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Reagent, Ligand and Catalyst Design: A Three-fold Approach to Organic Synthesis

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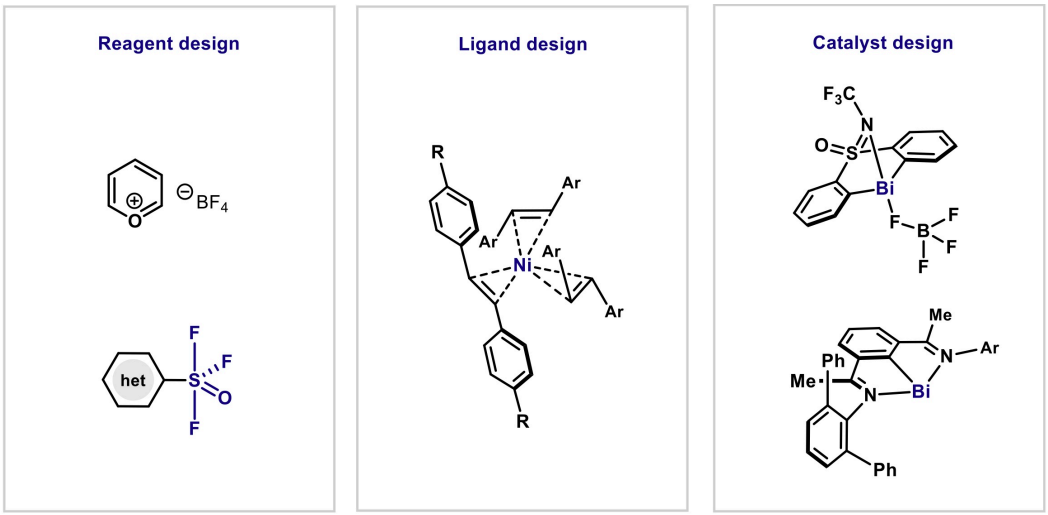
The main goal of our research group is to provide efficient, robust and sustainable methodologies for organic synthesis. To this end, our group has established a three-fold approach based on 1) the development of new organic reagents that enable practical and facile organic chemistry by streamlining synthetic routes; 2) the design of ligands that turn air-sensitive transition metals to robust complexes with remarkable stability toward oxidation and temperature; 3) the design of p-block elements, in particular bismuth (Bi), with the aim of designing novel catalytic redox processes akin to transition metals. We believe that this 3-fold approach is key to unlock new reactivity while allowing the discovery of fundamentally novel and unknown areas in chemistry. This talk will highlight the contributions of our group in these endeavors and will provide an overview of the recent developments.



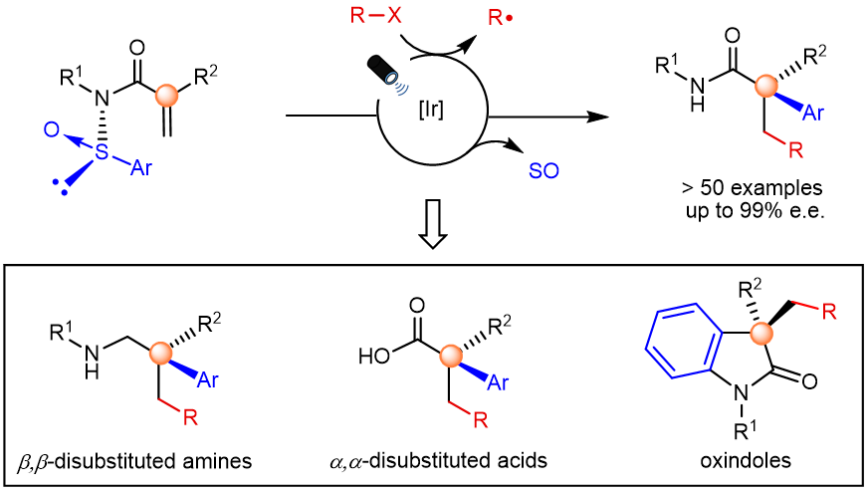
Asymmetric, visible light-mediated radical sulfinyl-Smiles rearrangement to access all-carbon quaternary stereocentres

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

[1]Department of Chemie University of Zurich

The development of novel strategies to disrupt symmetry at a molecular level is a longstanding pursuit within the organic chemistry community. Despite their importance in many biological active molecules, the asymmetric construction of all-carbon quaternary centers represents a major challenge for synthetic chemists. Acyclic systems are especially challenging due to the greater degrees of freedom, and steric congestion at the stereogenic center. Strategies involving both single and 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.[5] The reaction proceeds via a radical cascade Smiles rearrangement triggered by photoredox catalysis where a sulfoxide group serves as a chiral auxiliary before being expelled as SO. The *a*-all-carbon substituted amides obtained in this process are prevalent in pharmaceuticals, agrochemicals and bioactive natural products. Further, they can be transformed, in a single additional step, into highly valuable chiral building blocks difficult to obtain by other methods.



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Ethynylbenziodoxolones: Photocatalysis and Direct Excitation for Difunctionalisation and Deoxyalkynylation

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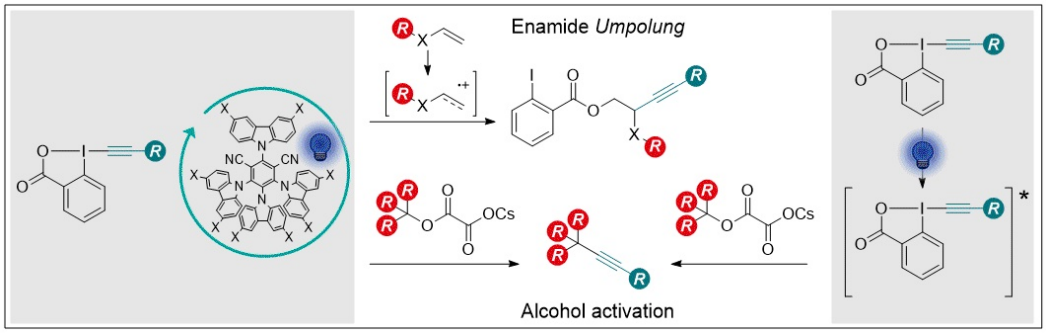
[1]Laboratory of Catalysis and Organic Synthesis

Alkynes are an important functional group for synthetic chemists but also present applications in biochemistry, medicinal chemistry and materials science. Broadening the scope of alkyne synthesis is of great importance. Ethynylbenziodoxolones (EBXs) when combined with photocatalysis have proven themselves to be efficient radical traps.[1] Our first strategy combines the use of photocatalysis to generate selectively enamide and enol-ether radical cationic intermediates that can then be trapped by the EBXs exploiting both the nucleophilic carboxylate and the somophilic alkyne moiety of these reagents.[2] This strategy overcomes the issues associated to the generation of highly reactive electrophilic radicals that has been used to date for radical enamide difunctionalisation. In our second strategy, we aimed to develop a redox neutral approach for deoxyalkynylation of tertiary alcohols using cesium salts. Interestingly, we discovered that not only could this reaction be developed using photocatalysis, it also proceeded through the direct excitation of the EBXs alleviating the need for a photocatalyst altogether.[3] This strategy allows the simple access to all-carbon quaternary alkynes under mild conditions.



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[3] Manuscript submitted.

Möbius Carbon Nanohoops

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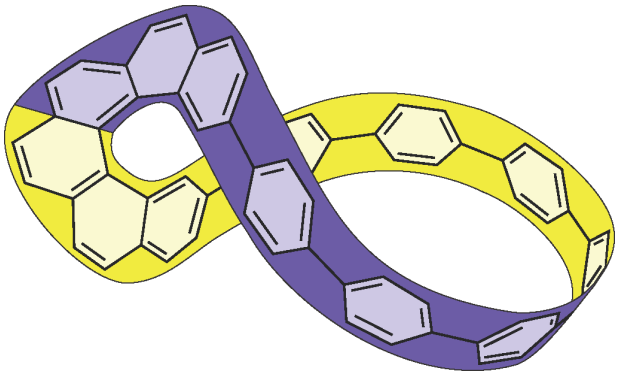
Prediction [1] and synthesis [2] of annulenes twisted into a Möbius strip introduced a new perspective on aromaticity, one of the most important topics in organic chemistry. The conceptually simplest approach to access a molecular Möbius strip is a combination of building blocks with linear and radial π-conjugation.[3] While the former are ubiquitous in π-conjugated systems, the latter require pyramidalization of sp^2-hybridized carbons, consequently introducing strain, which hampers the synthesis of these molecules.

One of the recent examples of radially conjugated π-systems are cycloparaphenylenes which possess a considerable strain energy. Preparation of such strained systems is challenging and usually utilizes aromatization as the driving force to overcome the energy penalty. Moreover, cycloparaphenylenes display size-dependent optoelectronic properties that are the direct consequence of radial π-electron conjugation. [4]

In this work, we incorporated [6]helicene into [7]cycloparaphenylene system creating a chiral helicene carbon nanohoop (Figure 1). [5] The helicene provides the necessary twist that transforms the radial π-conjugation of cycloparaphenylenes into the Möbius topology. We separated the enantiomers of the synthesized helicene carbon nanohoop using HPLC with a chiral stationary phase and demonstrated that its optoeletronic and chiroptical properties arise from the cycloparaphenylene and the helicene moieties, respectively. We investigated the dynamics of the synthesized nanohoop in solution by variable temperature ^{1}H NMR and DFT calculations . Furthermore, we studied the effect of the Möbius topology of the helicene carbon nanohoop and its derivatives on their global aromaticity.



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Tailoring a Sodium Amide (NaTMP) for Transition-Metal Free C-H Borylation of Arenes

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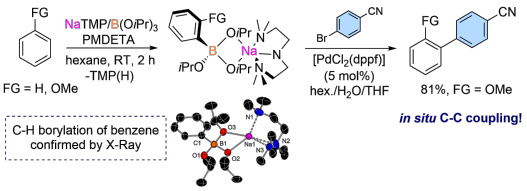
[1]University of Bern

Organoboron derivatives are key synthetic building blocks within everyday organic chemistry at both academic and industrial levels. One of their main applications is in Suzuki-Miyaura (SM) cross-couplings – a transformation which is estimated to represent over 65% of all C-C bond forming reactions performed.[1] Organoboron compounds are frequently prepared by C-H borylation, wherein a relatively inert C-H bond is transformed into a more versatile C-BR_2 bond.[2] The majority of current methods require the use of transition-metal catalysts. Although metal-free examples do exist, substrate scope is often limited to electron-deficient heteroarenes.[3]

Combining the efforts of NaTMP (TMP = 2,2',6,6'-tetramethylpiperidide) and commercially available B(O*i*Pr)$_3$, herein we introduce a new method for utilising a sodium amide as a metallating reagent in C-H borylation reactions. The reactivity of NaTMP is enhanced by the presence of tridentate Lewis donor PMDETA which induces its deaggregation, with B(O*i*Pr)$_3$ rapidly trapping and stabilising the metalated arene as shown in the scheme for benzene functionalisation. Isolation of key reaction intermediates provides important clues of the key roles of both Na and B in this borylation process. Showcasing the synthetic utility of this methodology, the newly formed sodium borate intermediates can then be used directly in SM cross-coupling reactions under moisture-tolerant conditions and in high yields.



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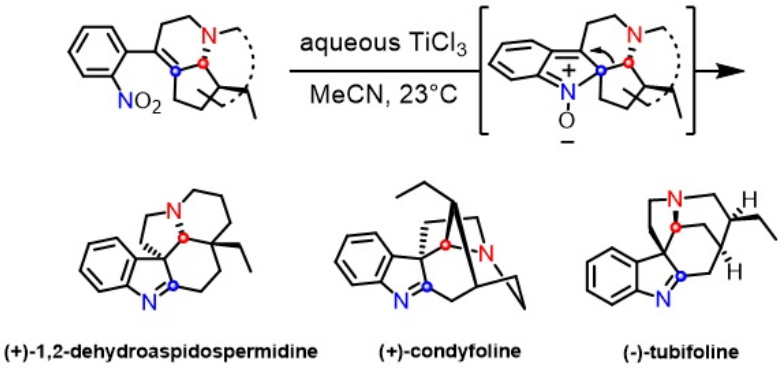
TiCl3-Mediated Synthesis of 2,3,3-Trisubstituted Indolenines: Total Synthesis of (+)-1,2-Dehydroaspidospermidine, (+)-Condyfoline, and (−)-Tubifoline

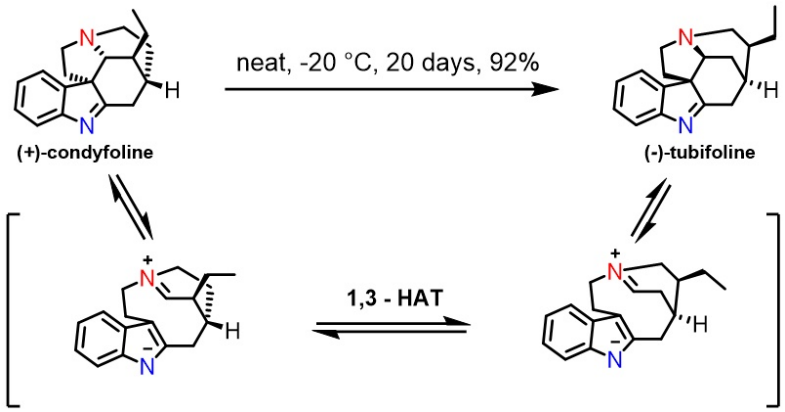
B. Delayre[1], C. Piemontesi[1], Q. Wang[1], J. Zhu[1]*

[1]EPFL-SB-ISIC-LSPN

2,3,3-Trisubstituted indolenine constitutes an integral part of many biologically important monoterpene indole alkaloids. We report an unprecedented access to this skeleton by a TiCl3-mediated reductive cyclization of tetrasubstituted alkenes bearing a 2-nitrophenyl substituent.[1] The proof of concept is demonstrated firstly by accomplishing a concise total synthesis of (+)-1,2-dehydroaspidospermidine featuring a late-stage application of this key transformation. A sequence of reduction of nitroarene to nitrosoarene followed by 6π-electron-5-atom electrocyclization and a 1,2-alkyl shift of the resulting nitrone intermediate was proposed to account for the reaction outcome.



A subsequent total synthesis of (+)-condyfoline not only illustrates the generality of the reaction, but also provides a mechanistic insight into the nature of the 1,2-alkyl shift. The exclusive formation of (+)-condyfoline indicates that the 1,2-alkyl migration follows a concerted Wagner–Meerwein pathway, rather than a stepwise retro-Mannich/Mannich reaction sequence.[2] The preservation of the stereochemical integrity of the migrating centres during the rearrangement process is significant, widening the scope of potential targets accessible using this strategy. Conditions for almost quantitative conversion of (+)-condyfoline to (−)-tubifoline by way of a retro-Mannich/1,3-prototropy/transannular cyclization cascade are reported.[3] The facile isomerisation of (+)-condyfoline to (-)-tubifoline at low temperature further supports our mechanistic hypothesis.



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Homogeneous catalysis using stable cyclometalated complexes

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Cyclometalated complexes of transition metals have received considerable attention since 1960s, in particular as the reactive intermediates of catalytic C-H functionalizations. However, only recently the unique catalytic properties of few bench stable complexes bearing anionic “carboligands” have been discovered.

This presentation will discuss the rational design of anionic C,N-ligands allowing for novel catalytic transformations. Our recent applications of iridium – ketimine catalysts towards acid-assisted ionic hydrogenation of oximes to hydroxylamines, anhydride-assisted amide hydrogenation and regioselective C-H-borylation will be highlighted.

Beyond transfer hydrogenation: Transfer hydroarylation by catalytic activation of strong C–C bonds

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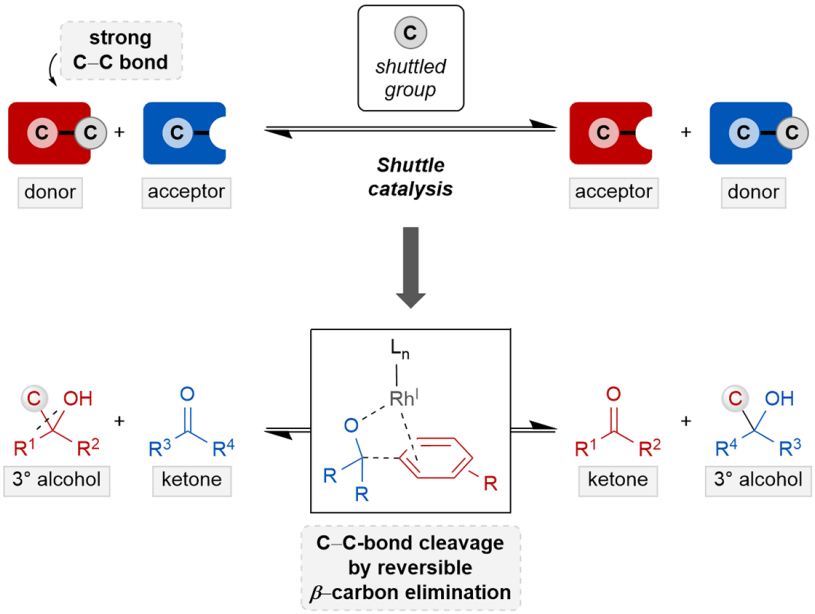
[1]Laboratory of Organic Chemistry, Department of Chemistry and Applied Biosciences, ETH Zürich, Vladimir-Prelog-Weg 3, 8093 Zürich, Switzerland

Carbon–carbon bonds are among the most abundant yet least reactive chemical bonds in organic molecules. The selective and mild activation of these bonds is an unmet challenge that offers great potential to break down and reorganize small molecules and polymers without the need for the tedious and challenging installation of functional groups. While progress has been made in the activation of strained cyclic and unstrained molecules with directing groups, methods that tolerate unbiased molecules are highly desirable. Here, we describe a catalytic transfer hydroarylation to interconvert alcohols and ketones by merging C–C bond activation with shuttle catalysis.



Using this method, alcohols serve as benign alternative to stoichiometric and highly reactive organometallic reagents to transfer aryl moieties to ketones. The method exhibits high chemoselectivity and tolerates functional groups that are vulnerable to traditional nucleophilic reagents (Grignard and organolithium compounds). Preliminary mechanistic experiments support a reversible β-carbon elimination/insertion mechanism. The work described herein represents a step toward valorizing renewable alcohols and paves the way to develop a platform for the creative manipulation of tertiary alcohols in catalysis.

