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Decoding the Biological Mechanisms of Buruli Ulcer Thanks to a modular Total Synthesis

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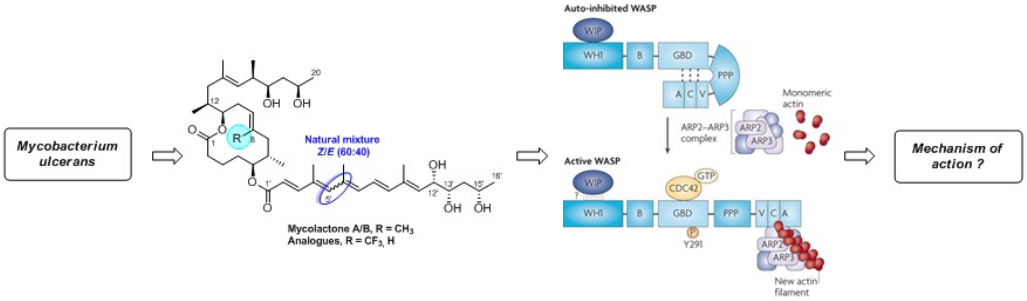
Buruli ulcer is a necrotizing skin disease present in more than thirty countries in the world, located mainly in West and Central Africa but also in Australia and now in Japan.[1] This infection is caused by *Mycobacterium ulcerans* (*M. u.*) that secretes a macrolide toxin called mycolactone, which is the first polyketide isolated from a human pathogen. The disease is characterized by the formation of progressive necrotic lesions combined with a lack of acute inflammatory response, and mycolactone is known to be directly involved in the biological mechanism. Recently, two important regulators of the actin cytoskeleton, WASP and N-WASP, have been discovered as the first proteic targets of the toxin.[2-3]

To date no specific and efficient treatment of Buruli ulcer has been developed, which correlates with the dramatic lack of understanding of the associated chemical and biological mechanisms. Moreover, the difficulty encountered by biologists to obtain this toxin from cultures of *M. u.*, led us to develop a diverted synthetic route for obtaining this toxin and its analogues with a high degree of purity in order to understand the onset of the disease.[4-5]



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Photoresponsive self-healing supramolecular hydrogels for light-induced release of bioactive guests

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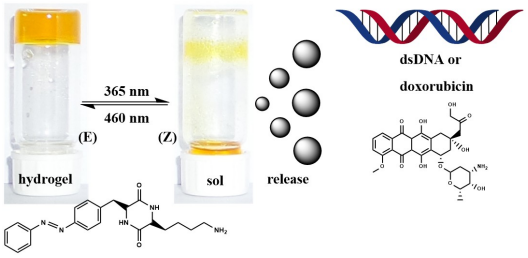
[1]Karlsruher Institut für Technologie (KIT)

Molecular photoswitches are small compounds that exhibit reversible changes of geometry, dipole moment, or rigidity upon exposure on light. Azobenzenes, diarylethylenes and spiropyrans are the most common classes of such compounds. [1,2] Our research effort is focused on application of azobenzene-derived molecular photoswitches for efficient photomodulation of macroscopic systems.

An azobenzene-containing cyclic dipeptide (PAP-DKP-Lys) is a photoresponsive low-MW hydrogelator. The gelation process can be triggered with temperature, pH light, and ionic strength. The resulting gels exhibit excellent self-healing properties. In presence of DNA the compound forms hydrogels that release the oligonucleotides upon irradiation. Hydrogels formed in presence of anticancer drug doxorubicin also release the cargo in a light-dependent manner. Such behavior can be explored in the future to design systems for light-induced delivery of drugs or therapeutic oligonucleotides. [3]



We will also demonstrate our recent results on the modifications of the azobenzene structure in order to optimize the photophysical properties of the switches, and on prospective applications of the resulting compounds for photoresponsive macroscopic systems such as hydrogels or metal-organic frameworks (MOFs).

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Paramagnetic Photoredox-Switchable Molecular Grippers:The Elements of Six-State Redox Switches

J. Milic[1], M. Zalibera[2], I. Pochorovski[1], J. Nomrowski[3], D. Neshchadin[4], L. Ruhlmann[5], C. Boudon[5], O. S. Wenger[3], G. Gescheidt[6], W. Lubitz[2]*, F. Diederich[1]*

[1]ETH Zurich, [2]Max Planck Institute for Chemical Energy Conversion, [3]University of Basel, [4]TU Graz, [5]Université de Strasbourg, [6]Graz University of Technology

Molecular grippers are able to mimic their macroscopic analogues by performing a controlled expansion and contraction in response to external stimuli that results in reversible encapsulation of small molecules. This behavior renders them applicable as miniaturized delivery systems, sensors, or elements in nanorobotics.[1,2] The usage of these molecular devices, however, depends on their receptiveness to electrical or electromagnetic stimuli.[1] We therefore developed the first redox-switchable molecular gripper based on resorcin[4]arene cavitand platforms with quinone (Q) walls that was inspired by the role of semiquinones (SQ) in natural photosynthesis.[2,3] The SQ state was generated chemically, electrochemically, and photochemically, and the properties were studied by cyclic voltammetry, UV/Vis spectroelectrochemistry, EPR, and transient absorption spectroscopy, as well as DFT calculations.[3] Introduction of the SQ-based cavitands opened the way to photoredox-switchable systems that can exist in three different redox states (Q, SQ, and HQ (hydroquinone)) and two different conformations (open and closed), which represent rare six-state redox switches (Figure 1). The tunable magnetic and binding properties of these switches, their high reversibility, and responsiveness to electrical stimuli can lead to a new generation of molecular devices.

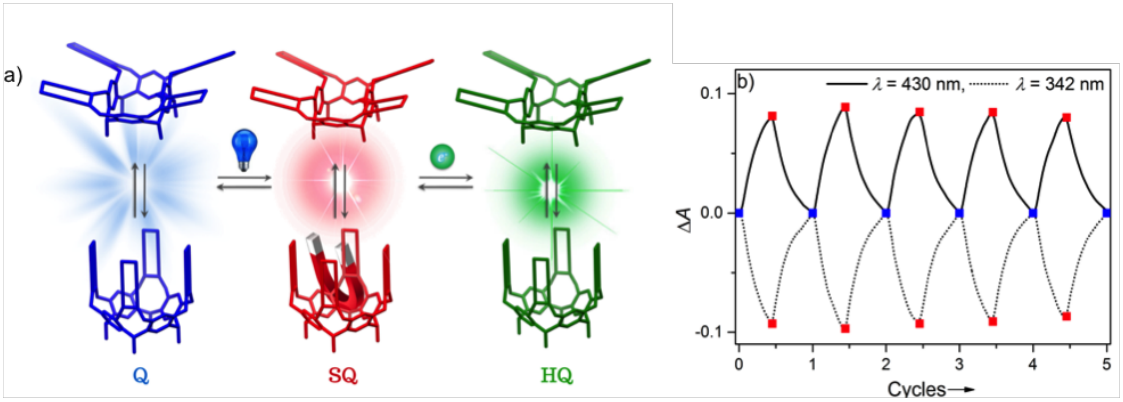

Figure 1. (a) Schematic of a resorcin[4]arene-based six-state photoredox switch that can exist in three different redox states (Q, SQ, and HQ) and two conformations (open and closed). (b) Electrochemical Q–SQ switching reversibility demonstrated by UV/Vis spectroelectrochemistry.

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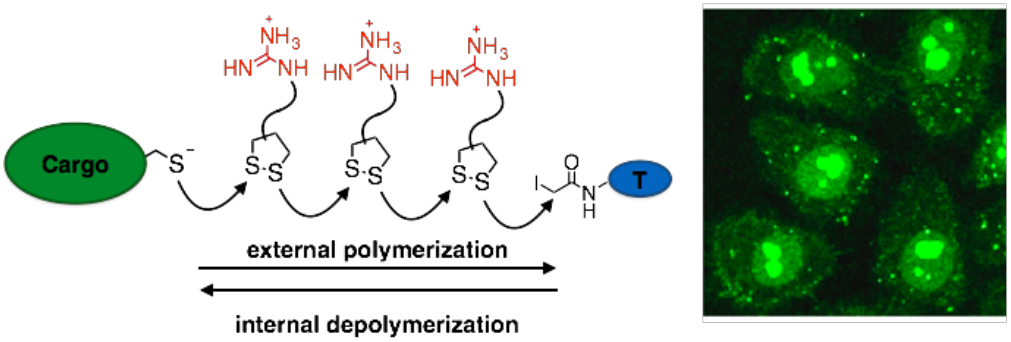
Cell-Penetrating Poly(disulfide)s

P. Morelli[1], G. Gasparini[1], N. Chuard[1], E. Bartolami[1], N. Sakai[1], S. Matile[1]*

[1]University of Geneva

Substrate-initiated cell-penetrating poly(disulfide)s (si-CPDs) are emerging as innovative molecular transporters due to their ability to deliver cargoes without cytotoxicity, through a proposed novel counterion thiol-mediated uptake mechanism [1]. Inspired by surface-initiated polymerization, we developed a conceptually new approach to grow CPDs on a variety of substrates through ring-opening disulfide exchange polymerization, in solution and under mild conditions. Thiolated fluorescent probes are commonly used as initiators, cyclic disulfides as monomers and iodoacetamides are used as terminators. Like cell-penetrating peptides (CPPs), CPDs are enriched with guanidinium groups which help the delivery of the cargo through the formation of micellar pores in the membrane. However, CPDs also contain a poly(disulfide) backbone which, through dynamic covalent disulfide-exchange, helps to increase uptake and, most importantly, eliminates the cytotoxicity which is common to many CPPs. Due to this dual uptake mechanism, our best performing CPDs were able to reach the nucleus of HeLa cells in 15 minutes and at nM concentration. Once internalized, the poly(disulfide)s are readily depolymerized thanks to the high concentration of glutathione in the cytosol. Recently, CPDs were used to achieve protein delivery through biotin-streptavidin technology [2], leading to the development of a general method to deliver other types of cargoes such as monobodies. Our focus is now oriented towards side chain and terminator modification [3] in order to achieve further CPD functionalization.



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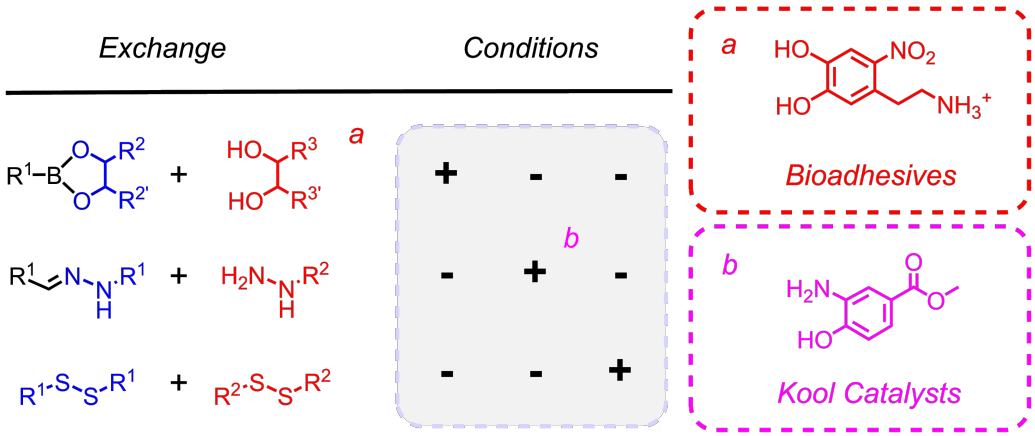
The Third Orthogonal Organic Dynamic Covalent Bond

S. Lascano[1], K. Zhang[1], R. Wehlauch[2], K. Gademann[2], N. Sakai[1], S. Matile[1]*

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

Dynamic covalent bonds are ideal tools for the construction of multicomponent functional systems due to their dual nature, permanent as covalent bonds or rapidly exchanging as non-covalent bonds. But their true potential lies in the use of more than one dynamic covalent bond at the same time. While the formation of three different dynamic covalent bonds has been reported [1-3], the selective exchange of each bond is still elusive. This calls for a third orthogonal dynamic covalent bond to add to the well-known and widely used hydrazones and disulfides.



For the first time, we demonstrated the existence of three fully orthogonal dynamic covalent bonds [4]. Thanks to particularly stable boronic esters and a new catalyst for hydrazone exchange, the once incompatible boronic ester and hydrazone exchange could be used simultaneously and fully orthogonally for the first time along with disulfides. The selective removal of an intact boronic ester by hydrazone exchange from a multicomponent surface architecture confirmed orthogonality of the three bonds in complex functional systems.

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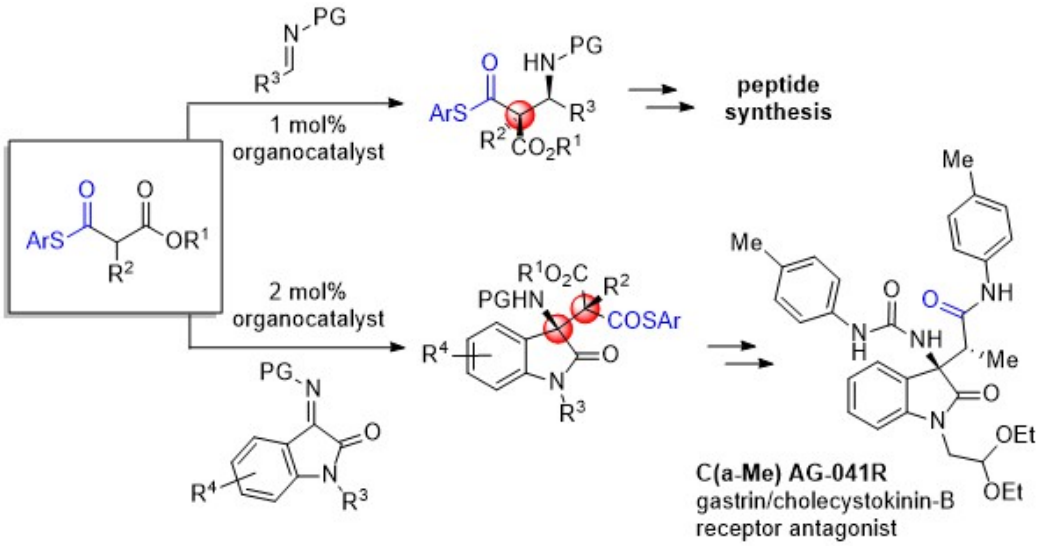
Stereoselective Metal-Free Synthesis of β-Amino Thioesters and their Synthetic Application

O. Engl[1], E. Cosimi[1], M.-O. Ebert[1], J. Saadi[1], H. Wennemers[1]*

[1]ETH Zurich

Thioesters are versatile building blocks for subsequent transformations into other functional groups such as ketones, aldehydes or amides. Nature utilizes malonic acid half thioesters (MAHTs) as thioester enolate equivalents in the biosynthesis of fatty acids and polyketides. MAHTs have also been used in organic synthesis but suffer from uncontrolled decarboxylation. Our group introduced mono thiomalonates (MTMs) as protected variants of MAHTs and versatile surrogates of thioester enolates.[1]

Herein we present the highly stereoselective synthesis of *β*-amino thioesters that proceeds under mild organocatalytic conditions through Mannich-type addition reactions of MTMs to *N*-Cbz and *N*-Boc protected imines. The method provides valuable building blocks for coupling-reagent-free peptide synthesis.[2,3] In addition, this methodology also allowed for the synthesis of 3-substituted 3-amino-2-oxindoles containing two adjacent tetrasubstituted stereocenters.[4] The synthetic value of the differentially functionalized oxindoles was showcased for the synthesis of derivatives of the bioactive *β*-amino acid AG-041R.[4]



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Palladium(0)-Catalyzed Asymmetric C(sp^3)–H Arylation: the Chiral Base Approach

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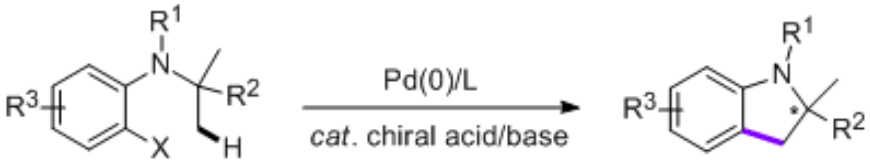
[1]University of Basel

In recent years, transition-metal-catalyzed asymmetric C(sp^3)–H activation has received increasing attention.[1] In this regard, the groups of Kündig,[2] Kagan,[3] and Cramer[4] reported the highly enantioselective construction of (fused) indolines using chiral N-heterocyclic carbene or phosphine ligands. In parallel, our group has reported the diastereo- and enantioselective synthesis of (fused) indanes containing up to three adjacent stereocenters by using chiral Binepine ligands.[5] Herein, we show that the enantioselective synthesis of chiral indolines containing 2^{ary} and 3^{ary} stereocenters (up to 98:2 e.r.) can be achieved *via* C(sp^3)–H activation using a catalytic chiral base, which is formed *in situ* upon deprotonation of a chiral acid, as the sole source of chirality.[6]



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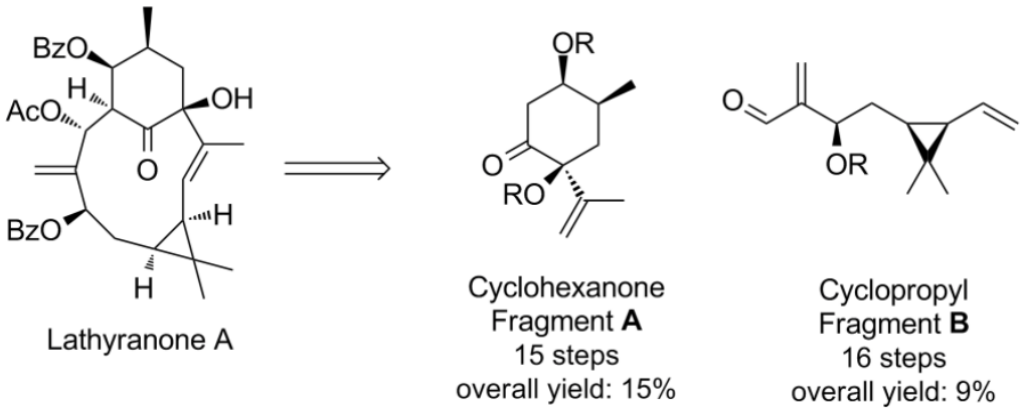
Towards the Total Synthesis of Lathyranone A

G. Rusconi[1], M. Arthuis[1], A. Lorente[1], C. Nevado[1]*

[1]University of Zurich

Lathyranone A is a diterpenoid macrocycle, that was isolated in 2007 from the seeds of *Euphorbia lathyris*[1]. Lathyranone A failed to inhibit the proliferation of some cancer cells lines[1], but the fact that the seeds of *Euphorbia lathyris* are used in the traditional Chinese medicine for the treatment of several diseases suggests that other biological targets for Lathyranone A may exist. For this reason we are interested in the total synthesis of this natural product. Our retrosynthetic analysis divides the molecule in two main fragments of similar size and complexity: **Cyclohexanone Fragment A**and **Cyclopropyl Fragment B**. The final assembly involves the addition of the enolate of **Fragment A** onto the aldehyde of **Fragment B**, to generate a highly advance intermediate that via RCM would produce the 11-membered ring.The challenges associated to the molecule's final assembly strategy will be presented here in detail.



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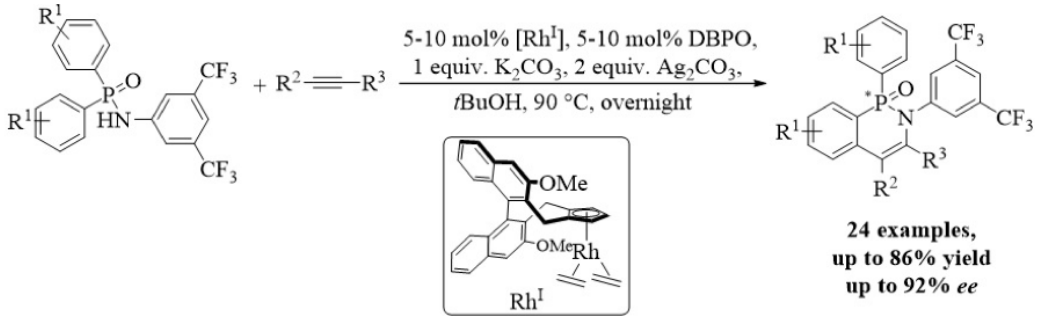
Rh(III)-catalyzed asymmetric synthesis of P-stereogenic heterocycles from phosphamides

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

[1]EPF Lausanne

Chiral *P*-stereogenic phosphorus compounds are widely applied in the fields of biology, agriculture as well as asymmetric synthesis.[1] However, their synthesis remains a challenging problem and novel efficient alternatives are highly desired.

Herein we report the development of the first example of chiral cyclopentadienyl Rh(III)-catalyzed asymmetric synthesis of *P*-stereogenic heterocycles from phosphamides.[2] The transformation proceeded with alkynes as coupling partner in the presence of base and an external oxidant. High yields and enantiomeric excesses were obtained for substrates with electron neutral and electron rich substituents. Good regioselectivities were obtained with unsymmetric alkynes. Kinetic studies review that the CMD is the stereo-determining step in combination with base which is different from the previously reported cases by our group.[3]



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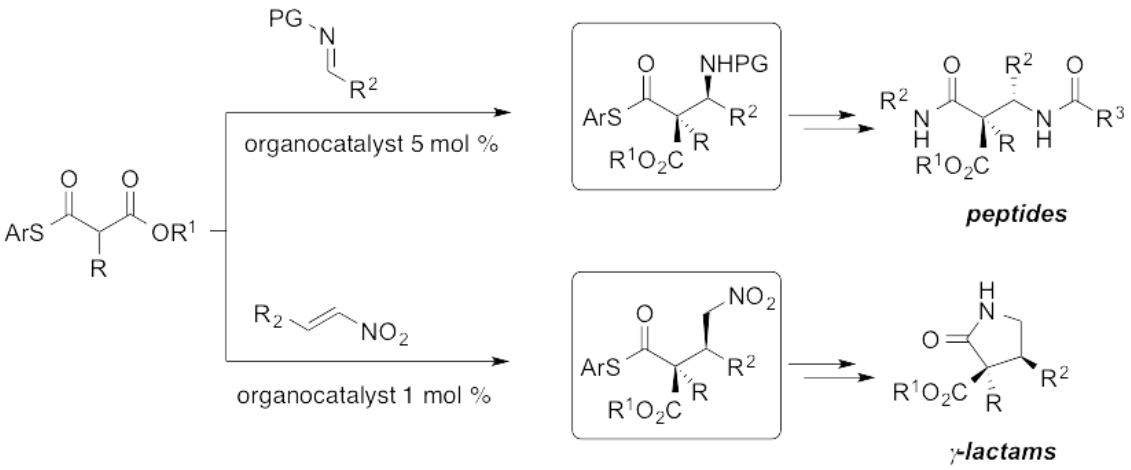
Stereoselective Organocatalyzed Synthesis of β-Amino Thioesters and γ-Nitro Thioesters and Their Synthetic Application

E. Cosimi[1], O. Engl[1], H. Wennemers[1]*

[1]ETH Zurich

Malonic acid half thioesters (MAHTs) are valuable thioester enolate equivalents for organocatalyzed decarboxylative addition reactions.[1] The unique reactivity of the thioester moiety allows for readily converting the addition products into the corresponding aldehydes, ketones or amides. Recently, our research group introduced monothiomalonates (MTMs) as protected variants of MAHTs, which allow for the use of low catalyst loadings in short reaction times.[2]

Herein we present highly stereoselective organocatalyzed addition reactions of MTMs to imines[3] and nitroolefins.[4] The methodology provides access to the corresponding *β*-amino thioesters, which allow for coupling reagent-free peptide synthesis, and *γ*-nitro thioesters, which were readily converted into, e.g., the corresponding γ-lactams.



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[4] E. Cosimi, J. Saadi, H. Wennemers, *manuscript in preparation*

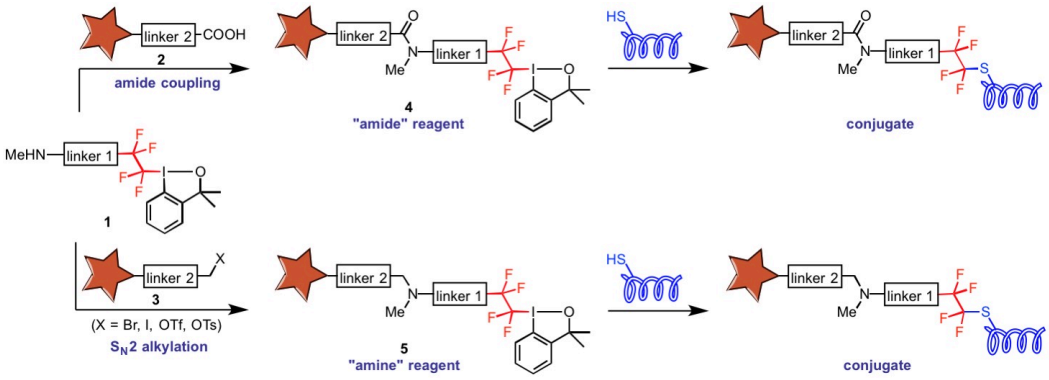
Modular electrophilic tetrafluoroalkylation reagents tailored for selective and irreversible thiol bioconjugation

J. Vaclavik[1,3], V. Matoušek[2], I. Klimánková[3], P. Beier[3]*, A. Togni[1]*

[1]ETH Zurich, [2]CF Plus Chemicals GmbH, [3]Academy of Sciences of the Czech Republic

Methods for late-stage selective introduction of fluoroalkyl groups into complex molecules are highly demanded for the development of pharmaceuticals, agrochemicals, advanced materials, etc. For this purpose, we recently reported a series of electrophilic tetrafluoroalkylation reagents [1]. Their applicability was demonstrated on S, O, P and C-nucleophiles, providing unique structures, often poorly accessible by other approaches. The shift from a terminal CF_3 group to CF_2CF_2X (X = S-Ar, O-Ar, Ar_{het}) opens a new dimension thanks to the functional group X. The reagents showed particularly high reactivity towards sulfur nucleophiles and the resulting conjugates were formed irreversibly.

