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Photoredox-catalysed Decarboxylative Alkynylation and Cyanation Using Cyclic Hypervalent Iodine Reagents

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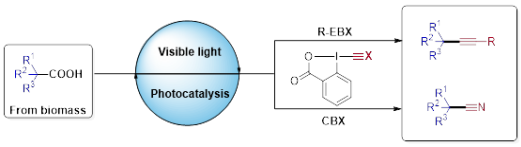
Photocatalysis has been gaining interest over the past decade. This new activation mode of small molecules has led to the development of various reaction strategies for accessing radical intermediates under mild reaction conditions, especially using decarboxylation. Carboxylic acids are preponderant in biomass, which makes them easily accessible and cheap starting materials for chemical transformations. Following earlier work using stoichiometric oxidants, photoredox catalysis has proven well adapted for initiating decarboxylation under mild environmentally friendly conditions.[1]

The alkynyl and cyano moieties are valuable as building blocks in organic synthesis. Developing new methods to introduce them into organic compounds has become one of the main research interests of our group. Recently, we developed a new method towards alkynylation[2] and cyanation[3] of carboxylic acids by combining an iridium photoredox catalyst with benziodoxolone reagents as privileged radical traps.[4] Herein, we will present our latest advances on decarboxylative functionalisation under metal free conditions.



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Development of Mild Procedure for Metal-Cp Complex Preparation to Enable in-situ Applications

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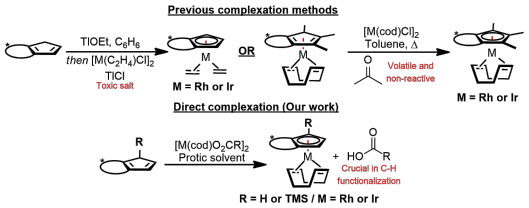
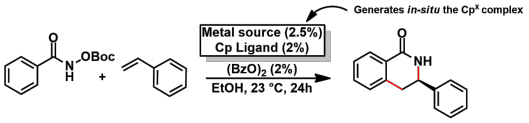
The cyclopentadienyl (Cp) ligand and its pentamethylsubstituted derivatives are of fundamental importance in organometallic chemistry.[1] In the last six years chiral Cp (Cp^x) versions have been designed and applied in atom-economic transformations, notably in C-H functionalization.[2] However, synthesis of chiral Cp^x metal complexes relies on undesirable reaction conditions, for example involving thallium alkoxide in benzene or requires derivatization.[3-4] We present here a novel method for the synthesis of highly valuable Rh(I) and Ir(I) Cp^x complexes (**Figure 1**). The newly formed complexes are obtained in high yields and enabled the synthesis of previously inaccessible ligand frameworks. Moreover, the new Cp^x complexes isolated via our methodology should promising results for known and future enantioselective processes.



This mild procedure allows *in-situ* formation of Cp^x complexes and can be directly subjected to further catalytic transformations without any purification (Figure 2). Particularly, the developed complex preparation would allow a rapid screening of chiral Cp^x backbone and carboxylic acids. The latest are notably known for being crucial in C-H functionalization proceeding through a concerted metalation-deprotonation (CMD) pathway.



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4-Epimerization of ascarosides downstream of the canonical β-oxidation cycle creates species specificity in nematode chemical signalling

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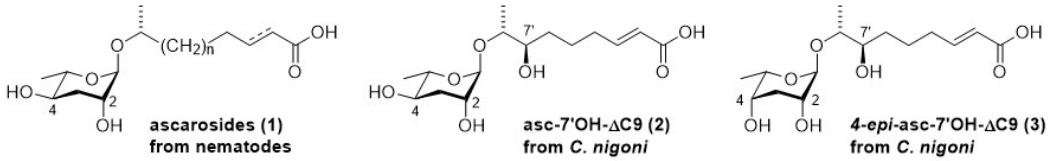
Nematodes like the model organism *Caenorhabditis elegans* excrete a large diversity of small molecules into their environment. The ascarosides (**1**), glycolipids of the 3,6-dideoxysugar L-ascarylose linked to fatty-acid aglycones derived from the peroxisomal β-oxidation cycle, are conserved in nematodes and regulate their behaviour and development. Small structural alterations of the side chain or the attachment of additional building blocks downstream of the β-oxidation cycle can dramatically change the biological activity of the ascarosides.[1]



We have previously developed mass spectrometric screens that facilitate the comprehensive detection of known as well as yet unidentified ascarosides in crude nematode exometabolome extracts. Comparative MS screening revealed some highly conserved components and facilitated the identification of species-specific ascaroside derivatives from *Caenorhabditis nigoni* including asc-7'OH-ΔC9 (**2**), which carries an (ω – 2)-hydroxylated aglycone.[2] Here, we describe the isolation and identification of the epimeric *4-epi*-asc-7'OH-ΔC9 (**3**) from *C. nigoni*. To confirm the structure assignment and obtain material for functional characterization, *4-epi*-asc-7'OH-ΔC9 (**3**) was synthesized by a 16 steps convergent synthesis. The *threo*-configured aglycone was prepared in 6 steps from methyl D-lactate while the *4-epi*-ascarylose building block was obtained in 8 steps from L-rhamnose using a regioselective epoxide ring-opening. The novel *4-epi*-asc-7'OH-ΔC9 (**3**) represents the first natural product carrying a 3,6-dideoxy-L-*lyxo*-hexose (*4-epi*-ascarylose) building block and reveals how nematodes utilize epimerization of the ascarylose moiety downstream of the canonical β-oxidation cycle to generate species-specific signalling components.

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Control of Through-Space Spin Interactions in Diradical Systems

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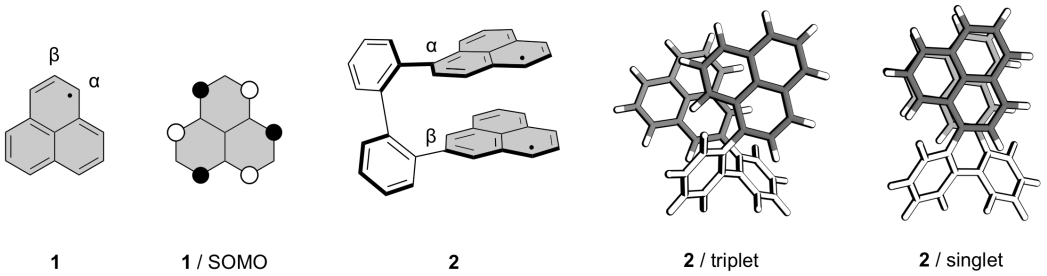
Spin-delocalization is a characteristic of π-conjugated systems that contain one or more unpaired π-electrons. A typical example of spin-delocalized systems is phenalenyl[1] (**1**), where one unpaired electron is delocalized uniformly between six positions (see the shape of the singly occupied molecular orbital (SOMO) of **1**). A unique feature of these systems is that they can form multicenter bonds[2] between cofacially oriented spin units, if the overlap between the SOMOs is favorable. The purpose of the current study is to investigate this bonding motif in dimeric diradical systems such as **2**, where two phenalenyl units (gray) are held in a close proximity to one another by an oligo-*ortho*-phenylene[3] spacer (white), which only allows the spin units to interact through space. This spacer also provides these systems with flexibility as well as ability to adopt a helical geometry, where the spin units are positioned on top of each other. The first aim is to find out which linkage pattern (αα, αβ (shown), or ββ) results in systems with a parallel orientation of the spins in the ground state (triplet), and which in systems with antiparallel orientation of the spins in the ground state (singlet). The poster presentation will include the synthesis of these target model compounds and the preliminary investigations of their properties and dynamics.



1 **1** / SOMO **2** **2** / triplet **2** / singlet

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Rapid and scalable synthesis of chiral bromolactones as precursors to α-exo-methylene-ϒ-butyrolactone-containing sesquiterpene lactones

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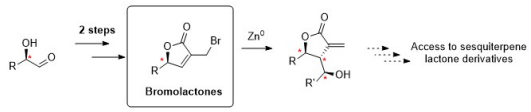
The sesquiterpene lactones cover a diverse and pharmacologically important diversity space. In particular, the electrophilic α-exo-methylene-ϒ-butyrolactone moiety that is preponderant in this natural product family has been shown to readily engage in covalent inhibition *via* conjugate addition of a cysteine residues in the target protein. However, the synthetic accessibility of sesquiterpenes or relative probes to investigate their mode of action remains laborious. Herein, we present a rapid and scalable route to chiral bromolactones as enabling precursors in the synthesis of sesquiterpene lactones.



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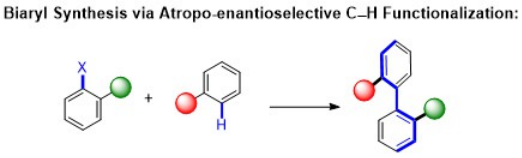
Axially Chiral Dibenzazepinones via a Pd(0)–Catalyzed Intramolecular Atropo-enantioselective C-H Arylation

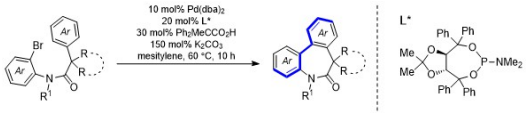
E. Braconi[1], C. G. Newton[1], J. Kuziola[1], M. D. Wodrich[2], N. Cramer[1]*

[1]Laboratory of Asymmetric Catalysis and Synthesis, [2]Laboratory for Computational Molecular Design, Ins

Atropoisomers are an important motif in a wide range of natural products and pharmaceuticals,[1] as well as in the field of asymmetric catalysis.[2] The conformational stability at the biaryl axis is the decisive factor in governing the pharmacological behaviour or chirality transfer properties of these molecules. In particular, axially chiral dibenzazepinones represent an interesting target, considering the importance of related benzazepinone and dibenzodiazepine containing drugs.



Despite their importance, atropo-enantioselective C–H functionalization approaches toward axially chiral molecules are rare and usually involve C–H functionalization *ortho* to an existing biaryl axis.[3] In contrast, controlling atropo-enantioselectivity, while simultaneously introducing the axis of chirality, appears significantly more challenging. Herein we report a highly atropo-enantioselective synthesis of dibenzazepinones *via* a palladium–catalyzed C–H functionalization.



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Enantioselective trifluoromethylation using hypervalent iodine based reagents : reaction development and mechanistic studies.

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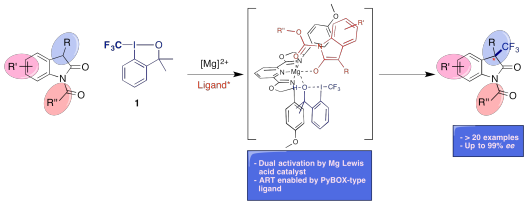
[1]Department of Chemistry and Applied Biosciences, Swiss Federal Institute of Technology, ETH Zürich

Taming highly reactive electrophilic CF_3 radical species to enable the construction of enantioenriched trifluoromethylated quaternary carbon centers remains a formidable challenge in the field of organofluorine chemistry. Herein, we report an asymmetric radical transformation (ART) exploiting hypervalent iodine reagent **1** as a CF_3 radical source in combination with a magnesium catalyst and a chiral PyBOX type ligand to generate trifluoromethylated oxindoles with excellent enantioselectivity.[1] Crucial to the reaction's success is magnesium's dual role as a Lewis acid, activating both reagent **1**, and the oxindole substrate.[2] The reaction demonstrates a versatile scope with consistently high *ee* values (90-99%) and excellent yields (up to 97%), and could be extended to the introduction of longer perfluoroalkyl chains. The reaction mechanism was probed *via* computational means, which corroborate with key experimental evidence in support of a radical reaction pathway. DFT calculations reveal that the transition state corresponds to an open shell singlet in which one part of the spin density lies on the CF_3 moiety, while the other resides on the oxindole. CF_3 radical transfer is believed to occur through an S_N2-type mechanism.[1]

The use of magnesium as a suitable activator for this class of hypervalent iodine reagents is unprecedented, and furthermore, reports on enantioselective trifluoromethylation using such reagents remain exceedingly scarce.[3] We anticipate that this study will offer valuable mechanistic insights to guide future efforts towards the realization of asymmetric perfluoroalkylation.



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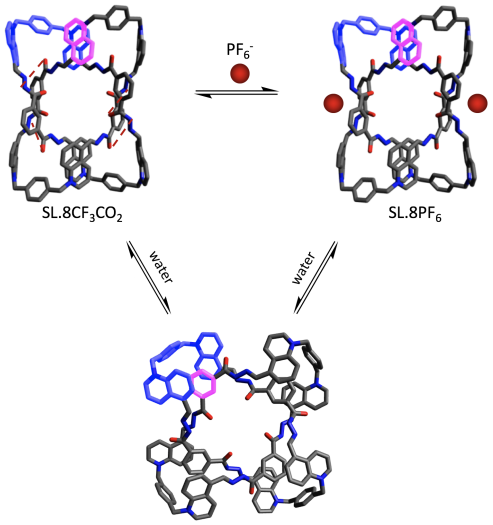
High cooperativity in a molecular switch

K. caprice[1]

[1]Departement of Organic Chemistry

Conventional approaches to the synthesis of molecular knots and links mostly rely on metal-templation[1-3]. We present here the formation of a Solomon link based on our strategy in which the hydrophobic effect[4,5] is the driving force for the synthesis of mechanically interlocked structures. The Solomon link produced is a switchable product which can adopt two different geometry. One stabilized by internal hydrogen bounding or binding to PF6 and the other one by binding to water.



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Catalyst-Controlled Stereodivergent Synthesis of Atropisomeric Multiaxis Systems

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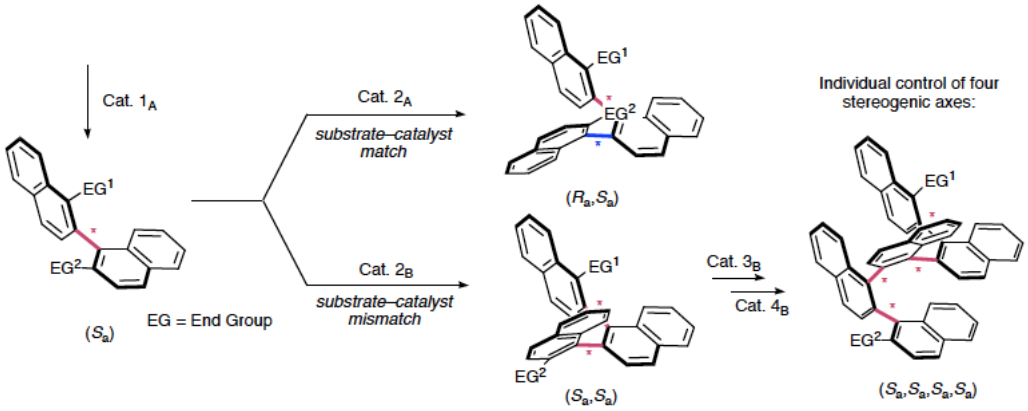
[1]Department of Chemistry

A well-defined spatial orientation of substituents in a molecular framework is an essential requirement for the synthesis of molecular systems with unique properties and applications. Due to their configurational stability, oligo-1,2-naphthylenes are particularly suitable to organize groups in space. A method that controls the configuration of each stereogenic axis is thus highly desirable. The poster outlines our approach for the stereodivergent synthesis of atropisomeric multiaxis systems based on the sequential addition of a building block to an aromatic aldehyde precursor, followed by an in situ double oxidation and stereoselective arene-forming aldol condensation. In order to overcome the substrate bias to divert atropodiastereoselectivity, efficient amine and ion-pairing catalysts that allow to individually control up to four stereogenic axes were identified.



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A Chiroptical and Magnetic Diradicaloid Photoswitch

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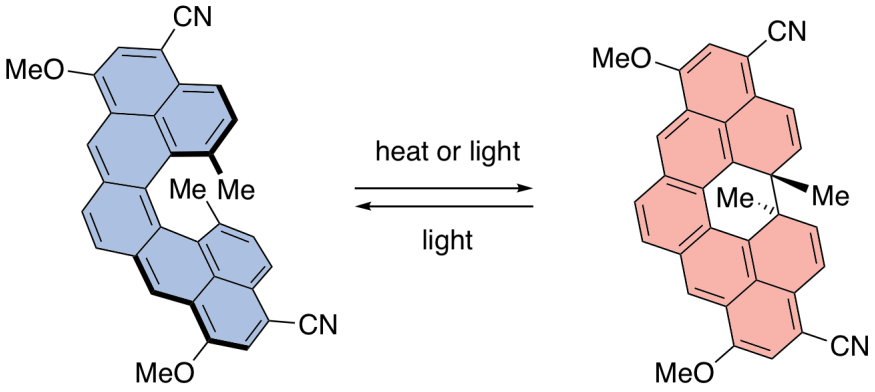
Cethrene[1] (highlighted in blue) is a helically twisted π-conjugated hydrocarbon with a Kekulé diradicaloid structure, characterized by a small HOMO–LUMO gap and a low-lying triplet excited state, which can be populated thermally. While the first characteristic results in a partial occupancy of both the HOMO and the LUMO by a total of two electrons in the ground state, the latter gives rise to magnetic properties of this system. Another consequence of the diradicaloid character is that the intramolecular electrocyclic ring-closure of cethrene proceeds[2] both thermally and photochemically, making cethrene one of the rare examples of the 'chameleons' of the Woodward–Hoffmann rules[3]. Recently, it has been shown in our group that cethrene equipped with two methyl substituents in the fjord region can act as a photochemical chiroptical switch between an open and a closed form. The only drawback of this system was that the energy gap between the singlet ground state and the triplet excited state was too large, which rendered the open form EPR silent. We therefore aimed to make a derivative of dimethylcethrene, which could also act as a magnetic photoswitch (figure). Computational screening revealed that a pair of methoxy and a pair of cyano substituents should be sufficient to make the open form (blue) EPR active, while the closed form (red) would remain EPR silent. The synthesis and properties of this prototype of a chiroptical and magnetic photoswitch will be presented.



