Photocatalytic deoxygenation of N–O bonds with Re complexes: from the reduction of N_2O to pyridine *N*-oxides

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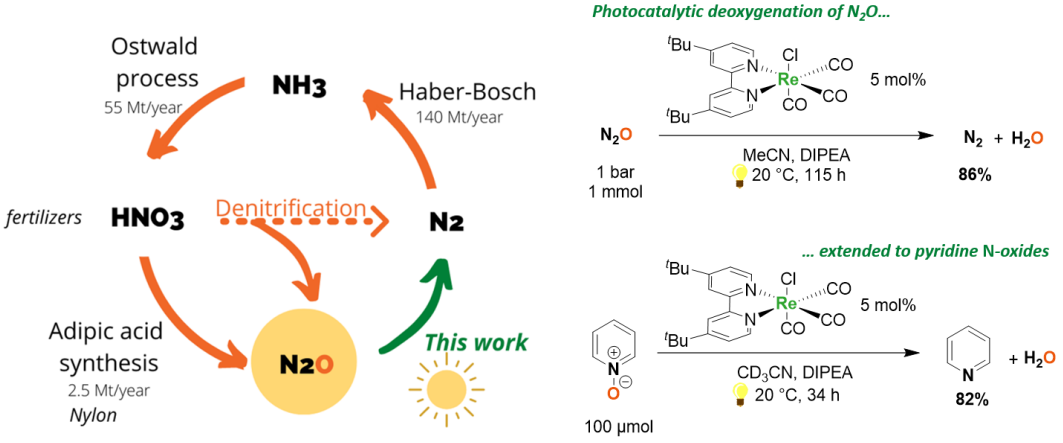
Commonly known as 'laughing gas', nitrous oxide is an ozone-depleting substance 298 times more powerful a greenhouse gas than CO_2. It accumulates in the atmosphere due to its kinetic stability (average lifetime of 120 years), thus contributing to 6% of anthropogenic greenhouse effect.[3,4] A solution would be the reduction of N_2O back to N_2, which would close the nitrogen cycle; however, few methods have been proposed due to the low reactivity of N_2O. Herein we describe a new pathway to reduce N_2O back to nitrogen at room temperature by means of visible light photocatalysis.

N_2O being isoelectronic with CO_2, inspiration came from previous work on the photoreduction of CO_2 to CO first disclosed by the group of Jean-Marie Lehn.[5] Remarkably, $[Re(bpy)(CO)_3Cl]$ proved successful as both catalyst and photosensitizer for the reduction of N_2O. GC monitoring gave out 83% conversion with a maximum TON of 18. To improve the conversion rate, the effect of substitution of the bpy ligands was studied. An efficient catalyst, $[Re(bpy\text{-}^tBu)(CO)_3Cl]$, was identified that gave out 86% yield.

Encouraged by this success, we extended this methodology to the reduction of other N–O bonds, leading to photocatalytic deoxygenation of the more challenging substrate pyridine *N*-oxide. A mechanistic study is underway to understand the fundamental mechanistic differences between both deoxygenative pathways of N_2O and of pyridine *N*-oxides.



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RENCONTRES de CHIMIE ORGANIQUE 2021

Synthesis and preliminary anticancer evaluation of new triazole bisphosphonate-based isoprenoid biosynthesis inhibitors

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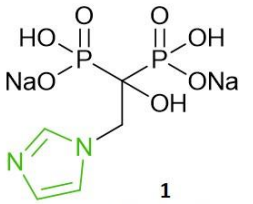
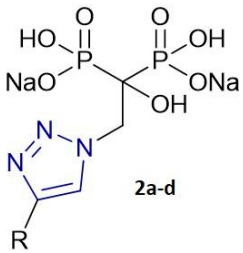
Nitrogen-containing 1-hydroxymethylene-1,1-bisphosphonates (N-HMBPs) such as zoledronate **1** are widely used for the treatment of skeletal disorders such as osteoporosis, Paget's disease, hypercalcemia or bone metastases. In addition, they also exhibit promising antitumoral properties such as inhibition of tumor cell proliferation, induction of apoptosis or inhibition of cell invasion and migration *in vitro* and *in vivo* by interfering with the mevalonate pathway. [1][2]