The aim of our current endeavours is to develop a platform allowing for modular, one-step synthesis of the CF_2CF_2X reagents. The irreversible and selective fluoroalkylation of thiols with functionalized tetrafluoroethyl moieties can serve as a basis for the development of a new approach toward thiol bioconjugation. The desired reagents can be prepared from the free amine reagent **1** by connecting linkers **2** and **3** bearing functional groups used in bioconjugation (fluorophore, azide, alkyne, biotin, etc.).



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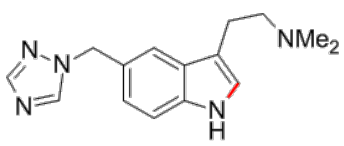
Aqueous Titanium Trichloride-Promoted Reductive Cyclization of o-Nitrostyrenes to Indoles

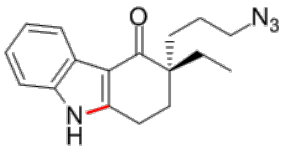
M. Mamboury[1], S. Tong[1], Z. Xu[1], Q. Wang[1], J. Zhu[1]*

[1]EPF Lausanne

Treatment of *o*-nitrostyrenes with aqueous $TiCl_3$ solution at room temperature afforded indoles through a formal reductive C(sp^2)–H amination process. A range of functions such as halides (Cl, Br), carbonyl (ester, carbamate), cyano, hydroxy, and amino groups were tolerated. From β,β-disubstituted *o*-nitrostyrenes, 2,3-disubstituted indoles were formed by a domino reduction/cyclization/migration process. Mild conditions, simple experimental procedure, ready accessibility of the starting materials and good to excellent yields characterize the present transformation. The methodology was used as a key step in a concise synthesis of rizatriptan and a formal total synthesis of aspidospermidine.



Rizatriptan



Precursor of *Aspidosperma* alkaloids

[1] Dr. Shuo Tong,† Dr. Zhengren Xu,† Mathias Mamboury, Dr. Qian Wang, Prof. Jieping Zhu, *Angew. Chem. Int. Ed.,* **2015**, 54, 11809-11812.

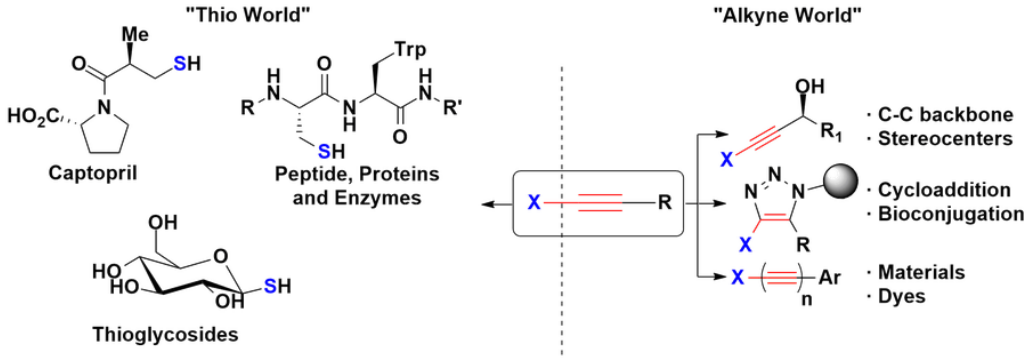
† These authors contributed equally to this work.

Fast and Highly Chemoselective Alkynylation of Thiols with Hypervalent Iodine Reagents

R. Tessier[1], D. Hari[1], R. Frei[1], J. Waser[1]*

[1]EPF Lausanne

Organosulfur compounds are a highly important class of molecules, and they play a vital role in biological mechanisms, through reactive cysteine residues. Due to the versatility of acetylene chemistry, methods that selectively transfer alkynes on sulfurs into multi-functionalized proteins would be highly useful in chemical biology. Thus, we reported a highly chemoselective thioalkynylation reaction[1], which served as platform for study post-translational modifications and bioconjugation[2]. Recent progress in the alkynylation of thiols in complexe (bio)molecules will be reported therein.



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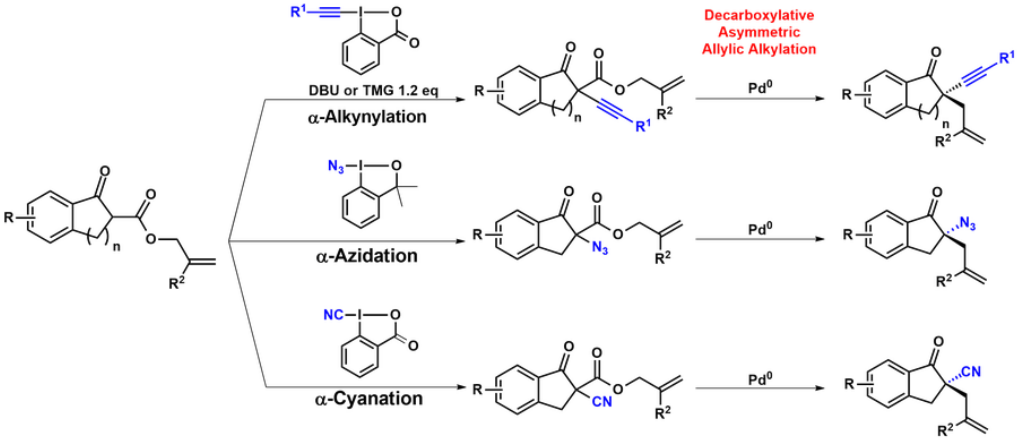
Pd(0)-Catalyzed Enantioselective Synthesis α-Alkynyl, Azido and Cyano Ketones

P. Caramenti[1], M. V. Vita[1], J. Waser[1]*

[1]EPF Lausanne

The asymmetric synthesis of α-functionalized ketones represents one of the most used strategy to increase complexity in organic molecules. In particular the decoration of the alpha position of a carbonyl with versatile functionalities such as alkynyl, azido and cyano groups is highly desirable. We present herein our unified approach to access them by an electrophilic alkynylation/azidation/cyanation-enantioselective palladium-catalyzed allylic decarboxylation sequence.[1] To access the required racemic α-functionalized β-ketoesters, a method based on the "Umpolung" of reactivity was developed. Since alkynes, azides and cyanides present inherent nucleophilicity, electrophilic cyclic hypervalent iodine reagents such as ethynyl, azido and cyano benziodoxol(on)e[2] were used. Subsequently a palladium-catalyzed allylic decarboxylation sequence was applied, with a catalytic system based on chiral biphosphine ligands developed by Trost and coworkers.[3]The products obtained were demonstrated to be versatile building blocks for the synthesis of fused or spiro polycyclic ring systems, as well as α- and β-aminoketones.



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New Approach Towards Nucleophilic Tetrafluoroethylation

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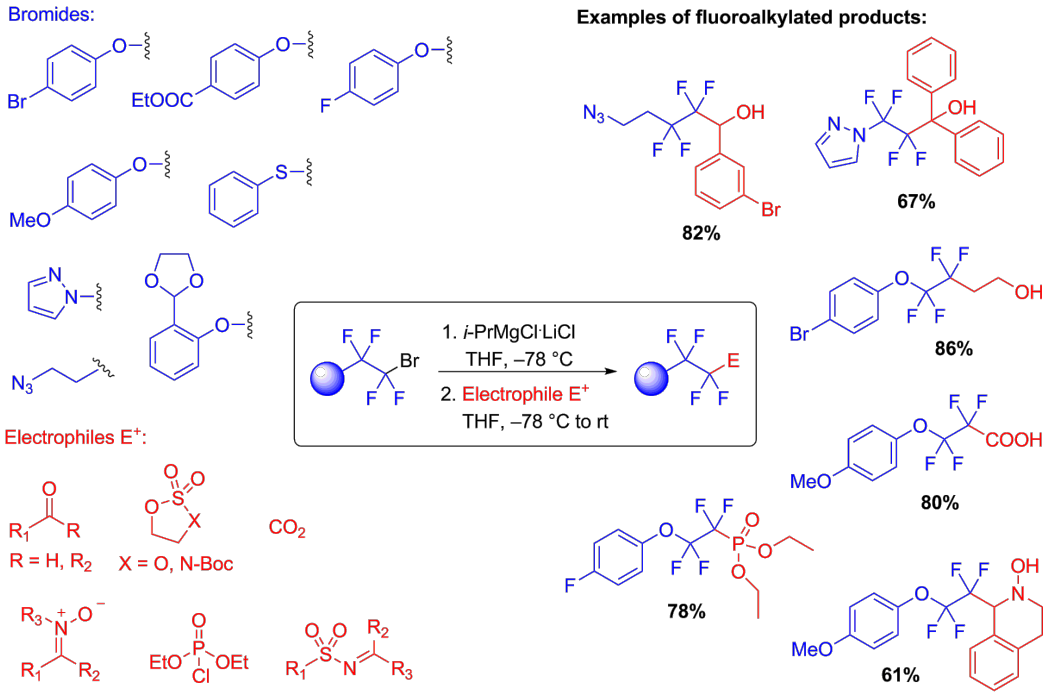
[1]Academy of Sciences of the Czech Republic, [2]ETH Zürich, [3]CF Plus Chemicals

The introduction of fluorine into organic molecules is a powerful tool to alter the physical, chemical and pharmacological properties of drugs, agrochemicals or advanced materials. The great number of applications is closely connected to the need of selective and efficient methods for the synthesis of such compounds.

The incorporation of tetrafluoroethylene (–CF_2CF_2–) groups can be achieved mainly by reagents for nucleophilic[1] and electrophilic[2] tetrafluoroethylation. This work further develops the nucleophilic approach and allows the introduction of substituted X–CF_2CF_2– (X = OAr, SAr, HetAr, C-alkyl) moieties. The starting tetrafluoroethyl bromides (X–CF_2CF_2–Br) are *in-situ* transformed into the X–CF_2CF_2–MgCl species, the application of which is demonstrated by corresponding reactions with various electrophiles.



Excellent reactivity has been observed towards diverse aldehydes and good-to-excellent yields were obtained with both aromatic and aliphatic ketones. Furthermore, other electrophiles (cyclic sulfates and sulfamidates, diethyl chlorophosphate, CO_2, sulfonyl imines and nitrones) also exhibited enhanced reactivity. Our work therefore represents an efficient one-pot procedure for the synthesis of a wide range of compounds bearing relatively rare X–CF_2CF_2– groups, which might find applications in life and material sciences.

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Efforts toward the Total Synthesis of Hyperforin via a Tandem Strategy

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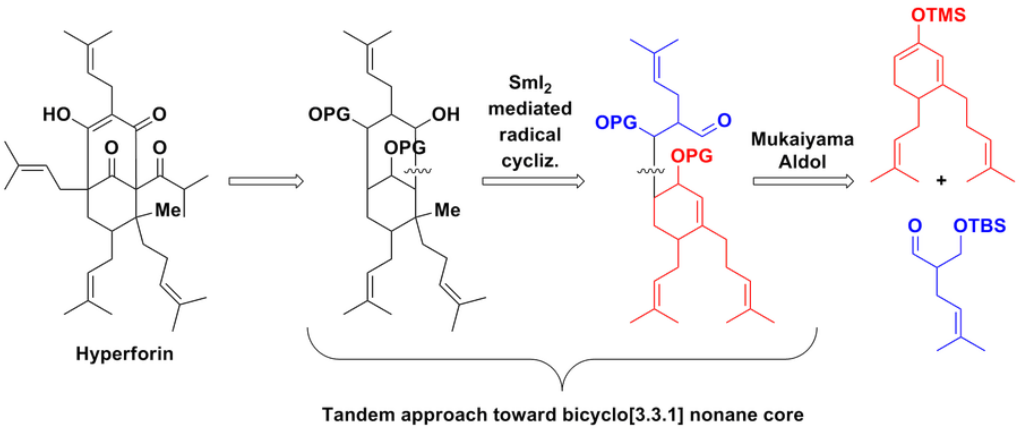
[1]University of Fribourg

Hyperforin is a natural product extracted from *Hypericum perforatum* (St-John wort) known for its mild antidepressive and antibiotic activities. It belongs to the polyprenylated acylphloroglucinols family of compounds bearing a bicyclo[3.3.1]nonane densely substituted with prenyl, homoprenyl and carbonyl groups, of which the synthesis, despite recent successes, remains a great challenge for the synthetic community.



Our approach consists in forming the bicyclo[3.3.1]nonane core of Hyperforin starting with readily accessible building blocks via a tandem cyclization and with a minimum of steps between the two key steps presented above. A synthetic pathway giving the suitable starting material for a SmI_2-mediated radical cyclization in gram quantities has been secured and the key step is currently under study to access Hyperforin in a total of 17 steps.

Lipid Linked Oligosaccharide (LLO) Analogues as Oligosaccharyltransferase (OST) Substrates

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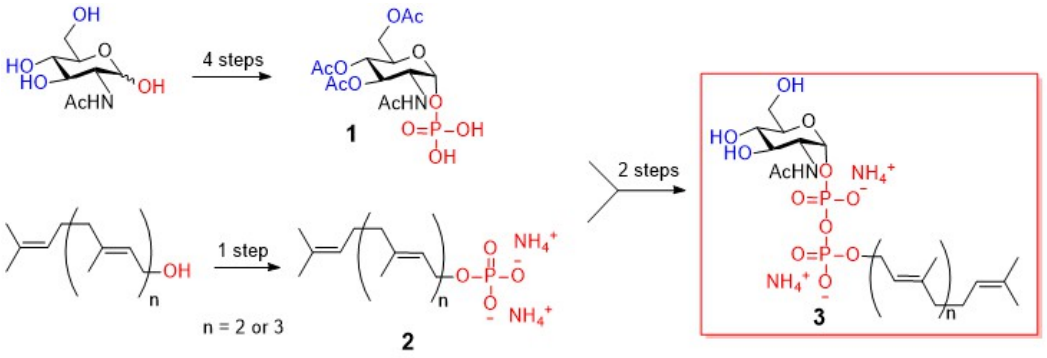
[1]University of Bern, [2]ETH Zürich

N-linked protein glycosylation is an essential post-translational modification that links glycans from a lipid carrier to the asparagine residues of polypeptide chains in bacteria, eukarya and archaea. These glycoproteins play a critical role in a wide variety of biological processes such as protein stability and rigidity, intracellular localization, cellular signaling and adhesion, and the immune response[1]. The structure of the gram-negative proteobacteria *Campylobacter Lari* OST was recently reported[2], leading to a revision of the proposed mechanism and allowing Structure Activity Relationship (SAR) on the polypeptide chain and on the LLO substrates. These studies led to further insight into the reaction mechanism and factors affecting substrate binding and enzyme turnover[3], [4]. LLOs described in Scheme 1 were recently synthesized and proved to be of interest to understand the structure and mechanism of an active LLO flippase, the ABC transporter PglK[5].This approach has now been extended to the synthesis of disaccharide containing LLOs suitable to study the eukaryotic OST Stt3.



Scheme 1: Synthetic pathway of LLO analogues synthesis.

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A green one-pot synthesis of a magnetic mesoporous carbon-containing Pd-Co nanoalloy. Applications for Suzuki couplings.

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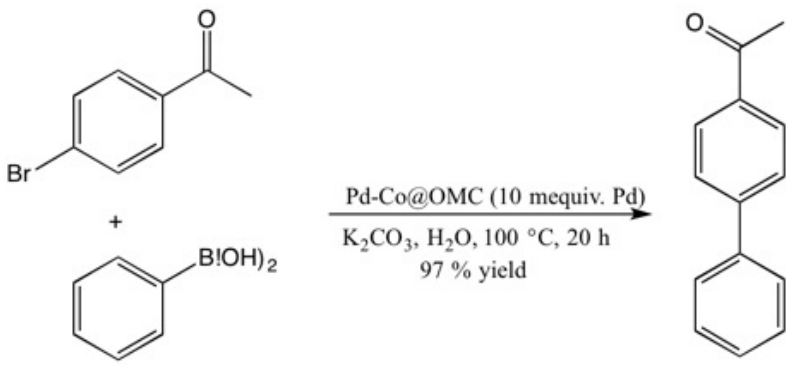
[1]Université de Haute-Alsace, Mulhouse, France

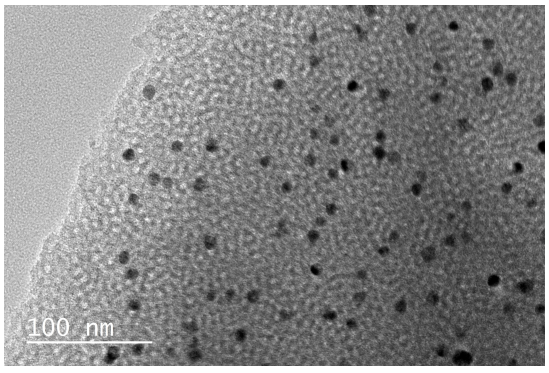
The Suzuki coupling is to date the most powerful reaction for the creation of aryl-aryl bonds under mild conditions. It finds widespread applications for the preparation of products possessing interesting pharmaceutical, biological or physical properties. The Suzuki reaction is generally performed in the presence of expensive homogeneous Pd catalysts that cannot be reused, and moreover often cause the presence of precious metal in products and wastes. A current challenge is the development of one-pot syntheses of heterogeneous Pd catalysts from easily available and inexpensive starting materials.[1] In addition these catalysts should be active in water and selectively recoverable for reuse.

We present here a simple and cheap direct synthesis of a magnetic mesoporous carbon containing a Pd-Co nanoalloy.[2] We show that this material is particularly efficient for Suzuki reactions in water.



OMC : ordered mesoporous carbon

TEM Image of Pd-Co@OMC



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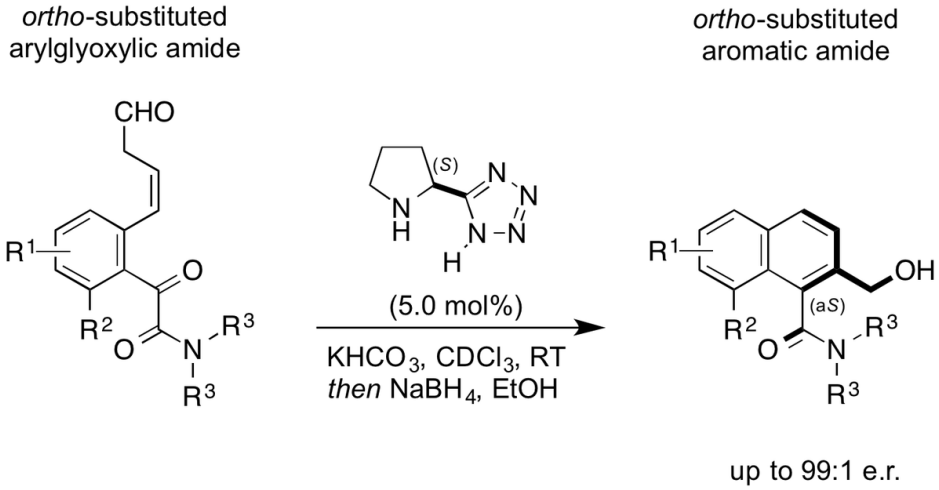
Stereoselective Arene-Forming Aldol Condensation: Synthesis of Axially Chiral Aromatic Amides

V. Fäseke[1], C. Sparr[1]

[1]University of Basel

Aromatic amides are among the most valuable structural motifs for the synthesis of bioactive compounds. In the case of a substitution pattern leading to a restricted Ar–CO rotation, complex conformational features and atropisomerism can frequently be observed. However, the selective preparation of these aromatic amide atropisomers still remains synthetically challenging. Today, only two strategies for the stereoselective catalytic preparation of Ar–CO rotationally restricted aromatic amides have been reported, while the importance of axially chiral aromatic amides as auxiliaries, ligands and organocatalysts is established.

The poster will outline the stereoselective synthesis of configurationally stable aromatic amides by an atroposelective arene-forming aldol condensation. *Ortho*-substituted arylglyoxylic amides precursors are converted into the corresponding axially chiral aromatic amides by a chiral secondary amine catalyzed process. Nearly complete transfer of the stereochemical information of the catalyst into axially chiral aromatic amides was achieved within minutes at ambient temperature to obtain highly enantioenriched *ortho*-substituted aromatic amides.



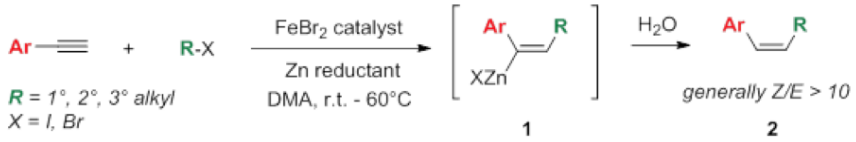
V. C. Fäseke, C. Sparr, *Angew. Chem. Int. Ed.*, **2016**, *55*, early view.

Highly γ-selective allylation of (E)-alkenylzinc iodides prepared by reductive coupling of arylacetylenes with alkyl iodides

F. Zhurkin[1], X. Hu[2]*

[1]Ecole Polytechnique Fédérale de Lausanne (EPFL), [2]EPF Lausanne

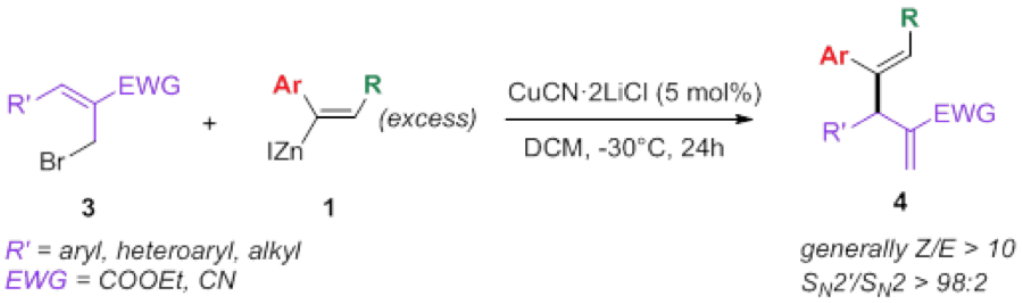
A general and efficient protocol for highly *Z*-selective reductive coupling of alkyl halides with terminal arylacetylenes was developed earlier in our laboratory[1]. Mechanistic studies showed that the reaction proceeds through the formation of (*E*)-alkenylzinc species **1** (Scheme 1).



Scheme 1. Iron-catalyzed reductive coupling of terminal arylalkynes with alkyl halides.

Coupling of the intermediates **1** with electrophiles would open a way to trisubstituted alkenes with high *Z*/*E* selectivity. The purpose of this project is to develop a protocol for selective allylic alkylation (AA) of these intermediates. Although a range of transition metals can catalyze such reactions, copper seems to be the most suitable catalyst for unstabilized organozinc nucleophiles[2-4]. We found that allylic bromides **3**[5], which are readily available from Baylis-Hillman alcohols, allow the highest regioselectivity. The presence of polar groups (EWG) makes possible isolation of the AA product **4** from the excess of *Z*-alkene **2** (Scheme 2).

The developed procedure affords the AA products in good yields (generally ›70%) as mixture of Z- and E-isomers (Z/E ›10) of almost exclusively S_N2' (γ) product. A wide range of functional groups (ester, ether, cyano, halogen, nitro, tertiary amine) are tolerated. 1,4-Dienes **4**, containing an activated double bond, are of potential synthetic utility.



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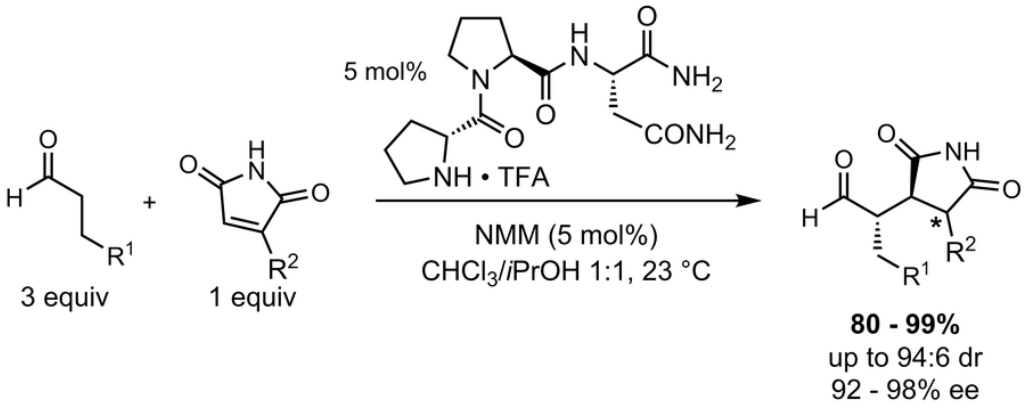
Peptide-Catalyzed Stereoselective Conjugate Addition Reactions of Aldehydes to Maleimides

C. Grünenfelder[1], J. Kisunzu[1], H. Wennemers[1]*

[1]ETH Zurich

Stereoselective conjugate addition reactions of aldehydes to unprotected maleimide offer an efficient entry into chiral succinimide derivatives which are present in natural products and drug candidates.[1] Typically, *N*-protected maleimides are used to avoid potential side reactions, which on the flip side requires a tedious additional deprotection step.[2] Tripeptides of the type Pro-Pro-Xaa (Xaa = acidic amino acid) have been introduced in our group as catalysts for conjugate addition reactions of aldehydes to nitroolefins.[3] Herein, we present H-dPro-Pro-Asn-NH_2 as a highly active and selective peptidic catalyst able to activate aldehydes and unprotected maleimides and to control the stereoselectivity of conjugate addition reactions. The obtained products were readily transformed into pyrrolidines, lactams, lactones, and peptide-like compounds.[4]



Scheme 1. Conjugate addition reactions of aldehydesand maleimides catalyzed by H-dPro-Pro-Asn-NH_2.

