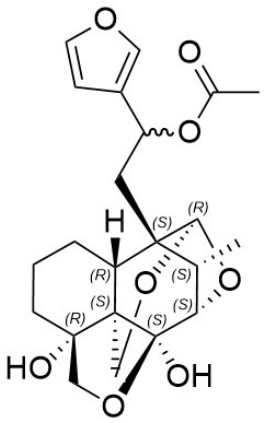
Teucrium polium subsp. *capitatum* (syn. *Teucrium capitatum*, Lamiaceae), popularly known as golden or felty germander, is a deciduous shrub that abundantly grows in Mediterranean regions of Europe, Northern Africa, and Southwest Asia. The aerial parts are traditionally used in Algeria as a decoction or ointment in the treatment of hypertension, diabetes, and wounds. In a previous study we reported the wound healing properties of a methanolic extract in a wound excision model in rabbits, and a comprehensive polyphenolic profile of this extract [1]. Further investigation of the methanolic extract focusing on the non-phenolic constituents afforded six furanoid neo-clerodane diterpenes, including 20-acetylauropolin and 6-acetylteucjaponin A, along with four previously undescribed congeners. The compounds were isolated by preparative HPLC-ESIMS after silica gel column chromatography. Their structures were established by extensive NMR analysis, HRESIMS, and by comparison with literature data of related compounds. The absolute configuration of 20-acetylauropolin was confirmed by single crystal X-ray crystallographic analysis. Some of the isolated diterpenes possess structural features uncommon in neo-clerodane diterpenes, such as a rare C-20 acetal function forming an oxepane ring to C-7 of the *trans*-decalin core structure such as in teupocapin C (**1**).



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Carboamination of propargylic alcohols via *in situ* tether formation

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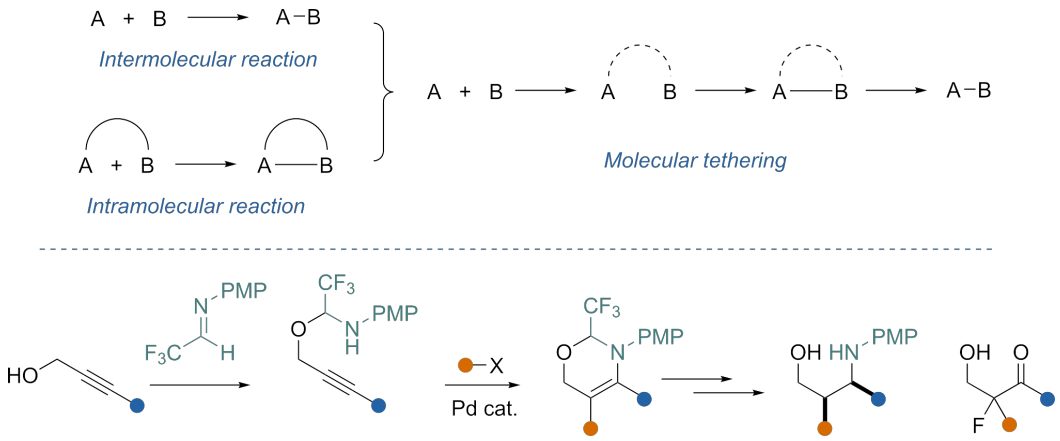
[1]Laboratory of Catalysis and Organic Synthesis (LCSO), Institute of Chemical Sciences and Engineering (ISIC), EPFL

Reactivity and selectivity are fundamental aspects of organic chemistry that must be mastered to allow the design of more efficient and environmentally friendly processes. Some reactions that are difficult to achieve in intermolecular setting can be greatly facilitated via substrate design – linking the reacting functionalities in favourable positions within the starting material. However, this strategy is limited by the accessible structural diversity. A potential alternative is to achieve intramolecularity via a strategic linkage that can be later easily cleaved, also known as molecular tethering (Scheme 1).

Selective difunctionalization of internal alkynes is an important organic transformation that provides access to geometrically defined tetrasubstituted olefins. However, for non-biased alkynes the regioselectivity is difficult to control [1]. Here we report the use of molecular tethering for selective carboamination of propargylic alcohols (Scheme 1). We found that a trifluoromethyl aldimine in combination with alkynyl bromides or aryl iodides provides 6-endo-dig selective cyclization to afford aminoarylation or aminoalkynylation products, respectively. The obtained compounds could be further functionalized by selective transformations of the double bond - hydrogenation or electrophilic fluorination.



Scheme 1. Carboamination of propargylic alcohols via in situ tether formation.

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Cu(I)-BOX Catalyzed Asymmetric 3-Component Reaction for the Synthesis of Trifluoromethylated Propargylic Ethers and Anilines

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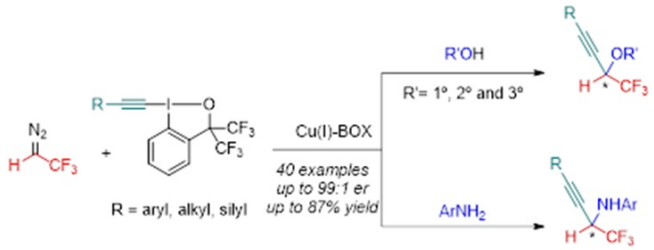
[1]EPFL-Laboratory of Catalysis and Organic Synthesis, [2]NCCR Catalysis

Chiral trifluoromethylated (CF_3) scaffolds are very important in organic and medicinal chemistry due to their excellent physical and pharmacological properties. Nevertheless, traditional methods often rely on the use of strongly basic reaction conditions, presenting a narrow scope. For this reason, it is important to find alternatives that allow the preparation of enantioenriched CF_3-compounds in a more efficient manner.[1] Propargylic ethers and anilines represent a versatile class of organic compounds in synthetically and medicinal chemistry due to the rigidity, electronic properties and easy post-functionalization of the alkyne group.

Multi-Component Reactions (MCRs) are often employed in medicinal chemistry because they facilitate the synthesis of libraries of compounds starting from easily accessible starting materials. Diazo compounds represent an important example of precursors in MCRs since they can react with both nucleophiles and electrophiles on the same reactive center, allowing the formation of multiple bonds in a single step.