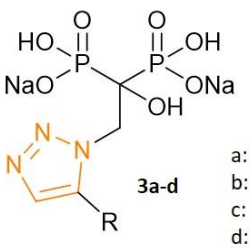
We have synthesized a new set of triazole bisphosphonates **2a-d**, **3a-d**, with an alkyl or phenyl substituent at the C-4 or C-5 position of the triazole ring under mild conditions according to a methodology previously developed by our group.[3][4] Preliminary biological evaluation of these compounds on MIA PaCa-2, MDA-MB-231 and A549 cancer cell lines revealed that compound **2b** exert an antiproliferative activity 4 to 12 folds higher than zoledronate. A structure-activity relationship study revealed that the potency of the antitumoral activity depends highly on both the presence of a long linear alkyl chain and the distance between the triazole ring and the HMBP moiety. Besides, molecular docking suggests that the compounds **2b** and **2c** could inhibit the geranylgeranyl pyrophosphate synthase (GGPPS), a key enzyme of the mevalonate pathway, by filling a lipophilic inhibitory pocket of the enzyme.
Thus, compound **2b** is an attractive lead for the development of new potent HMBP-based isoprenoid synthase inhibitors with improved anticancer properties.



1
Zoledronate



2a-d

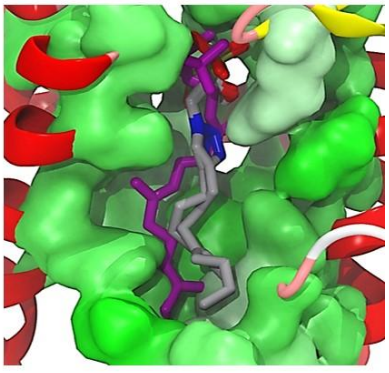


3a-d

a: R = butyl
b: R = hexyl
c: R = octyl
d: R =phenyl

Antiproliferative effects against various tumor cell lines

IC_{50} = 8.8 – 10.1 µM	IC_{50} = 0.75 – 2.4 µM	IC_{50} > 10 µM low activities



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RENCONTRES de CHIMIE ORGANIQUE 2021

Construction of enantioenriched bicyclic furans via a multicatalytic process merging gold catalysis and aminocatalysis

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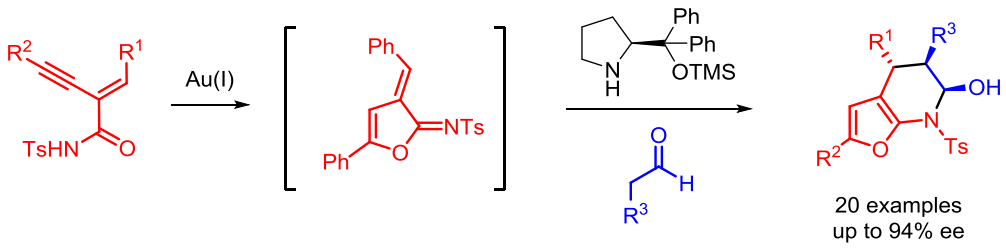
Asymmetric catalysis remains a challenge to synthetic chemists as the demand for enantiomerically enriched drug-like molecules continues to increase.[1] The development of multicatalytic processes using the complementary activation offered by a metal and an organocatalyst has allowed the construction of enantioenriched complex structures from readily available starting materials.[2]

In this communication, we will disclose an efficient, diastereo- and enantioselective asymmetric inverse electron demand aza-Diels–Alder reaction merging gold and amino catalysis to provide tetrahydrofuropyridinol frameworks. In this one-pot procedure, easily accessible ynamides undergo gold catalysed cycloisomerisation to generate transient azadienes that participates in an organocatalyzed asymmetric [4+2] reaction with the enamine. The resulting heterocyclic compounds containing three continuous stereogenic centers are obtained in good yields and high levels of stereoselectivity.



