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Radical cyclizations of α-oxy carbon centered radicals

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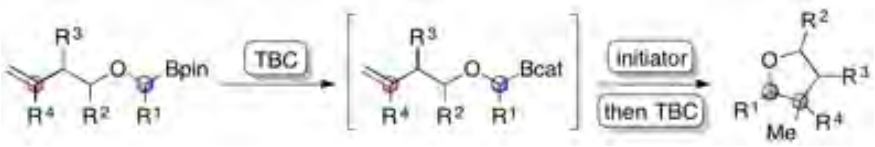
Oxolanes are ubiquitous in natural products and have long been an important class of bioactive heterocycles.[1] These oxacycles are readily accessible via radical cyclization reactions. Despite their importance, only a few papers have reported the cyclization of a-oxy carbon centered radicals, with a majority involving tin reagents.[2,3] Herein, we report a tin-free procedure to generate these radicals that uses air-stable organoboranes as precursors for the rapid construction of decorated oxolane derivatives.



This strategy involves the *in-situ* formation of α-oxy catecholboronic ester intermediates to side-step tricky isolations.[4,5] Full details of the method will be disclosed, such as the application to the synthesis of di-, tri- and tetrasubstituted oxolane derivatives, in good to high yields and diastereoselectivities.

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Cp*Rh(III)-catalyzed Cyclopropane Ring Expansion for the Synthesis of Pyrrolidinone

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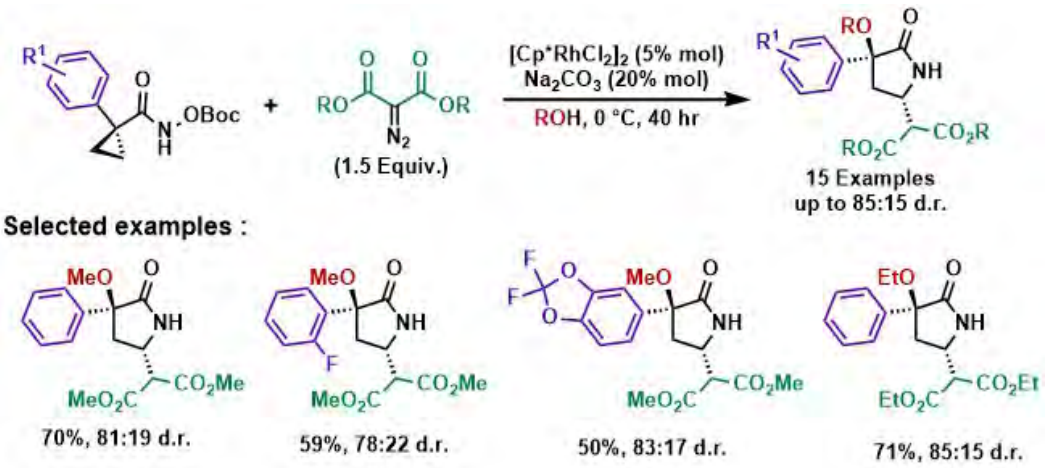
The cyclopentadienyl (Cp) ligand and its pentamethylsubstituted derivatives are of fundamental importance in organometallic chemistry.[1] Cp complexes are known for most transition metals, and have been widely applied in numerous catalytic processes, notably for C-H functionalization transformations. However, to date, only one example[2] exploit the potential of Cp*Rh(III) catalysts for C-C bond cleavage of strained ring.[3]

Heterocycles are very important structural, among them γ-lactams are ubiquitous in many biologically active natural products and pharmaceuticals.[4] Herein, we present an unprecedented synthesis of highly substituted pyrrolidinone (**Figure 1**), a precursor to pyrrole heterocycles. The developed transformation rely on a multicomponent process under mild conditions. Furthermore, examination of side-products structures combine with control experiments have shed light on the operative mechanism.



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One-Pot Alkene Hydroboration/Migratory Suzuki-Miyaura Cross-Coupling

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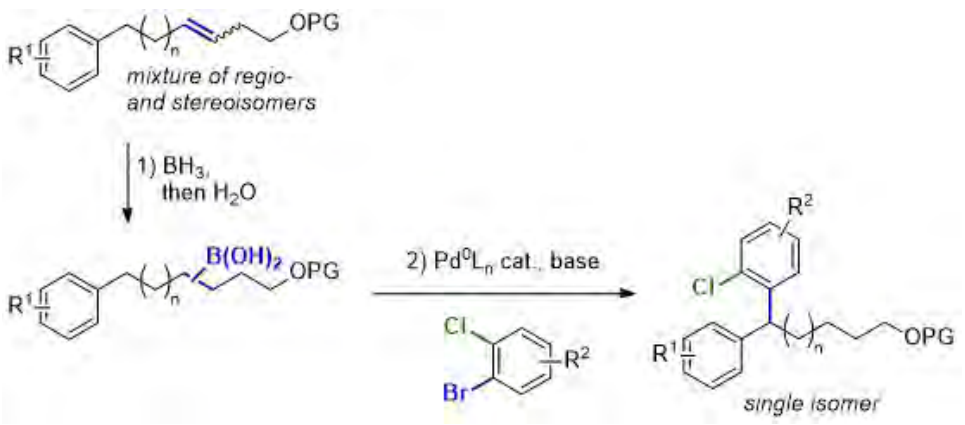
The development of C-H bond functionalization has exponentially increased since the start of the 21th century expanding the organic reaction toolbox. Challenging site-selective transformations were e.g. achieved with the introduction of a directing group or by exploiting the intrinsic reactivity of the substrates.[1] An alternative to these extensively researched methods exploits the controlled migration of the organotransition-metal species along an alkyl chain to the cross-coupling site.[2] Our group has been employing this strategy multiple times over the last years for the Pd-catalyzed β- or longer-range arylation of ester enolates, secondary organozinc reagents as well as surrogates.[3]

Here we report the one-pot hydroboration of unactivated internal olefins and migratory Suzuki-Miyaura cross-coupling to the benzylic position. The selectivity is achieved by careful selection of reaction conditions, the *o*-chlorine substituent on the electrophilic coupling partner and blocking the terminal position.



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Pancake Bonds in Dimeric Diradicals

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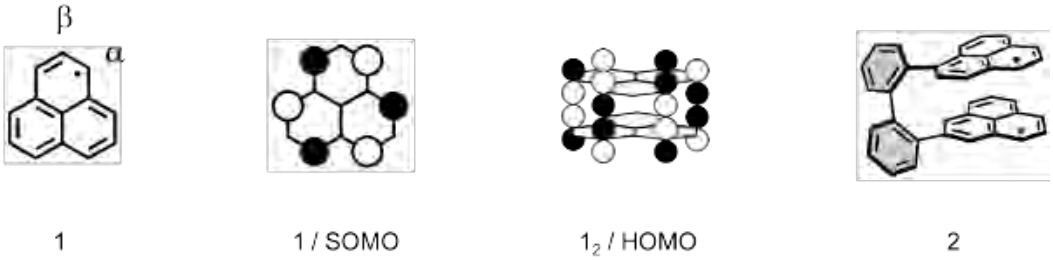
A central element of our research are π-conjugated systems that contain one or more unpaired π-electrons. Phenalenyl[1] (**1**) is a typical example representing spin-delocalized systems. The unpaired electron in phenalenyl is delocalized uniformly between six positions (see the shape of the singly occupied molecular orbital (SOMO) of **1**). The unique feature of these systems is their ability to form multicenter bonds[2], the so-called pancake bonds, between two or more cofacially assembled spin units ($\mathbf{1}_2$). This bonding motif gives these organic materials exceptional bulk properties such as magnetism and conductivity, which are commonly displayed by metals. Despite the potential in material science, little is known about the pancake bonding motif in the reported systems. To shed more light on the binding situation, our current study focuses on dimeric diradical systems such as **2**. This system consists of two phenalenyl units (white) that are held in a close proximity to one another by an oligo-*ortho*-phenylene[3] spacer (gray), which only allows the spin units to interact through space. This spacer provides these systems with flexibility and the ability to adopt a helical geometry, where the spin units are positioned on top of each other. Different linkage patterns (αα, αβ (shown), or ββ) will be used to study the effect of linkage on the spin coupling (triplet versus singlet) in the ground state of these molecules. The poster presentation will include the synthetic approach towards these target model compounds and the preliminary investigations of their properties and stereodynamics.



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Metastable-state photoacids: comparative study of substituent effects.

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Metastable-state photoacids (PAHs)[1] represent a very simple, yet powerful mean to convert visible light stimuli into a large and reversible pH variation. Upon irradiation these compounds undergo an intramolecular cyclization leading to proton dissociation, while under dark conditions they spontaneously relax back to their original, less acidic, state (Figure 1). This remarkable feature finds appealing applications in polymer science [2] and supramolecular chemistry [3]. However, these compounds are known also for their lability towards hydrolytic processes which limits their implementation in aqueous-based systems.[4] In light of this, we have synthesized a library of PAHs bearing methoxy groups in four different positions conjugated to central double bond (Figure 1), and carefully investigated the effects of each substitution pattern on the chemical stability and the photochemistry in water.

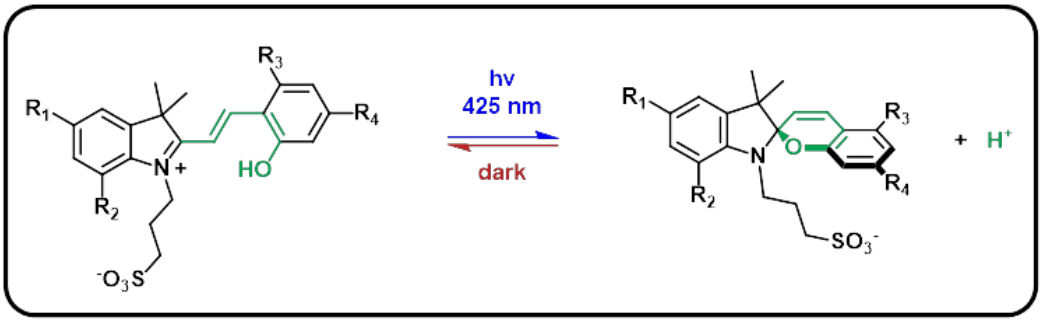

Figure 1. Schematic representation of light driven proton release of PAHs. Herein the library of compounds comprises the ones in which R1 or R2 or R3 or R4 is a methoxy group and the others are all hydrogen. The reference compound is the one in which all the substituents are hydrogen.

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Synthesis and reactivity of non-cyclometallated Au(III)-F: mild C(sp^2)-C(sp) bond formation

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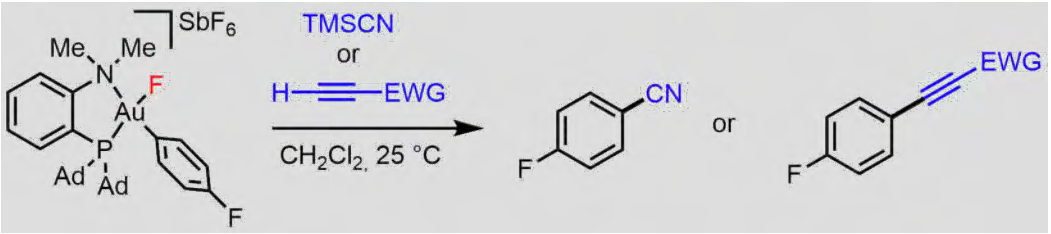
[1]University of Zurich

Late transition metal fluoride complexes raise interesting features in bonding and reactivity compared to their heavier halide analogues.[1] Although these species have been proposed to be key intermediates in catalytic cross-coupling and C-H activation reactions, their isolation and characterization is still extremely rare. Our group has recently isolated and characterized Au(III)-F using a highly stabilizing (N^C^C) ligand by a facile Cl/F ligand exchange reaction.[2] The lack of non-cyclometallated gold(III) monofluoride species encouraged us to synthesize and isolate the first bidentate (P^N) supported gold(III) fluoride complexes and further study their reactivity towards alkynes and trimethylsilyl-based nucleophiles. Our studies suggest an unprecedently fast reductive elimination to form new C(sp^2)-C(sp) bonds for this type of scaffold (Scheme 1).[3] Implications of this reactivity towards the developement of catalytic processes will also be presented here.



Scheme 1. Reactivity of (P^N) Au(III)-F with alkynes and TMSCN.

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Rh-Catalyzed Synthesis of Indenyl Triazenes

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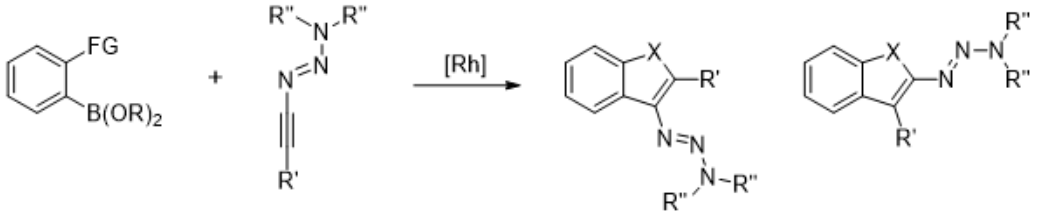
[1]Ecole Polytechnique Fédérale de Lausanne (EPFL)

Indenyl triazenes and their derivatives are compounds of interest because of the biological activity of indenes [1] and the synthetic possibilities afforded by the triazene group.[2] The only described example of the synthesis of an indenyl triazene suffers from the need for an indenyl Grignard reagent and low yield.[3] Building on the synthesis of indenes from ynamides as described by Lam et al., [4] we investigated the Rh-catalyzed reaction of 1-alkynyl triazenes with bifunctional boronic acids and esters.



The procedure tolerates air and requires the presence of water. Highly substituted indenyl triazenes were obtained in yields up to 90 % and regioselectivities up to >20:1 rr. The regioselectivity is determined by the choice of the alkynyl substituent R. Aromatic, alkylic and alcoholic substituents were suitable R’ groups, while the functional group (FG) on the boronic acid/ester could be an aldehyde, ketone, nitrile or a Michael-acceptor.

The acid-induced cleavage of the triazene group gave a variety of different products depending on the nature of X.

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Singlet or Triplet? That is the Question

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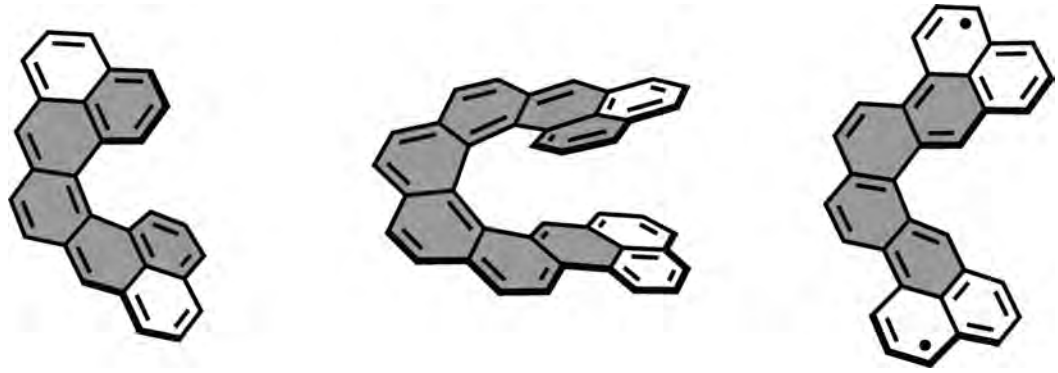
Polyaromatic hydrocarbons can be designed such that, depending on the topology or the extent of conjugation of the aromatic system, different ground states combined with different properties can be achieved. A class of such polyaromatic hydrocarbons are [n_k]cethrenes, molecules obtained by fusion of *n* benzenoid rings and featuring a [*k*]helicene backbone (highlighted in gray). Depending on the topology of fused benzenoid rings, cethrenes possess either a non-Kekulé diradical or a Kekulé diradicaloid electronic structure. Two typical features[1,2] of diradicaloid cethrenes are a small HOMO–LUMO gap and a low-lying triplet excited state that can be populated thermally. While the first characteristic results in a partial occupancy of both the HOMO and the LUMO in the ground state, the latter gives rise to magnetic properties of these systems. By extending the conjugation length, the magnitude of the HOMO–LUMO as well as the singlet–triplet energy gap is typically decreased. This structure–property relationship can be used to tune the magnetic properties in the series of cethrenes. Shown below are three homologs of this series, where, from left to right, is the parent[1,3] diradicaloid [7_5]cethrene, an extended diradicaloid [10_7]cethrene, and diradical [8_4]cethrene that is expected to display a triplet ground state. Using these molecules, we would like to study the effect of conjugation length and topology on the electronic structure. The poster presentation will include our efforts to synthesize these challenging but beautiful compounds.



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Dynamic-Covalent Benzopolysulfane Networks: A New Concept for Thiol-Mediated Cellular Uptake

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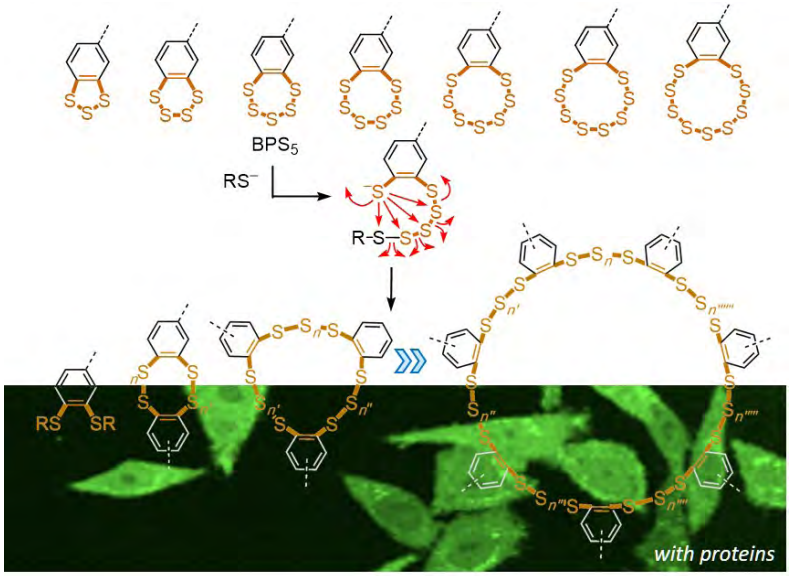
Cyclic oligochalcogenides (COCs) are emerging as powerful tools to penetrate cells through dynamic covalent dichalcogenide exchange with exofacial thiols on the cell surface[1]. Benzopolysulfanes (BPS) are COCs with unique rings of sulfur atoms fused to a benzene ring[2]. The cellular uptake of benzopentasulfides (BPS_5) far exceeds other reported COCs with efficient delivery to cytosol and nucleus, little endosomal capture, low toxicity, insensitivity to inhibitors of endocytosis. The transformation of BPS into in situ dynamic-covalent networks of extreme sulfur species with thiols, for selection and possibly amplification of the
best, appears to be crucial for this high cell-penetrating activity. Intracellular delivery of proteins assisted with BPS was then confirmed by the artificial metalloenzyme catalysis within cells[3]. Covalent BPS-streptavidin conjugates could also allow penetration of large proteins like anti-GFP nanobodies and antibodies into cytosol of cells.



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The Synthesis of Helically Chiral and Donor-Acceptor Carbon Nanohoops

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[1]University of Basel

Properties of molecules are tightly bound to their topology. Considering carbon-rich molecules, *e.g.* graphene, carbon nanotubes (CNTs) or fullerenes, each show distinct properties, although they are all made of sp2-hybridized carbon atoms. CNTs can be seen as nanoscale cylinders formed by rolling up graphene sheets followed by sealing of the graphene edges. Such top-down approach to CNTs synthesis does not lead, however, to uniform CNTs because graphene can be rolled up at many different angles. Therefore, hoop-shaped carbon macrocycles that represent small fragments of CNTs that retain information regarding chirality and diameter have been designed as templates for the synthesis of uniform CNTs.[1–3] In case of para-bound benzene subunits, such nanohoops are called cycloparaphenylenes (CPPs). Unlike in linear paraphenylenes, the HOMO and LUMO energies do not converge with increasing size of the CPP.[2,3] This leads to rather unique electronic properties of CPPs, particularly those with fewer repeating units. Breaking the symmetry of CPPs, *i.e.* changing the *para* connectivity to *meta* in one of the benzene subunits does not alter the electronic properties but changes the selection rules making the smallest macrocycles fluorescent.[4] Control of the electronic properties of CPPs by doping has been demonstrated.[5] However, fine-tuning of their the CPPs are also not chiral and could serve as templates only in the synthesis of armchair CNTs.

This contribution will describe the synthesis of nanohoops in which (a) a helical chirality or (b) donor-acceptor motifs are introduced. The former approach promises a new class of carbon-rich materials to be produced, while the latter allows for controlling the electronic properties of the CPPs and their derivatives.