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Conception de pillar[5]arene[2]rotaxanes liquides-cristallins chiraux

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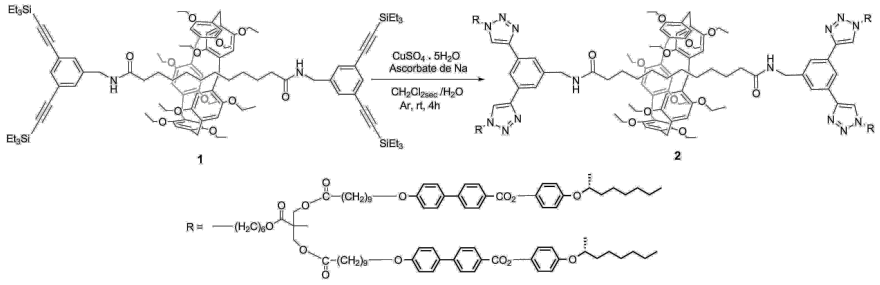
style="text-align: justify;">Les machines moléculaires (MIMs), comme les rotaxanes, représentent des candidats prometteurs pour l'élaboration de cristaux liquides (CL). En effet la combinaison des propriétés des MIMs avec les caractéristiques des CL peut nous offrir des supramolécules intéressantes. Nous nous intéressons à la conception de matériaux mésomorphes dendritiques chiraux à base de pillar[5]arene[2]rotaxanes. L'incorporation des rotaxanes dans les mésophases pourrait leur fournir un environnement dynamique organisé. [1]



Dans ce contexte, nous avons entrepris un projet de recherche visant à concevoir une synthèse efficace de [2]rotaxanes fonctionalisés par des dendrons polyesters aliphatiques chiraux, qui sont des précurseurs de phases smectiques chirales. Le but est d'induire des propriétés mésomorphes chirales au rotaxane par greffage de dendrons par chimie click. Le greffage se fait en deux étapes (voir la figure ci-dessus): dans la première étape, le rotaxane **1** [2] est déprotégé en présence de TBAF puis, dans la seconde étape, une cycloaddition alcyne-azoture catalysée par le cuivre(I) permet de greffer les dendrons. Des phases lamellaires de type smectique C^* ont été observées pour les dendrons et les rotaxanes. Ces résultats positifs seront consolidés par l'élaboration d'autres rotaxanes mésomorphes chiraux contenant des dendrimères avec des espaceurs différents. Les propriétés ferroélectriques seront ensuite étudiées.

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

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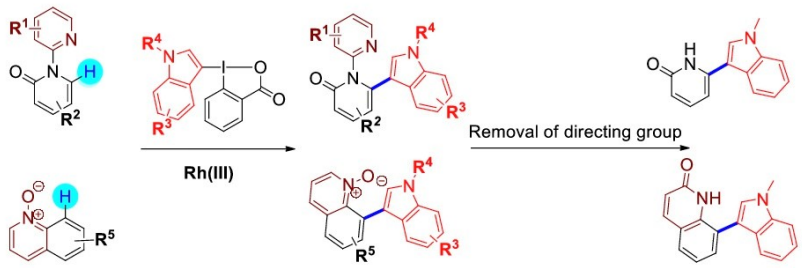
[1]Laboratory of Catalysis and Organic Synthesis, EPFL SB ISIC LCSO, BCH 4306, CH-1015 Lausanne, Switzerland

Indole heterocycles are widespread motifs in biologically active compounds and natural products[1]. Recently, our group introduced IndoleBenziodoXolones (IndoleBX)[2] as useful reagents for the efficient transfer of indole moieties. Herein, we present the application of these compounds to the directed C-H Indolisation of N-pyridyl pyridones and quinoline N-oxides under Rh(III) catalysis. This new reaction showed tolerance towards a broad range of functional groups and was highly regioselective (functionalization of C-6 for N-pyridyl pyridines, and C-8 for quinolone N-oxides). Upon removal of the directing groups, indole-containing pyridones and isoquinolones products could be easily obtained.



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Hypervalent Iodine reagents for fast and efficient peptide and protein modification

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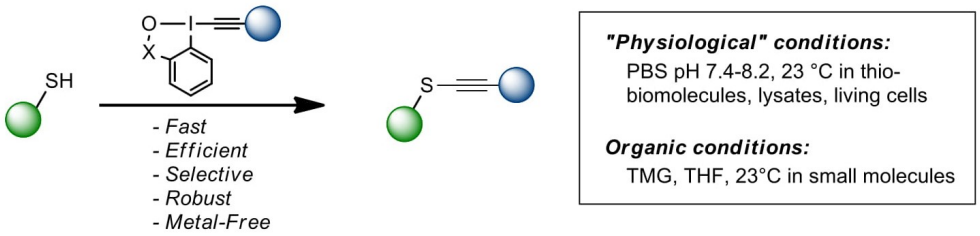
Efficient and flexible functionalization of peptides and proteins has been extensively used in modern biochemistry. The requisite for fast kinetics, mild reaction conditions and high chemoselectivity makes the development of practical labelling methods highly challenging. Despite their relatively low abundance, cysteines are vital for cellular biochemistry because of their critical role in structural stability and catalytic activity of proteins, furthermore their high nucleophilicity makes them an ideal target.

With the goal of cysteine targeting, our group developed highly efficient and chemoselective thio-alkynylation reactions, using the exceptional properties of hypervalent iodine (HI) reagents in both organic and more physiological conditions.[1,2] These reactions proceeds under mild organic and physiological conditions, without any metal assistance or thiol pre-functionalization, with very high robustness, efficiency and with reaction times of minutes.



In this work, we have expanded the HI-cysteine known reactivity to novel and efficient peptide modifications. The generated thio-alkyne group, is a stable and biorthogonal moiety that can hence be used for peptide stabilization or labelling, among many other potential applications.

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Nickel-Catalyzed Enantioselective Pyridone C-H Functionalizations Enabled by a Bulky N-Heterocyclic Carbene Ligand

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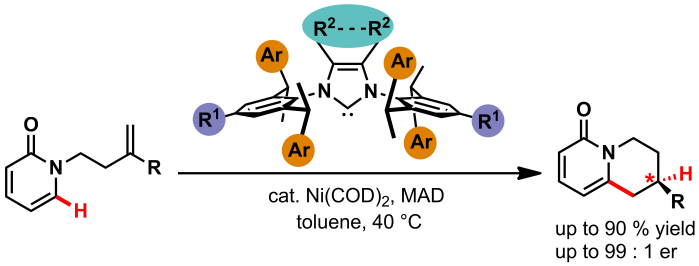
[1]Laboratory of Asymmetric Catalysis and Synthesis, EPFL CH-1015 Lausanne, Switzerland

2- and 4-pyridone rings are prevalent heteroaromatic structures, which are found in a broad variety of natural products, bioactive agents and approved drugs.[1] Over the past decade, rapid advances in C-H functionalization technology have been demonstrated to be of utility for the preparation of functionalized pyridones.[2] However nickel-catalyzed enantioselective C-H functionalizations are very rare and underdeveloped. Previously, we reported an *endo*-selective annulation protocol of *N*-alkenyl-2-pyridones. Cooperative Lewis acid/nickel(0)-catalysis and application of *N*-heterocyclic carbene ligands (NHCs) enabled C-H activation and regioselective cyclization under formation of chiral annulated 2-pyridones.[3] A variety of known chiral NHCs have failed to achieve a synthetically useful control of enantioselectivity.
Here, we introduce a class of sterically demanding chiral NHCs with large modulation opportunities, enabling the nickel(0)-catalyzed C-H functionalization of 2- and 4-pyridones in excellent yields and enantioselectivities.[4] Their close relationship to the achiral privileged ligand IPr holds the promise of enabling further catalytic enantioselective transformations with different transition metals.



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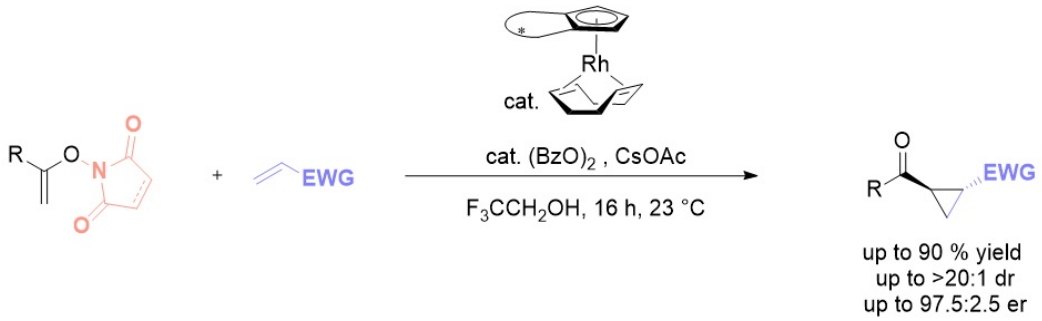
$Cp^xRh(III)$-Catalyzed Enantioselective Cyclopropanation via Alkenyl C-H Activation

C. Duchemin[1], N. Cramer[1]*

[1]Laboratory of Asymmetric Catalysis and Synthesis,

Optically active cyclopropanes are prevalent in many biologically active compounds and natural products. Several methods, such as the Simmons–Smith reaction, Michael addition-initiated ring-closure reactions, and cyclopropanations of olefins with metallocarbenes have been developed in asymmetric manners. Rovis and coworkers reported a rhodium(III)-catalyzed *trans* -cyclopropanation *via* alkenyl C-H activation.(1)

Our group pioneered the development of highly efficient chiral Cp ligands for transition metal catalysis.(2) Their potential was demonstrated in combination with various metals for a variety of transformations.(3) Herein, we report the application of chiral cyclopentadienyl complexes to enantioselective alkenyl C-H activation leading to the formation of *trans*-cyclopropanes *via* a formal [2+1] annulation in good yields and excellent diastereoselectivities and enantioselectivities.



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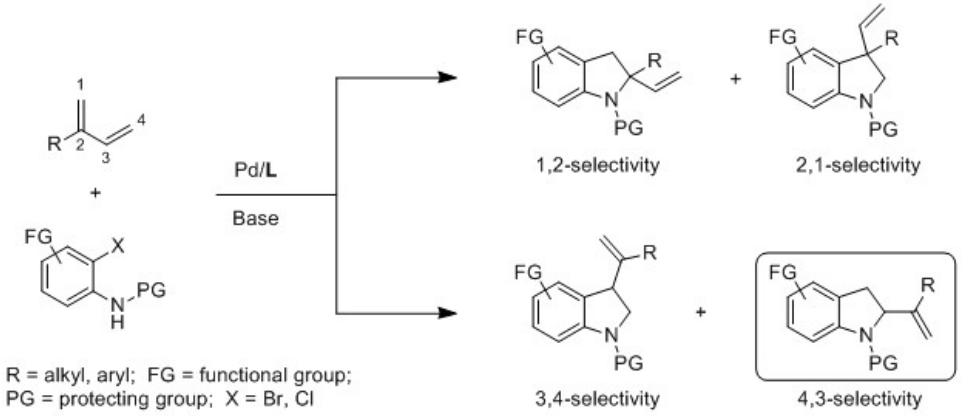
Pd-catalyzed carboamination of 2-substituted conjugated 1,3-dienes

M. Garbo[1], G. M. Borrajo-Calleja[1], C. Mazet[1]*

[1]Université de Genève

Nitrogen-containing heterocycles are ubiquitous in biologically active compounds: they are present in 59% of unique small-molecule drugs approved by the FDA.[1] A strategy for the rapid synthesis of such moieties is represented by the carboamination of alkenes, a reaction in which a C-C and a C-N bond are formed concomitantly.[2]
We recently reported the palladium-catalyzed carboamination of 2,3-dihydrofurans.[3] To expand the scope of olefinic cross-coupling partners, we focused on the use of 2-substituted conjugated 1,3-dienes.[4] Selective functionalization of this class of substrates poses several challenges which – if successfully overcome – provides expedient access to valuable chiral indoline derivatives.
We present herein our efforts towards the development of a Pd-catalyzed 4,3-selective carboamination of 2-substituted conjugated 1,3-dienes.



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Decarboxylative alkynylation of peptides C-terminal using photoredox catalysis.

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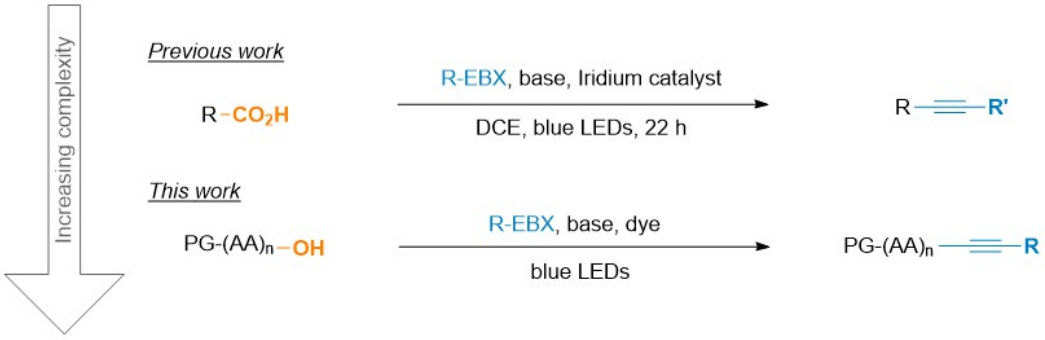
[1]Laboratory of Catalysis and Organic Synthesis, EPFL SB ISIC LCSO, BCH 4306, CH-1015 Lausanne, Switzerland

While being highly appealing, efficient methods for peptides C-terminal labeling remain rare. Our group had previously developed a photoredox catalyzed decarboxylative alkynylation of amino acids.[1][2] Alkynes are introduced starting from free carboxylic acids in one step using hypervalent iodine reagents and photoredox catalysis. We envisioned the extension of this methodology to larger biomolecules. A metal-free C-terminal selective decarboxylative alkynylation of peptides has been developed. Efficient and fast functionalization of peptides with bioorthogonal functional groups was achieved. Work is ongoing towards large bioactive peptides labeling.



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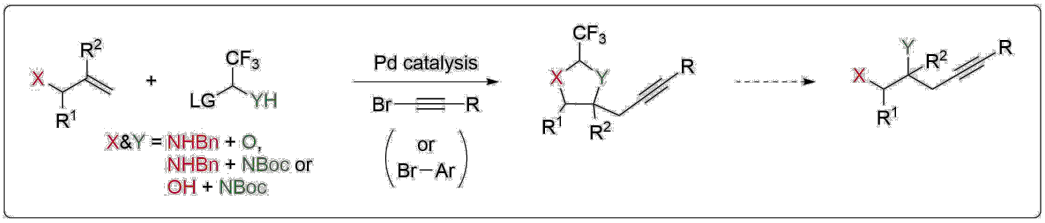
Trifluoroaldehyde-Based Tethers for Palladium Catalysis

P. D. Greenwood[1], J. Waser[1]*

[1]Laboratory of Catalysis and Organic Synthesis, EPF

The palladium catalyzed di-functionalization of alkenes containing hydroxy or amino groups has been established as an effective synthetic approach to access a diverse range of heterocycles and other highly functionalized compounds.[1,2] Recently, our group has demonstrated the expedient use of trifluoroacetaldehyde-tethered hydroxy and amino nucleophiles in the Pd^0 catalyzed di-functionalization of alkenes in conjunction with electrophilic sp and sp^2 sources. Initially, this strategy was applied to allylic amines to yield vicinal amino alcohol[3] or diamine[4] scaffolds and more recently vicinal masked amino alcohols were obtained from allylic alcohols.[5] The resulting aminals could then be hydrolysed to give rise to the free aminoalcohols and diamines or the aminal could act as a protecting group to allow further functionalisation and diversification of the product.
Herein, we will present further advances in the use of trifluoroaldehyde-based tethers in palladium catalysis.



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Reactivity of the key intermediate of gold catalysed olefin hydroamination

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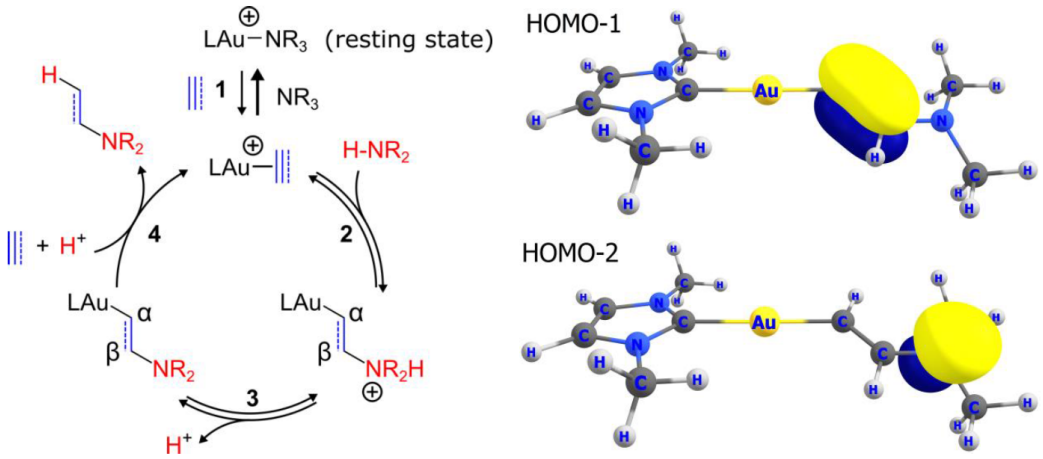
[1]ETH Zürich, Laboratorium für Organische Chemie

In gold(I) catalysis, amines can only be added to olefins with difficulty. Alkynes are generally more reactive than olefins. Gas phase measurements showed that both substrates bind with similar energy to cationic gold species [1]. The displacement of more strongly coordinating amines from the catalyst (step **1**) occurs to a similar extent.



