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Access to heterocycles bearing emergent fluorinated substituents — as FAR as possible

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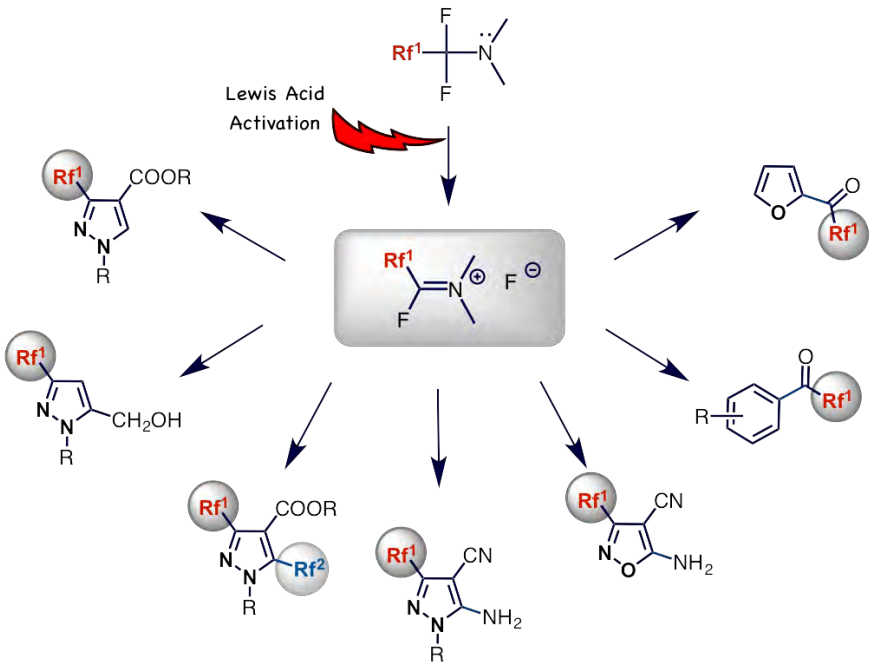
Organofluorine compounds play a key role in modern drugs and crop protection. Fluoroalkyl groups are popular functional groups and their introduction can significantly improve biological activity of active ingredients. α,α-Difluoroalkylamines like TFEDMA (HCF_2CF_2-NMe_2), Yarovenko ($HCFClCF_2$-NEt_2) or Ishikawa (CF_3CFHCF_2-NEt_2) reagents belong to the so-called **F**luoroalkyl **A**mino **R**eagents (**FAR**) and can be readily prepared from commercially available fluoro-olefins (monomers used for polymers production) and secondary amines. While these reagents have previously been used for the replacement of OH with fluorine in alcohols and carboxylic acids, we recently became interested in their use to prepare fluoroalkyl-pyrazoles. It has been demonstrated that FARs, after activation with Lewis acids such as BF_3 and $AlCl_3$, afford iminium salts with Vilsmeier-type activity. We have exploited this reactivity to prepare different fluorinated heterocycles, which are important building blocks for Life Science oriented research.[1-5]



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Irreversible cysteine-selective labelling of a protein using modular electrophilic fluoroalkylation reagents

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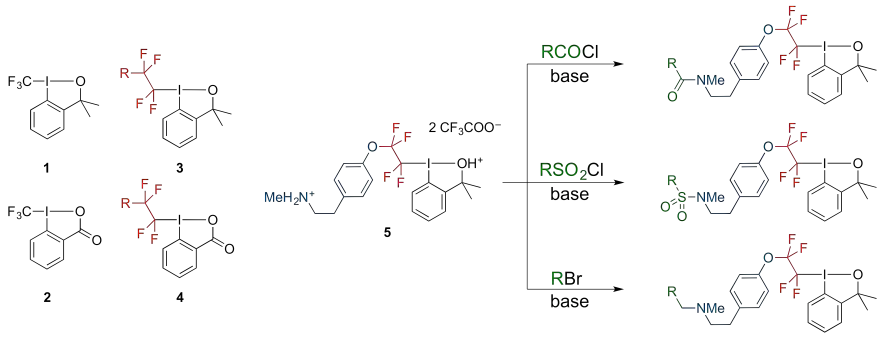
Hypervalent iodine-based compounds **1** and **2** have become popular reagents for formally electrophilic trifluoromethylation owing to their ease of use and reactivity with a broad variety of nucleophilic substrates [1]. In 2016, we extended the reagents bearing the terminal trifluoromethyl group by synthesizing a series of λ^3-iodanes **3** and **4** containing a CF_2CF_2R motif (where R = SAr, OAr, *N*-heterocycle) [2]. As the reactivity of the resulting reagents was comparable with that of the original ones (**1**, **2**) and the tetrafluoroethylene moiety can serve as a linker, giving the possibility of functional applications, we explored the potential of this concept further.