The conformational properties of the catalyst were studied by ^{1}H NMR spectroscopic, crystallographic and computational means. These investigations highlighted the importance of hydrogen bonding between catalyst and maleimide for the observed stereoselectivity and activation of the maleimide electrophile.[4]

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Volcano Plots: Computational Tools for Screening Homogeneous Catalysts

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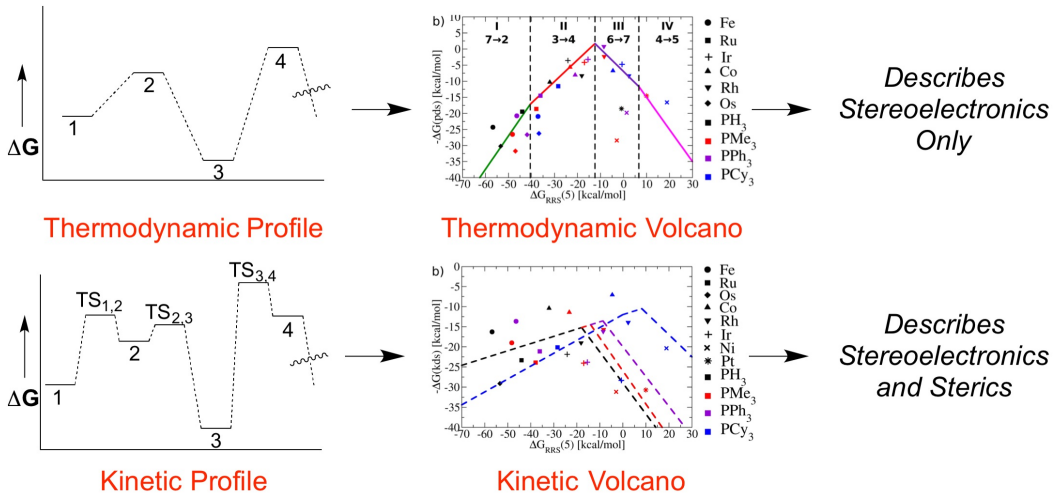
[1]EPF Lausanne

Volcano plots are common tools used by the heterogeneous catalysis and electrochemistry communities to compare the thermodynamic profiles of different catalysts. These plots pictorially represent Sabatier's principle, which states that the interaction between a substrate and a catalyst should be neither too weak nor too strong.[1] Despite their inherent ability to identify attractive catalysts and to facilitate understanding of the roles that metal and ligand choice have on cycle energetics, volcano plots describing homogeneous catalysis remain unrealized. Recently, we created volcano plots examining the thermodynamics of Suzuki cross-coupling,[2] a prototypical homogeneous catalytic reaction, that capably reproduced experimental trends. However, homogeneous catalysts often contain bulky ligands that facilitate a desired chemical transformation, the resulting steric interactions of which are rarely reflected in thermodynamic profiles (upper graphic). This makes kinetic aspects of the catalytic cycle of paramount importance. Building on our previous work, we now create kinetic volcano plots[3] (lower graphic) that provide essential information relevant to homogeneous catalysts extending beyond thermodynamic volcanoes. Moreover, we demonstrate how kinetic volcanoes derived from structure-activity relationships are able to estimate the transition state barriers associated with key steps of the catalytic cycle with minimal computational cost.



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N-Heterocycles via Pd(0)-Catalysed C(sp^3)-H Functionalisation

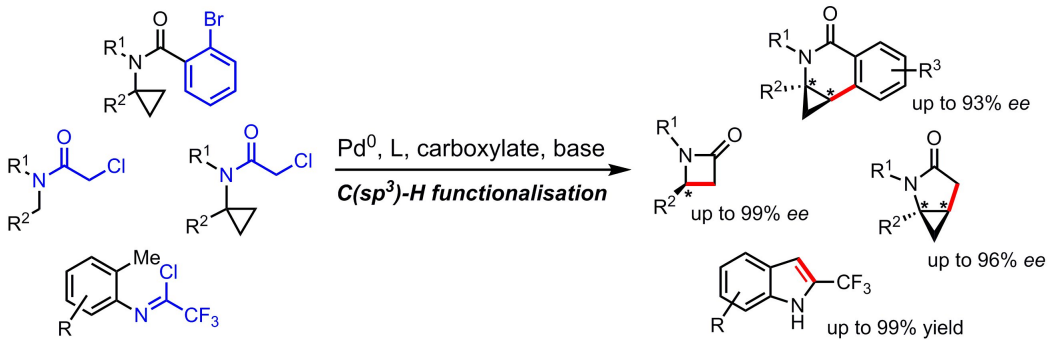
J. Pedroni[1], N. Cramer[1]*

[1]EPF Lausanne

Nitrogen-containing heterocycles are prevalent motives in biologically active compounds.[1] In the past years, the enantioselective access to benzannulated *N*-heterocyclic building blocks *via* intramolecular Pd(0)-catalysed C-H arylation has been extensively investigated in our research group.[2]

Recently, we have expanded the scope of Pd(0)-catalysed C(sp^3)-H functionalisations beyond aryl halides. Readily accessible chloroacetamides are cyclized to valuable chiral β-[3] and γ-lactams[4] in high yields and enantioselectivities, bringing the elusive Pd(0)-catalysed C(sp^3)-C(sp^3) bond formation to a synthetically useful level.

Encouraged by the increasing interest in trifluoromethylated compounds for drug development, we have investigated the C(sp^3)-H functionalisation of trifluoroacetimidoyl chlorides, obtained in one step from the corresponding anilines. The efficient cyclisation under Pd(0)-catalysis does not require the use of stoichiometric trifluoromethylating reagents or protective groups, thus providing an economic strategy for the synthesis of 2-CF_3-indoles.[5]



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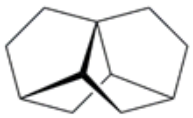
[5] J. Pedroni, N. Cramer, *Org. Lett.* **2016,** *18*, 1932

Synthesis of a Tetracyclic Derivative of Norbornane

L. D. Bizzini[1], M. Mayor[1]*

[1]University of Basel

One of the challenges of synthetic organic chemistry is structural diversity, in particular, at the level of small molecular building blocks.[1] New compounds and compound classes in the size range of small molecules (less than 500 g/mol) are of interest since they may display unforeseen properties and lead to new structural motifs.[2] The computer-assisted enumeration of the chemical space addresses this challenge by generating all possible molecules for a give number of atoms (excluding hydrogen) under consideration of specific rules.[3] One particular example found in the chemical universe database (GDB-11) is the yet unknown tetracyclic hydrocarbon **1**. This esthetically pleasing, *C*2-symmetrical, chiral molecule is comprised of three partially superposed norbornyl units. It is surprising that this unstrained molecule has not yet been synthesized in over 100 years of norbornane chemistry.[4] The goal of this project is to synthesize and study the properties of hydrocarbon **1**. The total synthesis of this compound will be presented in the presentation.



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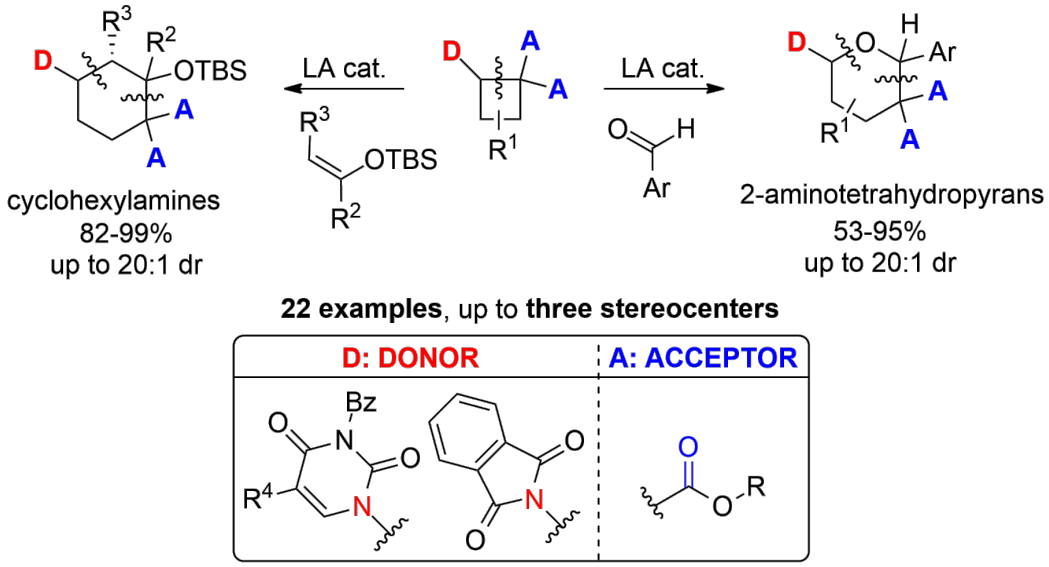
[4+2]-Annulations of Aminocyclobutanes

D. Perrotta[1], S. Racine[1], F. de Nanteuil[1], J. Waser[1]*

[1]EPF Lausanne

In the domain of small rings chemistry, donor-acceptor cyclopropanes have been widely used in annulations to generate complex cyclic structures. However, the use of their analogues 4-membered rings have been less investigated up to now. Herein we report for the first time the use of donor-acceptor aminocyclobutanes in [4+2]-annulations with aldehydes and silyl-enol ethers.[1] The 2-aminotetrahydropyrans and cyclohexylamines obtained are recurring motifs in biologically active molecules. [4+2]-annulation of substituted aminocyclobutanes with aldehydes delivered products bearing three stereocenters, using scandium triflate or iron trichloride as catalyst. The use of thymine- or fluorouracil-substituted cyclobutanes gave direct access to six-membered ring nucleoside analogues. Finally, the [4+2]-annulation between aminocyclobutanes and silyl enol ethers led to the corresponding cyclohexylamines.



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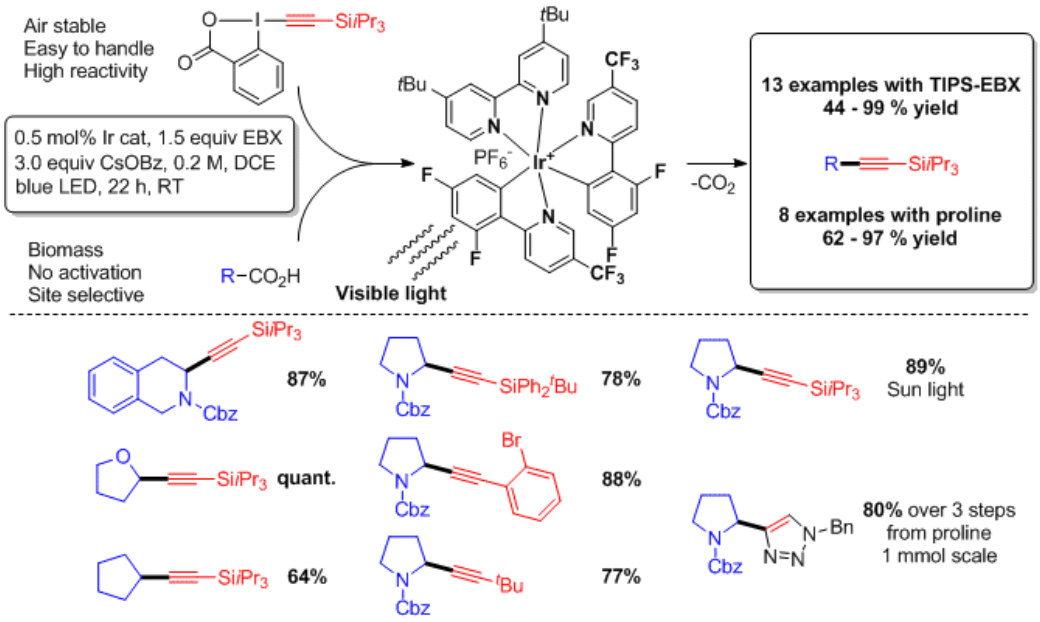
Room-Temperature Decarboxylative Alkynylation of Carboxylic Acids Using Photoredox Catalysis and EBX Reagents

F. Le Vaillant[1], T. Courant[2], M. Wodrich[1], J. Waser[1]*

[1]EPF Lausanne, [2]Université Paris Descartes

Alkynes are broadly used in organic but also in medicinal chemistry and material sciences due to their versatile properties. Therefore, efficient methods for their synthesis are necessary. Herein, we report the introduction of alkynes by a decarboxylative process of carboxylic acids at room temperature under visible light irradiation.[1] This transformation was achieved in good yields under mild conditions using iridium photocatalysts and EthynylBenziodoXolone (EBX) reagents. Interestingly, silyl-, aryl- and alkyl- substituted alkynes can be successfully transferred to a broad variety of carboxylic acids such as α-amino and α-oxo acids, as well as less reactive aliphatic carboxylic acids, all derived from the biomass. Further applications, especially the transfer of other groups than alkynes and mechanistic insights will be described in the poster.[2]



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Alleno-Acetylenic Cages (AACs): Conformational Chirality Switch and Molecular Recognition

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[1]ETH Zurich

Enantiomerically pure 1,3-diethinylallenes proved to be superior chiral entities for the construction of alleno-acetylenic oligomers and macrocycles with outstanding chiroptical properties[1]. Transferring these exceptional properties to supramolecular assemblies allowed us to exploit the sensitivity of electronic circular dichromism (ECD) for chiroptical sensing[2].

We present new optically pure alleno-acetylenic cages (AACs), which undergo solvent size and polarity dependent conformational changes. Controlled switching between two conformations leads to cage cavities of different sizes with the ability to complex small molecules. Conformational switching of the enantiomerically pure AACs shows dramatic changes in the absorption of circularly polarized light (ECD), enabling conformation-dependent differentiation between left and right circularly polarized light[3]. Reversible encapsulation of small molecules in combination with dramatic conformation-dependent ECD absorption render AACs ideal for applications in chemosensors[3].

The selective binding of small molecules at very low concentration was studied in solution and supported by X-ray co-crystal structures. Structure-based design was followed by molecular recognition studies of nonchromophoric small molecules. Optically pure AACs show enzyme-like chiral recognition properties towards optically active ligands. The highly preorganized cage structure induces binding of the ligand in unexpected high-energy conformations[3].

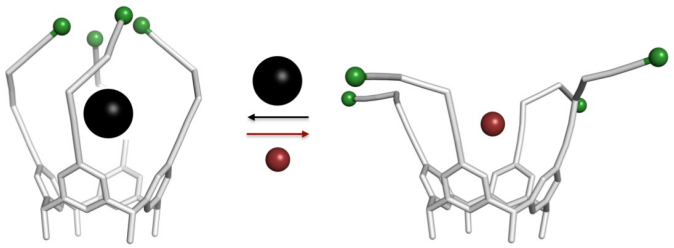

Figure 1. From controlled conformational switching of (P_4)-AACs to chiral recognition (simplified structure shown).

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Conformational Analysis of Tripeptide Catalysts Using Computational Methods and NMR Spectroscopy

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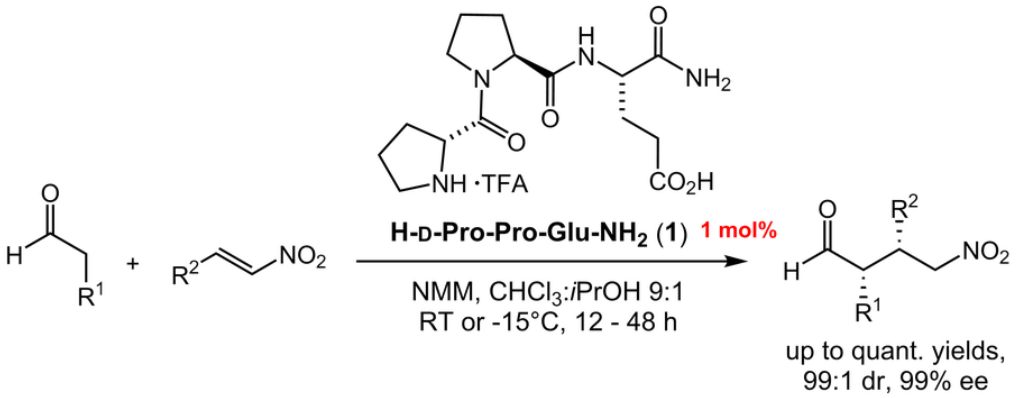
[1]ETH Zurich

Our group has previously shown that peptides of the type H-Pro-Pro-Xaa are useful catalysts in aldol and conjugate addition reactions.[1-3] Among these, the tripeptide H-DPro-Pro-Glu-NH_2 (**1**) is a highly active and robust catalyst for the conjugate addition of aldehydes to nitroolefins.[2] Catalyst loadings of ‹1 mol% can be used to access addition products in high yields and stereoselectivities. Previous investigations have provided insight into the mechanism of these reactions.[4-6] Crystal structure data of related catalytically active tripeptides have also highlighted key hydrogen-bonding interactions that are present within the catalysts, as well as in the trifluoroacetate adducts.[7] While these studies shed light onto the catalytic cycle, a more complete picture of the catalyst's solution structure would allow us to better comprehend how the right combination of rigidity and flexibility can affect substrate specificity. This will not only aid in the development of new catalysts, but also lead to a deeper understanding of this structural balance that is also prevalent in enzymes.



Herein we describe the use of computational analysis and NMR spectroscopy to identify an ensemble of solution structures for H-DPro-Pro-Glu-NH_2, H-DPro-Pro-Glu(OMe)-NH_2, and their corresponding enamine intermediates. Computational methods include molecular dynamics simulations using the CHARMM force field and conformational searches followed by DFT optimization of low-energy conformations. Distances, vicinal coupling constants, and residual dipolar coupling constants were extracted from 2D NMR data and used as restraints. The methods, simulated structures, and comparison to experimental data will be discussed.

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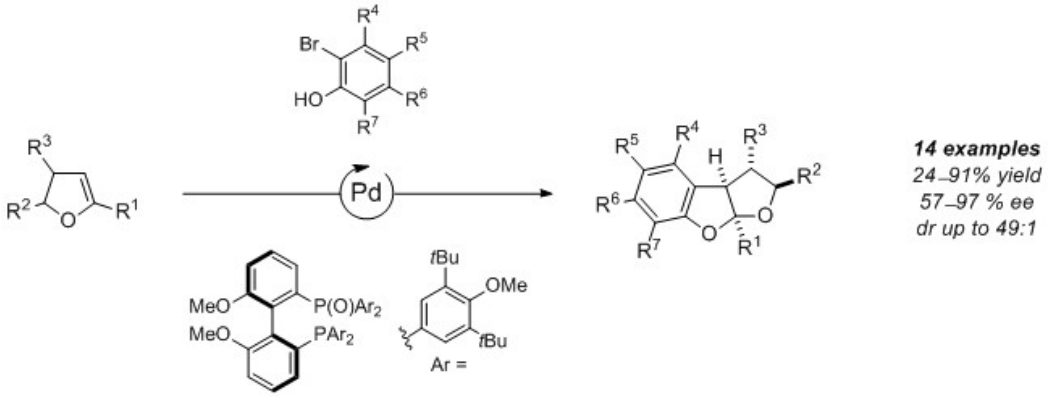
Palladium-Catalyzed Enantioselective Intermolecular Carboetherification of Dihydrofurans

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

[1]University of Geneva

In recent years, efforts have been focused on the development of new methodologies for carbon-heteroatom bond formation,[1]owing to the ubiquity of aryl C-N and C-O bonds in agrochemicals, pharmaceuticals and natural products.
Among these methodologies, the Pd-catalyzed carboetherification of alkenes has emerged as a powerful strategy. Despite remarkable advances in the field, most reported examples proceed via intramolecular reactions and their enantioselective variants are still scarce.[2,3]
Herein we describe a novel intermolecular carboetherification that gives direct access to fused tetrahydrofurobenzofurans; a scaffold that can be found in numerous biologically active compounds and which is tipically accesible via long and unpractical synthetic routes.[4] Under optimized conditions and using readily available starting materials, the final cross-coupling products are systematically obtained in high yield, enantio- and diastereoselectivity.[5] A key feature of our methodology is the *in situ* formation of a chiral bisphosphine mono-oxide (BPMO).



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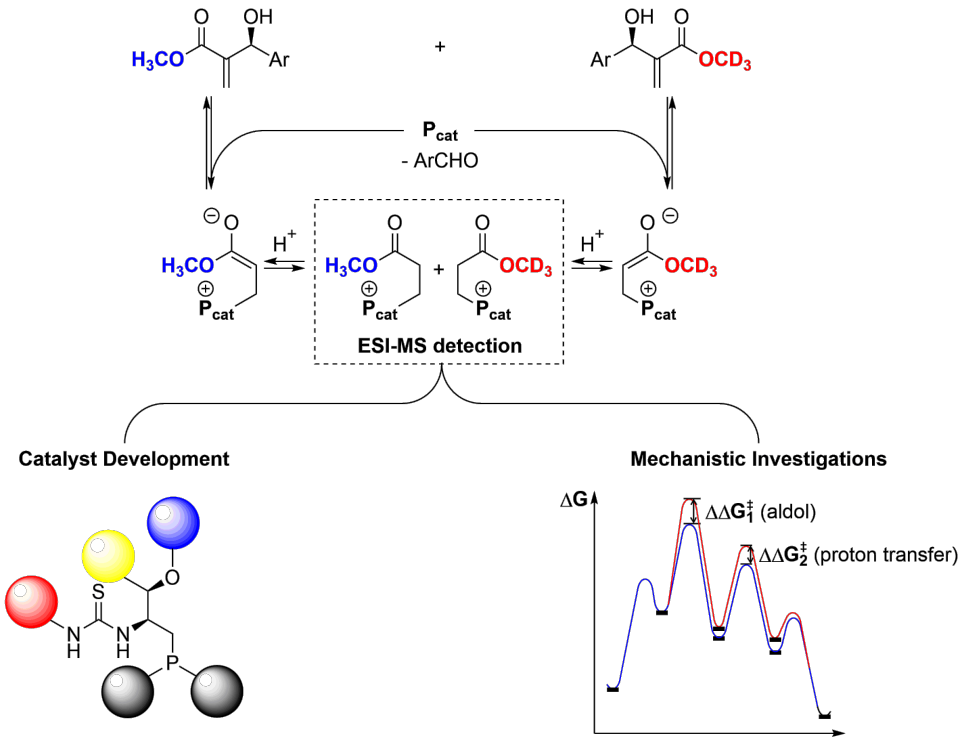
Asymmetric Morita-Baylis-Hillman Reaction: Catalyst Development and Mechanistic Insights

P. Isenegger[1], A. Pfaltz[1]*

[1]University of Basel

The Morita-Baylis-Hillman (MBH) reaction is a powerful method for the formation of a C-C bond between the α position of a Michael acceptor and an electrophile. The resulting products are highly functionalized building blocks, which can be easily modified in various ways. In the last decade substantial progress has been made in the development of enantioselective MBH reactions. However, although many chiral catalysts have been reported that give access to enantioenriched MBH products, their scope is generally limited. Especially for MBH reactions of simple acrylic esters with aldehydes, more efficient catalysts with a broader application range are needed. Herein we report a combinatorial approach to the development of chiral phosphine catalysts based on a mass spectrometric screening method devised in our laboratory, which has led to improved bifunctional chiral phosphine catalysts for MBH reactions of methyl acrylate with aldehydes. In addition, the data from mass spectrometric screening also allowed us to gain mechanistic insights and to identify the enantioselectivity-determining step in the catalytic cycle.[4]



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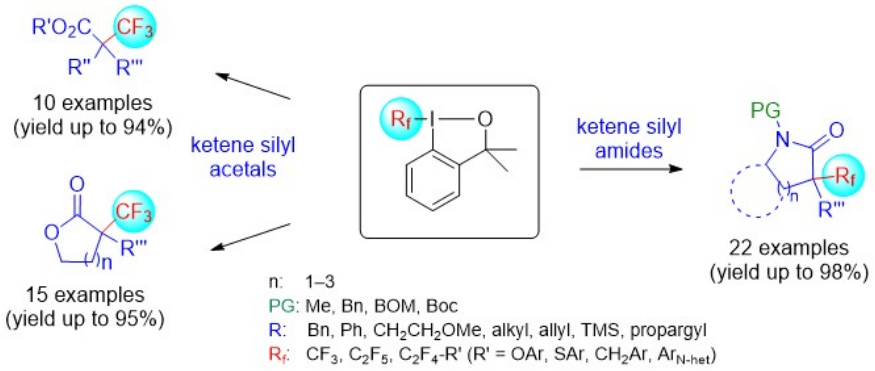
Lewis Acid-Catalyzed α-Perfluoroalkylation of Ketene Silyl Acetals and Ketene Silyl Amides

D. Katayev[1], V. Matousek[2], J. Vaclavik[3], A. Togni[1]*

[1]ETH Zurich, [2]CF Plus Chemicals GmbH, [3]ETH Zürich

We report efficient methods enabling the rapid installation of trifluoromethyl and functionalized fluoroalkyl groups by an electrophilic perfluoroalkylation of ketene silyl acetals and ketene silyl amides using hypervalent iodine reagents. [1-2] The reactions proceed under mild conditions in the presence of a catalytic amount of trimethylsilyl triflimide ($TMSNTf_2$) (1–2.5 mol%) as a Lewis acid providing a direct access to a variety of secondary, tertiary and quaternary α-perfluoroalkyl esters, lactones and lactams in high yields. For a certain class of ketene silyl acetals and amides the reaction can be performed without catalyst. Moreover, we have devised a one-pot protocol that allows the installation of the trifluoromethyl group directly onto a variety of lactams, requiring no isolation or purification steps of the intermediates. Mechanistic investigations led to conclude that radical species are likely reactive intermediates in these transformations. [3-4] The synthetic utility of these methods has been demonstrated by the conversion of α-trifluoromethylated products into synthetically useful organofluorine building blocks such as β-CF_3 alcohols, α-CF_3 esters and amides.