β-amino vinyl gold intermediates, that are formed in step **3** from alkynes, possess a C=C bond. Natural bond orbital (NBO) identified the π(C=C) orbital as HOMO-1, and hence accessible for electrophiles like H^+. Essentially at the same energy lies the nitrogen lone-pair. Products are formed when the C=C bond is protonated, but reactants are obtained when the nitrogen is.

There is no π(C=C) bond in β-amino ethyl gold intermediates that are generated from olefins. Instead, a low-lying filled orbital is expected to be involved in protonation. This would slow step **4** down and limit the TOF [2].

An independent preparation for β-amino ethyl gold complexes was developed and their reactivity studied in the gas phase and by NMR.

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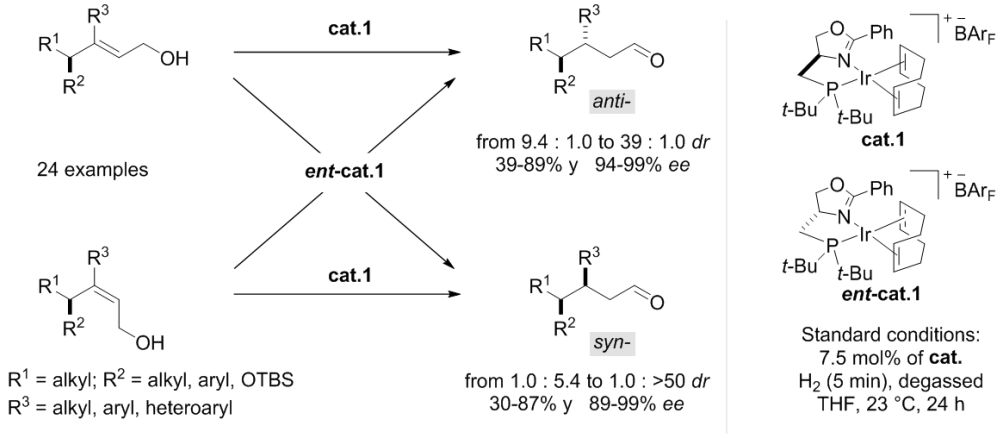
Catalyst-Controlled Diastereoselective Isomerization of Acyclic Opctically Active Primary Allylic Alcohols

J. Guillemin[1], H. Li[1], C. Mazet[1]*

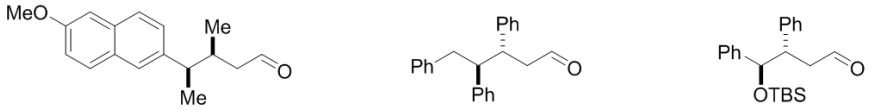
[1]Department of Organic Chemistry, University of Geneva

The development of diastereoselective methods where a chiral catalyst must control the absolute configuration of a given stereocenter independently of a stereochemically complex environment is a contemporary problem in selective catalysis.[1,2]

Herein, we describe the catalyst-controlled diastereoselective isomerization of acyclic optically active primary allylic alcohols. Under identical experimental conditions with iridium catalysts supported by a chiral (P,N) ligand, both *anti*- and *syn*- aldehydes could be obtained with high enantioselectivity, diastereoselectivity and in moderate to good yields.[3]



Representative results



from (R)-(Z), 97% ee
48%, 46:1, 89% *ee*

from (R)-(Z), 99% ee
60%, 30:1, 99% *ee*

from (S)-(E), 98% ee
59%, 12:1, 99% *ee*

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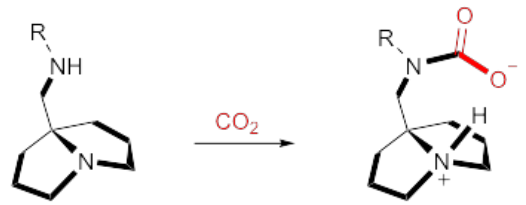
Pyrrolizidines for Direct Air Capture and CO_2 Conversion

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

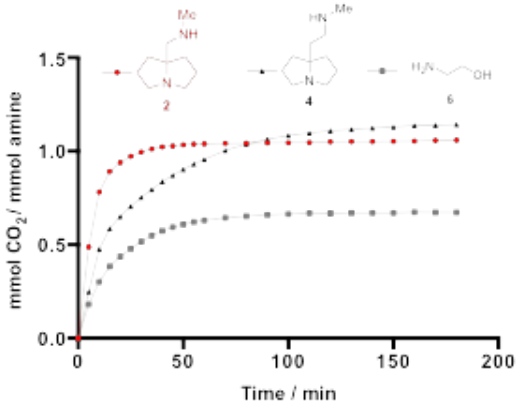
[1]University of Zurich, [2]University of Basel

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

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



R = alkyl, aryl or H



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Towards an Excited State Hammond Postulate

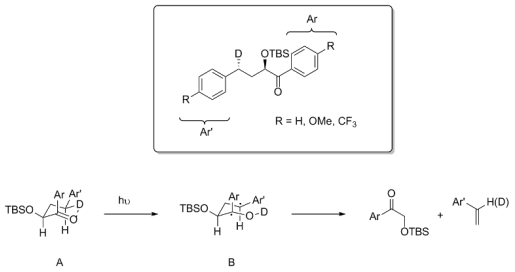
F. Harvey[1], C. Bochet[2]*

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

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

In previous experimental work on photolysis of *o*-nitrobenzyl derivatives[1,2], it was observed that the Bell-Evans-Polanyi principle was followed, and the position of the CI also varied with the substituents. This suggests that Hammond's postulate may be applicable to CIs in the excited state.

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



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

The above substrates will be synthesised then submitted to a series of photolyses, and the ratio of styrene/styrene-*d*1 will be analysed as a function of the substituent Ar. The reaction will be performed for both isomers in order to take into account the isotope effect.

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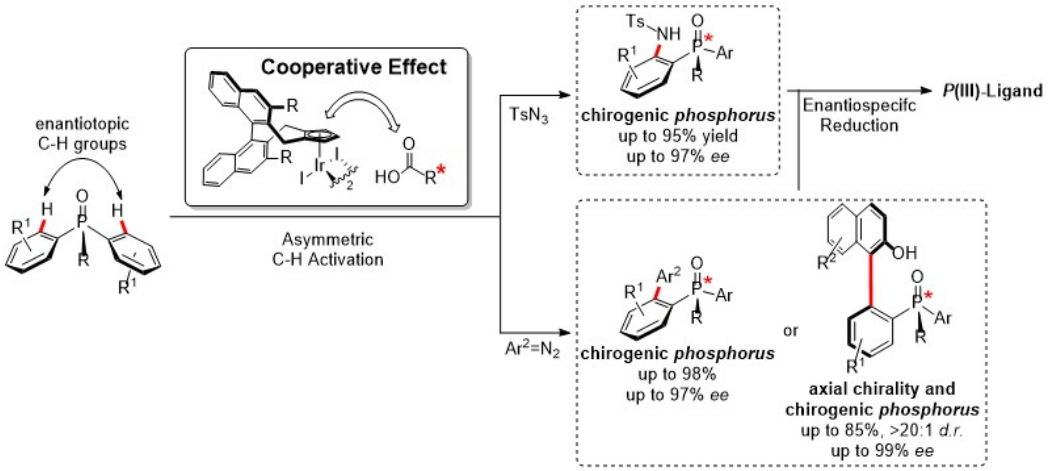
Enantioselective $Cp^{X}Ir^{III}$-Catalyzed C-H Amidations and Arylations Give Access to P-Chiral Phosphorus (V) Compounds

Y. Jang[1], N. Cramer[1]*

[1]Laboratory of Asymmetric Catalysis and Synthesis, EPFL

Chiral phosphorus(III) compounds are important monodentate ligands for asymmetric catalysis.[1] While chiral backbones are well established species, chiral-at-phosphorus ligands remain underutilized due to their laborious synthesis.[2] However, *P*-chiral ligands are highly sought after, because the stereogenic element is closer to the reactive center of a catalyst and can therefore induce its chiral information more effectively.[3]

Recently, we reported an asymmetric iridium catalyzed C-H amidation, which afforded phosphine oxides that can be enantiospecifically reduced to the respective phosphine. Key for the success of this transformation was the combination of a chiral $IrCp^{X}$ catalyst[4] and a chiral carboxylic acid.[5] We extended this approach to access biaryl phosphine oxides in one step. This technology not only allowed for the syntheses of *P*-chiral phosphine oxides in high yields and excellent enantiomeric ratios, but also for the introduction of axial chirality with high yields, excellent diastereomeric and enantiomeric ratios.[6]



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[6] Manuscript in Preparation.

[8]Cethrene: A Helical Non-Kekulé Triplet Diradical

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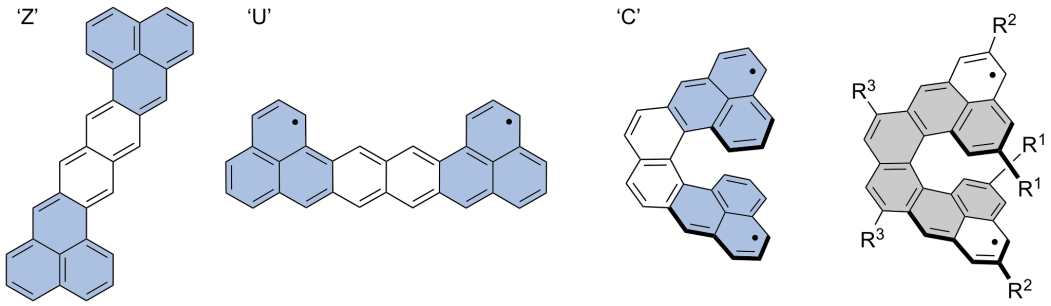
[1]University of Zurich, Department of Chemistry, Winterthurerstrasse 190, 8057 Zurich

Phenalenyl[1] (highlighted in blue) is the smallest triangular graphene fragment that contains an unpaired electron (S = 1/2) delocalized over the entire π-conjugated system. When two phenalenyl units and additional benzenoid rings are fused together, two types of polycyclic π-conjugated hydrocarbons can be obtained, Kekulé and non-Kekulé. In Kekulé systems, all π-electrons are paired to give a closed-shell system with a singlet ground state (S = 0), while in non-Kekulé systems, two electrons remain unpaired to give a diradical open-shell system with a triplet ground state (S = 1). Figure below shows typical examples of both types, Kekulé [8]zethrene[2] ('Z') and non-Kekulé [8]uthrene ('U'), the structures of which differ in the way that two phenalenyl subunits (blue) are fused to the central naphthalene moiety (white). Although Kekulé systems such as [8]zethrene have been studied[3] intensively over the past two decades, the chemistry of non-Kekulé systems remains largely unexplored, because of extremely high reactivity of these species. The goal of this project was synthesize the first helical non-Kekulé graphene fragment, [8]cethrene ('C'), a diradical isomer of [8]uthrene. In this molecule, two phenalenyl subunits are fused to a naphthalene moiety such that a twisted [6]helicene backbone (highlighted in gray) is obtained. As a result, [8]cethrene will have a helical geometry, which might, in concert with bulky substituents installed to protect the most reactive positions, improve stability of these systems and make them isolable as solid materials. In addition, spin density in [8]cethrene will be delocalized over a chiral backbone, which will make this system suitable for investigation of phenomena that arise from the interplay of magnetism and chirality. The synthesis and properties of a derivative of [8]cethrene equipped with six substituents will be presented.



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Double-Stranded RNA-Specific Templated Reaction with Triplex Forming PNA

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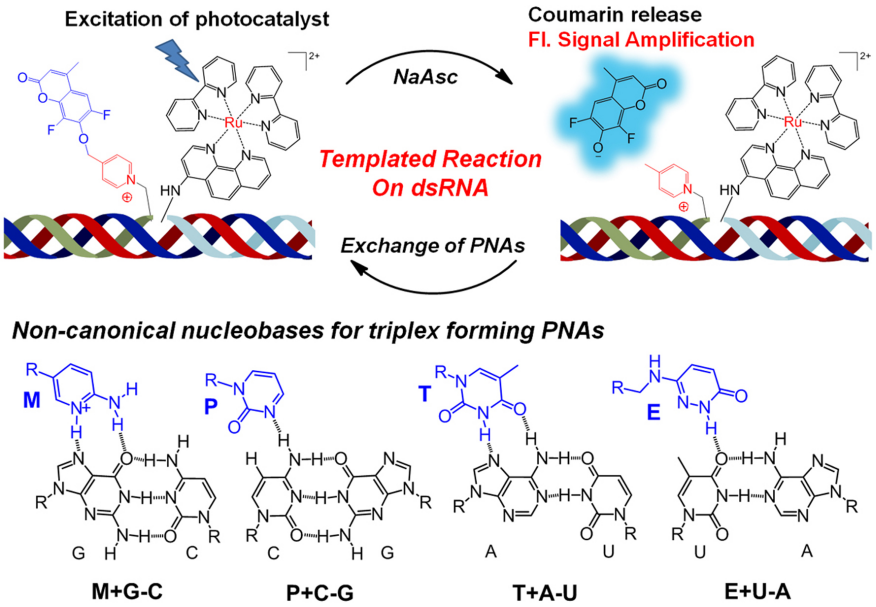
[1]Department of Organic Chemistry, NCCR Chemical Biology, Faculty of Science, University of Geneva, 30 quai Ernest Ansermet, 1211 Geneva, Switzerland.

Non-coding (ncRNA) is emerging as an important regulator in cellular processes. Since ncRNAs tend to adopt diverse folds with stretches of double-stranded RNA (dsRNA), there is a need for technologies to reliably detect such RNAs for biological research. Herein we present dsRNA-specific templated reaction achieved by sequence-specific triplex formation of PNAs having non-canonical nucleobases. The PNAs bring a ruthenium photocatalyst and a profluorophore within reactive distance through dsRNA-PNA triplex and lead to immolation of a pyridinium linker and unmasking a profluorophore. The reaction proceeded with signal amplification and was selective for dsRNA over DNA as well as single-stranded RNA. The technology was applied to detection of pre-microRNA-31.



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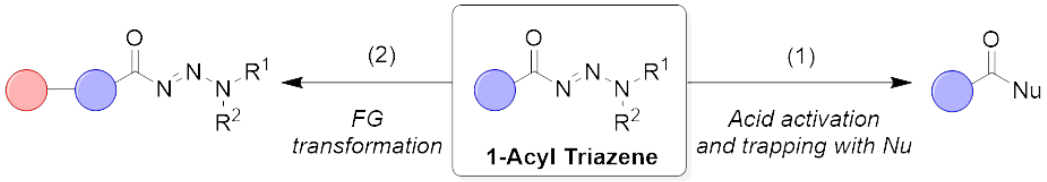
Synthesis of 1-Acyl Triazenes by Gold(I)-Catalysed Oxidation of 1-Alkynyl Triazenes

I. R. Landman[1], K. Severin[1]*

[1]LCS, ISIC, Ecole Polytechnique Fédérale de Lausanne (EPFL), 1015 Lausanne, Switzerland

Triazenes are a “versatile tool in organic synthesis” for numerous applications, such as in pharmacology, total synthesis and polymer technology.[1] We have previously reported a new method for the synthesis of 1-alkynyl triazenes, using nitrous oxide as N-atom donor.[2] Building on the high intrinsic reactivity of 1-alkynyl triazenes, we have developed a method to synthesize 1-acyl triazenes via gold(I)-catalysed oxidation reactions. In contrast to 3-acyl triazenes,[3] 1-acyl triazenes have not been described before. A key advantage of these acylated triazenes is that via acid activation they act as acylation or amidation reagent (1). This reactivity could open-up new pathways for organic synthesis. In addition, functional group transformation of 1-acyl triazenes (2) could lead to building blocks that enable late-stage functionalization.



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Synthèse de tris-[60]fullérodendrimères liquides-cristallins pour la conception de matériaux ferroélectriques

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Mots-clés : métathèse croisée, fullerène, cristaux liquides, matériaux ferroélectriques

La combinaison des caractéristiques des cristaux liquides et des propriétés électrochimiques et photophysiques du [60]fullerène (C_{60}) est intéressante pour le développement de matériaux multifonctionnels applicables dans les dispositifs optoélectroniques (par exemple, les cellules photovoltaïques). Nous nous intéressons au développement de fullérodendrimères liquides-cristallins riches en fullerène possédant des propriétés ferroélectriques [1]. Pour atteindre cet objectif, le composé **1** a été construit par la réaction de métathèse croisée d'oléfines. Le mésomorphisme est induit par la présence de 16 mésogènes chiraux sur les dendrons poly(aliphatiques esters) de troisième génération [2]. Nous discutons l'influence du fullerène sur l'organisation supramoléculaire ainsi que la possibilité d'augmenter le nombre de C_{60}.