Reagents **3** and **4** were limited to rather basic structures as most functional groups would not tolerate the synthetic pathway. Hence, a reagent containing a secondary amine was prepared (**5**) and investigated in late-stage derivatization *via* mild formation of amides, sulfonamides and tertiary amines. Eventually, we arrived at 22 modular reagents containing manifold functional units (*e.g.*, tetraethylene glycol, biotin, and several fluorophores) [3].

All the reagents (**1**–**5**) display high reactivity toward thiols. Therefore, we envisaged that the modular λ^3-iodanes derived from **5** could be useful as reagents for cysteine-selective tagging of biomolecules. Indeed, when tested with artificial retro-aldolase RA95.5–8 S25C K210M, the exposed cysteine site was labelled selectively [3]. In contrast, the enzyme's active site containing a reactive lysine was left intact, which was not the case with conventional reagents based on maleimide and iodoacetamide. Therefore, the reagents' applicability goes beyond pure organic synthesis – they have the potential to constitute the basis of a new approach to protein labelling.



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Enantioselective Total Synthesis of (+)-Peganumine A

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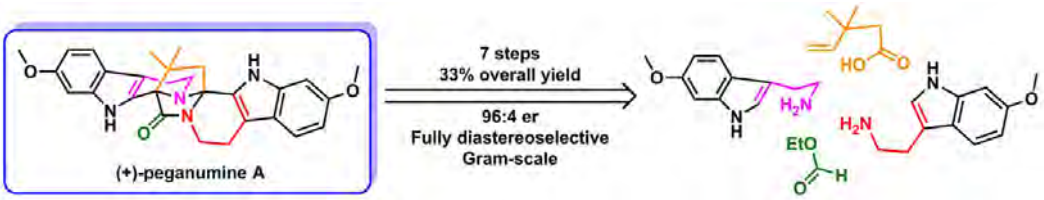
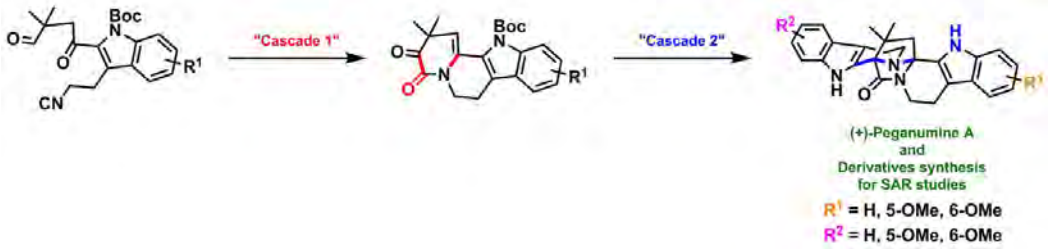
(+)-Peganumine A, a dimeric tetrahydro-β-carboline alkaloid, was isolated in 2014 from *Peganum harmala* L. by Li, Hua and coworkers.[1] This unprecedented octacyclic compound contains two quaternary stereocenters embedded in a unique 3,9-diazatetracyclo[6.5.2.0.0]pentadec-2-one scaffold. This molecule shows low μM cytotoxicity against various cancer cell lines.



The intriguing molecular architecture in conjunction with its significant bioactivity and extremely low isolation yield prompted us to undertake the total synthesis of peganumine A. Starting from simple commercially available materials, we used two key cascade reactions to reach the final target:

- "Cascade 1": A one-pot construction of an indolo[2,3-a]quinolizine tetracyclic skeleton from an ω-isocyano-γ-oxo-aldehyde *via* a sequence of an unprecedented C-C bond forming lactamization and a transannular condensation.
- "Cascade 2": A one-pot process merging two achiral building blocks into the final enantioenriched octacyclic structure *via* a sequence of asymmetric Pictet-Spengler reaction followed by an acid-catalyzed transannular cyclization. This domino process created two quaternary stereocenters with concurrent formation of two spirocycles and the 2,7-diazabicyclo[2.2.1]heptan-3-one unit with control of both the absolute and the relative stereochemistry.