In this context, Hypervalent Iodine Reagents (HIR) have been widely used in organic chemistry for the Umpolung of the reactivity of nucleophiles [2], but barely in MCRs with diazo compounds. In the last years, our group has reported different multi-component reactions with HIR and diazo compounds as starting materials. [3,4] Here, we report the first enantioselective 3-CR reaction between diazo compounds, nucleophiles and HIRs allowing the asymmetric synthesis of trifluoromethylated propargylic ethers or anilines catalyzed by a simple Cu(I)-BOX catalytic system. The reaction proceeds with a broad functional group tolerance, since primary, secondary and tertiary alcohols as well as both electron-rich and electron-poor anilines can be used as nucleophiles. Regarding the electrophilic partner, aryl-, alkyl- and silyl-substituted alkynes can be successfully introduced. In the case of chiral natural alcohols, the reaction proceeds with high catalyst control, achieving the synthesis of the trifluoromethylated propargylic ethers with very high diastereoselectivity [5]



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Electronically flexible pyridylidene amide ligands for palladium-catalyzed α-arylation of ketones

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Electronically flexible ligands such as pyridylideneamides (PYAs, Fig. 1A) can vary their degree of donor ability and may stabilize several intermediates of a catalytic cycle.[1] This ligand flexibility is a highly desirable feature in catalytic processes, especially when different oxidation states are involved.[2] In their zwitterionic form, these ligands exhibit strongly donating properties that facilitate oxidative additions on the coordinated metal center. Furthermore, their ease of production, low-cost synthesis and high tunability make them efficient alternatives to carbenes and phosphines. Surprisingly, the potential of such donor-flexible PYA ligands has been poorly investigated in palladium-catalyzed cross-coupling processes. Here we introduce different bidentate pyridyl-PYA ligands coordinated to palladium(II), which afford highly active and robust ketone α-arylation catalysts with unprecedented turnover numbers (TONs) for N-based ligands in this transformation (Fig. 1B).[3] Moreover, we will discuss mechanistic details that emerged from using these well-defined precatalysts.

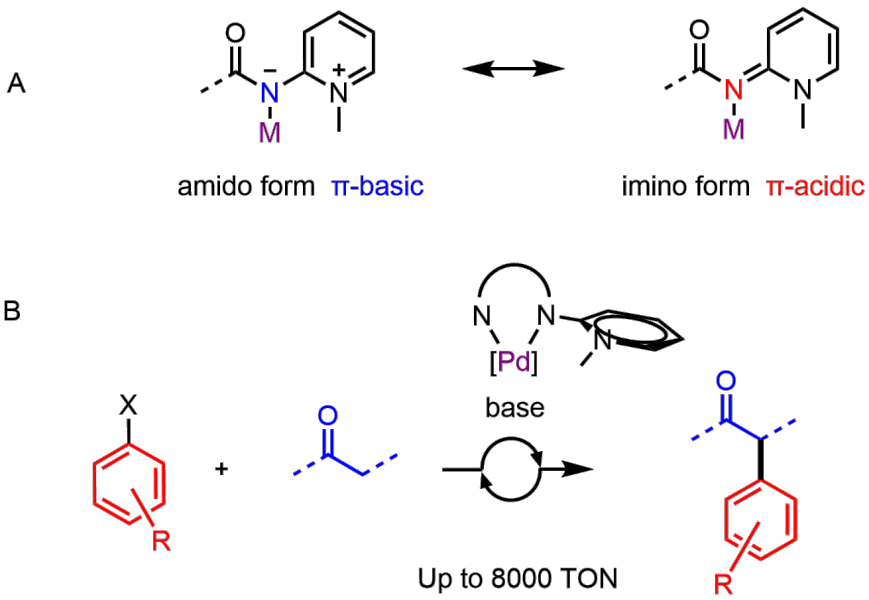

Figure 1. A: Resonance forms of the PYA ligand. B: Schematic representation of a palladium complex containing a pyridyl-pyridylidene amide ligand that is active in the α-arylation of ketones.

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Donor-Acceptor Aminocyclobutane Monoesters: Synthesis and Silylium-Catalyzed (4+2) Annulation with Indoles.

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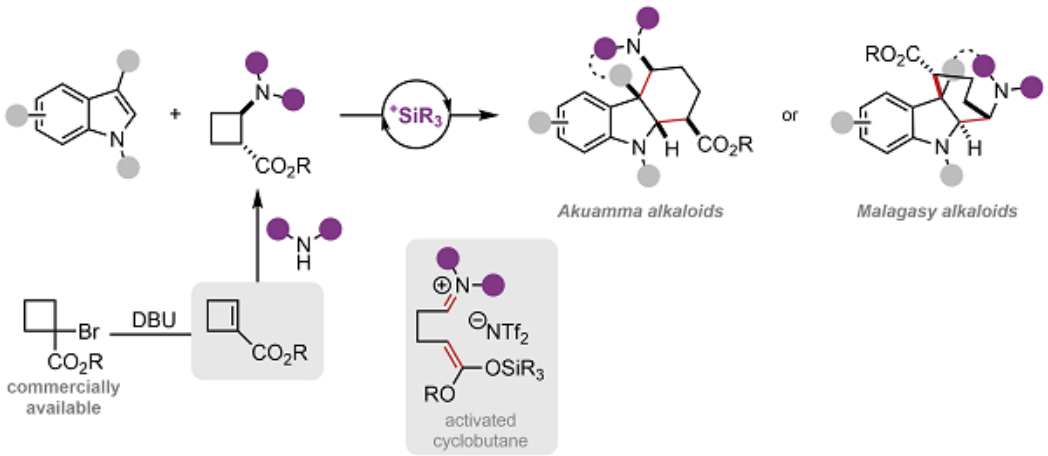
Donor-acceptor (DA) cyclopropanes vicinally substituted with electron-donating and electron-accepting groups are among the most studied strained ring motifs.[1] The corresponding cyclobutanes have been considerably less studied, despite their similar ring strain energy. Progress in this area is highly desirable, as cyclobutanes stand out as advantageous precursors in the construction of saturated ring systems. In particular, (4+2) annulations between cyclobutanes and indoles have proved to be very effective to rapidly form complex alkaloid skeletons containing a 6-membered ring.[2] In that regard, the use of aminocyclobutanes would enable more convergent synthesis of alkaloid building blocks. However, only few methods for the synthesis and annulation of nitrogen substituted DA cyclobutanes have been reported so far.