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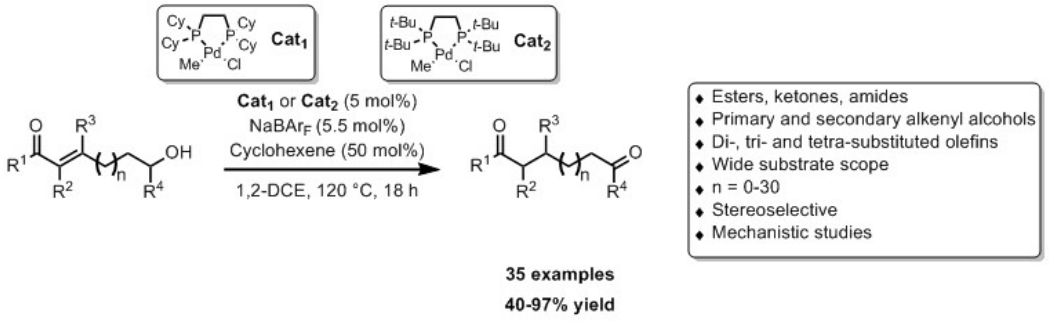
Palladium-Catalyzed Long-Range Deconjugative Isomerization of Highly Substituted α,β-Unsaturated Carbonyl

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

[1]University of Geneva

The long range isomerization/refunctionalization of olefins has emerged as an effective method for the construction of functionalized molecules starting from readily available precursors. This redox neutral methodology relies mostly on the use of transition metal complexes, with the economic and environmental advantage to avoid the formation of stoichiometric waste.[1] However, the main challenges for the successful development of such processes are (i) the difficult coordination of highly substituted (prochiral) olefins with metal catalysts,[2] severely narrowing the scope of these methodologies, and (ii) the control of the regioselectivity of metal hydride insertion across the C=C bond.[3]
Building on previous studies in our group,[4] we report herein the application of two Pd catalysts to the deconjugation, isomerization and refunctionalization of α,β-unsaturated carbonyls in good to high yields. Our system successfully isomerizes di-, tri- and tetra-substituted olefins to highly valuable aldehydes and ketones regardless the chain length (›35 examples). We also conducted mechanistic studies in order to understand the factors that govern such reaction. Preliminary results of the asymmetric variant of the reaction will also be presented.



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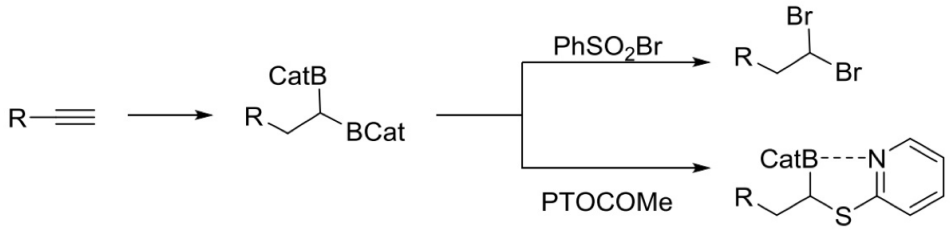
Radical Chemistry of Gem-Diboronates

A. Kuzovlev[1], M. Lüthy[1], P. Renaud[1]*

[1]University of Bern

Organoboranes, commercially available or easily prepared via hydroboration of olefins, represent a very attractive source of alkyl radicals.[1] Dihydroboration of terminal alkynes by borane was discovered by Brown.[2] We report here, that gem-dicatecholboranes, obtained by hydroboration of terminal alkynes, are suitable precursors for the generation of radicals. Depending on the nature of the trap, mono- or bis-reactions are observed.



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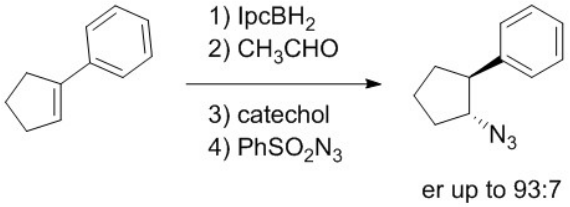
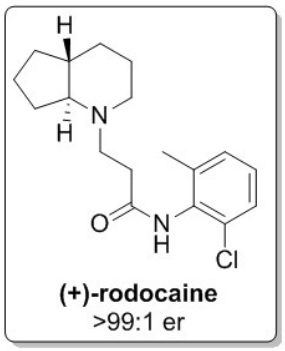
Radical-Mediated Enantioselective Hydroazidation of Alkenes

D. Meyer[1], P. Renaud[1]*

[1]University of Bern

The formation of carbon-nitrogen bonds using organic azides as radical traps has attracted the attention of many different research groups. We recently described a radical procedure for the *anti*-Markovnikov hydroazidation using catecholborane as hydroboration agent followed by reaction with benzenesulfonyl azide as radical trap.[1] We developed now an enantioselective type of this reaction using isopinocampheylborane as chiral hydroboration agent.[2] This four-step-one-pot procedure includes the further conversion of the chiral alkylborane into the diethyl boronic ester,[3] transesterification to the alkylcatecholborane and final radical azidation.





In order to demonstrate the utility of the method, the first enantioselective synthesis of (+)-rodocaine was achieved.

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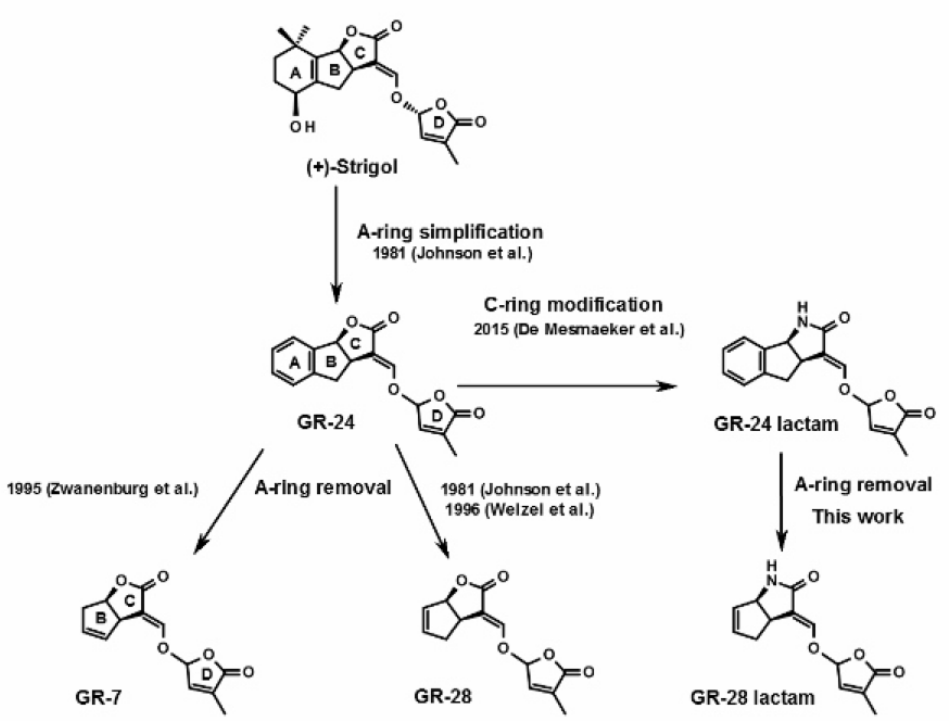
Simplified strigolactams as potent analogues of strigolactones for the seed germination induction of Orobanche cumana Wallr.

A. Lumbroso[1], E. Villedieu-Percheron[1], D. Zurwerra[1], C. Screpanti[1], M. Lachia[1], P.-Y. Dakas[1], L. Castelli[1], V. Paul[1], R. Fonne-Pfister[1,1], A. de Mesmaeker[1]*

[1]Syngenta Crop Protection AG

Strigolactones play an important role in the rhizosphere as signaling molecules stimulating the seed germination of parasitic weed seeds and hyphal branching of arbuscular micorrhiza and also act as hormones in plant roots and shoots. Strigolactone derivatives e.g. strigolactams could be used as suicidal germination inducers in the absence of a host crop for the decontamination of land infested with parasitic weed seeds.

We report the stereoselective synthesis of novel strigolactams together with some of their critical physicochemical properties such as water solubility, hydrolytic stability, as well as their short soil persistence. In addition, we show that such strigolactams are potent germination stimulants of *Orobanche cumana* parasitic weed seeds and do not affect the seed germination and the root growth of sunflower.



Emmanuelle Villedieu-Percheron , Mathilde Lachia, Pierre Jung, Claudio Screpanti, Raymonde Fonné-Pfister, Sebastian Wendeborn, Didier Zurwerra, Alain De Mesmaeker, *Chimia*, **2014**, 68, 654-663

Claudio Screpanti, Raymonde Fonné-Pfister, Alexandre Lumbroso, Stefano Rendine, Mathilde Lachia, Alain De Mesmaeker, *Bioorg. Med. Chem. Lett*., **2016**, DOI : 10.1016/j.bmcl.2016.03.072

Preparation of Alkylated Pyridine Derivatives via Radical Addition toN-Methoxypyridinium Salts

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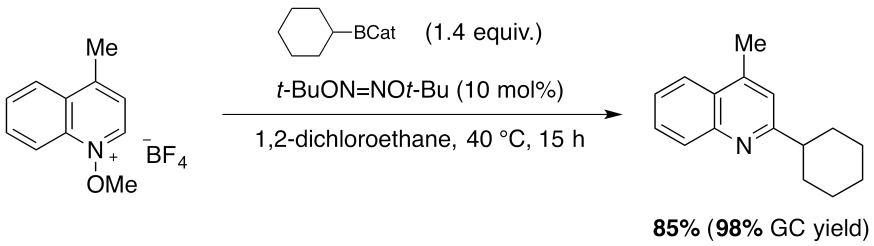
[1]University of Bern

The Minisci reaction consists of alkylation or acylation of a protonated, electron-poor heteroaromatic base using a nucleophilic carbon-centered radical. Due to polar effects, the reaction shows selectivities that would be impossible to obtain under Friedel-Crafts reaction conditions.[1]
However, the reaction suffers from drawbacks such as use of a stoichiometric amount of oxidant, low regioselectivity and polyalkylation.
Due to the viability of this method for late stage functionalization of organic compounds, it is of great interest to overcome these limitations.
Herein, we describe a method that uses non-protic activation of the substrate. Alkylboranes (RBCat[2], R_3B) react with *N*-methoxypyridinium salts in the presence of a radical initiator to afford substituted pyridines. Interestingly, no external oxidizing agent is required to run this reaction. The scope and limitation of this reaction will be discussed.



85% (**98%** GC yield)

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Photo Chemical Amplifier Based Self-Immolative Spacer

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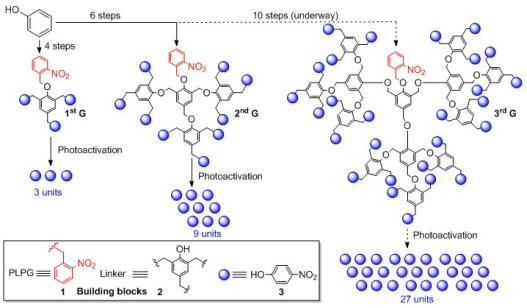
[1]University of Fribourg

A molecular amplifier could be defined as a device capable of transforming a weak chemical (physical) input into a large chemical 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) a controlled drug delivery as well as 2) a solubilizing agent 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.

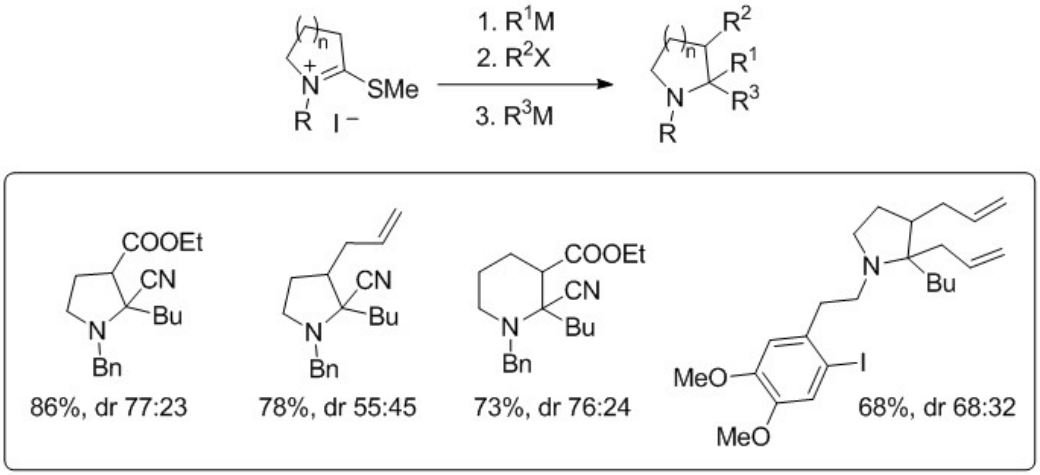
Trialkylation of cyclic thioiminium ions

M. Mojzesova[1], P. Mateo[1], P. Renaud[1]*

[1]University of Bern

Thioiminium ions are excellent bis-electrophiles for the preparation of symmetrical *gem* -dialkylated cyclic amines. [1] More recently, we have developed the addition of organocopper reagents to thioiminium ions for the functionalization of the α-position of nitrogen atom, a method to prepare non-symmetrical *gem*-dialkylated cyclic amines. [2]

Here, we report an extension of this work, where a cyclic thioiminium ion is converted into trialkylated cyclic amines in a one-pot process via successive treatment with nucleophile (R^1M), an electrophile (R^2X) and a second nucleophile (R^3M). The scope and limitation of this reaction as well as its mechanism will be discussed.



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New access to quaternary aminocyclobutanesvia nucleophilic additions on cyclobutaniminium salts

A. Kolleth-Krieger[1], A. Lumbroso[1], G. Tanriver[2], S. Catak[2], S. Sulzer[1], A. de Mesmaeker[1]*

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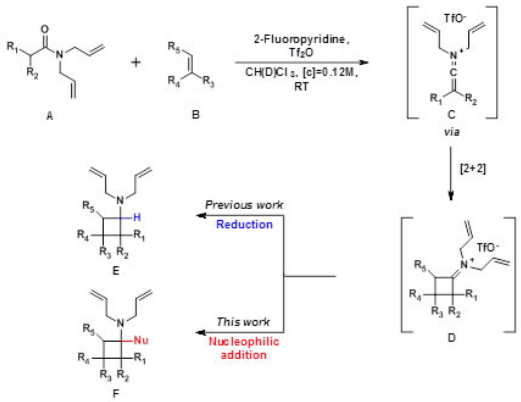
We describe the first [2+2] cycloaddition between a keteniminium salt and an alkene followed by a nucleophilic addition. This one-pot sequence enable the formation of quaternary centers with high level of stereoselectivity and is largely applicable to the synthesis of highly strained intermediates as well as precursor for spirohydantoïns. Moreover, DFT calculations support deuterated experiments showing that no spontaneous iminium-enamine tautomerization can exist during the [2+2] cycloaddition process.



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Template-free high hierarchical self-assembly of a pyrene derivative into supramolecular nanorods

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Supramolecular chemistry goes beyond the simple molecular recognition principle. Complex architecture can be realized but the design of supramolecular structures with a precise control on the dimensional organisation remains a challenge.

Herein, we report the synthesis of a new pyrene derivative that self-assembles into well-defined nanorods. We designed the pyrene derivative to present three main features: the ability to form intermolecular stacking; an H bond donor and acceptor functional group and the presence of bulky chemical functions that can be further exploited to functionalize the self-assembled structure. X-ray crystallography allowed elucidating the packing of the pyrene within the self-assembled nanorods.

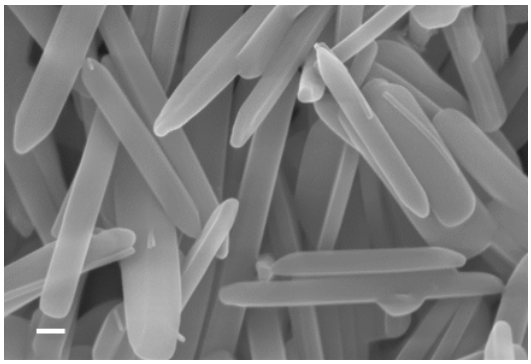

Figure 1. FESEM micrographs of self-assembled supramolecular nanorods of pyrene derivative 1 (scale bar 200 nm).

Exploring Site Selectivity of Iridium Hydride Insertion into Allylic Alcohols:Serendipitous Discovery of a Mild and General Catalyst for the Vinylogous Peterson Elimination

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The 1,2-migratory insertion of an olefin into a transition metal hydride is a fundamental elementary step in organometallic chemistry that constitutes the basis of a plethora of catalytic processes.[1] In recent years, our group has pursued the development of iridium complexes of general formula [(P,N)Ir(cod)]BAr_F for the enantio- and diastereoselective isomerization of primary allylic alcohols to aldehydes.[2] Productive isomerization proceeds via an intermolecular hydride-type mechanism involving insertion of the in situ generated [Ir−H] intermediate across the C=C bond of the allylic alcohol, followed by β-hydride elimination and tautomerization to deliver the carbonyl compound.[2a]

Herein we describe how attempts to control site-selectivity of [Ir−H] insertion by introduction of a silyl substituent in the vicinity of the C=C bond of the allylic alcohol led to the serendipitous discovery of cationic iridium catalyst **1** for a vinylogous Peterson elimination.[3] Optimization of this rather underdeveloped reaction was pursued to afford a variety of 1,3-dienes in excellent yields. Remarkably, the mild reaction conditions under which **1** operates are compatible with sensitive functional groups that would not be tolerated by more conventional acidic or basic reagents. Along these lines, preliminary studies also point to an unprecedented mechanism.[4]
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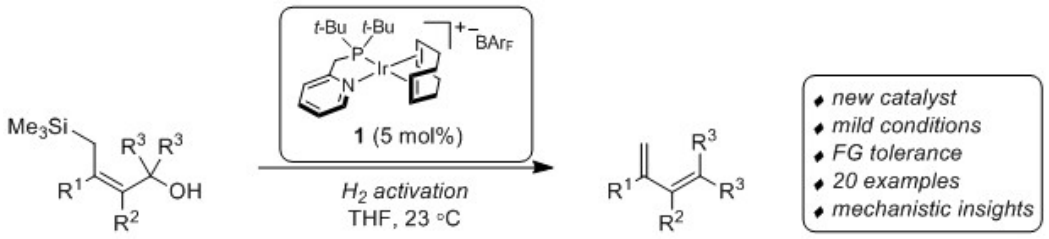

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Terminal-selective arylation of alkyl chains by regioconvergent Negishi coupling

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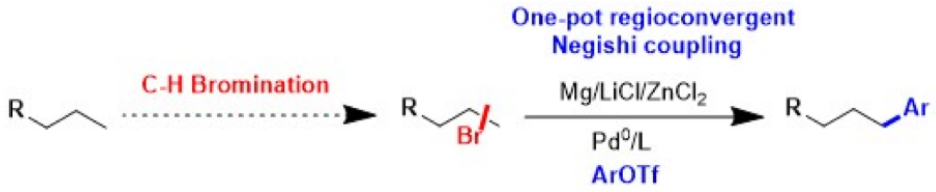
Palladium-catalyzed C(sp^2)-C(sp^3) cross-couplings are particularly valuable tools in synthetic chemistry and hence a great deal of interest has emerged in this area.[1] Recently, our group has developed a new cross-coupling strategy based on the migration of an organopalladium species along an alkyl chain.[2] Through experimental and theoretical mechanistic studies, we have shown that this migration occurs through a beta-H elimination/rotation/insertion sequence.[3]

In this work, we have extended this migrative-coupling to simple and commercially available alkyl bromides. Under practical Barbier-type conditions involving magnesium insertion and transmetallation with $ZnCl_2$, a series of linear arylated products could be obtained in a regioconvergent manner with good to excellent linear/branched selectivities, thanks to the use of a flexible phosphine ligand. Moreover, this strategy could be coupled to a non-selective radical bromination process, which allowed the functionalization of simple alkanes in just two steps.[4]



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Synthesis of amino-cyclobutanes via [2+2] cycloadditions involving keteniminium intermediates

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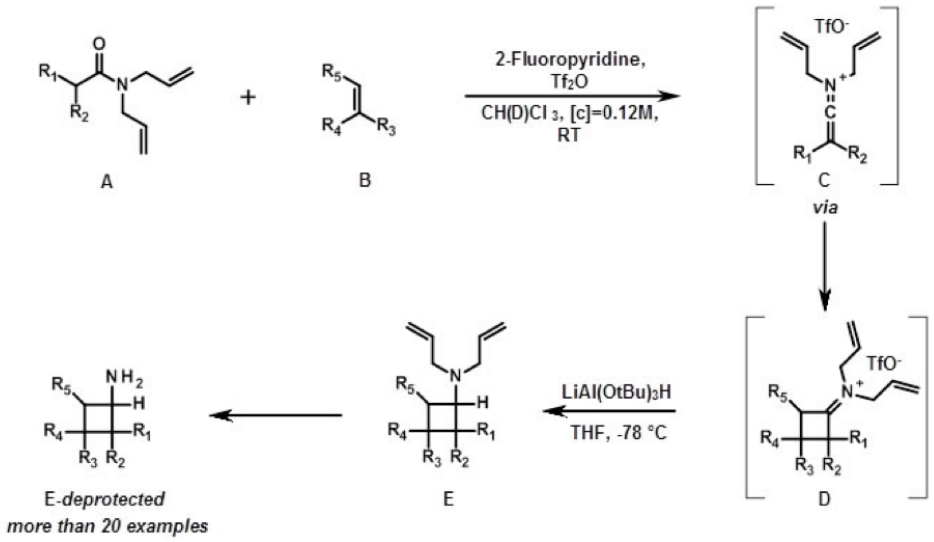
An efficient method has been developped for the synthesis of aminocyclobutanes *via* a [2+2] cycloaddition between a keteniminium salt and an alkene, followed by a stereoselective reduction step. The use of easily removable *N*-allyl moieties as protecting groups increases the potential of this method to access, in a few steps, highly functionalized cyclobutaneamines-containing building blocks. Moreover, competition reactions as well as DFT calculations verify the compatibility of *N*-allyl and *N*-propargyl keteniminiums in [2+2] cycloaddition reactions.



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Anion-π Interactions and Chalcogen Bonding in Functional Systems

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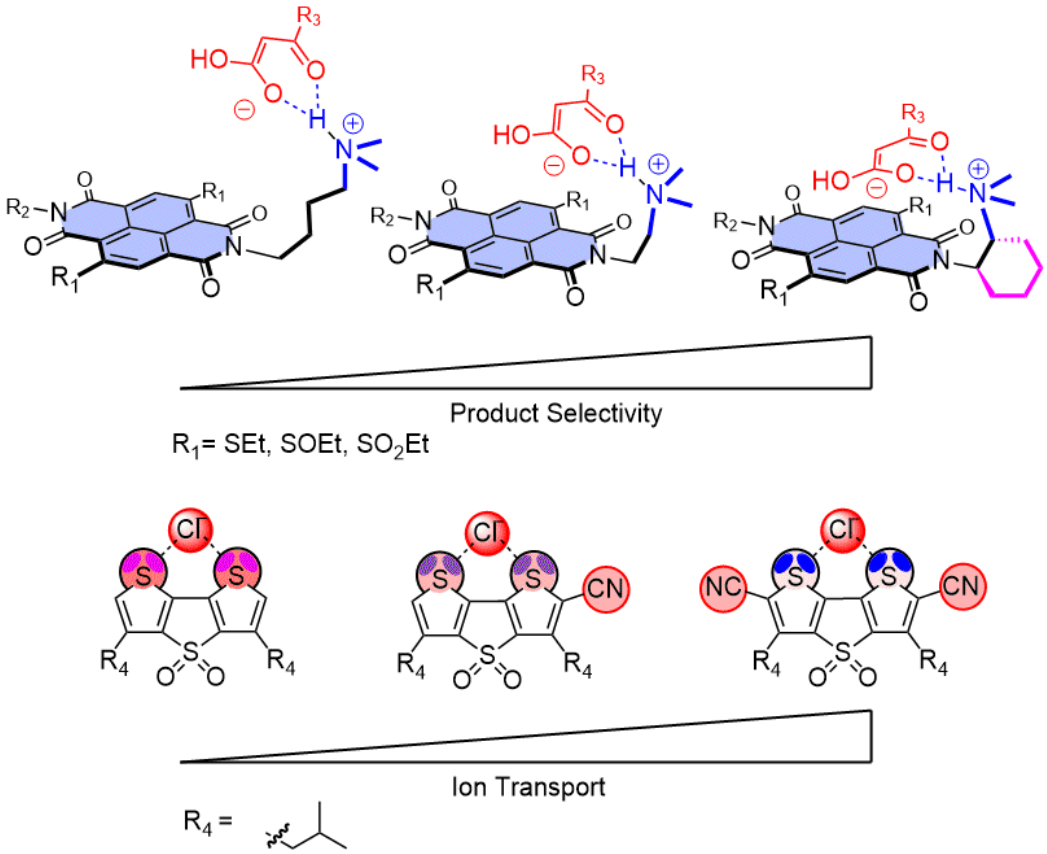
[1]University of Geneva

Anion-π interactions have recently been applied to decarboxylative addition of malonic acid half thioesters (MHTs) to nitroolefins [1]. Strongly electron-deficient naphthalenediimides (NDIs) are proficient to stabilize negatively charged intermediates leading to addition via anion-π interactions, favoring the formation of addition product over the otherwise preferred decarboxylation. In the current study [2], catalyst efficiencies were further improved by introducing a rigid cyclohexyl Leonard linker, which leads to ideal preorganization of the substrate on the aromatic surface.