In a single pass, we have synthesized gram-quantity of (+)-peganumine A in 7 steps and 33% overall yield.[2] This convergent route allowed us to synthesize the derivatives of peganumine A for future structure-activity relationship studies.



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Exploration of Pd(0)-Catalysed C(sp^3)–H Functionalisation Beyond Aryl Halides

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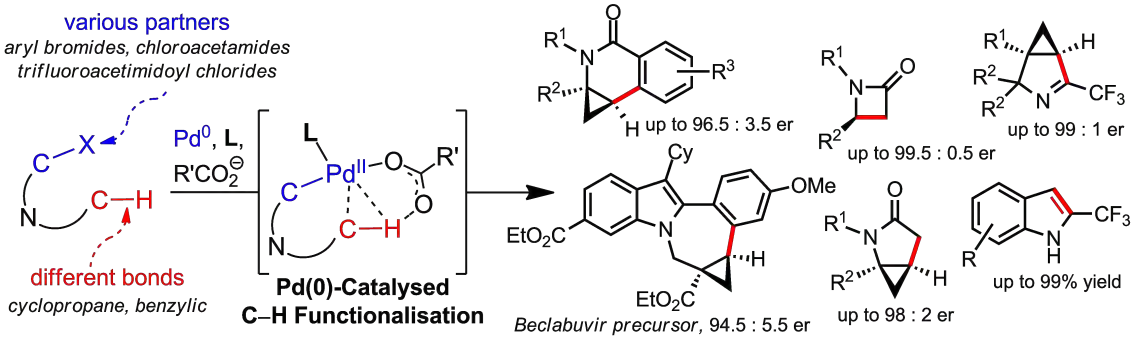
Nitrogen-containing heterocycles are prevalent motifs in biologically active compounds.[1] Transition metal catalysed enantioselective C–H functionalisations have become attractive alternatives for the selective synthesis of such scaffolds.[2] In the past years, the enantioselective synthesis of benzannulated *N*-heterocyclic building blocks *via* intramolecular Pd(0)-catalysed C(sp^3)–H bond arylation has been extensively investigated.[3] In this context, we have developed intramolecular aminocyclopropane arylations towards dihydroisoquinolinones and the Beclabuvir ring system.[4]

Our recent studies broaden the scope of Pd(0)-catalysed C–H functionalisations by using electrophilic partners other than aryl halides. Readily accessible chloroacetamides are efficiently functionalised, yielding valuable chiral b- and g-lactams in high yields and enantioselectivities with formation of a C(sp^3)-C(sp^3) bond.[5,6] Furthermore, indoles and versatile chiral imines bearing a CF_3-group are obtained by C–H functionalisation of trifluoroacetimidoyl chlorides.[7]



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Stereoselective Organocatalyzed Synthesis of α-Fluoro β-Amino and α-Fluoro γ-Nitro Thioesters

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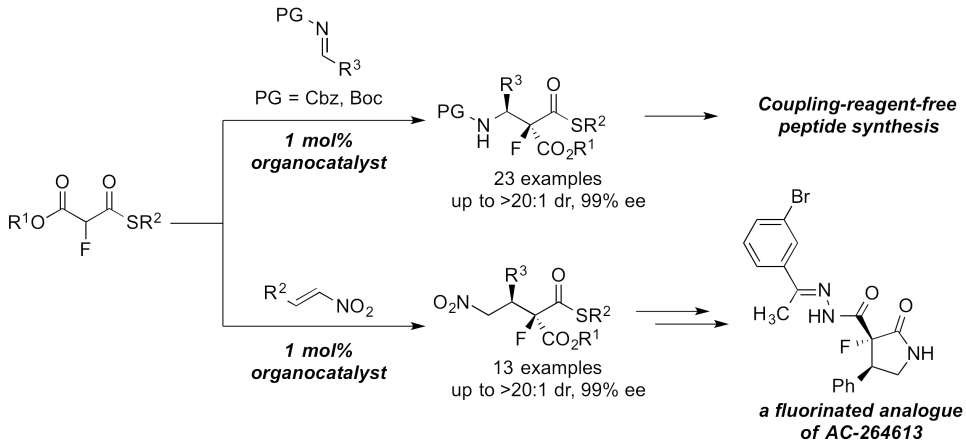
[1]Laboratory for Organic Chemistry, D-CHAB, Switzerland