Driven by the pursuit of efficiency and atom economy, we developed the first synthesis of bench stable donor-acceptor aminocyclobutane monoesters in one single step from commercially available building blocks.[3] We then disclose the first catalytic annulation reaction involving aminocyclobutane monoesters.[3] Activated by silylium catalysis, aminocyclobutane monoesters were able to perform (4+2) annulation with indoles providing valuable alkaloid scaffolds. Using this method, tetracyclic structure of either *akuamma* or *malagasy* alkaloids were obtained selectively depending on the temperature of the reaction.



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Heteroleptic Covalent Organic Cages

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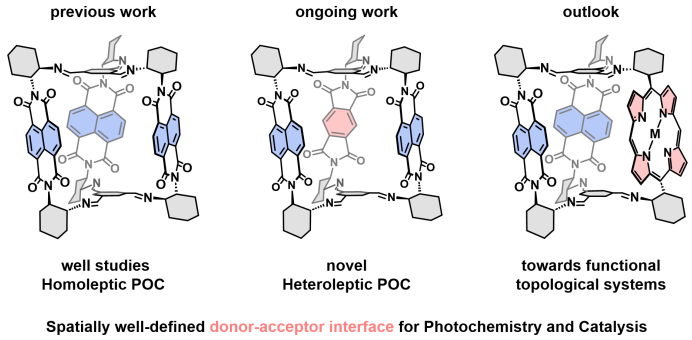
Over the past decade, the field of porous organic cages (POCs) based on dynamic covalent chemistry (DCC) has emerged, offering access to a wide range of crystalline microporous materials.[1] Molecular organic materials distinguish themselves from porous bulk polymers by absence of intermolecular bonding in the solid-state. This characteristic provides higher degrees of accessibility for functionalization and superior solution processability.[1] With their combination of diverse optoelectrical properties, shape-persistent porosity, and ease of handling, POCs present an intriguing platform for further investigations. Šolomek and colleagues developed porous organic cages (POCs) based on photophysically and redox-active rylene diimide dyes leading to properties including long-lived charge separation, delayed fluorescence, and the selective adsorption of gases.[1-4]



Due to supramolecular self-sorting, as a consequence of the thermodynamic reaction control in DCC, the formation of POCs has been limited to the formation of homoleptic cages of higher symmetry. However, decreasing the symmetry holds the potential to introduce desirable properties for photochemistry and catalysis, leveraging the directional electronic field between well-arranged donor-acceptor interfaces. Recent scrambling experiments suggest that the selective formation of heteroleptic porous, shape-persistent POCs are achievable through kinetic reaction control. The current work focuses on selectively forming heteroleptic POCs by better understanding the stabilities of key synthetic intermediates. Recently the desired target molecules have been observed by means of HR-MS and NMR spectroscopy, albeit in a mixture with competing homoleptic POCs. To overcome this challenge, efforts are being made to minimize competing decay processes of key synthetic intermediates, which have hindered selectivity thus far. By doing so, it should be possible to obtain the desired heteroleptic POCs in sufficient purities, allowing for structural characterization and subsequent investigations of their physical, electronic, and photochemical properties. Allowing to access a novel class of POCs with extraordinary physical properties, which can be tuned for specific tasks at hand with.

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Deciphering the Mechanism of Thiol-Mediated Uptake: µMap Strategy for Labeling Transient TMU Partners

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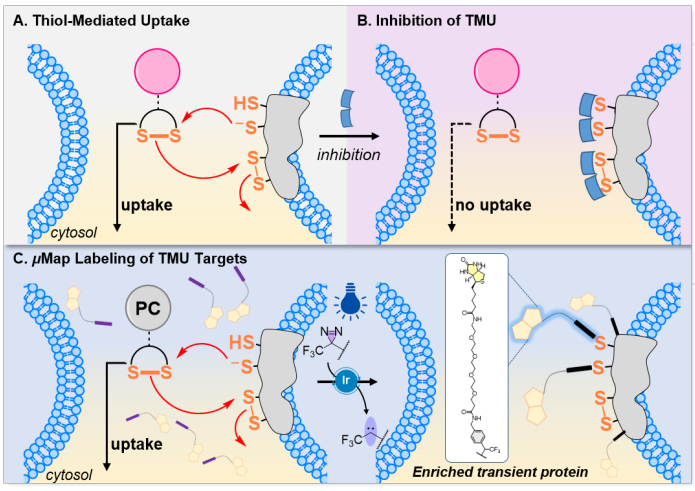
style="text-align: justify;">The cell membrane is the natural biological barrier of the cell that maintains its integrity, *i.e.* shape and size, and assures an exclusive exchange of molecules, from ions to proteins, with the outer matrix through several internalization processes. Thus deciphering its complete mechanism to exploit its full potential for drug delivery remains a challenging task with extremely high benefits in medicinal chemistry and pharmaceutics. Among the various studied internalization pathways, thiol-mediated uptake (TMU) has been recently given a lot attention due to its efficient transport of a wide range of substrates into the cytosol, from small molecules to HMW proteins. It is thought that this efficient method relies on a dynamic covalent cascade exchange (CAX) between a disulfide rich molecule, and exofacial thiols of transmembrane proteins on the cell surface. Despite the recent advances over the last years, the mechanism of uptake is still poorly understood.[1] This might be partially explained by the dynamic nature of the process that lacks of any exploitable steady state. Furthermore, recent studies validated TMU as a multi-target process,[2] thus adding a layer of complexity to the uptake mechanism. To elucidate this process, our toolkit was initially limited to classical chemical proteomics approaches, inefficient for labeling any transient interactions in this dynamic cascade exchange. To overcome this problem, the recently developed *µ*Map® strategy from the MacMillan group[3] appeared to be suitable for our project: the method relies on the use of a photocatalyst (PC) that upon blue light irradiation activates in a determined range, the UV-sensitive diazirines through a Dexter energy transfer (DET). The generated carbene reacts with its surrounding in a fast covalent manner, consequently, labeling the proximity of the photocatalyst. In our case, the CAX equipped with a PC could be a powerful tool to label the TMU pathway by highlighting all the transient interactions in the cell wall, thus, opening new perspectives on TMU mechanism.