Developing the concept of preorganization further, two thiophene units are concisely held together by a sulfone bridge to enable bidentate binding of chloride through chalcogen bonding. These dithienothiophenes are exploited to transport anions through lipid bilayer membranes.

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Atom Economical Transformation of Ethynylbenziodoxol(on)e (EBX) Reagents: Oxy-Alkynylation of Diazo Compounds

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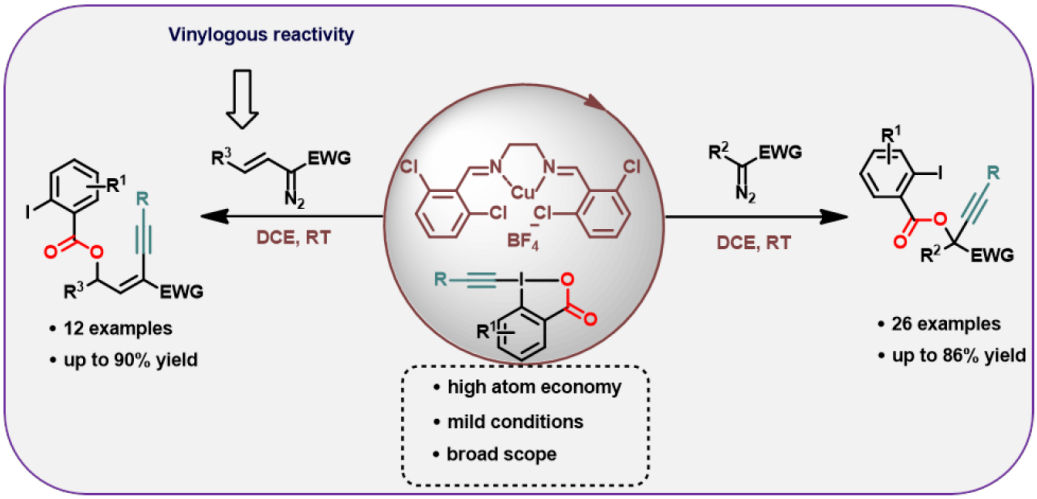
[1]EPF Lausanne

In recent years, electrophilic alkynylation has shown a great potential to make acetylene synthesis much more flexible and efficient.[1] However, electrophilic alkynylations using hypervalent iodine reagents generates one equivalent of an iodoarene as a side-product which is a significant waste of atom economy.[1,2] Here, we describe a strategy that involves the atom economical transformation of ethynylbenziodoxol(on)e (EBX) reagents by utilizing the diazo chemistry.[3] This reaction is remarkable in its broad scope with both ethynylbenziodoxol(on)e (EBX) reagents and diazo compounds. In addition, vinyl diazo compounds worked efficiently to furnish enynes as a single geometric isomers. The obtained products were efficiently transformed into useful building blocks such as α-hydroxy acids, triazoles, and isocoumarins. In addition, new results will also be presented.



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Pd(0)-Catalyzed Enantioselective C–H Functionalization of Enamide Phosphates

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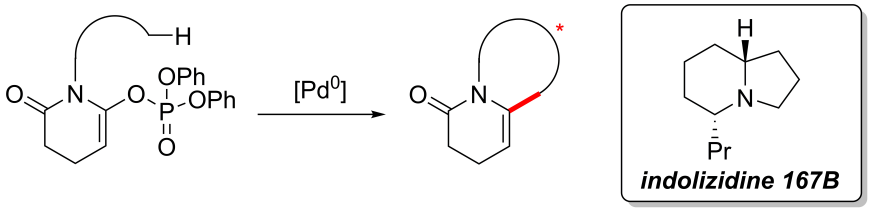
[1]EPF Lausanne

Transition metal-catalyzed C–H functionalization reactions have emerged as a central theme within organic chemistry.[1] Although many transformations have been extensively developed, several limitations still exist. For example, commonly employed substrates – such as aryl and alkenyl triflates – are often expensive, and can suffer from low stability and consequently poor yields in coupling reactions. In contrast, the corresponding phosphates are readily accessible from cheap and less toxic reagents, and in some cases exhibit greatly enhanced stability.[2] However, despite their great potential, only one example of a C–H functionalization employing phosphates, in an achiral manner, has been reported.[3]

The enantioselective synthesis of *N*-heterocycles *via* Pd(0)-catalyzed C–H arylation has been one of the main focuses in our research group.[4] These compounds are of the utmost importance in organic chemistry, thus new approaches can be of enormous value. Herein we present the first example of an enantioselective C–H functionalization of alkenyl phosphates enabling the synthesis of fused heterocycles resembling indolizidines.



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Carbohydrate mimics for therapeutic applications: exploring their conformational preference in the gas and micro-hydrated phases

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Carbohydrates are a group of the ubiquitous biomolecules, which play an important role in the human body for example in energy storage, immune response, infection, inflammation and tumor metastasis.[1] Nevertheless, carbohydrates are barley used as drugs, due to their complex structure, high polarity and weak binding affinity. However, recent developments provide evidence, that carbohydrate mimics have a huge potential in many therapeutic areas[2], taking advantage of their extraordinary properties of molecular recognition.

In order to rationally optimize the 3D structure, physico-chemical properties as well as the biological activity of carbohydrate mimics, first we need to understand how surrounding water molecules may 'sculpt' the structure of highly polar carbohydrates by restraining their conformational landscape or promoting specific bioactive conformations.[3]

We synthesized mimics of trisaccharide Lewis^X in order to explore the solvation effects at the atomic level by Gas phase laser spectroscopy in combination with *ab initio* quantum chemical calculations, which if compared to bound (X-ray crystallography) or solvent-phase conformation (NMR, MD simulations) could significantly improve our insight into the forces driving preferred carbohydrate conformations.

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Toward a Computationally Holistic View of Homogeneous Catalysis

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Computationally predicting novel catalysts for organic reactions requires exploring the detailed reaction mechanism for a single chemical transformation of interest. This fundamentally differs from electrochemical and heterogeneous applications where a significantly larger number of catalysts are screened using a simplified reaction mechanism. Linear scaling relationships established during the screening process describe the relative stability of intermediates with respect to a descriptor variable and allow qualitative analysis of the limitations associated with a chemical reaction[1,2]. Volcano plots constructed from these scaling relationships permit the behavior of individual catalysts to be analyzed and compared based on Sabatier's principle, which assumes that an ideal catalyst binds reactants and releases products in an equally facile manner. Catalysts matching this profile appear atop the volcano (**II** in Fig. 1) while deviations from this behavior cause catalysts to either be dominated by the release of the product (**I** in Fig. 1) or by the binding of the reactant (**III** in Fig. 1).

Recently, we transferred the concept of volcano plots to homogeneous catalysis by examining Suzuki coupling[3]. However, despite this success, organic reactions are frequently more complicated than can be illustrated in a typical 2D volcano plot that only describes a correlation between catalytic activity and a single descriptor. For instance, this simple picture fails to describe the influences brought about by co-catalysts, different reaction mechanisms, or variations in reactants and products. Here, we present a method that addresses these shortcomings using improved 2D and 3D volcano plots. These concepts form the basis of tools that predict active catalysts for reactions central to organic chemistry.

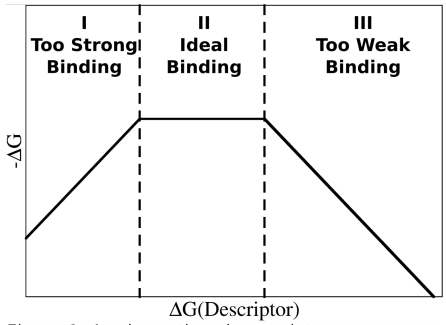

Figure 1: A schematic volcano plot.

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Ruthenium-Catalyzed [2+2] Cycloaddition Reactions of Bicyclic Alkenes with 1-Alkynyltriazenes

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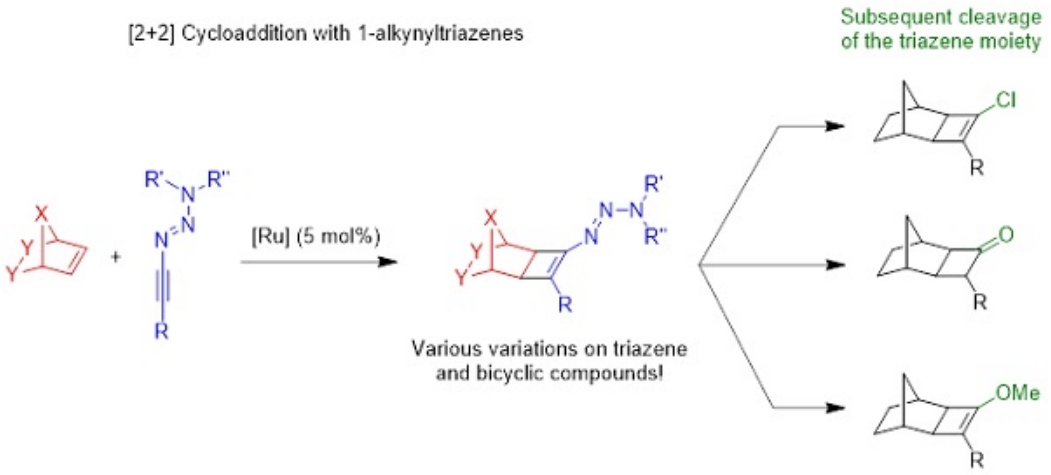
[1]EPF Lausanne

Recently, our group reported a procedure which allows preparing 1-alkynyltriazenes by a simple one-pot-reaction using nitrous oxide.[1] Subsequently, we have shown that 1-alkynyltriazenes react as activated alkynes with a reactivity profile similar to ynamides.[2] We continued the exploration of the triazenes reactivity by using them in Ru-catalyzed [2+2] cycloadditions reactions with bicyclic alkenes. As catalyst precursors, we have employed the stable and easy-to-access sandwich complex [Cp*Ru(η^6-$C_{10}H_8$)](BPh$_4$) in combination with [NBnEt$_3$]Cl as chloride source. This system appears to be an interesting alternative to the standard catalyst precursor Cp*Ru(COD)Cl. The cycloaddition reactions with 1-alkynyltriazenes proceed rapidly under mild conditions to give the corresponding adducts in good yields. A unique advantage of using 1-alkynyltriazenes for [2+2] cycloaddition reactions is the fact that the triazene group in the products can be replaced under acidic conditions.



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Enantioselective a-arylation of protected aliphatic alcohols via sparteine-mediated asymmetric lithiation and Negishi coupling

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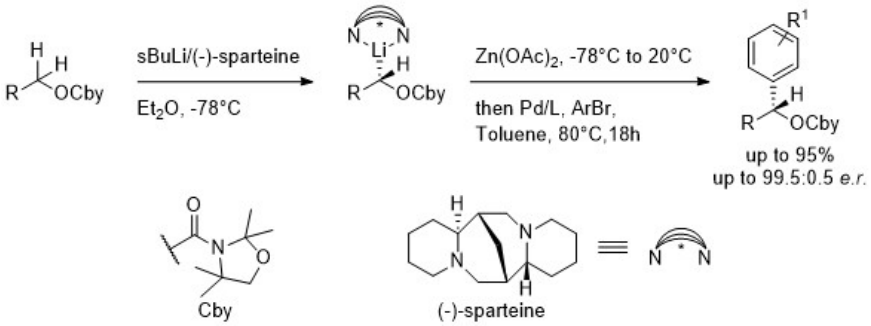
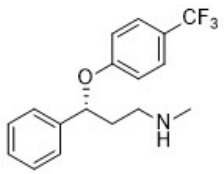
[1]University of Basel

The enantioselective a-arylation of protected aliphatic alcohols is described. Hoppe's technology allows to perform the enantioselective a-lithiation in presence of sparteine.[1] After Li-Zn transmetalation and Negishi cross-coupling, highly enantioenriched benzylic alcohols are accessed. The method is compatible with a wide range of (hetero)aryl bromides and aliphatic alcohols.



After deprotection, the highly enantioenriched benzylic alcohols provide valuable building blocks to construct naturally occurring and bioactive compound, notably (*R*)-Fluoxetine, an important antidepressant.[2]



(R)-Fluoxetine (Prozac)
Antidepressant

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Study of Gold(III)-fluoride complexes: Key Intermediates in Gold Catalyzed Transformations

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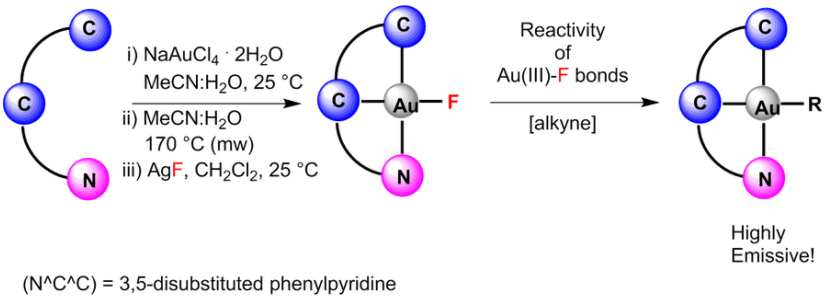
Gold-catalyzed oxidative cross-couplings have bloomed in the past few years postulating gold(III) fluorides as productive reactive intermediates.[1] However, experimental support for these species is to-date scarce due to their labile nature, and thus the reactivity of Au-F bonds remains largely unexplored.[2]Here, we report the synthesis of monomeric, easy to handle, bench-stable Csp^2-Au(III)-F complexes. Key for the success in the preparation of these valuable compounds is the use of a Cl/F ligand-exchange reaction enabled by a novel (N^C^C)-pincer ligand framework to stabilize the Au(III) center. Devoid of oxidative conditions or stoichiometric use of toxic Hg salts, our method was applied to the preparation of multiple Csp^2-Au(III)-F complexes, which were used as mechanistic probes for the study of the unique properties and intrinsic reactivity of Au-F bonds.[3] Interestingly, the (N^C^C) framework entices improved photophysical properties in the corresponding gold(III) complexes compared to widely used (C^N^C)-pincer ligand systems.



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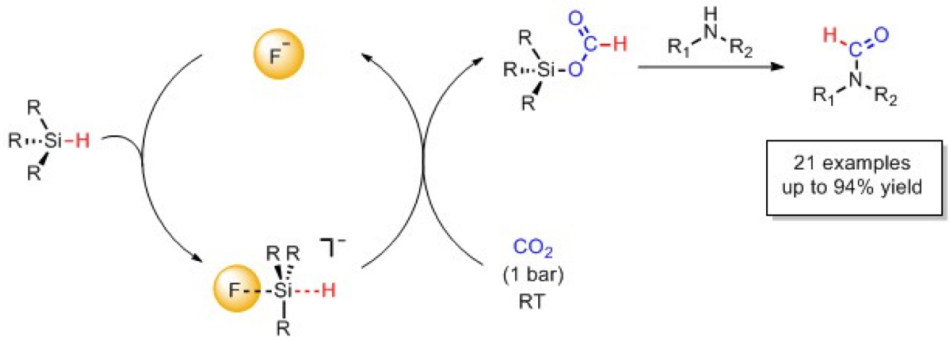
N-formylation of Amines with CO_2 Catalyzed by Fluoride and Hydroxide Anions

M. Hulla[1], F. D. Bobbink[2], S. Das[3], P. Dyson[2]

[1]EPFL, [2]EPF Lausanne, [3]Georg-August-Universität Göttingen

N-formylation of amines with CO_2 can be achieved with hydrosilane reducing agents and simple fluoride and hydroxide salt catalysts. Fluoride and hydroxide anions activate the hydrosilane reducing agent leading to reactivities comparable to $NaBH_4$ or $LiAlH_4$. Reduction of CO_2 and subsequent N-formylation of amines is then achieved at room temperature and atmospheric pressure without the need for precious metal catalysts. Excelent yields and selectivities are achieved with TBAF and phenyl silane for both aliphatic and aromatic amines.

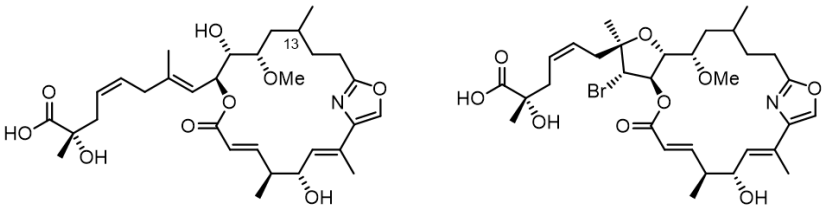


Towards the Total Synthesis of Leiodolide A

A. Edenharter[1], K.-H. Altmann[1]*

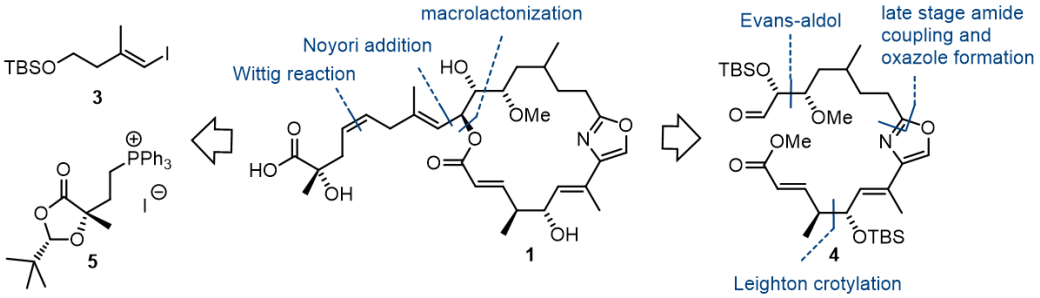
[1]ETH Zurich

Leiodolide A (**1**) is a 19-membered marine macrolide of mixed polyketide/non-ribosomal peptide synthase origin, which was isolated in 2006 by Fenical and co-workers from a deep-water sponge of the rare genus *Leiodermatium*, together with the structurally closely related leiodolide B (**2**). Leiodolide A (**1**) has been reported to exhibit significant *in vitro* antiproliferative activity against a range of human cancer cell lines, in particular those of myeloid lineage.[1] It thus represents a potentially valuable new scaffold for anticancer drug discovery.



In light of its interesting biological properties and in order to unambiguously confirm the intriguing structure with a still unassigned stereocenter at C13, we have embarked on the total synthesis of **1**, based on the retrosynthesis depicted below.

According to this strategy, **1** will be assembled by a zinc-mediated Noyori addition of vinyl iodide **3** to aldehyde **4** and subsequent ring- closure, followed by a Wittig reaction with phosphonium salt **5** to introduce the head of the side chain. Aldehyde **4** has been efficiently built up by means of oxazole formation from two fragments, which were derived from citronellal and L-serine as chiral pool building blocks, respectively. The stereocenters in aldehyde **4** were established by Evans-aldol chemistry and Leighton crotylation.



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The Mechanism of Stereospecific Cyclization: Key Step on the Way to Optically Active Chromans

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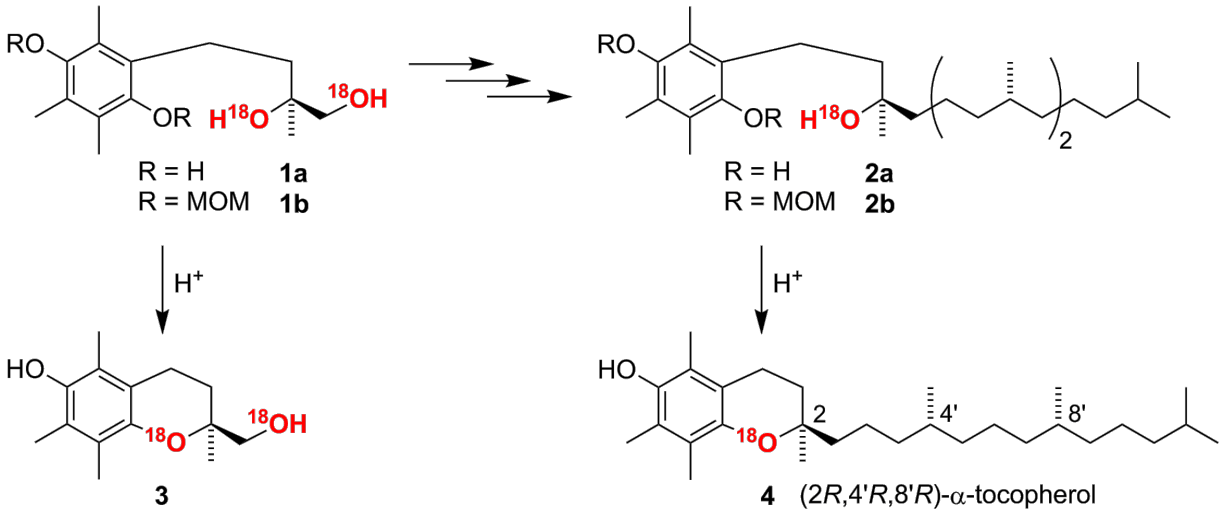
[1]DSM Nutritional Products, 4002 Basel

Naturally occurring tocopherols and tocotrienols are single-isomer vitamin E compounds. (2*R*,4'*R*,8'*R*)-α-Tocopherol (**4**) as a prominent example is of high commercial interest due to its biological and antioxidant properties.[1] Although the stereospecific cyclization reaction of intermediates and precursors such as **1a**/**2a** to chromans **3**/**4** under carefully controlled acidic conditions is known for a long time [2] and has been used as a key step in many total syntheses,[3] the mechanism of this transformation is unknown.



We investigated the course of the acid catalyzed ring closure reaction by starting from doubly ^{18}O-labelled derivative **1b** (synthesized via stereoselective bishydroxylation). Chromans **3** and **4** (via intermediate **2b**) obtained by applying standard literature procedures showed complete (over 95%) chirality transfer as well as ^{18}O-incorporation. The mechanism proposed will be discussed in comparison to findings documented in previous research papers.

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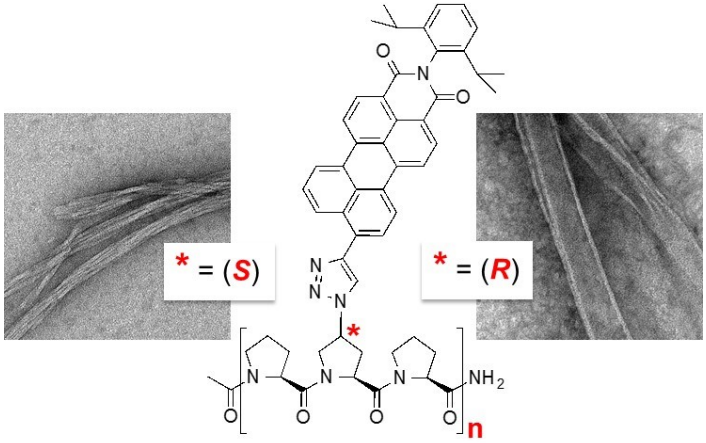
Oligoprolines as a Versatile Platform for the Self-Assembly of π-Systems

U. Lewandowska[1], W. Zajaczkowski[2], W. Pisula[2,3], N. Ochs[1], S. Steppert[2], C. Li[2], K. Müllen[2]*, H. Wennemers[1]*

[1]ETH Zurich, [2]Max Planck Institute, Mainz, Germany, [3]University Lodz, Poland

Incorporation of building blocks bearing specific functionality into larger entities has enormous potential for material science due to the possibility of bridging the gap between the molecular and macroscopic scale in terms of order, when precise control of the self-assembly process is achieved.[1,2] Efforts have been made to create well-ordered, functional structures based on DNA and polypeptide, which can be easily decorated with the desired functionality. Until now the use of rigid peptidic scaffolds for such purposes has been limited.[3]



Supramolecular order: (*R*) > (*S*)

n = 1 < 2 < **3** ≥ 4 > 5

Functionalizable, azidoproline-containing oligoprolines were chosen as scaffolds for the directed self-assembly of π-conjugated systems as they adopt already at a short chain lengths of six residues the conformationally well-defined polyproline II (PPII) helix, in which every third residue is stacked on top of each other in a distance of ~1 nm.4 We have shown that both the length and the stereochemistry of the peptide backbone affect the supramolecular assembly of oligoproline–PMI conjugates significantly 5,6 and allowed for achieving hierarchical self-assembly of various chromophores from fibers, through nanosheets to well-defined hexagonal microcrystalline material (Figure 1). The aim of the project is to create and control nanostructured materials for the generation of ordered mesoscopic materials that could be applied in macroscopic organic electronic devices.

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Tailor-made Concave Ligands for the Encapsulation and Functionalization of Nanoparticles

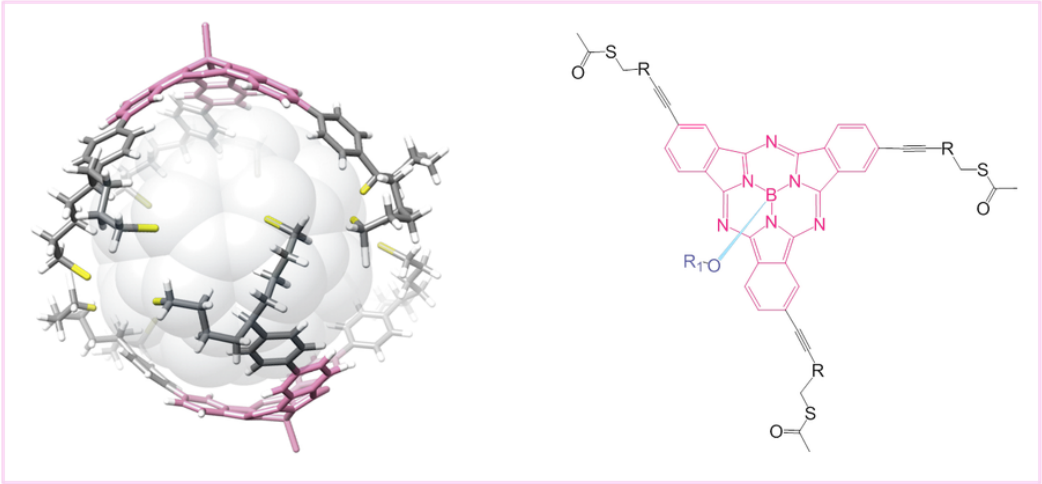
A. Gallego[1], M. Mayor[2]*

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

Nanoparticles are on the focus of many investigations due to its unique size-dependent electronic and optical properties. However, the potential applications are often limited by the restrained functionalization that hinders its further manipulation. Different synthetic approaches have being tested to control the number and functionality along the particles surface[1]. However, the overall control over the number and specific reactivity of the particles is still challenging.