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ACCESS TO C-ARYL/ALKENYLGLYCOSIDES BY DIRECTED PD-CATALYZED C-H FUNCTIONALISATION OF THE ANOMERIC POSITION ON GLYCAL-TYPE SUBSTRATES

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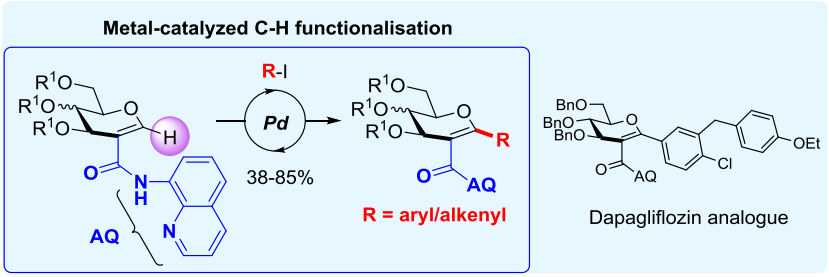
The involvement of glycoconjugates in numerous biological processes promotes the development of new access to these compounds. Analogues possessing an unnatural C-C bond (C-branched sugars) are largely studied due to their enzymatic and chemical stabilities and their conformational similarity towards C-O and C-N natural links. Metal-catalyzed processes revealed to be popular powerful tools to build C-C bond on the sugar backbone. Nevertheless, these types of transformation on sugars remain limited.[1][2]
We already described a new access to C2-amidoglycals via an aminocarbonylation reaction between 2-iodoglycals and amines in the presence of "CO" source. Diverse amines could be successfully linked on glycals leading to original glycolipid and glycopeptide mimics.[3] These obtained structures appear to be ideal for C-H functionalisation of the anomeric position, directed by the 8-amidoquinoline in position 2.
Herein, we present a Pd-catalyzed directed C-H functionalisation of the anomeric position on C2-amidoglycals leading to C-aryl/alkenylglycosides.[4] Diverse aryl/alkenyl iodides and glycals could be successfully engaged with good to excellent yields. This methodology could be applied to the synthesis of glycosylated amino acids and of a Dapagliflozin analogue.



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Reaction of Phosphines with 1-Azido-(2-halogenomethyl)benzene Giving Aminophosphonium-Substituted Indazoles

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The Staudinger reaction named after J. Meyer and H. Staudinger, who described more than a century ago, the oxidation of a phosphine by an azide, to form, upon release of N_2 gas, a phosphinimine (or an iminophosphorane) featuring a P=N linkage. [1]

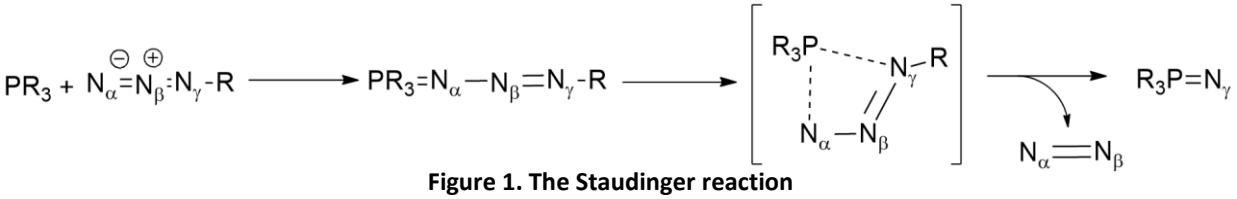

Figure 1. The Staudinger reaction

The reaction goes through the intermediary of a phosphazide, which was first considered as a transient low stable species but could be isolated by tuning the temperature of the reaction and the nature of the substituents or by coordinating to group d or p elements.[2,3]

Trapping the transient phosphazide with carbonyl derivatives has also allowed to synthesize nitrogen heterocycles.[4]

For coordination chemists, the Staudinger reaction is a powerful tool to prepare iminophosphorane ligands used to develop catalysts for example.[5]

With the objective to synthesize bifunctional phosphonium-iminophosphorane species we investigated the reaction of a phosphine with 1-azido-(2-halogenomethyl)benzene and discovered that the outcome of the reaction highly depends on the conditions and nature of the reagents.

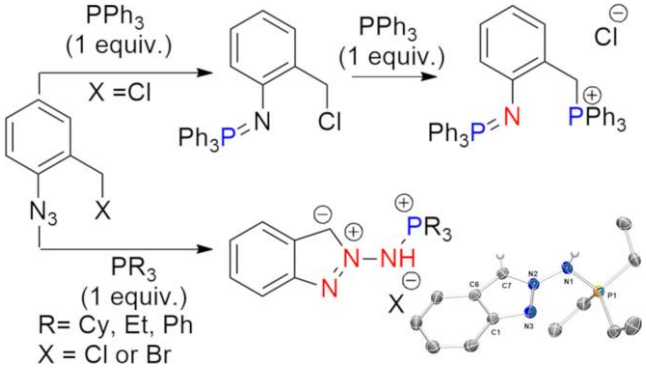

Figure 2. Reactivity of 1-azido-(2-halogenomethyl)benzene with phosphines.