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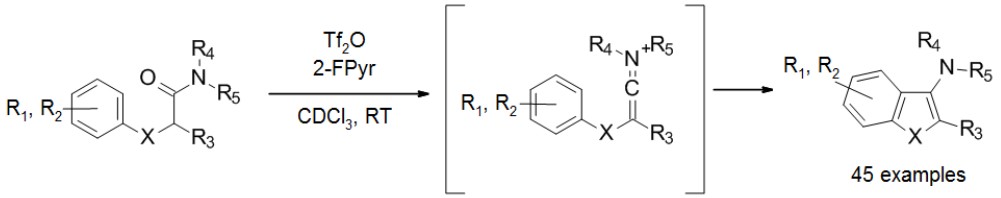
The keteniminium chemistry as an efficient tool for the synthesis of 3-aminoheteroles

D. Dagoneau[1], A. Kolleth[1], A. Lumbroso[1], P. Quinodoz[2], G. Tanriver[3], S. Catak[3], S. Sulzer-Mossé[2], A. De Mesmaeker[2]*

[1]Syngenta Crop Protection, [2]Syngenta Crop Protection AG, [3]Bogazici University

Based on our previous methods to synthesize 3-amino(benzo)thiophenes, using keteniminium as key intermediate, we will present the expansion of this chemistry towards the formation of other 3-aminoheteroles. Control and competition experiments will be also highlighted.



Straightforward Synthesis of 3-Aminothiophenes Using Activated Amides

D. Dagoneau[1], A. Kolleth[1], A. Lumbroso[1], P. Quinodoz[2], G. Tanriver[3], S. Catak[3], S. Sulzer-Mossé[2], A. De Mesmaeker[2]*

[1]Syngenta Crop Protection, [2]Syngenta Crop Protection AG, [3]Bogazici University

We will present a facile approach towards the synthesis of diversely substituted 3-aminothiophenes. A wide range of functional groups can be incorporated at the C-2, C-4 and C-5 positions of the thiophenes and this route is also suitable for the synthesis of fused bicyclic heterocycles such as 3-aminotetrahydrobenzothiophenes. This methodology relies on a *6p* -electrocyclization involving a vinyl sulfide linked to a keteniminium salt, the latter being formed *in-situ via* activation of the corresponding amide with triflic anhydride.

Stereoselective Synthesis of Z-Enamides and Enol Ethers from Hypervalent Iodine Reagents

N. Declas[1], P. Caramenti[1], R. Tessier[1], M. D. Wodrich[2], J. Waser[1]*

[1]Laboratory of Catalysis and Organic Synthesis, EPFL Lausanne, [2]Laboratory for Computational Molecular Design, EPFL Lausanne

Enamides and enol ethers are important building blocks in synthetic organic chemistry.[1] However, their stereoselective synthesis remain challenging. Furthermore, their nearly exclusive use as nucleophiles for C-C bond formation limits the number of possible disconnections, and the availability of electrophilic synthons would greatly enhance the flexibility of organic synthesis. The polarity of many functional groups was successfully inverted using hypervalent iodine compounds,[2] and their potential for functional-group transfer has been broadly explored during the past decades.[3] Herein, we present the stereoselective synthesis of *Z*-enamides and enol ethers-based benziodoxolones. These compounds were synthesized from the corresponding ethynylbenziodoxolones (EBX) through the stereoselective addition of N- and O- nucleophiles. The so obtained vinylbenziodoxolones (VBX) reagents were engaged in metal-catalyzed and metal-free reactions. These transformations proceed at room temperature and granted access to various *Z* -enamides and enol ethers.[4]

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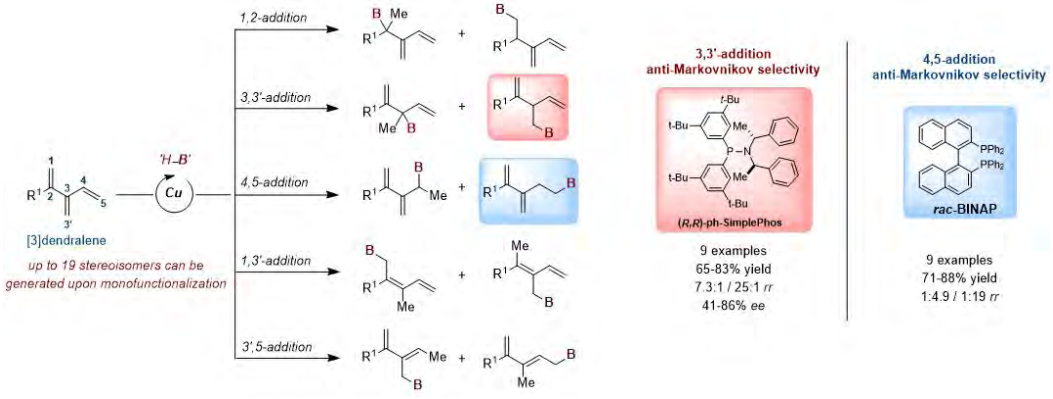
Ligand-Controlled Chemodivergent Copper-Catalyzed Borylations of 2-Substituted [3]Dendralenes

C. Desfeux[1], C. Mazet[1]*

[1]Department of Organic Chemistry, Université de Genève

Dendralenes are cross-conjugated polyolefins that can be either cyclic or acyclic. Acyclic dendralenes are typically accessed by iterative cross-coupling strategies. The intriguing physical properties of acyclic dendralenes have been extensively studied in the past ten years, and their use in cycloadditions to generate complex polycyclic carbon frameworks has been investigated in details (e.g. in diene transmissive Diels-Alder reactions). [1][2] To date, their use as substrates for transition metal-catalyzed selective functionalizations has been barely explored. This may be because functionalizations of polyconjugated dienes pose challenges both in terms of *reactivity* (mono- vs. poly-functionalization) and *selectivity* (chemoselectivity, regioselectivity, diastereoselectivity, enantioselectivity…).



To tackle these challenges, we directed our efforts towards the development of complementary site-selective Cu-catalyzed protoborylations of [3]dendralenes. Herein, we present the results of these investigations and the identification of two complementary catalytic systems for the (i) 4,5-addition with anti-Markovnikov selectivity and the (ii) 3,3'-addition with anti-Markovnikov selectivity. In the latter case, the corresponding skipped-dienes were not only obtained with excellent chemoselectivity but also with high levels of enantiocontrol. Successful application of these two methods to higher homologues will also be presented.

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Nickel-Catalyzed Enantioselective C–H Functionalizations of Heterocycles Enabled by Bulky N-Heterocyclic Carbene Ligands

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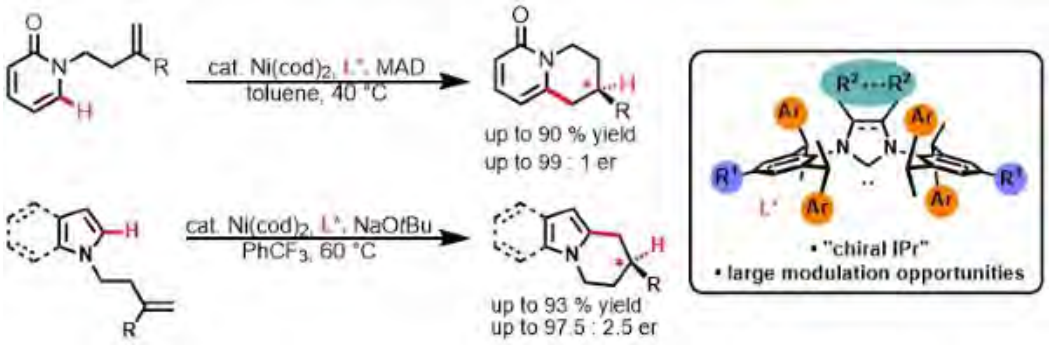
Heterocycles such as 2- and 4-pyridones, as well as indoles and pyrroles are prevalent heteroaromatic structures, which are found in a broad variety of natural products, bioactive agents and approved drugs.[1] Over the past decade, rapid advances in C–H functionalization technology have been demonstrated to be of great utility for the preparation of functionalized pyridones,[2] as well as indoles.[3] However nickel-catalyzed enantioselective C–H functionalizations are rare and underdeveloped. Chiral *N*-heterocyclic carbenes (NHCs), pairing steric and electronic tunability with an appreciated robustness of mono-ligated transition-metal species, have become more common in asymmetric catalysis and in particular in nickel(0)-catalyzed transformations.[4] Here we present a cooperative Lewis acid/nickel(0)-catalyzed C–H activation to form chiral annulated pyridones.[5] Additionally we introduce nickel(0)-catalyzed undirected C–H functionalizations of indoles and pyrroles.[6] Both transformations rely on a new class of sterically demanding chiral NHCs with large modulation opportunities, enabling the nickel(0)-catalyzed C–H functionalization of heterocycles in excellent yields and enantioselectivity.



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A green chemical synthesis of reusable palladium nanoparticles from phytochemical resins. Applications for mild and chemospecific hydrogenations of nitroarenes

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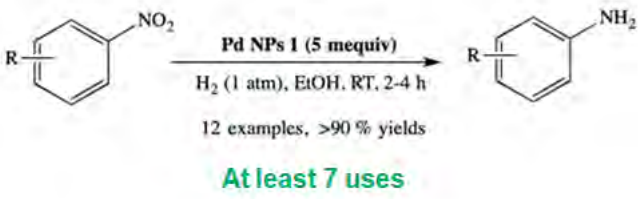
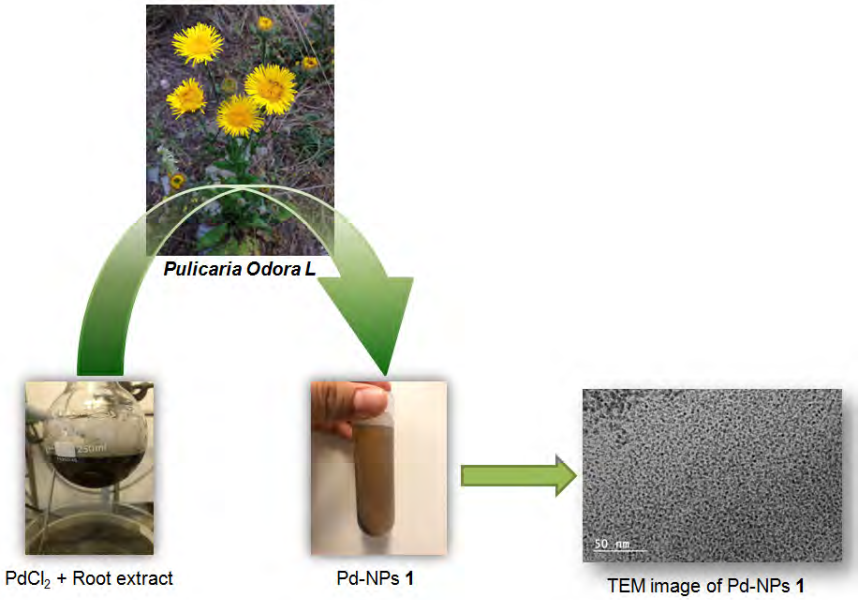
A fast and efficient green preparation of Pd nanoparticles (NPs) using a root extract from *Pulicaria odora L.* and $PdCl_2$ in water is reported. The obtained Pd NPs **1** surrounded by phytochemical resins present a homogeneous size between 2 and 4 nm depending on the preparation conditions. The Pd NPs **1** were characterized by different techniques (TEM, HRTEM, XRD and XPS) and have been successfully used for the chemospecific hydrogenations of nitroarenes at RT in EtOH under H_2 (1 atm) in the presence of only 5 mequiv. of Pd. The Pd NPs **1** were easily recovered and could be reused at least seven times without loss of efficiency. The Pd leaching is very low (< 0.1 % of the introduced amount).





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Direct Access to Chiral Secondary Amides by Copper-Catalyzed Borylative Carboxamidation of Vinylarenes with Isocyanates

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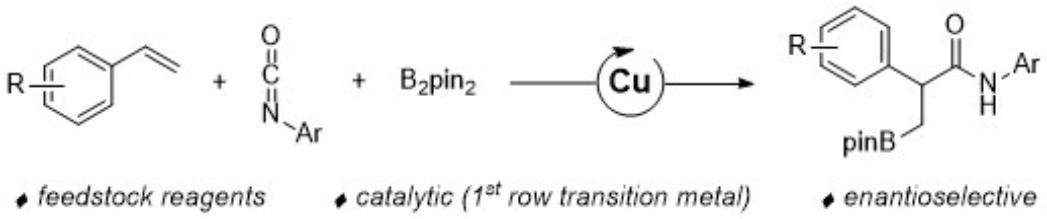
The dehydrative condensation of an amine and a carboxylic acid is the most common method for amide-bond formation. [1] A major drawback of such an approach is the use of elaborated and expensive coupling reagents that critically affect the efficiency and atom economy of the process. Therefore, the quest for alternative amidation protocols – ideally catalytic, atom-economic and relying on low-cost feedstock reagents – is of primary importance in contemporary organic chemistry. Several innovative strategies that fulfil some of these requirements have been recently devised. [2] In this context, isocyanates stand as attractive electrophiles for amide synthesis by C–C rather than the more conventional C–N bond formation approach.[3] Despite remarkable advances, the current portfolio of isocyanate-based amidation processes lacks of a catalytic protocol for the cross-coupling of isocyanates with alkenes. Such a method would provide a sustainable and cost-effective access to α-chiral secondary amides and, in principle, an enantioselective variant could also be elaborated.



Herein, we describe a copper-catalyzed borylative carboxamidation of vinylarenes with isocyanates, enabling access to chiral secondary amides bearing a α-stereocenter and a β-boronate handle. An enantioselective variant of this transformation was developed, affording a set of chiral amides with unprecedented levels of enantioselectivity. [4] Overall, our approach holds promise for the development of new catalytic asymmetric strategies in amide-bond formation.

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An Enantioselective/Diastereoconvergent [Cu/Rh] Catalytic Sequence to Access Polyfunctionalized 7-Membered Rings from 1,3-Dienes

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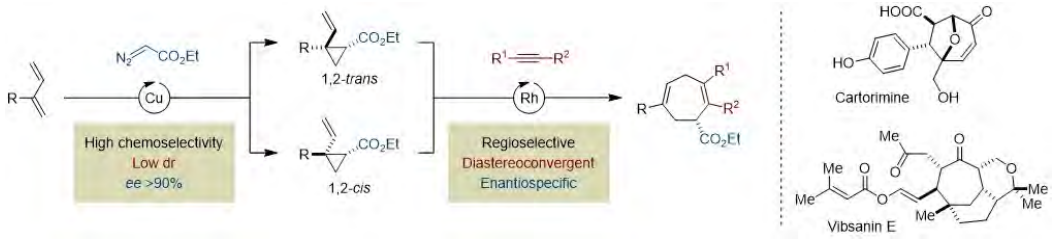
[1]Université de Genève

Seven-membered carbocycles are a common motif in natural products and biologically active compounds, in particular within the terpenoid familiy.[1] Methodologies for their stereoselective preparation are not nearly as much developed as for six-membered cycles and often rely on cycloaddition reactions. Despite fundamental advances over the last two decades, there is no report to date of an intermolecular and enantioselective [5+2] cycloaddition.[2,3] Its development would constitute an undoubtedly useful addition to the current portfolio and provide access to valuable stereochemically complex 7-membered rings.

Herein, we report the successful realization of this objective. Our approach is based on the development of a multimetallic sequential enantioselective cyclopropanation / diastereoconvergent cycloaddition starting from readily available conjugated 1,3-dienes.



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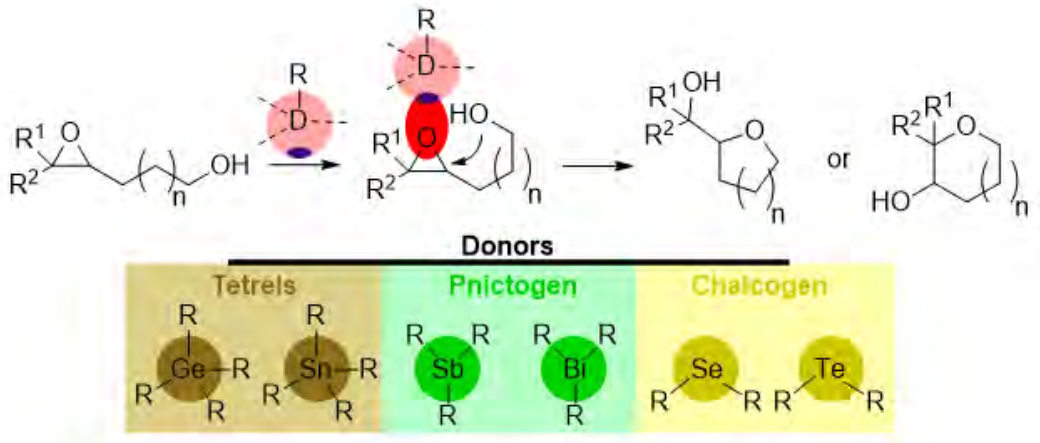
Epoxide opening ether cyclization mediated by exotic σ-hole interactions

A. Gini[1], M. Paraja[1], N. Sakai[1], S. Matile[1]*

[1]Department of Organic Chemistry, University of Geneva

The long journey into non-covalent interactions is far to be ended. In the last decade the exploitation of halogen-[1] and chalcogen-bond[2][3] donor as catalyst opened new routes on the application of the so-called sigma-hole interactions over more classical non-covalent bond, such as hydrogen bonding. However, the closely related pnictogen- and tetrels-bond interactions are still poorly explored. Indeed, only recently antimony-based organocatalyst has been revealed as a valid mediator for chloride-binding catalysis in Reissert-type reaction on isoquinoline.[3] Thus, other applications on negative-site activation are still demanding to describe the potentiality and the limitations of such unusual pnictogen- and tetrels-bond interactions.



In this perspective, inspired by the nature, the epoxide opening ether cyclization resulted a valid alternative to accomplish exotic non-covalent catalysis. Recently this reaction has been efficiently mediated by anion-π catalysis.[4] Following this concept, herein we present the first examples of tetrels-, pnicotgen- chalcogen-bond catalysed epoxide opening ether cyclization. The reaction of various epoxide and poly-epoxide of different length was studied in the presence of organo-tetrels, -pnicotegn and -chalcogen catalysts. In addition, the influence of diverse polyfluoro-phenyl substituents was tested.

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Non-oxidative ring opening of strained rings with gold: a mechanistic study

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The activation of C-C bonds in highly strained cyclic systems, such as cyclopropane and methylenecyclopropanes derivatives (MCP) is a useful and straightforward strategy to achieve molecular complexity.[1] Transition metals can activate either the single or the double C-C bond in a MCP via one out of the four different reaction patterns shown in Fig 1a.[2] Surprisingly, despite its synthetic potential, only a few studies of the reactivity between MCPs and gold have been reported up to date[3]

In this work we demonstrate, for the first time, a non-oxidative C-C bond cleavage delivering a new type of bench stable cyclometallated (N^C)gold(III) complexes (Fig 1b). The mechanism of this transformation has been extensively studied by means of kinetic measurements, linear free-energy relationships and isolation of reaction intermediates. The rate-determining step seems to involve a concerted ring-opening reaction via a four-membered transition state. Further applications of these systems in catalysis are underway in our group and will be presented here.

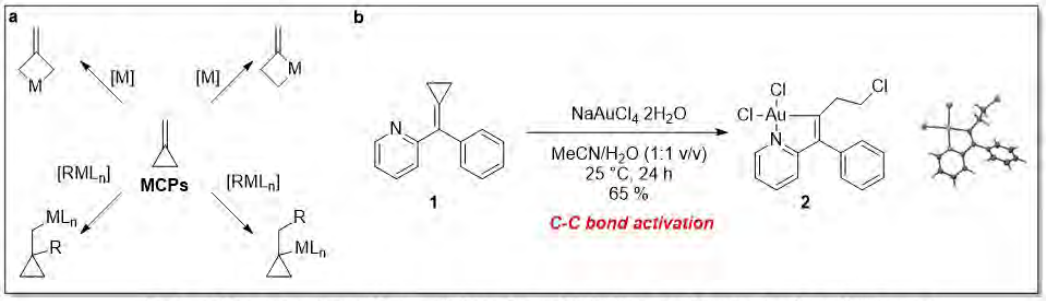

Fig 1. a) Reaction patters of MCPs with transition metals b) Reaction between 1 and a gold(III) source

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Investigating the Herbicidal Properties of Streptol and its Analogues

T. D. Grayfer[1], A. Georgiou[2], A. Bailly[2], J. Michel[1], S. Sieber[1], L. Eberl[2], K. Gademann[1]*

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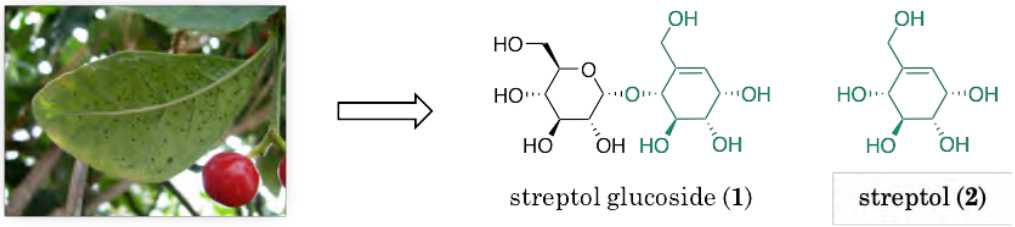
Natural products have always fascinated scientists due to their structural diversity and varied biological activities. Among them, selective and non-toxic pesticides have gained increasing attention in the recent years. Working on a rare symbiotic plant-bacterium system, our group has recently isolated a structurally unusual plant growth inhibitor, streptol glucoside (**1**).[1],[2] It is a pseudosugar bearing a glucose moiety and a carbasugar core known as streptol (**2**). Intriguingly, streptol was also previously described as a plant growth inhibitor[3] and was shown to be non-cytotoxic to mammalian cells;[4] however, its mechanism of action has never been reported. Our group has shown that streptol can be detected alongside streptol glucoside in the aforementioned symbiotic system. Given the novelty of this scaffold as compared to commercially available pesticides, this project set out to explore and enhance the plant growth inhibitory activity of streptol and streptol glucoside.