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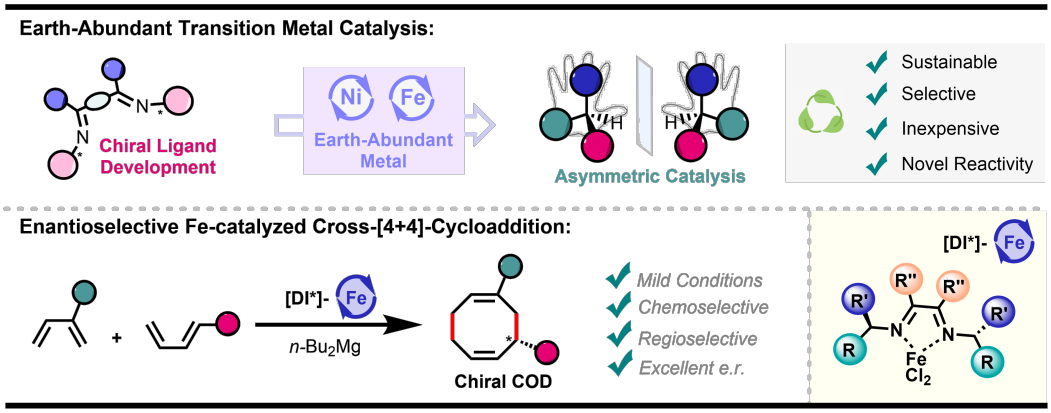
Towards Sustainable Catalysis: Development of Chiral α-Diimine Iron Complexes for Asymmetric Cycloadditions of 1,3-Dienes

E. Braconi[1], N. Cramer[1]*

[1]EPFL SB ISIC LCSA (Laboratory of Asymmetric Catalysis and Synthesis)

The advent of **catalysis** has had a life-changing impact on modern society. A**symmetric transformations** are nowadays in high demand due to the **reduced environmental footprint** of single enantiomer production. Despite the majority of synthetic catalysts contain noble metals (e.g. palladium and platinum), biological transformations are mostly catalyzed by **Earth-abundant metals (EAM)**, such as iron and nickel. Their **higher terrestrial abundance** and **lower price** is the reason for a gradual switch towards a more **sustainable metal catalysis**.[1] Moreover, the different electronic properties displayed by noble and 3d-metals open the possibility for **exploring unusual reactivity** and discovering novel transformations.



Chiral cyclooctadienes (CODs) are a frequently occurring scaffold in **natural products** and specialty chemicals, and are used as steering **ligands for asymmetric catalysis**. They are among the most difficult rings to synthesize, mainly because of unfavorable entropic and transannular penalties, and accessing them in an efficient asymmetric fashion has been a longstanding unsolved issue.

We present the first **highly enantioselective iron-catalyzed cross-[4+4]-cycloaddition** of 1,3-dienes to form substituted cyclooctadienes in a single step from feedstock materials and under very mild conditions.[2] A **highly tailored chiral α-diimine iron complex**, easily accessible and tunable, is key for the success of this transformation, providing a balanced performance between reactivity, excellent cross-selectivity and very high enantioselectivity. Analysis of the steric maps of the microenvironment around the iron center helps account for the observed selectivity.

Furthermore, the application of the developed catalyst class in other cycloaddition reactions will be disclosed for the first time.[3]

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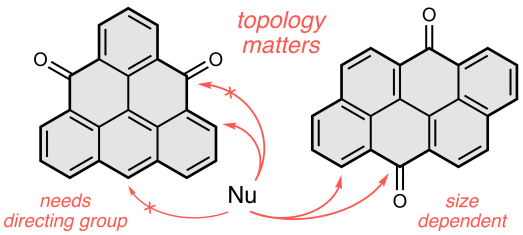
[3] *Work in Progress.*

Functionalization of zigzag graphene fragments: Tales of the unexpected

L. Valenta[1], P. Ribar[2], T. Rosa de Araujo[1], O. Blacque[1], T. Šolomek[3], M. Juríček[1]*

[1]University of Zurich, Department of Chemistry, [2]University of Basel, Department of Chemistry, [3] Department of Chemistry, University of Basel

The synthesis of new zigzag nanographenes is key to understand the properties of semiconducting and magnetic materials based on graphene for applications in molecular electronics. The practical issues associated with nanographene compounds are low stability and low solubility, which make routine processability and characterization highly challenging. These obstacles can be overcome by the installment of substituents around the periphery. Nucleophilic addition of carbon-centered nucleophiles to nanographene ketones represents a convenient late-stage method for the peripheral functionalization that can solve the aforementioned problems. The use of this method, however, is rare in the chemical literature, which is surprising considering the vast number of nanographene ketones that have been reported up to now. We reasoned that the scarcity of this method is due to the lack of understanding of the rules that govern it. We therefore explored the nucleophilic addition in more detail, using two topologically different zigzag model systems, non-Kekulé triangulenedione (left) and Kekulé anthanthrone (right). Over the course of this exciting study, we identified unexpected regioselectivities, which we could all rationalize as an interplay of the electronic effects, expressed by the Fukui functions, and sterics related to the size of nanographene and nucleophile.[1] We compiled these findings into a set of rules, which can be used to not only explain the few known examples with unexpected selectivity, but also to predict the selectivity for unknown compounds. As a result, this method can now be used to prepare new nanographene derivatives, which would otherwise only be accessible via long multistep synthesis. This presentation will also include our latest unpublished results, where we utilized these rules to construct stable derivatives of highly reactive longer acenes.



Peter Ribar, Leoš Valenta, Tomáš Šolomek, Michal Juríček, *Angew. Chem. Int. Ed.,* **2021**, DOI: 10.1002/ange.202016437

Catalyst Repurposing Sequential Catalysis

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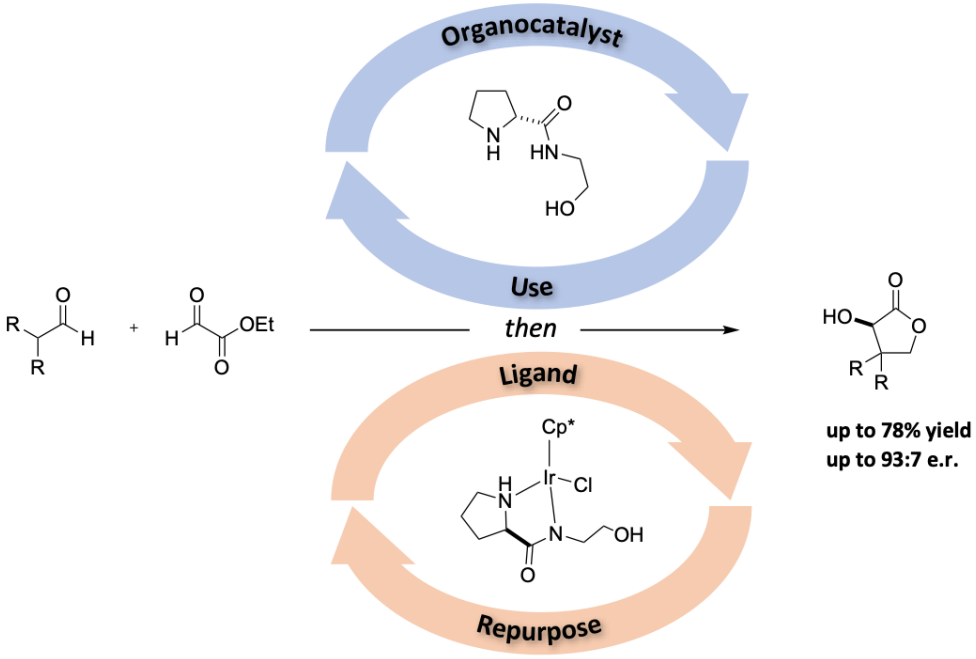
The development of operationally simple multicatalytic systems by combining the advantages of both metal- and organocatalysis enables distinct transformations or reaction cascades otherwise inaccessible by single catalyst systems. This allows for unique possibilities for the formation of valuable organic frameworks. We herein describe an efficient and general catalyst repurposing strategy for the asymmetric synthesis of α-hydroxy-γ-butyrolactones. Starting from inexpensive and readily available starting materials our method is based on a sequential aldol addition/transfer hydrogenation/lactonization sequence by exploiting the inherent functionalities of prolineamides to serve as both an organocatalyst in an initial stereoselective aldol addition and as a ligand to promote a highly efficient transfer hydrogenation. This approach therefore represents an operationally simple, economic and efficient method for the preparation of the desired scaffolds. Furthermore, the developed catalyst repurposing sequential catalysis (CRSC) strategy was successfully applied for the selective preparation of key industrial intermediate (*R*)-pantolactone (vitamin B_5 precursor), offering an attractive alternative to the currently established resolution strategy.[1]



- **Catalyst repurposing in sequential catalysis**
- **Stereoselective aldol addition/transfer hydrogenation/lactonization sequence**
- **Efficient and scalable synthesis of enantioenriched α-hydroxy-γ-butyrolactones**

[1] F. Bourgeois, J. A. Medlock, W. Bonrath, C. Sparr, *Org. Lett.* **2020**, *22*, 110 – 115.

Palladium Catalysed Mild C−H Arylation of Arenes

J. Dhankhar[1], E. G. Fernández[1], C. Dong[1], T. K. Mukhopadhyay[1], A. Linden[1], I. Čorić[1]*

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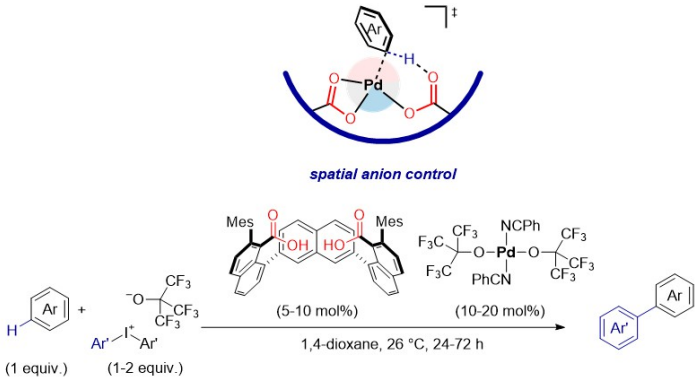
Transition metal catalysed C–H activation is a transformative methodology for synthesis of complex molecules, allowing new retrosynthetic pathways and late-stage diversification. Non-directed, arene-limited palladium-catalysed C–H functionalisation reactions, such as olefinations, can be accelerated with various neutral and anionic ligands which proceed through CMD mechanism.[1,2] However, the direct arylation of C–H bonds without the use of directing groups remains challenging and requires excess of the arene, high temperatures, transition-metal additives, or is limited to certain classes of substrates.[3,4]

We describe the design of rigid bis(carboxylate) anions which provide spatial anion control on Pd(II), enabling non-directed C–H arylation of arenes at ambient temperature. The catalytic system utilizes palladium(II) precatalysts and iodine(III) arylation reagents with nonafluoro-*tert*-butoxide anions, which were rationally designed to avoid the use of silver(I) compounds and any other potentially interfering additives or anions.[5] The mild conditions enable late-stage structural diversification of biologically relevant small molecules. The calculations show that appropriately spatially positioned carboxylates are powerful cooperative ligands for C–H activation on Pd(II), and could facilitate functionalisation through Pd(IV) intermediates. The concept of spatial anion control offers a general strategy for design of catalytic sites for C–H activation and might find broad use in transition-metal catalysis.



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Selective C-H azidation of amino acids and peptides

E. M. Allouche[1], R. Simonet-Davin[1], J. Waser[1]*

[1]Laboratory of Catalysis and Organic Synthesis (LCSO), Institute of Chemical Sciences and Engineering (ISIC), Ecole Polytechnique Fédérale de Lausanne (EPFL), Avenue Forel 2, Lausanne, Switzerland.

Azides figure among the most versatile and useful functional groups in synthetic chemistry. They can undergo multiple transformations leading to nitrogen-containing compounds with important applications in several research domains such as organic synthesis, drug discovery, chemical biology and materials science. The azidation of amino acid-containing biomolecules is of particular interest as more and more established pharmaceutical companies are including peptide-based molecules in their drug-development program.
In this poster presentation, we will present our recent work on the discovery and development of a selective C-H azidation of amino acids and peptides.

Desymmetrization of Difluoromethylene Groups by C–F Bond Activation

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[1]ETH Zurich, [2]University of California, Berkeley, CA, USA

Enantioenriched tertiary alkyl fluorides are valuable targets in medicinal chemistry as they mimic common tertiary stereocenters but exhibit distinct properties. Despite their importance, strategies to access these compounds are limited. In my master thesis, significant contributions to the development of the unprecedented desymmetrization of a difluoromethylene group by C–F bond activation are described. By combining a chiral iridium phosphoramidite catalyst with a fluorophilic activator that accelerates C–F oxidative addition, the desymmetrization of allylic difluoromethylene groups occurs in high yield and selectivity. [1]

1. Optimization of the desymmetrization with silyl ketene acetals as nucleophiles [1]

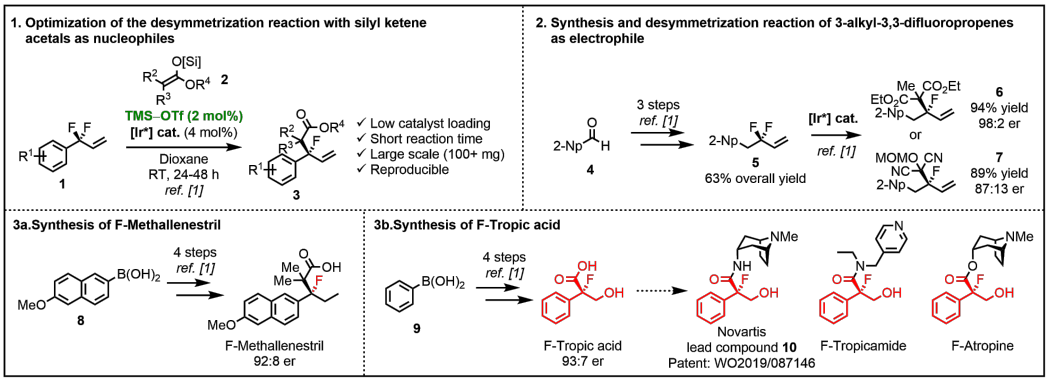
The Ir-catalyzed allylic substitution of 3-substituted-3,3-difluoropropenes with silyl ketene acetals required long reaction times (72-96 h), high catalyst loadings (8 mol%) and exhibited a non-reproducible induction period which hindered efforts to scale the reaction above 0.02 mmol (4 mg). By adding 2 mol% of TMS–OTf both the reaction time and the catalyst loading were successfully reduced, the former to 24-48 hours, the latter to 4 mol%. In the synthesis of F-Methallenestril the addition of 2 mol% TMS–OTf allowed the Ir-catalyzed allylic substitution on 100 mg scale.

2. Synthesis and desymmetrization of 3-alkyl-3,3-difluoropropenes as electrophile [1]

While the nucleophile scope has been conducted with several aryl electrophiles, alkyl substrates were not investigated. It was unclear how to prepare 3-alkyl-3,3-difluoropropenes and whether they would participate in the present reaction due to their reduced reactivity. In this work a novel synthesis for 3-alkyl-3,3-difluoropropenes has been developed. A Barbier reaction of aldehyde **4** and 3-bromo 3,3-difluoropropene followed by a Barton deoxygenation gave **5** in 63% overall yield. The optimization studies involving e.g. other fluorophilic activators like $Ba(OTf)_2$ ultimatly allowed the desymmetrization with malonate derivatives as nucleophiles.

3. Synthesis of fluorinated bioactive molecules [1]

To demonstrate the synthetic applicability and value of this method, fluorinated analogues of bioactive molecules were prepared. In fact, the fluorinated analogue of Methallenestril (a nonsteroidal estrogen) and Tropic acid, (a building block present in several drugs e.g. Atropine), have successfully been synthesized in 4 steps from commercial starting materials. The desymmetrization step gave excellent yields and high enantiomeric ratios. In a Novartis' patent from 2019, biologically active compounds derived from racemic F-Tropic acid (such as **10**) are investigated, highlighting the potential industrial benefit of the developed enantioselective method.



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Imaging Membrane Tension During Endocytosis

L. Assies[1], F. Piazzolla[1], V. Mercier[2], J. López-Andarias[1], A. Roux[2], N. Sakai[1], S. Matile[1]*

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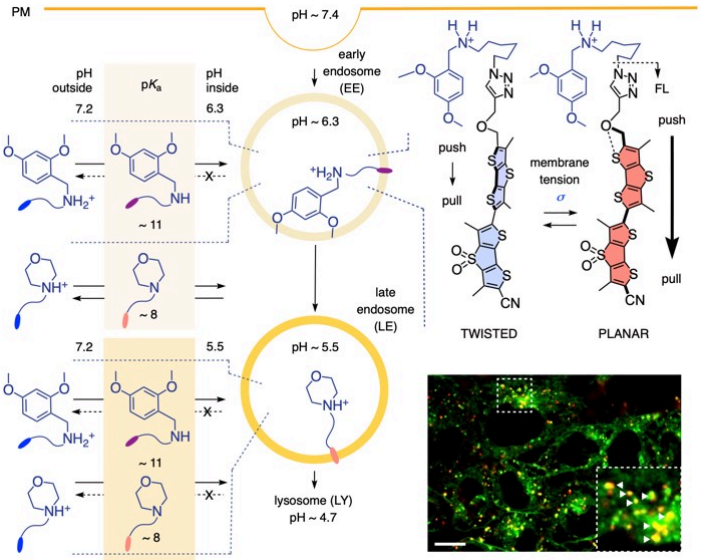
Fluorescent flipper probes have been introduced by our group to image membrane tension in living cells, [1,2] and strategies to target these probes to specific membranes to study biological processes are emerging. [3,4] The changes in membrane tension during the process of endocytosis are particularly interesting and targeting the endolysosomal network without the use of protein engineering is especially appealing.[5] We have developed a class of early endosome (EE) targeting flipper probes, using substituted benzylamines as head groups. The varying pK_a values of these head groups lead to different localization of the probes in the endolysosomal network. All flipper probes target late endosomes (LE) and lysosomes equally but colocalization experiments showed that probes with higher pK_a values lead to better staining of the EE, as they are also protonated at the higher pH in the EE. The resulting EE flipper probes are mechanosensitive and can be used for studies of endocytic processes. Different headgroups with even higher pK_a values are currently under investigation.



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Exploring Bimetallic Cooperation for the Rational Design of Nucleophilic Silyl Reagents

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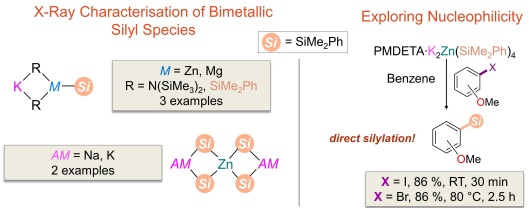
The high natural abundance of silicon and its non-toxic nature are just some of this element's advantages, strengthened by the popular use of organosilicon compounds within cross-coupling reactions.[1] Therefore, there stands a natural drive to easily access such useful organosilicon building blocks. Extensive studies by Oestreich have employed $Zn(SiR_3)_2$ reagents in combination with catalytic amounts of Cu salts to promote facile silyl-zincation reactions of synthetically-attractive scaffolds.[2] Complementary work by Uchiyama has showcased the benefits that heterobimetallic reagents can offer (e.g. $[LiZn(SiR_3)R_3 \bullet MgCl]$, R = alkyl, alkoxide), whereby nucleophilic installation of silyl groups to organic molecules is possible without precious metal additives.[3] Despite these advances, a gap in the knowledge still exists with regards to (i) fundamental characterisation and understanding of these bimetallic reagents employed and (ii) the *modus operandi* which they follow.

In an effort to bridge this gap, this work exploits the high reactivity of alkali-metals (e.g. K) combined with the better selectivity of lower-polarity metals (Mg and Zn) as a platform for accessing and finely tuning the synthesis and reactivity of novel, nucleophilic silyl complexes. The results presented include X-ray crystallographic characterisation of these bimetallic silyl reagents, and our preliminary understandings surrounding their nucleophilic capabilities in the direct silylation of haloarenes.



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Sigma- or pi-dimer?