In this communication, we will discuss the formation of the rather unusual aminophosphonium substituted indazole obtained (Figure 1), its structure and reactivity.[6]

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Iron-Catalysed Intermolecular Aziridination of Alkenes

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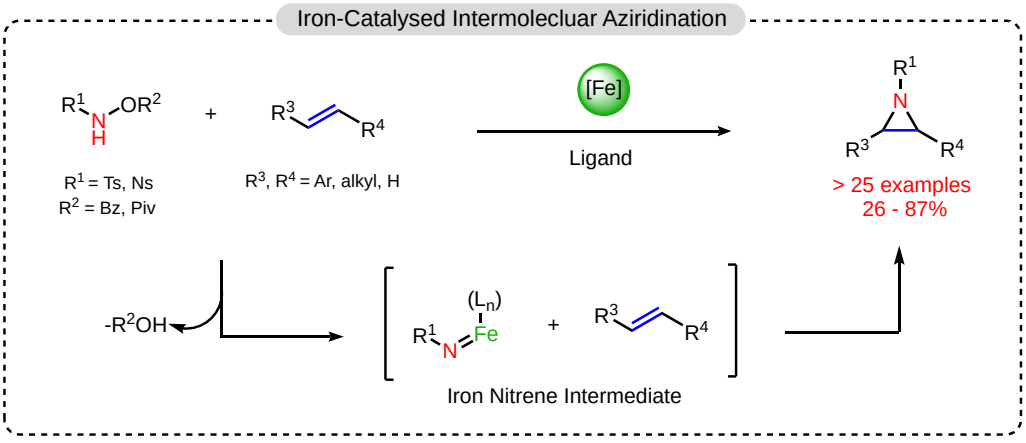
As the smallest nitrogen-containing heterocycles, aziridines are valuable building blocks in organic synthesis. Since nitrogen atoms are ubiquitous in biologically active compounds, there has been an ongoing effort into the development of new and efficient methodologies for C–N bond formation.
Catalytic nitrenes are a powerful tool for the formation of C–N bonds and have led to the development of efficient processes such as C–H functionalisation and aziridination of alkenes.[1] Most of these developed processes are poorly atom economical, due to them requiring external oxidants, and are also based on the use of non-sustainable materials such as rare and expensive transition metal catalysts (Rh, Pd, Etc.). Hydroxylamine derivatives, in the presence of a ruthenium or copper complex, can form a metal-nitrene intermediate avoiding the requirement for external oxidants, since the presence of an N–O bond acts as an endogenous oxidant.[2] Surprisingly, the generation of metal nitrenes from hydroxylamine derivatives and cheap, abundant and non-toxic iron sources has been scarcely studied.[3]
Following our previous studies[4] on the reactivity of iron nitrenes deriving from hydroxylamine derivatives, we will present the development of an intermolecular iron-catalysed aziridination of alkenes using hydroxylamine derivatives as a nitrogen source. This sustainable process allows for efficient access to protected aziridines in good-to-excellent yields. Further development and mechanistic studies are currently ongoing.



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RENCONTRES de CHIMIE ORGANIQUE 2021

Bulky Pd-NHC cinnamyl supported catalysts, efficient in Buchwald-Hartwig C-N cross-couplings and suitable for industrial applications