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Chiral Boramidines: New Boron-Based Materials with Efficient Circularly Polarized Luminescence

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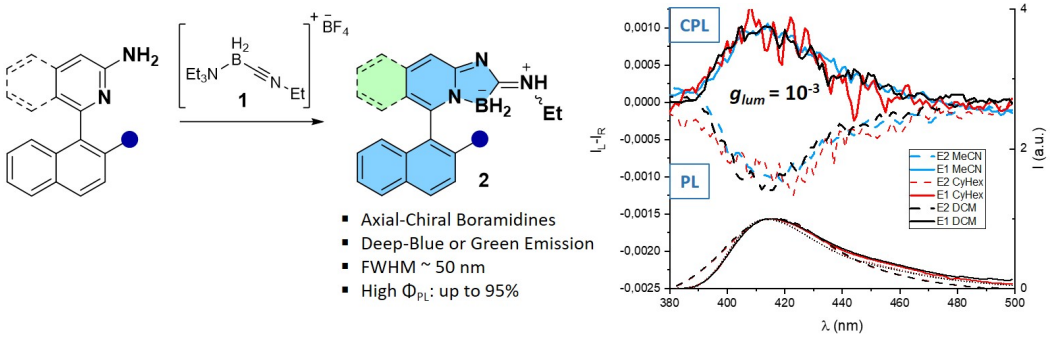
There is currently significant interest in developing novel organic molecules that exhibit a pronounced circularly polarized luminescence (CPL) due to their possible applications in 3D displays, optical sensors, and optical information storage or encryption.[1] An elegant approach to modifying the inherent characteristics of the original conjugated π-systems is the incorporation of main group elements into their π-conjugated structures. This strategy leads to the emergence of appealing optoelectronic properties that cannot be achieved with traditional carbon- or metal-based materials.[2] In this regard, the boron-based conjugated systems have drawn immense attraction because they offer excellent photophysical properties, and have recently been reported as new and exciting thermally activated delayed fluorescence moieties.[3]

Despite the abundance of boron-based platforms prepared mainly from BX_3, sodium cyanoborohydride-derived N-alkylnitriliumboranes (**1**) were found to be versatile precursors for the synthesis of novel stable luminescent B-containing heterocycles.[4] Inspired by the work of Yudin and co-workers,[4] new chiral boramidine derivatives (**2**) were prepared. These fluorophores show interesting (chir)optical properties, such as the incorporation of triplet state, narrow emission bands, high PLQY, and emission of CPL with remarkable g_{lum} values.



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An artificial hydrogen bond relay in a supramolecular capsule enables highly selective β-glycosylation

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Carbohydrates are of central importance in biology. Their selective chemical synthesis, however, and in particular the selective formation of the thermodynamically labile β-glycosidic bond still pose a challenge in various cases. The Tiefenbacher group recently demonstrated that a hexameric molecular capsule catalyzes the selective formation of globally protected β-glycosides independent of the substrate's substitution pattern and configuration.[1,2] Interestingly, the proposed mechanism involves synchronized activation of the glycosyl donor and acceptor inside the supramolecular capsule via a relay involving seven hydrogen bonds. While such activation is known for enzymes, it is unprecedented for man-made catalysts. The state-of-the-art mechanistic picture is that the capsule-catalyzed pyranosylation exclusively proceeds through a loose S_N2 transition state while furanosyl donors additionally allow the transformation in a highly β-selective S_N1 fashion. Glycosyl donors are very suitable electrophiles for the proton-wire catalyzed reaction mode. Although analogous substitutions can also be performed with non-glycosidic electrophiles such as allylic, propargylic, and aryl halides, the yields are generally low. The main limit of this methodology is due to the confined space inside the molecular capsule, which naturally limits the reaction scope concerning the size of reactants. A detailed investigation revealed that approaching the maximum cavity packing, the β-selectivity of glycosylation reactions remains generally very good. Further, the production of glycosides can be performed utilizing solvents obtained from renewable sources, improving its applicability as compared to the toxic and petroleum-based solvents previously known for this catalyst.

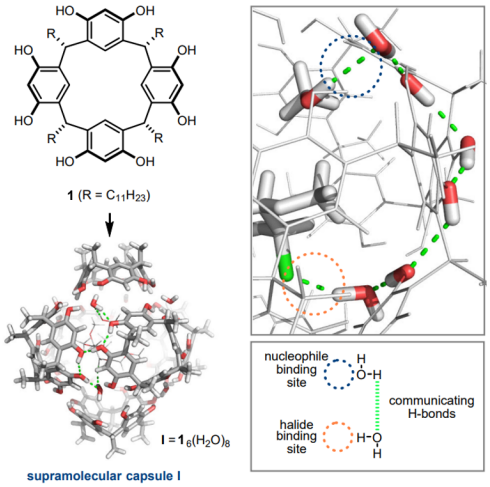

Figure 1. Capsule **I** self-assembles in apolar solvents from six resorcinarene units and eight water molecules forming a network of sixty hydrogen bonds. This catalyst facilitates glycosylation reactions by synchronizing both reaction partners through a proton relay (depicted as green dotted lines).