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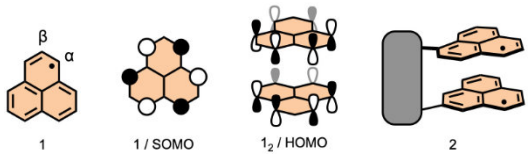
Phenalenyl[1] (**1**) is a prototype of spin-delocalized open-shell π-systems, with one unpaired electron delocalized equally between six α-positions. A feature of fundamental interest is the ability of **1** and related systems to form multicenter bonds[2], known as pancake bonds, between cofacially π-stacked spin units ($\mathbf{1}_2$). This bonding motif gives rise to bulk properties such as magnetism and conductivity, which are typically associated with metals. Derivatives of **1** that display pancake bonding in the solid state were reported,[2] however, there are fewer examples of studies in solution,[3] where the equilibrium is shifted towards the radical, because of the rather weak strength of the pancake bond.

To investigate pancake bonding in solution, we study dimeric diradical systems (**2**), in which two phenalenyl units are held in a close proximity by a linker that controls their relative orientation and allows them to interact only through space. A system with two β-linked phenalenyl units was synthesized and investigated by NMR, EPR and UV/Vis spectroscopy as well as DFT calculations. This diradical is unexpectedly stable and our results suggest stabilization via a dynamic interplay of sigma and pancake bonds. Currently, we investigate the nature of this stabilizing interaction and how it is affected by the linkage pattern. With these new insights, we aim to achieve tunability and switching between this system's paramagnetic and diamagnetic states, which makes it interesting for applications in spintronics.



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Alkynyl hypervalent iodine reagents: improved synthesis for their *in situ* generation

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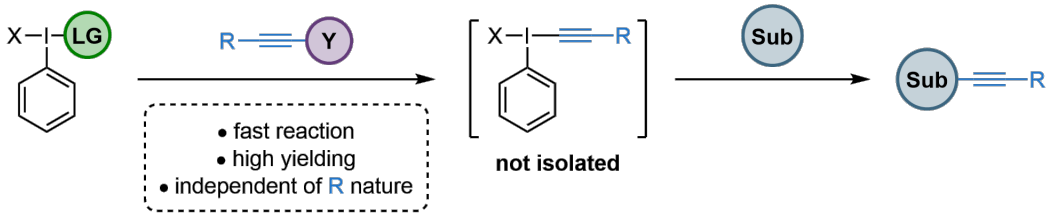
In the last decade, hypervalent iodine compounds proved to be particularly useful reagents to perform Umpolung reactions. Under a variety of conditions, they allow the transfer of the functional group linked to the I(III) center in an electrophilic fashion.[1] One major drawback of those methodologies is the synthesis of the reagents, usually requiring two steps. This is particularly problematic in the case of alkyne transfer where variation of the substituent on the triple bond is highly desirable. Currently, each diversification will require the synthesis, isolation and purification of the corresponding reagent, sometimes in poor yields depending on the alkyne substitution.[2] In this context, a method allowing their *in situ* formation and subsequent reaction would allow a straightforward transfer of various alkynes starting from a common intermediate. We find out that by choosing the right hypervalent iodine precursor and alkyne partner, alkynyl reagents can be accessed in high yield and short reaction time independently of the nature of the R group (Scheme 1). Using these conditions, they could be generated and subsequently used to transfer the alkyne without isolation.



Scheme 1: One-pot two-step formation of hypervalent iodine reagents and alkyne transfer.

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Organophotocatalytic Aerobic Oxygenation of Phenols in a Visible-Light Continuous-Flow Photoreactor

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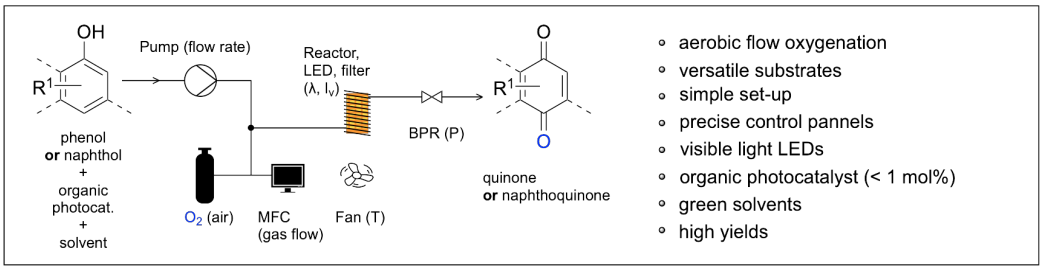
A mild photocatalytic phenol oxygenation enabled by a continuous flow photoreactor using visible light and air overpressure is presented herein. Products for wide-ranging applications, including the synthesis of vitamins, were obtained in high yields by means of a simple set-up with precise control panels. The reactor design permits the use of low photocatalyst loadings to promote singlet oxygen generation. It is anticipated that the efficient gas-liquid reaction for the high-yielding formation of quinones with air contributes to a circular economy and sustainable synthesis by bypassing the production of hazardous metal waste streams and avoiding the use of chlorinated solvents.



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Cyclopentadienone Iron Complex Catalyzed Hydrogenation of Ketones: An *Operando* Spectroscopic Study Using Pressurized Sample Infusion Electrospray Ionization Mass Spectrometry

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In recent years, cyclopentadienone iron complexes have received increased attention [1][2]. Their simple preparation from affordable and available starting materials and their catalytic activity in hydrogenation and transfer hydrogenation reactions make them ideal candidates towards developing more sustainable catalytic systems which do not rely on noble metal containing catalysts. The mechanism for the reduction of ketones and aldehydes to the corresponding alcohols has been proposed but needs to be proven [3]. Additionally, an *operando* spectroscopic investigation has, to the best of our knowledge, not been performed. To this end, Electrospray Ionization Mass Spectrometry (ESI-MS) using a Pressurized Sample Infusion (PSI) [4] approach for sample introduction lends itself to observing reaction intermediates in real time and thus allows determining what species are present in the reaction mixture under the actual reaction conditions.

In this work, we have prepared both positively [5] and negatively charge tagged cyclopentadienone iron complexes. They are capable of reducing ketones in water as solvent under hydrogen pressure (7.5 – 10 bar) and elevated temperatures (90 – 120 °C). Using custom made reaction vessels bearing inlets for standard HPLC PEEK tubing, we were able to introduce aliquots into the mass spectrometer (Thermo Finnigan TSQ Quantum) under pressure. Aliquots were stored in a 20 µl sample loop on a Rheodyne valve before entering the mass spectrometer, so that the collected sample could be subsequently pushed into the spectrometer using a water containing syringe mounted on a syringe pump. This was done to avoid excessive flow rates. Using the Rheodyne valve as a gateway also allowed the collection of samples for product analysis by ^{1}H NMR. Thus, using this setup, for each sample collected at a certain time, both conversion determined by ^{1}H NMR and a mass spectrum showing the species present in the reaction mixture could be obtained. Additionally, we are using Cryogenic Ion Vibrational Predissociation (CIVP) Spectroscopy [6] to further investigate the nature of the species present in the reaction mixture (see Vladimir Gorbachev's virtual poster).

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IBM RoboRXN: Automating Chemical Synthesis Remotely with AI and Cloud

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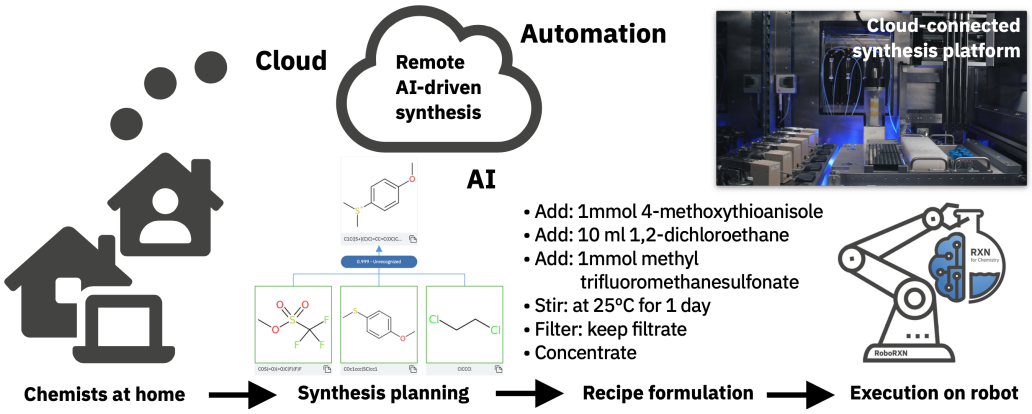
[1]IBM Research Europe

Automation is a key requirement to increase the efficiency and safety of manual processes, allowing robots to autonomously execute tedious routine or even dangerous operations. While many fields benefit from the use of automated systems, in the typical research chemistry laboratory environment, most of the work is done manually by trained chemists. In this poster, we present IBM RoboRXN, a novel cloud-based platform that combines artificial intelligence (AI) and automation. The AI assists the chemist by suggesting one or several synthetic routes to the desired target molecule, which can then be executed autonomously by the platform with as little human intervention as possible. We will critically review a selection of organic synthesis targets, highlighting strengths and areas of improvement. RoboRXN can also be accessed remotely, enabling with the power of AI even non-trained personnel to execute chemical reactions safely and efficiently.

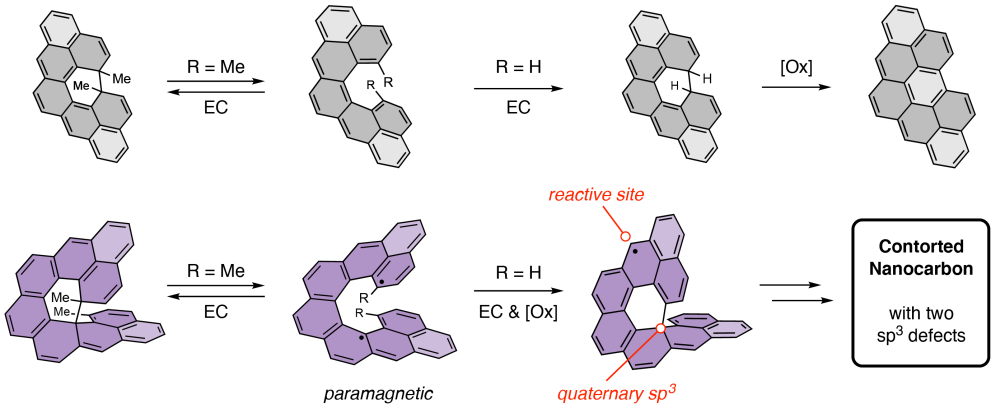


Nonacethrene Unchained: A Method Toward Contorted Nanocarbons

D. Čavlović[1], P. Ravat[2], D. Häussinger[3], O. Blacque[1], M. Juríček[1]*

[1]University of Zurich, Department of Chemistry, [2]University of Würzburg, Institute of Organic Chemistry, [3]University of Basel, Department of Chemistry

The intriguing electronic structure of diradicaloid π-conjugated hydrocarbons is in the center of current research activities in the field of polycyclic aromatic hydrocarbons. Even though this class of compounds has been widely studied for their magnetic properties, their reactivity is largely unexplored. In our group, we develop a helical branch of diradicaloids, named cethrenes,[1] which undergo a facile formally forbidden thermal electrocyclic (EC) ring closure. The nature of this rare transformation is of great fundamental interest because of its surprisingly low activation energy.[2] The initial studies of the reactivity of parent cethrene (gray) with R = H or Me inspired us to conceptualize[3] the working principle of a magnetic photoswitch. To validate this principle, we designed a π-extended system (purple), in which switching between magnetically active and inactive states would be enabled by light. The switching process of the substituted π-extended cethrene (R = Me) is currently under investigation, however, we discovered[4] an unexpected reaction cascade of its naked analog (R = H). The electrocyclic ring closure leads to formation of one quaternary sp^3-center, which "protects" this system from going flat like the parent cethrene (gray). What follows is an irreversible rearrangement, which enables an additional sequence of steps including another "forbidden" electrocyclization. This unprecedented reaction cascade comprising eight steps in total from the dihydro-precursor affords a contorted all-conjugated hydrocarbon with two precisely built-in sp^3 defects. Full details of these unexpected discoveries, which manifest the great potential of diradicaloid chemistry to develop new methods toward nanocarbons, will be discussed during the presentation.



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Synthesis of Highly Functionalized Cyclopentanes through Atom Transfer Radical Addition Cyclization Cascade

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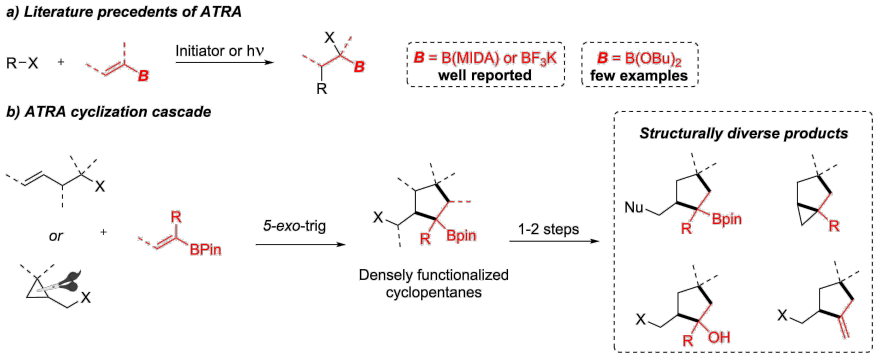
Aryl and alkylboronic esters are useful synthetic handles that can undergo further transformations. A plethora of deborylative carbon-carbon and carbon-heteroatom bond forming reactions allows to introduce various functional groups such as amines, halides, alcohols, alkenes, alkynes, and others.[1,2] Addition of radicals to vinylboronates is a useful entry to such a class of compounds. Atom/group radical addition of electron poor alkyl halides with electron rich vinylboronic acid MIDA esters and trifluoroborates proceeds smoothly and has been explored by several groups.[3-5] On the contrary, only a few examples of atom transfer radical addition (ATRA) of electron poor alkyl halides with non-complexed alkenylboronic esters have been demonstrated, due to the polarity mismatch and the high stability of α-boryl radical intermediate (Scheme 1a).[6,7] Despite the known challenges, we set out to design an ATRA cyclization cascade between non-complexed alkenylboronic esters and electron poor alkyl halides bearing a non-activated tethered alkene. Indeed, such a cascade enabled the synthesis of highly functionalized cyclopentanes, that could be easily diversified to afford useful building blocks (Scheme 1b).



Scheme 1. Synthesis of alkylboronic esters by the means of radical chemistry.

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Nickel-Catalyzed Asymmetric Synthesis of α-Arylbenzamides

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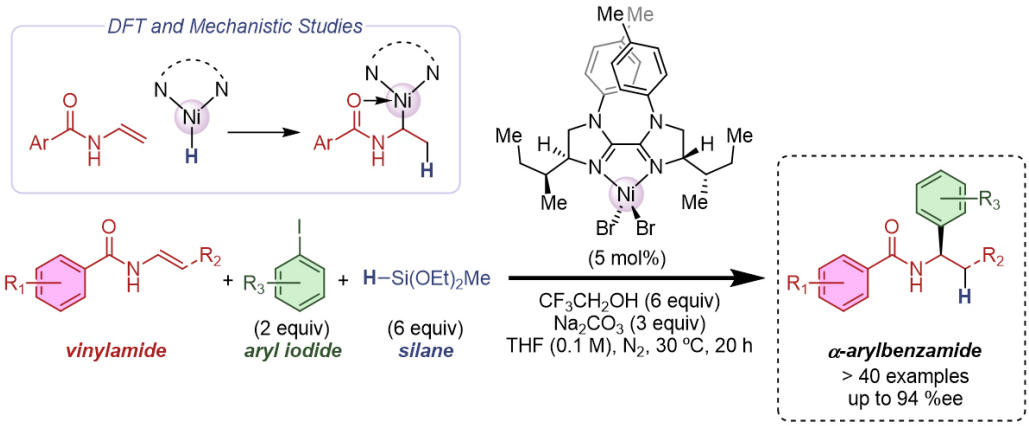
α-Arylbenzamides are pharmacologically relevant and ubiquitous motifs, present in anti-cancer agents,[1a] SARS-CoV PLpro inhibitors[1b] and anti-depressants among many other bioactive molecules.[1c] However, despite their unquestionable importance, straightforward methods to access these enantiomerically enriched motifs are still elusive. Currently established strategies include the direct enantioenriched arylation of the corresponding C-H bond[2a] or the hydrogenation of α-amidostyrenes[2b] among others. Our methodology relies on an elegant 3-component asymmetric hydroarylation of vinylamides,[3] catalyzed by a chiral Ni-bisimidazoline complex. Control experiments and DFT calculations support a mechanism based on the addition of an *in situ*-formed Ni-hydride complex onto the olefin. The excellent enantiomeric excess (up to 94 %ee) is explained by the coordination of the carbonyl group to the Ni atom. The broad scope (> 40 examples) demonstrates that the reaction tolerates different functional groups (nitrile, ketone, ester, boronic ester, etc.) and electronic properties in the aryl ring (EWG and EDG), both in the vinylamide as well as in the aryl iodide. Examples using ortho-substituted aryl iodides, vinyl bromides, benzyl bromide and more complex substrates bearing additional stereocenters are also included in this work.



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Synthesis of chiral benzylic amino alcohol: Molecular tether approach

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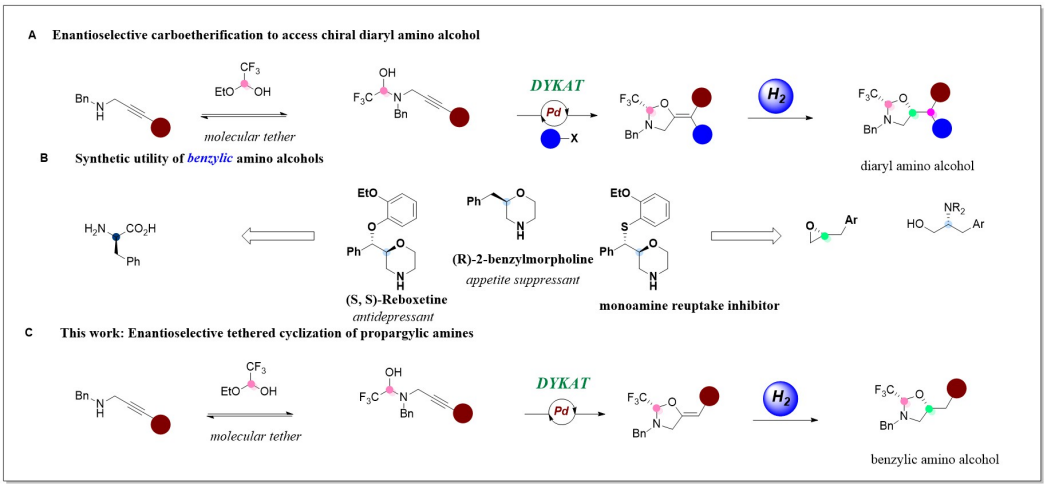
[1]Laboratory of Catalysis and Organic Synthesis (LCSO)

Asymmetric synthesis is generally based on two classical approaches: chiral auxiliary and asymmetric catalysis. Our group recently reported diastereoselective synthesis of chiral diaryl amino alcohol precursors by combining chiral auxiliary and asymmetric catalysis approach (scheme A).[1][2] We developed a palladium catalysed carbo-etherification, especially in three component fashion, which rapidly lead to chiral oxazolidine intermediate, involving DYKAT, starting from propargylic amine, aryl iodide and trifluoro acetaldehyde derived molecular tethers. The installed stereocenter then directs the diastereoselective hydrogenation of the double bond to access enantioenriched chiral diaryl amino alcohol precursors.