Remarkably, the streptol core closely mimics α-glucose, which prompted us to propose several biological pathways in which the former could be involved instead of the latter *in planta*. Namely, we speculated that streptol could target glucosidases or cell wall construction of plants. In order to probe for these targets and pinpoint the pharmacophore moieties of streptol, we synthesised a small library of its structural analogues. The synthesis of these new compounds was designed in a highly chemodivergent and scalable manner.

Our synthetic approach as well as structure-activity relationship studies will be presented in this talk. We believe that, beside their fundamental interest, these data could prove useful to pave the way towards selective and potent herbicides with a potentially novel mode of action.

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Rh(III)-Catalysed C-H (Hetero)arylation of Pyridones and Quinolines with IndoleBX

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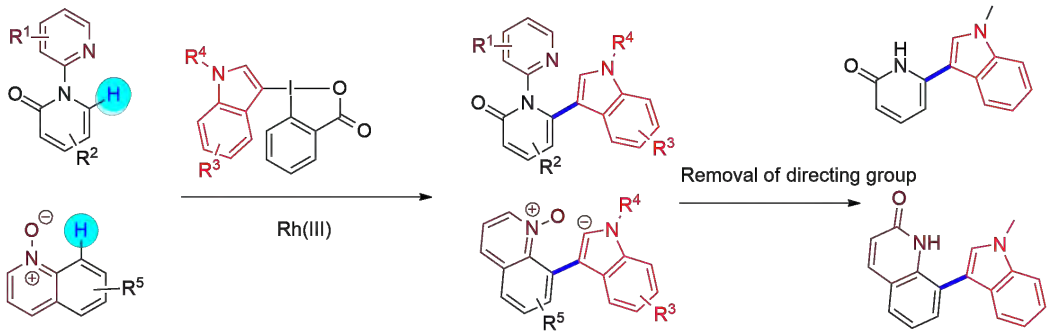
Indole heterocycles have been found in a diverse range of biologically active compounds and natural products. [1] Recently, our group developed IndoleBenziodoXolones (IndoleBX) [2] as useful reagents for the efficient transfer of indole moieties. The indole moiety can be installed through directed C-H bond functionalization under Rh(III) catalysis on N-pyridyl pyridines and quinolone N-oxides [3]. This new reaction showed tolerance towards a broad range of functional groups and was highly regioselective (functionalization of C-6 for N-pyridyl pyridines, and C-8 for quinoline N-oxides). Upon removal of the directing groups, indole-containing pyridones and isoquinolones products could be easily obtained.



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Peptide Stapling by the Means of Selective Cysteine Alkynylation Using Hypervalent Iodine Reagents

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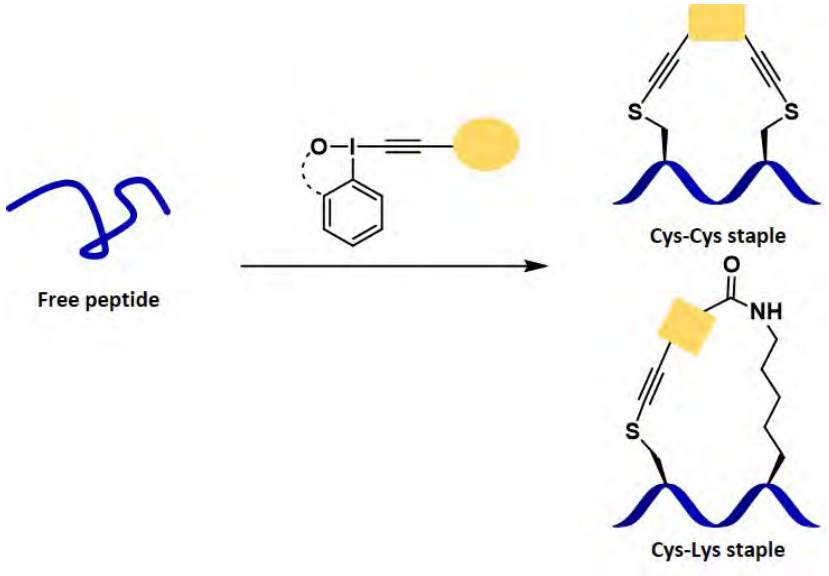
A stapled peptide is formed via a covalent linkage of two amino acid side chains. Such cross-linking can be used to stabilise short α-helices. This secondary structure is commonly mediating protein-protein interactions (PPIs). Thus, stapled peptides bearing helicity have a potential to inhibit PPIs, making them a desirable target. [1]

Selective cysteine alkynylation using hypervalent iodine reagents has been previously developed in the group. [2,3,4] This method has been further extended to cysteine-cysteine and cysteine-lysine stapling by the introduction of novel reagents. Herein, we will present the recent progress and discoveries towards our metal free peptide stapling method that utelises natural amino acid residues.



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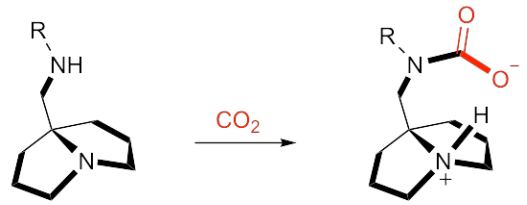
Scorpion-Like Designer Amines for Efficient and Reversible CO_2-Capture from Gas Mixtures

J. M. Hanusch[1], I. P. Kerschgens[1], F. Huber[1], M. Neuburger[2], K. Gademann[1]*

[1]University of Zurich, [2]University of Basel

The increase of the atmospheric CO_2 concentration is currently regarded as a major environmental problem. Therefore, new and more efficient ways to remove CO_2 from flue gas or directly from air are needed to address this challenge. Since decades, amine absorbents are the state-of-the-art approach to perform post-combustion CO_2 capture or remove CO_2 from natural gases in the so-called gas sweetening process. These methods often lack in selectivity, stability or demand high energy during release. Moreover, the captured CO_2 could be used as a cheap and green C1 source to convert into value-added products.

On this poster, we report on the investigation of a new type of low molecular weight diamines with high CO_2 capture capacity and high selectivity towards CO_2. Moreover, these amines demonstrated fast uptake and release kinetics due to special structural features, good stability over multiple capturing cycles and lower energy demand for recycling. In addition, given the high affinity towards CO_2, these amines could also be used in direct air capturing which still remains a main challenge in this field of research. Furthermore, NFC is modified and used as a carrier to get the big advantage of solid CO_2 absorbents.



R = alkyl, aryl or H

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Anion-π Catalysis on Epoxide-Opening Cascade

X. Hao[1], X. Zhang[1], A. Bornhof[1], J. López-Andarias[1], W. Liu[1], J. Wang[1], A. Pham[1], N. Sakai[1], S. Matile[1]*

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Anion−π catalysis, functioning through stabilizing anionic transition states or intermediates on π-acidic aromatic surfaces, has emerged in recent years.[1] Since then, anion–π catalysis has been explored with enolate,[2] enamine,[3] iminium,[4] transamination[5] and oxocarbenium[6] chemistry, and the first anion–π enzyme[2b] has been created.

Recently, we focused on epoxide-opening reaction, which is potent and practical pathway in the synthesis of the biologically interesting polycyclic polyether natural products. The primary anion−π catalysis on epoxide-opening reaction has been unveiled with the discovering of autocatalysis and violation of Baldwin rules. [7] Herein, the primary anion−π catalysis on epoxide-opening cascade reactions with diepoxide and triepoxide are disclosed.

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Towards an Excited State Hammond Postulate

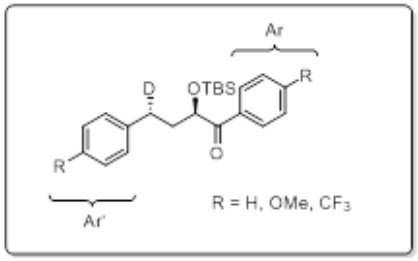
F. Harvey[1], C. Bochet[2]*

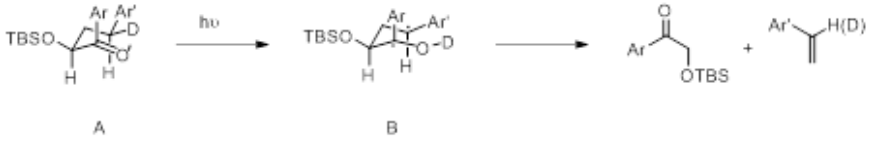
[1]University of Fribourg, [2]University of Fribourg

Classical thermal reactions can be studied by estimating the location of the transition state along the reaction coordinate using Hammond's postulate. Photochemical reactions, however, lack simple qualitative tools to determine the location of the conical intersections (CI) on the potential energy surfaces leading to the products, and complex quantum mechanics calculations are necessary in order to predict the outcome of a reaction.

In previous experimental work on photolysis of o-nitrobenzyl derivatives [1] it was observed that the Bell-Evans-Polanyi principle was followed, and the position of the CI also varied with the substituents. This suggests that Hammond's postulate may be applicable to CIs in the excited state.

To probe the influence of the position of the CI with respect to the energy level of the reactants and products, the following reaction system was designed:





A B

A reactant-like CI should be stereochemically biased (A), whereas a product-like CI should be stereochemically unbiased (B). Ar and Ar' influence both the energy level of the reactant and the position of the CI.

The above substrates will be synthesised then submitted to a series of photolyses, and the ratio of H/D-styrene will be analysed as a function of the substituent Ar. The reaction will be performed for both isomers in order to take into account the isotope effect.

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Visible light mediated enantioselective formation of all-carbon quaternary centers on acyclic systems

C. Hervieu[1], T. Suarez[1], M. Müller[1], E. Merino[1], C. Nevado[1]*

[1]University of Zurich

The enantioselective synthesis of all-carbon quaternary stereocenters within acyclic systems represents a major challenge for synthetic chemists. Strategies involving both single or multiple C-C bond-forming events per chemical step have been developed but sensitive reagents and careful temperature control are typically required. [1,2,3,4] Here, we present the enantioselective synthesis of α-aryl-β-substituted amides bearing an all-carbon quaternary center. The reaction proceeds via radical cascade Smiles rearrangement triggered by a photoredox catalyst. In this process, a sulfoxide group serves as a chiral auxiliary being removed during the reaction. This novel method allows the production of a wide variety of derivatives not only in good yields, but also excellent levels of stereospecifity. [5]

• Dual role of sulfoxide group: Chirality at sulfur controls absolute configuration / Traceless reagent
• Soft reaction conditions • Stereospecific method • 36 examples, 37-95% yields, up to 99:1 *er*

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Synthesis of Chiral and Redox-Active Covalent Organic Cages and Macrocycles

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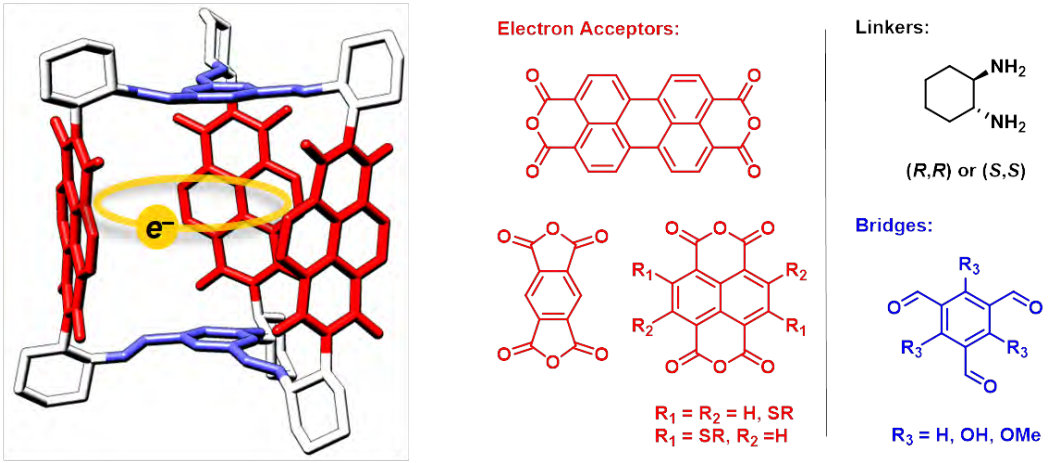
[1]University of Basel

Despite the promising characteristics of fullerenes in semiconductor composites, they suffer from several drawbacks, such as chemical accessibility, modularity or weak visible light absorption, which hamper the structure-property relationships in such materials to be established. Rylene-based materials, in contrast, offer versatile chemical modifiability. Electronic and optical properties of rylene-based materials can be tailored by introducing suitable substituents, which could allow overcoming these challenges.[1] However, rylene-derivatives are planar and tend to aggregate, unlike spherical fullerenes, which often has a detrimental impact on the efficiency of devices that employ them.

Recently, a chiral covalent organic cage with three built-in redox-active naphthalene diimide (NDI) units[2] assembled by dynamic imine chemistry[3-5] was reported. The three-dimensional structure prevents the three redox-active units from aggregation. In addition, the precise spatial arrangement of the NDI units provides a great platform to study electron transfer processes. Here, synthesis of a series of rylene-based chiral organic cages with a variety of optical and redox properties will be presented.



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Synthesis and characterization of new oxazolidine derivatives

M. Karamash[1], M. Giannantonio[1], A. Crochet[1], K. M. Fromm[1]*

[1]Fromm Group, Department of Chemistry, University of Fribourg

Due to the rapid increase in cancer cases all over the world, the research of new potential anticancer agents is an important research field. Oxazolidinones are a class of azoles, with the carbon between the nitrogen and oxygen in a 5-membered saturated ring. They appear to be promising pharmaceutical candidates as anticancer and/or antibacterial agents. [1-4]

In this research, a new approach to the synthesis of oxazolidine derivatives has been applied and analyzed. Consequently, a possible mechanism was proposed. A library of new oxazolidine derivatives was synthesized and characterized by different NMR spectroscopic methods, mass spectrometry, and X-ray single-crystal diffraction.

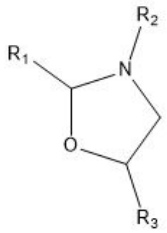

Figure 1. Oxazoline derivatives.

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Synthesis of the First Persistent Helical Non-Kekulé Triplet Diradical [8_6]Cethrene

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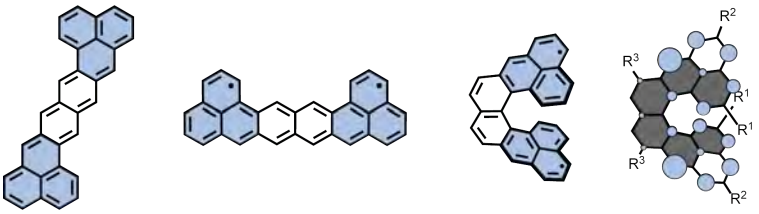
Phenalenyl[I] (highlighted in blue) is the smallest triangular graphene fragment that contains an unpaired electron (S = 1/2) delocalized over the entire π-conjugated core. When two phenalenyl units and additional benzenoid rings are fused together, two types of polycyclic π-conjugated hydrocarbons can be obtained, Kekulé and non-Kekulé. While in Kekulé systems all π-electrons are paired to give a closed-shell system with a singlet ground state (S = 0), in non-Kekulé systems, not all electrons can be paired, which results in an open-shell system with a unique feature of highest possible multiplicity in the ground state ($S \geq 1$). As a consequence, these materials are highly reactive and their syntheses are challenging. Even though preparation of persistent non-Kekulé graphene fragment is hard, it is crucial for gaining a deeper insight into the properties of these unique materials. Figure below shows typical examples of both types: Kekulé [8]zethrene[2] ('Z' shape) and non-Kekulé [8]uthrene ('U' shape), the structures of which differ in how two phenalenyl subunits (blue) are fused to the central naphthalene moiety (white). Although Kekulé systems such as [8]zethrene have been studied[3–4] intensively over the past two decades, the chemistry of non-Kekulé systems remains largely unexplored, because of extremely high reactivity of these species. The goal of this project is to synthesize the first helical non-Kekulé graphene fragment, [8_6]cethrene ('C' shape), a diradical isomer of [8]uthrene. In this molecule, two phenalenyl subunits are fused to a naphthalene moiety such that a twisted [6]helicene backbone (highlighted in gray) is obtained. As a result, [8_6]cethrene will have a helical geometry, which might, in concert with bulky substituents installed to protect the most reactive positions, improve kinetic stability of these systems and make them isolable as solid materials. In addition, spin density in [8_6]cethrene is delocalized over a chiral backbone, which makes this system interesting for investigation of phenomena that arise from the interplay of magnetism and chirality. The synthesis and properties of a derivative of [8_6]cethrene equipped with six substituents will be presented.



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1-Acyl Triazenes: Synthesis and Reactivity

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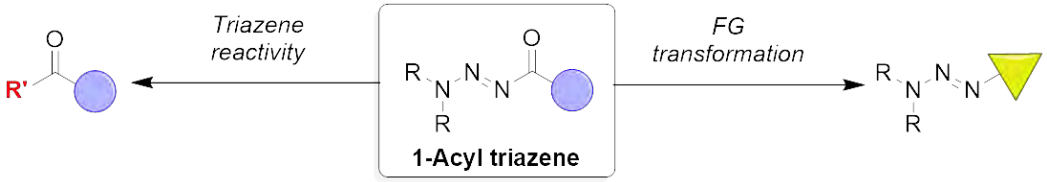
[1]LCS, ISIC, École Polytechnique Fédérale de Lausanne

3-Acyl triazenes are well-studied compounds with applications in medicinal and synthetic chemistry.[1,2] In contrast, there are hardly any reports about triazenes with acyl groups attached to the N1 atom, and general methods to prepare these compounds are missing. Here, we show that 1-acyl triazenes are readily accessible by acid-catalysed hydration of 1-alkynyl triazenes, or by gold- or iodine-catalysed oxidation of 1-alkynyl triazenes.[3] Crystallographic analyses show that 1-acyl triazenes are characterized by very short N2-N3 bonds. 1-Acyl triazenes display high thermal and hydrolytic stability, and tolerate oxidative and strong basic conditions. Under strong acidic conditions, 1-acyl triazenes acts as acylation reagents. This reactivity could open-up new pathways for organic synthesis. In addition, functional group transformation of 1-acyl triazenes could lead to building blocks that enable late-stage functionalization.



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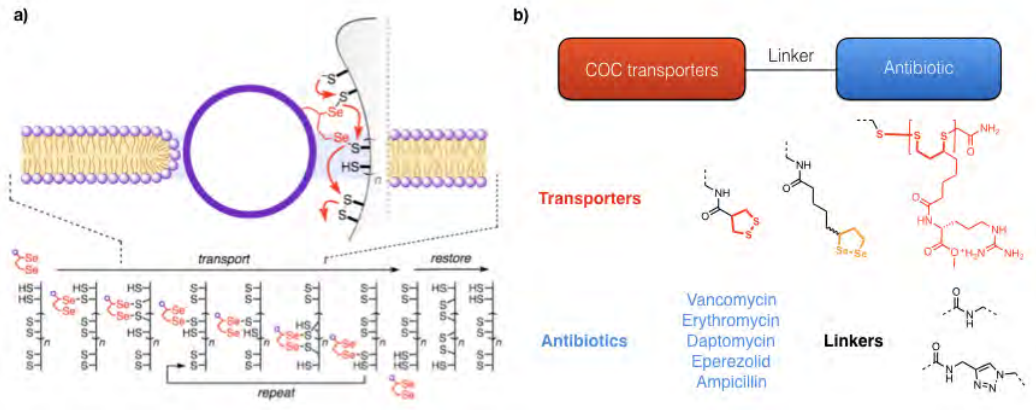
Ring Opening of 1,2-Dithiolane and 1,2-Diselenolane, Consequences for Cellular Uptake and Probing of Thiol-Mediated Uptake into Bacteria

Q. Laurent[1,2], M. Berthet[1,2], S. Barluenga[1,2], N. Sakai[1,2], N. Winssinger[1,2]*, S. Matile[1,2]*

[1]Department of Organic Chemistry, University of Geneva, [2]NCCR Chemical Biology

Cyclic oligochalcogenides (COCs) have emerged as powerful tools for the cytosolic delivery of biologically relevant substrates (proteins, peptides, quantum dots, ...).[1] Understanding the uptake mechanism of such transporters is of the utmost importance. Upon thiol-mediated ring opening of 1,2-dithiolanes and 1,2-diselenolanes, we were able to determine that the nucleophile attacks specifically the secondary chalcogen atom, which is followed by fast intramolecular rearrangement to the primary chalcogen atom. The clarification of this regioselectivity is of importance in poly(disulfide)s and cellular uptake. Based on this study, we proposed a mechanism of molecular walker to explain the particularly efficient diselenolane-mediated delivery of large substrates (Figure 1, a).[2] Experiments are in progress to elaborate on this working hypothesis. Inspired by well-established siderophore-based *Trojan Horse* strategy,[3] COCs have been attached to Gram-positive antibiotics to probe for thiol-mediated uptake in bacteria, with the hope of providing them with activity against Gram-negative bacteria (Figure 1, b).