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Reaction-Agnostic Featurization of Bidentate Ligands for Bayesian Ridge Regression of Enantioselectivity

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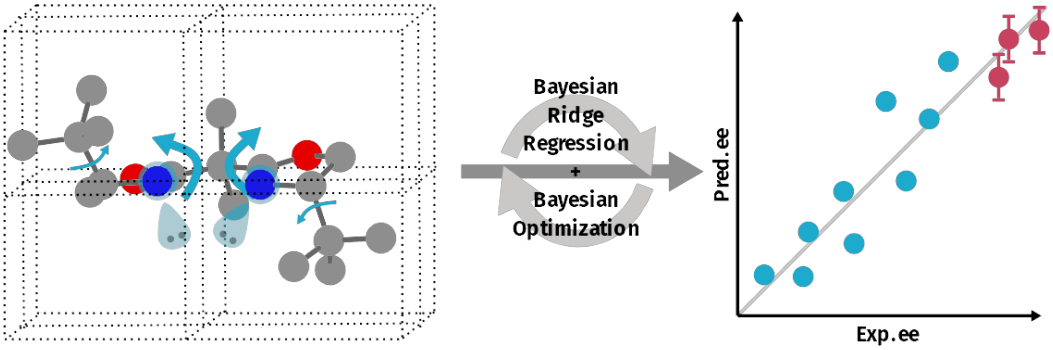
Chiral ligands are important components in asymmetric homogeneous catalysis, but their synthesis and screening can be both time-consuming and resource-intensive. Data-driven approaches have the potential to reduce the time and resources needed for reaction optimization by more rapidly identifying an ideal catalyst than random screening, but are often non-transferrable across reactions.
Here, we introduce a general featurization strategy for bidentate ligands, coupled with an automated feature selection pipeline and Bayesian ridge regression (BRR) for multivariate linear regression (MLR) modeling. Our approach, which is applicable to any reaction, incorporates electronic, steric, and topological features, such as rigidity/flexibility, branching, geometry, or constitution, and is well-suited for early-stage ligand optimization. With only 19 to 30 data points per dataset, we validate our workflow for the prediction of enantioselectivity in four metal-catalyzed asymmetric reactions. BRR provides uncertainty estimates that can be used in Bayesian optimization (BO) to efficiently explore pools of prospective ligands. We screen 312 chiral bidentate ligands extracted from a crystallographic repository and suggest promising ligand candidates for a challenging asymmetric oxy-alkynylation reaction.



Cyanine Renaissance: Light-Operated Medicine

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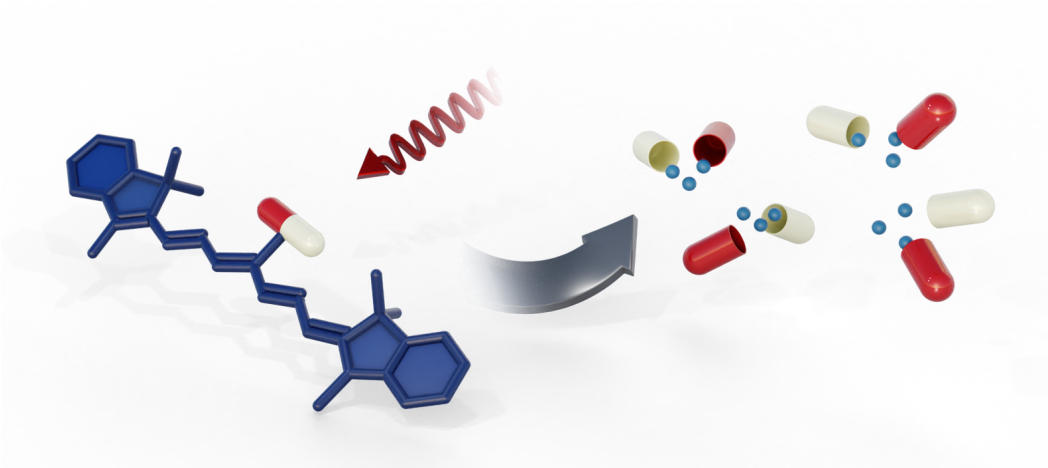
Cyanine dyes represent an indispensable class of chromophores in modern chemistry and biology. Especially heptamethine cyanines (Cy7) are appreciated for their absorption and emission in the tissue-penetrating near-infrared region (NIR; 650–850 nm). Herein, I will demonstrate how the development of a synthetic methodology for the introduction of various substituents along the central cyanine chain enables tailoring their photochemical and photophysical properties within three orders of magnitude.[1,2] Exercising this control over the structure–property relationship by a single substituent was subsequently harnessed in a number of distinct applications in various fields including fluorescent probes, single molecule localization microscopy, biosensors or upconversion nanoparticles.[3] Finally, I will showcase how our synthetic strategy kick-started a novel class of cyanine-based photocages.[4] These molecules efficiently release a broad palette of organic payloads in aqueous media and human cells using a single NIR photon as the trigger with the focus on therapeutic applications.



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Studies towards the total synthesis of macplocimine A

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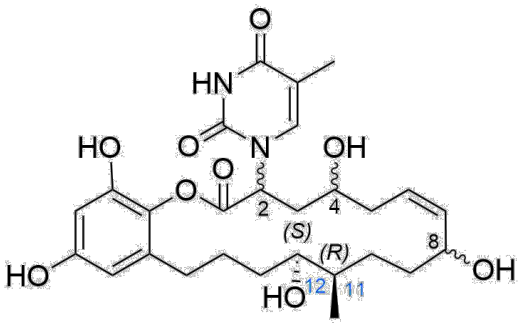
Macplocimine A (**1**) is an 18-membered macrolide that was isolated from the marine-derived filamentous sulfur bacteria *Thioploca sp.* (benthic microbial mat, Chile) by Magarvey and co-workers in 2013.[1] As a unique structural feature among all known natural macrolides, macplocimine A (**1**) incorporates a nucleic acid base attached to the macrolactone ring.

No biological data has been reported for this natural product to date. However, given its structural relatedness to resorcylic lactones (RALs), which are known to exhibit a wide range of biological activity, in combination with the presence of a thymine moiety as a hydrogen bond donor/acceptor motif, the compound should have the potential to be biologically active.

Likewise, the stereochemistry of macplocimine A (**1**) has not been elucidated, except for the relative configuration of the stereocenters C(*11*) and C(*12*), which was established to be *anti*. No synthetic work on **1** has been documented in the literature.

Enticed by its intriguing structural features and the associated synthetic challenges and in order to enable its biological assessment, we have embarked on the total synthesis of diastereomers of macplocimine A (**1**). The strategy towards the synthesis of the various diastereoisomers of macplocimine A (**1**) is outlined in Scheme 1.