Substituted chiral morpholine derivatives are widely present in many pharmaceuticals (scheme B).[3] The synthetic route of especially (R)-2-benzyl morpholine category structures is quite limited and multistep. The synthesis often relies on Sharpless asymmetric epoxidation to install chiral centre,[4] or starting from chiral amino acids,[5] or stereospecific rearrangements of N-alkyl 1,2-amino alcohol [6] to access the key benzylic alcohol derivatives.

Herein, we will present our recent investigation towards the developments of an enantioselective tethered cyclization of propargylic amine to access wide variety of trisubstituted olefins which under stereoselective hydrogenation process leads to enantioenriched benzylic amino alcohol derivatives (scheme C).



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Development and Molecular Understanding of Cyanation of Aryl Boronic Acids Through High-Throughput Experimentation and Data Analysis

J. De Jesus Silva[1], N. Bartalucci[1], B. Jelier[1], S. Grosslight[2], T. Gensch[3], C. Schünemann[4], B. Müller[4], P. Kamer[4], M. S. Sigman[2], C. Copéret[1]*, A. Togni[1]*

[1]ETH Zurich, Department of Chemistry and Applied Biosciences, [2] University of Utah, Department of Chemistry, [3]TU Berlin, Department of Chemistry, [4]Leibniz-Institute for Catalysis e. V.

The widespread application of aryl nitriles in various fields of chemical synthesis has fueled the continuous search for protocols to achieve the cyanation of aromatic substrates under catalytic conditions.[1] While a large amount of these protocols still rely on the use of toxic, (masked) nucleophilic cyanide sources,[2] the design of these catalytic reactions remains mostly serendipitous due to the multidimensionality of the reaction conditions, among which ligand selection is a significant challenge.

Herein, we describe a palladium-catalyzed electrophilic cyanation of aryl boronic acids, using bench stable *N*-cyanosuccinimide as the cyanating agent. A combined high-throughput experimentation-data analysis approach is used to identify key ligands and to trace a structure-activity relationship between yield and readily accessible ligand descriptors (see **Figure 1**). In this study, we evaluated 90 ligands, highlighting Buchwald-type monophosphines and XantPhos-type bisphosphines as the most efficient ligands for this reaction, and revealing σ-donating abilities and ligand lability, as key parameters, which govern the observed reaction yields of the desired product.

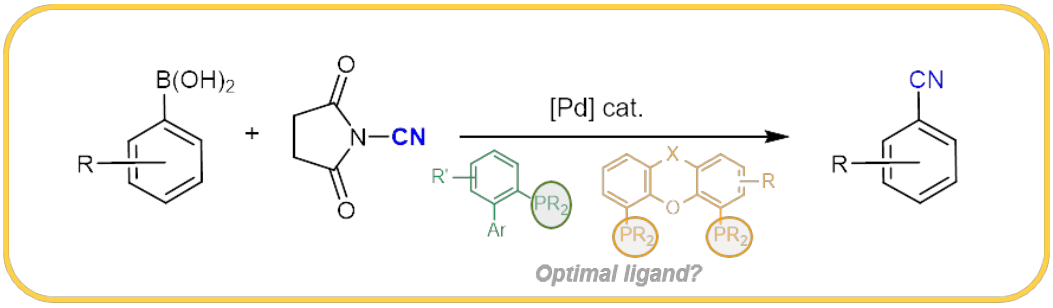

Figure 1. Design of a new cyanation protocol and identification of key ligands through a combined high-throughput experiment-data analysis approach.

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Stereoselective Synthesis of Hetero-Vinylbenziodoxolones Reagents and Their Reactivity as Oxy-Allyl Cation Synthetic Equivalents.

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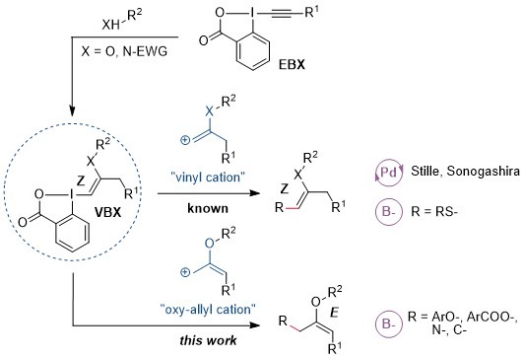
Hypervalent iodine reagents are widely used in organic synthesis as efficient group transfer reagents via Umpolung of nucleophiles.[1] Enolates, enol ethers and enamines are among the most important nucleophilic synthons in synthetic chemistry,[2] and the Umpolung of enolates with hypervalent iodine reagents is well established.[3] However, the transformations involve highly reactive intermediates formed in situ, and an access to stable reagents is of a high interest.[4] In 2019, our group published a highly stereoselective synthesis of Z-enamides and enol ethers based vinylbenziodoxolone reagents (N- and O-VBX), in two steps from silyl alkynes.[5] The enhanced reactivity of the hypervalent bond allowed their use as formal vinyl cations in presence of nucleophiles. Under specific conditions, O-VBX reagents, could act as oxy-allyl cation synthetic equivalents, a reactivity that differs from the well-established "vinyl-cation" behavior of alkenyl iodonium salts.[6] The new transformation, promoted by an excess of base, is working especially well with phenol nucleophiles, leading to aryl enol ethers bearing an allylic ether with complete E-stereoselectivity. In absence of external nucleophiles, the 2-iodobenzoate group of the reagent could be transferred. Under oxidative conditions, the obtained products were transformed in alpha-functionalized ketones, offering a new synthetic pathway to access functionalized ketones from alkynes in three to five steps.[7]



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Atom economic difunctionalisation: the addition of acid chlorides across unsaturated C–C bonds

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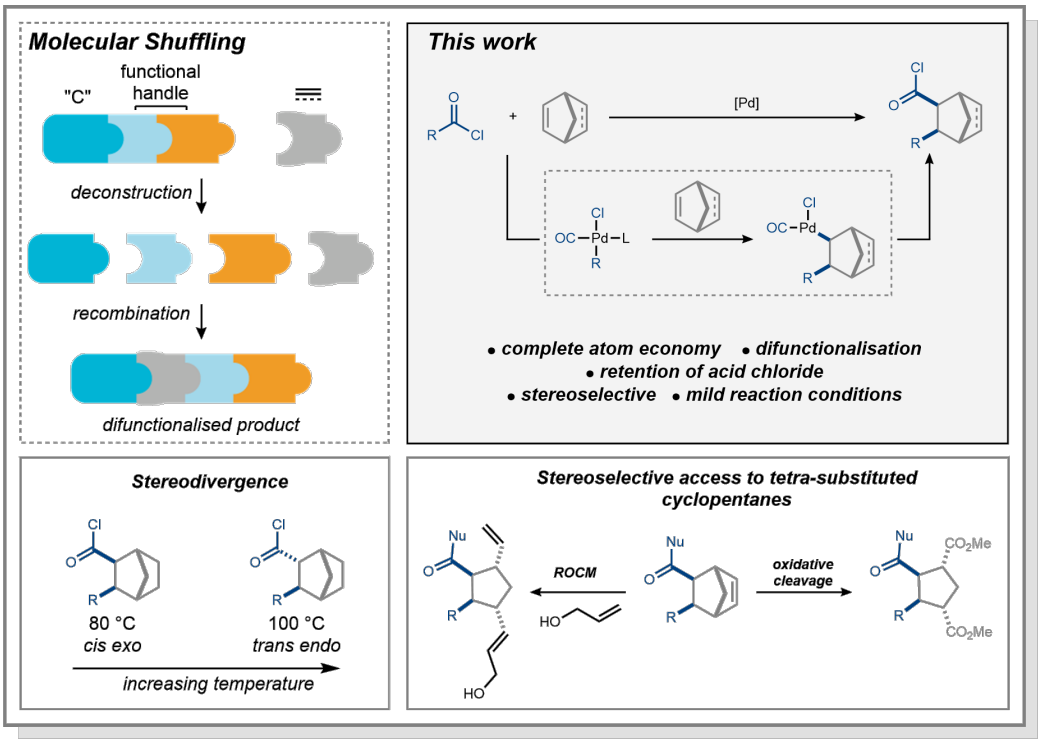
Atom economy and synthetic utility are two concepts that are often antagonistic. For example, efficient difunctionalisation reactions of unsaturated C–C bonds are scarce. Currently, functional handles are used in a “single-use” fashion to access these compounds. As a result, the functional handle is not retained in the product, resulting in a loss of synthetic utility and atom economy. In an effort to unite these seemingly disparate concepts, we considered an alternative approach in which the functional handle serves to enable a transformation while being retained in the product via a molecular shuffling approach. Overall, this would represent an increased molecular complexity with complete atom economy while conserving synthetic utility by retaining the functional handle of the starting material. Here, we present the realisation of this concept, in which the R–COCl bond of an acid chloride is cleaved and then added across an unsaturated C–C bond to generate two new C–C bonds. Notable features of the reaction include the synthesis of highly reactive acid chloride products without the need for exogenous carbon monoxide, excellent stereoselectivity, complete atom economy, and a rare example of temperature-dependent stereodivergence. The products can be used to access tetra-substituted cyclopentanes by oxidative cleavage or ring-opening cross-metathesis. Further, computational studies rationalise the observed stereochemical outcome and support a plausible reaction mechanism.



At the Core of Dynamic Polymers: The Self-Assembly of Twisted Aryl Amines

M. El Bitar Nehme[1], M. Rickhaus[1]*

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

Triphenylamines (TPAs) and its derivatives have received considerable attention over the past years thanks to their attractive properties that enable their use in photovoltaic applications. Their molecular configurations and electronic properties greatly influence their aggregation states as well as their charge carrier-transporting properties. Previous studies reported that substituting the TPA with at least one amide group could induce supramolecular polymerization that can form helical structures via tri-intermolecular H-bonds. To date, there is no reliable method to predict how exactly a given building block will organize itself in solution or the solid state, consequently allowing us to formulate the following questions:

What rules govern supramolecular order? And how do we encode these rules into molecular building blocks?

Can we predict new properties that emerge as a result of an assembly of subunits?

To address these seminal goals, we aim to study the influence of systematic variations of the core of a triarylamine trisamide (TATA) core unit, while keeping the outer layer (i.e. sidechains) constant. This ensures that the main driving force for the assembly (the hydrogen bonds) located at the periphery remain in place, leading to columnar stacking. For this purpose, we have devised Family A, which aims at highlighting different parameters such as geometry, steric hindrance, size, and flexibility. Family A (Figure 1) will be dedicated to a series of TATA derivatives with distorted cores. Besides the TPA core, these systems feature a secondary alkyl linkage of different length (C0- C3) that connects each aryl with its neighbor. The length of the bridge is anticipated to induce different degrees of twist to the core, distorting the available π-surface. The main objective in this family is thus to investigate if it is possible to find a direct relationship between the distortion of the flat surface and the observed degrees of supramolecular order.

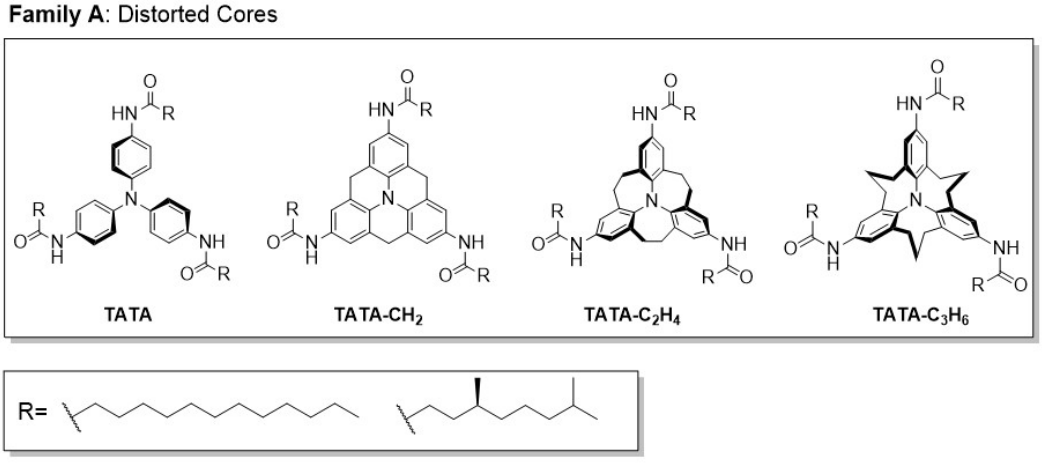


Figure 1. The molecular structures of the desired compounds

Through Bond and Space: Curved Light Harvesting Arrays

L. Gallego[1], M. Rickhaus[1]*

[1]University of Zurich, Department of Chemistry

The properties of flat π-rich molecules have been widely studied and are well known for their use as conductive and optical materials. We know that distorting the systems away from planarity can substantially impact their behaviour, but we know little to what extent. Curved, cyclic, conjugated systems have been lately used in energy transfer processes, with porphyrin nanorings and their linear analogues standing out, showing enhanced electronic delocalization throughout the system.

Here we show our approach towards studying the properties of carpyridine (CP) based oligomers. CP is a novel porphyrinoid-related, metal-containg macrocycle bearing two carbazole and two pyridine units alternately connected through ortho aryl-aryl bonds. This arrangement results in a saddle shaped secondary structure. What makes CPs intriguing from a materials perspective is that the carbazoles and the pyridines are decoupled due to the bending. Each monomer by itself has thus limited delocalization. However, when connected through ethynyl bridges to build different size oligomers, the conjugation passes from linker via pyridine and goes through the metal. Given the geometry of the monomer, linear and cyclic oligomers could be obtained, expecting a change in their photophysical and chemical properties. The presence of the metal in the CP units also enables hosting a guest by coordination, and when using an acceptor guest, this would allow the study of energy transfer processes from the oligomers through space towards the acceptor.

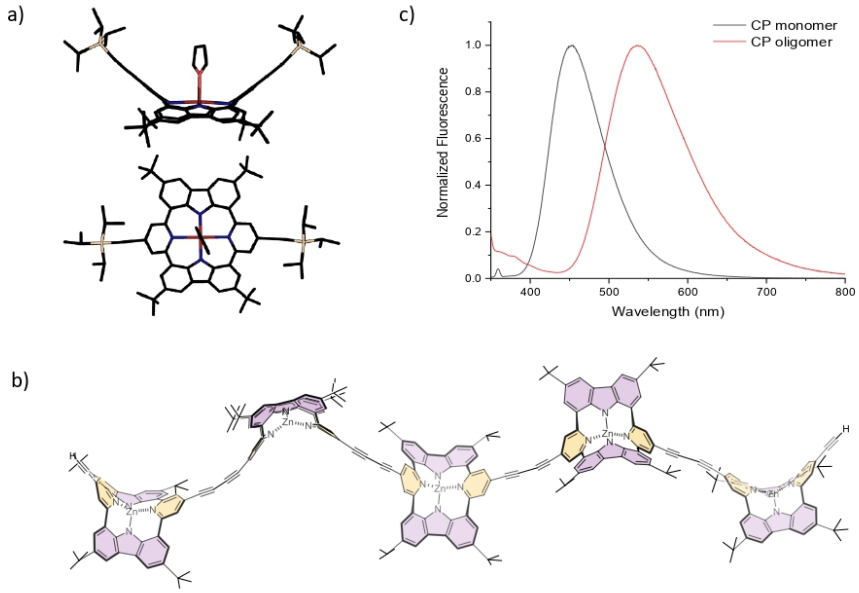


***Figure 1**: a) X-Ray structure of a CP obtained by slow evaporation from THF, b) Chemical structure of a [5]-CP oligomer and c) Emission spectra of the CP monomer and oligomer*

Ir(III)-catalyzed C(sp3)-H directed amidation for the synthesis of 1,2-aminoalcohols

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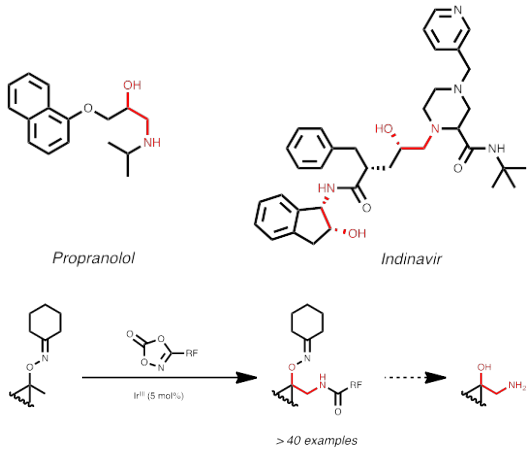
[1]Department of Chemistry, University of Basel, [2]Novartis

The 1,2-aminoalcohol motif is a recurrent feature found across a large panel of natural products, active pharmaceutical ingredients and agrochemicals (Scheme 1.a). The traditional elaboration of this motif calls upon amino-hydroxylation of olefins, epoxide or aziridine opening, or multistep sequences.[1],[2] In this context, we aimed at developing a novel, robust and efficient methodology for the installation of this particular moiety in secondary and tertiary alcohols.[3],[4],[5],[6] We report an oxime-directed Ir(III)-catalyzed C(sp^3)–H amidation process, which is compatible with primary C–H bonds of both 2^{ary} and 3^{ary} alcohol-derived substrates (>35 examples). Further applicability to secondary C–H bonds in cyclic systems is also demonstrated (10 examples) (Scheme 1.b). Additionally, our approach involves the use of a new fluorinated 1,4,2-dioxazol-5-one reagent that results in amide products which undergo facile cleavage at room temperature under basic conditions.



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Transmetalation of Monocyclometalated Gold(III) Complexes with Boronic Acids: Novel Selectivity and Mechanistic Insight

J. A. González[1], F. Verdugo[2], J. L. Mascareñas[2], F. López[2], C. Nevado[1]*

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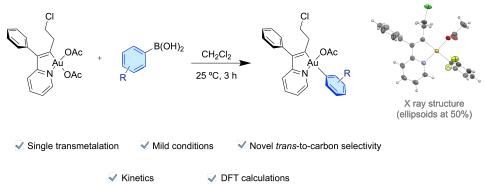
In recent years, gold has re-captured attention in modern chemistry and material science. In particular, oxidative homogenous gold-catalyzed reactions have proven to be an extraordinary tool in organic synthesis. Thus, remarkable efforts have been invested to synthesize and understand the reactivity of organometallic gold(III) species. For these purposes, monocyclometalated 2-phenyl-pyridine gold(III) derivatives have enabled a detailed characterization of elementary steps such as olefin insertion, transmetalation and reductive elimination. In the case of the transmetalation, i.e. the transfer of ligands between two metals, the selectivity observed (aryl *trans*-to N) in the corresponding monoarylated gold(III) product has been a topic of interest. This is because the observed geometry around the gold(III) center does not reflect the *trans* influence differences (N *vs* C) displayed in the 2-phenyl-pyridine gold(III) precursors.[1,2]

Scheme 1. Direct monotransmetalation in a novel [C^N]Au(OAc)$_2$ complexes



Based on our previously reported work,[3] we synthesized a new monocyclometalated pyridine-alkenyl gold(III) bis(acetato) complex that is able to undergo direct monotransmetalation with aryl boronic acids to deliver the corresponding monoarylated product. Interestingly, in all cases, the products display a geometry around the gold center (*trans*-to-C) that has not been reported up to date, **Scheme 1**. Furthermore, DFT and kinetics revealed that the transmetalation occurs in two steps: a fast acid-promoted equilibrium between the gold complex and the boronic acids and then, a rate-determining step where the aryl moiety is transferred from boron to gold. In summary, this work describes an unprecedented reactivity on cyclometalated gold(III) complexes, where the selectivity of transmetalation is dictated by the *trans*-influence differences in the ground state.