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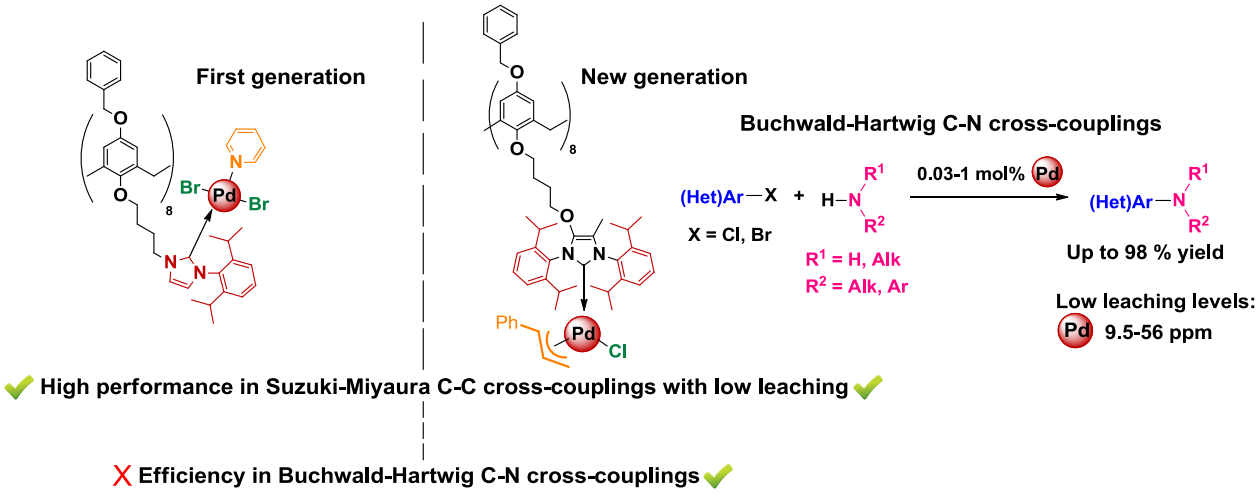
Transition-metal catalysis is crucial in organic synthesis; it enables obtaining a wide range of functionalized motifs in a short reaction time. In industry, one of the major challenges is the removal of the catalysts, thus avoiding the contamination of final products with toxic metal traces. In this context, catalysts immobilization on filterable supports has been reported, leading to their simple elimination without significant metal leaching. However, the existing supported catalysts may suffer from a lack of activity in line with a poor reproducibility. This is not suitable for industrial requirements and explains their low utilization until now. We propose here reproducible, scalable and performant filterable catalysts, synthesized through a homogeneous route. Air stable Pd-NHC complexes were supported on benzyloxycalix[8]arene macromolecules developed by our group.[1] The PEPPSI-type[2] 'first generation' of such catalysts proved to be highly efficient in Suzuki-Miyaura C-C cross-couplings using aryl bromides.[3] In order to extend their reactivity to the Buchwald-Hartwig C-N cross-couplings, a 'new generation' of catalysts was prepared: the steric hindrance around the carbene and the palladium ligand were modified.[4] Herein we present our convenient synthetic procedure towards a 'new generation' of Pd-NHC cinnamyl supported catalysts. Low catalytic loadings are needed to perform efficient Buchwald-Hartwig C-N cross-couplings using aryl chlorides and bromides and a variety of alkyl and aryl amines. Delightfully, low palladium leaching levels are detected in the final products after a simple filtration.[5]



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Rhodium-Catalyzed Asymmetric Transfer Hydrogenation/Dynamic Kinetic Resolution of 3-Benzylidene-Chromanones