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An Eco-friendly Route to Reusable Pd-containing Mesoporous Carbons for Mild and Chemospecific Hydrogenations of Nitroarenes

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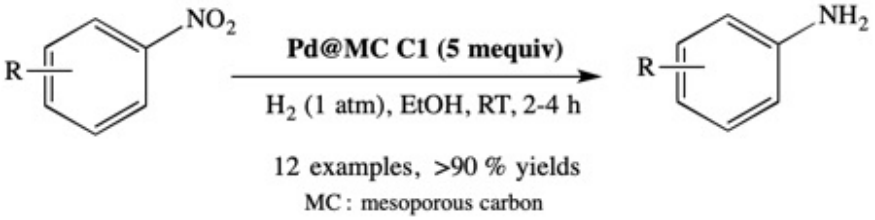
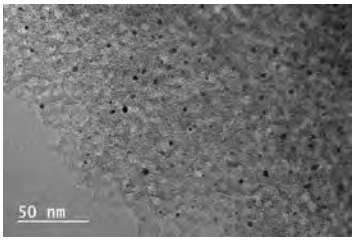
[1]Université de Haute Alsace, CNRS, IS2M UMR 7361

Mesoporous carbons containing Pd nanoparticles (**C1**) were prepared by a fast, efficient and eco-friendly route from readily available and non-toxic carbon precursors (phloroglucinol, glyoxal), a porogen template (pluronic F127) and a palladium salt. These materials were characterized by several techniques (TEM, STEM, N_2 sorption, XRD and XPS) and used successfully for mild hydrogenations of nitroarenes at RT under an atmosphere of hydrogen. The Pd-leaching was very low (< 0.1% of the initial amount) and the catalysts were reused several times with no significant loss in efficiency. Almost pure arylamines were obtained directly after reaction in excellent yields.



TEM Image of Catalyst **C1**



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Copper Catalyzed Chemo-, Regio- and Enantioselective Borylation of 1,3-Diene

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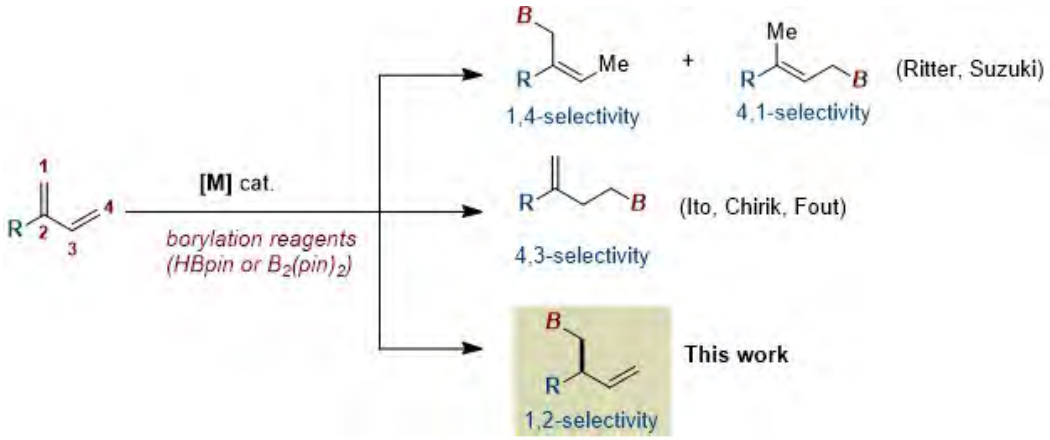
[1]Department of Organic Chemistry, Université de Gen, [2]Université de Genève

Overcoming the selectivity challenge in organic synthesis (including chemo-, regio- and enatioselectivity) to achieve only favored compound among different possible products is the core problem to be solved for organic chemists. The readily avalilable conjugated 1,3-dienes represent a particularly attractive platform for selective functionalizations.[1] However, selective functionalization of conjugated 1,3-dienes is a significant challenge because of the possibility of the addition of two different double bonds or conjugated addition, leading to chiral and achiral products.[2] Transition metal-catalyzed hydroborations and borylations of unsaturated bonds have emerged as attractive strategies providing access to functionalized structural motifs. Especially for 2-substituted 1,3-dienes, the selectivity challenge is highlighted by the fact that up to six different isomers can be generated upon exclusive mono-functionalization. The borylation of conjugate or less substituted double bond has been realized by several research groups.[3] To our knowledge, methods to access unusual 1,2-selective borylation of 1,3-diene are absent from the current literature. Herein, we established a perfectly Cu-catalyzed 1,2-selective borylation of 2-substituted 1,3-dienes to access valuable enantioenriched homoallylic boronates.[4] More important, this successful methodology represents the excellent uniform and harmony of chemo-, regio- and enatioselectivity in organic reactions.



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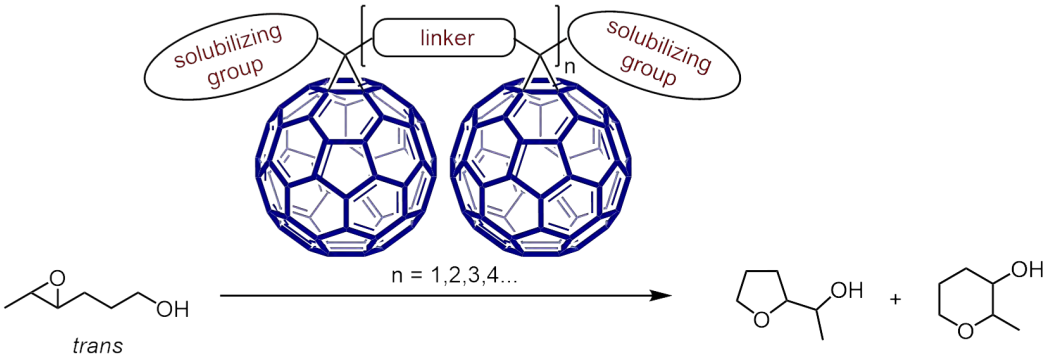
Anion-π Catalysis on Functional Fullerene Oligomers

W. Liu[1], J. Wang[1], A. Bornhof[1], X. Zhang[1], J. López-Andarias[1], X. Hao[1], A. Pham[1], N. Sakai[1], S. Matile[1]*

[1]Department of Organic Chemistry, University of Geneva

Anion−π catalysis, functioning through stabilizing anionic transition states or intermediates on π-acidic aromatic surfaces, has emerged in recent years.[1] Fullerenes with large spherical π surfaces can catalyze the decarboxylative aldol reaction of malonic acid half thioester (MAHT) as well as Diels-Alder reactions.[2-3] For further studies, herein, we design and synthesize a series of functional fullerene oligomers with larger π surfaces. These fullerene oligomer catalysts have been utilized in the epoxide ring-opening cyclization[4] and show better activities that the fullerene monomer.



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Bioinspired Synthesis of Lignans

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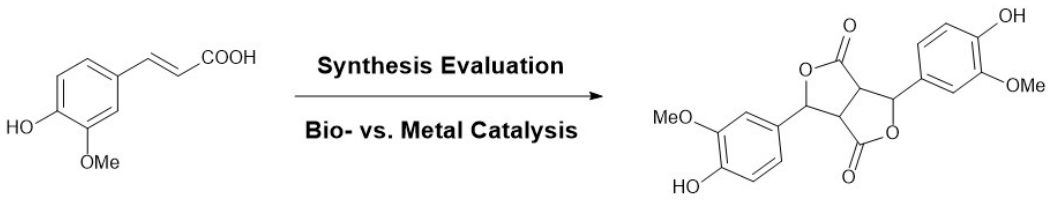
[1]HES-SO Haute école spécialisée de Suisse occidental, HEIA Fribourg, Institute ChemTech

The lignans are a large group of polyphenols found in plants. These plant lignans have been shown to be transformed in the gut by microorganisms to physiologically more active and bioavailable mammalian lignans like enterodiol or enterolactone. These phenolic compounds have an interest regarding their antioxidant potential and health benefits of lignans have been linked to the prevention of cardiovascular disease, hypercholesterolemia, and various cancers [1].



Ferulic Acid bis-Lactone

Here, we present our work, which is on a bioinspired synthesis of a key intermediate in the synthesis of secoisolariciresinol (SECO), a bis-lactone based on dimerization of ferulic acid. Several synthetic approaches, including biocatalysis [2], were evaluated regarding selectivity, yield and “practicality” on scale. The most promising synthesis was scaled-up to multi-gram scale.

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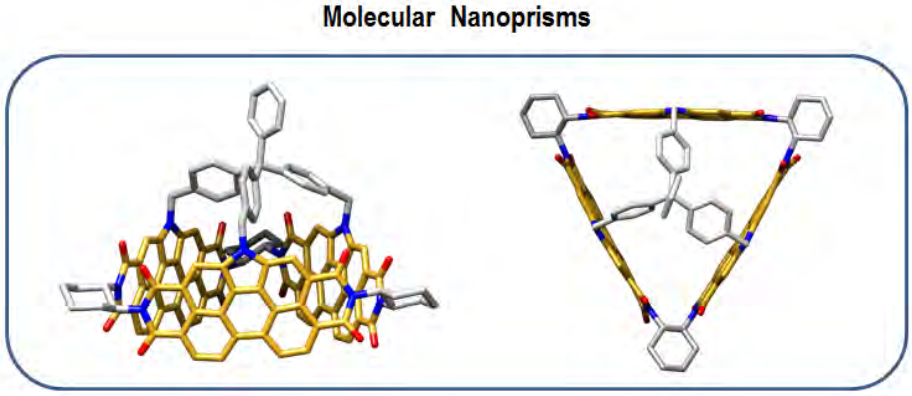
Synthesis of Molecular Nanoprisms Based on Perylene-3,4,9,10-dicarboximides

C. G. Martinez[1], T. Šolomek[1]*

[1]University of Basel

The consumption of energy in our society is expected to increase rapidly due to growing world population.[1] Therefore, producing the energy in a clean and sustainable way is a keystone to control climate change. Here, solar energy has a great potential because it is inexhaustible and at the same time its environmental impact is low. Organic photovoltaic (OPV) technology appears as a promising alternative offering a great series of advantages. However, the challenge with OPVs is in improving their power conversion efficiency by understanding the internal physical processes in an OPV. Specifically, organic materials must absorb light, dissociate excitons, transport the free charges and collect them efficiently.[2] Among them, fullerenes have been the most successful electron acceptors in OPVs until very recently. Although fullerenes are great acceptors, they absorb sunlight weakly, are difficult to modify and expensive to manufacture.[3]

Here, a strategy for obtaining molecular nanoprisms (Figure 1) based on perylene-3,4,9,10-dicarboximides (PDIs) will be discussed. These compounds, like fullerenes, exhibit high symmetry and rigidity, and will display electron delocalization and transport in three dimensions. PDI units were selected because they absorb visible light with large molar absorption coefficients, are air- and photostable, display good redox properties and electron mobilities, and their structure can be easily modified.[4] Such simple model systems will allow studying the effect of electron delocalization on charge separation and recombination thereby improving our understanding of OPVs.



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Synthesis of possible protein biomarkers as reference materials for retrospective verification of exposure to Chlorine

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Chemical warfare agents (CWA's) became well known since World War I. Even though 97% of all declared chemical weapons stockpiles have been verifiably destroyed[1], CWA's are still present in the modern world despite the majority of the states have ratified the Convention on the Prohibition of the Development, Production, Stockpiling and Use of Chemical Weapons and on their Destruction (CWC)[2]. Since 2012, about 336 chemical weapons attacks were reported in the Syrian Arabic War. Beside the use of the nerve and blistering agents like Sarin and sulfur mustard, another chemical regained a lot of popularity – Chlorine[3]. Chlorine gas, being a toxic but widely used chemical in industry with numerous civilian applications[4], serves as a parade example for the dual-use problem.

Nowadays, only few biomarkers[5] for the unambiguous verification of exposure to Chlorine gas are known. Facing this specific problem, possible Chlorine-modified protein biomarkers are synthesized for analytical investigation. Unequivocal methods to verify exposure strongly contribute to strengthening the verification regime of the CWC. Furthermore, theses biomarkers can give important indications about the action of Chlorine in the human body.

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Dual-photoredox/Ni catalyzed three-component carbofunctionalizations of alkenes

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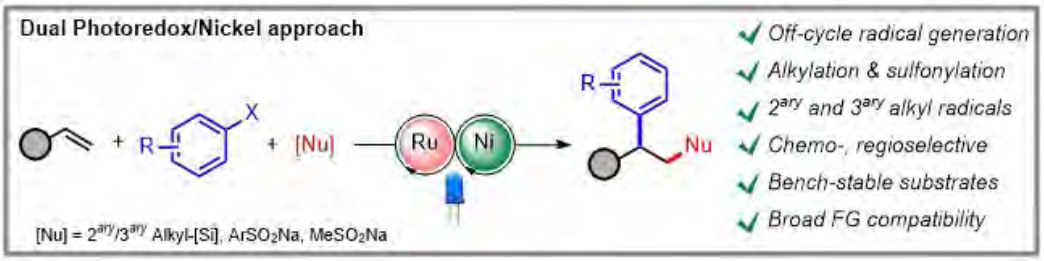
[1]University of Zurich

Intermolecular difunctionalization of alkenes represents a powerful strategy to construct complex aliphatic structures by concomitant formation of C-C and/or C-X bonds across the π-system.[1] Herein, we report a multicomponent difunctionalization of olefins merging photoredox and nickel catalysis under visible light irradiation. This transformation unveils addition of alkyl and aryl/alkyl sulfonyl radical regioselectively to the terminal position of the olefin and simultaneous arylation of the internal carbon in a single step under mild reaction conditions. The process, devoid of stoichiometric additives, benefits from the use of bench-stable and easy-to-handle reagents, is operationally simple and tolerates a wide variety of functional groups. [2]



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Palladium-catalyzed Intermolecular Biaryl Atropoenantioseletive C–H Functionalization

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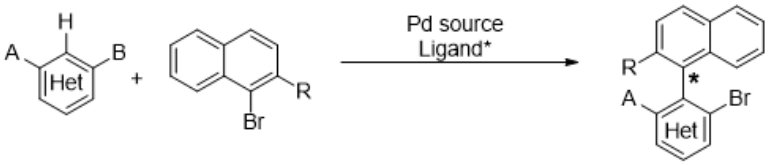
[1]Laboratory of Asymmetric Catalysis and Synthesis, EPF Lausanne, [2]Department of Chemistry, University of Basel

A considerable amount of natural products, pharmaceuticals as well as asymmetric catalysts exhibit rotational restriction about a biaryl axis. Such atropisomers are largely achieved by dynamic kinetic resolution. The aim of this research is to develop a Pd^0/Pd^{II} catalytic system with carefully designed ligands that facilitates the arylation of heteroarenes in an atropoenantioselective manner.



Advanced wastewater treatment to abate micropollutants with granular activated carbon (GAC) alone and combined with partial ozonation (O_3/GAC)

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In Switzerland, since January 2016 a new legislation is implemented with the aim to enhance surface water quality. The target is to reduce the micropollutant load discharged by the wastewater treatment plant (WWTP). Conventionally, WWTPs are designed to reduce the biological and chemical oxygen demand and to remove suspended solids and nutrients. The Swiss Federal Office for the Environment has established a list of 12 indicator substances to monitor the efficiency of upgraded WWTPs. These compounds are not easily or not biodegradable and are usually not removed by a conventional WWTPs. The average abatement of the 12 compounds should be >80%. To reach this goal, ozonation or treatment with powdered activated carbon (PAC) is recommended. However, different technologies are also possible. The treatment with granular activated carbon (GAC) has many benefits as it is easier to be operated and has a smaller CO_2 footprint, but best practice to be economic is not available yet.

In this project, the competitiveness of GAC in wastewater treatment and the combination of GAC with a low dose pre-ozonation is evaluated. The project is focusing on the WWTP of Glarnerland and is in collaboration with the engineer consultant Hunziker AG. It is currently receiving the wastewater from 6 communities and the wastewater of several industries (total 70’000 person equivalents). The different industries are producing paper, textiles or pharmaceuticals. Due to this inflow, the WWTP has to deal with a wide range of DOC coming in (5-15 mgDOC/L from 2015-2018).

For chemical analysis, a method using high pressure liquid chromatography coupled to high resolution mass spectrometry (HPLC-HRMS with the QExactive from Thermo) or coupled to triple quad MS (HPLC-QQQMS from Agilent 6495) was applied to around 60 target compounds. In a pilot plant, 4 different types of granular activated carbon are used and compared. Two GAC columns with two of the above material are additionally run with a pre-ozonation at a low dose of around 0.2 gO_3/gDOC. Overall, there is a good abatement of the 12 indicator substances observed. The first results that compare the GAC efficiency of the four materials have shown that the GAC density influences the sorption. The GAC with the lowest density showed a lower efficiency than the other columns, as there is less carbon in the column at the same volume. The combination with a pre-ozonation results are promising. The elimination of micropollutants over the GAC column that followed the pre-ozonation is overall better than over the GAC column that did not have a pre-ozonation. With the combination O_3/GAC, the goal of average 80% removal of the 12 indicator substances are archived up to 40’000 bed volumes (BV) with an ozone dose of 0.2 gO_3/gDOC. With the GAC alone, the average removal fell below the 80% already at 12-15’000 BV. Currently, the economic aspects of GAC treatment and O_3/GAC combination are evaluated.

Chiral $Cp^xCo(CO)I_2$ Complexes in Asymmetric C–H Functionalization

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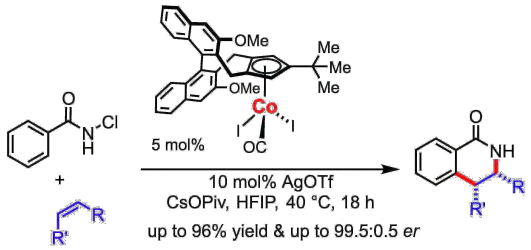
[1]Laboratory of Asymmetric Catalysis and Synthesis, EPFL

In recent years, 3d metal catalysts have proven their potential in C–H activation reactions.[1] In particular, cobalt has received considerable interest as a non-noble congener of rhodium. In line with our interest in the development of asymmetric catalytic transformations, we have recently shown the first application of chiral $Cp^xCo(CO)I_2$ complexes by demonstrating their use in asymmetric synthesis of dihydroquinolinones.[2]



The developed method gives access to the target compounds in high yields and *er* up to 99.5:0.5. Notably, the obtained enantioselectivities are typically superior to those previously reported for rhodium catalysis.

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Enantioselective Synthesis of Benzonorcaradienes by Chiral Cyclopentadienyl Ruthenium Catalysis

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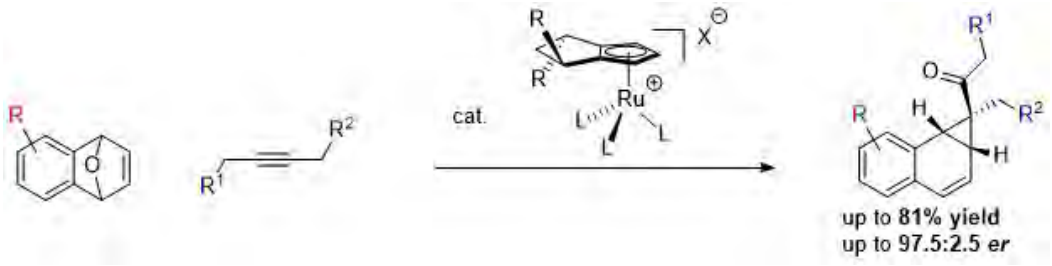
[1]Laboratory of Asymmetric Catalysis and Synthesis, EPF Lausanne

Cyclopentadienyl ligands (Cp) and their corresponding transition-metal complexes have broad application on catalysis.[1] On this basis, chiral cyclopentadienyl ligands (Cp^x) have been developed and utilized with transition-metals such as Rh^{III}, Ir^{III} and Ru^{II}, showcasing their high potential for asymmetric reactions.[2][3] In spite of the high demand for chiral cyclopentadienyl ligand, the development of a concise synthetic route is still at an early stage. Hence, in our previous research, we presented readily accessible and novel class of Cp^x ligand.[4] Herein, we report a related Cp^xRu^{II}catalyzed highly diastereo- and enantioselective coupling of oxabenzonorbornadienes and internal alkynes for the synthesis of benzonorcaradienes with up to 97.5:2.5 er.[5] The reaction illustrates the potency of this CpxRuII type catalyst for asymmetric catalysis.