Our strategy aims on the encapsulation of the particles with two concave ligands whose complementary bowl-shape to the spherical particles would direct the formation of **bi-funcionalized nanoparticles** (see *figure 1, left*). Subthalocyanines are ideal for this aim due to its concave structure and versatile reactivity[2]. Furthermore, its encapsulation capabilities were already demonstrated with fulerenes[3].

Thus, we designed and synthesized a series of subthalocyanines (*figure 1, right)* functionalized with protected thiols in terminal positionsconnected through organic groups of different lengths and rigidity (R) in order to further evaluate its influence and determine the most efficient encapsulating structure.



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Organocatalytic enantioselective Michael addition of α-alkyl substituted α-nitroacetates to phenyl vinyl selenone

A. Clemenceau[1], J. Zhu[1], Q. Wang[1]

[1]EPF Lausanne

Synthesis of enantio-enriched α-quaternary α-amino-acids has remained an active research area. We have recently described a *Cinchona* alkaloid-catalyzed Michael addition reaction of methyl α-aryl-α-isocyanoacetates to phenyl vinyl selenone. The resulting enantioenriched α-aryl-α-(2'-phenylselenonylethyl)- α-isocyanoacetates were subsequently converted into α-aryl-α-(2'-FG-alkyl)- α-amino acids and medicinally important heterocycles as well as natural product trigonoimine A.1 To access α,α-dialkyl substituted α-amino acids, a novel *Cinchona* alkaloid-catalyzed enantioselective Michael addition reaction has been developed using α-alkyl substituted α-nitroacetates and phenyl vinyl selenone as reaction partners. Under optimized conditions, α-alkyl-α-(2'-phenylselenonylethyl)-α-nitroacetates were obtained in good to excellent yields and enantioselectivities. The broad substrate scope and the easy modification of the nitro and phenylselenonyl groups made this reaction a useful alternative for the synthesis of α,α-dialkyl substituted α-amino acids and other chiral building blocks.2

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Helical oligophenyl Geländer molecules

R. Mannancherry[1], M. Mayor[1]*

[1]University of Basel

Polycyclic aromatic compounds (PACs) gained the attention of fundamental researchers and material scientists since the concept of molecular chemistry was born. Especially chiral PACs have attracted strong interest for material applications due to their unique physical properties. Additionally their structural beauty represents an exciting and interesting challenge for chemists.[1]

Recently, our group succeeded in synthesising a new type of Geländer molecules with a terphenyl backbone and a bannister oligomer.[2-4] These interesting results motivated us to extend our research into three new approaches. The first one is to synthesise longer oligomers (**figure 1a**) in order to achieve one full turnover of the helical structure and determine, if the chiral information is further transferred to the next phenyl unit. Secondly, we design a fully hydrogen-carbon Geländer oligomer (**figure 1b**), to obtain a closer-packed system which is expected to prohibit the racemisation process after once the enantiomers are separated at the HPLC with a chiral packed column. The final purpose of study these structures at the nanoscale, our third aim is to introduce a 9,9′-spirobifluorene group in the *para* position of one of the most external phenyl units, providing the molecule with an anchoring group capable to immobilize the helical Geländer system on a metal surface (**figure 1c**).

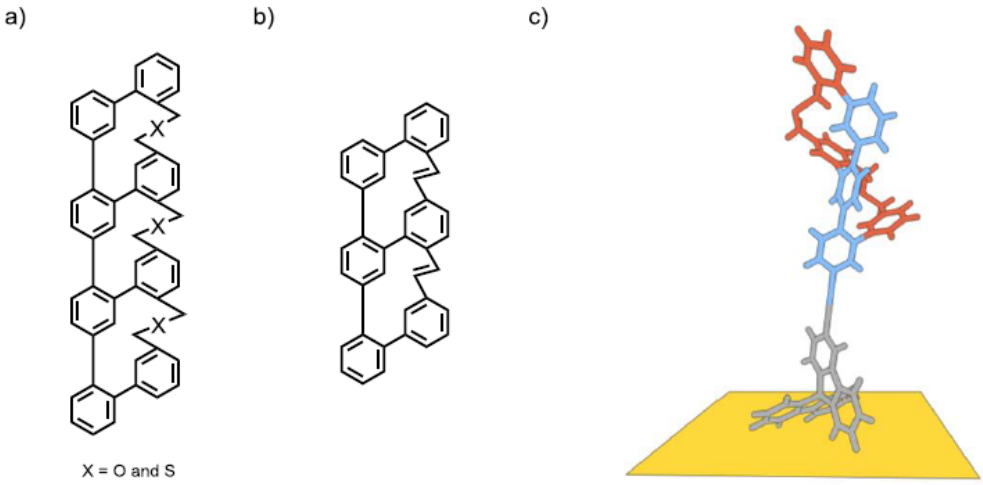

Figure 1: Three new strategies to investigate chiral PACs properties. a) Design of the higher-order oligomer species. b) Helical Geländer system containing only hydrogen and carbon atoms. c) 3D illustration of the immobilized Geländer molecule on a metal surface.

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Multifold-Linked Fe(II) Terpyridine Cage Complexes

T. Brandl[1], M. Mayor[1]*

[1]University of Basel

Alfred Werner paved the way for supramolecular chemistry with his pioneering work on inorganic coordination compounds.[1] Since the last century metal complexes have drawn great attention in the community due to their exceptional physical properties. In this regime iron(II) complexes became the workhorse of the arising and fascinating field.

Due to the electron configuration of Fe(II), it offers six coordination sites that fit perfectly to coordinate two tridentate terpyridine molecules in an octahedral geometry. Iron complexes itself can be found in different spin states – the high-spin and the low-spin. Depending on the spin state, the colour of the complex varies.[2] Due to the ability of these complexes to undergo spin crossover (SCO) phenomena[3], these complexes are interesting for information storage systems.[4] The idea of the proposed interlinked iron complex (Figure 1) is to fine tune the ligand-field about the Fe(II) and observe if the spin crossover system can be considered as a modification in the geometry. The rigidified iron complex adsorbed on an Au(111) surface can then be analysed using a Scanning Tunnelling Microscopy (STM) technique. If the complexes remain in their low-spin state, it would be interesting to perform SCO experiments by exertion of an external force.

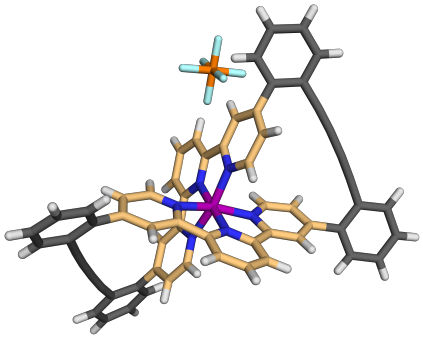

Figure 1: Crystal structure of twofold-linked Fe(II) terpyridine complex.

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Studying the conformational ensemble of b^3/b^2-peptides using ROEs, J-couplings and RDCs

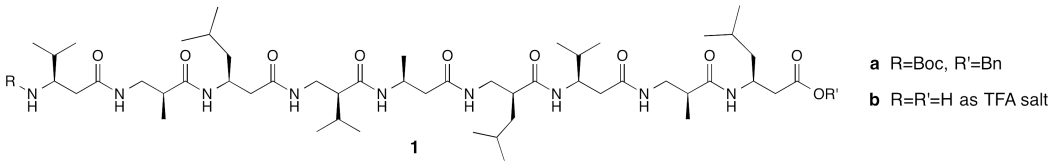
C. Rigling[1], B. Kolesinka[2], M.-O. Ebert[1]*

[1]ETH Zurich, [2]University of Lodz, Poland

NMR spectroscopy is the method of choice for determination of the three-dimensional structure of molecules in solution. Commonly, it is assumed that a single dominant molecular conformation in solution can represent all the experimental NMR data. However, molecules are constantly subjected to conformational changes in solution and representing the conformational ensemble as single structure can lead to over-restraining and thus to misinterpretation of the available data. Efforts to overcome this problem have mainly been focused on large biomolecules. For small and medium-sized molecules the small density of available restraints still renders a full description of the conformational ensemble difficult.

We have studied the solution-structure of the mixed b^3/b^2-peptides **1a** and **1b** in detail. It is known that b^3/b^2-peptides can exhibit antimicrobial activity, and only recently they were found to penetrate the lipid bilayer of eukaryotic cells [1]. Earlier studies suggested that a 12/10 helix is the dominant conformation of the terminally protected b^3/b^2-nonapeptide **1a** in methanol. Deprotection (**1b**) is believed to lead to an equilibrium between a 10/12 and a 3_{14} helix [2].

To investigate this hypothesis in more detail we have used an extended set of experimentally derived restraints, including RDCs, and a multi-copy simulated annealing procedure. The RDCs were measured using a stretched polyvinyl acetate gel in methanol. For comparison the structures were also calculated with the common single conformation procedure. The structures resulting from the two different methods are discussed.



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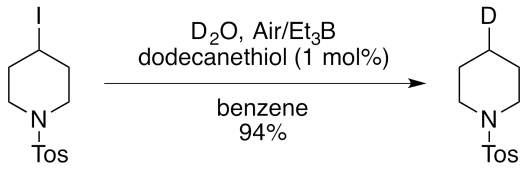
Thiol-Catalyzed Radical Deuteration of Alkyl Iodides Mediated by Triethylborane and Deuterium Oxide

V. Soulard[1], G. Villa[1], D. Vollmar[1], P. Renaud[1]*

[1]University of Bern

Preparation of organic compounds selectively labelled with deuterium atom, remains a challenging synthetic problem [1]. Radical deuteration of alkyl halides is one of the most efficient approach to perform this task. It is usually run using organotin deuterides [2] but this method has three major drawbacks: organotin deuterides are expensive, toxic [3] and led to product contamination.

We report here a method to deuterate alkyl iodides via a radical pathway with deuterated water or methanol as source of deuterium atom. Triethylborane is used to initiate and propagate the chain and dodecanethiol is used as a catalyst [4]. High deuterations and yields are obtained using this method.



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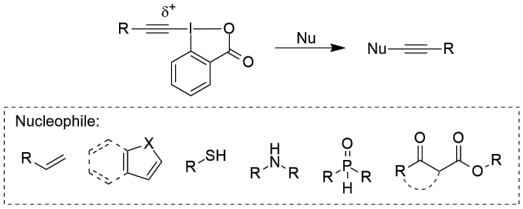
EthynylBenziodoXolone (EBX) Reagents for Alkynylation Reactions

L. Schouwey[1], J. Waser[1]*

[1]EPF Lausanne

Hypervalent iodine (III) reagents are nowadays widely used for electrophilic group transfer reactions.[1] Within this class of compounds, cyclic reagents such as benziodoxolones (**1**) have shown increased stability, but still sufficient reactivity.[2] Ethynylbenziodoxolones in particular have been highly successful in electrophilic alkynylation reactions. In order to develop new reactions and overcome the current scope limitations, new reagents have to be developed. Recent progress in this respect will be presented herein.



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Organocatalyzed 1,4-addition reactions of aldehydes to nitroolefins – Mechanistic studies

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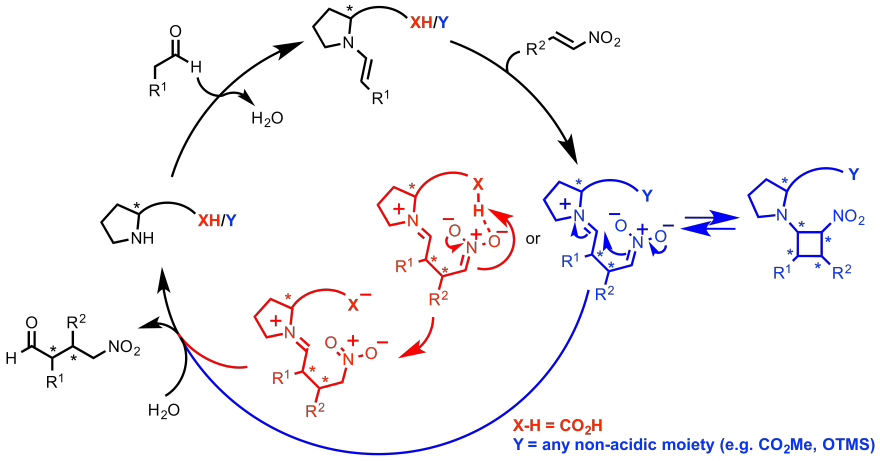
[1]ETH Zürich

Organocatalysis has become a pillar of asymmetric catalysis but comparatively few mechanistic investigations have been carried out. Addition reactions between aldehydes and nitroolefins using chiral amine-based catalysts are among the most studied reactions.[1] Our group showed that the presence or absence of a proton donor within the catalyst significantly affects the reaction pathway and rate-determining step.[2] Furthermore, mass spectrometric monitoring of back reactions of quasi-enantiomeric products provided proof that reactions with catalysts containing a suitably positioned proton donor proceed *via* enamine intermediates.[3]

We have now extended our mechanistic studies with a combination of different spectroscopic techniques and will present new insights into the reaction pathway. We will also present how these findings allowed for further optimizing the reaction conditions.



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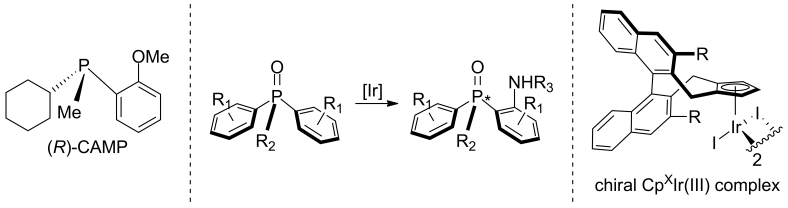
Chiral Cp^XIr(III) Catalyzed C-H Amidation Leading to P-Chiral Arylphosphine Oxides

Y. Jang[1], M. C. Dieckmann[1], N. Cramer[1]*

[1]EPF Lausanne

Organophosphorus compounds with *P*-stereogenic centers are valuable motifs in pharmaceuticals, agrochemicals, organocatalysts and ligands.[1] Chiral phosphorous ligands, such as CAMP, play a key role in current asymmetric synthesis.[2] However, despite the importance of molecules that are chiral-at-phosphorous, only a limited number of catalytic enantioselective approaches have been developed.[3]

Chang *et al.* recently disclosed an Ir(III) catalyzed asymmetric amidation of arylphosphine oxides, however only low yields and enantioselectivities were observed.[4] Application of our recently developed chiral Cp^XIr(III) complex has enabled a more mild and efficient C-H amidation process, resulting in a highly enantioselective transformation that proceeds in good yield.[5] This methodology has also been expanded to the synthesis of phosphinamides and phosphinates.



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Retention of Absolute Configuration in Hydrogen Atom Transfer/Cyclisation Cascade

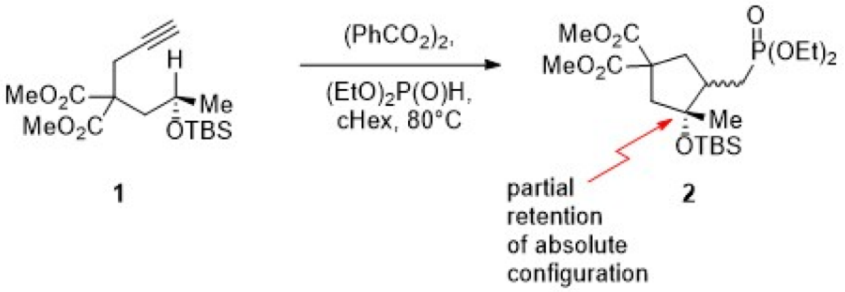
C. Gloor[1], I. Kovalova[1], V. Soulard[1], P. Locher[1], Y. Kavanagh[1], M. Pichowicz[1], P. Renaud[1]*

[1]University of Bern

Due to the nature of radicals, few stereoselective reactions are known in which a radical is generated at a chiral center with retention of the absolute configuration. In an early report by Heiba and Dessau, the formation of an optically active lactone was observed although the reaction proceeds through a radical at the chiral center *via* a 1,5-H shift.[1] The level of retention was however unknown. Recently, Curran and coworkers published a related cyclisation process of a-amide radicals involving retention of chirality.[2, 3]

Meanwhile, our group reported a radical cyclisation involving phosphonyl and thiyl radicals to access cyclopentane derivatives.[4] We decided to use this reaction as the starting point to study whether retention of chirality is possible and the factors influencing the stereochemical outcome.

The alkynyl malonate **1** was readily synthesized in a five-step procedure strating from (*S*)-(–)-ethyl lactate. Treatment of **1** with diethylphosphite afforded the cyclic product **2** with partial retention of configuration (Scheme 1)



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Neutral Radicals Derived From Imidazolium Dyes

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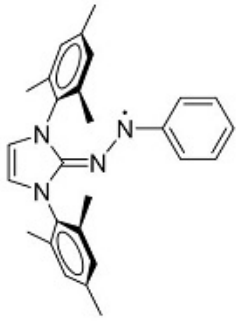
[1]EPF Lausanne

The synthesis and the characterization of a new class of aminyl radicals is reported. The neutral monoradical **1** was obtained by reduction with potassium of azoimidazolium dye featuring N-mesityl substituent at the heterocycle. Structural, spectroscopic and computational data suggest that the spin density is centered on the nitrogen atom next to the imidazolin-2-iminato group. Furthermore, we have shown that the reduction of a dimeric dye with an octamethylbiphenylene bridge between the azo groups results in the formation an open-shell diradical (**2**). Compound **2** is structurally related to compounds of the formula $[R_2N\text{-}(C_6H_2R'_2)_2\text{-}NR_2]^{2+}$, which have received considerable attention in recent years. A unique feature of **2** is the fact that it has an overall charge of zero, as opposed to +2, and strong diradical character. Both, the monoradical **1** and the diradical **2** were found to display high stability in solution as well as in solid state. The stability can be attributed to the steric shielding of the N-aryl substituents, as well as to the stabilizing effect of the imidazolin-2-iminato group. Potential applications of these new aminyl radicals (e.g. as as electrochromic dyes) are currently explored in our laboratory.



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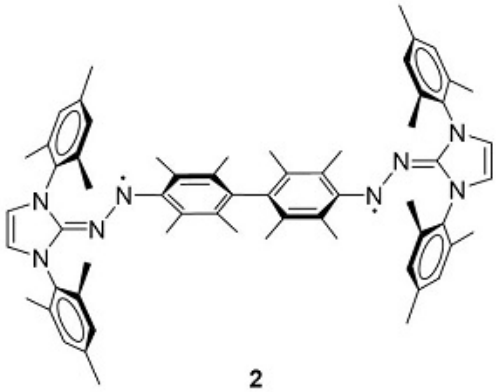


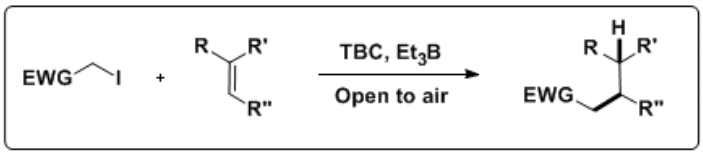
2

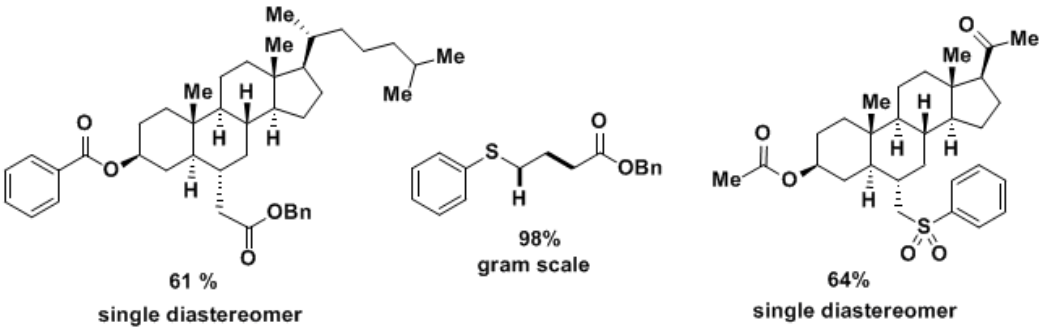
Catechol Mediated Intermolecular Carbohydrogenation of Terminal and Non-Terminal Alkenes

S. R. Suravarapu[1], S. Rieder[1], G. Povie[1], P. Renaud[1]*

[1]University of Bern

A few years ago, we have reported a radical chain reduction of organoboranes to alkanes with a very inexpensive 4-*tert*-butylcatechol under very mild conditions [1]. More recently, we have extended this procedure for the efficient deiodination of alkyl iodides with a mixture of 4-*tert*-butylcatechol and triethylborane [2]. Herein, we disclose that this reagent can be used for amazingly efficient carbohydrogenation of terminal and even non-terminal alkenes.





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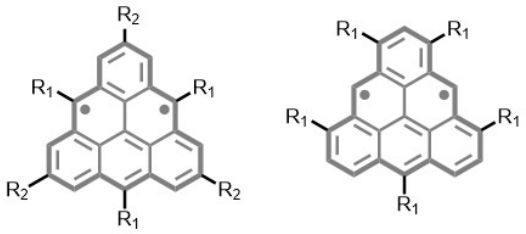
Synthesis of Persistent Derivative of Open-Shell Graphene Fragment Triangulene

P. Ribar[1], M. Juricek[1]

[1]University of Basel

Non-Kekulé graphene fragments (GFs) are promising candidates for applications in future molecular quantum electronic devices. These molecules are composed of sole carbon and hydrogen atoms with open-shell electronic structure [1] that determines their unique properties but also their high chemical reactivity and, therefore, low stability. Only a handful of open-shell GFs are known to this day. These rather rare examples, however, were only detected under strictly oxygen-free conditions and at low temperatures. Strategies to stabilize a non-Kekulé compound triangulene (in grey, see figure) with a triplet ground state [2] will be discussed. The synthetic efforts to prepare and fully characterize, both in solution and in the solid state, persistent derivative of triangulene by enclosing its sensitive diradical core inside a protective shell, in the form of the set of bulky substituents, will be presented and supported by EPR measurements and quantum chemical calculations.



Synthesis of the starting materials is known from the literature [2-3]. In the case of 5-substituted derivative, the synthesis will be started with a Suzuki cross coupling reaction followed by a series of Grignard additions. Reduction of hydroxy groups will lead to the final precursor.6-substituted derivative will be prepared by a Suzuki cross coupling reaction followed by an addition of a organocerrium reagent. Preparation of a precursor will also require a reduction of all hydroxy groups.The final triangulene derivatives will be prepared by presursor oxidation using *p*-chloranil.

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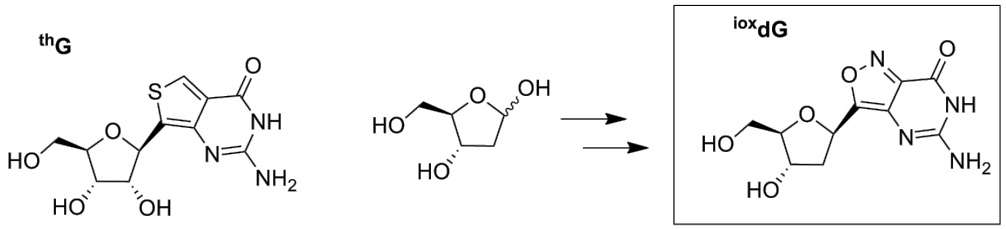
Development of fluorescent nucleoside isosteres

A. Johnson[1], N. W. Luedtke[1]*

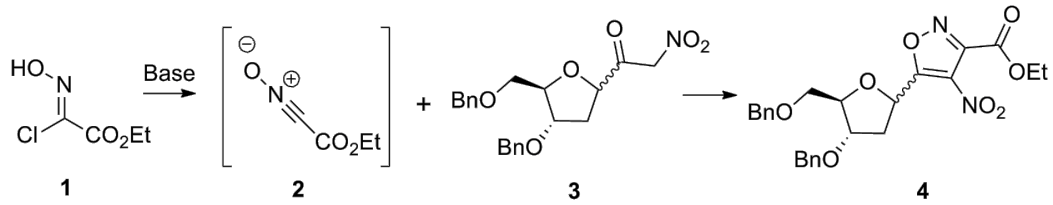
[1]University of Zurich

The secondary structure of nucleic acids is relevant to many cellular processes. Developing efficient probes for their detection can give valuable information on their biological roles. A variety of fluorescent nucleosides have been synthesized and used for *in vitro* analysis, however; there is little precedence for application of these probes *in vivo*.[1] This is mainly due to the large structural differences between the fluorescent analogues and the native nucleosides. Due to the relatively small π-system of the naturally occurring nucleobases, it is very difficult to obtain a sufficient level of photophysical activity without greatly perturbing the nucleoside structure.[2] Traditional methods include extension of the π-system and tethering of a fluorescent moiety. ;

One of the best examples in the literature of a sufficiently fluorescent nucleoside with minor structural modification of the nucleobase is th**G**.[3] One drawback of this analogue is the lack of a *N*7 hydrogen bond acceptor, which is crucial to the formation of G-quadruplex structures. To maintain this capability, we are synthesizing the analogue ^{iox}**dG** as an improved mimetic, which we expect to have red-shifted absorbance and emission maxima.