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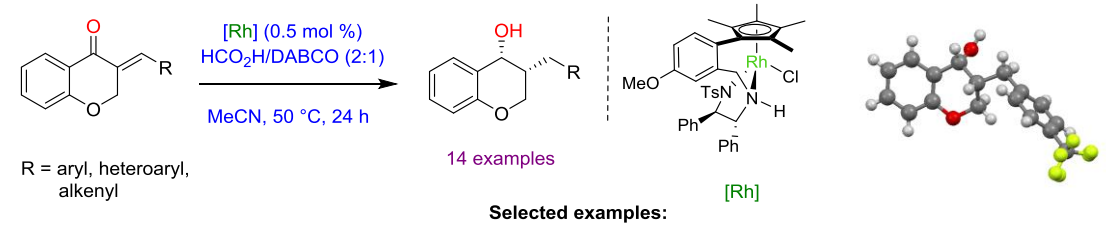
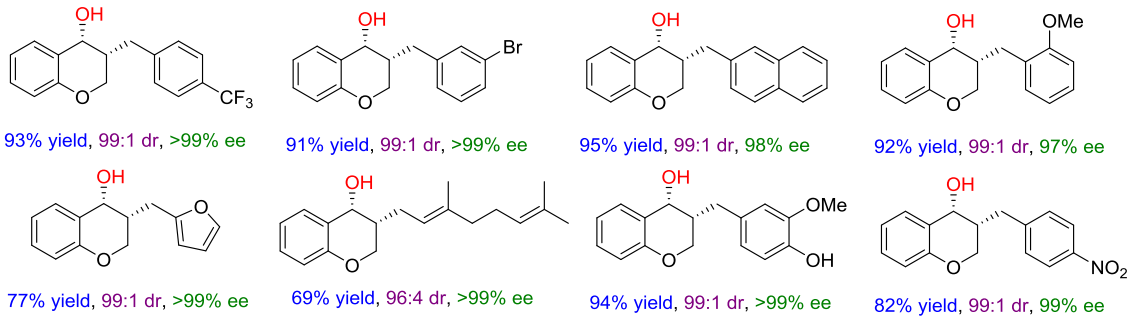
Homoisoflavonoids are a widespread family of molecules, naturally occurring in plants, which possess a promising set of biological activities. Among those, benzyl chromanols are an encouraging family that could be accessed through a key step of asymmetric transfer hydrogenation combined with a dynamic kinetic resolution process (ATH/DKR)[1]. Continuing our interest in asymmetric transfer hydrogenation (ATH) [2] we developed a straightforward access to enantiomerically enriched *cis*-3-benzyl-chromanols from (*E*)-3-benzylidene-chromanones through a Rh-catalyzed asymmetric transfer hydrogenation. This transformation allowed the reduction of both the C=C and C=O bonds and the formation of two stereocenters in high yields with excellent levels of diastereo- and enantioselectivities (up to >99:1 dr, up to >99% ee) in a single step through a dynamic kinetic resolution process using a low catalyst loading and HCO_2H/DABCO as the hydrogen donor. This efficient and straightforward catalytic route provides access to synthetically useful chromanol derivatives and valuable chroman pharmacophores as well and tolerates a broad range of functionalities.[3]



Selected examples:



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Anion Receptors Combining Anion-π interaction and Hydrogen Bonding: Cooperative or Anti-Cooperative?

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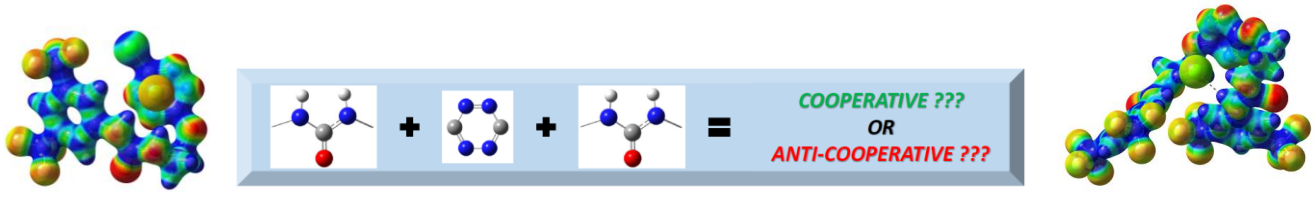
Anions are widely spread in several areas such as biology, medicine, catalysis and environment. [1] As an example, anions have a predominant role in channelopathies such as cystic fibrosis or Dent's disease [1].

Therefore, the development of anion receptors is a milestone in today's organic chemistry. Despite the widespread use of cation receptors, molecular recognition of anion receptors is still in his infancy. The prediction, the determination of the three-dimensional architecture of the receptor-anion complex involved and their potential applications, are among the challenges of this rising area of chemistry.

The development of such molecules is based on the use of one or multiple weak interactions such as π-anion interactions, halogen or hydrogen bonding, but also hydrophobic effects. [1] These weak interactions individually contribute to the structuration and properties of complex three-dimensional receptors. However, associated within a single polyfunctional molecular platform, a combination of several weak interactions is likely to generate interesting cooperative effects, thus modulating existing or forthcoming properties. [1]

Moreover, numerous publications are based on anion receptors bearing fluorescent probes that enable colorimetric or photophysical detection/characterization of binding/transport properties. [2] In this context, we designed new anion receptor platforms comprising both a hydrogen-bond donor and a π-deficient heterocycle not only able to generate π-anion interactions but also act as a fluorophore. [3,4] The synergistic roles of hydrogen bonding and π-anion interaction towards anion recognition are evidenced by DFT calculations. Then, the complexation process will be characterized by a broad scope of experimental methods (MS^n mass spectrometry, NMR, UV-Visible, Fluorescence and decays titrations), highlighting interesting cooperativity effects both in ground and excited states. [3,4]