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[8] & [9]Cethrenes: Chiroptical & Magnetic Switches

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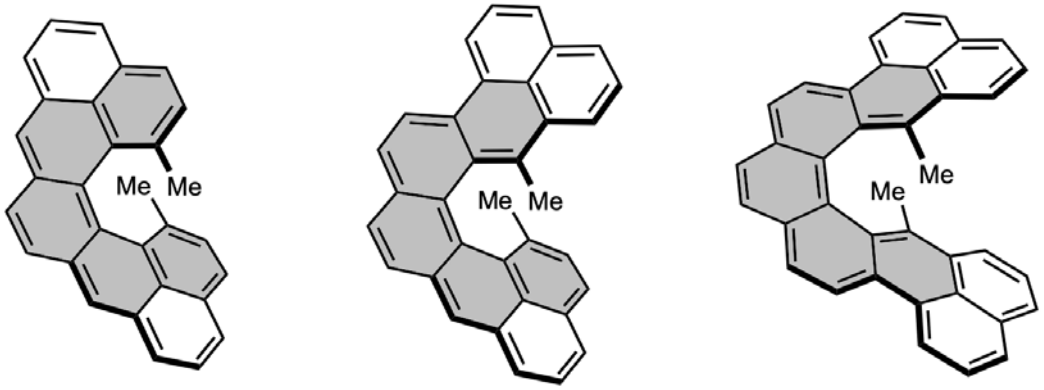
[1]University of Zurich, Department of Chemistry, Winterthurerstrasse 190, 8057 Zurich

Diradicaloid π-conjugated hydrocarbons[1] are characterized by small HOMO–LUMO gaps and low-lying triplet excited states that can be populated thermally. In our group, we investigate diradicaloid systems with helical geometries, called cethrenes[2], where through-space orbital interactions, which affect the energies of the ground and excited states, arise. These systems can also act[3,4] as photochemical switches between an open and a closed form, which show distinct magnetic and chiroptical properties. The goal of this project was to evaluate the effect of conjugation length on the energy gap between the singlet ground state and triplet excited state in a series of compounds based on [5]helicene (gray-filled rings), which differ in the number of additional fused benzenoid rings (white-filled rings). This knowledge will allow us to establish design principles that can be used to fine-tune the properties of this class of materials. Synthesis and characterization of two new model compounds, [8_5]- (middle) and [9_5]cethrene (right), extended homologs of [7_5]cethrene (left) previously reported[4] by our group, will be presented.



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Gold Nanoparticle Dimers via Acetylene Homocoupling

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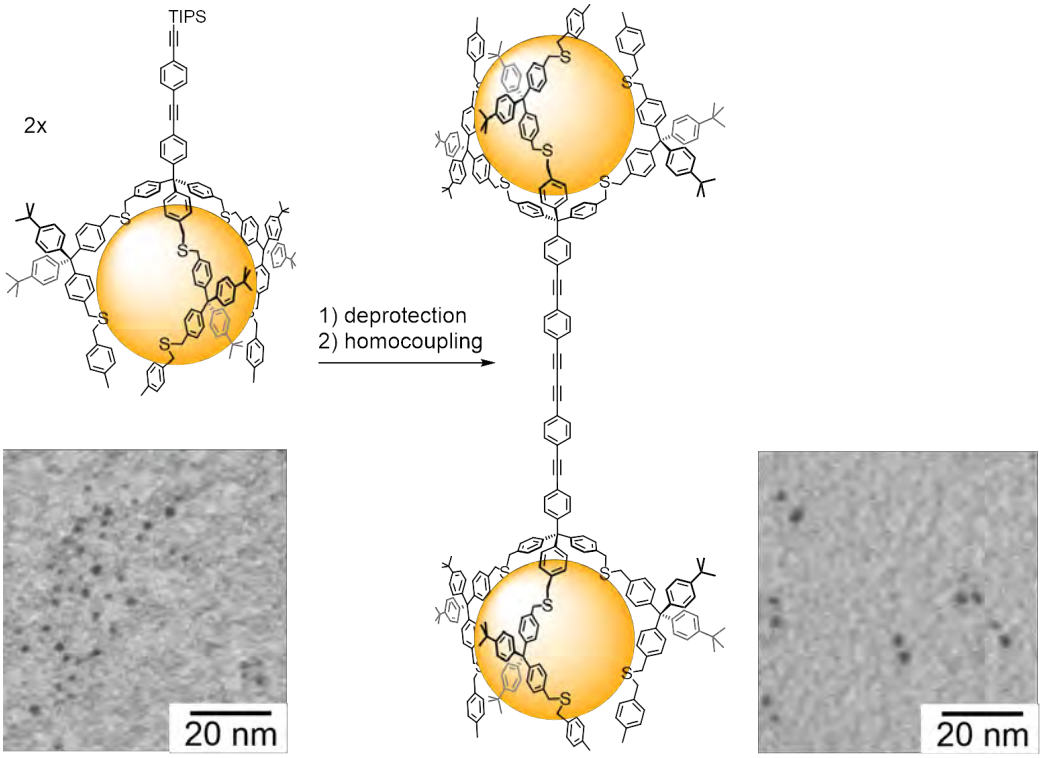
[1]University of Basel

Due to their unique properties, functional gold nanoparticles (Au NPs) are of major interest for molecular electronics. [1-3] We have synthesized a tripodal thioether-based ligand which stabilizes Au NPs in a 1:1 ligand-to-NP ratio and offers further chemical functionality by exposing a protected acetylene in perpendicular orientation to the particle. The Au NPs have a narrow size distribution (1.20 ± 0.26 nm) and withstand thermal stress up to 105 °C. The Au NPs were used to synthesize dimers via standard acetylene deprotection-homocoupling protocol. The dimer-dimer distance is in agreement with molecular modeling. Furthermore, the dimers can be isolated by size-exclusion chromatography and are stable for an extended period.



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Scenes of Tension Inside the Cell with Selective Mechanosensitive Fluorescent Probes

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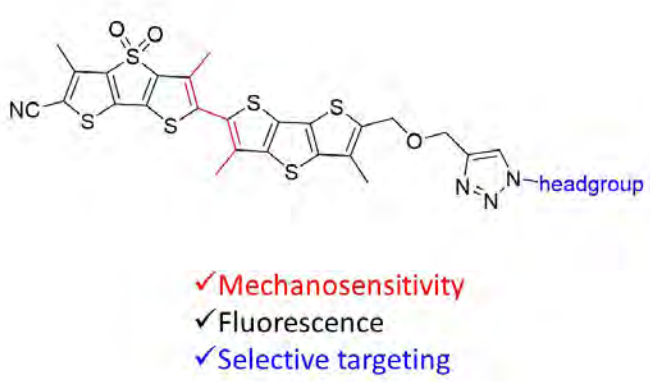
[1]Department of Organic Chemistry, University of Geneva

The development of practical and reliable strategies to measure mechanical forces inside cells is still a difficult challenge for chemists and biologists.[1]

For this purpose, the well-known fluorescent mechanosensitive flipper scaffold has been identified as the ideal building block to synthetize selective organel targeting probes.[2] The flipper push-pull system, displaying a peculiar deplanarization in the ground state, has been thus coupled with suitable headgroups to ensure the selectivity.

Further tailoring of this scaffold is now expected to give a fine tuning of its selective confinement in differently acidic endocellular compartments, like the various endosomal subpopulations.

In this way imaging and membrane tension measurement of these compartments will be achieved and further understanding of their role in various physiological and pathological processes will be possible.



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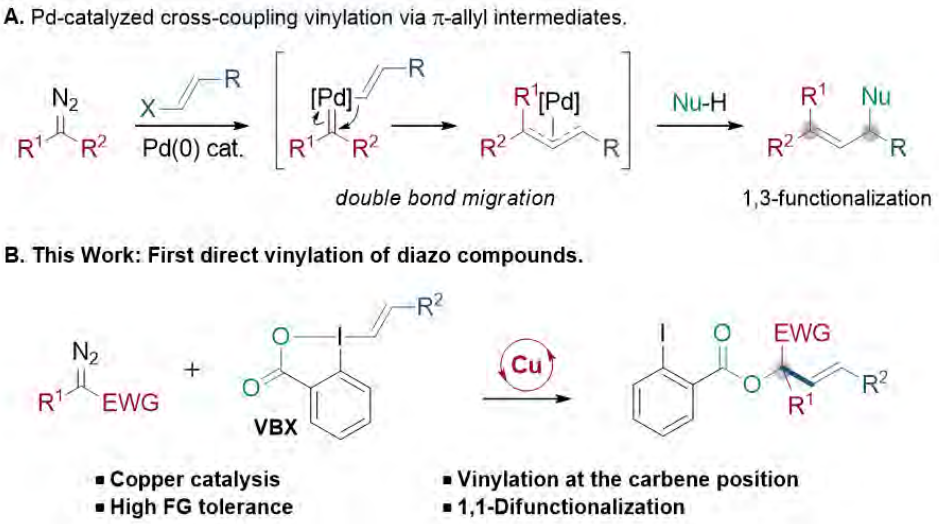
Copper-Catalyzed Insertion of Diazo Compounds into Vinyl Hypervalent Iodine Reagents to Generate Allylic Esters

G. Pisella[1], J. Waser[1]

[1]Laboratory of Catalysis and Organic Synthesis

Metal carbenes are highly versatile intermediates, easily generated from diazo compounds, which have been extensively used in synthetic chemistry (cyclopropanation, Nu-H insertion, ylide chemistry).[2] Recently, metal carbenes have emerged as a new type of cross-coupling partners for the formation of C−C bonds.[3] In this context, the generation of palladium carbene intermediates for the cross-coupling with vinyl halides has been highly successful for the synthesis of functionalized olefins, but resulted in the formation of isomerized 1,3-alkene products through double bond migration (Scheme 1A).[4]



Scheme 1. Cu-catalyzed vinylation of diazo compounds with VBX reagents.

To develop the first direct vinylation of diazo compounds (Scheme 1B), we identified vinylbenziodoxolone (VBX) reagents as ideal coupling partners:[5] The hypervalent bond confers a highly electrophilic character to the vinyl motif and the benzoate group can act as a nucleophilic oxygen source. VBX reagents have been much less used than the more established EBXs (ethynylbenziodoxolones).[6] The use of inexpensive and earth-abundant copper associated to the high atom-efficiency of the reaction are notable advantages of the methodology. The transformation is tolerant to a wide range of functional groups and provides ready access to a broad scope of allylic esters in very high yields.

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Synthesis of benzazepinones via intramolecular cyclization involving ketene iminium intermediates

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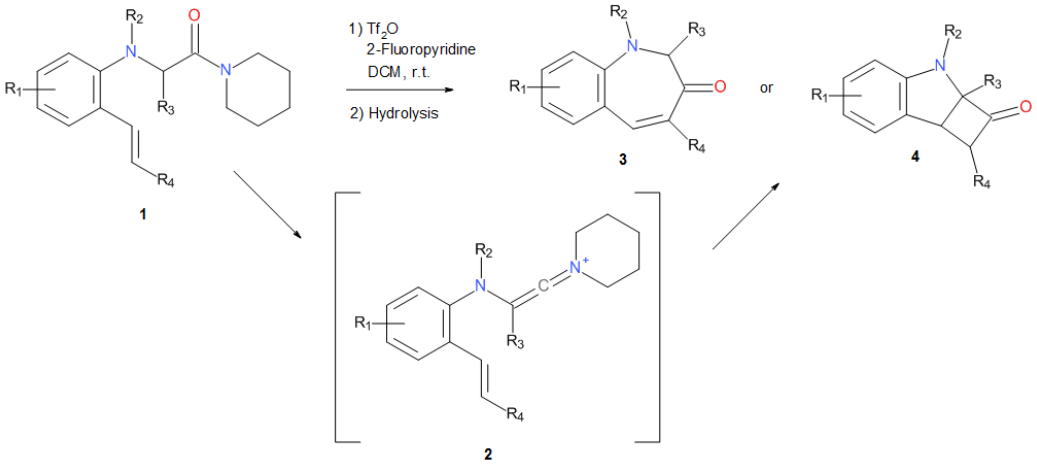
[1]Syngenta Crop Protection AG

The reactivity of styrenic anilines **1** towards triflic anhydride was explored and described herein. The activation of the amide moiety generates a keteniminium salt **2**, that could react in two different ways depending on the electrodensity of the aniline (see scheme).



When the nitrogen is substituted with a strong electron-withdrawing group, cyclobutanones **4** are formed preferentially by a [2+2] cycloaddition, otherwise a Friedel-Crafts type cyclization occurs leading to benzazepinones **3**. The scope as well as mechanistic aspects of these reactions will be discussed.

Catalytic Cascade Reactions Inspired by Polyketide Biosynthesis

F. C. Raps[1], V. C. Fäseke[1], D. Häussinger[1], C. Sparr[1]*

[1]University of Basel

The biosynthesis of aromatic polyketides by non- or partially reducing polyketide synthases involves the controlled folding of poly-β-carbonyl chains by a complex enzymatic machinery. Compared to polyene cyclizations and epoxide-opening cascades, an extraordinary number of folds lead to great structural variability. Given the versatility of processes controlling the folding mode in biomimetic polyketide cyclizations with catalyst-control is yet unprecedent, despite the seminal early efforts in the area of stoichiometric reactions.[1]

The poster outlines our stepwise approach to catalyst-controlled biomimetic polyketide cyclizations by gradually increasing the size and flexibility of the poly-β-carbonyl substrates. Noncanonical hexacarbonyl chains were selectively converted into aromatic products with a new-to-nature oxygenation pattern with high selectivity originating from a careful catalyst design.[2] A putative folding by an extended hydrogen-bond network is proposed and various applications of the products will be presented.

By taking inspiration from early stereochemists and in particular the concepts of macrocyclic stereocontrol, transannular cyclizations of cyclic poly-β-carbonyl substrates leading to structurally complex products with a high degree of catalyst-control were investigated.[3] The poster will highlight reaction cascades from substrates identical to a hypothetical polyketide macrocyclization, transannular aldol reactions and cleavage steps allowing to reenter biosynthetic sequences.

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Pd^0-Catalysed C(sp^3)-H Activation: From Direct to Remote Functionalization for the Construction of Medium-Sized Rings

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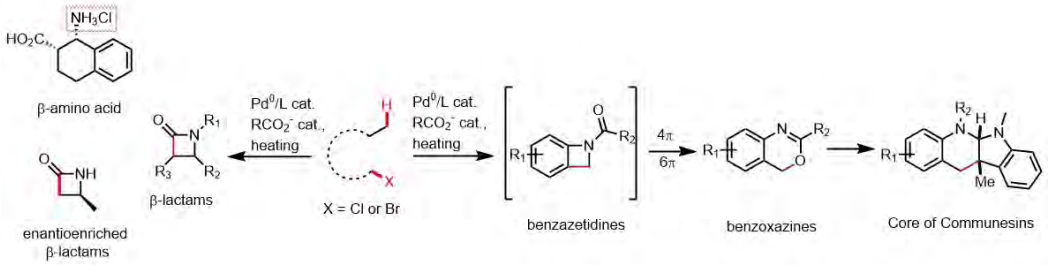
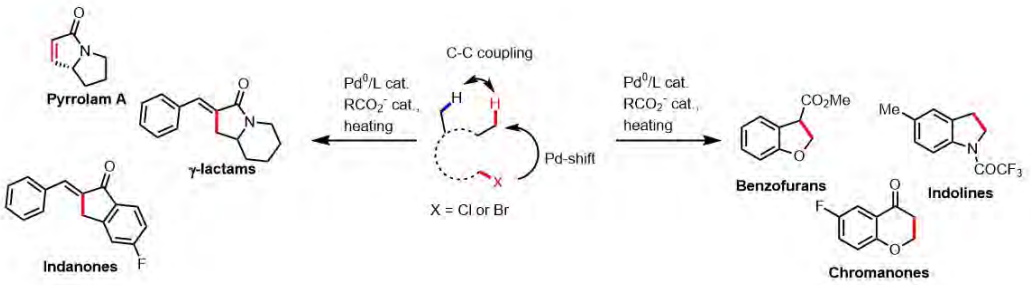
[1]Universität Basel, Basel, Switzerland, [2]Department of Chemistry, University of Basel

With the recent development of palladium catalysed C-H activation, direct functionalization of C(sp^3)-H bonds has proved to be a method of choice to access valuable building blocks. [1] [2] Taking advantage of this methodology, we recently proposed new direct functionalization of C(sp^3)-H bonds to access b-lactams [3] and benzoxazines. [4] The applicability of the reactions were demonstrated with the derivatizations of the obtained compounds to access respectively valuable beta-amino acids or natural products core.



In addition to direct functionalization, the ability of palladium to undergo a 1,4-through-space shift allows the functionalization of distal positions. [5] This interesting feature was developed and combined with C-H activation on different systems, to access a wide range of gamma-lactams, indanones, benzofurans, chromanones and indolines. [6][7]



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[7]: R. Rocaboy, O. Baudoin, *unpublished results*

Preparation of Indolenines via Nucleophilic Aromatic Substitution

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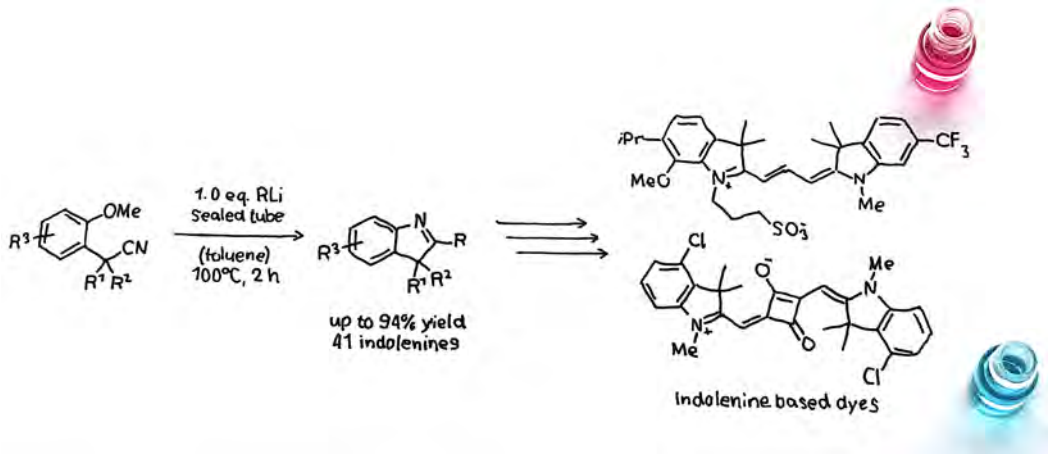
[1]University of Zurich

The indole and indolenine core structure is a popular motive among many natural products.[1] Besides its use in natural product synthesis, indolenines are also used as precursors in the synthesis of indolenine based dyes that are employed in many differed fields such as *in vivo* and *ex vivo* imaging.[2] For the synthesis of indolenines the interrupted Fischer indolization is mostly used, which application is mainly limited to substitutions at the 5-position.[3] In this context, we have developed a new method for the preparation of indolenines via a nucleophilic aromatic substitution using easy accessible benzyl nitriles as starting materials.[4] This cyclization method is high yielding (up to 94%) and tolerates a wide range of different functional groups, which is exemplified by the substrate scope of 41 indolenines. Substitutions at all possible positions of the aromatic ring as well as electron rich and poor benzyl nitriles are well tolerated. Furthermore, we investigated the mechanism of the nucleophilic aromatic substitution reaction. Finally, we applied this new method for the synthesis new indolenine-based dyes, which are difficult to access with currently literature known procedures.



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Enantioselective C(sp^2)-H arylation for the synthesis of warped molecules

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Enantioselective Pd^0-catalyzed C-H activation reactions rely on the use of a chiral ancillary ligand and/or a chiral base [1]. Our group recently developed a new family of chiral bifunctional phosphine-carboxylate ligands for asymmetric C(sp^2)-H arylation [2]. Application of this new approach to the preparation of enantioenriched fluoradenes and related structures is described herein.

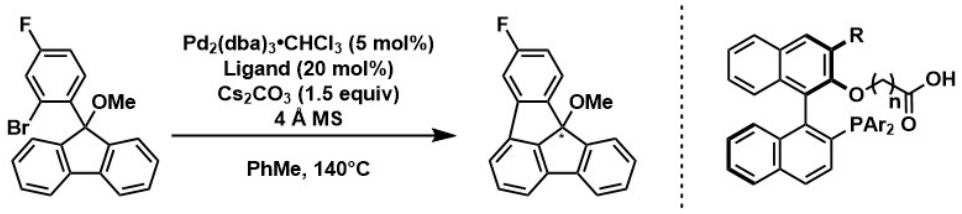

Figure 1 Enantioselective synthesis of fluoradenes

The reaction conditions and the ligand structure were optimized using the model substrate shown on Figure 1. These conditions were then applied to the preparation of other warped molecules. Moreover, starting from these C-H activation products a second cyclization reaction could allow the preparation of enantioenriched bowl-shaped molecules from achiral building blocks. Efforts towards this goal are also discussed.