Fluorination and the incorporation of β-amino acids into peptides represent powerful strategies to enhance their proteolytic stability and to control their conformation.[1] These features are combined in α-fluoro-β-amino acids, which influence the conformation of β-peptides.[2] Recently, our group developed a stereoselective method to access fluorinated aldol products using fluorinated malonic acid half thioesters (F-MAHTs) as building blocks.[3] Herein we present highly stereoselective organocatalyzed Mannich reactions between fluorinated monothiomalonates (F-MTMs) and N-Cbz and N-Boc protected imines as well as Michael reactions between F-MTMs and nitroolefins.[4] These reactions require only 1 mol% of organocatalyst and provide access to the corresponding α-fluoro β-amino thioesters and α-fluoro γ-nitro thioesters, respectively. α-fluoro β-amino thioesters can be directly used for peptide synthesis in solution and on solid phase, whereas α-fluoro γ-nitro thioesters can be transformed into the corresponding fluorinated lactams, as showcased in the synthesis of a fluorinated analogue of AC-264613.[5]



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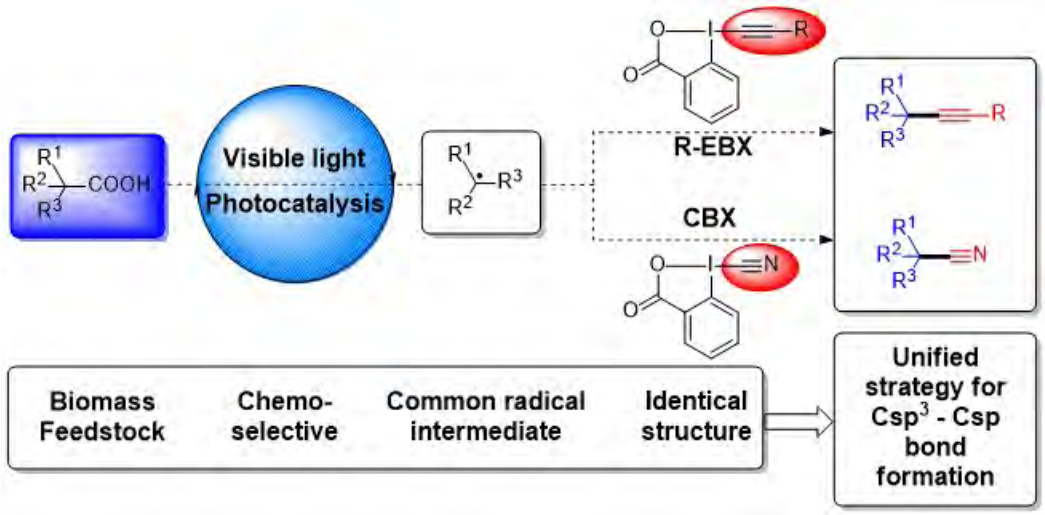
Decarboxylative Alkynylation and Cyanation using Photoredox Catalysis and Hypervalent Iodine Reagents

F. Le Vaillant[1], M. Wodrich[1], T. Courant[2], J. Waser[3]*

[1]EPF Lausanne , [2]Université Paris Descartes, [3]EPF Lausanne

Aliphatic alkynes and nitriles are functional groups of great significance, naturally occurring and broadly used as versatile building blocks in organic synthesis. They find applications from material to medicinal and pharmaceutical sciences. A unified strategy to access both classes of compounds under eco-friendly conditions is, therefore, highly desirable. Herein, we describe the straightforward decarboxylative alkynylation[1] and cyanation[2] of broadly available carboxylic acids using photoredox catalysis and cyclic hypervalent iodine reagents. In both reactions, the simplest benziodoxolone reagent was the most successful. Functional groups tolerance is high and reactions can be scaled up to generate useful intermediates in drug synthesis. According to computational and experimental studies, two different mechanisms can be proposed, based on the oxidation potential of the reagents: via radical intermediates for alkynylation, and carbocation intermediates for cyanation.