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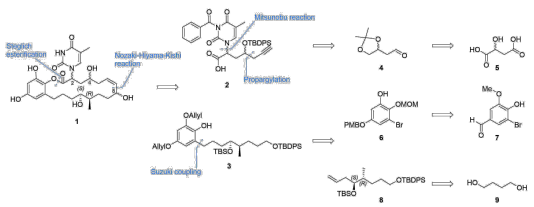
Macrocycle formation was planned to be achieved *via* intramolecular Nozaki-Hiyama-Kishi reaction. The requisite macrocyclization substrate would be assembled from building blocks **2** and **3** *via* Steglich esterification. The former can be accessed from *D*- or *L*-malic acid (*D*- or *L*-**5**) *via* aldehyde **4** by Barbier-type propargylation and introduction of the thymine base under Mitsunobu conditions. Phenol **6** can be elaborated from bromovanilline (**7**) and butane-1,4-diol (**9**).

In this contribution, we will present efficient and scalable routes to building blocks **2** and **3** from **5** and **9**, respectively; as well as the building block assembly and macrocycle formation, for which we have established proof-of-concept. Finally, we will discuss the status of our work on the final steps of the total synthesis of selected diastereomers.



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Anion-π catalysis induced epoxide-opening ether cyclizations on different surfaces

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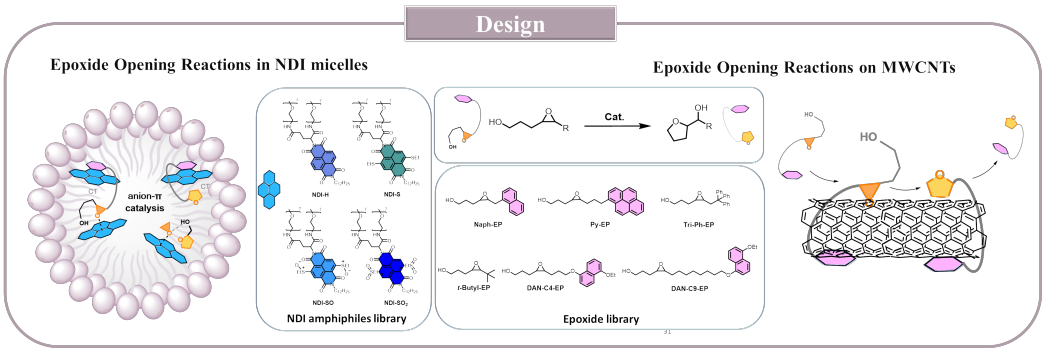
[1]Department of Organic Chemistry, and University of Geneva, 1211 Geneva, Switzerland

Anion-π catalysis, that is the stabilization of anionic transition states and reactive intermediates on π acidic aromatic surfaces, is rare in nature and has been ignored for a long-time in chemistry.[1] Since anion-π catalysis was reported in 2013 firstly, with the enolate addition chemistry in place, anion-π catalysts up to π-stacked foldamers, fullerenes and carbon nanotubes could be developed, which then were used to realize different reactions like asymmetric enamine, iminium, Diels-Alder, transamination or epoxide-opening chemistry [1,2].

Naphthalenediimides (NDIs) are well known by its π-acidity when different electron withdraw substituents were installed on its core structures, and the anion-π interaction promoted autocatalysis of epoxide-opening ether cyclizations was first observed on sulfone-NDI derivatives[2]. Herein reported anion-π catalysis in various NDI micelles (e.g., sulfoxide, sulfone) which could provide a space-confined and solvent-free environment in where epoxides could become more concentrated and pre-organized, so that significant rate enhancement and autocatalytic behavior were realized when compared with reactions either in organic solvents or other surfactants.

Meanwhile, carbon nanotubes were known for its induced π acidity in response to the binding of anions or anionic transition states due to the repulsion of the nearby π electrons toward the other end of the π system, thus enabling and strengthening anion binding on the π surface[3]. Therefore, MWCNTs have been applied in our work to serve as a powerful anion- π catalysts due to their high polarizability. And further electronic field assisted anion-π catalysis on MWCNTs surfaces was also proved promising and practical.



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

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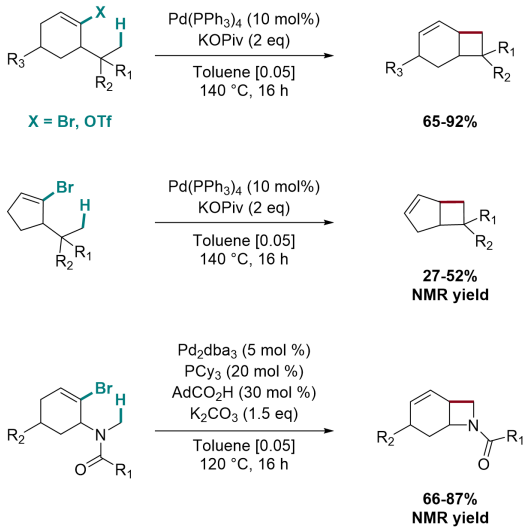
1,4-Palladium shift has been established as an elegant approach towards the functionalization of remote C–H bonds.[1,2] However, its application is restricted to using aryl halides as precursors.[3-5] In this work, we have successfully extended its application to C(sp^2)–X alkenyl precursors. As a result, we report an unprecedented cyclobutanation protocol towards fused cyclobutane derivatives using alkenyl (pseudo)halides through a Pd^0-catalyzed C(sp^3)–H activation process. This reaction takes place via 1,4-Pd shift followed by intramolecular Heck coupling. The methodology performs best with cyclohexenyl precursors giving access to a variety of substituted bicyclo[4,2,0]octenes, and also shows a potential for accessing smaller ring systems starting from cyclopentenyl halides. Replacing the alkyl chain with N-methyl amides gives access to fused azetidines via the same mechanism. Early kinetic studies indicate a primary kinetic isotope effect establishing the C–H activation as the rate-determining step, while deuterium incorporation suggests an irreversible 1,4-Pd shift process, – probably arising from the fast trapping of the *σ*-alkylpalladium species through Heck coupling.