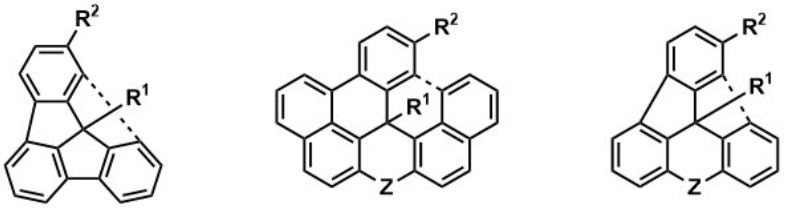

Figure 2 Examples of warped molecules and related bowls (dashed bonds)

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Synthesis of Novel 3-Monosubstituted s-Tetrazines and Application in the Labeling of Macromolecules

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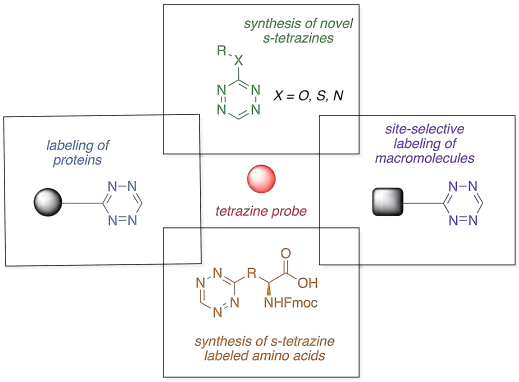
[1]University of Zurich

Since the first discovery of *s*-tetrazines in the late 19th century,[1] *s*-tetrazines have been employed in the development of organic electronics (e.g OPVs and OFETs),[2] energetic materials,[3] total synthesis[4] and coordination chemistry.[5] More recently, research interest shifted to their application in the context of bioorthogonal chemistry, due to their high potential as substrates for inverse-electron demand Diels-Alder reactions with strained alkenes and alkynes. Thus, there is a continuous interest in the development of novel *s*-tetrazines.



Based on our interest in the developement of novel chemical probes for the labeling of macromolecules, we synthesized a novel *s*-tetrazine and investigated its chemical properties. The synthesis of novel 3-monosubstituted *s*-tetrazines and *s*-tetrazine labeled amino acids could be accomplished and the potential in the site-selective labeling of macromolecules and peptides as well as the employment in the labeling of proteins was demonstrated.

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Cγ-SUBSTITUENTS AS TOOLS TO INFLUENCE THE REACTIVITY AND STEREOSELECTIVITY OF PROLINE BASED CATALYSTS

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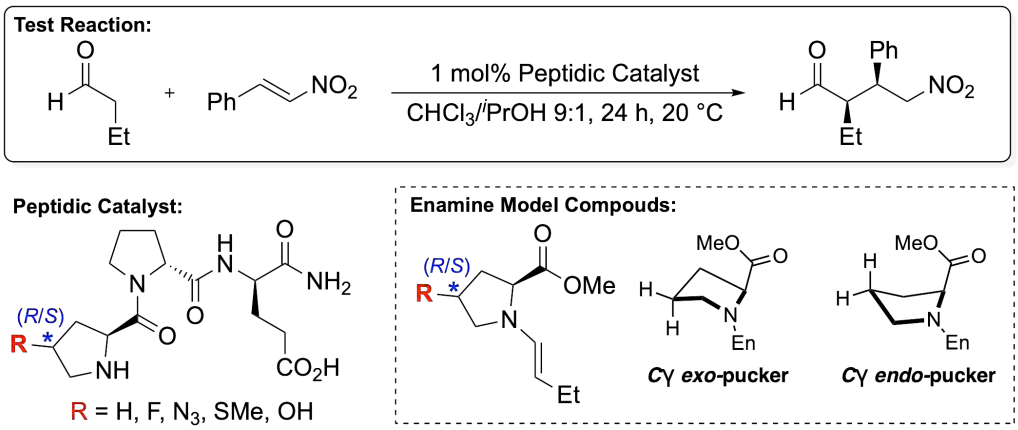
[1]Laboratorium für Organische Chemie, D-CHAB, ETH Zürich

Tripeptides of the H-Pro-Pro-Xaa type are highly reactive and stereoselective catalysts for asymmetric aldol reactions and conjugate addition reactions of carbonyl compounds to nitroolefins, dicyanoolefins and unprotected maleimide [1]. For example, as little as 0.1 mol% H-DPro-Pro-Glu-NH_2 suffices to catalyze conjugate addition reactions of aldehydes to nitroolefins in high yields and excellent stereoselectivities [2]. Mechanistic studies showed, that the catalytic cycle proceeds *via* an enamine intermediate, which takes part in the rate- and stereodetermining C–C-bond formation step [3]. We envisioned that the enamine reactivity and stereoselectivity can be influenced by changing the conformation of the *N*-terminal proline. We introduced substituents at the Cγ-position of the proline ring, which are known to favor different ring puckers [4]. We used the conjugate addition reaction of butanal to nitrostyrene as testing ground to analyze the performance of the Cγ-substituted catalysts by *in situ* IR- and NMR-spectroscopic experiments. We complemented our findings by studies on enamine model compounds, which were derived from Cγ-substituted proline methyl esters. Our investigations provided insight into the effect of different ring puckers on the reactivity and stereoselectivity of proline derived catalysts.



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Synthesis of α-aminoboronic acids and α-tertiary amines from potassium acyltrifluoroborates (KATs)

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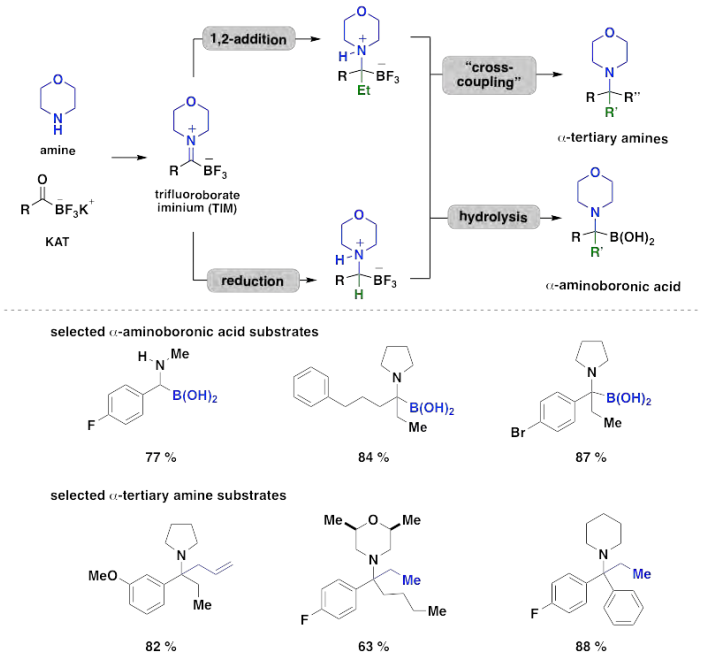
[1]ETH Zürich

The application of potassium acyltrifluoroborates (KATs) for the synthesis of α-aminoboronic acids and α-tertiary amines – which are important motives in modern drug discovery – is described. KATs are stable, commercially available compounds for which several synthetic routes have been developed. They undergo iminium formation with primary and secondary amines to give zwitterionic trifluoroborate-iminiums (TIMs). These can be further treated with a hydride source or Grignard reagents to give α-aminotrifluoroborates. These α-aminotrifluoroborates can be hydrolyzed to give α-aminoboronic acids using $SiCl_4$ as Lewis acid. The α-aminotrifluoroborates can be coupled with Grignard reagents to achieve the synthesis of *N,N*-substituted α-tertiary amines in a process involving a unique, distal oxidation of the carbon–boron bond.



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Modular Synthesis of α-Amanitin

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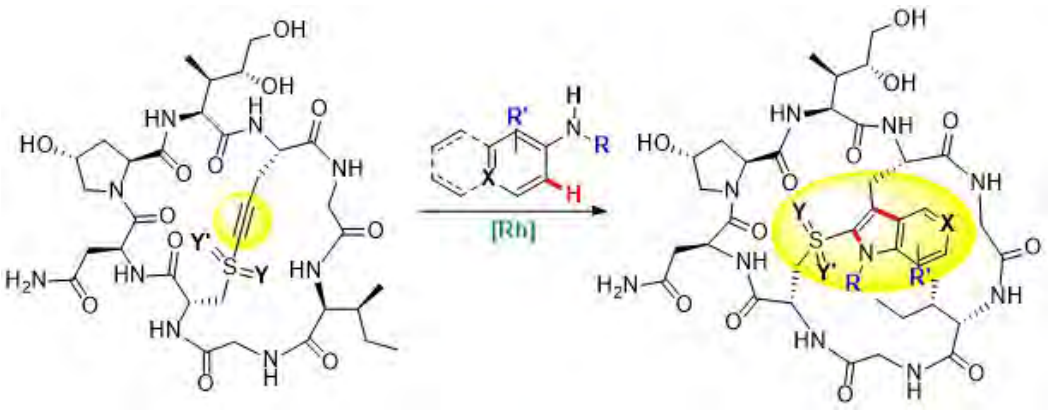
[1]Laboratory of Asymmetric Catalysis and Synthesis– , [2]Laboratory of Asymmetric Catalysis and Synthesis,

Amatoxins are ribosomally synthesized and post-translationally modified bicyclic octapeptides biosynthesized by the deadly basidiomycete fungus *Amanita phalloides*. They form a class comprised of a range of macrocycles with an eight-amino acid core sequence, IWGIGC(N/D)P, and exhibit varying degrees of hydroxylation. Amongst this group, α-amanitin is most prominent. It binds very selectively to the 140 kDa subunit (SB3) of DNA-dependent RNA polymerase II in nuclei of all eukaryotic cells, with subnanomolar dissociation constants.[1] Interaction of α-amanitin with Pol II leads to inhibition of the translocation of the RNA polymerase along the DNA template, therefore blocking the synthesis of mRNA, and as a consequence protein synthesis.[2] This interaction is responsible for the toxic effect of *Amanita phalloides*, leading to death after 4-8 days.[3] There is significant interest in investigating α-amanitin and its derivatives in order to gain further insight into the transcription mechanism, and its properties make it a target scaffold for potential new drugs.[4]

The most characteristic structural feature of α-amanitin is the linkage between cysteine and 6-hydroxy-tryptophan, which effectively cross-links the main chain peptide cycle. However, relatively little is known on the structure activity relationship of the molecule, especially with regards to this moiety.

We disclose our synthesis of α-amanitin *via* an unprecedented Rh(III)-catalyzed tryptathionine formation reaction, which permits access to a range of potential new derivatives to be investigated for their biological activity.



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Synthesis of Tetraarylethene and Triazoline AIE Emitters

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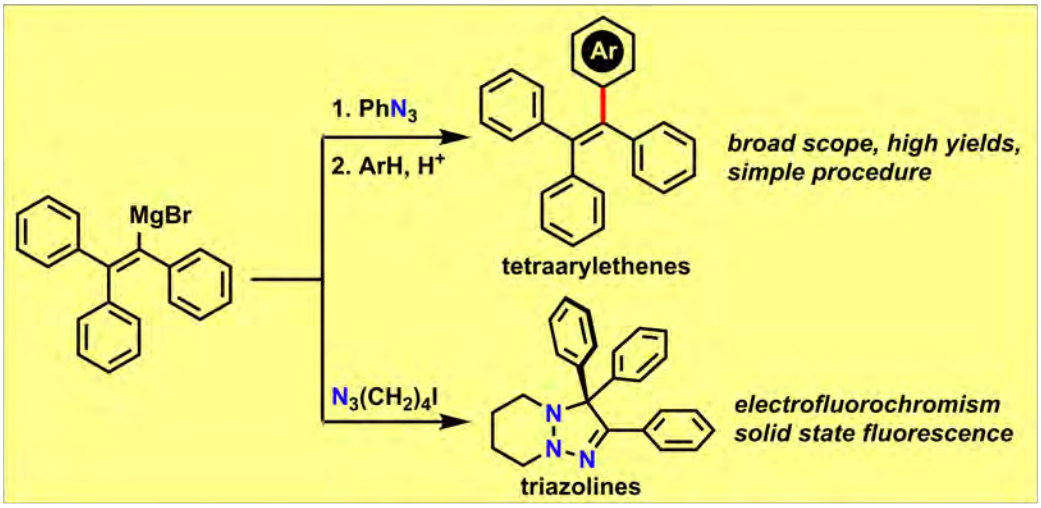
[1]École Polytechnique Fédérale de Lausanne

Compounds showing aggregation-induced emission (AIE) properties have found numerous applications in analytical chemistry, imaging, materials sciences, and biology. Tetraarylethenes are particularly popular in this context. During our investigations of chemistry of vinyl triazenes,[1-3] we have developed a novel route towards tetraarylethene AIE emitters via metal-free C-H triarylvinylation of aromatic compounds with vinyl triazenes.[4] Scope of the coupling includes simple unactivated arenes, functional arenes, heteroarenes and aromatic polymers. Within the course of this study, we have accidentally found a new class of solid state emitters based on Δ^3-triazolines.[5] These molecules display electrofluorochromism: it is possible to convert them reversibly into stable non-fluorescent radical cations.



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Atom transfer radical addition of a-boryl carbon centered radicals to alkenes for a new cyclopropanation manifold

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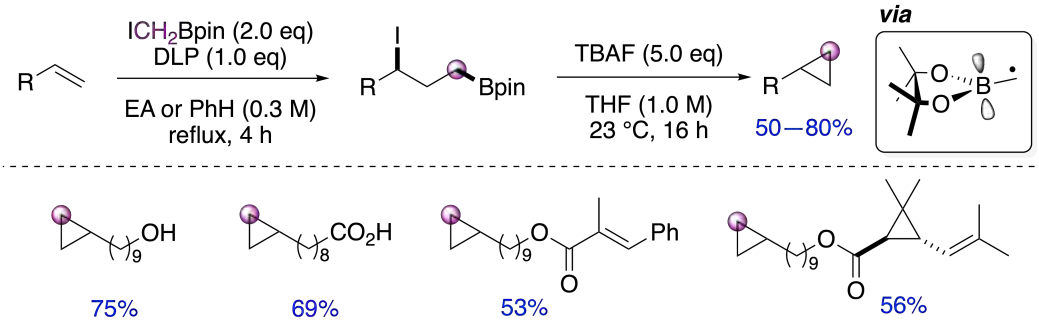
[1]Universität Bern, [2]University of Lancaster, [3]University of Strathclyde

The hitherto underexplored yet commercially available and bench-stable ICH_2Bpin,[1,2] may undergo atom transfer radical addition (ATRA) over unactivated, terminal alkenes in the presence internal electron-rich or electron-poor olefins. The resulting g-iodoboronic esters are infrequently found in the literature despite containing two proximal and orthogonally transformable carbon–heteroatom bonds.[3]



For efficient addition, we rely on the stabilizing influence of the vacant boron p-orbital on a radical formally located on its adjacent carbon atom.[4,5] The reaction can be telescoped into an operationally simple, one-pot protocol with a subsequent nucleophilic treatment to trigger a 1,3-cyclization. Full details of the chemoselectivity and complementarity of this cyclopropanation in comparison to other methods will be discussed in more detail.

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Divergent Total Synthesis of (+)-Epicoccin G and (-)-Rostratin A Enabled by Double C(sp^3)-H Activation

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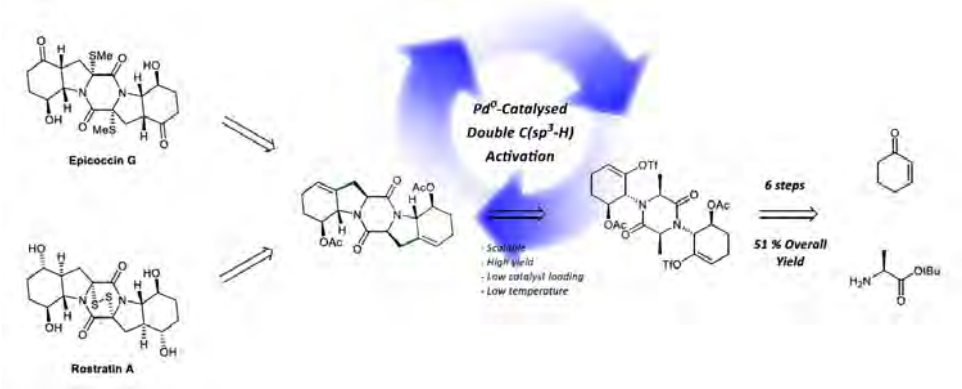
Dithiodiketopiperazine (DTP) natural products comprise a large number of metabolites, which display a wide range of biological activities including antiviral, antibacterial, antiallergic, antimalarial and cytotoxic properties.[1] DTPs, characterized by sulfur atoms on a fused diketopiperazine (DKP) structure, have gained significant interest from the synthetic community, due to their unique structural and biological properties. In particular, the groups of Nicolaou, Reisman and Tokuyama have reported elegant total syntheses of DTP molecules containing a pentacyclic ring system.[2,3,4] The innovative strategy reported herein is based on a Pd(0)-catalysed double C(sp3)-H activation key step allowing straightforward, high-yielding and concise access to a common advanced intermediate bearing the pentacyclic DKP scaffold.[5,6] The latter can be readily derivatised into several DTP natural products. Herein, we report the application of this C(sp3)–H activation-based strategy to the divergent enantioselective synthesis of epiccocin G and rostratin A, which are synthesized for the second and first time, respectively.



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Catalysis in the Supramolecular Resorcinarene Capsule

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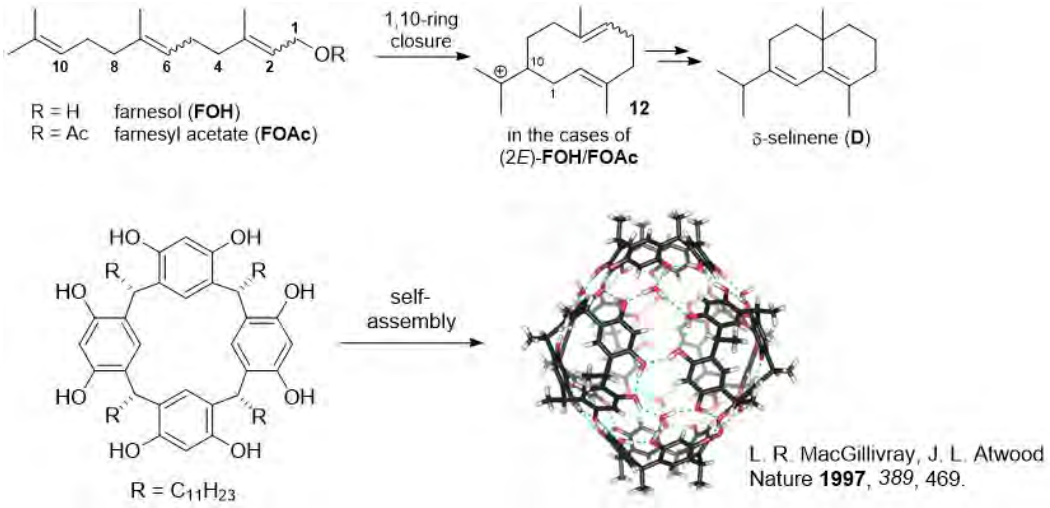
Nature's extraordinary elegance when performing chemical reactions has fascinated and inspired chemists for decades. Arguably, one of the most complex organic transformations performed in living organisms, is the tail-to-head terpene (THT) cyclization (see Fig.1 for one example).[1,2] It allows the construction of the most diverse class of natural products, namely terpenes, via nature's way of combinatorial chemical synthesis. Thousands of different natural products are formed from just a handful of simple, acyclic starting materials: geranyl pyrophosphate (monoterpenes), farnesyl-PP (sesquiterpenes) and geranylgeranyl-PP (diterpenes). Nature utilizes enzymes, termed cyclases or terpene synthases, to carry out this complex transformation. Building upon our initial results,[3-6] we explore possibilities to utilize supramolecular structures to mimic such complex transformations in the laboratory.