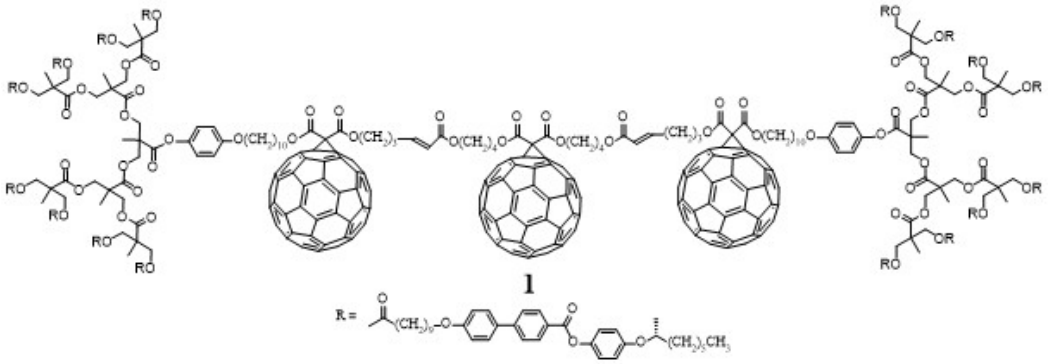

Figure 1 : *Tris*-[60]fullérodendrimère liquide-cristallin

Nous avons observé que la température d'isotropisation des [60]fullérodendrimères est plus élevée que celle pour le composé sans fullerène (*tris*-malonate), démontrant que la présence du fullerène stabilise l'état mésomorphe. De plus, la phase smectique C chirale (SmC*) a été observée pour plusieurs composés démontrant ainsi que des matériaux supramoléculaires ferroélectriques sont accessibles.

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An eco-friendly route to Pd-containing mesoporous carbons for hydrogenations and C-C bond forming reactions in ethanol or water

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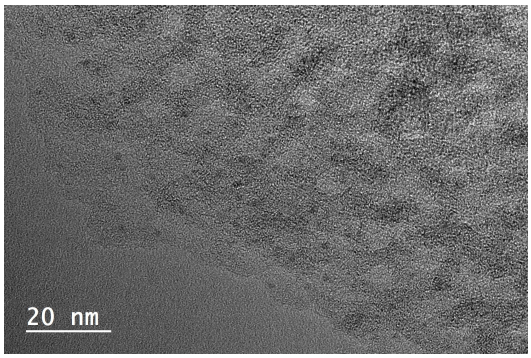
Mesoporous carbons containing Pd nanoparticles or PdM (M = Co, Rh, etc...) nanoalloys were prepared by a fast, efficient and eco-friendly route(1) from readily available and non-toxic carbon precursors (phloroglucinol, glyoxal), a porogen template (plutonic F127) and metallic salts which could be introduced either before or after the calcination. These materials were successfully used as heterogeneous catalysts for "green" Suzuki-Miyaura, Mizoroki-Heck and hydrogenation reactions at room temperature. These catalysts could also be reused several times.



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Harnessing photoredox-catalyzed decarboxylation as a key step in the functionalization of carboxylic acids and cyclic alkylketones using hypervalent iodine reagents

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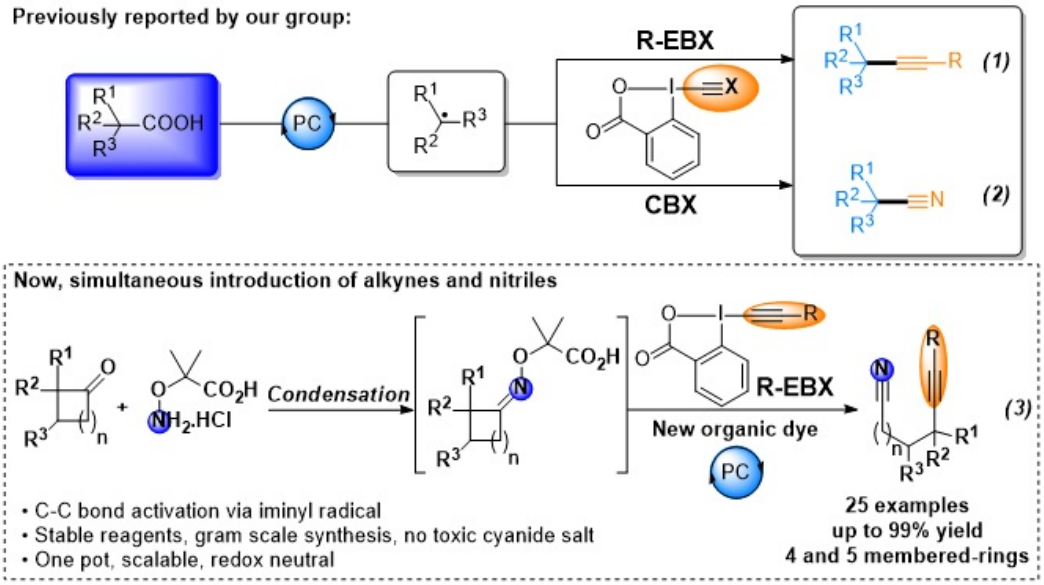
[1]Laboratory of Catalysis and Organic Synthesis

Aliphatic alkynes and nitriles are functional groups of great significance, naturally occurring and broadly used as versatile building blocks in organic synthesis. We developed a unified strategy to access both classes of compounds from carboxylic acids, using photoredox catalysis and hypervalent iodine reagents.[1,2] According to computational and experimental studies, two different mechanisms can be proposed: via radical intermediates for alkynylation, and carbocation intermediates for cyanation. Herein, we describe the remote alkynylation cyanation of cyclic alkylketone oxime ethers via a photoredox catalyzed radical cascade.[3] The reaction is redox neutral and avoid toxic cyanide salts. Fine-tuned organic dyes and one-pot procedure are also reported.



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Towards the Total Synthesis of the Antimycobacterial Natural Product Amicetin and SAR Studies

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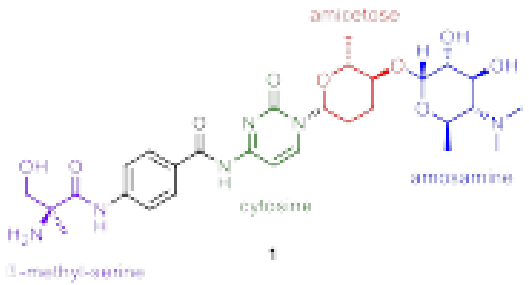
[1]ETH Zürich

Emerging drug-resistant bacterial pathogens pose an acute threat to public health and require the discovery of new antibacterial drugs.[1] Nucleoside antibiotics represent an important and versatile class of natural products with diverse bioactivities, including activity against various types of pathogenic bacteria. Thus, they are interesting lead structures for the development of new antibacterial agents.[2] The disaccharide pyrimidine nucleoside antibiotic amicetin (**1**) was first isolated in 1953 by DeBoer *et al.* from *Streptomyces vinaceus-drappus* and *Streptomyces fasciculatis* and found to inhibit the growth of *Mycobacterium tuberculosis*, *Staphylococcus aureus* and *Escherichia coli*. While its precise mode of action remains to be elucidated, amicetin (**1**) is believed to target the peptidyl transferase activity of the 70S ribosome and thus to interfere with peptide bond forming processes in bacteria. Structurally, a particularly intriguing feature of **1** is the unique α-(1-4)-glyosidic bond between amosamine and the 2-deoxy sugar amicetose.



The primary goal of our work was the development of a first total synthesis of **1**. In subsequent steps, the chemistry developed in the course of the total synthesis work is planned to be exploited for the synthesis of structural analogs of **1** for structure-activity relationship (SAR) studies. In particular, these studies should shed light on the importance of the specific disaccharide moiety in **1** for its biological activity. At this point, a concise synthesis of the complete amicetin (**1**) backbone has been established. However, major final glycosylation and deprotection issues prompted us to re-evaluate the design of the two single pyranose fragments and the order of coupling events of the individual building blocks.

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Proline-rich cyclic peptides for cation recognition

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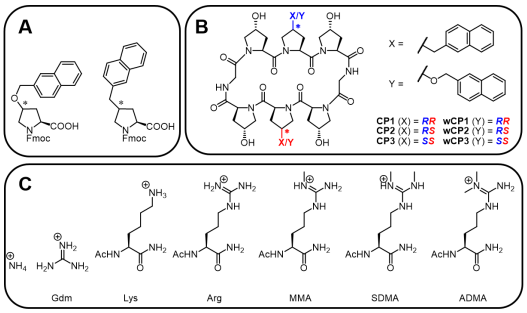
Gene expression, translation and transcription is regulated by a plethora of different and complementary signalling cascades. One of those regulatory processes is the methylation of lysine and arginine residues in histones.[1,2] Abnormal methylation of lysines or dysregulation of arginine methylation on histones has been linked to a number of diseases among them cancer.[3] The interest in understanding those methylations led to investigations of binding to lysine and methylated lysines using synthetic receptors.[4] But to date, there is no single example of a small molecule host that has a high degree of selectivity towards arginine and its methylation states over lysine.

We designed and synthesized proline-rich macrocycles **CP1**-**3** and **wCP1**-**3** with Gly-Pro and Hyp-Pro as turn inducing motifs. Binding studies revealed a selectivity of the macrocycles **CP1**-**3** for Arg over Lys in acetone and this selectivity is thought to arise from size differences between the cations as well as shape complementarity between arginine and the cavity of the macrocycle. Binding studies in water were performed with the receptors **wCP1**-**3** and showed reversed selectivity for binding Arg over Lys when going from the "*SS*"- to the "*RR*"-diastereoisomer. With this research we hope to get insight into key features necessary for the distinction of different cations and facilitate the development of new small molecule receptors for cation recognition.



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Toward the Total Synthesis of Puraquinonic Acid via Pd(0)-Catalyzed Enantioselective C(sp3)-H Arylation as the Key Step

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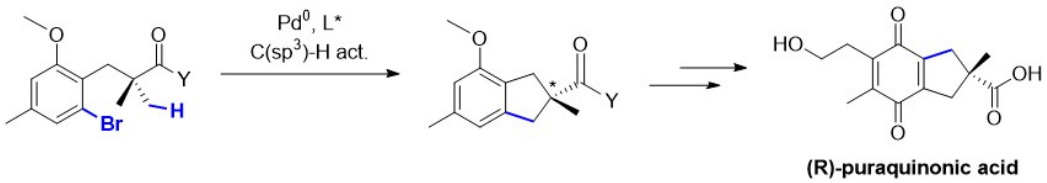
Puraquinonic acid is a fungal metabolite from 15-norilludalane family, first isolated in 1997 from *Mycena Pura*. This molecule showed mild differentiation-inducing activity toward HL-60 cells [1]. Due to the presence of the highly symmetrical quaternary stereocenter, its enantioselective total synthesis proved to be challenging and lengthy [2]. To solve this problem, we planned to employ a Pd(0)-catalyzed intramolecular enantioselective C(sp^3)-H arylation reaction. In the last decade, asymmetric C-H activation proved to be an efficient tool for the construction of tertiary [3], and more recently quaternary stereocenters [4]. Herein, we report our latest results toward the enantioselective total synthesis of puraquinonic acid [5].



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Palladium-Catalyzed Carboamination of Allylic Alcohols Using a Removable Tether

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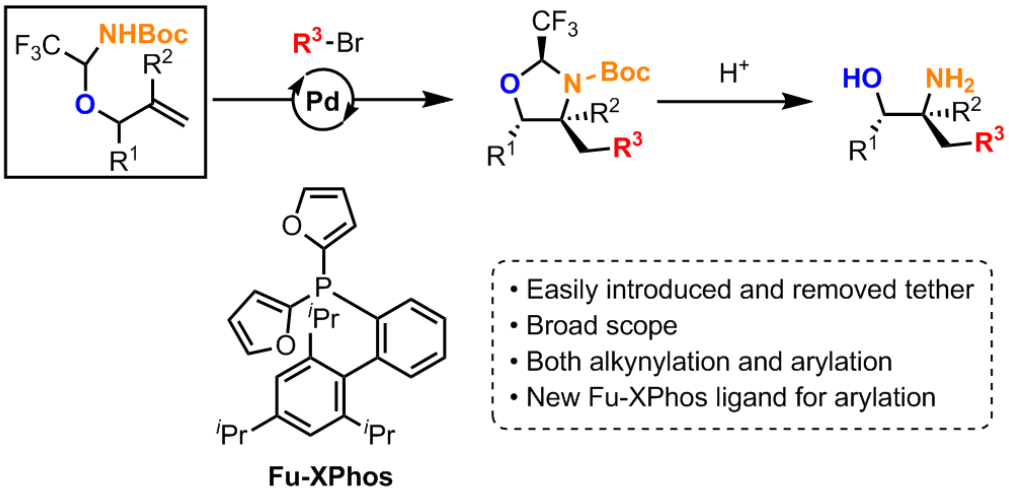
The functionalization of olefins mediated by transition metals has emerged as a straightforward approach for a rapid increase in molecular complexity. In this context, the use of removable tethers combined with Pd-catalyzed olefin functionalization has known intense developments in recent years and has proved to be an efficient strategy for the selective installation of new functionalities on an alkene in a 1,2 relationship.[1] Recently, our group has introduced (hemi)aminal tethers derived from trifluoroacetaldehyde for the carboetherification and carboamination of allylic amines to give aminoalcohols and diamines.[2] Herein, we would like to report the successful implementation of this strategy to allylic alcohols. The synthesis of a stable hemiaminal could be achieved, followed by a Pd-catalyzed carboamination that could install concomitantly a C-N bond and a highly valuable C-C bond.[3] Aminoalkynylation was first realized using alkynyl bromides and commercially available phosphine ligands. For aminoarylation, a new biaryl phosphine ligand, “Fu-XPhos”, had to be introduced to suppress a competitive Heck pathway. The carboamination products were obtained in high yields and diastereoselectivity, and the tether could be easily removed to give value-added amino alcohol building blocks. Our latest achievements in the field will also be presented.



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Development of New Hypervalent Indole(D)BX reagent And Its Application to Regioselective Arylation of Indoles

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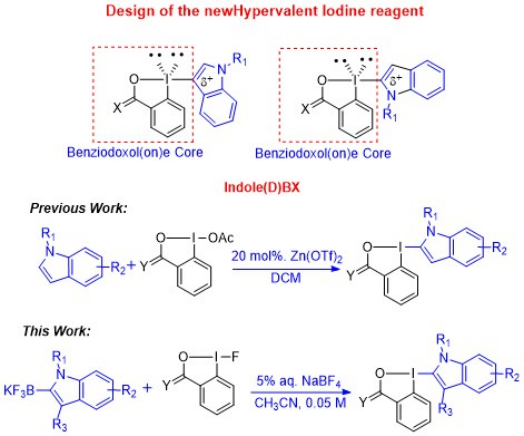
Indole ("*The Lord of the Rings*" of aromatic compounds)[1] after 150 Years of its discovery (Adolf von Baeyer, 1869),[2] it is still a privileged structure in the field pharmaceuticals, agrochemicals, and functional materials. Most of the time umpolung character, involves the oxidation of the indole nucleus or the presence of strong electron-withdrawing groups on it. In this context, cyclic hypervalent iodine reagents are recognized for their high reactivity, which can lead to the formal umpolung of functional groups. During past one decade our group made enormous effort on development of many useful cyclic hypervalent iodine reagents.[3,4] Previously our group demonstrated[5] an one-step synthesis of the bench-stable hypervalent iodine reagents IndoleBX. Very recently [6] we have developed a new metal free protocol to obtain IndoleBX reagent at C2 connectivity of Indole. We present herein the novel synthesis of a series of electrophilic Indole(D)BX reagents. These new reagents are bench stable, highly functionalized and their synthesis is facile and scalable. They can be applied in metal-free oxidative cross couplings with electron-rich (hetero)arenes.