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Divergent Regio- and Enantioselective Synthesis of Spirocycles *via* Phenol-Directed Cobalt(III)-Catalyzed Dearomative Annulations with Alkynyl Triazenes

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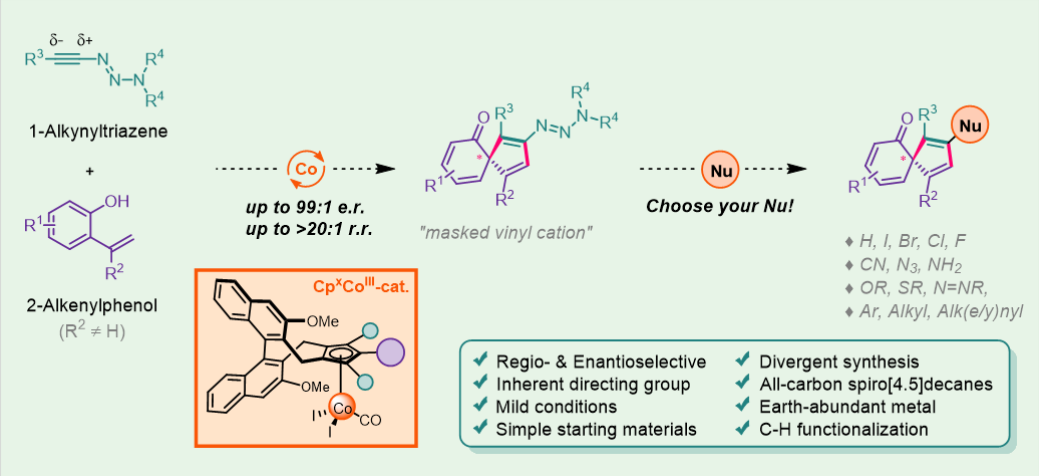
Answering the global call for sustainability, we aim to trade the use of precious noble metals in catalysis for Earth-abundant 3d-metals, such as cobalt, considering their vastly reduced environmental footprint, substantially lower cost, and significantly reduced toxicity.[1] Notably, it also holds tremendous potential, since they can display both similar as orthogonal reactivity patterns compared to their 4d- and 5d-congeners.

Herein, we disclose the ongoing development of a highly regio- and enantioselective dearomative [3+2] C-H annulation reaction of 2-alkenylphenols with 1-alkynyltriazenes, catalyzed by an Earth-abundant cobalt(III) complex bearing a tailored chiral cyclopentadienyl (Cp^x) ligand. The asymmetric transformation occurs under mild aerobic conditions, and provides rapid access to attractive all-carbon spiro[4.5]decane derivatives, using straightforward raw materials that are readily prepared *via* one-step or one-pot procedures. The obtained enantioenriched spirocycles possess substantial and divergent derivatization potential due to the presence of a valuable triazene moiety, which allows installing a plethora of other functionalities by tapping into its very broad reactivity portfolio.[2,3] Additionally, the use of a simple, inherent phenol directing group, which gets incorporated in the product, contributes further to the good step-economy and sustainability of this methodology.



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Facile access towards trans-hydroxyoctahydroazulenone core and total synthesis of diterpenoids Randainin D and Shortolide C

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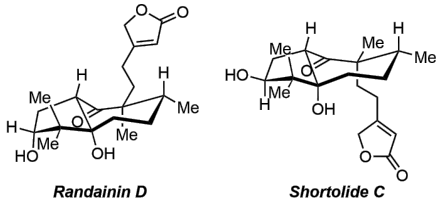
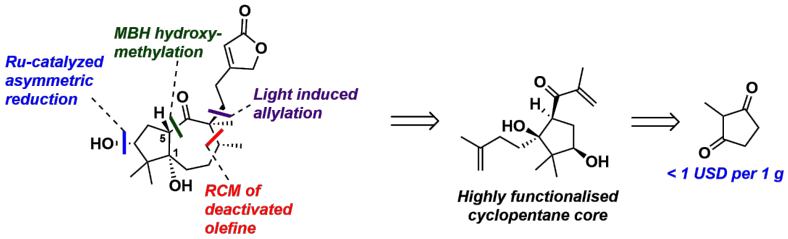
Hydroazulene is an abundant framework found in *guaiane-type* sesquiterpenes [1]. Recently Shen [2] and Williams [3] groups isolated novel natural products (*Randainins A-D* and *Shortolides B-C*) possessing simultaneously *hydroxyoctahydroazulene* skeleton and *butenolide* moiety. Such framework features make these natural products unique, being structurally related to both, *guaiane-type* sesquiterpenes and *labdane-derived* diterpenoids. *Randainin D* is a moderate inhibitor of superoxide-anion generation and elastase release, *Shortolide C* (**Fig. 1**) reduces the growth of *Staph. aureus*. Such biological activity and intriguing structures (trans-5/7-ring scaffold, five stereocenters, four – contiguous, and two – quaternary), make these unusual natural products attractive and challenging synthetic targets.



Our goal is to develop a divergent total synthesis of *Randainin D* and *Shortolide C.* It was found that Ru-catalyzed asymmetric reduction of 2,2-dimethylcyclopentane-1,3-dione creates the stereocenter at C3, which leads to the desired trans-junction at C1-C5, through the sequence of diastereoselective steps. Assembly of the 7-membered ring was realized via challenging Ru-catalyzed RCM leading to the tetrasubstituted enone. The endgame is a novel light-induced allylation that provides access to the butenolide fragment.



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Head-to-Tail dimerization of N-heterocyclic Diazoolefins

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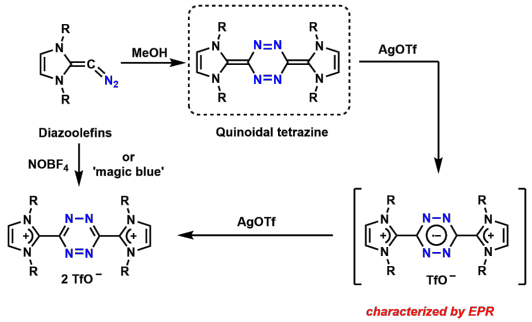
Room temperature stable N-heterocyclic diazoolefins were isolated by our group[1] and by Hansmann's group[2] in 2021. N-heterocyclic diazoolefins can undergo [2+3] cycloaddition reactions. The ylidic carbon can also coordinate with metal complexes and Lewis acids. Our group recently discovered an unprecedented type of cycloaddition reaction for N-heterocyclic diazoolefins: the head-to-tail dimerization.[3] This formal [3+3] cycloaddition gives strongly reducing quinoidal tetrazines. The oxidation of quinoidal tetrazines proceeds in a stepwise manner, with an isolable and room temperature-stable radical cation as an intermediate. The radical could be characterized by EPR spectrometry, and a singlet with hyperfine splitting due to the coupling to four ^{14}N nuclei was observed. The final oxidation product contains a tetrazine core with two imidazolium substituents. The dication can also be prepared from diazoolefins directly by reactions with oxidants like nitrosonium tetrafluoroborate or 'magic blue'.