The key step in the synthesis of ^{iox}**dG** is a [3+2] cyclization. Hydroximic acid chloride **1** in the presence of base generates nitrile oxide **2** *in situ*.[4] Cyclization with *α*-nitroketone **3** affords an isoxazoline, which dehydrates to give the desired isoxazole scaffold. To the best of our knowledge, this is the first example of such a reaction using aliphatic substrates.



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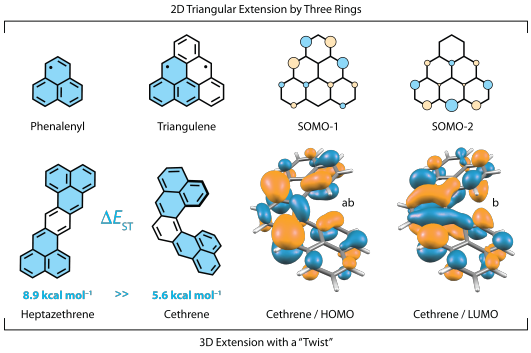
Spin-Delocalized Hydrocarbons With or Without Twist

M. Juricek[1], P. Ravat[1], P. Ribar[1], T. Solomek[2]

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

One of the future challenges in the field of molecular spintronics is the development of multifunctional devices that employ spins of unpaired electrons. Open-shell molecules with delocalized spin density are promising candidates for fulfilling this task as they can display a combination of magnetic and conducting properties. We design and synthesize neutral spin-delocalized hydrocarbons and study their properties that arise from their unusual electronic structure to understand the interplay of electron communication *through space and backbone*, which is crucial for balancing the intra- and intermolecular spin interactions that dictate the bulk material properties.



The prototypical spin-delocalized hydrocarbon is phenalenyl (blue), a three-ring system with an unpaired electron uniformly delocalized between six carbon atoms. To explore new features of spin-delocalized systems, we extend the phenalenyl motif in 2D and 3D. The 2D triangular extension leads to systems with a ground state of highest possible multiplicity. We explore strategies to kinetically stabilize the second homolog in this series, namely, triangulene, a non-Kekulé hydrocarbon containing two unpaired electrons predicted to have a triplet ground state. The 3D extension is achieved by inducing a helical twist into the backbone, which gives rise to *intramolecular* through-space interactions. We have recently demonstrated[1,2] the effect of such helical twist in *cethrene*, a biradicaloid hydrocarbon with a singlet ground state and [5]helicene backbone, in which the singlet–triplet energy gap is lowered when compared to its planar isomer heptazethrene, on account of through-space interactions (ab = antibonding, b = bonding) within the HOMO and the LUMO that arise as a result of the helical twist.

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Studies on the alkene-tetrazine ligation for DNA labeling

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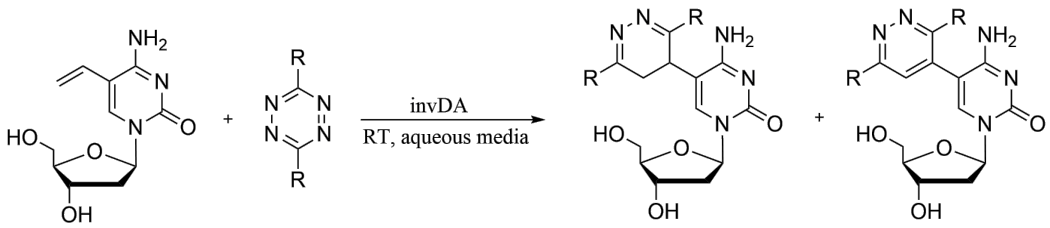
[1]University of Zurich

Fluorescent labeling of DNA can be used for the visualization of nucleic acids in living cells. The most frequently used label is 5-bromo-2'-deoxyuridine (BrdU), which can be incorporated into the DNA of replicating cells and detected using fluorescent antibodies.[1] However, due to its limited detection, 5-ethynyl-2'-deoxyuridine (EdU) was developed, which can be visualized by a bioorthogonal “click” reaction with a fluorescent azide.[2] The greater sensitivity of EdU detection is achieved at the cost of its increased toxicity. These effects can be avoided by using F-ara-EdU (5-ethynyl-2'-fluoro-2'-deoxyuridine) [3] or VdU (5-vinyl-2'-deoxyuridine), [4] which label the DNA with almost no influence on the genome function.
VdU is employed in the inverse electron demand Diels-Alder reaction (invDA) with an electron-deficient diene to give a highly fluorescent product. This cycloaddition is chemically orthogonal to the “click” reaction, allowing multi-color labeling of DNA synthesis.

We focused our interests on the further study of the invDA reaction, using VdC (5-vinyl-2'-deoxycytidine) as a potential metabolic label. Our goal is to find a suitable tetrazine, which can react with VdC under biological conditions to give a cycloaddition product with interesting fluorescence properties *in vivo*.



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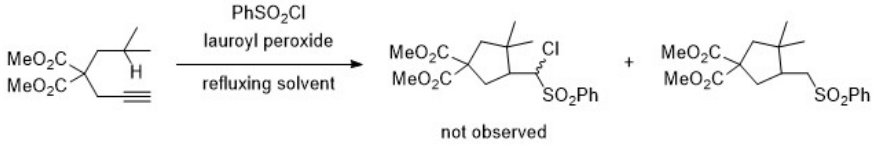
Sulfonyl Radical Mediated Addition/Translocation/Cyclization Cascade

C. Gloor[1], F. Dénès[2], P. Renaud[1]*

[1]University of Bern, [2]Université de Nantes

Our group developed a radical addition/translocation/cyclization cascade for the synthesis of substituted cyclopentanes.[1] In order to have a facile access to natural product cores, we were interested in performing a similar reaction cascade reaction with sulfonyl radicals.

The reaction was tested on the model system which we used to optimize all our addition/translocation/cyclization cascades. Interestingly, the reaction did not furnish the expected cyclic chlorosulfone but rather the cyclic dechlorinated sulfone. After optimization, this reaction proved to be very efficient and high yielding. The scope and the mechanism will be discussed in detail.



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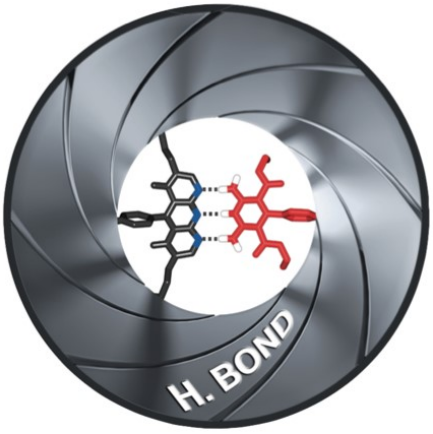
Supramolecular achitectures based on a novel AAA-DDD triple hydrogen bonding motif

J. Grolms[1], K. Severin[1]*

[1]EPF Lausanne

Design, synthesis and characterization of different supramolecular architectures based on a novel AAA-DDD triple H-bonding motif is reported. A facile and flexible method for the synthesis of the building blocks was previously developped in our laboratory. Janus-type ditopic supramolecular building blocks with precisely oriented AAA and DDD groups are thus accessible in few steps. These building blocks were used for the assembly of a macrocycles as well as a supramolecular polymer.



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Intermolecular H-Atom Abstraction in Radical C-H Activation

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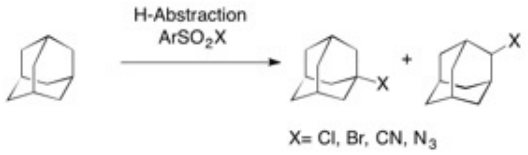
[1]University of Bern

Intermolecular C-H functionalization of unactivated hydrocarbons are of great importance in the synthetic organic chemistry. Selective activation of aliphatic C-H bond can be performed using transition metal catalysis[1,2] or radical reactions[3,4]. Control the regioselectivity of radical mediated C-H activation is a challenging field[5,6].



We describe here a general approach using different kinds of highly reactive radicals to abstract the hydrogen atoms and sulphonyl reagents to trap the intermediate alkyl radicals. A strategy to control the regiochemistry by varying the abstracting radical will be presented.

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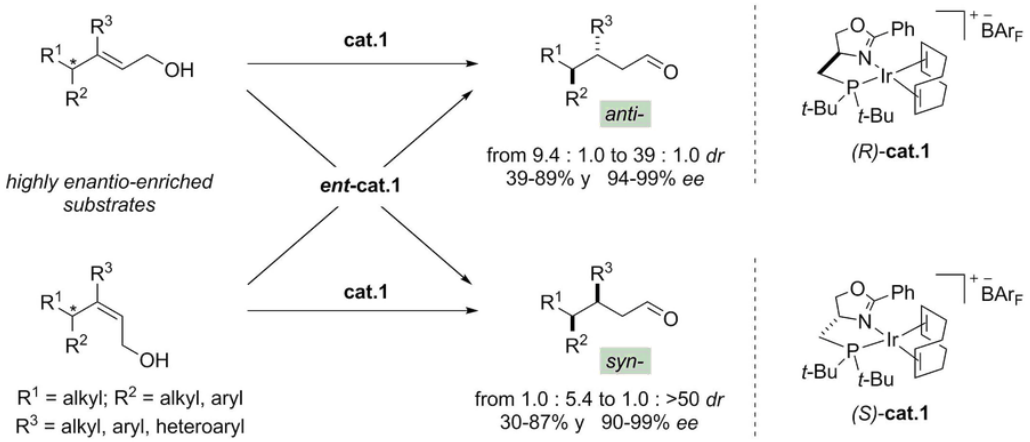
Catalyst-Controlled Diastereoselective Isomerization of Acyclic Primary Allylic Alcohols

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

[1]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] To assess the potential of the iridium-catalyzed isomerization of primary allylic alcohols in such a context, diastereoselective isomerizations of chiral racemic substrates was first explored.[2,3] Recently, our group has developed a catalytic strategy for the perfectly stereocontrolled installation of C20 of stereoidal derivatives, basing our strategy on the selectivity principle used for prochiral olefinic substrates in stereospecific enantioselective transformations.[3] Following on this study, we wished to extend our approach to more challenging acyclic systems.

Herein, we describe the highly diastereoselective isomerizations 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 good yields.[4] The scope of this transformation will be presented in details.



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High resolution F1-decoupled NMR spectra for the analysis of mixture of compounds with similar structure

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[1]University of Geneva

The analysis of congested spectra of mixtures of structurally similar compounds pose a real challenge to organic chemists. Simplification and improved resolution of 1D and 2D proton spectra is highly desired to facilitate the spectral analysis hampered by severe signal overlap over narrow range of chemical shifts. The presence of the $J_{H,H}$ scalar coupling causing signal splitting greatly contributes to the complexity of the spectra. Homonuclear decoupling, leading to a reduction of multiplets into singlets in proton spectra greatly improves the spectral resolution.

Here we present a series of homonuclear 2D experiments (2D DIAG [1], CLIP-COSY [2] and TOCSY [3]) with singlet structure in F1 and multiplets containing the J-coupling information in the F2 dimension. These experiments use indirect homodecoupling based on the *nemoZS* [1], PSYCHE [4] or BIRD [5] decoupling schemes. The increased information content of the spectra when compared to standard ^{1}H 2D experiments such as DQF-COSY will be demonstrated for a case of a mixture of carbohydrates.

The combination of homonuclear decoupling and spectral aliasing leads to high-resolution spectra that can be acquired in a few minutes.

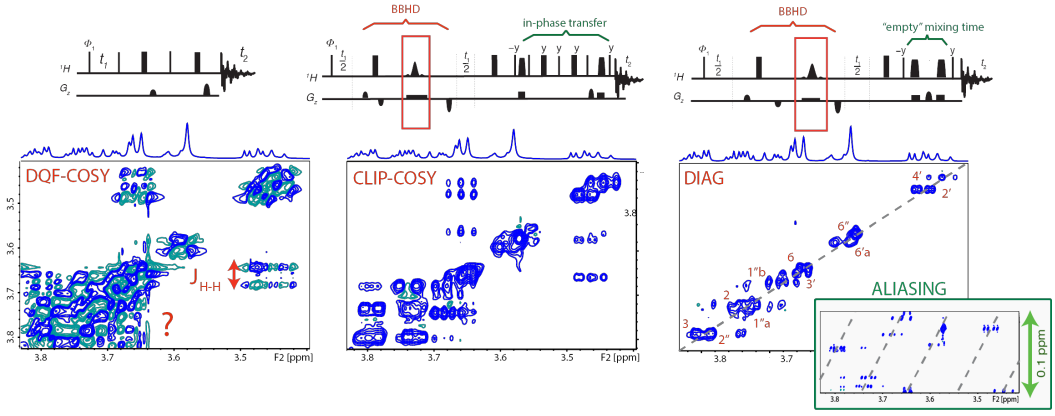

Figure 1. *Simplification of the 2D spectra (left to right: normal DQF-COSY, F1-decoupled CLIP-COSY, F1-decoupled DIAG) of a sample of raffinose.*

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Atomistic simulations of Claisen rearrangement reaction in solution and enzyme environment

S. Brickel[1], M. Meuwly[1]*

[1]University of Basel

Claisen rearrangement is a [3,3]-sigmatropic rearrangement with importance in organic synthesis and biology, via the transformation of chorismate to prephenate by chorismate mutase (CM)[1]. In solution and in the enzyme the reaction is catalysed by the stabilisation of the cyclic transition state (TS).

The Claisen rearrangement reaction of allyl-vinyl-ether to pent-4-enal is studied by Multisurface Adiabatic Reactive Molecular Dynamics (MS-ARMD[2]) simulations. The focus lies on analysing the mechanistic details, especially the effect of the catalysis, and to show the versatility of MS-ARMD. This efficient method is used to follow the dynamics and energetics of a reaction. Compared to previous works by other groups, using QM/MM methods, this approach comes with approximately the cost of conventional force field, which allows extensive studies of the system as well as calculating converged reaction rates. The quality of the simulation is dependent on the quality of the reference points used for parametrising the force field (FF). The reactive FF utilised here is parametrised to *ab initio* reference points at the MP2/6-311++G(2d,2p) level of theory.

The calculated TS energy in gas phase compares well to experiment values[4] (29.8 kcal/mol compared to 30.6 kcal/mol), with the deviation being below 1 kcal/ mol. Comparing the potential of mean force from umbrella sampling in condensed phase with MS-ARMD to QM/MM results[3] establishes the quality of the force field.

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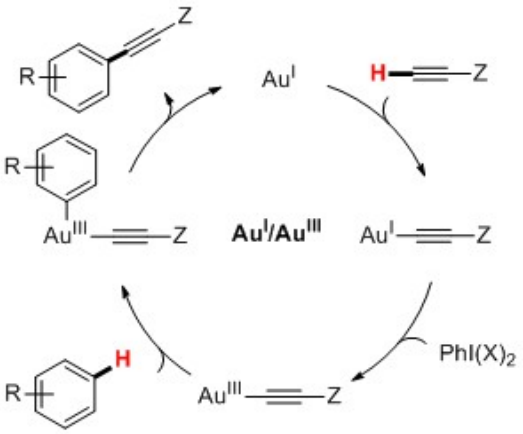
Gold-Catalyzed Alkynylation of Arenes: Mechanistic Insights and Evidence for Au^{I}/Au^{III} Redox Catalytic Cycles

M. Hofer[1], T. De Haro[1], E. Gomez-Bengoa[2], R. Kumar[1], C. Nevado[1]

[1]University of Zurich, [2]Universidad del País Vasco

Au^{I}/Au^{III}-catalyzed, oxidative cross-coupling reactions have been developed in recent years as a powerful tool for C-C and C-X bond formation. However, the mechanistic understanding of these transformations is still limited and detailed investigations to elucidate their mechanism are rare.[1] Given our ongoing interest in the oxidative chemistry of gold,[2] we decided to investigate the mechanism of the gold catalyzed alkynylation of arenes previously developed in our group. This reaction enables the intermolecular coupling of Csp^2-centers of electron rich arenes with Csp-centers of electron deficient terminal alkynes in presence of gold as catalyst and $PhI(OAc)_2$ as stoichiometric, external oxidant.[3] Kinetic analysis and NMR monitoring of species formed in the reaction mixture together with control experiments and DFT calculations, have unravelled a sequence of steps to generate the product including: 1) Transfer of the alkyne to the gold(I) complex via C-H activation; 2) Oxidation to an alkynylgold(III) complex by an *in situ* generated oxidant; 3) C-H Activation of the arene on the gold(III) oxidation state and subsequent reductive elimination. Interestingly, the reactivity of the gold(III) intermediates is governed by the anionic ligands: only the acetato ligands are displaced by the arene yielding the Csp^2-Csp coupling products, while chloride ligands show no reactivity thus highlighting the importance of catalyst and oxidant speciation in gold-catalyzed oxidative couplings.[4]



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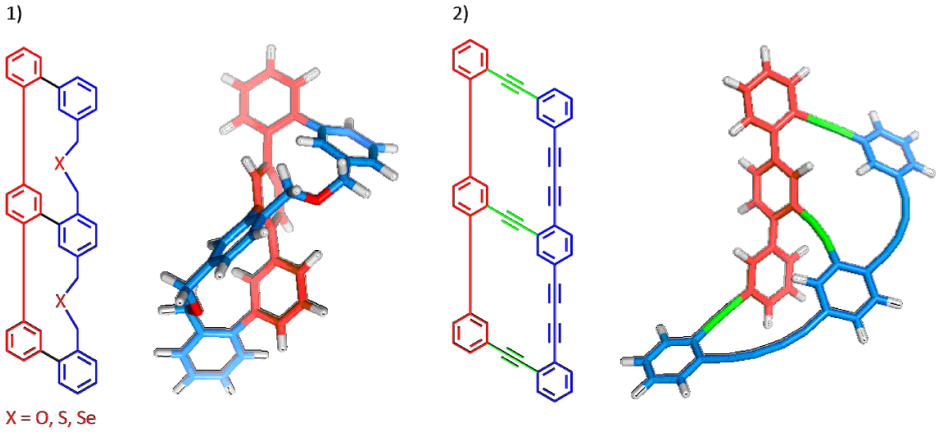
Synthesis towards a new Diacetylene Bridged Geländer-Type Oligomer

L. M. Bannwart[1], M. Mayor[1]*

[1]University of Basel

Atropisomers are chiral compounds that do not contain sterogenic centres, but a stereogenic axis. While the synthesis of chiral compounds containing chiral centres has been an important field of research for a long time, little was known about atropisomeric compounds which were treated as an academic curiosity. The interest in atropisomers started with the discovery that the configuration around a biphenyl axis is an important factor to control the pharmacological properties of bioactive compounds. Combined with their usefulness as catalysts in asymmetric synthesis, biphenyls became prominent and well-studied examples of “chiral compounds without stereogenic centre”.



Vögtle *et al.*[1] described a new class of bridged terphenyl compounds called "geländer oligomers". In the classical geländer oligomers the optical inactive *meso* form is more stable than the pair of enantiomers. Recently, our group reported a novel type of geländer oligomers that cannot exist as a *meso* form.[2],[3],[4] However this benzyl ether, sulfur and selenium-bridged molecules (**1**) have all low barriers of racemisation. Therefore, we designed a new diacetylene-bridged molecule (**2**), which is expected to be more rigid. Consequently the racemisation process in this molecule should be significantly slower.

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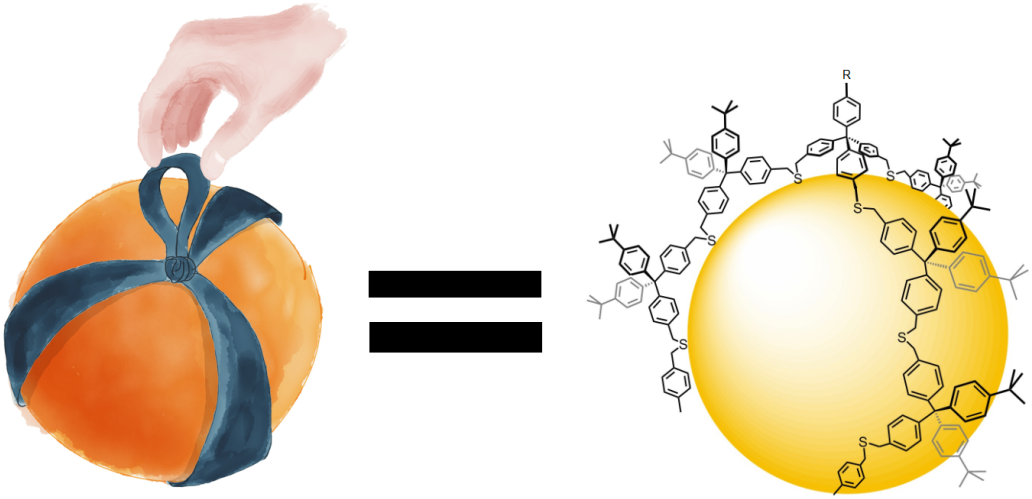
Gold Nanoparticles Reaching out for Molecular Electronics via Tailor-Made Ligands

E. H. Peters[1], M. Lehmann[1], M. Mayor[1]*

[1]Universität Basel

Due to their unique properties [1], gold nanoparticles (Au NPs) are of major interest In the growing field of molecular electronics [2,3]. A novel, thiol-based, central tripodal subunit has been synthesized, as well as a range of branch-like side-chain elongations, enabling dendritic coverage of Au NPs, reaching out for tailor-made thioether ligand-stabilized NPs. All successfully synthesized NPs show narrow size distributions and are of the same size within statistical error (1.32 ± 0.37 nm, 1.14 ± 0.33 nm, and 1.16 ± 0.29 nm) despite variation of the side-chains, indicating that not the side-chain architecture, but rather the conformation of the central linking subunit dictates the curvature, and therefore dimensions of the NP. A typical coverage of 1 to 3 ligands per NP was found by thermogravimetric analysis. Further work will comprise improved ligand design towards reliable single-ligand coverage of the Au NPs as well as the introduction of an electronically addressable moiety, enabling the integration of the Au NPs in electronic devices.



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Synthetic Low Density Lipoprotein with Surface Functionalization

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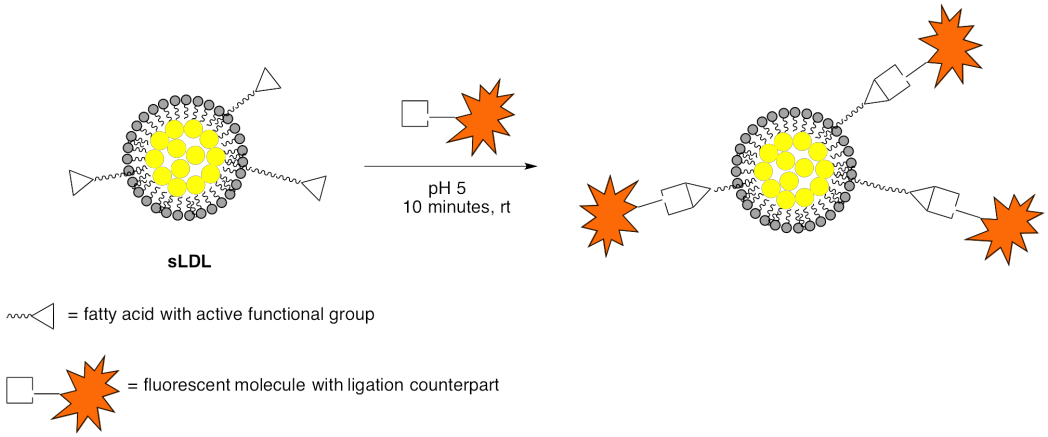
[1]ETH Zurich, Vladimir-Prelog-Weg 3, CH-8093. Zurich, Switzerland

Low-density lipoproteins (LDL) is one among other nanocarriers that have been of research interest in the field of drug delivery and diagnostics. Lipoprotein nanoparticles are biocompatible, which allows for longer blood circulation and efficient delivery to the targeted disease tissues and, more importantly, for being able to be broken down by cells without attacking the immune systems [1].

However, using native LDL, which requires isolation from fresh donor serum, has some disadvantages, such as limited availability and potential infection from donor's blood that can cause serious side effects. Due to this reasons, synthetic LDL (sLDL) was developed and proved to be a promising delivery tool that retains biocompatibility of the native lipoprotein [2].

Inspired by our previous work, where LDL-nanoparticles as delivery agents have been used for *in vivo* imaging in mice [3], we have developed a novel method for versatile surface functionalization on synthetic LDL. The sLDL was prepared from triolein, cholesterol oleate and phosphatidyl choline in the presence of oleic acid derivative with a functional group for chemical ligation, that tolerates aqueous conditions. Subsequent addition of the fluorescein derivative allowed successful covalent attachment of fluorescein on LDL surface sufficiently to provide chemically modified sLDL.



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Synthesis and characterization of novel cross-linked ionic polymers and their application for carbon dioxide cycloaddition to epoxides.

A. van Muyden[1], F. D. Bobbink[1], P. J. Dyson[1]*

[1]EPF Lausanne

Carbon dioxide is under the spotlight as an abundant, non-toxic and inexpensive carbon source. The cycloaddition of CO_2 and epoxides to cyclic carbonates (CCE) is already an industrialized reaction. However, it suffers from energy demanding separation of the products from the catalyst. Ionic polymers were reported to be efficient for this reaction and could simplify this task to a filtration. Herein, di-cationic imidazolium-based cross-linked ionic polymers bearing linkers with various functional group were synthesized. The linkers were chosen to assess how they influence the catalytic activity. The synthesis followed a two-step procedure, first, synthesis of the di-cationic monomer and, second, polymerization of the monomer using radical initiation. They were used as catalysts for the CCE reaction and exhibit similar activities and selectivity than the best heterogeneous catalyst. In addition, the cross-linked polymers were stable up until 300 °C and insoluble in common organic solvents. Simple product separation and catalyst recovery is enables by these polymers.