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Developing Chiral 1,3,2-Diazaphospholenes for Enantioselective Catalysis

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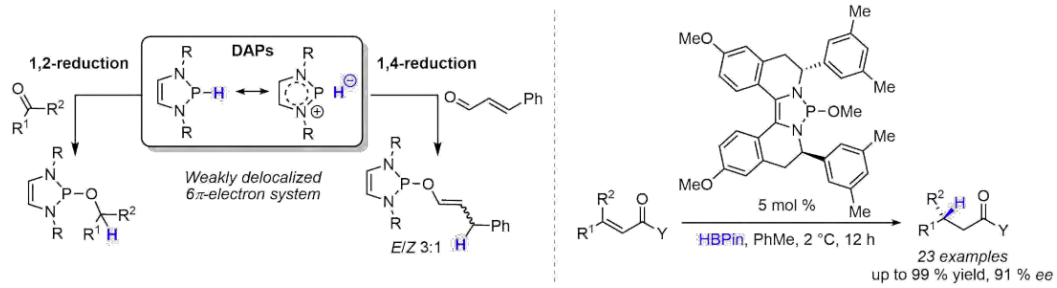
Organocatalysts offer complementary reactivity to transition-metal based catalysts while obviating the need for expensive and rare metals. As a result of their σ-aromaticity, secondary 1,3,2-diazaphospholenes display an umpolung of the P–H bond, rendering them as organic molecular hydride donors (**Figure 1**).[1] They have shown competency as catalysts for the reduction of carbonyl compounds and their derivatives, showing high selectivity for the 1,4-reduction of α,β-unsaturated carbonyl compounds.[2-5]



We introduce a family of chiral 1,3,2-diazaphospholenes, characterized by a rigidified backbone that enable the asymmetric reduction of a variety of α,β-unsaturated carbonyl compounds with excellent levels of enantiocontrol.[6] Furthermore, examination of the solid state single crystal X-ray diffraction analysis combined with nuclear magnetic resonance spectroscopic studies have shed light on the operative mechanism.

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The Hemiasterlin / E7974 Couple as Training Set for Organic and Natural Products Chemistry Courses in the Field of Life Sciences

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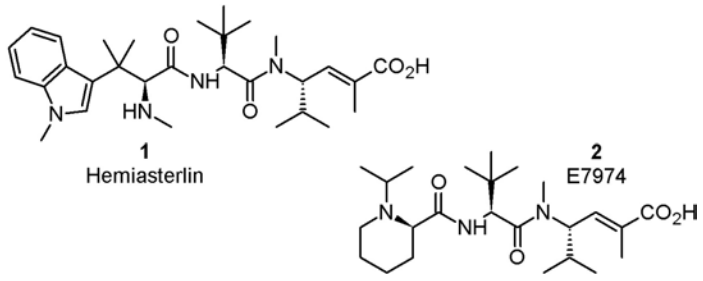
In memoriam Prof. Dr. Walther Schmid - an outstanding teacher of Organic Chemistry

Hemiasterlin **1** is a highly cytotoxic natural tripeptide of marine origin. It has been isolated from several marine sponges[1-3] and consists of three unusual and structurally highly interesting amino acids. The unique substructures have made[4] and still make[5] **1** an interesting target for total synthetic approaches. The cytotoxic action of **1** is due to tubulin binding and prevention of tubulin polymerization;[6] the *in vivo* application of **1** as anticancer agent, however, obviously suffers from general toxicity.[6] Exchange of just one amino acid has led to the synthetic derivative E7974**2** **w**ith improved pharmacological profile,[6] which has already been evaluated in several phase I clinical trial studies.



We will demonstrate how **1** and **2** and their unique structural features can be used in Life Sciences to improve knowledge and attract students' interest for peptide-related research already in basic courses dealing with Organic and Natural Products Chemistry.

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Electron diffraction: A new tool for the structural chemist.

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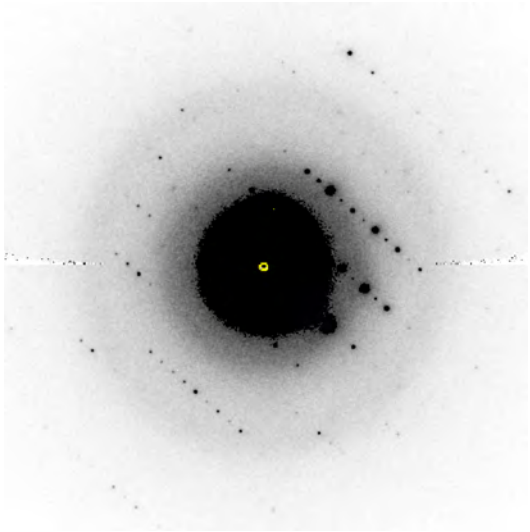
Atomic structure determination is essential to chemistry, since the atomic structures of matter reveal their function and destiny. For many decades X-ray crystallography and high resolution transmission electron microscopy have been the dedicated tool for structural chemistry. Both techniques however require crystalline and radiation-resistant matter in the micrometer-size regime. Yet, most crystalline substances like catalysts, pharmaceuticals and semiconductors are abundant as powders with crystalline particles in the submicrometer-range and suffer from beam-induced damage. Here, due to the lower radiation intensity used and the higher elastic scattering cross section, electron diffraction has been developed. The recent advances in detector technology gave new opportunities to this field, which we here exploited on samples, where usual structure determination would fail. Therefore, we equipped a conventional FEI 30 electron transmission microscope with an Eiger 1M X detector and yielded a customised electron diffractometer. We solved the structure of the active pharmaceutical compound paracetamol based on the powder blend of the cold medicine “Grippostadt®”. Though data was incomplete, their high quality revealed the atomic coordinates of the hydrogen atoms. The next case was resembled by the salt of a methylene blue derivative, whose submicrometer-sized needles did not show sufficient diffraction with synchrotron radiation. Here electron diffraction did not reveal the molecule only, it was also capable of resolving a crystallographic disorder of a BF4 – -anion. The atomic coordinates were in high agreement with the X-ray crystallographic structure yielded later on. Experimental structure determination proceeded with the same time investment as for any standardised X-ray crystallographic measurement. These results elevate electron diffraction to a level with the other established tools for atomic structure determination in chemistry. The simplicity of the experimental set-up and the use of the freely available X-ray crystallography software XDS and SHELX allows its durability at any research institution in the world.



An electron diffraction pattern contains structural information, even if dynamical scattering is present.

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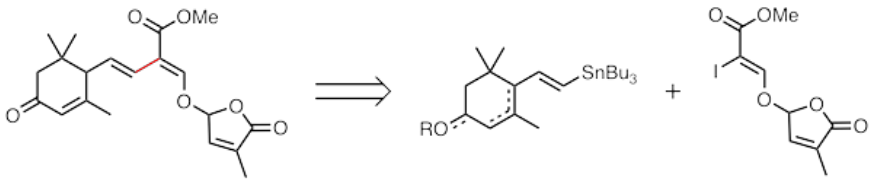
Total Synthesis of Heliolactone

M. Yoshimura[1], M. C. Dieckmann[2], P. Quinodoz[2], A. De Mesmaeker[2]*

[1]ETH Zürich, [2]Syngenta Crop Protection AG

Strigolactones are one family of plant hormones, which affect diverse aspects of plant growth and development. Recently, heliolactone has been isolated as a non-canonical type of strigolactone from the root exudates of sunflower, and it could be involved in crop enhancement. However, the biological activity is yet to be elucidated due to the inherent chemical instability and the low natural abundance. To disclose the biological contribution of heliolactone to crops, we herein synthetically provided heliolactone and its related derivatives by using Stille cross-coupling as the key step.



Heliolactone

A Mild Diversification Strategy Providing Direct Access to Nitroalkenes, Nitrohydrins, Isoxazolines and Isoxazoles from an NO_2-Redox Active Scaffold

K. Zhang[1], B. J. Jelier[1], A. Passera[1], G. Jeschke[1], D. Katayev[1]*

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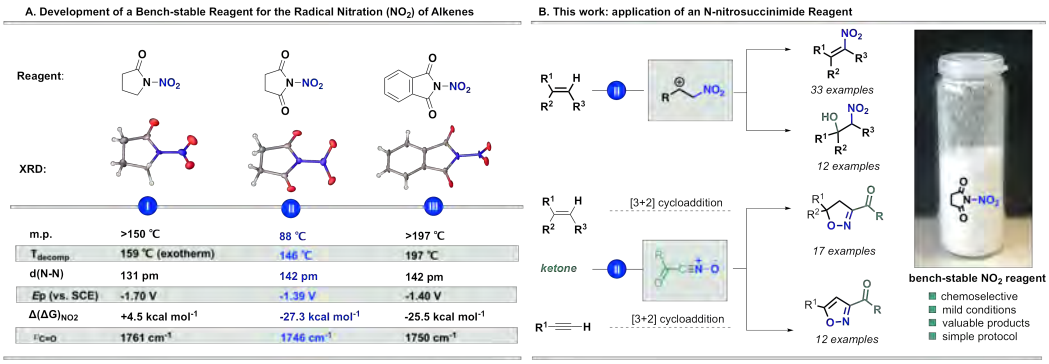
The plurality of nitration methods in the chemist's repertoire is fixated on the use of cationic and anionic forms of nitrogen dioxide to construct a C–NO_2 bond.[1] Currently, both approaches present several limitations from practical and synthetic perspectives, especially in more delicate syntheses or upon reaction scale-up.[2] Spurred by the presence of the nitro motif in drug-like molecules and the synthetic importance of the nitro group in functional group interconversions, we have designed a new class of NO_2-transfer reagents mitigating many of the classical challenges.

We evaluated a class of neoteric N–NO_2 heterocycles based on the pyrrolidinone scaffold. While the synthesis of N-nitropyrrolidinone I, N-nitrosuccinimide II and N-nitrophthalimide III has been rudimentarily noted more than fifty years ago, surprisingly no demonstrated reactivity has been described since. Herein, the slow liberation of nitrogen dioxide from a bench-stable reagent under catalytic conditions allows for a mild and selective β-nitration of alkenes. Remarkably, when carried out in the presence of water or ketones, difunctionalized alkenes are rapidly accessed with the same reagent providing a convenient route to synthetically valuable β-nitrohydrins or biologically active isoxazole derivatives, respectively.[3] Mechanistic insight including cyclic voltammetry, photophysics, DFT, and EPR suggest a mesolytic N–N bond fragmentation affording a nitryl radical as the key intermediate.



[1] Y. Nieves-Quinones, D. A. Singleton, *J. Am. Chem. Soc*. **2016**, 138, 15167−15197.
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[3] K. Zhang, B. J. Jelier, A. Passera, G. Jeschke and D. Katayev, *manuscript submitted.*

Divergent 1,3-Difunctionalization of Aminocyclopropanes

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Aminocyclopropanes are important building blocks in synthetic chemistry. Their reactivity was explored mainly by utilizing transition-metal catalysis to form a metallocyclobutane intermediates, or by photoredox chemistry to oxidize the amino group to a radical cation species.[1] Our group has focused in the past on the ability of donor-acceptor substituted aminocyclopropanes (D-A aminocyclopropanes) to react as zwitterionic synthons(Figure 1A),[2] we herein report a different strategy for the activation of mono-substituted aminocyclopropanes giving access to biscationic synthons(Figure 1B).

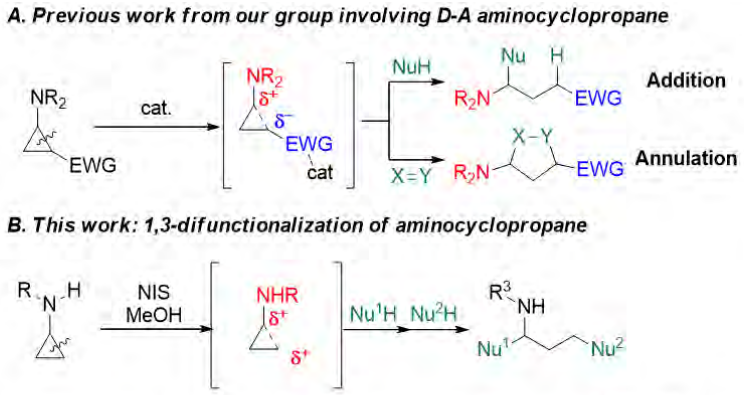

Figure 1. Our previoius work of D-A aminocyclopropanes (**A**). This work: radical-initiated ring opening strategy towards α, γ-difunctionalized amines (**B**).

We developed a mild ring-opening strategy to transform acyl, sulfonyl or carbamate protected aminocyclopropanes into 1,3-dielectrophiles bearing halide atoms (Br, I) and hemi-aminals. Substitution of the halides by a series of nucleophiles can be done under basic conditions via S_N2 pathway while replacing the alkoxy group of the hemi-aminal can be done under acidic conditions via an elimination-addition pathway, thus generating a wide range of 1,3-difunctionalized propylamines in one pot or in two steps.

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Unravelling the conductance path throughsingle-porphyrin junctions

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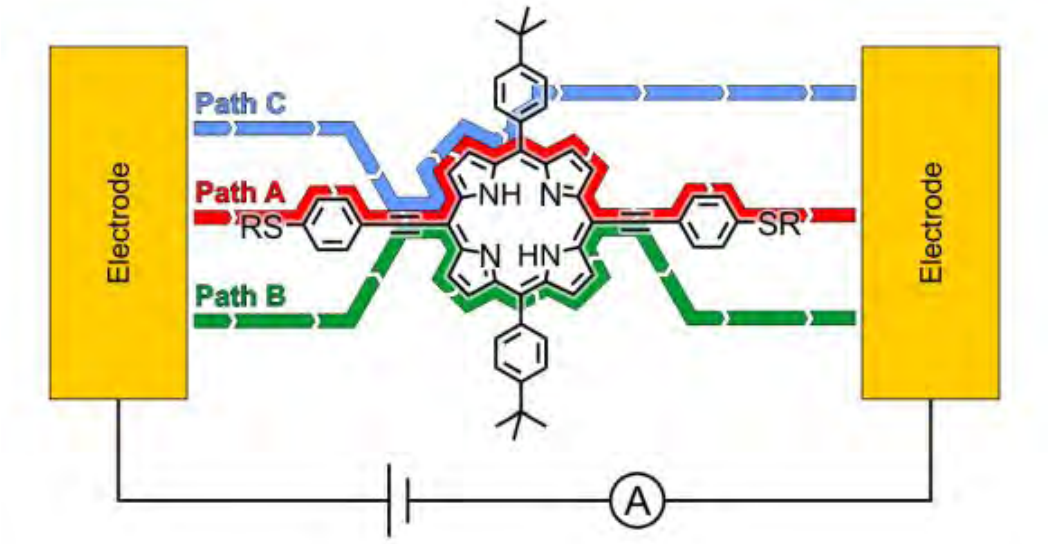
Porphyrin derivatives are key components in nature machinery enabling to store sunlight as chemical energy. In spite of their prominent role in cascades separating electrical charges and their potential as sensitizers in molecular devices, reports concerning their electronic transport characteristics are inconsistent. Here we report a systematic investigation of electronic transport paths through single porphyrin junctions. The transport through seven structurally related porphyrin derivatives was repeatedly measured in an automatized mechanically controlled break-junction set-up and the recorded data was analyzed by an unsupervised clustering algorithm. The correlation between the appearances of similar clusters in particular sub-sets of the porphyrins with a common structural motif allowed to assign the corresponding current path. The small series of model porphyrins allowed to identify and distinguish three different electronic paths covering more than four orders of magnitude in conductance.



A General Approach Towards Collagen Heterotrimers

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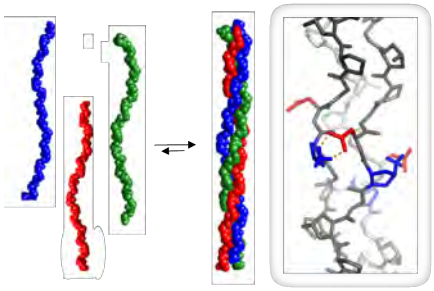
Collagen is an abundant fibrous protein in the extracellular matrix of connective tissues.[1] A characteristic feature of collagen is the triple helical structure formed by three polypeptide strands. Depending on the type of collagen, the triple helix is composed of three identical chains (A_3 homotrimers), or of two or three different chains (A_2B or ABC heterotrimers).[2] In order to enable biomedical applications of collagen-mimetic materials, it is desirable to gain synthetic access to heterotrimeric collagens. However, while nature employs enzymes to precisely control the folding and assembly of single collagen chains into heterotrimers, it is challenging to recapitulate this specificity in synthetic systems. Previously, we were able to prepare highly stable heterotrimeric triple helices from collagen model peptides using covalent oxime linkages.[3] We now sought an alternative approach that uses selective non-covalent interactions for accessing synthetic collagen assemblies.

Here we present a new salt bridge between aminoproline[4] and aspartic acid to guide the self-assembly of distinctly different peptide strands by selective non-covalent interactions into heterotrimers. Notably, the formation of only three salt bridges enabled the assembly of a specific ABC-type heterotrimer from a mixture of three different strands. NMR and CD spectroscopic studies, as well as native MS analysis[5] confirmed that the strands fold into a unique triple helix out of $3^3 = 27$ possibilities. Furthermore, we highlight the utility of our design to access triple helices of any desired composition and register by the formation of AAB and ABA-type systems. These findings represent the first general approach towards the preparation of self-assembled collagen heterotrimers and significantly advance the field of engineered collagen structures.



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Siegfried's Process R&D – From chemical feasibility to multi ton production

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Siegfried is one of the leading Contract Manufacturing Organisations worldwide. Our company has extensive experience in chemical and pharmaceutical process development and manufacturing of active pharmaceutical ingredients (APIs), intermediates and finished dosage forms on multi ton scale.

Starting from experimentations on chemical feasibility the major challenges within our process R&D projects involve optimization of manufacturing costs and reaction yields as well as investigations on critical reaction parameters, side reactions and process safety.

Siegfried labs and production plants are designed to carry out all typical organic chemical reactions and enzyme-catalysed transformations. Reaction conditions range from -100°C to 300°C and from 1 mbar to 40 bar.

Using synthesis machines, such as LabMax, RC1, parallel synthesis (ChemSpeed ASW 2000P) and Crystal 16 ensures we generate process data and information in the most effective way, speeding up development lead times and gaining greater understanding of reaction parameters.

In addition, Siegfried pays special attention to crystallization & product isolation processes, as these are vital for product yield and purity. Manufacturing processes for clearly defined crystal modifications and particle size distribution are developed – aided by various analytical techniques – and complemented by milling processes. Further techniques to manipulate physical form include spray drying, micronization and pre-formulation mixtures.

Finally, our process and chemical development capabilities are fully supported through the regular use of an array of analytical techniques & equipment, including NMR, HPLC, UPLC, GC, LCMS, GCMS, DSC/TGA, and Malvern, Microtrac and Helos PSD equipment.

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Harnessing Nature's Toolbox for Selective Halogenations: New Concepts for an Old Problem

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Although the halogenation of organic molecules is one of the most widespread techniques for the functionalization of substrates, efficient catalytic methods for the selective (regio-, chemo-, and in particular stereoselective) construction of carbon-halogen bonds are rare. In contrast, Nature has evolved different strategies to create carbon-halogen bonds in a highly effective and specific manner.

Our research therefore focuses on the exploration of the mechanism as well as the structure-function relationship of such halogenation catalyzing enzymes. Based on these findings mild, generally applicable, and selective catalytic methods for the formation of carbon-halogen bonds (brominations, chlorinations and even fluorinations) are developed combined with their application to access medically relevant target structures in efficient ways. Selected examples of our group imitating Nature's concepts of halogenation reactions will be presented, in particular those utilizing hypervalent λ^3-iodanes[1]and Lewis base-Lewis acid cooperative networks.[2]These strategies help to push the boundaries of chemical space as they grant access to a rich diversity of novel chemical structures that often cannot be approached by our current standard method repertoire.

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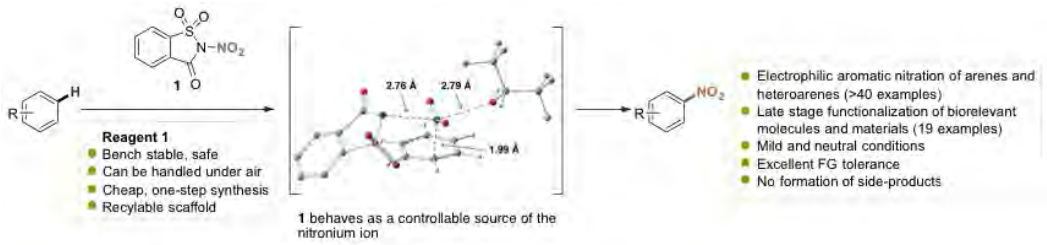
Facile Access to Nitroarenes and Nitroheteroarenes Using N-Nitrosaccharin: An Electrophilic Nitrating Reagent

R. Calvo[1], D. Katayev[1]*, K. Zhang[1], A. Passera[1]

[1]Department of Chemistry and Applied Biosciences, Swiss Federal Institute of Technology, ETH Zürich

Electrophilic aromatic nitration remains one of the most extensively studied transformations in organic synthesis, and nitroaromatics and nitroheteroaromatics have become an essential class of compounds which serve as key building blocks and intermediates in the preparation of a variety of industrial products. Nevertheless, there remains a lack of mild and practical methodologies to access these compounds. Electrophilic nitration using a mixture of HNO_3 and H_2SO_4 remains the fundamental process for the production of nitro(hetero)aromatics on both a laboratory and industrial scale, however, the reaction presents a number of critical drawbacks including poor functional group tolerance, the formation of side products and the generation of nitrogen oxides and superstoichiometric amounts of acidic waste [1].