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Flipper and flap: two mechanosensitive probes

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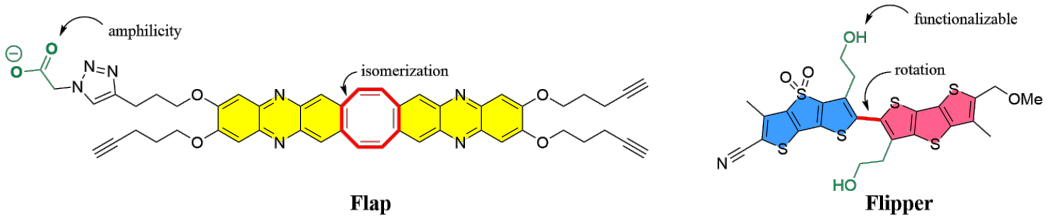
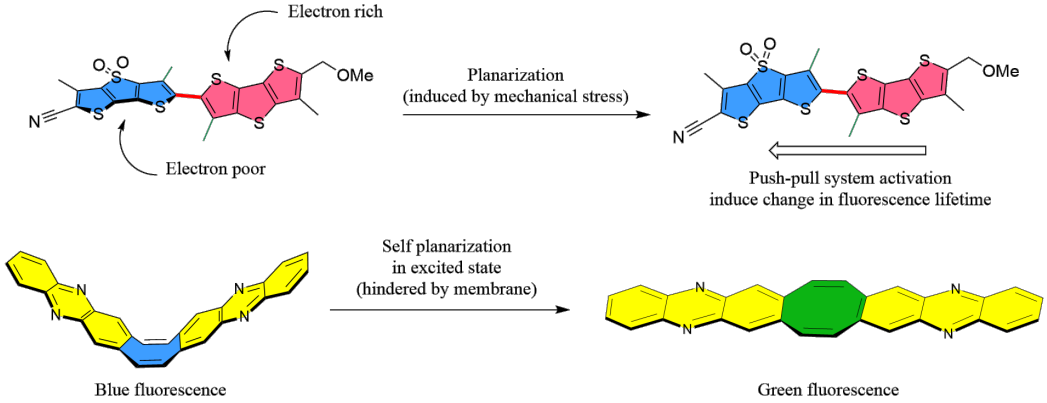
[1]Department of Organic Chemistry, University of Geneva, [2]Department of Chemistry, Kyoto University

Sensing and reporting the physical forces in polymeric materials[1] and living systems[2] are key challenges to better understand their behavior. To tackle these challenges, the incorporation of probes into polymers or cells can allow the visualization of mechanical stress events. Flippers[3] and flaps,[4] two mechanosensitive molecules, both exhibit a change in their fluorescent properties under mechanical stress. Herein we present a variation of the flipper[3] probe that could be embedded in a polymer and a new amphiphilic flap.



The new synthetic strategy to access this flipper probe allows the functionalization close to the rotational axle. The strategic placement of these attachment points allows planarization of the bis-dithienothiophene system by applying mechanical stress in between the two dithienothiophene units. Conjugation of the push-pull system upon planarization gives rise to an increased fluorescence lifetime.[3] In the case of the flap probe, the addition of an acid group grants the molecule amphiphilic properties, enabling membrane insertion. The restricted environment in the membrane hinders the planarization of the molecule resulting in a shift in fluorescence.



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Introduction of Peripheral Side Groups to the Octulene Scaffold

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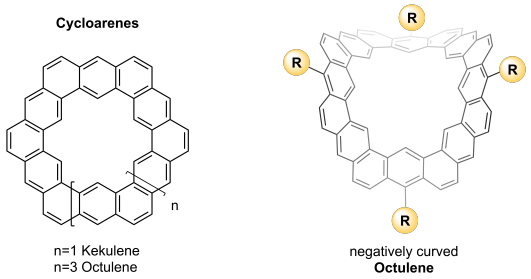
[1]University of Zurich, Department of Chemistry

The field of polyaromatic hydrocarbons received great attention over the last decades, owing to the manifold structure possibilities resulting in utterly diverse materials. The bottom-up approach of precisely synthesizing defined materials gave rise to a multiplicity of functional materials, with diverse electronic, photophysical and solid-state properties, yielding a wide range of applications. Substituents can play a crucial role for solubility and intermolecular interaction in those materials, allowing the possibility to control effects like aggregation or assembly into long-range ordered systems.

Among polyaromatic hydrocarbons, cycloarenes are a class of macrocycles, consisting of annulated benzene rings with C-H bonds pointing into the formed cavity of the macrocycle. The first studied representative of this group of macrocycles was kekulene, which consists of 12 annulated benzene rings (figure 1, n=1).[1] More recently, the extended macrocyclic analogue octulene (figure 1, n=3) was reported for the first time.[2-3] Due to the strain introduced by the larger ring size, octulene has no longer a planar structure, but exhibits persistent negative curvature (figure 1, right). The increased cavity size of octulene additionally enables the binding of a chloride anion in the center of the macrocycle. Therefore, the octulene scaffold is an interesting platform to be further studied, as modification of its properties can path the way for various applications.



Herein, we present the introduction of varying peripheral side groups into the octulene core scaffold. Besides the feasibility of different synthesis approaches, the impact of those substituents will be presented and compared to the corresponding planar kekulene derivatives.

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The Taming of Helical Triplet Diradical

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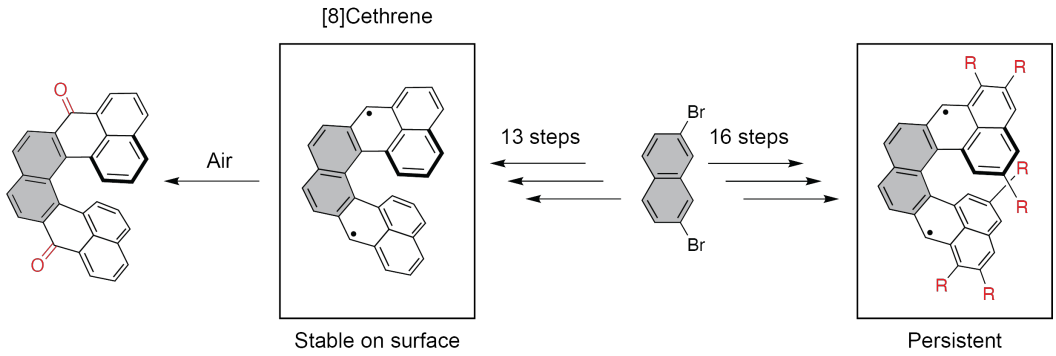
[1]University of Zürich, Department of Chemistry

Molecular materials that can spin-filter electric current hold potential as components of future information processing devices. Our group's approach towards such materials relies on the use of chiral molecules, which display bulk magnetic and conducting properties. Although most of magnetic and conducting materials are based on metals, we employ metal-free open-shell fragments of graphene as molecular building blocks. In order to achieve a chiral open-shell system, we designed a helical hydrocarbon [8]cethrene composed of two phenalenyl units (white-filled rings) fused to a naphthalene unit (gray-filled rings) such that a [6]helicene scaffold is obtained. This hydrocarbon belongs to the class of non-Kekulé molecules, with two "frustrated" electrons that cannot pair leading to a diradical structure, which is predicted to possess a triplet ground state. Although Kekulé closed-shell systems have been studied intensively, the chemistry of non-Kekulé systems remains unexplored in the solid state, mainly because of their extremely high reactivity. To synthesize and isolate a persistent [8]cethrene diradical, we set out to prepare a derivative, in which all reactive positions would be protected by a bulky a substituent (R, in red). This compound was synthesized in 16 steps from 2,7-dibromonaphthalene. In addition, the "naked" parent [8]cethrene was prepared in 13 steps. As expected, the naked system is not stable and in solution, it undergoes oligomerization or oxidation at the most reactive positions to a diketo compound. As a result, it could only be generated and studied on a gold surface under ultra-high vacuum using scanning probe microscopy techniques. Six bulky substituents substantially improve the kinetic stability and we are currently isolating and characterizing these species in the solid state.



Catalyst-free Photochemical C(sp^3)-H Arylation of Amides in a Solvent-Caged EDA Complex

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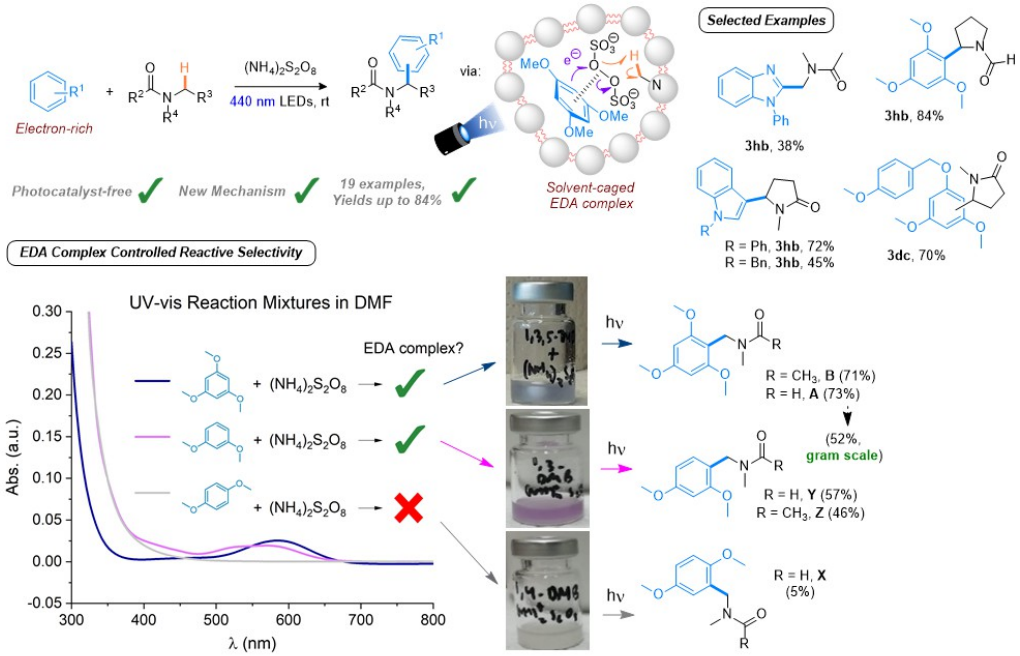
Amides and lactams are important moieties in polymers, peptides, functional materials and bioactive organic molecules. An alternative approach to the condensation of amines with carboxylic acids is the direct C(sp^3)-H functionalization of simple amide feedstocks.[1] Hydrogen atom transfer (HAT), affording alpha-amido radicals, is an elegant vehicle for the functionalization of amides that circumvents otherwise high oxidation potentials needed for their activation by single electron transfer. Radicals derived from persulfate are ideally matched to engage amide C(sp^3)-H bonds. The activation of persulfate in this way can be achieved at high temperatures,[2] but also under ambient conditions using visible light.[3,4] For example, Stephenson and co-workers reported an elegant photochemical method employing transition metal photocatalyst $[Ru(bpy)_3]^{2+}$ and ammonium persulfate for a C(sp^3)-H arylation of amides with electron rich arene partners.[4] We serendipitously found this reaction proceeds without any photocatalyst, using only visible light at ambient temperature.[5] UV-vis spectra revealed an electron-donor acceptor (EDA) complex between electron rich arenes and persulfate is key to reactivity. Mechanistic studies including quantum yield measurements and radical trapping experiments corroborated the reaction taking place within a solvent cage, offering promise to the ability to control photochemical reaction outcomes through confined spaces.



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Selective Tetrafunctionalizations on Phenolic Macrocycles: Diversifying the Calix[4]arene Family

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Calix[4]arene along with its sister molecules resorcin[4]arene and pyrogallol[4]arene are rigid, bowl-shaped, phenol-based macrocycles (Figure 1a).[1-2] While a multitude of derivatives of these frameworks are reported, selective derivatization with high specificity via short synthetic routes remains challenging. We have expanded the toolbox of such fourfold transformations that allowed us to synthesize new functional molecules from one common starting material (Figure 1b-d).[3-5]

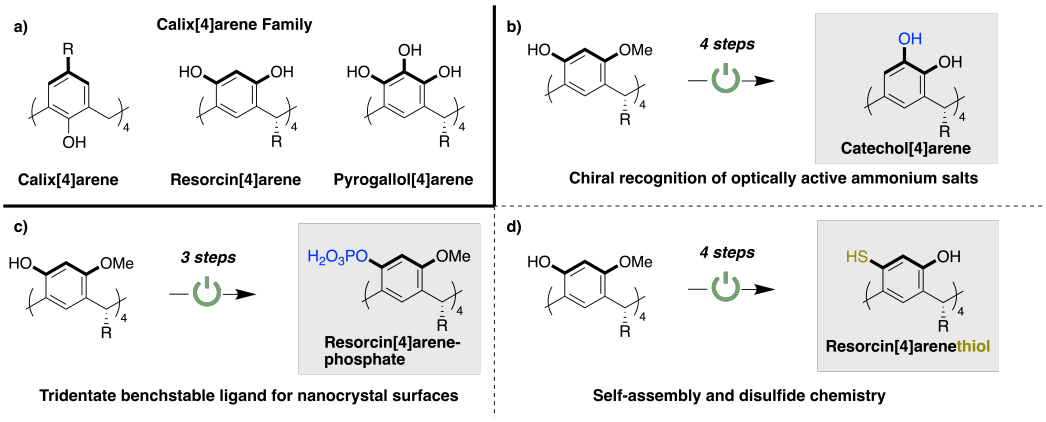

Figure 1. a) Structures of important members of the calix[4]arene family. b) Synthesis of Catechol[4]arene, an inherently chiral receptor for optically active ammonium salts. c) Synthesis of Resorcin[4]arenephosphate, a tridentate ligand for nanocrystal surfaces. d) Synthesis of Resorcin[4]arenethiol, a tetrathiol explored for its capabilities for self-assembly and disulfide chemistry.

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Organic Building Blocks for 2D Interwoven Molecular Textiles

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[1]University of Basel, Departement of Chemistry, St.

Materials consisting of interwoven yarns *i.e.* textiles, are of great importance in our every day life due to their excellent structural properties as stability, flexibility and shape adaptability.[1] These extraordinary properties gave a rise of interest to investigate the possibility to interweave 1D single strain polymers in order to form textiles on a molecular scale. Recent advantages by Mayor, *et al* who investigated 2D interweaving utilizing a SURMOF process, and Leigh, *et al*. who used a 9 fold metal complex showed the synthetical and analytical challenges of such highly ordered structures.[2,3] Our research focuses on the design and synthesis of well controllable organic building blocks that can be utilized to form 2D molecular textiles by interwoven 1D linear polymers.

Profiting from static and dynamic control, a building block featuring a cross-like 3D conformation was designed (Fig 1a). The required conformational shape arises from bridging two tetraphenyl moieties by two esters (Fig. 1b). This structural feature allows for the specific arrangement of the monomers offering both functionalities (amine and aldehyde) regarding the directional polymerization utilizing Schiff-base condensation after monolayer assembly (Fig. 1c-d). The dynamic control arises from the interconnecting ester bonds, which upon cleavage converts the cross-linked network into a 2D interwoven molecular textile (Fig. 1e).

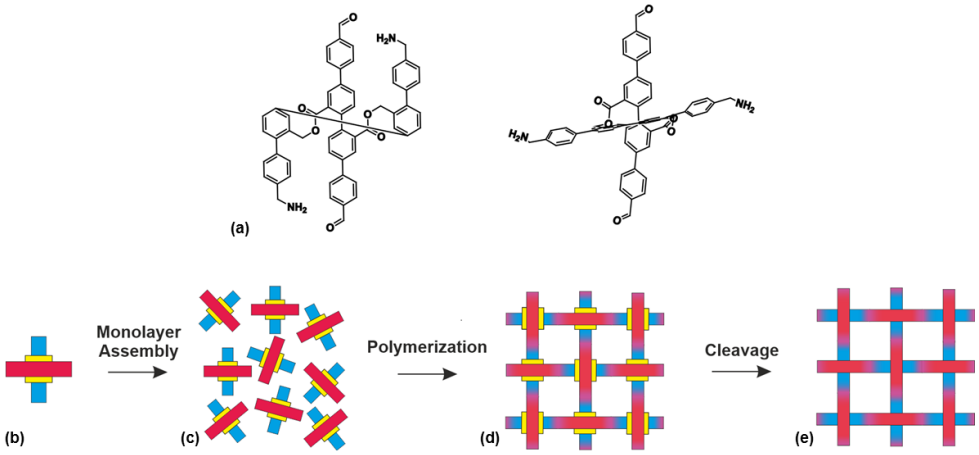

Figure 1: a) Design of building block and 3D conformation. Schematic representation of b) cross-like monomer c) Assembled mono-layer d) 2D Crosslinked network e) 2D interwoven molecular textile

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Accessing Monosubstituted Cyclopentadienyl Rhodium(I) and Iridium(I) Complexes by a Simultaneous Nucleophilic Addition-Metalation Approach to Fulvenes

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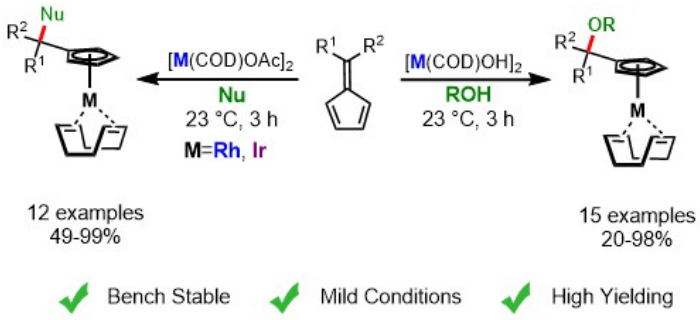
Despite advances in the synthesis of polysubstituted cyclopentadienyl metal-complexes, the rapid access to a library of monosubstituted Cp bearing-metal complexes remains challenging. A convenient and general method to access a broad range of monosubstituted cyclopentadienyl rhodium(I) and iridium(I) complexes is presented (**Scheme 1**). The process involves a direct nucleo-metalation of fulvenes with widely available metal precursors, affording a set of $CpRh^{I}(olefin)_2$ and $CpIr^{I}(olefin)_2$ complexes in high yields. A broad range of oxygen-, nitrogen- and carbon-based nucleophiles were found competent for the process and offer good tuning abilities of the cyclopentadienyl portion.