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Catalysis with and without Metals towards the Total Synthesis of Tocopherols

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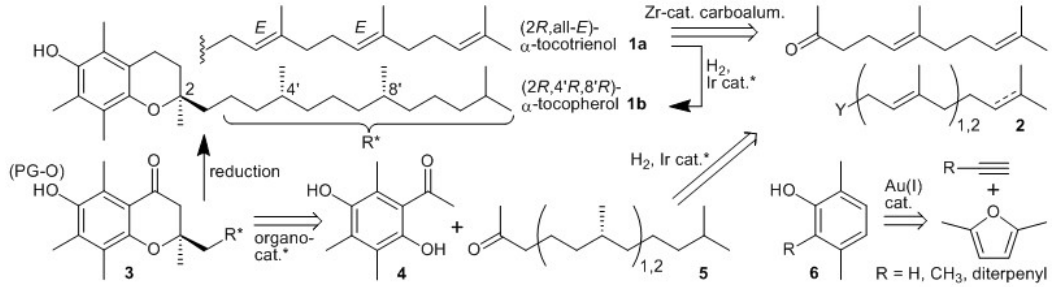
(2*R*,4'*R*,8'*R*)-α-Tocopherol (**1b**) is an industrially important target due to its highest biological potency of all vitamin E compounds. [1] Novel routes by total synthesis including the creation of the quarternary chroman stereocenter [2] will be presented. In continuation of our efforts together with academic partners [3-7] we discovered an enamine-based organocatalytic condensation to chromanone **3** [8] from hydroxyacetophenone **4** with chiral isoprenyl ketones of type **5** accessible from olefins **2** via asymmetric hydrogenation with highly selective and active iridium complexes. [9] Alternative strategies will also be discussed. An additional topic deals with the synthesis of aryl key building blocks **6** by Hashmi's gold-catalyzed furan-yne-cycloisomerization addressing the replacement of fossil resources by bio-renewables. [10]



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Control of Spin Interactions in Helical Diradicaloids

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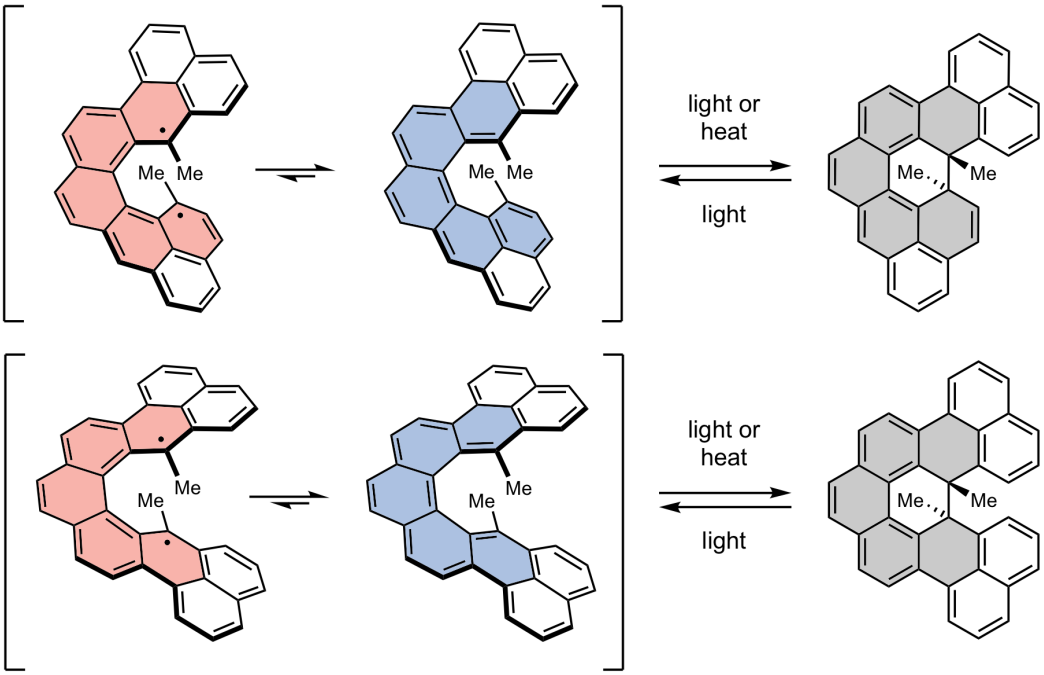
Diradicaloid π-conjugated hydrocarbons[1] are characterized by small HOMO–LUMO gaps and low-lying triplet excited states that can be populated thermally. In our group, we investigate diradicaloid systems with helical geometries, called cethrenes[2], where through-space orbital interactions, which affect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



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Gold Nanoparticle Dimers via Acetylene Homocoupling

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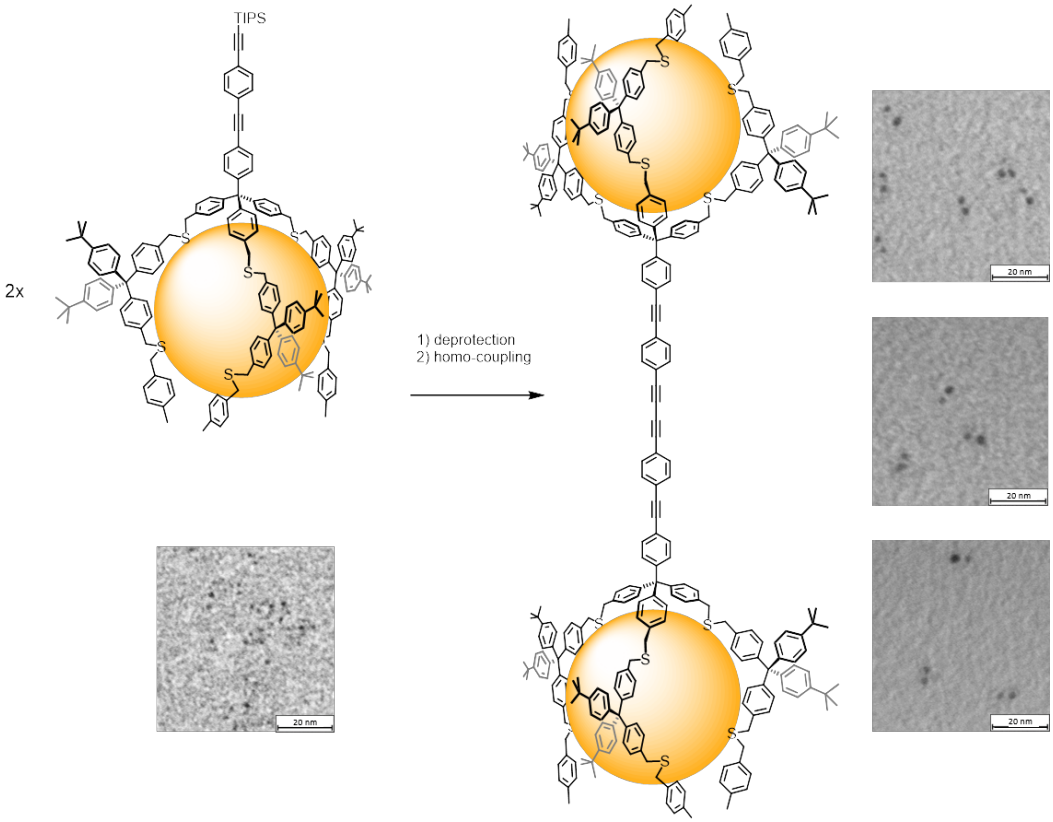
[1]University of Basel

Due to their unique properties, functional gold nanoparticles (Au NPs) are of major interest for molecular electronics. Au NPs have successfully been stabilized by a single tripodal thioether-based ligand which offers further chemical functionality by exposing a protected acetylene. The Au NPs are of narrow size distribution (1.20 ± 0.26 nm) and withstand thermal stress up to 105 °C. The Au NPs were used to synthesize dimers via previously implemented acetylene deprotection-homocoupling protocol.[1,2] The dimer-dimer distance is in agreement with molecular modeling. Furthermore, the dimers can be isolated by size-exclusion chromatography and are bench stable for an extended period.



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Synthesis of molecular probes targeting ER flippases

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Most proteins that enter the secretory pathway become glycoproteins, *i.e.* they are modified by sugars, such as N-glycans. The absence of N-glycans is lethal, and alterations in glycosylation patterns may lead to devastating diseases, including cancer. The assembly of the canonical oligosaccharide donor for N-glycosylation requires the flipping of dolichol-containing glycolipids from the cytoplasmic to the luminal side of the endoplasmic reticulum (ER). This process implies the existence of proteins (flippases) that facilitate the otherwise very slow movement of polar glycolipids through the membrane (**Figure 1**).[1] The goal of this study is the synthesis of molecular probes, which should serve as tools for the identification of the proposed ER flippases (**Figure 1**).

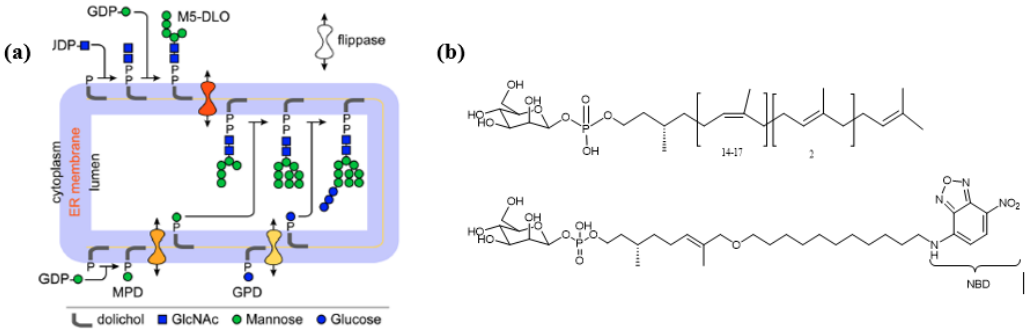

Figure 1 (a) Illustration of some of the steps involved in the protein N-glycosylation pathway, located in the ER membrane. **(b)** Structure of the natural substrate (top) and the corresponding fluorescent analogue (bottom).

We are synthesizing lipid analogs for the purpose of assaying, capturing and isolation of candidate flippase proteins. For this purpose, we are synthesizing fluorescent mimics of the natural substrates, with an ω-terminal fluorophore (NBD, see **Figure 1**). Additionally, we are synthesizing analogs with chemically reactive moieties for crosslinking to the target proteins are required. The chemical synthesis of these probes will be presented.

This work is part of an interdisciplinary project supported by the Swiss National Science Foundation (SNSF) – Sinergia Project *Molecular identification of lipid transporters for protein glycosylation*.

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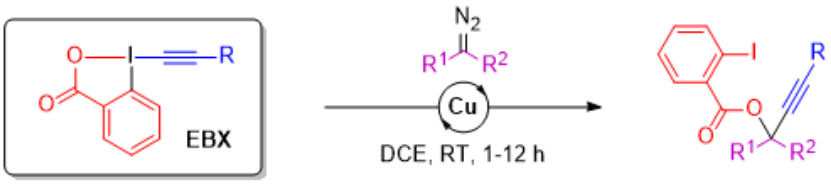
Copper-Catalyzed transformation of Diazo Compounds with Hypervalent Iodine Reagents

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

[1]Laboratory of Catalysis and Organic Synthesis

In order to develop atom economical transformations with Benziodoxolone-based reagents, the transfer of both functionalities attached to the hypervalent iodine center has to be achieved. Our group reported the oxy-alkynylation of diazo compounds using EBX reagents and cheap copper catalyst.[1]



New transformations using a similar strategy with other hypervalent iodine reagents will be presented.

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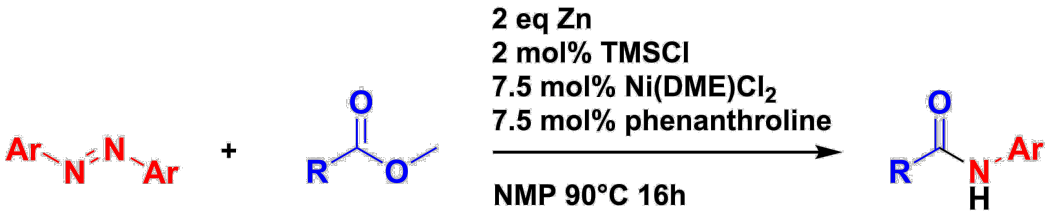
Mechanistic Insights into Azobenzene-Ester Coupling: Evidence for Nickel Imide Intermediates

M. L. Ploeger[1], A. Daru[2], J. N. Harvey[2], X. Hu[1]*

[1]EPF Lausanne, [2]KU Leuven

The development of methods for the synthesis of azobenzenes has received considerable attention recently, because of their wide range of applications.[1] As a result, using them as synthetic intermediates becomes increasingly attractive. Recently, we reported the nickel catalyzed coupling between nitroarenes and esters to form amides, in which azobenzene derivatives play a crucial role as reaction intermediate.[2] To enable the further development of azobenzene-derived chemistry, a deeper mechanistic understanding of this intriguing reactivity is of considerable interest. We present kinetic experiments, stoichiometric reactions and computational studies relating to nickel catalyzed azobenzene-ester coupling. The combined results indicate intermediacy of a nickel imide. This is interesting, because nickel imides are known to undergo a variety of reactions.[3] Since their generation normally requires hazardous reagents, the finding that they are formed in a catalytic cycle from stable and easily accessible azobenzenes provides opportunities for improvement of various synthetic methods.



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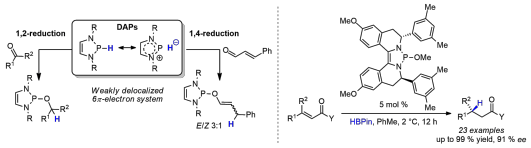
Developing Chiral 1,3,2-Diazaphospholenes for Enantioselective Catalysis

J. H. Reed[1], S. F. Miaskiewicz[1], P. Donets[1], C. Oliveira[1], N. Cramer[2]*

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

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



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

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Synthesis of Nitrogen Heterocycles by Palladium(0)-Catalyzed C(sp^3)–H Activation

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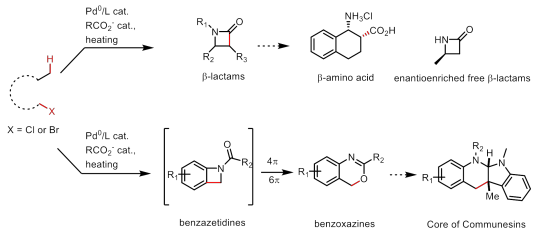
[1]Universität Basel, Basel, Switzerland

Nitrogen heterocycles are omnipresent in small-molecule pharmaceuticals, representing almost 60 % of drugs recently approved by the U.S. Food and Drug Administration.[1] In the last decades, synthetic methods have been widely developed to access these building blocks, notably through the use of a metal catalyst. In particular, methods based on C(sp^3)-H activation have been introduced, including by our group,[2] to access N-heterocycles in a straightforward manner from easily accessible precursors. Herein, we report the synthesis of beta-lactams[3] and benzoxazines,[4] with the latter arising from the electrocyclic rearrangement of benzazetidine intermediates, via palladium(0)-catalyzed intramolecular C(sp^3)-H activation.



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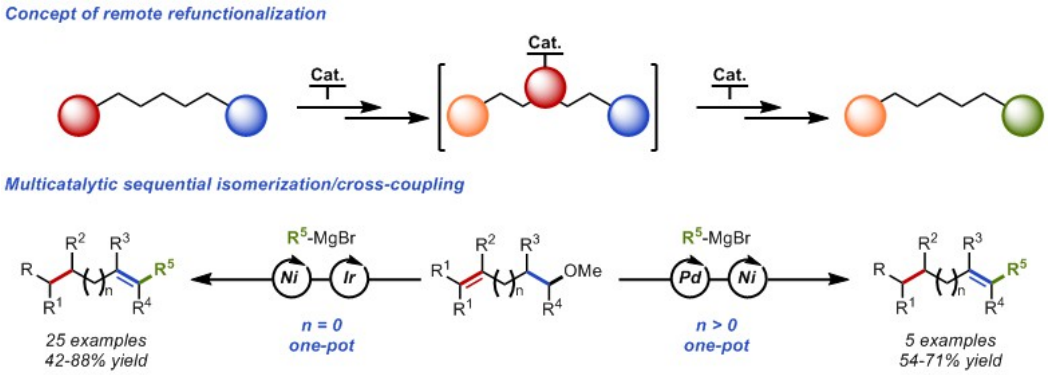
Increasing Molecular Complexity by Remote Refunctionalization: Merging Olefin Isomerization and Cross-Coupling

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

[1]Université de Genève

The long-range isomerization/refunctionalization of olefins has emerged as an effective method for the construction of functionalized molecules starting from readily available precursors.[1] Our group has previously reported the development of Ir- and Pd- catalysts for the effective isomerization of allyl- and alkenyl-alcohols to aldehydes and ketones. While high enantioselectivity were achieved with the iridium catalyst,[2] the palladium catalyst proved to be also competent in the deconjugative isomerization of a,b-unsaturated carbonyls bearing a remote alcohol functionality into the corresponding a,w-dicarbonyl compounds.[3] We found that isomerization was not restricted to alkenyl alcohols but could be extended to alkenyl methyl ethers. Thus, we envisioned the possibility to merge isomerization and cross-coupling reactions by the development of multicatalytic one-pot sequential processes which enable the preparation of substituted alkenes. First, a cationic iridium catalyst was found to be suitable for stereoselective short-range isomerization and was shown to be compatible with a nickel catalyst for the subsequent cross-coupling using Grignard reagents. Subsequently, a highly stereo- and enantioselective variant of this [Ir/Ni] sequence was developed using a chiral iridium precatalyst. Finally, a complementary [Pd/Ni] sequence was optimized for the long-range isomerization/cross-coupling of alkenyl methyl ethers with a distal C=C bond. The methodology enabled the formation of C(sp^2)-C(sp^2) and C(sp^2)-C(sp^3) bonds and afforded substituted alkenes that would be otherwise difficult to access.[4]



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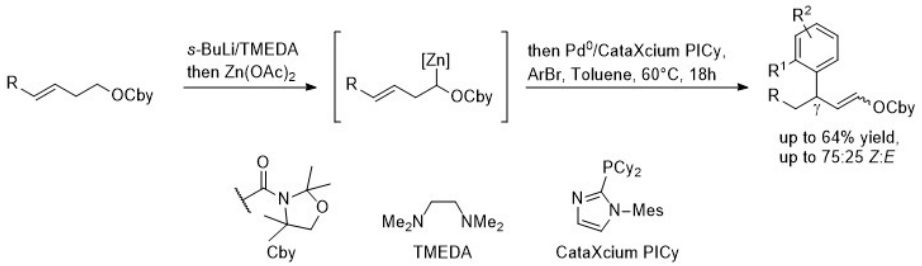
Pd-Catalyzed γ-Arylation of γ,δ-Unsaturated O-Carbamates via an Unusual Haptotropic Rearrangement.