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New entries into amino-benzonorbornene chemistry

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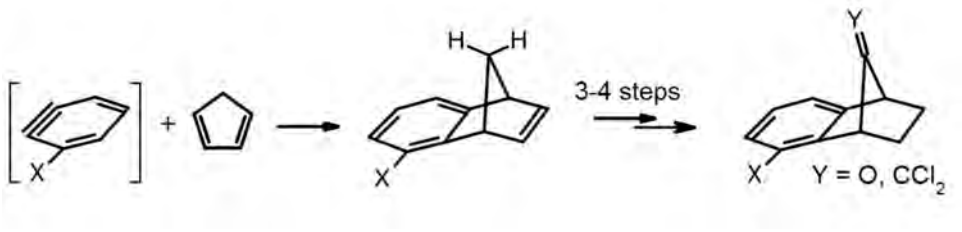
Cationic rearrangements based routes, from early Process Research towards two key intermediates of fungicidal active ingredients, will be disclosed. The synthesis of functionalized benzonorbonenes from cycloaddition between cyclopentadiene and benzynes, followed by rearrangements to adjust the substitution pattern and the functional groups, will be presented from the point of view of route scouting and novel reactions assessments.



The chemistry developed for targeting specific amino-benzonorbornene derivatives[1,2] will be broadened to, and exemplified by, other substrates. Rare or unprecedented electrophilic acylations and alkylations of double bonds by cations, triggering *in situ* further cationic 1,2-Wagner-Meerwein shifts will be disclosed; in both cyclic and acyclic series, [1,2]-shifts of aromatic rings led by β-cation stabilisation by silicon groups will also be exemplified.

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Enantioselective α-Arylation of O-Carbamates via Sparteine-Mediated Lithiation and Negishi Cross-coupling

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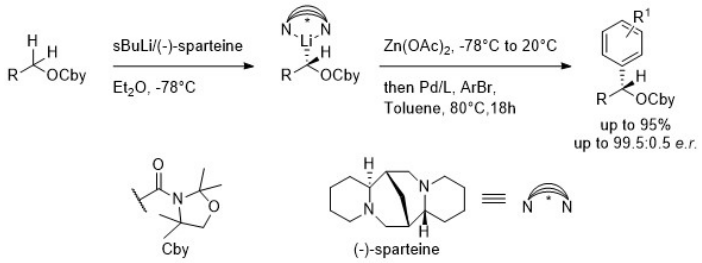
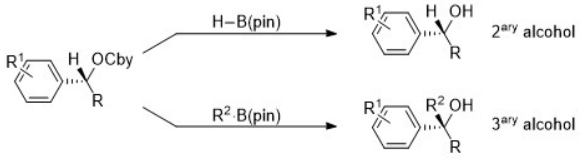
The enantioselective α-arylation of protected aliphatic alcohols is described. Hoppe's technology allows to perform the enantioselective α-lithiation in presence of sparteine. [1] After Li-Zn transmetalation and Negishi cross-coupling, highly enantioenriched benzylic alcohols are accessed. The method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



Application of Aggarwal's lithiation-borylation sequence [2] provides a short and divergent access to a variety of enantioenriched secondary and tertiary benzylic alcohols. [3]



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Radical Deuteration of Alkyl Iodides Catalyzed by Thiol and Mechanistic Studies on Deoxygenation Reactions of Xanthates

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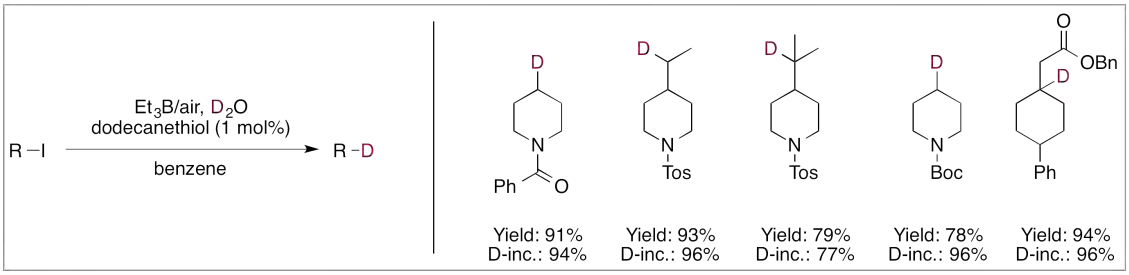
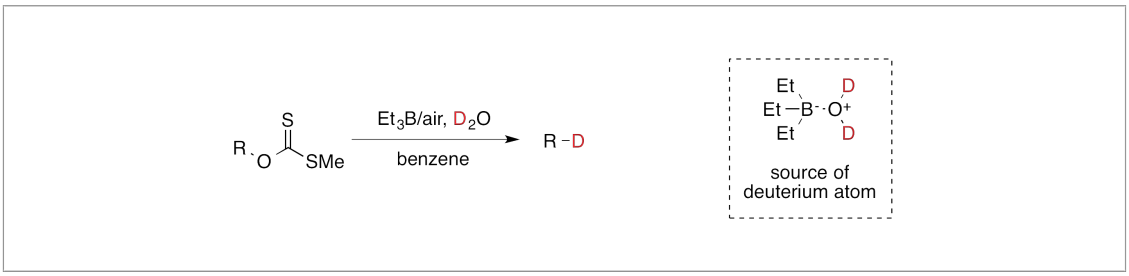
[1]University of Bern