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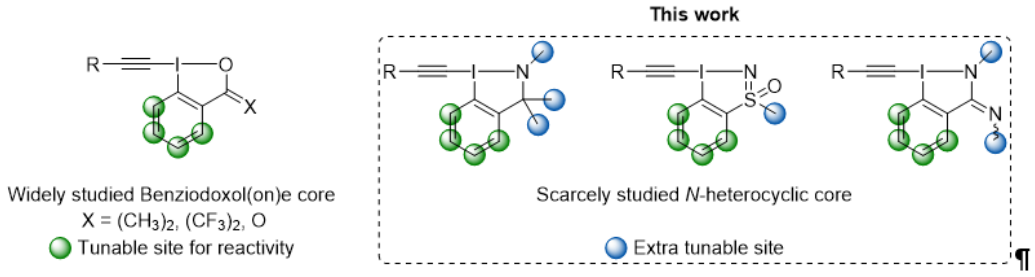
Structure and Reactivity of New Cyclic Alkynyl Hypervalent Iodine Reagents

E. Le Du[1], T. Duhail[2], M. D. Wodrich[1], R. Scopelliti[3], F. Fadaei-Tirani[3], E. Anselmi[3,4], E. Magnier[2]*, J. Waser[1]*

[1]Laboratory of Catalysis and Organic Synthesis, Ecole Polytechnique Fédérale de Lausanne, EPFL SB ISIC LCSO, BCH 4306, 1015 Lausanne, CH, [2]Institut Lavoisier de Versailles, Université Paris-Saclay, UVSQ, CNRS, UMR 8180, 7800 Versailles (France), [3]Institute of Chemical Sciences and Engineering, Ecole Polytechnique Fédérale de Lausanne, EPFL SB ISIC GE, BCH 2111, 1015 Lausanne, CH, [4]Université de Tours, Faculté des Sciences et Techniques, 37200, Tours (France)

Hypervalent iodine reagents (HIR) have been established as versatile and environmentally benign oxidant and group transfer reagents.[1] Among them, cyclic HIR have become mainstream reagents for organic chemistry and exhibit higher stability than their iodonium salt equivalents.[2] For instance, benziodoxol(on)e based reagent have been intensively studied in functional group transfer reactions.[3] However, these reagents offer only few possibilities to modulate their reactivity by structural modification due to the presence of an oxygen in the iodoheterocycle. Herein, we present the syntheses, structural investigations and reactivity of new *N*-heterocyclic HIR bearing additional tunable sites.[4]



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Inhibitors of Thiol-Mediated Uptake

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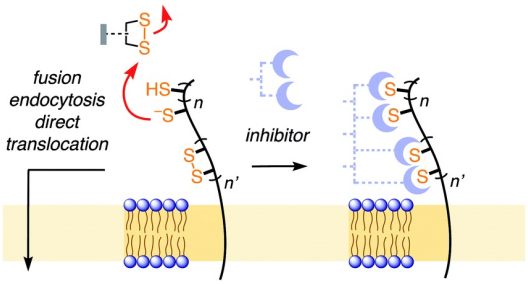
Thiol-mediated uptake has so far focused on efficient cellular uptake of biologically active molecules attached to thiol-reactive groups. The only inhibitor to demonstrate thiol-mediated uptake has been Ellman's reagent (DTNB), which has a weak inhibitory performance. In efforts to develop potent inhibitors of thiol-mediated uptake, we explored thiol-reactive compounds with the systematic and effective assay system using fluorescent cyclic oligochalcogenides that can enter the cell by thiol-mediate uptake. The most potent inhibitor exhibits more than 5000 times higher activity than DTNB. In addition, the inhibition of SARS-CoV-2 lentivirus cellular entry by thiol-mediated inhibitors was identified. Further structural optimizations are underway to develop promising inhibitors with enhanced antiviral activity.



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Oligomers of Cyclic Oligochalcogenides for Enhanced Cellular Uptake

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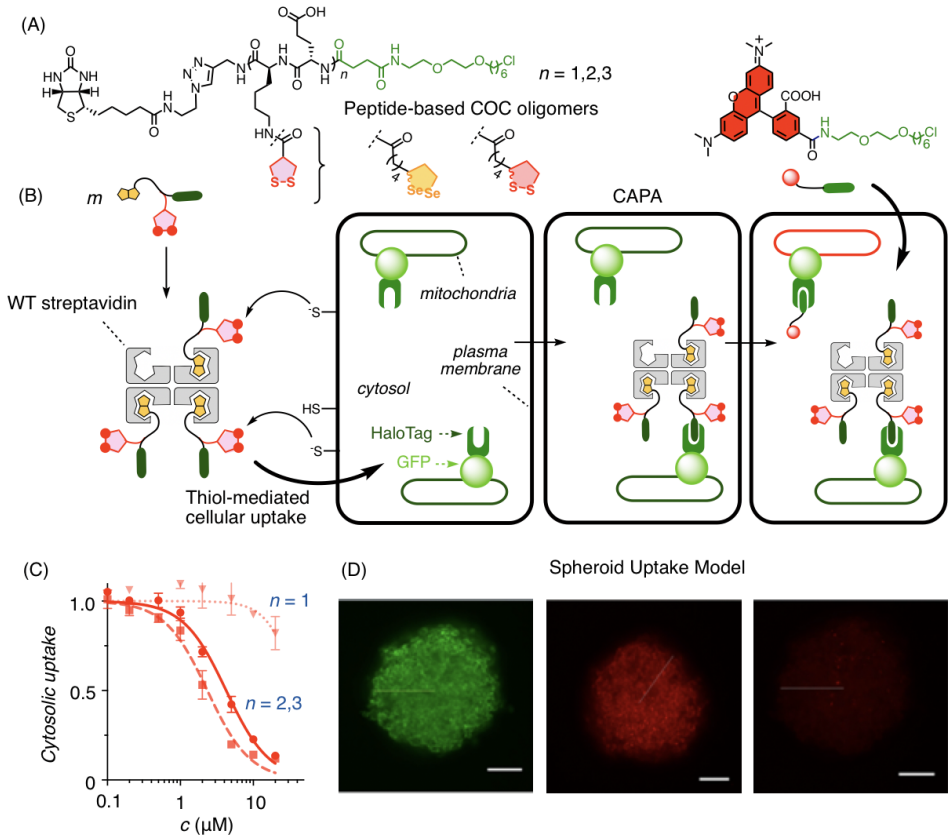
The recent discovery of cell-penetrating polydisulfides (CPDs),[1] and monomeric cyclic oligochalcogenides (COCs)[2] as powerful thiol-mediated uptake transporters called for the introduction of COC oligomers.[3] To explore COC synergism emerging from multivalent interactions with membrane thiols (Figure 1B), we designed peptides with *n* alternating units (*n* = 1,2 3) containing a lysine and glutamic acid, to attach the COCs and to increase water solubility, respectively. Next, the N-terminus was capped with the chloroalkane reporter to perform the invaluable penetration assay named CAPA[4] (Figure 1B). In addition, supramolecular oligomeric effects were explored using biotin/streptavidin biotechnology. The latest results also proved a remarkable sequence-dependence of the peptide structure on cellular uptake as well as an outstanding ability to penetrate multicellular assemblies such as spheroid models (Figure 1D).



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N-heterocyclic substituted aldehydes in organocatalyzed conjugate addition reactions

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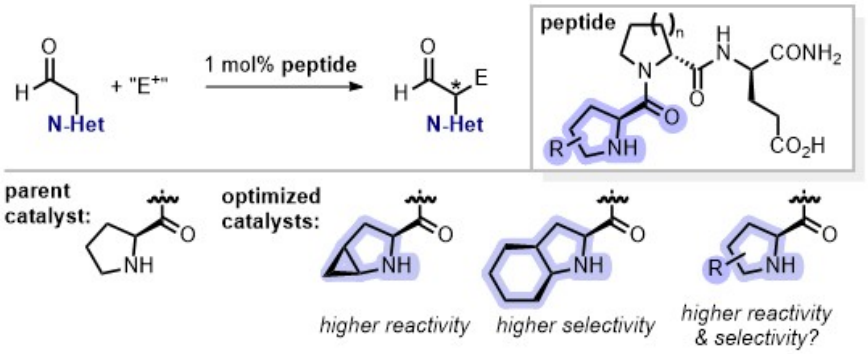
Chiral secondary amines are powerful catalysts for stereoselective C–C bond forming reactions *en route* to chiral bioactive molecules.[1] Half of all small-molecule based drugs are chiral and a majority contains at least one N-heterocyclic substituent.[2] For organocatalytic transformations, unprotected and even protected N-heterocyclic moieties often pose though a major challenge due to undesired interactions with the catalyst or reaction intermediates. Any interference would be severe if the conformation and/or reactivity of the catalyst, or the intermediate involved in the C–C bond forming step, *e.g.* the enamine, is affected. This explains why only very few reports describe the use of N-heterocyclic substituted substrates in organocatalytic reactions. Catalysts need to be sufficiently robust and stereoselective to enable such transformations, ideally at low catalyst loadings.

Our group has developed peptides of the type H-Pro-Pro-Xaa as highly reactive and stereoselective catalysts for C−C bond formations.[3] Recently, we showed that the reactivity of proline derivatives can be increased by defining the pyramidalization of the nitrogen of the enamine intermediate that then reacts with the electrophile.[4] This finding allowed for organocatalytic conjugate addition reactions between aldehydes and a broad range of nitroolefins bearing N-heterocyclic moieties, as well as other electrophiles.[5] Now, we expanded this methodology and introduce additional tools to improve 2° amine based catalysts to allow also for the incorporation of N-heterocyclic substituted aldehydes in organocatalyzed conjugate addition reactions.



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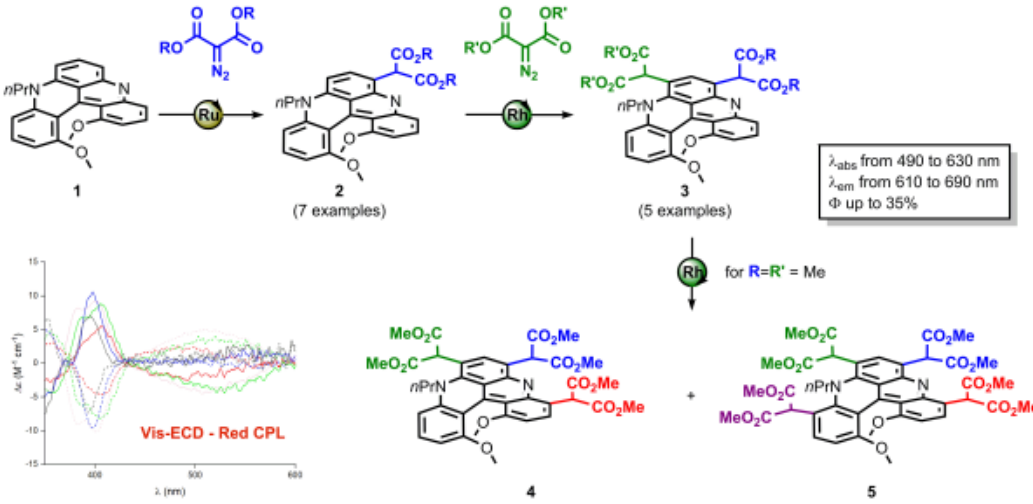
A novel functionalization of pH-sensitive diaza[4]helicenes based on metal carbene insertion mechanism

Y. Nikolova[1], B. Fabri[1], P. Moneva Lorente[1], A. de Aguirre[1], F. Zinna[2], L. di Bari[2], A. I. Poblador-Bahamonde[1], J. Lacour[1]*

[1]University of Geneva, Department of Organic Chemistry, [2]University of Pisa, Department of Chemistry and Industrial Chemistry

Electrophilic metal carbenes, readily generated via decomposition of diazo reagents with metal complexes, are known to provide selective and effective ylide forming reactions [1-2] but also a range of X-H and C–H insertions [3-5]. Herein, with chiral quinacridine-containing aza[4]helicenes (**1**) as substrates, exclusive C-H reactivity is observed. In addition, full regioselectivity and chemoselectivity are afforded thanks to controlled metal catalysis. In fact, clean mono insertion of malonate moieties occurs under $[CpRu(CH_3CN)_3][PF_6]$ catalysis, while $Rh_2(Oct)_4$ complex leads to the formation of di-, but also tri- and tetra-functionalized derivatives. Thanks to DFT calculations, detailed explanations on the reactivity and regioselectivity will be presented. Finally, of importance, the malonate substituents impact key chemical and physical properties – from pKa tuning to improved electronic circular dichroism (ECD) and circularly polarized luminescence (CPL) in the red domain of the visible light spectrum.



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Asymmetric Catalysis by Chiral Cp^XCo^{III} Complexes

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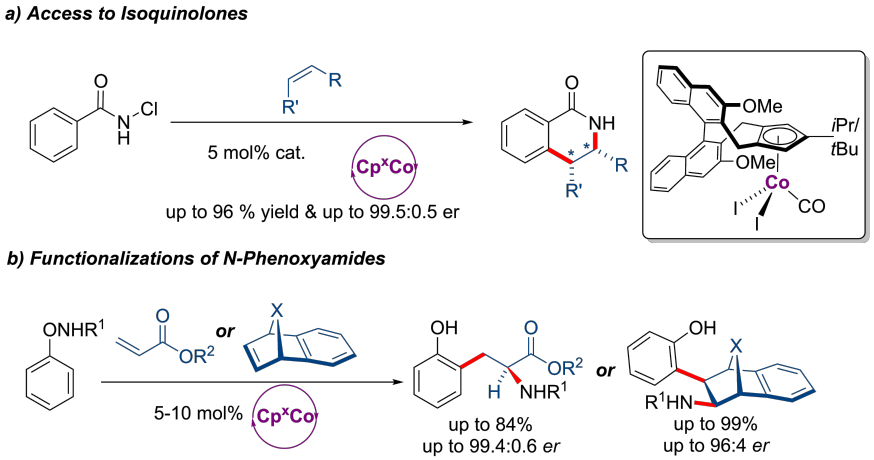
[1]Laboratory of Asymmetric Catalysis and Synthesis, École Polytechnique Fedérale de Lausanne, Lausanne CH-1015, Switzerland

The C–H activation has contributed to an increased synthetic efficiency and allows for late-stage functionalizations. Lately, a significant interest has appeared towards the application of non-noble metals in C–H activation.[1] The rapid progress in this field now demands to carry out such transformations in an enantioselective manner. Our group has shown for the first time the preparation of the chiral Cp^XCo(III) complexes. Their catalytic performance was demonstrated in a benchmark reaction towards isoquinolones (Scheme 1a).[2] The observed enantioselectivities were superior to those previously reported under Cp^XRh catalysis. In the further work, we showed that this catalytic system is also applicable in the non-annulative carboaminations of Michael acceptors and strained bicyclic alkenes (Scheme 1b).[3] Notably, these transformations are known to be restricted to CpCo(III) catalysis and cannot be carried out with the rhodium analogues.[4,5]



Scheme 1. Cp^XCo catalysts in C–H Functionalizations

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α-Diazo-ynonesters - a Versatile Scaffold Towards Formation of Hydroxypyrroles & Hydroxypyrazoles

R. Pertschi[1], A. de Aguirre[1], C. Besnard[2], A. I. Poblador Bahamonde[1], J. Lacour[1]*

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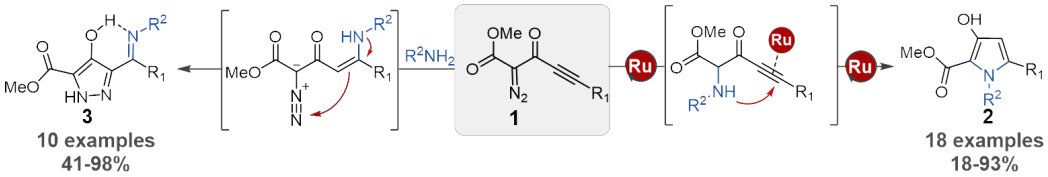
Pyrroles and pyrazoles are key structural building blocks in natural products and medicinal chemistry owing to their biological properties.[1] In this context, a modular approach toward their formation is presented, *via* the unique scaffold of α-diazo-ynonesters **1**. On one hand, the formation of hydroxypyrroles **2** is achieved thanks to the ability of cyclopentadienyl Ru(II) complexes to generate electrophilic metal carbenes but also to activate alkynes by their intrinsic π-acidity.[2] Details on the sequence of metal carbene NH-insertion / Hydroamination will be provided during the presentation. On the other hand, in metal free conditions, the Michael acceptor properties of α-diazo-ynonesters **1** are harnessed to form hydroxypyrazoles **3** *via* a Hydroamination / Nucleophilic addition sequence.



Acknowledgments
The Swiss National Science Foundation for funding.

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Peptide Stapling with Anion-π Catalysts

A. Pham[1], N. Sakai[1], S. Matile[1]*

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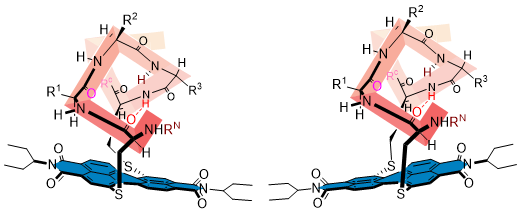
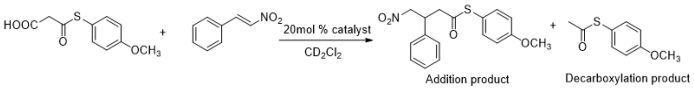
Cation-π interactions were reported to play a central role in variety of biological processes. One of the most important examples is the contribution of cation-π interactions in the enzymatic biosynthesis of terpenes and steroids using polyenecyclases.[1] In contrast, the complementary, counter interactions – anion-π interactions rarely occurs in nature. Even though, anion-π catalysis has emerged recently as a promising tool for performing a wide range of chemical transformations, most examples are limited only in the context of organic synthesis.[2] To examine the potential applications of anion-π interactions in more biologically relevant processes, we incorporated anion-π catalysts into several short peptides and evaluated their activities in catalysis.



Using naphthalenediimides (NDIs) as a covalent linker to staple one turn of α-helix allowed the formation of catalysts with relatively stable secondary structure. The catalytic activities of these catalysts in the addition of malonic acid half thioesters to enolate acceptors (MAHT reaction, Figure 2) are in agreement with an α-helix like structure.[3] Even though anion-π catalysis next to peptides occurs with record chemoselectivity, enantioselectivity was weak. To improve enantioselectivity of the system, perylenediimide (PDIs) was used to replace NDIs. Introducing substituents at bay-areas of PDIs led to twisting of the aromatic surface and added another dimension of chirality into the system (axial chirality). NMR studies supported helix-like structures of new catalysts. The catalytic performance of these catalysts could be improved with addition of aromatic electron deficient surfaces. These results encourage integration of aromatic electron poor motifs into designs of supramolecular systems for different purposes, including anion-π enzymes.



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Organic Molecules with Inverted Gaps between First Excited Singlet and Triplet States and Appreciable Fluorescence Rates

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One recent proposal for designing state-of-the-art emissive materials in organic light-emitting diodes (OLEDs) is thermally activated delayed fluorescence (TADF). The idea is to enable facile thermal upconversion of excited-state triplets, which are generated upon electron-hole recombination, to excited-state singlets. Minimizing the corresponding singlet-triplet energy difference facilitates devices with up to 100% internal quantum efficiency. Ideal emissive materials potentially surpassing TADF emitters should have both inverted singlet-triplet gaps (herein termed the INVEST property) and substantial fluorescence rates to maximize reverse intersystem crossing (ISC) rates from excited triplets to singlets while minimizing ISC rates and triplet state occupation, leading to long-term operational stability. However, molecules with negative singlet-triplet gaps are extremely rare, and until now none of them emissive. Herein, based on computational studies, we find molecules with negative singlet-triplet gaps and considerable fluorescence rates and show that they are more common than hypothesized previously.

Two recent publications appeared almost simultaneously, sparking new interest in INVEST molecules and their potential applications in OLEDs [1,2]. The two molecules reported were both based on phenalene with a distinct degree of nitrogen substitution. In these structures, the inverted gaps emerge as a result of both very small exchange integrals, due to minimal spatial overlap between the HOMO and the LUMO, and significant double excitation character in the electronic transitions leading to stabilization of the first excited singlet state relative to the first excited triplet state. Importantly, both reported INVEST molecules have symmetry-forbidden fluorescence from the first excited singlet, which makes them very inefficient emitters. Provided that INVEST molecules with appreciable fluorescence rates were found, they could have the potential to become the next generation of OLED materials. Based on computational evidence, we herein reveal many organic INVEST molecules with appreciable fluorescence rates. Overall, we observe that the singlet-triplet gap, the fluorescence rates, and the absorption wavelength can be tuned by modification, especially nitrogen substitution, of the phenalene core. We also observe that substitution with electron-donating and electron-withdrawing groups, via the “push-pull” effect can lead to azaphenalenes with increased fluorescence rates, while maintaining inverted singlet-triplet gaps. Finally, we observe that systematic optimization of substituted azaphenalenes for high oscillator strength, small singlet-triplet gap, and absorption wavelength leads to a rich chemical space of highly emissive INVEST molecules covering the entire visible light spectrum.