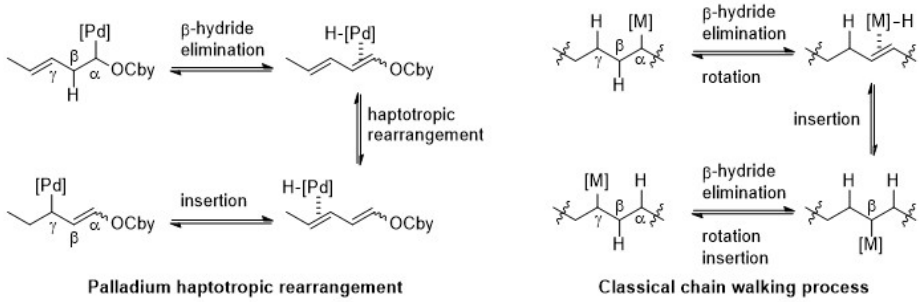
T. Royal[1], O. Baudoin[1]*

[1]Department of Chemistry, University of Basel

Within our research program dedicated to the control of site-selectivity in the Pd-catalyzed cross-coupling of secondary nucleophile, [1] we recently developed the enantioselective α-arylation of *O*-carbamates via Negishi cross-coupling. [2] In our effort to extend the methodology to its ligand-controlled migratory version, we uncovered a new reactivity of γ,δ-unsaturated substrates. These latter, after α-lithiation and transmetalation to zinc, undergo selectively γ-arylation with a variety of *o*-substituted aryl bromides.



The reaction proceeds via an unusual haptotropic rearrangement [3] of the organopalladium intermediate, in contrast to the classical chain-walking process. [4]



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Synthesis of α-amanitin via a Rh(III)-catalyzed tryptathionine formation

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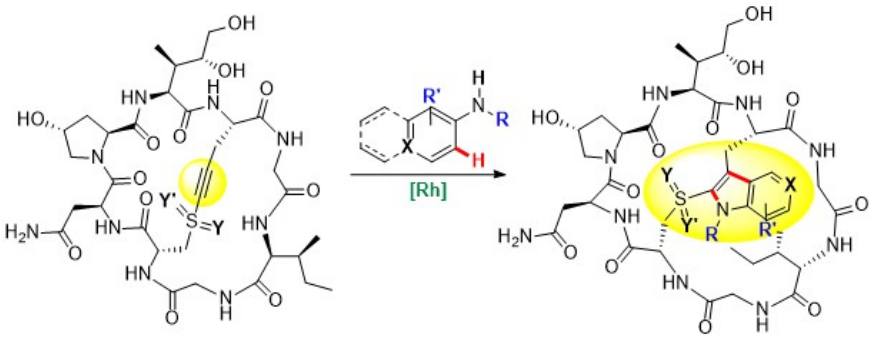
[1]Laboratory of Asymmetric Catalysis and Synthesis– EPFL BCH 4305, CH-1015 Lausanne, Switzerland

Amatoxins are ribosomally synthesized and post-translationally modified bicyclic octapeptides biosynthesized by the deadly basidiomycete fungus *Amanita phalloides*. They form a class comprised of a range of macrocycles with an eight-amino acid core sequence, IWGIGC(N/D)P, and exhibit varying degrees of hydroxylation. Amongst this group, α-amanitin is most prominent. It binds very selectively to the 140 kDa subunit (SB3) of DNA-dependent RNA polymerase II in nuclei of all eukaryotic cells, with subnanomolar dissociation constants.[1] Interaction of α-amanitin with Pol II leads to inhibition of the translocation of the RNA polymerase along the DNA template, therefore blocking the synthesis of mRNA, and as a consequence protein synthesis.[2] This interaction is responsible for the toxic effect of *Amanita phalloides*, leading to death after 4-8 days.[3] There is significant interest in investigating α-amanitin and its derivatives in order to gain further insight into the transcription mechanism, and its properties make it a target scaffold for potential new drugs. [4]The most characteristic structural feature of α-amanitin is the linkage between cysteine and 6-hydroxy-tryptophan, which effectively cross-links the main chain peptide cycle. However, relatively little is known on the structure activity relationship of the molecule, especially with regards to this moiety.

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



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AzidoBenziodoXolone (ABX) & Analogues: Development of a New Reaction and Safety Studies

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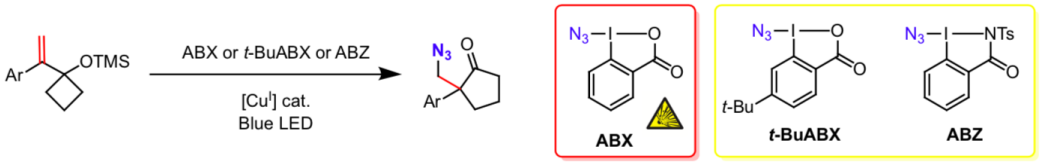
[1]Laboratory of Catalysis and Organic Synthesis, EPFL SB ISIC LCSO, BCH 4306, CH-1015 Lausanne, Switzerland, [2]TÜV SÜD Schweiz AG, Mattenstrasse 24, CH-4002 Basel, Schweiz, [3]Group of Chemical and Physical Safety (GSCP), EPFL-ISIC-GSCP, CH J2 502 | Station 6, CH-1015 Lausanne, Switzerland

Organic azides figure among the most versatile and useful compounds in synthetic chemistry. These high-energy molecules can undergo a multiplicity of transformations, leading to nitrogen-containing products with important applications in organic synthesis, biology, medicine, and materials science.[2] In recent years, AzidoBenziodoXolone (ABX)[1] – the Zhdankin reagent – has received increasing attention as an effective azidation reagent, which has been utilized in several azide-transfer processes, relying either on radical-based or Lewis acid-mediated pathways.[3]



Herein, we present the use of ABX in a new photoredox-driven reaction to access azide-containing cyclic ketones. During the optimization of this reaction, we became aware of the safety hazard originating from the explosive nature of ABX. Therefore, we present here a full safety study of this compound and introduce two new analogues, *t*-BuABX and ABZ, proven to be safer. We also show their reactivity as ABX substitute for the presented reaction, as well as other azidation processes, such as photoredox-driven azidolactonization.[4]

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Thio-catalyzed Hydroalkylation of Alkenes Employing Water as Source of Hydrogen

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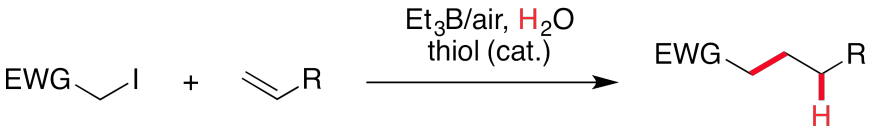
[1]Universität Bern

After a large advance in transition-metal catalyzed aryl-aryl, aryl-alkenyl, and aryl-alkynyl cross coupling reactions, there is now a large effort to develop a similar set of $C(sp^3)$-$C(sp^3)$ cross coupling methodologies. Free radical intermediates are an effective choice for this process under mild conditions. The process benefits from a large tolerance to functional groups since the reactive organometallics required in conventional approaches are bypassed. The addition of a carbon-centered radical to alkenes, followed by its reduction was first developed by Giese, employing AIBN as initiator and Bu_3SnH as reductant for this hydroalkylation process.[1] However, the use of tin for this reaction is expensive, toxic and leads to product contamination.[2] A few years later, transition metal-free methods developed by Roberts, Fukuyama and Renaud are good alternatives to this reaction.[3]



We showed recently that iodides could be deuterated efficiently in the presence of a trialkylborane, heavy water (D_2O), and a catalytic amount of thiol.[4] We report here, an extension of this method to a hydroalkylation reaction catalyzed by a thiol. This process, transition metal-free, is an easy, cheap, and eco-friendly way to perform the reaction under mild conditions. The mechanism of the hydroalkylation catalyzed by a thiol as well as the scope and limitations of the reaction are discussed.

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Studies Towards the Total Synthesis of Nahuoic Acid A

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[1]Departement of Chemistry and Applied Biosciences, Institute of Pharmaceutical Sciences, ETHZ

Nahuoic acid A (**1**) (Fig. 1) is a highly hydroxylated marine polyketide that was isolated in 2013 by Andersen and co-workers from a culture of *Streptomyces* sp. found in tropical marine sediments. Nahuoic acid (**1**) is a member of a small group of structurally related natural products (Fig. 1) and it was the first selective *S*-adenosylmethionine (SAM)-competitive inhibitor of the lysine methyl transferase SETD8 ever to be identified.[1,2] So far, only one total synthesis of a nahuoic acid family member, i. e. nahuoic acid C (**3**), has been successfully completed by Smith and co-workers.[3]

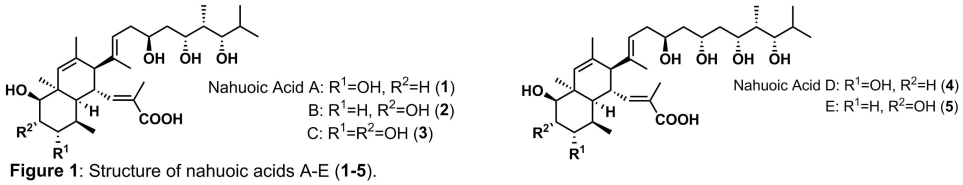
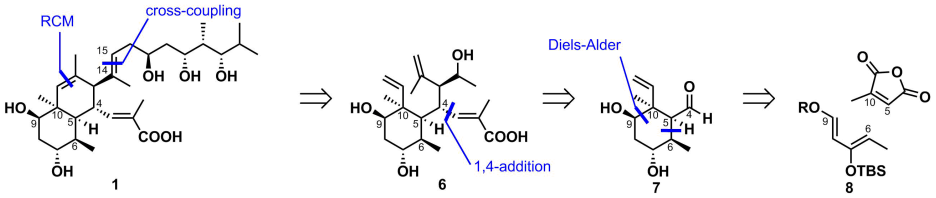


Figure 1: Structure of nahuoic acids A-E (**1-5**).

Enticed by its highly challenging substituted *cis*-decalin core structure and its interesting biological activity, we have embarked on the total synthesis of nahuoic acid (**1**). As illustrated in Scheme 1, our strategy toward **1** envisions its final assembly by a late stage sp^2-sp^3 cross-coupling to form a trisubstituted C14-C15 double bond. The *cis*-decalin core is planned to be accessed by ring closing olefin metathesis (RCM) of triene **6**, in which the C4 side chain should be installed in a stereoselective, substrate-controlled 1,4-addition. The stereochemistry of the four contiguous stereocenters at C5, C6, C9, C10 was foreseen to be installed in an *endo*-selective Diels-Alder reaction of diene **8** and citraconic anhydride.
Our work so far has led to the development of an efficient, stereoselective route for the synthesis of the intermediate aldehyde **7**. This contribution will discuss the chemistry involved in the preparation of **7** together with our ongoing efforts on the further elaboration of **7** *en route* to nahuoic acid (**1**).



Scheme 1: Retrosynthetic approach to nahuoic acid A (**1**).

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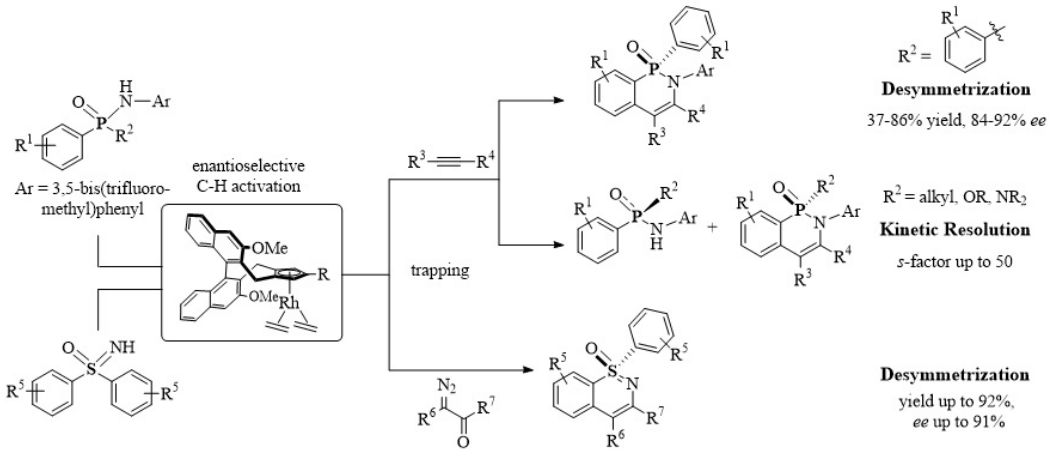
Rh(III)-Catalyzed Asymmetric Synthesis of Heteroatom-Stereogenic Compounds

Y. Sun[1], N. Cramer[1]*

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

Phosphorus- and sulfur-stereogenic compounds are being widely used as ligands in asymmetric transition-metal-catalysis and as organocatalysts.[1] These molecules also show important potential for pharmaceutical and agricultural use.[2] However, synthesizing these heteroatom-stereogenic compounds remains a challenge.

Herein we report a chiral cyclopentadienyl[3] Rh(III)-catalyzed enantioselective C-H activation enabling access to *P*- and *S*-stereogenic compounds. For prochiral phosphinamide substrates, enantioenriched heterocycles were accessed *via* annulation with internal alkynes.[4] In addition, chiral phosphinamides were kinetically resolved, yielding both cyclic phosphinamides and unreacted starting materials, with selectivity-factors of up to 50.[5] In contrast, prochiral sulfoximines were trapped with diazo compounds to render enantioenriched benzothiazine 1-oxides regioselectively, while releasing only water and nitrogen as side products.[6] Kinetic studies revealed that a concerted-metalation-deprotonation is the stereo-determining step when an inorganic base is employed, in contrast to previous reports from our group.[7]



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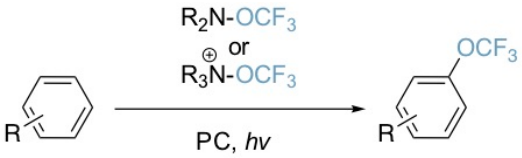
Development of Novel Reagents for the C–H Trifluoromethoxylation of Arenes

P. F. Tripet[1], B. J. Jelier[1], I. Franzoni[2], G. Jeschke[1], A. Togni[1]*

[1]ETH Zürich, [2]University of Toronto

Due to its unique properties, the trifluoromethoxy (OCF_3) group has attracted growing attention in pharmaceutical, agrochemical and material science.[1] Despite this interest, the incorporation of OCF_3 into organic molecules is generally regarded as a major unsolved problem in synthetic chemistry.[2] In part, development of trifuoromethoxylation reagents has been hampered by the inherent instability and poor nucleophilicity of the OCF_3 anion.[3] In contrast to anionic-based approaches, the present work investigates the generation and reactivity of the largely unexplored trifluoromethoxy radical.[4] Key to this goal is the synthesis and exploration of novel reagents capable of undergoing N–O bond homolysis under photoredox conditions.[3] Thus, electron deficient arenes can undergo unselective C–H functionalization in moderate yield to afford the desired trifluoromethyl aryl ethers as mixtures of regioisomers.[5] Furthermore, contemporary challenges in the harnessing of highly reactive radical species will be discussed.



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Organic linker molecules designed to provide regional control over MOF growth.

D. Vogel[1], M. Mayor[1]*

[1]University of Basel

Metal-organic frameworks (MOF) are grown in a self-assembly process with no regional control over the MOF growth. To gain regional control over the MOF forming process, a modified layer-by-layer growth process will be presented. The MOF growth will be restricted to a specific region, using organic bidentate linker molecules with one masked coordination site. The masked coordination site is available for selective unmasking via an external stimulus restricting the growth in the next layer-by-layer growth cycle to this specific unprotected coordination site. Therefore, we present a bidentate organic linker with a thermo- and/or light-sensitive protection group to mask one coordination site.

Lewis Acid catalyzed enantioselective desymmetrization of donor-acceptor meso-diaminocyclopropanes

M. Wang[1], J. Waser[1]*

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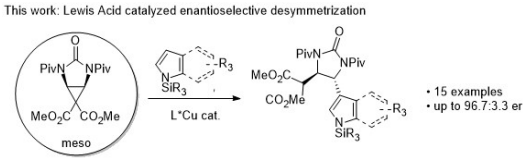
D-A cyclopropanes are versatile building blocks in organic synthesis.[1] Ring strain combined with bond polarization enables regioselective ring opening, annulation and rearrangement reactions upon Lewis or Brønsted acid activation. By varying the substituents on the cyclopropane and the reaction partners, a plethora of structures can be accessed. Enantiomerically enriched compounds can further be obtained by performing asymmetric transformations. In this regard, D-A cyclopropanes are often themselves chiral, leading to two possible scenarios: kinetic resolution and DYKAT (dynamic kinetic asymmetric transformation).[2] The latter is often the strategy of choice as it displays higher efficiency. Our group applied it for the first time to donor-acceptor aminocyclopropanes [3] but the desymmetrization of achiral *meso* substrates was still challenging and never reported.[4] We therefore designed a novel *meso*-diaminocyclopropane. The transformation displayed high enantioselectivity and complete diastereoselectivity, together with a broad scope of indoles as well as a pyrrole. Beyond constituting an important proof of concept, the methodology delivered enantioenriched urea derivatives as products, which are highly important core structures in natural and bioactive compounds. The design of a new subclass of BOX ligands was essential for obtaining high enantiomeric ratios.