Recently, there has been a growing interest in the pharmaceutical industries to incorporate deuterium in drugs candidates to improve their metabolism and pharmacokinetic properties[1]. A significant number of deuterated drug candidates (heavy drugs) have been synthesized and forwarded to clinical trials, such as Deutetrabenazine (Austedo®, TEVA pharmaceuticals) which is the first deuterated drug on the market. However, preparation of organic compounds selectively labelled with deuterium atom, remains a challenging synthetic problem. 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 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 which is compatible with a large range of functional groups.



The development of the deuteration method led us to discoveries that incite us to reinvestigate the mechanism of xanthates deoxygenation described by Wood *et al.*[5] (see below) who used heavy water activated by trialkylboranes as a source of deuterium atom.



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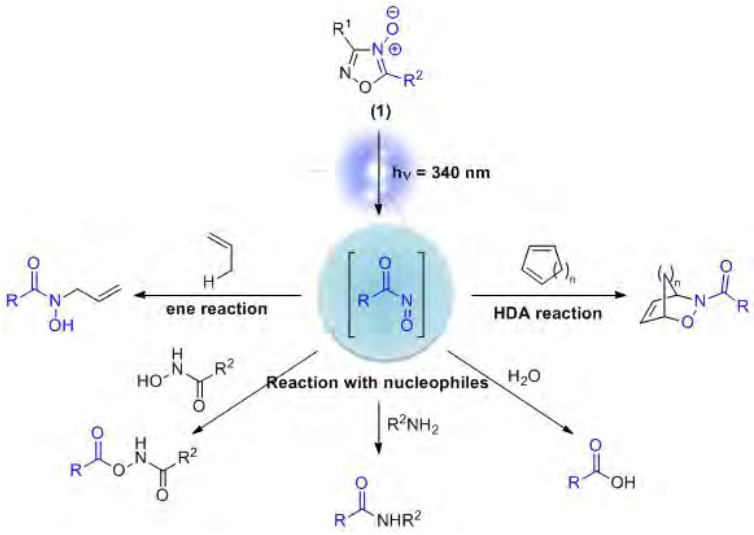
Photocleavage of 1,2,4-oxadiazole-4-oxide: A powerful tool for organic synthesis.

J. Loup[1], C. G. Bochet[1]*

[1]University of Fribourg

Nitrosocarbonyl species are very reactive compounds that have found many applications in organic synthesis[1]. These intermediates are involved in several useful reactions whose products serve as a versatile platform for further transformations.



The most common method to access to these molecules is by oxidation of the corresponding hydroxamic acid which prevents their use for sensitive substrates. In 1997, Caramella *et al.* showed that photolysis of 1,2,4-oxadiazole-4-oxide **1** allowed the smooth formation of these reactive intermediates[2]. This new method allows an easy access to the useful nitrosocarbonyl species without using any harsh conditions and could find many unique applications in organic synthesis. The first part of the project focuses on the development of a more robust and scalable synthetic road to access to 1,2,4-oxadiazole-4-oxide **1**. Once a reliable method will have been established, synthetic applications of photolysis of **1** will be addressed.