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Simple carbonyl a-deuterations via keteneiminium intermediates

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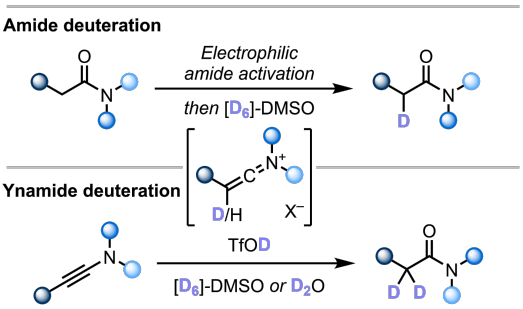
Isotope labelling is a powerful tool that enables the precise monitoring of specific atoms and as such, constitutes a common strategy to study and elucidate reaction mechanisms.[1] Importantly, the introduction of isotopic labels is also employed for the investigation of behavior and metabolic pathways of drug candidates.[2] Due to the kinetic isotope effect, deuterium incorporation in specific sites of drug molecules can slow down cytochrome P450 metabolism, optimize pharmacokinetic properties or reduce toxicity.[3] Expanding the synthetic toolbox to enable convenient and mild deuterium incorporation in organic molecules is, therefore, highly desirable.

Here, we present two recent methodologies developed in our team for the synthesis of deuterated amides and imides.[4,5] In both cases, the transformations hinge on transient keteniminium ions, formed either by electrophilic amide activation or by treatment of ynamides with a (deuterio)-Brønsted acid. As will be shown, the deuterated products were obtained in good yields with high degrees of deuterium incorporation.



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Asymmetric epoxidation and cyclopropanation using a catalytically formed chiral auxiliary

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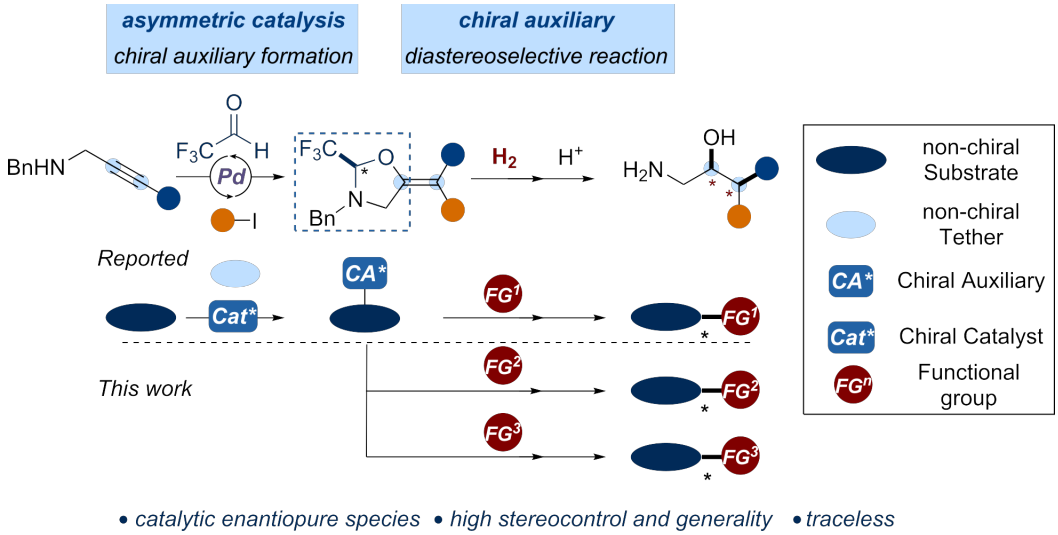
For the asymmetric synthesis of chiral molecules, one can either employ chiral auxiliaries or enantioselective catalysts. The fundamental difference between the two approaches is that for chiral auxiliaries the control of stereoselectivity is achieved without influencing the reactivity. Thus, chiral auxiliaries can be used to impart stereocontrol in multiple, mechanistically unrelated transformations. [1] However, this strategy suffers from the need of stoichiometric amount of enantiopure molecules, as well as low step and atom efficiency.
Recently we reported the concept of catalytically formed-chiral auxiliary (Scheme 1). [2] We developed an unprecedented Pd-catalysed DYKAT process for the enantioselective tethered carboetherification of propargylic amines using trifluoroacetaldehyde and aryl iodides. The installed stereocenter was then used to control a hydrogenation reaction. In the process precursors of highly biologically relevant amino alcohols were formed in enantio- and diastereodivergent manner. Here we report the use of the catalytically formed chiral auxiliary in asymmetric cyclopropanation and epoxidation.



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Cu(I)-Catalyzed *gem*-Amino Alkynylation of Diazo Compounds: Straightforward Synthesis of Fluorinated Propargylic Amines

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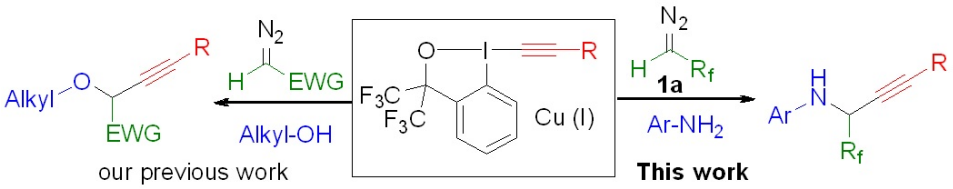
[1]Laboratory of Catalysis and Organic Synthesis (LCSO), EPFL

Fluorinated propargylic amines are versatile building blocks in medicinal chemistry due to the great synthetic versatility offered by the alkyne and fluorine groups. Traditional approaches for the synthesis of this type of compounds rely on the addition of metal acetylides to fluorinated imines,[1] or the reduction [2] of alkyne-substituted fluorinated ketimines, among other examples. Nevertheless, the imines used in these methods are often unstable and need to be prepared *in situ*. In this context, the use of fluorinated diazo compounds has been well described in Multi-Component Reactions involving amines as nucleophiles for the synthesis of different building blocks.[3]

To access the propargylic amines from diazo compounds and amines, the use of an electrophilic alkyne transfer reagent would be necessary. Our group has experience in the use of ethynylbenziodoxol(on)es (EBX) as electrophilic alkynylation agents. Recently, we have reported the three-component reaction between diazo compounds, EBX and alcohols as nucleophiles.[4] Herein, we report the extension of this multi-component reaction to anilines, resulting in the straightforward synthesis of fluorinated propargylic amines catalyzed by a simple Cu(I) salt.[5]



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Diversification of Phosphine Ligands by Formal Substitution at Phosphorus

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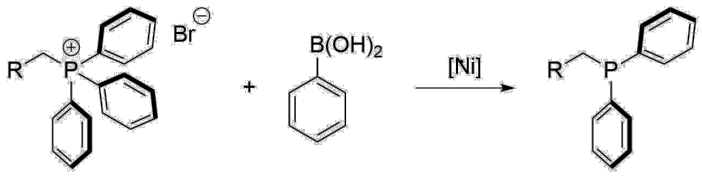
Ligands tune the reactivity of transition metal catalysts by imposing steric bulk in proximity of the reactive center and modifying the electronic properties of the metal. The design of new ligands is a major driving force in the development of more active catalysts and helps to unlock novel reactivity modes.

Phosphines are a privileged class of ligands because of their high tunability. A variety of phosphine ligands is commercially available, but their structural diversity is quite limited in many aspects. The synthesis of phosphine ligands is often cumbersome and requires handling of highly reactive and toxic building blocks. As a result of this, many chemists only evaluate commercial ligands for the design of new reactions and might therefore fail to identify more active or selective catalysts.

It has been shown that tetraarylphosphonium salts can be engaged as electrophiles in a range of cross coupling reactions, delivering functionalized arenes.[1–3] These reactions presumably also generate phosphines as byproducts, but the synthetic utility of this process has not been realized so far.

We report a novel synthesis of phosphines that allows to selectively introduce a diverse range of alkyl groups into phosphine scaffolds. Alkylarylphosphonium salts are selectively dearylated in a nickel-catalyzed Suzuki reaction to form alkylated phosphine products.



The phosphonium salt starting materials can be prepared by a simple alkylation reaction of the starting phosphine. The overall process can therefore be described as a formal substitution of aryl for alkyl groups at the phosphorus center and provides a straight forward process for the structural diversification of phosphines to access new ligand space.

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Reversible Michael Acceptors for Thiol Mediated Cellular Uptake and Inhibition

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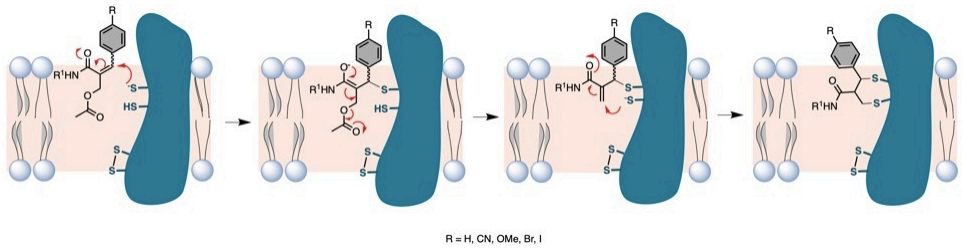
Michael acceptors have been widely used for thiol labeling and disulfide modifications of proteins.[1] Variations of the structure of Michael acceptors allow their use for nonreversible and reversible modifications. For example, covalent binding to thiols allows the development of targeted inhibitors[2], while reversible thiol-Michael addition gives access to self-healing hydrogels[3] or real-time imaging of biological thiols.[4] Thiol-mediated cellular uptake (TMU) relies on exofacial thiols at the cell surface to perform cytosolic delivery.[5] The dynamic character of thiol addition to Michael acceptors makes them promising candidates for TMU. In our work we use benzalcyanoacetamides as reversible and irreversible inhibitors of TMU. Where substituents on the phenyl ring play an important role in their reactivity towards thiols.[6] Moreover, modifying the structure by introducing a leaving group, such as acetate, in β position results in divalent reversible Michael acceptors. Which can be used for cascade exchange reaction with vicinal thiols to also perform intracellular delivery.



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Induced Axial Chirality by a 2,5-Substituted Cofacial *para*-Phenylene-Ethynylene Framework

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Chiral chromophores belong to a group of molecules that have caught the attention of chemists for years. Combining spectroscopic properties of chromophores (e.g., absorption and luminescence) with chirality induces remarkable properties such as circular dichroism (CD) and circularly polarized luminescence (CPL). Chiroptical materials that have found application in technology are often self-assembled nanostructures or polymeric aggregates.[1] This way, powerful chromophores such as rylenes, porpyhrins or other polyaromatic hydrocarbons, which are usually planar and therefore inherently achiral, can be assembled in chiral superstructures, and thus be equipped with the respective chiroptical properties. However, compared to higher ordered structures, single chiral molecules have some important advantages, such as higher solubility and easier synthetic access.[2] Inspired by this, we envisioned to induce chirality into planar chromophores by designing a rigid framework that allows bringing four achiral chromophores in a fully optically stable chiral environment and excitonically couples the chromophoric transitions. Using 6-methoxynaphthalene as a model chromophore, we present the synthesis, structural analysis and spectroscopic investigation of our designed framework, and show that this simple yet potent framework might prove useful to enrich the structural diversity of chiral materials.[3]

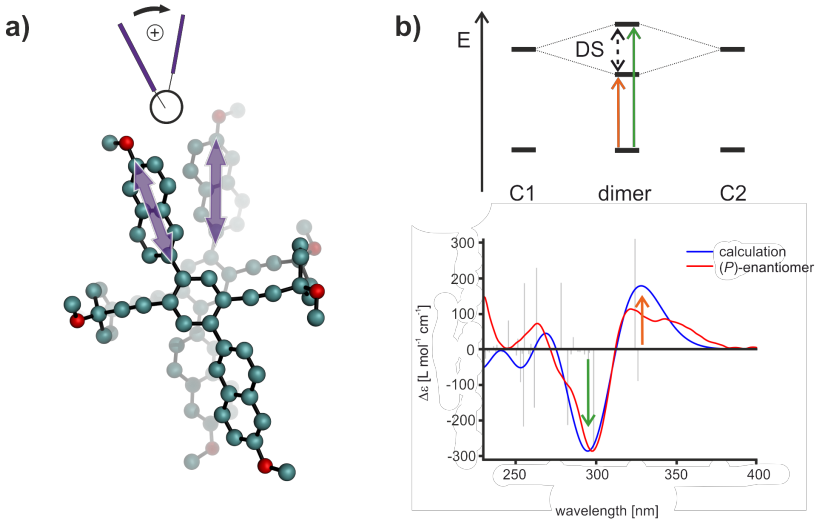

Figure 1: a) Representation of the (*P*)-enantiomer and the chromophores associated transition dipole moments. b) *Top*: Energy diagram of the transitions of isolated chromophores (C1 and C2) and the resulting *Davydov* splitting (DS) upon dimerization in a chiral configuration. *Bottom*: The calculated and measured CD spectra of the (*P*)-enantiomer showing the bisignate signal due to the DS.

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Radical azidation of cyclopropenes for the synthesis of quinolines

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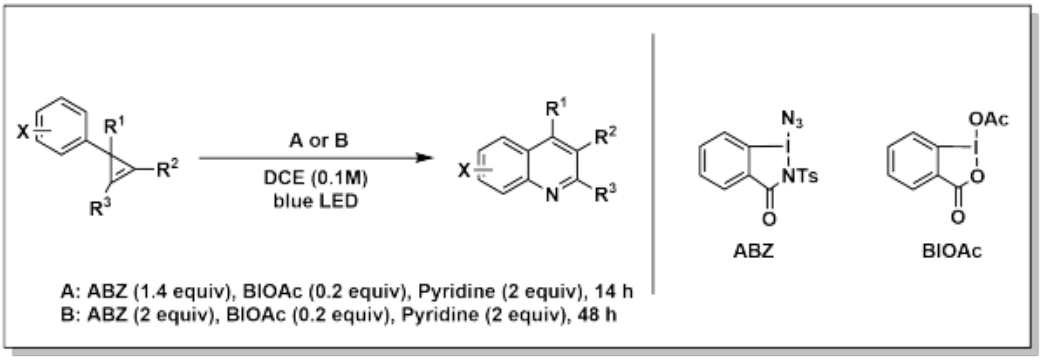
Cyclopropenes represent the smallest cyclic alkenes. Due to the simultaneous presence of ring strain and the double bond cyclopropenes are unique 3-carbon synthons in organic synthesis. Starting from the 1950s, many synthetic methods that involve cyclopropenes have appeared.[1] Nevertheless, reactions relying on the addition of radicals to cyclopropenes remain scarce. Therefore, our group became interested in these transformations.[2] Herein, we report a radical azidation of cyclopropenes leading to the formation of quinoline products. The transformation is enabled by the use of the safe hypervalent iodine(III) azidating reagent (ABZ) under blue LED irradiation. The utility of the transformation was demonstrated by the synthesis of diversely substituted quinoline products.



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Optimized iminium-catalyzed 1,4-reductions inside the resorcinarene capsule: Achieving >90% *ee* with proline as catalyst

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The self-assembled resorcinarene hexamer **I** (Fig. 1a), first reported by Atwood[1] in the solid state in 1997, assembles from six resorcinarene units **1** and eight water molecules. It can entrap guest molecules temporally inside its cavity due to the dynamic nature and is used in catalysis.[1–3] In 2016, our group reported that iminium-catalyzed 1,4-reduction of α,β-unsaturated aldehydes can be performed inside capsule **I** (Fig. 1b).[4,5]

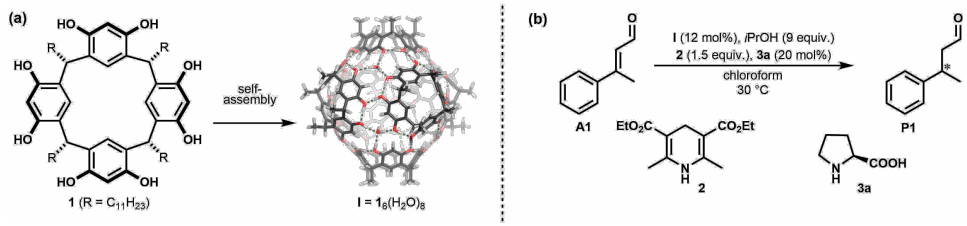

Figure 1. (a) Self-assembly of monomer **1** into hexameric capsule **I**. (b) General scheme of iminium-catalyzed 1,4-reduction inside capsule **I**.

Our understanding of capsule **I**-catalysis improved substantially over the last years. For instance, the importance of HCl as a co-catalyst for a selection of reactions inside **I** was elucidated.[6] However, the influence of HCl on iminium-catalyzed reactions inside **I** remains unknown. We here report the results of (1) elucidating the role of HCl for the iminium catalysis inside **I**; (2) reducing the amount of capsule catalyst required; (3) optimizing the reaction conditions to improve the enantioselectivity.