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A Readily Accessible Class of Chiral Cp Ligands and their Application in Ru(II)-Catalyzed Enantioselective Syntheses of Dihydrobenzoindoles

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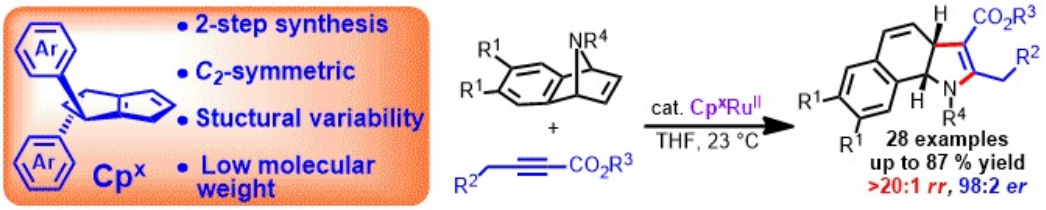
Chiral Cp^x ligands have a large application potential in enantioselective transition-metal catalysis. However, the development of concise and practical routes to such ligands remains in its infancy stage.[1] We present a convenient and efficient synthesis of a novel class of chiral Cp^x ligands with tunable sterics that can be readily used for complexation giving $Cp^xRu(II)$, $Cp^xRh(I)$, and $Cp^xIr(I)$ complexes. The synthetic access to this ligand family is remarkably facile. A class of chiral Cp^x ligands are efficiently accessed with excellent enantiopurity in just two steps from cyclopentadiene and cinnamaldehydes. The potential of this ligand class is demonstrated with the Ru(II)-catalyzed enantioselective syntheses of dihydrobenzoindoles with high levels of chemo- and enantioselectivity.[2]



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Chitosan/Carboxymethyl Cellulose Sulfuric Acid Hydrogels and Their Nanocomposits: Preparation and Application in Tartrazine Removal

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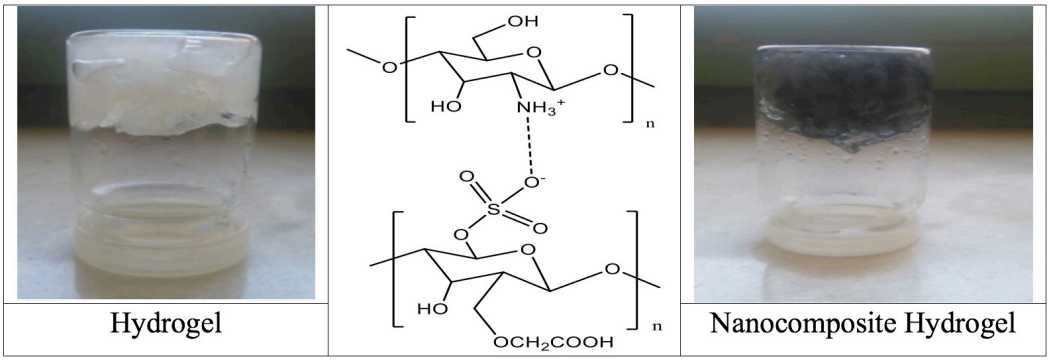
Synthesis of hydrogels based on chitosan has gained much attention. Non-covalent interactionssuch ashydrogen bonds and electrostatic between amino and hydroxyl groups of chitosan with different cross-linkers leads to formationof physically cross-linked chitosan hydrogels. The cross-linking of chitosan not only improve their resistance to acidic environments, but also increase their absorption capacity.

Herein, at first, carboxymethyl cellulose sulfuric acid (CMC-SO_3H) was prepared through reaction of chlorosulfonic acid with carboxymethyl cellulose. Then, preparation of physically cross-linked hydrogels was carried out by simple mixing of chitosan and CMC-SO_3H in acetic acid (0.1%, v/v) solution. The mixture was stirred vigorously with a mechanical stirrer for approximately 1-2 min at room temperature. The variousratios of chitosan : CMC-SO_3H mixtures (1 : 0.25, 1 : 0.5, 1 : 0.75, 1 : 1, 1 : 1.25, 1 : 1.5, w/w) were used for synthesis of hydrogels. In continuation, their hydrogel nanocomposites were prepared by crosslinking of chitosan and CMC-SO_3H (with ratio of 1 : 1, w/w)in the presence of 0.25% and 0.5% (w/w) multi-walled carbon nanotubes (MWCNTs).

The adsorption of tartrazine, by prepared hydrogels was investigated using batch equilibration method at different pHs (PH: 4, 7). It was found that chitosan : CMC-SO_3H hydrogel with ratio of 1:1 was the appropriate adsorbent for tartrazine. Therefore, the hydrogel with ratio of 1:1 was selected. The effect of PH was studied for the adsorption of tartrazine at different PHs (4, 7) by chitosan : CMC-SO_3H hydrogel (1:1). It was observed that the best result was obtained at PH 7 (adsorption capacity about 91%).Introducing MWCNT-COOH in the structure of chitosan : CMC-SO_3H hydrogels has an effect on the adsorption of tartrazine. It was seen that the maximum and best adsorption capacity was obtained for hydrogel nanocomposites (0.25%). The maximum percentage of tartrazine adsorption for nanocomposite hydrogel (0.25%) was 94%.



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Synthesis and Reactivity of Vinyl Triazenes

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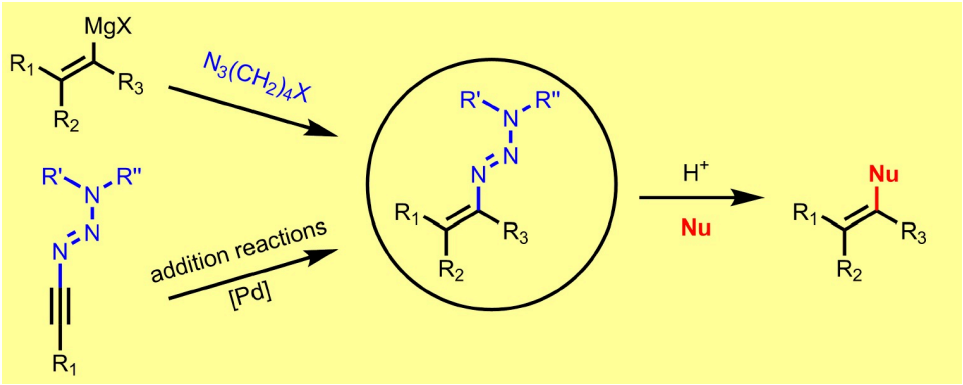
Vinyl triazenes represent convenient precursors for generation of vinyl cation intermediates. First vinyl triazenes were described in the literature in 1967.[1] Due to the lack of versatile methods for the preparation of vinyl triazenes, their synthetic utility remained underexplored for the next 50 years.[2] We have developed two general approaches for the synthesis of vinyl triazenes. The first approach is based on a coupling reaction between vinyl Grignard reagents and organic azides.[3] This method allows preparing simple cyclic and noncyclic vinyl triazenes in moderate to good yields. The second method relies on addition reactions to 1-alkynyl triazenes.[4] Palladium-catalyzed hydrogenation, hydroarylation and haloallylation reactions afford a variety of functionalized vinyl triazenes with high yields and selectivities. We have also demonstrated the utility of vinyl triazenes by substitution of the triazene group by broad range of nucleophiles under mild and metal-free conditions.



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Electrophilic Indole and Pyrrole Reagents for C-H Functionalization

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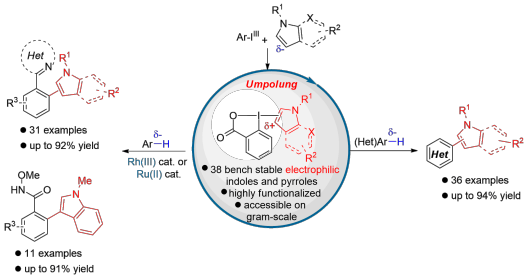
[1]Ecole Polytechnique Fédérale de Lausanne

Amongst all the azoles present in nature, electron-rich pyrroles and indoles are the most ubiquitous.[1] In particular, the subclass of mixed bi-(hetero)arenes is encountered in top selling drugs,[2] optoelectronic materials and natural bioactive compounds.[3] Even if many methods for the formation of the (hetero)arene-indole or -pyrrole bond have been reported,[4] low regioselectivity, homo-coupling, de-aromatization and polymerization are common limitations. To overcome the intrinsic nucleophilic properties of electron-rich indoles and pyrroles, a “umpolung” approach can be considered to allow new synthetic disconnections. Hypervalent iodine reagents are known to invert the reactivity of various nucleophiles,[5] but have been only rarely used in the case of electron-rich heteroarenes.



We present herein the synthesis of 38 novel electrophilic indole and pyrrole benziodoxolone reagents.[6] These new reagents are bench stable, highly functionalizable and their synthesis is facile and scalable. They can be applied in metal-catalyzed C-H activation transformations as well as metal-free oxidative cross couplings with electron-rich (hetero)arenes.[7] In both methods the desired products were obtained with high regioselectivity and could not be synthesized using previously reported metal catalyzed C-H arylation processes.

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Total Synthesis of the Antibiotic Disciformycin B

P. Waser[1], K. Altmann[1]*

[1]Department of Chemistry and Applied Biosciences, Institute of Pharmaceutical Sciences, ETHZ

Disciformycins A (**1**) and B (**2**) are macrolide glycosides that were isolated in 2014 from myxobacterium *Pyxidicoccus fallax* by Müller and co-workers *(Figure 1).* Structural motifs of the natural products include a 12-membered macrolactone ring, an unusual angelic acid-derived C-11 side chain and a *D*-(-)-arabinofuranoside moiety with an α-glycosidic linkage to the macrocyclic core. Biological assessment revealed that **1** and **2** show significant antibacterial activity against methicillin- and vancomycin-resistant *Staphylococcus aureus* (MRSA/VRSA) strains.[1]

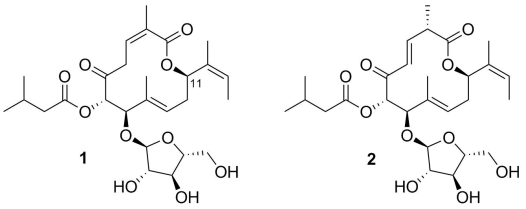
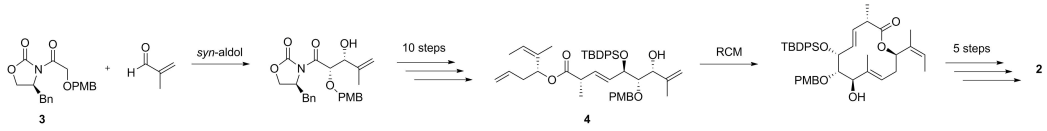


Figure 1. Structures of disciformycin A (**1**) and B (**2**).

Given the interesting structural and biological features of **1** and **2**, we have embarked on a project aiming at the total synthesis of these antibiotics, in order to provide a basis for the subsequent synthesis of analogs for structure-activity relationship (SAR) studies. So far, only one total synthesis of **1** and **2** has been reported in the literature by Fürstner and co-workers.[2] We have accomplished the total synthesis of **2** in 17 linear steps starting from known imide **3** (*Scheme 1*). Key steps of our synthesis include (1) a highly efficient *syn*-aldol reaction between imide **3** and methacrolein; (2) ring-closing olefin metathesis (RCM) of tetraene **4** to afford the macrocyclic core; (3) late-stage dehydrative glycosylation for introduction of the arabinofuranoside moiety; and (4) mild chemoselective allylic alcohol oxidation that completed the total synthesis.



Scheme 1. Total synthesis of disciformycin B (**2**).

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A Photochemical Amplifier Based on Self-Immolative Spacers

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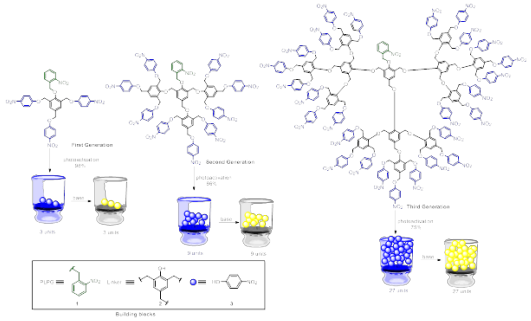
[1]University of Fribourg, [2]University of Fribourg

A molecular amplifier could be defined as a device capable of transforming a weak chemical (physical) input into a large chemical (physical) output. In this work, we will present a molecular amplifier capable of releasing multiple chemical entities upon activation by a single photochemical event (scheme 1).



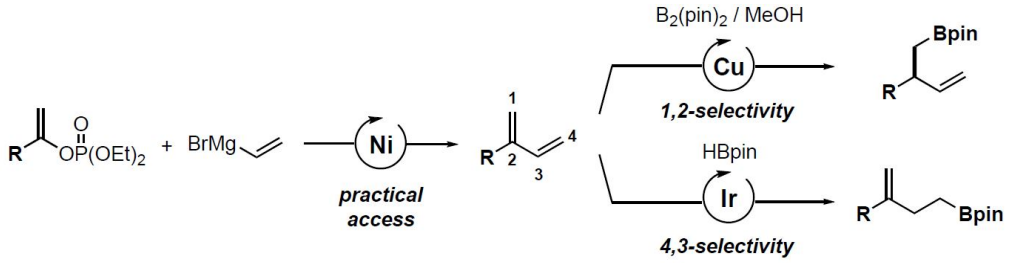
Our system could be used as 1) indicator 2) solubilizing agent and 3) as controlled drug delivery system, and is based on readily available building blocks, such as 1) a photolabile protecting group (2-nitrobenzyl) to induce an increase of the stability in the system, 2) a self immolative linker to connect two or more entities and be able to fragment upon activation and 3) nitrophenol, a colored releasable group.

2-Substituted 1,3-Dienes as Platform for (Enantio)Selective Metal Catalysis

D. Fiorito[1], Y. Liu[1], S. Folliet[1], C. Mazet[1]*

[1]Department of Organic Chemistry, Université de Genève

Conjugated 1,3-dienes represent a particularly attractive platform for selective functionalization. They find widespread use as building blocks for organic synthesis as well as in polymerization processes. From a selectivity standpoint, functionalization of 1,3-dienes poses a significant challenge due to the numerous coordination and insertion modes conceivable for a transition metal catalyst. [1] In recent years, efforts to develop selective catalytic transformations have been essentially focused on *linear* 1,3-dienes (i.e. 1-substituted 1,3-dienes).[2] Until recently, the limited synthetic accessibility of *branched* 1,3-dienes (i.e. 2-substituted 1,3-dienes) has severely limited their use in the development of selective transformations.[3] Whitin this context, our laboratory recently reported a general Ni-catalyzed protocol which streamlines access to 2-substituted 1,3-dienes from readily available synthons.[4] Herein we describe our results in the selective hydroboration and protoboration of this underexplored class of conjugated olefins. An enantioselective Cu-catalyzed protoboration of 2-substituted 1,3-dienes has been developed.[5] The use of a chiral phosphanamine ligand is essential in achieving high chemo-, regio- and enantioselectivity, providing rapid access to a variety of synthetically relevant homoallylic boronates/alcohols. A complementary approach based on iridium catalyzed hydroboration of dienes affords perfect 4,3-selectivity, providing valuable homoallylic boronates.[6] Overall, we present two catalytic strategies that solve critical challenges posed by conjugated dienes both in terms of *reactivity* (mono- vs. di-functionalization, parasitic reduction, competing isomerization) and *selectivity* (chemoselectivity, regioselectivity, enantioselectivity).



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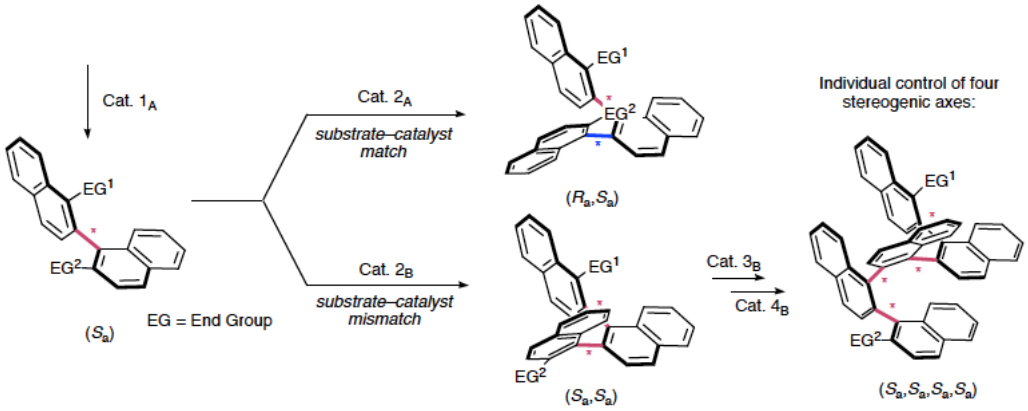
Catalyst-Controlled Stereodivergent Synthesis of Atropisomeric Multiaxis Systems

A. Castrogiovanni[1], D. Lotter[1], C. Sparr[1]*

[1]Department of Chemistry

A well-defined spatial orientation of substituents in a molecular framework is an essential requirement for the synthesis of molecular systems with unique properties and applications. Due to their configurational stability, oligo-1,2-naphthylenes are particularly suitable to organize groups in space. A method that controls the configuration of each stereogenic axis is thus highly desirable. The presentation outlines our approach for the stereodivergent synthesis of atropisomeric multiaxis systems based on the sequential addition of a building block to an aromatic aldehyde precursor, followed by an in situ double oxidation and stereoselective arene-forming aldol condensation. In order to overcome the substrate bias to divert atropodiastereoselectivity, efficient amine and ion-pairing catalysts that allow to individually control up to four stereogenic axes were identified.