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Selective functionalization of furfural and its derivatives

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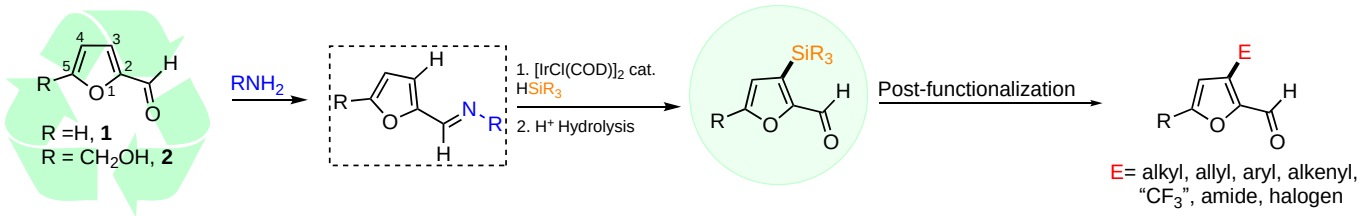
In order to develop an ever more eco-compatible synthetic chemistry, it is nowadays essential to synthesize intermediates and added-value chemical compounds starting from substrates derived from biomass rather than those from fossil resources. Furfural **1** and 5-(hydroxymethyl)furfural (HMF) **2** are among the most promising bio-based molecules.[1] Obtained by dehydrating lignocellulosic biomass from agricultural residues and dedicated crops, these molecules have great potential as renewable platforms for the sustainable production of fine chemicals.[2]

In particular, the direct functionalization of furfural, without prior modification of the redox state of the aldehyde function, by selective C–H activation[3] is an emerging field that is attracting considerable interest. In this contest, our team has recently developed protocols for functionalizing furfural-derived imines at the 3-position by ruthenium-catalyzed alkylation,[4] arylation[5] and acylation.[6]

Herein, we disclose a directed C3–H silylation of furfural derivatives under iridium catalysis. This new selective functionalization is achieved on furfuryl imines with triorganosilanes or organodisilyloxysilanes in the presence of a hydride scavenger. This transformation gives access to even more versatile platforms that can be further functionalized using the C(sp^2)–Si bond as handle. Post-functionalizations through TM-catalyzed cross-coupling reactions[7] or Brook-type rearrangements[8] are investigated; especially through fluoride anion activation. Discovery of these reactivity, as well as optimizations and scopes of these methods will be described.



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Low-valent titanium(II) mediated intramolecular alkyne/alkoxyallene reductive coupling reactions