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Dynamic kinetic resolution of racemic amines with stereogenic nitrogen centers

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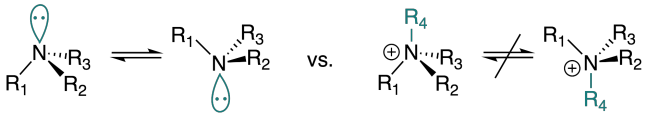
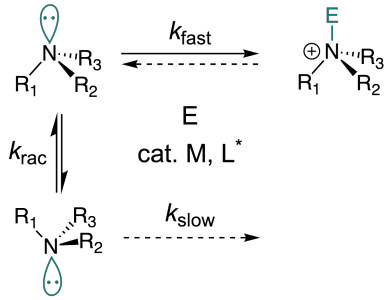
Within the last decades, much attention from the chemical community has been directed at the development of asymmetric reactions. Just as a tetrahedral carbon atom, nitrogen with three different substituents can be a stereogenic centre. Such tertiary amines, however, usually do not show optical activity due to a low lying transition state for nitrogen inversion, which results in a rapid equilibrium between the enantiomers. This inversion can be prevented by conformational strain such as the one observed in Tröger's base[1], or by a quaternization of the nitrogen atom.[2]



Chiral ammonium salts are widely used as phase-transfer catalysts[3] and recently also as stereo-controlling cations[4]; they can be found in nature[5] and some exhibit pharmacological activity.[6] Current strategies for the synthesis of such compounds are based on the resolution techniques of diastereoselective adducts or salts.[7]

Recently we published the first example of the Pd-catalyzed enantioselective allylation of tertiary amines, where we could realize excellent conversions and significant stereoselectivities.[8] Hence, our research is focused on the dynamic kinetic resolution of racemic amines with stereogenic nitrogen centers via TM-catalyzed transformations.



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Enantioselective Synthesis of α-Aminoboronic Acid Derivatives via Copper-Catalyzed N-Alkylation

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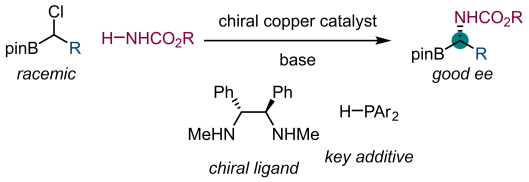
Optically active α-aminoboronic acids, bioisosteres of natural α-amino acids, find application in medicinal chemistry as antitumor, antiviral, and antibacterial agents and for the treatment of type II diabetes. Herein, we present a new direct synthetic strategy based on the enantioselective cross-coupling of readily available racemic α-chloro boronates with carbamates using an earth-abundant copper catalyst with commercial DMPEDA and a diaryl phosphine as the ligands. These reaction conditions originated from a detailed mechanistic study of a photoinduced system.



reaction development: driven by mechanistic studies

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C_{60}-Based Switchable Fluorescent Probes

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[1]ETH Zurich

C_{60} is an excellent acceptor molecule in both electron- and energy-transfer reactions. A number of fullerene-based donor-acceptor systems have been reported in the few last decades, especially aimed towards the development of electronic devices. However, only few studies on biocompatible fullerenes donor-acceptor system have been reported, mainly due to the extremely low solubility of C_{60} in either water or water-miscible solvents.
In this study, we synthesized water-soluble C60-fluorophore conjugates as donor-acceptor systems. The donor and acceptor molecules are connected with an enzyme-reactive peptide linker, are highly water-soluble, and form small aggregates (60, indicating successful intermolecular quenching. Upon addition of an enzyme, which is known to react with the peptide linker, the fluorescence intensity increased both dramatically and time-dependently. Currently, preparation of in vitro cell assays using this probe are in progress.
Corresponding

Bis-cyclometallated iridium catalysts for ortho directed C-H borylation

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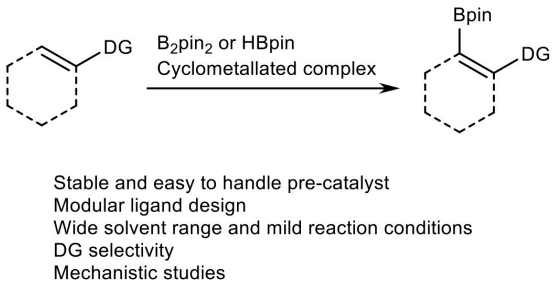
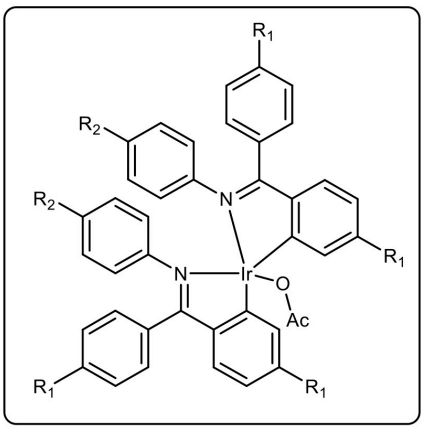
Over last few decades C-H activation has gained continuous scientific interest and over time has transformed from an academic curiosity to new practical applications in industry.[1] Cyclometallated complexes are emerging as a new class of catalysts for different C-H functionalizations, and they can be used for Late-stage functionalization (LSF) of complex molecules.[2]





Here we report the synthesis and application of novel bis-cyclometallated iridium catalysts. These catalysts can be prepared from different iridium precursors and are soluble in a wide range of organic solvents. The new complexes exhibit high air stability and directing group selectivity for *ortho* selective C-H borylation of wide range of different molecules including natural products and drug derivatives.

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