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Pd(0)-Catalyzed Desymmetrizations Allow for Facile Synthesis of Chiral Isoindoles

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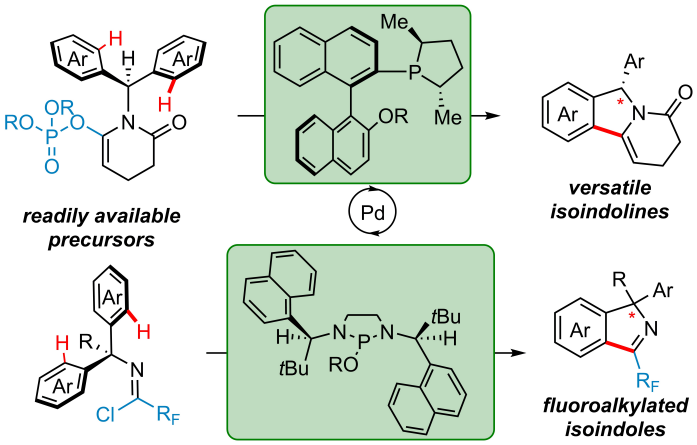
[1]Laboratory of Asymmetric Catalysis and Synthesis, EPFL SB ISIC LCSA, CH-1015 Lausanne, Switzerland

The isoindole scaffold is an ubiquitous motif in natural products and pharmaceuticals.[1] However the synthetic approaches to this valuable skeleton remain limited to conventional methods. In this respect a stereocontrolled C–H functionalization serves as an attractive complimentary strategy, allowing for the rapid construction of elaborate structures from simple precursors.[2] Whilst aryl (pseudo)halides have been extensively employed as electrophiles in enantioselective Pd(0)-catalyzed syntheses of heterocycles, alternative partners for C–H functionalizations are far less developed.

We have shown for the first time that ketene aminal phosphates are competent electrophiles for Pd(0)-catalyzed desymmetrization.[3] This transformation delivers versatile chiral isoindolines in good yields and high enantioselectivities. Intending to introduce sought after fluorine-containing substituents we have studied C–H functionalization of imidoyl chlorides allowing for efficient asymmetric synthesis of densely substituted fluoroalkylated isoindoles. High levels of stereocontrol in both transformations are achieved by careful design of bulky chiral monodentate ligands: binaphthyl-derived phospholanes and diazaphospholanes.[4]



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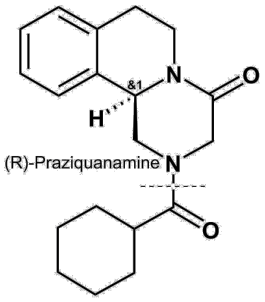
Praziquantel: an old product with new challenges! Performance Materials, Merck KGaA Darmstadt Germany

A. Wächtler[1,2], D. Maillard[1]

[1]Performance Materials Merck KGaA Darmstadt Germany, [2]Consultant

For more than 30 years, Praziquantel (2-Cyclohexylcarbonyl-1,2,3,6,7,11b-hexahydro-4H-pyrazino[2,1-a]-isochinolin-4-one, ATC Code P02BA01), discovered and co-developed by Merck and Bayer, has been the recommended by the World Health Organization for the treatment of schistosomiasis, a neglected tropical disease caused by the genus Schistosoma, which affects more than 240 million people worldwide especially in Africa, Middle East, Southeast Asia, and South America [1]

Currently approved for the treatment of school-aged children (aged six and over), Praziquantel is administered as racemate at a dose of 40 mg/kg body weight. Unfortunately the bitter taste, the large tablet size (600 mg) and lack of pediatric clinical data hamper its use for pre-school aged children. In view of developing a pediatric formulation, a chiral switch from racemic Praziquantel to the actual active ingredient (*R*)-Praziquantel is currently being investigated.



(*R*)-Praziquantel

Here we will describe the chemistry of Praziquantel and the options for a rapid and inexpensive development at industrial scale to access (*R*)-Praziquantel as well as the final choice.

This work is supported within the Pediatric Praziquantel Consortium by the Bill & Melinda Gates Foundation and by the Global Health Innovative Technology Fund (GHIT) as well as by Merck.

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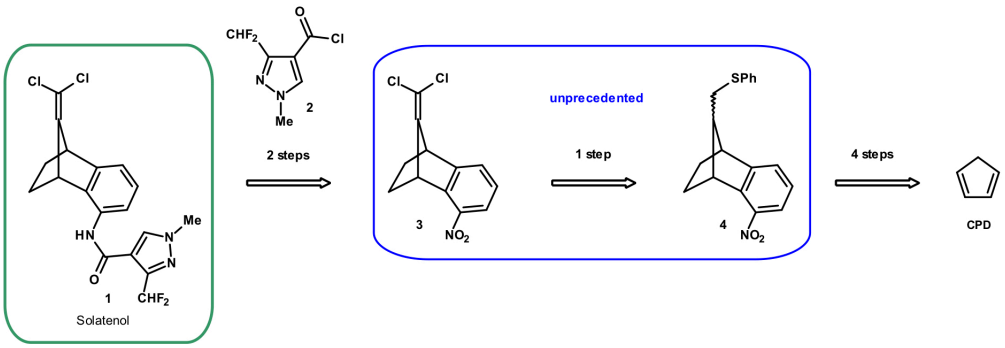
The Solatenol Process Challenge How Manufacturing Restrictions Can Boost Creativity

R. Beaudegnies[1], M. Baalouch[1]

[1]Syngenta Crop Protectsion AG, Research Chemistry, Schaffhauserstrase 101, CH-4332 Stein, Switzerland - renaud.beaudegnies@syngenta.com



*Solatenol*fungicide is a last generation succinate dehydrogenase inhibitor (SDHI) launched by Syngenta in 2016 and exhibits an outstanding activity against the key pathogen *Phakopsora pachyrhizi*.

Its unusual and complex structure has triggered challenging process work prior to manufacturing.

We report the development of an original synthetic strategy matching the tight requirements of active ingredient (AI) production on industrial scale.

In particular, we have established the unprecedented one-step transformation of thioether substrate (4) into the corresponding dichlorovinyl derivative (3) as a key step; demonstrating how strong synthetic constraints can spark innovative solutions.

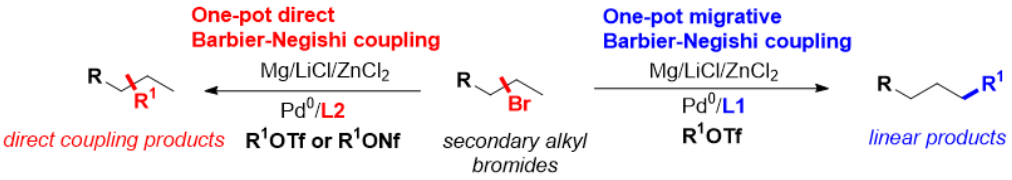
Ligand-Controlled Selectivity in Palladium-Catalyzed Barbier-Negishi Couplings of Secondary Alkyl Bromides

K. Zhang[1], O. Baudoin[1]

[1]Department of Chemistry, University of Basel

Palladium-catalyzed C(sp^2)-C(sp^3) cross-couplings are particularly valuable tools in synthetic chemistry and hence a great deal of interest has emerged in this area.[1] Although great progress has been made in the last decades, important challenges still exist, such as the preformation of organometallic species and the control of the coupling site-selectivity due to competing *β*-H elimination.[2,3]

Herein, an operationally simple and mild Barbier-Negishi coupling of secondary alkyl bromides is described. Whereas newly developed sterically hindered phosphine ligands favor the direct cross-coupling, more flexible phosphine ligands induce migrative couplings through a *β*-H elimination/rotation/insertion sequence.[4]



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Direct C-H Trifluoromethoxylation of Arenes Triggered by Visible Light Mediated Redox Fragmentation of Pyridinium Reagents

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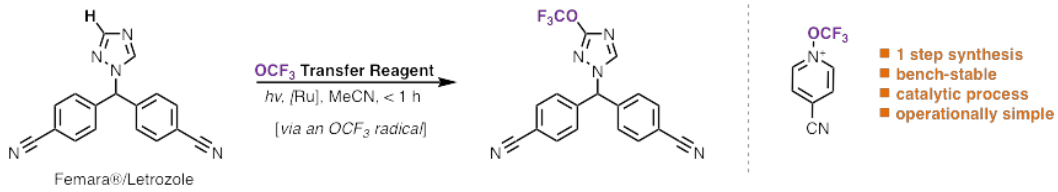
Although the trifluoromethoxy substituent is prevalent in a wide range of pharmaceuticals, agrochemicals and materials, methods to introduce this motif into aryl scaffolds are highly underdeveloped and limited. The synthesis of complex aryl trifluoromethyl ethers typically requires building blocks prepared in multiple step syntheses with difficult to handle and often harsh reagents and conditions. Furthermore, many of these approaches either suffer from poor substrate scope or require the use of highly reactive, toxic or thermally unstable reagents. Herein, we present a simple trifluoromethoxylation methodology that enables non-directed functionalization of C–H bonds on a range of substrates to provide direct access to aryl trifluoromethyl ethers. This light driven process is distinctly different than conventional protocols and occurs through an OCF_3 radical mechanism mediated by a photoredox catalyst, triggering a light-driven neutral N–O fragmentation of a novel, bench-stable pyridinium reagent. Furthermore, we will showcase our efforts in developing high intensity photoreactors suitable for high throughput screening that may be applicable to the wider community interested in harnessing light driven processes for reaction discovery.



Palladium-Catalyzed Synthesis of Ketenimines with Isocyanides

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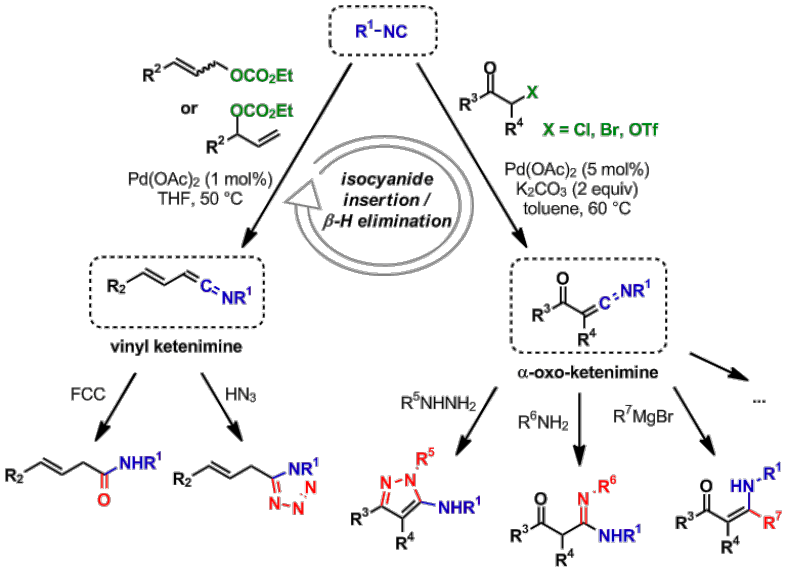
The last 15 years have witnessed significant progress in palladium-catalyzed isocyanide insertion reactions. In this context, we recently reported two new syntheses of ketenimines by taking advantage of a palladium-catalyzed isocyanide insertion / β-hydride elimination sequence.

The first protocol allowed the generation of vinyl ketenimines from isocyanides and allyl carbonates.[1] The *in-situ* formed ketenimines were readily hydrolyzed to β,γ-unsaturated carboxamides upon FCC on silica gel. Alternatively, a novel three component reaction with HN_3 was subsequently developed for the regioselective synthesis of 1,5-disubstituted tetrazoles. The second protocol delivered α-oxo-ketenimines from isocyanides and α-haloketones.[2] Reaction of these relatively stable α-oxo-ketenimines with nucleophiles such as hydrazines, amines and Grignard reagent afforded pyrazoles in one-pot, β-keto-amidines and enaminones with high chemoselectivity. Whereas amines and Grignard reagent attacked exclusively on the ketenimine functions, the formal [3+2] cycloaddition with *N*-monosubstituted hydrazines was initiated by nucleophilic addition to the carbonyl group.



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Synthesis of Fluorescent Nucleoside Analogues

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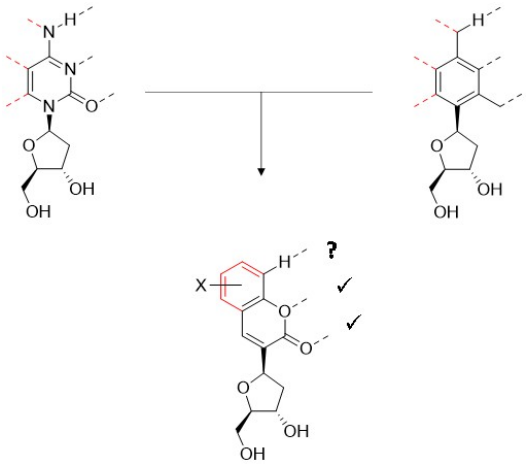
Nucleosides with fluorescent properties can be employed as powerful tool for probing DNA structure. A broad range of fluorescent nucleobases have been synthesised since the 1960s, when the first analogue was reported. This design process can be quite challenging due the necessary balance between canonical nucleobase mimicry and sufficient fluorescence for application. Most of the isomorphic derivatives developed suffer from poor photophysical properties, whereas the most fluorescent analogues cannot be used as native mimics.[1] This spectrum of extremes leaves a gap in which we hope to explore and develop nucleosides which fulfil both criteria.

Furthermore, another cleft can be observed between C-C and native C-N nucleosides. Despite this allowing the access to a myriad of other nucleobases, C-C nucleosides are rather underutilised in comparison due to the difficulties with forming their glycosidic bond.[2,3] We also endeavoured to employ C-C nucleosides to examine some well-established fluorescent structures as Watson-Crick face mimics.

One such candidate we have developed contains a coumarin moiety. The advantages of coumarins are firstly their novelty as nucleobases. Secondly, their fluorescent properties have been extensively studied. Finally they have a partial Watson-Crick hydrogen bonding face, which allows for some mimicry of native cytosine. Thus far, minimal investigation have been carried out into the interactions of C-H moieties acting as a hydrogen bond donor within a DNA duplex.



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Influence of the trans/cis Conformer Ratio on the Stereoselectivity of Peptidic Catalysts

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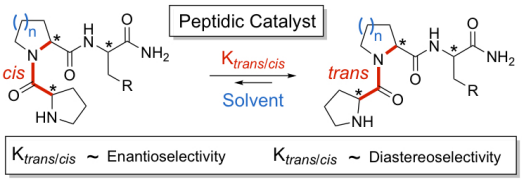
The *trans*/*cis* isomerization of Xaa-Pro amide bonds (Xaa: any amino acid) is key for the structure and function of several enzymes. In recent years, numerous versatile peptidic catalysts have been developed that bear Xaa-Pro amide bonds. We envisioned that control over the *trans*/*cis* amide bond ratio might provide a tool to optimize the catalytic performance of peptidic catalysts.[1,2]

Our group developed peptides of the H-Pro-Pro-Xaa type that are highly reactive and stereoselective catalysts for organocatalytic C-C bond formations, such as aldol reactions and conjugate addition reactions of aldehydes to nitroolefins and unprotected maleimide.[2] Here, we shed light on the influence of the amide bond conformation on the stereoselectivity and reactivity of H-DPro-Pro-Xaa-NH_2 type catalysts in conjugate addition reactions.[3] The middle Pro residue within the tripeptides was replaced with analogues of varying ring sizes (azetidine carboxylic acid, Aze, and piperidine carboxylic acid, Pip) to produce different *trans*/*cis* ratios in different solvents. Our investigations revealed a direct correlation between the *trans*/*cis* amide bond ratio and the enantio- and diastereoselectivity of the tripeptidic catalysts. This ultimately led to the identification of the H-DPro-Pip-Glu-NH_2 a catalyst that allows C−C bond formations in the presence of as little as 0.05 mol %, which is the lowest catalyst loading yet achieved for organocatalyzed reactions that rely on an enamine-based mechanism.



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Synthesis and Reactivity of Vinyl Triazenes

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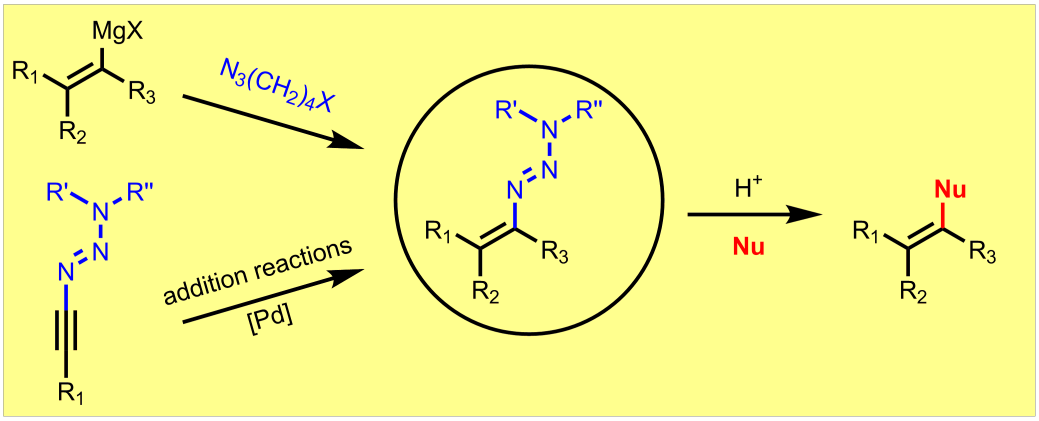
Vinyl triazenes represent convenient precursors for generation of vinyl cation intermediates. First vinyl triazenes were described in the literature in 1967.[1] Due to the lack of versatile methods for the preparation of vinyl triazenes, their synthetic utility remained underexplored for the next 50 years.[2] We have developed two general approaches for the synthesis of vinyl triazenes. The first approach is based on a coupling reaction between vinyl Grignard reagents and organic azides.[3] This method allows preparing simple cyclic and noncyclic vinyl triazenes in moderate to good yields. The second method relies on addition reactions to 1-alkynyl triazenes.[4] Palladium-catalyzed hydrogenation, hydroarylation and haloallylation reactions afford a variety of functionalized vinyl triazenes with high yields and selectivities. We have also demonstrated the utility of vinyl triazenes by substitution of the triazene group by broad range of nucleophiles under mild and metal-free conditions.



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