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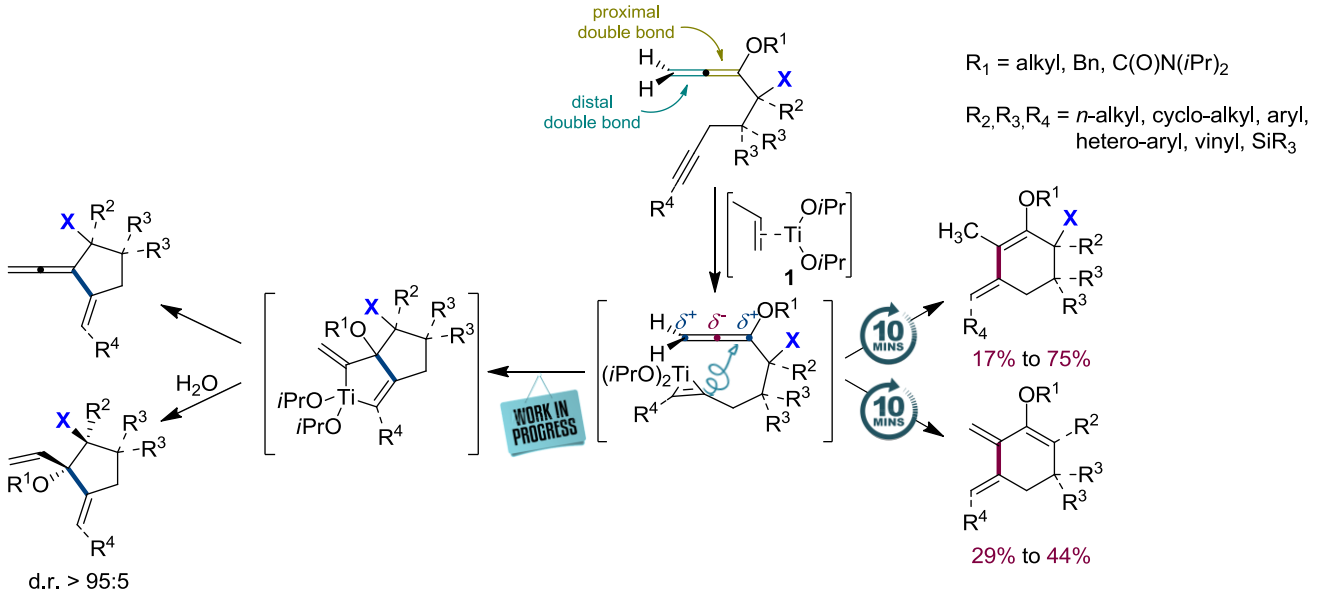
Since the beginning of the 1990s, the chemistry of low-valent titanium(II) complexes has shown significant advances[1] thanks to the Kulinkovich cyclopropanation.[2] It can be mentioned that these complexes are eco-friendly and low-cost since titanium is part of the most abundant elements (9th in the Earth's crust) and titanium alkoxides are non-toxic. More specifically, various methodologies have been developed around reductive couplings with titanacyclopropene species,[1b] resulting from a ligand exchange between (η^2-propene)Ti(OR)$_2$ **1** (Scheme 1) and an alkyne moiety. To date, concerning titanacyclopropenes in presence of an alkoxyallene, only two intermolecular examples have been reported with a complete regioselectivity toward the electrophilic carbon of the distal double bond.[3] Herein, we highlighted and optimized titanium mediated intramolecular alkyne/alkoxyallene coupling reactions for a straightforward access to various functionalized systems (16 examples) thanks to fine switches of reaction conditions and modulation of X. A singular and innovative regioselectivity *in favor of an addition onto the nucleophilic carbon of the alkoxyallene moiety* appears to be the key step for most of the structures.



Scheme 1: Intramolecular reactivity of titanacyclopropenes toward alk*oxyallenes*

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Modular approach to substituted pyridoazepinones

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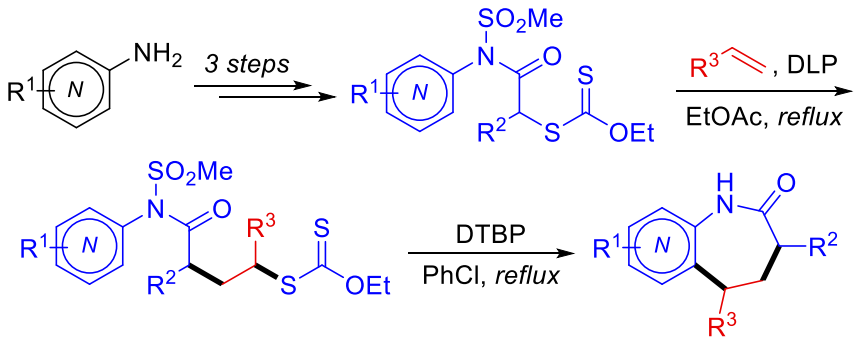
Pyridoazepinones are a pyridine-containing scaffold, that is present in several natural products and in synthetic medically-relevant compounds.[1] It also may serve as a classical isostere of benzazepinone motif, that is a part of various biologically active substances. However, no general method for the preparation of pyridoazepinones has been described until these days.

The proposed strategy toward pyridoazepinones is based on the construction of the seven-membered ring by C-C bond formation via xanthate addition-transfer process with non-activated alkenes, radical cyclization, and re-aromatization of the pyridine ring enabled by homolytic cleavage of the sulfonamide bond.[2]



• 24 examples • derivatization • one-pot and gram-scale synthesis

This method allowed the preparation of pyridoazepinones with various substituents both in the pyridine core and in the seven-membered cycle (24 examples), and was found to be tolerant toward various functional groups, such as protected amines, esters and boronate esters. The further derivatization of the obtained products was also performed. Finally, the synthesis was accomplished on gram scale and in a one-pot manner to show the applicability of the presented approach for industrial purposes.

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