Using *N*-nitrosaccharin **1** as an organic, bench stable nitrating reagent, we demonstrate a general protocol for the direct nitration of an extensive range of arenes and heteroarenes under mild and neutral conditions, and demonstrating an exceptionally broad functional group tolerance. Our methodology was also applicable to the late stage functionalization of biorelevant molecules, pharmaceuticals, agrochemicals and materials which would be unsuitable substrates for existing nitration methods. The reagent can be synthesized in one step and in excellent yield from saccharin, and the saccharin by-product following nitration can be recovered and recycled [2].



Comprehensive experimental work in combination with computational studies support a polar electrophilic aromatic nitration. The unique and highly ordered transition state found by DFT elucidates how our reagent behaves as a controllable source of the nitronium ion, enabling such a general and functional group tolerant reaction [2]. We anticipate that our practical and mild electrophilic aromatic nitration will find application across a broad range of disciplines at both an academic and industrial level.

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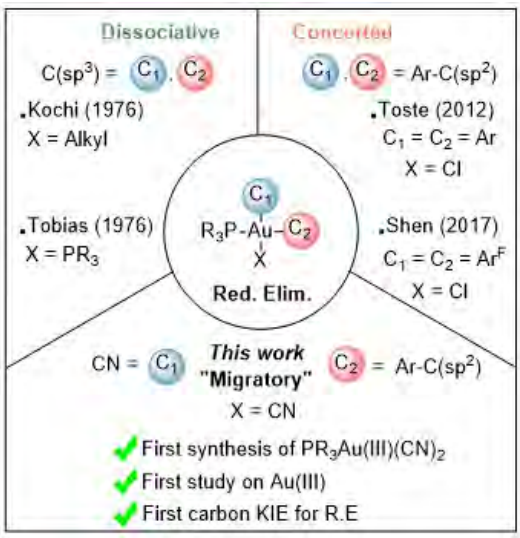
Novel “migratory” C(sp^2)-C(sp) reductive elimination on Gold(III) complexes: a mechanistic insight

A. Genoux[1], J. González[1], E. Merino[1], C. Nevado[1]*

[1]University of Zurich

In recent years, gold-catalyzed cross couplings have come to the forefront of synthetic methods for the formation of both C-C and C-X bonds.[1] Reductive elimination at a gold(III) intermediate precedes the formation of the desired bond and is one of the key steps in these reactions. An in-depth understanding of the factors that affect the rate and selectivity of the elementary organometallic processes underlying the reaction mechanism is crucial to develop more efficient catalytic systems. Herein, we present a combine detailed experimental and computational study on the C(sp^2)-C(sp) reductive elimination at monophosphine arylcyanogold(III) complexes. Our investigations unravel a “migratory” reductive elimination mechanism not observed previously in well-studied C(sp^3)-C(sp^3)[2] and C(sp^2)-C(sp^2)[3] reductive elimination processes at highly oxidized gold centers.[4]



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Studies towards the Synthesis of Shearinine Natural Products

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[1]Laboratory of Organic Chemistry, Department of Chemistry and Applied Biosciences

Shearinines are indole triterpenoids isolated from a variety of fungi.[1] They were selected as targets both because of their complex molecular scaffolds and their interesting bioactivities. Among others, Cichewicz and coworkers found shearinine D and shearinine E to be potent inhibitors of biofilm formation by *Candida albicans*. They additionally observed synergistic effects when the alkaloids were employed in combination with amphotericin B,[2] a compound which has a long history in our research group.[3] Our highly convergent synthetic strategy relies on the late-stage assembly of two complex fragments and allows for the straightforward implementation of various modifications enabling a structure–activity relationship study on the shearinine natural products.

R = H **Shearine D**
Me **Shearinine E**

Shearinines D and E present a formidable synthetic challenge due to their complex nonacyclic structures bearing eight stereocenters, wherein two are vicinal quaternary carbons. Our campaign has led to the completion of the first total synthesis of shearinine D.

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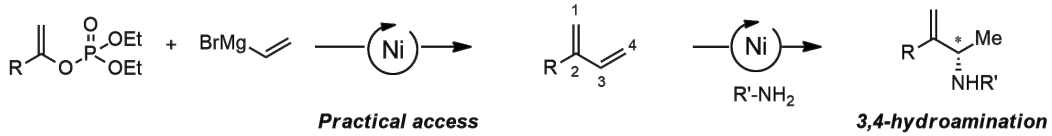
Enantioselective Nickel-Catalyzed Amination of 2-Substituted 1,3-Dienes

G. Tran[1], W. Shao[1], C. Mazet[1]*

[1]Université de Genève

Conjugated 1,3-dienes are a particularly versatile platform in the context of selective functionalization, and have been widely used as building blocks for organic synthesis. However, selective functionalization of 1,3-dienes is particularly challenging due to the numerous coordination and insertion modes conceivable for a transition metal catalyst.[1] In recent years, efforts toward the development of selective catalytic transformations have been mainly focused on *linear* 1,3-dienes,[2] while the limited synthetic availability of *branched* 1,3-dienes has severely hampered their use in the development of selective transformations.[3] Within this context, our laboratory recently reported a general Ni-catalyzed protocol which streamlines access to 2-substituted 1,3-dienes from readily available materials.[4]



Herein we describe our results in the selective nickel-catalyzed hydrofunctionalization of this underexplored class of conjugated olefins. Using a (P,P) chiral ligand, 2-substituted 1,3-dienes could be hydroaminated by primary amines. High yields, regioselectivities and enantiomeric excesses were obtained for a wide variety of substrates.[5] A mechanistic study combining kinetic analysis, stoechiometric experiments and supporting organometallic chemistry allowed us to gain in-depth understanding of the subtleties of this reaction, thus paving the way for its extension to other classes of substrates. Overall, we will disclose a catalytic strategy that solves critical challenges arising from the use of conjugated dienes, both in terms of *reactivity* (mono- *vs.* di-functionalization, parasitic reduction, competing isomerization) and *selectivity* (chemoselectivity, regioselectivity, enantioselectivity).

[1] Jessada Mahatthananchai, Aaron M. Dumas, Jeffrey W. Bode *Angew. Chem., Int. Ed.* **2012**, *51*, 10954.
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[5] Gaël Tran, Wen Shao, Clément Mazet, *Manuscript in preparation*

Pd^0-Catalysed $C(sp^3)$-H Activation: From Direct to Remote Functionalization for the Construction of Medium-Sized Rings

R. P. Rocaboy[1], O. Baudoin[2]*

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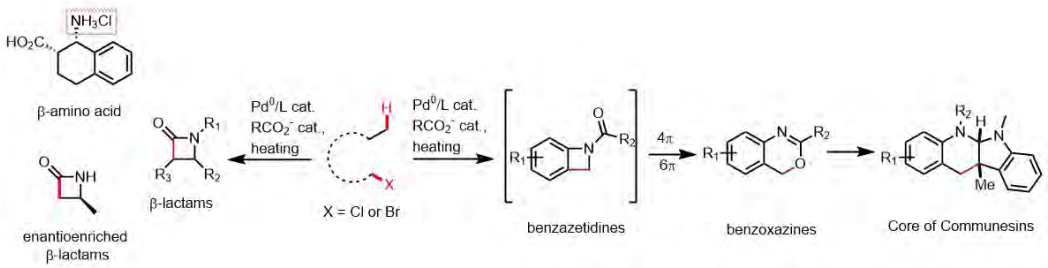
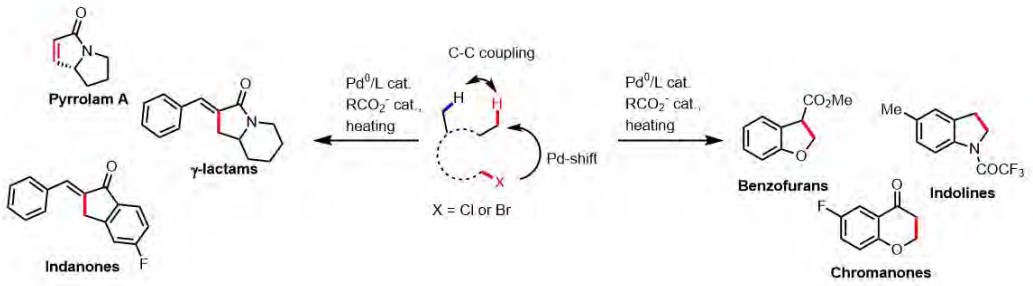
In the context of the recent developments of palladium-catalysed C-H activation, the direct functionalization of $C(sp^3)$-H bonds has proved to be a method of choice to access valuable building blocks. [1] [2] Taking advantage of this methodology, we recently proposed new direct functionalizations of $C(sp^3)$-H bonds to access beta-lactams [3] and benzoxazines. [4]



In addition to direct functionalization, the ability of palladium to undergo a 1,4-through-space shift allows the functionalization of distal positions. [5] This interesting feature was combined with $C(sp^3)$-H activation reaction on different systems, to access a wide range of gamma-lactams, indanones, benzofurans, chromanones and indolines. [6][7]



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Asymmetric Synthesis of Esketamine

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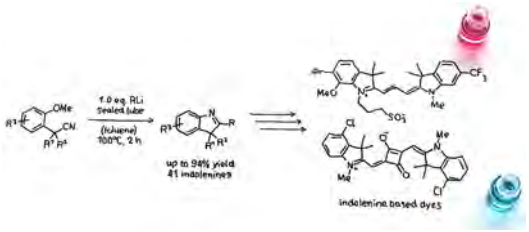
The U.S. FDA has recently approved Spravato™ (esketamine) nasal spray as a rapidly acting antidepressant for adults with treatment-resistant depression (TRD), which represents one of the most significant milestones for depression treatment in decades. The drug substance has been produced for decades via a racemic synthesis of ketamine and its resolution. We herein wish to disclose an asymmetric synthesis of esketamine based on catalytic enantioselective transfer hydrogenation of enone and [3,3]-sigmatropic rearrangement of allylic cyanate. The catalytic asymmetric route to esketamine (99.9% ee, 50% overall yield) forms the base for the future development of the drug.

Preparation of Indolenines via Nucleophilic Aromatic Substitution

J. Roesslein[1], F. Huber[1], K. Gademann[1]*

[1]University of Zurich

The indole and indolenine core structure is a popular motive among many natural products.[1] Besides its use in natural product synthesis, indolenines are also used as precursors in the synthesis of indolenine based dyes that are employed in many differed fields such as *in vivo* and *ex vivo* imaging.[2] For the synthesis of indolenines the interrupted Fischer indolization is mostly used, which application is mainly limited to substitutions at the 5-position.[3] In this context, we have developed a new method for the preparation of indolenines via a nucleophilic aromatic substitution using easy accessible benzyl nitriles as starting materials.[4] This cyclization method is high yielding (up to 94%) and tolerates a wide range of different functional groups, which is exemplified by the substrate scope of 41 indolenines. Substitutions at all possible positions of the aromatic ring as well as electron rich and poor benzyl nitriles are well tolerated. Furthermore, we investigated the mechanism of the nucleophilic aromatic substitution reaction. Finally, we applied this new method for the synthesis new indolenine-based dyes, which are difficult to access with currently literature known procedures.



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Chiral Cyclopentadienyl Ligands: Structural Insights and Application in Enantioselective Cyclopropanation

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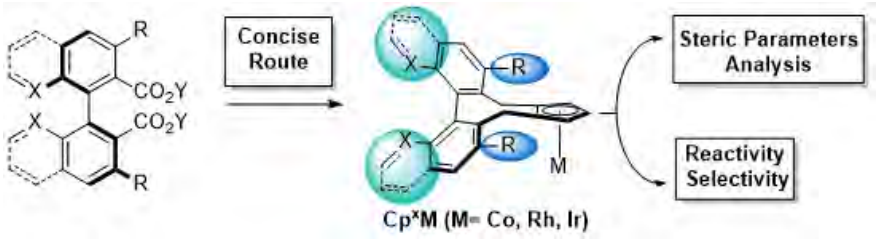
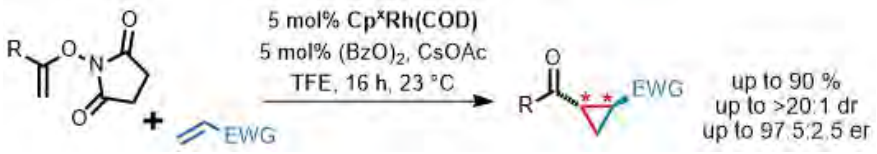
The design of complex molecular architectures has evolved considerably thanks to transition metal catalyzed functionalization of C-H bonds. The half-sandwich cyclopentadienyl (Cp) metal complexes of the group 9 are precious catalysts for the development of challenging transformations. Our group pioneered the development of highly efficient chiral Cp ligands for catalysis.[1] Their potential was demonstrated in combination with various metals for a variety of enantioselective reactions.[2] Herein, we present a detailed analysis of under-explored biaryl Cp^x ligands, obtained from concise syntheses. Upon complexation to group 9 metals, the catalysts were characterized by X-Ray analysis and their performances were explored towards benchmark C-H activation transformations.[3]



In a second part, we report the application of Cp^xRh complexes to enantioselective and diastereoselective cyclopropanation *via* activation of vinyl C-H bonds. Combined with the one-step Au(I)-catalyzed formation of the *N*-enoxyimides substrates from alkynes, the synthetic utility of this method is demonstrated by concise syntheses of KMO inhibitor UPF-648 and members of the oxylipin family of natural products.[4]



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Stereodivergent Catalyst Control of Two Stereogenic Axes

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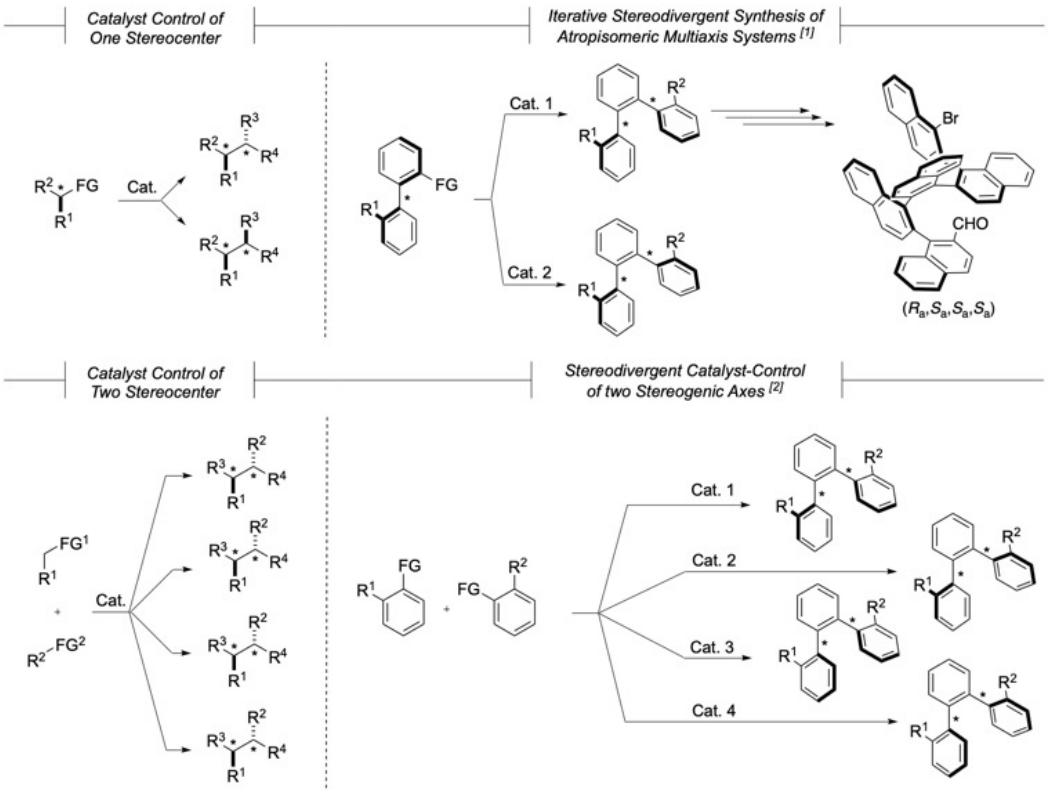
The implications of stereoisomerism on biological activity is well known and versatile methods for their selective synthesis is hence required. Most molecules important to life have multiple stereogenic moieties and catalyst-control over diastereomers is therefore particular relevant. The simultaneous creation of more than one stereocenter in a single synthetic step is thus highly desirable and provides the basis for straightforward and short routes to complexes molecular scaffolds. Our group recently developed an iterative method for the catalyst-controlled stereodivergent synthesis of atropisomeric multiaxis systems.[1]We now present a stereodivergent diastereo- and enantioselective method with simultaneous catalyst-control over two stereogenic axes. Along with controllable *syn*- or *anti*-configuration, the products show useful levels of enantiopurity. The structurally well-defined scaffolds bear two stereogenic axes and are envisioned to provide ligands, catalysts and molecular building blocks.[2]



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Reactivity and synthetic utility of a-boryl carbon centered radicals: two opposing reaction manifolds

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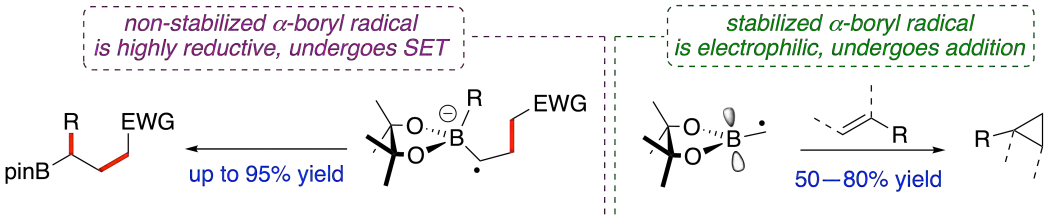
[1]Universität Bern, [2]University of Lancaster, [3]University of Strathclyde

The vacant boron p-orbital in organoboranes has a stabilizing influence on a radical formally located on an adjacent carbon atom.[1,2] The stabilized radical precursor ICH_2Bpin performs atom transfer radical addition (ATRA) to alkenes to furnish g-iodoboronic esters. In an alternative manifold, occupying the vacant p-orbital on vinylboronic esters with a ligand eradicates any stabilization, and generates an excellent trap for electrophilic radicals.[3-5] This time the mechanism operates through a single electron transfer (SET).



Our investigations concluded with two operationally simple, one-pot protocols; an ATRA/ 1,3-cyclization to yield cyclopropanes or a three-component coupling reaction of an organolithium, electrophilic halide, and vinylboronic ester. The scope, mechanism, and chemoselectivity of these two a-boryl radical chain processes will be discussed.

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A Tethered Approach to the Palladium Catalyzed Dual Functionalization of Alkynes.

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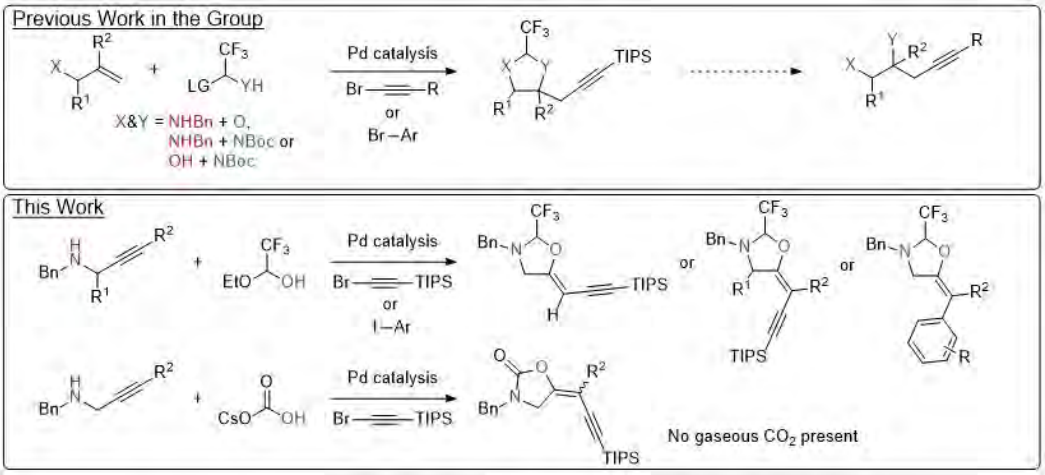
[1]Laboratory of Catalysis and Organic Synthesis, EPFL Lausanne

The palladium catalyzed di-functionalization of alkenes containing hydroxy and amino groups has been established as an effective synthetic approach to access a diverse range of heterocycles and other highly functionalized compounds [1,2]. Recently, our group has demonstrated the expedient use of trifluoroacetaldehyde-tethered hydroxy and amino nucleophiles in the Pd0 catalyzed difunctionalization of alkenes using either an alkynyl bromide or aryl iodide as electrophile. This approach, when applied to allylic amines and alcohols, gave acess to a range of vicinal amino alcohols [3,4] or diamines [5]. The resultant aminals and acetals could be hydrolysed to give rise to the free aminoalcohols. Herein, the extension of this strategy to propargylic amines to synthesise highly substituted enynes and complex α-amino ketone derivatives is presented. The generated oxazolines could be further transformed into a range of different compounds[6]. During the development of this method, a carboxylation alkynylation reaction using carbonate salt as carbon source was discovered serendipitously and gave access to oxazolidinones[7].



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