As a highlight of these studies, unprecedented enantioselectivity (up to 92% *ee*) was achieved for the 1,4-reduction of α,β-unsaturated aldehydes inside capsule **I** using simple L-proline as the sole source of chiral information. This is of high interest as proline in a regular solution setting is unable to deliver high enantioselectivity for 1,4-reductions.[7]

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Non-innocent electrophiles unlock exogenous base-free coupling reactions

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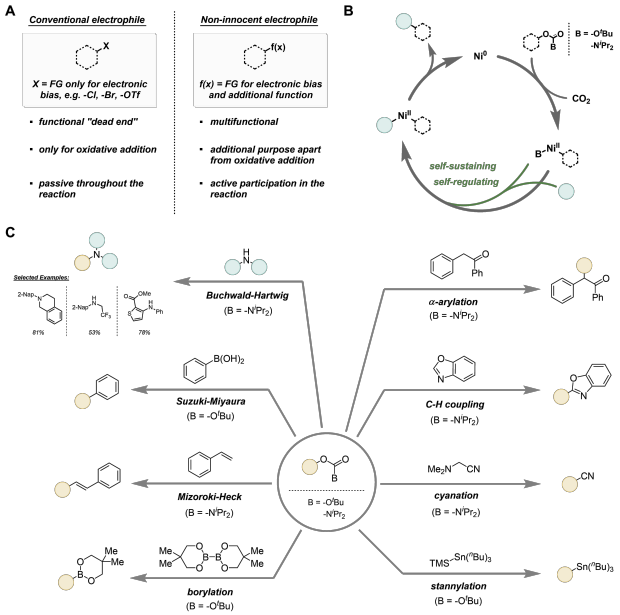
Electrophiles are key parts in countless catalytic reactions and serve almost exclusively two general purposes through their functional group: first, locating the bond-forming site at the corresponding substrate and second, providing the electronic bias for the initiation of the catalytic cycle. Apart from that, such conventional electrophiles are passive throughout the reaction rendering the functional group and the corresponding prior synthetic efforts to install it highly sacrificial. This work introduces the concept of non-innocent electrophiles, a class of multifunctional electrophiles endowed with a functionality which actively participates in the reaction after oxidative addition (Fig. 1A). This concept was used as a platform for the development of exogenous base-free coupling reactions. Considered an inherent requisite for catalytic turnover in numerous transition metal catalyzed couplings, the use of stoichiometric bases simultaneously affects this class of reactions by limiting the accessible chemical space, generating additional waste, and oftentimes rendering reaction conditions heterogeneous thereby restricting the application of emerging technologies such as flow chemistry or high-throughput experimentation. Therefore, a general approach that eludes the need for exogenous bases in coupling reactions would be beneficial in various aspects. In summary, the study confirmed the hypothesis and diisopropylcarbamates as well as *tert*-butyl carbonates were found to release a competent base after oxidative addition. Notably, this catalytic release mechanism generates the base on-demand, establishing self-sustaining catalytic systems with intrinsic self-regulation and efficiently overrides the deleterious effects caused by the use of an exogenous base. As a result multiple coupling reactions (8 distinct reactions) which traditionally rely on the addition of stoichiometric base could be turned into exogenous base-free, homogeneous processes, that were compatible with base-sensitive functional groups. Importantly, C–H/C–O coupling scenarios proved feasible representing a promising avenue for sustainable catalysis (Fig. 1B and 1C).[1]



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Enabling Cyclization Strategies through Carbonyl Ylide Mediated Synthesis of Malonate Enol Ethers

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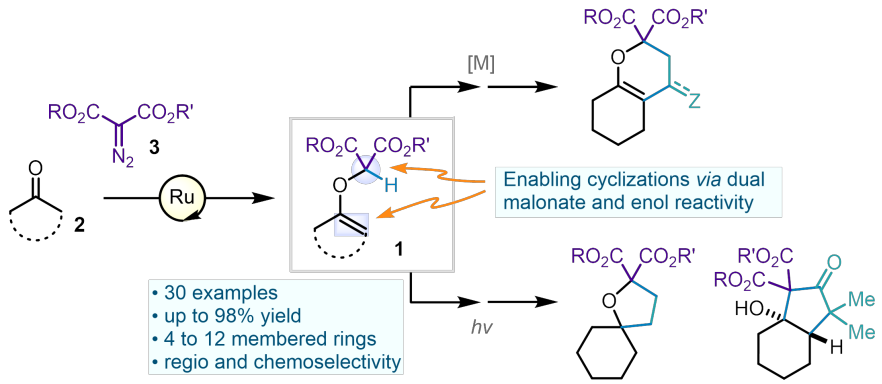
Diazo reagents substituted with two electron-withdrawing groups are amongst the most stable diazo derivatives,[1] amenable yet to decomposition reactions that form highly reactive electrophilic carbenes.[2] In this context, combinations of $[CpRu(CH_3CN)_3][X]$ (X= PF_6 or BAr_F) salts and diimine ligands can be used as catalysts and original reactivities are then afforded for the resulting metal carbenes.[3]

Herein, with α-diazodiesters as reagents, we report the effective formation of malonate enol ethers **1** by condensations of ketones **2** with metal carbenes derived from α-diazomalonates **3** and $[CpRu(CH_3CN)_3][BAr_F]$ as catalyst. Malonate enol ethers **1** of different ring sizes and geometries are obtained in good to excellent yields, often as single regioisomers, and their mechanism of formation is elucidated based on DFT calculations. Furthermore, they are interesting building blocks for annulation strategies and several fused and spiro heterocycles are generated under Lewis-acid mediated conditions or visible light photoredox catalysis. The dual reactivity of these 2-vinyloxymalonates can be used to expand the classical range of cyclizations derived from carbonyl ylide intermediates.



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Methylthio-benzothiazole based self-assembled monolayer for quantitative functionalisation by thiolated substrates.

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Various thin films consisting of linker molecules interconnecting a silicon surface to a functionality of interest on the respective silicon surface were previously reported.[1] Post modifications of these thin films with alkylthiols is a great challenge up to today and requires ether tedious multistep processes or low yielding reaction steps.[2,3] To increase the yield and reduce the reaction time required for thiol nucleophile based post modifications, we present a novel benzothiazole based linker. The chemisorption of this methylthio-benzothiazole based linker produces a thin film passivating the surface. Subsequently, the passivated thin film is activated by an oxidation. The activated thin film, in contrast to the beforehand passivated thin film, provides high reactivity towards nucleophiles, in particular thiols. Most importantly, this novel benzothiazole based linker provides convenient access to silicon thin film functionalization using thiol nucleophiles (even alkyl thiols) without the need for tedious multistep processes. All solid phase reactions were monitored and analysed by contact angle goniometry and X-ray photoelectron spectroscopy (XPS) and compared to their by classical batch synthetic method synthesized deposited analogue.

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Oxidative Ring-Opening Reactions of Aminocyclopropanes

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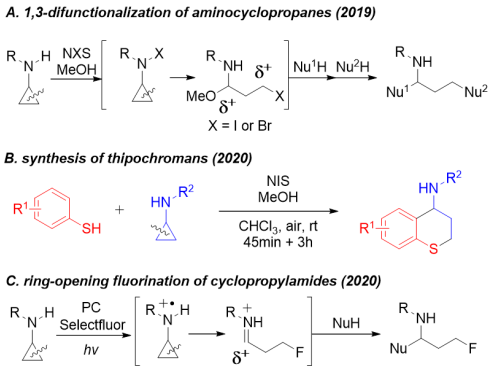
Aminocyclopropanes are important building blocks in synthetic chemistry. Their reactivity was explored mainly by utilizing transition-metal catalysis to form a metallocyclobutane intermediates, or by photoredox chemistry to oxidize the amino group to a radical cation species.[1] Our group has focused in the past on the ability of donor-acceptor substituted aminocyclopropanes (D-A aminocyclopropanes) to react as zwitterionic synthons[2] and recently, we reported a different strategy for the activation of mono-substituted aminocyclopropanes giving access to biscationic synthons (Figure 1A).[3] We further demonstrated the synthetic utility of this strategy by applying it for the efficient synthesis of 4-aminothiochromans (Figure 1B).[4]



We herein reported a mild ring-opening fluorination of cyclopropylamides enabled by photoredox catalysis (Figure 1C).[5] The amide nitrogen was oxidized to form a radical cation species which induced ring opening fluorination by reacting with F^+ source like Selectfluor. Introducing a series of nucleophiles to the imine carbon center can be done under acidic conditions, thus generating a wide range of 3-fluorinated propylamides in one pot.

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Synthesis of Carpyridines

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Porphyrins are a well-researched class of aromatic chromophores due to their range of uses as ligands in biology and roles in larger supramolecular structures,[1,2] as well as their electronic and optical properties.[3,4] A largely unexplored but related construct are macrocycles composed of pyridine and carbazole subunits, initially reported by Müllen,[5] which we term ‘carpyridine’. The inclusion of two oppositely facing five membered rings within the carbazole moiety allows carpyridines to exhibit a negative curvature, which is confirmed by crystallography.[5] Despite bending within the macrocycle, the cavity still provides a vacancy for coordination to a metal adopting a square planar geometry. Unoccupied axial sites of a coordinated metal present an opportunity for metal-metal interactions with other monomers to take place such that a relay of communication may occur between units and should be evident upon inspection of optical properties. Several metals have been successfully coordinated into these carpyridines through use of microwave radiation at elevated temperatures and this has a stark effect upon the photochemical properties of the system (Figure 1).

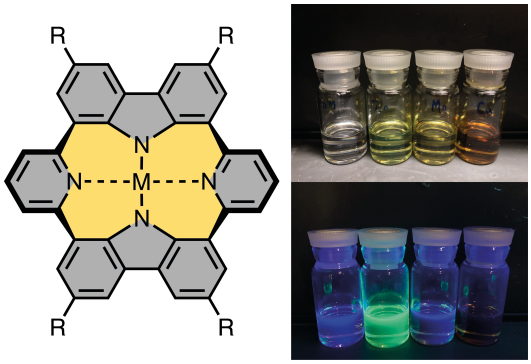

Figure 1. A tuneable carpyridine monomer, left, and photographs of metalated carpyridines, right, under 365 nm irradiation (bottom) and by eye (top).

Modification of carpyridine side chains will also alter the behaviour of the monomers, and in turn, an effect is had upon the optical properties. Bulky, branched groups (R = *t*Bu) will prevent aggregation due to steric crowding whereas linear alkyl chains (R = *n*-$C_{12}H_{25}$) promote association and may lead to aggregation induced emission in the absence of a metal or quenching with the inclusion of one.

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Atropo-Enantioselective Oxidation-Enabled Iridium(III)-Catalyzed C–H Arylations with Aryl Boronic Esters

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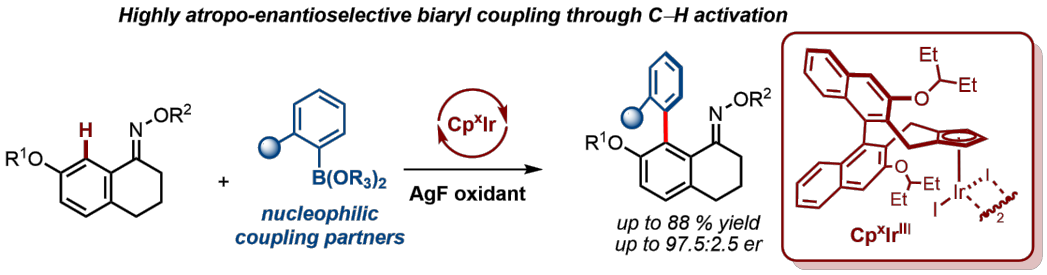
[1]EPFL SB ISIC LCSA

Atropo-enantioselective biaryl coupling through C–H bond functionalization is an emerging technology allowing direct construction of axially chiral molecules. [1] This strategy directly forges the chiral axis from simple precursors, however, the hefty steric requirements to form stable atropisomers is a challenge for the catalyst performance and requires a very high efficiency to accommodate such hindered substrates. We and others reported capable Pd-, Ir- and Rh-catalysts, which enable highly atropo-enantioselective C–H arylation with electrophilic coupling partners namely aryl bromides and quinone diazides. [2-4] An attractive, complementary choice of coupling partners would engage widely available and versatile carbon nucleophiles such as aryl boronic esters and silanes. This approach, however, is largely underdeveloped. [5]

Herein, we present a highly atropo-enantioselective C–H arylation of tetralone derivatives paired with aryl boronic esters as nucleophilic components. [6] The transformation is catalyzed by chiral cyclopentadienyl (Cp^x) iridium(III) complexes and enabled by oxidatively enhanced reductive elimination from high-valent cyclometalated Ir-species. [7] The method provides an efficient access to unexplored atropochiral oxime-derived α-tetralones, as well as chromanone and flavone products. Moreover, this exemplifies that oxidation-induced eliminations are suitable to improve catalytic performance of otherwise relatively stable chiral cyclometalated Cp-iridium(III) complexes.



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Direct Photochemical C(sp^3)-H Fluorination of Complex Molecules via a Photosensitized Auxiliary Approach

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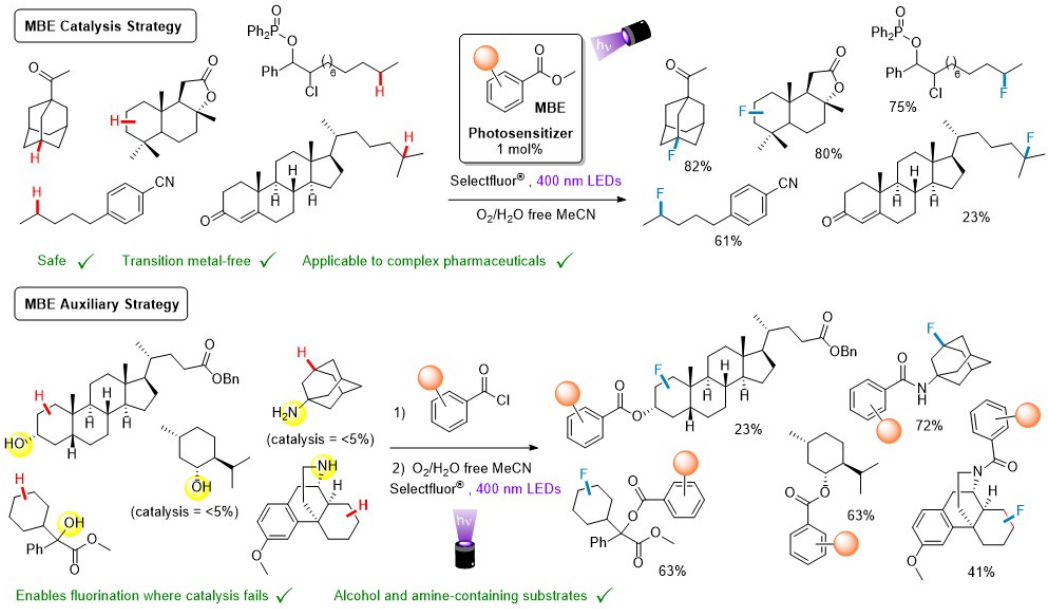
Exchanging a hydrogen for a fluorine atom profoundly increases the stability, bioavailability and lipophilicity of organic molecules in a biological system, as well as providing a handle for their radiolabelling. The privileged nature of fluorinated compounds in pharmaceutical and agrochemical sciences has demanded new and improved synthetic fluorination strategies, of which direct C(sp^3)–H fluorination is the most ideal. Although numerous methods exist for fluorinations,[1] few allow the direct fluorination of unactivated C(sp^3)–H bonds[2,3] and of these many rely on precious transition metal catalysis. Photochemical C–H fluorination with cheap organic photosensitizers allows alternative selectivity by a radical mechanism, which operates under mild, ambient conditions. Seminal reports by the groups of Chen and Tan achieved direct, unactivated C(sp^3)-H fluorinations using anthraquinone or acetophenone as photosensitizers.[4,5] However, reactivity and selectivity were restricted by the innate reactivity of substrate molecules. Alcohol and amine containing substrates generally required protection for success. Herein, we report the discovery of a modified benzoate ester (MBE) as a novel photosensitizer. As an exogenous photosensitizer catalyst, MBE effects the C(sp^3)-H fluorination of a range of substrates including complex molecules (29 examples, 24-82% yields). A key advantage of MBE as a photosensitizer compared to previous approaches,[4,5] is its use as an 'auxiliary' that can be attached to alcohol and amine containing substrates. Our auxiliary method enables the fluorination of a much broader scope of substrates including those where the catalytic method failed, corroborating a pre-association of the MBE and Selectfluor to increase reactivity.



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Synthesis of Twisted Triaryl Amines

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In the past 60 years, Triarylamine (TAA) based covalent polymers have been studied extensively due to their attracting electronic and optical characteristic[1]. However, the examples of TAA type supramolecular polymers have been reported very recently. For example, Giuseppone group achieved columnar supramolecular stacks in 2010 by adding supplementary hydrogen bonding moieties such as amide group in periphery[2] and illustrated that the associated supramolecular polymerization mechanism involves a nucleation step of high activation energy, which requires the flattening of the triarylamine core. This mechanism suggests the core structure of building block is crucial for supramolecular assembly order. However, it is still unclear that can we quantitatively control or predict the supramolecular self-assembly by adjusting the core.

To figure out these questions, we need more complicated core units that can introduce different parameters such as geometry, steric hindrance, size and flexibility. Thus, we proposed a series of twisted TAA cores (Figure 1), which have a secondary alkyl linkage of different length (C1-C3) that connects each aryl with its neighbor. These building blocks will be useful for investigating the relationship between the distortion of the flat surface and the observed degrees of supramolecular order after lateral modifications.

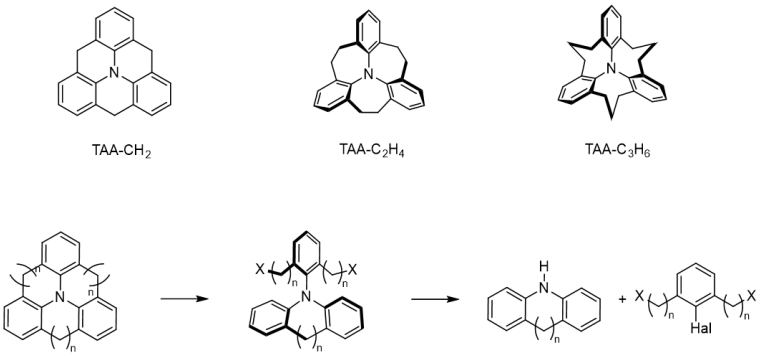

Figure 1. Retrosynthesis analysis of twisted TAA family.

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Photo-induced Charge Transfer in Azapyrene-Tetrathiafulvalene Triads

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Tetrathiafulvalene (TTF)-based donor-acceptor (D–A) ensembles have attracted a lot of attention due to their unique (opto)electronic properties and potential applications in organic semiconductors, photovoltaics, sensors, switches and molecular electronics.[1-3] To develop high-performance electronic devices, control over multiple charge-transfer (CT) pathways in D-A ensembles is of prime importance. Recently, we have demonstrated chemical and ultrafast optical regulation of distinct photo-induced charge flows within such D-A systems.4,5 As a continuation of our ongoing work, we herein describe redox and optical properties of new D–A ensembles (Chart 1) which were prepared by covalent linkage of two TTF donor units to a central azapyrene acceptor either with or without two tert-butyl groups. A detailed experimental and theoretical study of electronic interactions between D and A units and ICT processes in these triads is presented.

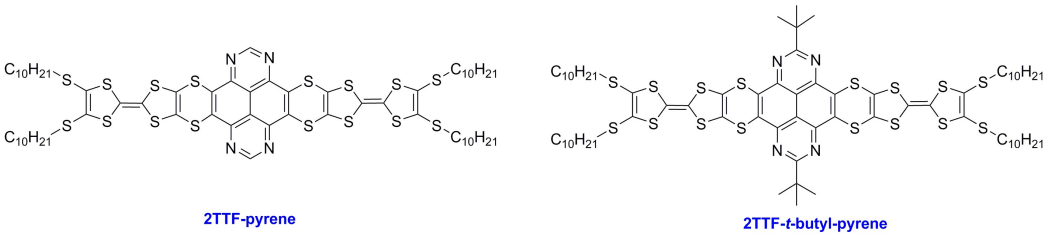

Chart 1. Chemical structures of triads 2TTF-pyrene and 2TTF-*t*-butyl-pyrene.

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Palladium(0)-Catalyzed Enantioselective Intramolecular Arylation of Enantiotopic Secondary C–H Bonds

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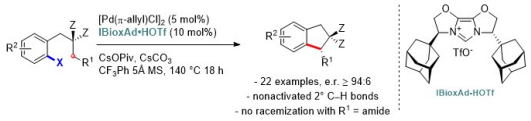
Enantioselective C–H activation is a current topic of high interest providing access to structures of great complexity from easily accessible precursors in a step economical manner. Despite efforts from the Cramer, Kündig, Kagan and our group in asymmetric Pd^0-catalyzed C–H activation, methods where the stereogenic center is formed at the activated site remain scarce.[1] The synthesis of β-lactams by activation of benzylic C(sp^3)–H bonds by Cramer remains the only example to this date.[2] Herein, we report the highly enantioselective synthesis of indanes using IBiox-type NHC[3,4] ligands.



High yields (up to 95%) and enantioselectivies (e.r. up to >99:1) were obtained across a variety of products. The reaction tolerates a wide range of substituents including electron donating and withdrawing groups on the aromatic part and different functionalities on the chain undergoing C-H activation. Additionally, the synthesis of tertiary amides with a labile stereogenic center was achieved without erosion of enantioselectivity. [5]

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