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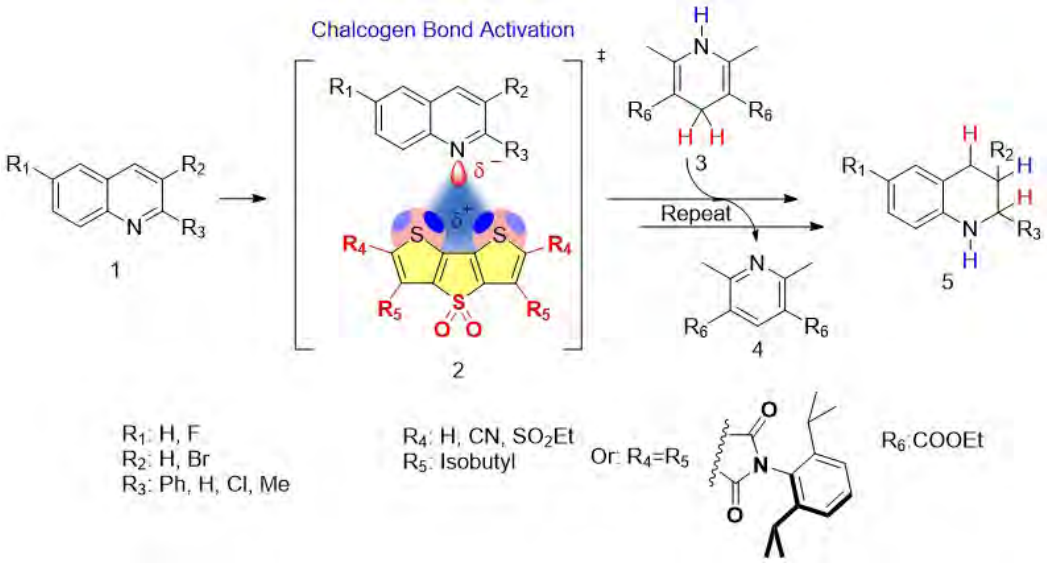
Chalcogen Bonding in Catalysis

S. Benz[1], J. López-Andarias[1], N. Sakai[1]*, S. Matile[1]*

[1]University of Geneva

Weak noncovalent interactions are the key to tailor make complex chemical systems to realize a specific function. Our most recent efforts geared towards expanding the toolbox of noncovalent interactions resulted in the application of chalcogen bonds to transmembrane transport and catalysis.[1,2] Chalcogen bonds arise when the electron deficient σ* orbitals, on sulfur, selenium or tellurium interact with a lewis-basic partner. Ideal spatial orientation of the sigma holes led us to select the scaffold of Dithieno[3,2-b;2',3'-d]thiophenes (DTTs) for bidentate chalcogen binding



Through interaction with the nitrogen lone pair DTTs are a privileged motive to activate imines and quinolines for Hantzsch ester mediated transfer hydrogenation. Over a 1000-fold rate enhancement, stronger activities with deeper σ holes and wider bite angles, chloride inhibition and correlation with computed binding strengths yield strong evidence for operational chalcogen bonds. Lessons learned are being currently applied to asymmetric catalysis with selenium based chalcogen binders.

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Transforming Olefins into Dinucleophiles

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

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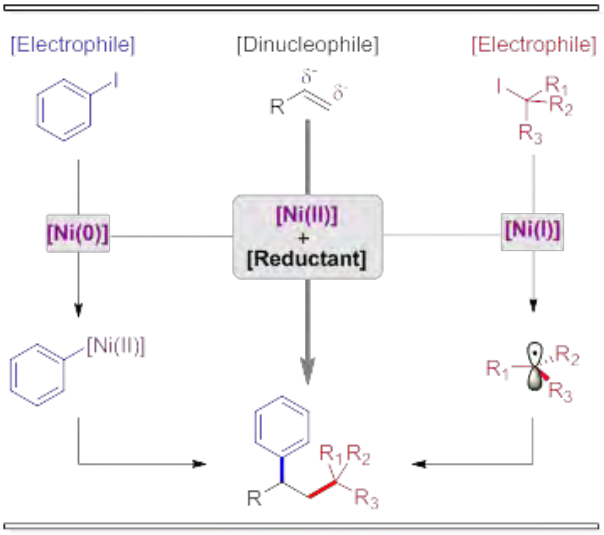
Addition of two hydrocarbon derivatives across π-systems has been traditionally carried out using formally a nucleophile and an electrophile as reaction partners[1]. The multiple bond is thus conceptually considered as a (+/-)-dipole, which justifies the extensive use of electronic biased substrates.[2] Alkylative procedures that can be applied to a wide range of substrates independently of their intrinsic nature are still in high demand. Here, we present the first example of an intermolecular, three-component reductive dicarbofunctionalization of olefins with aryl iodides and alkyl iodides as reaction partners.[3] In contrast to previous methods[4], the reaction tolerates a wide range of olefins and the carbon sources do not require any additional functionalization. Interestingly, this process is characterized by the present of two different nickel cycles interconnected by the action of both, the unsaturated partner and the reductant.



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