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Profragrance chemistry as interdisciplinary research area and key technology for fragrance delivery

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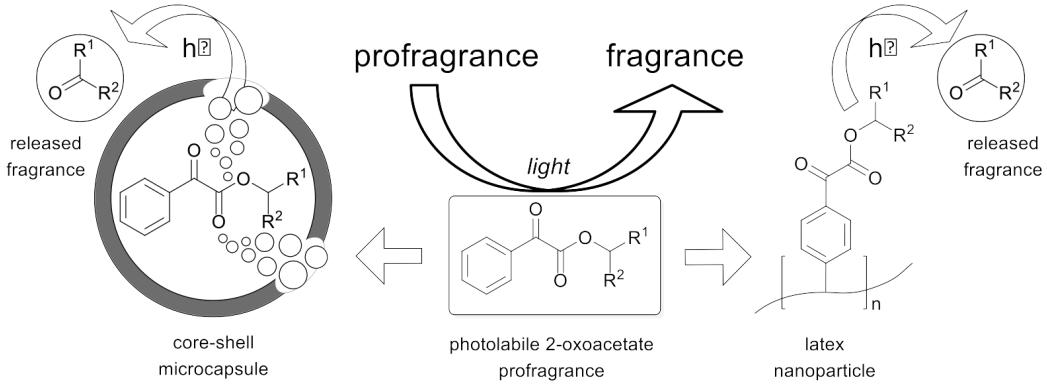
The performance of perfumed consumer articles is often judged on the duration of fragrance perception. To slow down the evaporation of highly volatile perfumery compounds, the development of non-volatile precursors, so-called profragrances, which release perfumery compounds by covalent bond cleavage during application, has become an important reserach area in the perfume industry [1]. Reaction conditions, which may serve as a trigger to deliver fragrances from their corresponding precursors, have to be mild to occur during the use of the respective consumer articles in an everyday life environment. Temperature variations, exposure to (day)light, the presence of oxygen or water (including changes in pH) and the action of enzymes have been identified as being suitable for this purpose.



The general concept of profragrance development and its interdisciplinarity, spanning from organic synthesis *via* analytical chemistry to various aspects of materials science, will be demonstrated at the example of light-sensitive delivery systems [2]. On exposure to ambient daylight, 2-oxoacetates degrade to form an aldehyde or ketone together with a molar equivalent of CO and/or CO_2. The compounds have been used as light-activated profragrances to control the release of volatile carbonyl compounds in functional perfumery. However, when stored in aqueous media, 2-oxoacetates (partially) hydrolyse, thus resulting in an undesired premature degradation of the precursors. To overcome this inherent hydrolytic instability, two different approaches, namely the copolymerisation of 2-oxoacetate monomers into latex nanoparticles [3] and the encapsulation of the profragrances into core-shell microcapsules [3,4], have been investigated (see Scheme). While the formation of of CO and/or CO_2 as side-products of the photoreaction has no impact on the fragrance release from 2-oxoacetate monomers or polymers, we could demonstrate that the gas formation inside core-shell microcapsules generated an overpressure, which rapidly led to the extension or burst of the capsule wall and thus to an efficient fragrance release [4]. Both delivery systems fulfilled the expected requirements in terms of performance; photolabile 2-oxoacetates thus offer a broad range of applicability for the light-induced delivery of fragrances.

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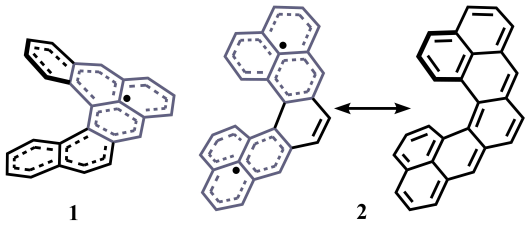
Helically Chiral Open-Shell Polycyclic Aromatic Hydrocarbons

P. Ravat[1], M. Juricek[1]

[1]University of Basel

The combination of chirality and magnetic properties integrated in a single molecule is scarce, but it is potentially useful for development of spintronic devices.[1,2] The spin-delocalized chiral molecular systems are not only of fundamental value to obtain “three-dimensionally” delocalized spin structure but also of great interest to generate chiral magnets and access electron-spin qubit systems using a polarized photon. Helicenes, *ortho*-annulated polycyclic aromatics, possess a non-planar helically chiral π-conjugated structure. By creating a helicene system bearing one or more unpaired electrons, one should thus be able to combine (i) the magnetic properties, related to the non-zero spin of a molecule, and (ii) the chiroptical properties, stemming from the inherent chirality of the molecule.



We have designed and synthesized the first helically chiral phenalenyl hydrocarbons, radical **1** and biradicaloid **2**. The [5]helicene backbone gives rise to the inherent chirality and the phenalenyl substructure provides one unpaired electron. While compound **1** has an open-shell doublet ground state, compound **2** has a singlet ground state and a thermally accessible triplet excited state. We named[3] compound **2** as “Cethrene” because of its “C”-shape and chirality. Cethrene can be represented by either a biradical or a quinoidal resonance form. At room temperature, cethrene gave a well-resolved EPR spectrum on account of population of the triplet state. The EPR signal intensity decreased upon decreasing the temperature and almost diminished at 200 K. The Bleaney Bower’s fit gave the singlet–triplet (S–T) energy gap of 5.6 kcal mol–1, which is significantly smaller than that of its planar analog heptazethrene (8.9 kcal mol–1), as a result of helical twist that gives rise to through-space antibonding and bonding interactions within the HOMO and the LUMO, respectively. The detailed synthetic strategy, structure–property relationship, chiroptical and magnetic properties, and the theoretical investigation of compounds **1** and **2** will be discussed during the presentation.

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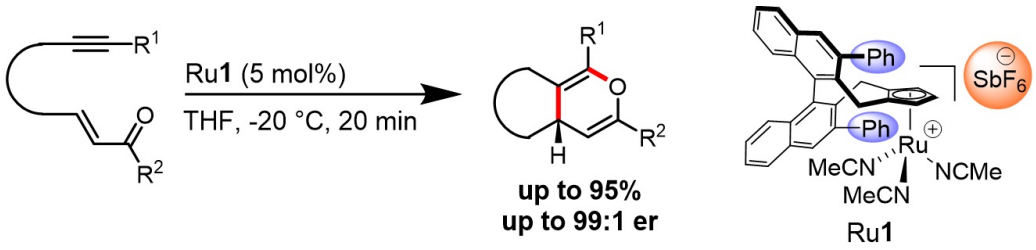
Chiral Ruthenium-cyclopentadienyl Complexes as Versatile Catalysts for Enantioselective Transformations

D. Kossler[1], N. Cramer[1]

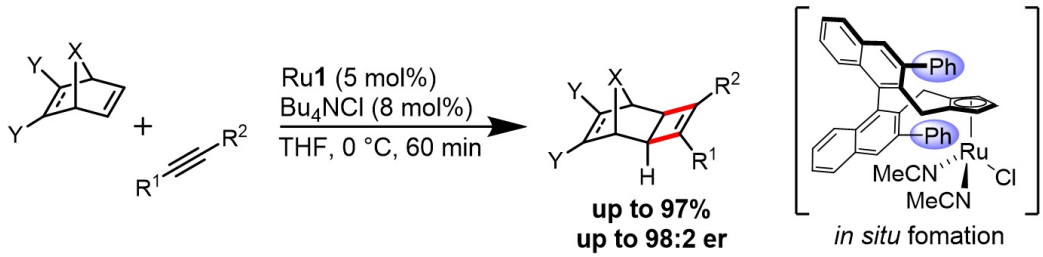
[1]EPF Lausanne

The cyclopentadienyl (Cp) ligand is of fundamental importance for organometallic chemistry and as such found in countless transition-metal catalysts. Chiral versions of these catalysts often employed tethering strategies to the complexed metal, which goes to the expense of free coordination sites. Our group has developed chiral versions of these ligands, which keep the maximum number of coordination sites unoccupied and therefore available in the catalytic cycle.[1]

Ruthenium catalyzed cycloisomerizations offer a rapid access to complex molecular frameworks in an atom economical fashion.[2] Therefore the cationic $[CpRu(MeCN)_3]PF_6$ complex found widespread application in organic synthesis. Recently we reported the synthesis of a set of chiral cationic Ru(II) catalysts bearing our chiral Cp^X ligands and their application in the formal [4+2] cyclization of yne-enones to the corresponding pyrans in high enantioselectivity.[3]



In the course of this project we discovered a considerably large influence of the counterion on the reactivity and selectivity of the transformation. We opted to explore these effects with particular emphasis on covalently binding anions, thus obtaining a chiral congener of the well-established neutral Cp*Ru(cod)Cl catalyst. This idea proved to be feasible and let to the development of an asymmetric version the Ruthenium catalyzed formal [2+2] reaction of strained bicyclic alkenes with internal alkynes to chiral *exo*-cyclic cyclobutenes.[4]



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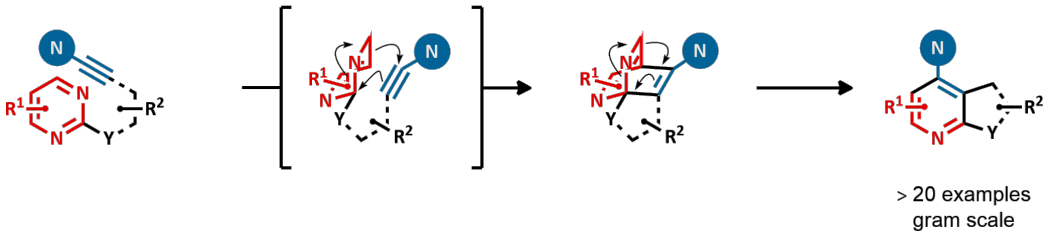
Inverse Electron-Demand [4 + 2]-Cycloadditions of Ynamides: AccesstoNovel Pyridine Scaffolds

G. Duret[1], R. Quinlan[1], R. E. Martin[2], B. Yin[1], P. Bisseret[3], M. Neuburger[4], V. Gandon[5], N. Blanchard[3]*

[1]Strasbourg University, [2]F. Hoffmann-La Roche AG, [3]CNRS - Université de Strasbourg, [4] University of Basel, [5]ICSN

Functionalized polycyclic aminopyridines are central to the chemical sciences, but their syntheses are still hampered by a number of shortcomings. These nitrogenated heterocycles can be efficiently prepared by an intramolecular inverse electron demand hetero Diels−Alder (ihDA) cycloaddition of ynamides to pyrimidines. This ihDA/rDA sequence is general in scope and affords expedient access to novel types of aminopyridinyl scaffolds that hold great promise in terms of exit vector patterns.

We report an efficient method to prepare various fused aminopyridines and spiro-amino pyridines through the first inverse electron demand hetero Diels−Alder cycloadditions of ynamides. [1] More than twenty original examples were obtained with good yields and the scale up of this method was efficiently obtained using flow chemistry. DFTcalculations provide mechanistic insights suggesting that the overall process is favored both onkinetic and thermodynamic grounds.



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[1] Guillaume Duret, Robert Quinlan, Rainer E. Martin, Philippe Bisseret, Markus Neuburger, Vincent Gandon, Nicolas Blanchard*Org. Lett.*,**2016**, 18, 1610−1613.b

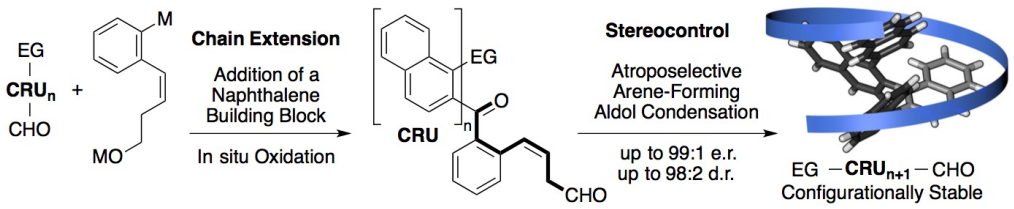
Stereoselective Arene-Forming Aldol Condensation:Synthesis of Configurationally Stable Oligo-1,2-naphthylenes

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

[1]University of Basel

Structurally well-defined oligomers play a fundamental role in the function of natural systems, such as peptides or DNA. Synthetic counterparts, e.g. truncated helicenes, are often characterized by a low configurational stability and typically pose a substantial synthetic challenge.

The presentation will outline our approach to the catalyst-controlled synthesis of oligo-1,2-naphthylenes. Based on the hindered rotation about the aryl-aryl single bonds, these oligomers show high configurational stability. For the efficient oligomer assembly, an building block addition approach was developed. An *in situ* double oxidation followed by a stereoselective arene-forming aldol condensation elongates the oligomer by one unit. The shape, such as the *P*-helix secondary structure is thereby transcribed from a chiral amine catalyst and excellent atropoenantio- and atropodiastereoselectivity of up to 99:1 was achieved.



CRU: constitutional repeating unit; EG: end-group

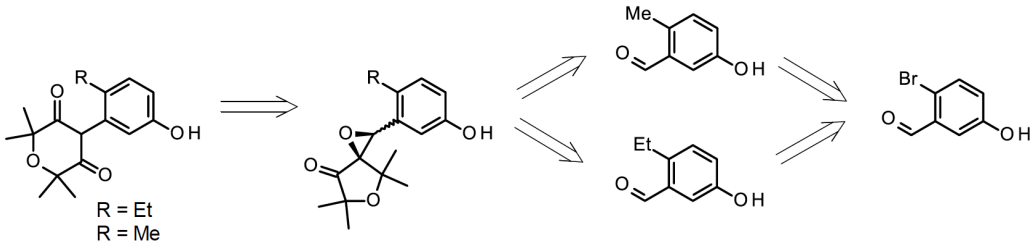
D. Lotter, M. Neuburger, M. Rickhaus, D. Häussinger, C. Sparr, *Angew. Chem.* **2016**, *128*, 2973–2973; *Angew. Chem. Int. Ed.* **2016**, *55*, 2920–2923. br /

Optimization of Manganese Coupling Reaction for Kilogram-scale Preparation of two Aryl-1,3-dione Building Blocks

T. Smejkal[1]

[1]Syngenta Crop Protection AG, Research Chemistry, Schaffhauserstrasse 101, 4332 Stein, Switzerland

The inhibition of acetyl-CoA carboxylase (ACCase) is one of the most commercially important modes of action for the control of grass weeds. To support our discovery program of new ACCase-inhibiting carbocyclic aryl-1,3-diones an efficient synthesis of two building blocks was required.



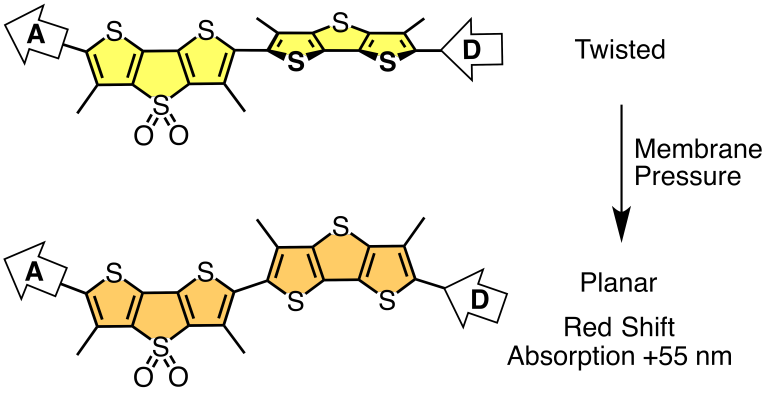
A concise kilogram-scale synthesis was developed employing manganese-catalysed cross coupling and semi-pinacol rearrangement/ring expansion.

Mechanosensitive Fluorescent Membrane Probes

Q. Verolet[1], S. Soleimanpour[1], M. Dal Molin [1], A. Colom[1], A. Roux[1], N. Sakai[1], S. Matile[1]*

[1]University of Geneva

The bilayer membrane characteristics such as lateral tension, fluidity and polarity are crucial parameters in many biological processes. Inspired by the lobster pigmentation and the origin of its impressive color variation after cooking, our group proposed a new class of fluorescent probes that exploits the combination of chromophore planarization and polarization to report on its environment [1]. The fluorescent push-pull probe is built with at least two aromatic moieties linked by a sigma bond. The sensitivity towards fluidity change arises from the flattening of the aromatic scaffold in the ground state induced by the passage to a more rigid environment. This planarization red shifts the absorption spectrum enough to discriminate the phase transition from L_d to S_o lipid bilayer membranes with the naked eye. Finally, a charged head is connected to the chromophore to control the internalization and the position of the probe inside the membrane. To maximize the mechanosensitivity and the fluorescence of the probe, a screening of the length, deplanarization [2], nature [3] and push-pull [4] of the aromatic moiety was accomplished.



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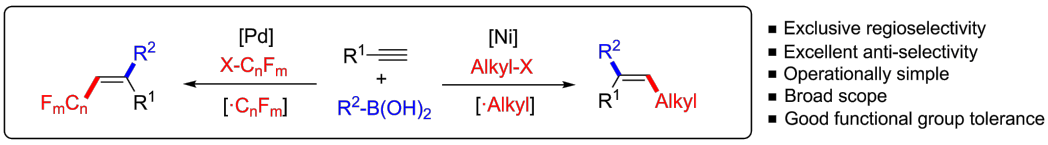
Metal-Catalyzed Stereoselective Dicarbofunctionalization of Alkynes

A. García-Domínguez[1], Z. Li[1], C. Nevado[1]

[1]University of Zurich

Intermolecular processes involving the regio- and stereoselective formation of two new C-C bonds across an alkyne are in high demand as they provide an efficient access to tri- and tetra-substituted olefins.[1] In this context, single step proceduresinvolving bench stable reagents and catalysts are still scarce.[2] Here, we report two different metal-catalyzed three-component reactions of terminal alkynes with alkyl halides and organoboronic acids.[3] In case of using palladium as a catalyst, perfluoroalkyl iodides were efficiently installed whereas the use of nickel enabled the incorporation of α-carbonyl derivatives or unactivated alkyl groups. These methods, which proceed via radical mechanisms, allow the preparation of the corresponding alkenes under mild conditions in a regiocontrolled manner with excellent anti-selectivities. In addition, the stability of all reaction partners makes these reactions operationally simple and widely applicable.



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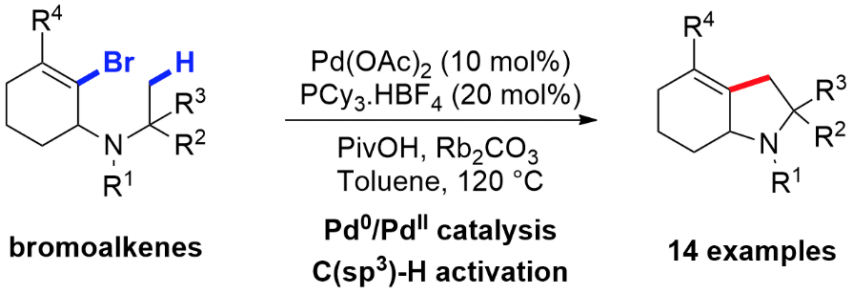
Development and applications of C(sp^3)–H Alkenylation

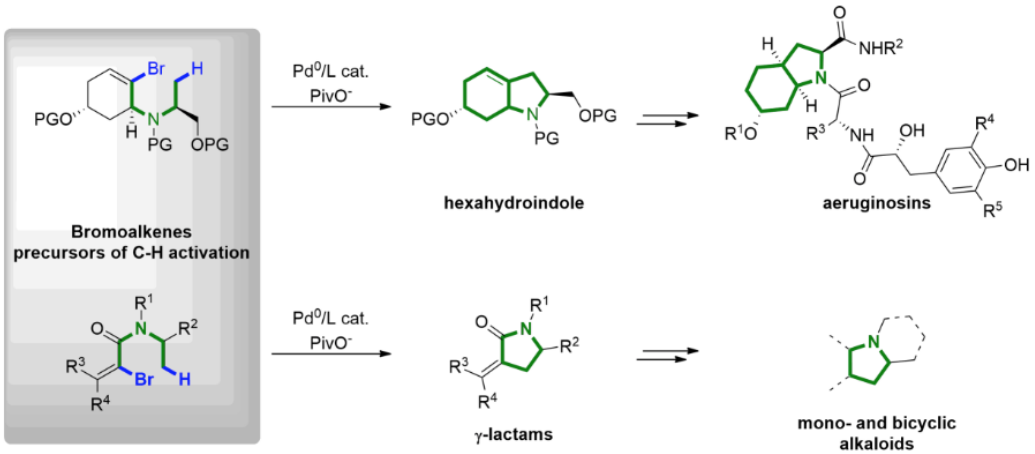
D. Dailler[1]

[1]University of Basel

In the last decade, the transition metal-catalyzed intramolecular activation of unactivated C-H bonds has emerged as powerful method to transform otherwise inert entities.[1] Within this field, we recently developed a straightforward access to hexahydroindoles by intramolecular C(sp^3)-H alkenylation starting from bromoalkenes.[2]



In this communication, we will report access to alkaloids by use of this intramolecular C(sp^3)-H alkenylation. Firstly, the combination of this methodology with a directed C(sp^3)-H arylation allowed to achieve a divergent synthesis of aeruginosins.[3] In a second part, the development of a modular C(sp^3)-H alkenylationleading to g-lactams,[4] which are prevalent scaffolds found in numerous bioactive natural molecules, will be described.



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A family of low molecular-weight, organic catalysts for reductive C-C and C-N bond formation

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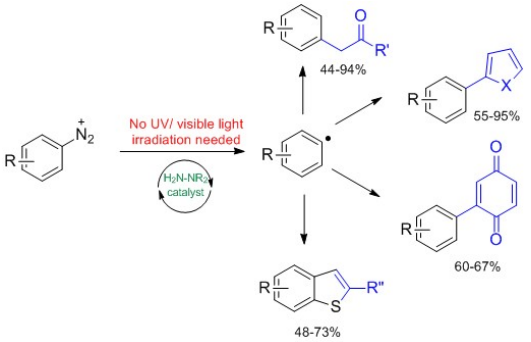
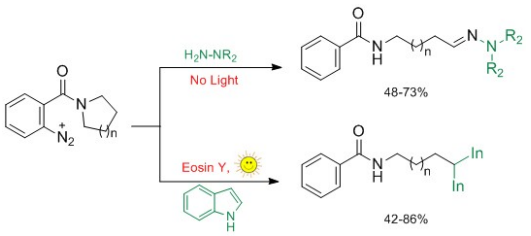
Diazonium salts function as ideal sources of organic radicals that engage in several important transformations [1]. Recently, the use of photocatalysts in conjunction with a visible light source proved to be an efficient method for achieving different transformations with diazonium salts[2]. Our group has developed a family of low molecular-weight, organic catalysts that promote a range of C-C bond forming reactions of diazonium salts, and achieve so without the need for any metal adjuvant or irradiation with light[3]. These catalysts efficiently promote a range of transformations with competitive yields (Scheme 1)



We additionally report a metal-free, mild procedure for redox-neutral α-amino functionalization[4] with concomitant C-N[5] as well as C-C bond formation[6] (Scheme2).



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Size-controlled nanoparticle formation in aqueous media with a thiol-free tripeptide

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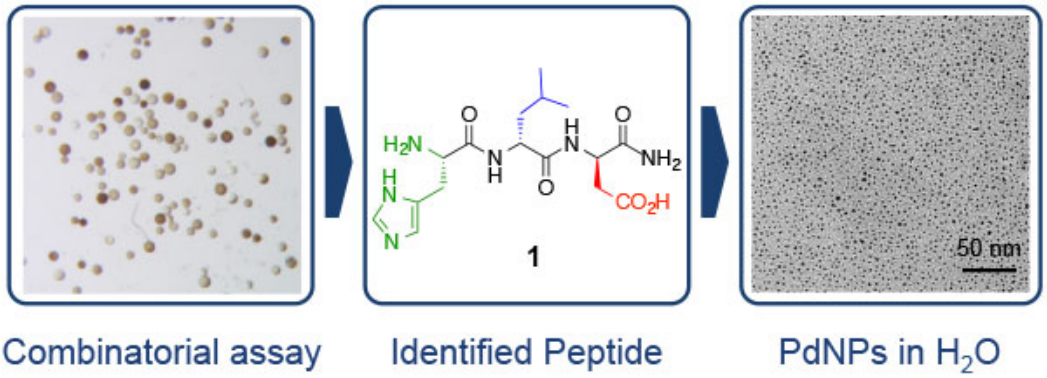
Nature uses interactions between metals and proteins for a variety of purposes ranging from catalysis to biomineralization. The modularity of peptides renders them attractive as additives for the formation of nanoparticles (NPs) and opens attractive avenues for the preparation of novel materials with specific functions and a broad range of applications.[1]
Our group has previously developed a combinatorial assay for the identification of peptides that control the formation of silver NPs within one-bead-one-compound libraries.[2] Now, we applied this combinatorial methodology for the identification of peptides that control the formation of palladium NPs and identified H-His-D-Leu-D-Asp-NH_2 (**1**) as an additive for the generation of highly stable, monodisperse, and water-soluble PdNPs with average diameter of 2.8 ± 0.8 nm. Tripeptide **1** proved to be applicable for the preparation of gold and platinum NPs with, again, excellent control over their size-distribution.[3]



Studies with close analogues of tripeptide **1** revealed the specific role of each amino acid in the sequence, His as surface-binding motif, D-Leu to build a hydrophobic shell, and D-Asp to provide water-solubility and additional stability by charge repulsion. Additional analyses provided insight into the structure of the peptidic self-assembled monolayer. These findings open interesting prospects for the formation of functionalized PdNPs.[3]

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