SISOC XIII

4-6 SEPTEMBER 2022 – TARRAGONA (SPAIN)

13th Spanish-Italian Symposium on Organic Chemistry

BOOK OF ABSTRACTS

UNIVERSITAT ROVIRA i VIRGILI

ICIQ

Institute of Chemical Research of Catalonia

Designed and edited by:
Jaume Capdevila
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Welcome to SISOC XIII

Dear colleagues:

After two years of delay, due to the pandemic situation, we are pleased to welcome you to the 13th Spanish-Italian Symposium on Organic Chemistry in the historical city of Tarragona.

Thanks to all the researchers that have agreed to present their latest results, we are confident that this Symposium will be successful for all participants

We take this opportunity to express our gratitude to the scientific committees, both Spanish and Italian for the selection of lecturers and grants. We would also like to thank the companies and institutions that have sponsored the symposium, as well as those which have enabled our participants to taste products from our land.

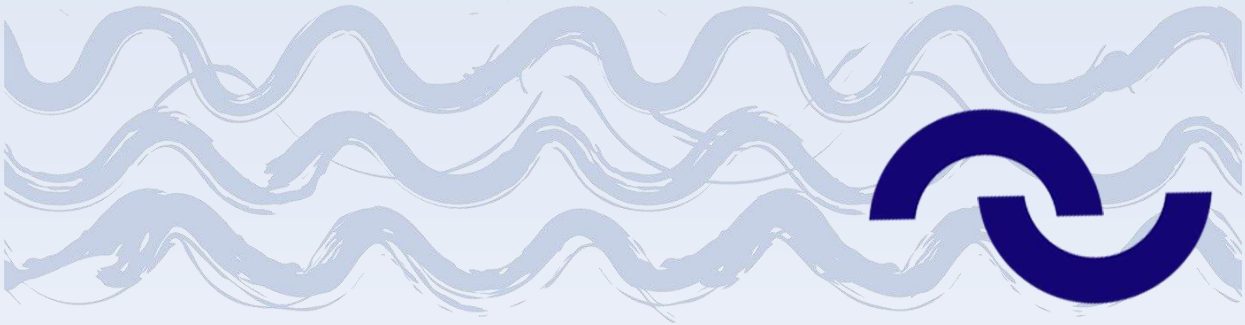
The organizers sincerely hope that SISOC-XIII will be an exciting and inspiring scientific meeting, with a fruitful exchange of new ideas that will lead to future successful work in Organic Chemistry. In addition, we believe that the organized social events will create new friendly relationships among researchers, from which new scientific collaborations will grow. To do so, we have the best ally, the city of Tarragona, which, with its sunny weather, lovely views, beautiful monuments and peacefulness will certainly help us to achieve this goal.

We would not want to end this welcome without an emotional memory of Kilian Muñiz, who was an enthusiastic member of the organizing committee at the beginning of this adventure. We will always remember and miss you dearly, Killian. This symposium is in your honor!

We wish you a pleasant stay in our city and an interesting exchange of knowledge.

Prof. Maribel Matheu
Chairperson of Organising Committee

The meaning of the SISOC XIII logo



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Special Invited Lecture

SPECIAL INVITED LECTURE

CATALYTIC SELECTIVE FUNCTIONALIZATION OF DIENES. THE CASES OF AZIRIDINATION AND TELOMERIZATION

Sergio Castillón

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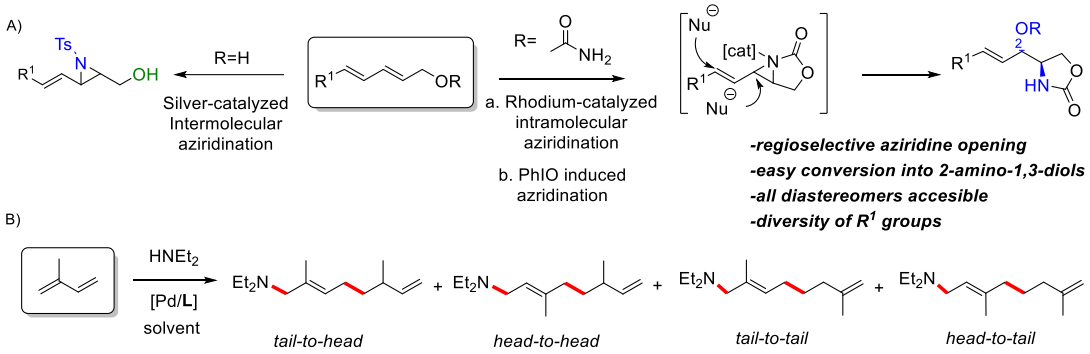
Selective functionalization of 1,3-dienes are important reactions in organic synthesis. Concerted cycloadditions are the most widely used method for diene functionalization. Moreover, selective transition metal-catalyzed alkene functionalization reactions attracted the interest of researchers in the last years because it allows a perfect control of regio- and stereoselectivity.

Here we will present two different processes for selective diene functionalization, aziridination [1] and telomerization [2]. Aziridination of hydroxymethyl-dienes affords vinylaziridines, which can be selectivity opened to afford 2-amino-1,3-diols in a regio- and stereoselective manner. 2-Amino-1,3-diols are present in different natural products as sphingosines. Different approaches of aziridination reactions such as intermolecular silver-catalyzed, intramolecular rhodium-catalyzed or metal free PhIO-promoted reactions will be analyzed (A).



Diene telomerization is an industrial process, and in Tarragona there is a plant for 1,3-butadiene telomerization. The telomerization of isoprene (2-methyl-1,3-butadiene) poses a formidable problem of regioselectivity since up to 4 different main isomers can be obtained. We will show that palladium-catalyzed isoprene telomerization allows the regioselective preparation of 3 of the 4 isomers (B).

Acknowledgement: Ministerio de Ciencia y Innovación (Spain). IFF

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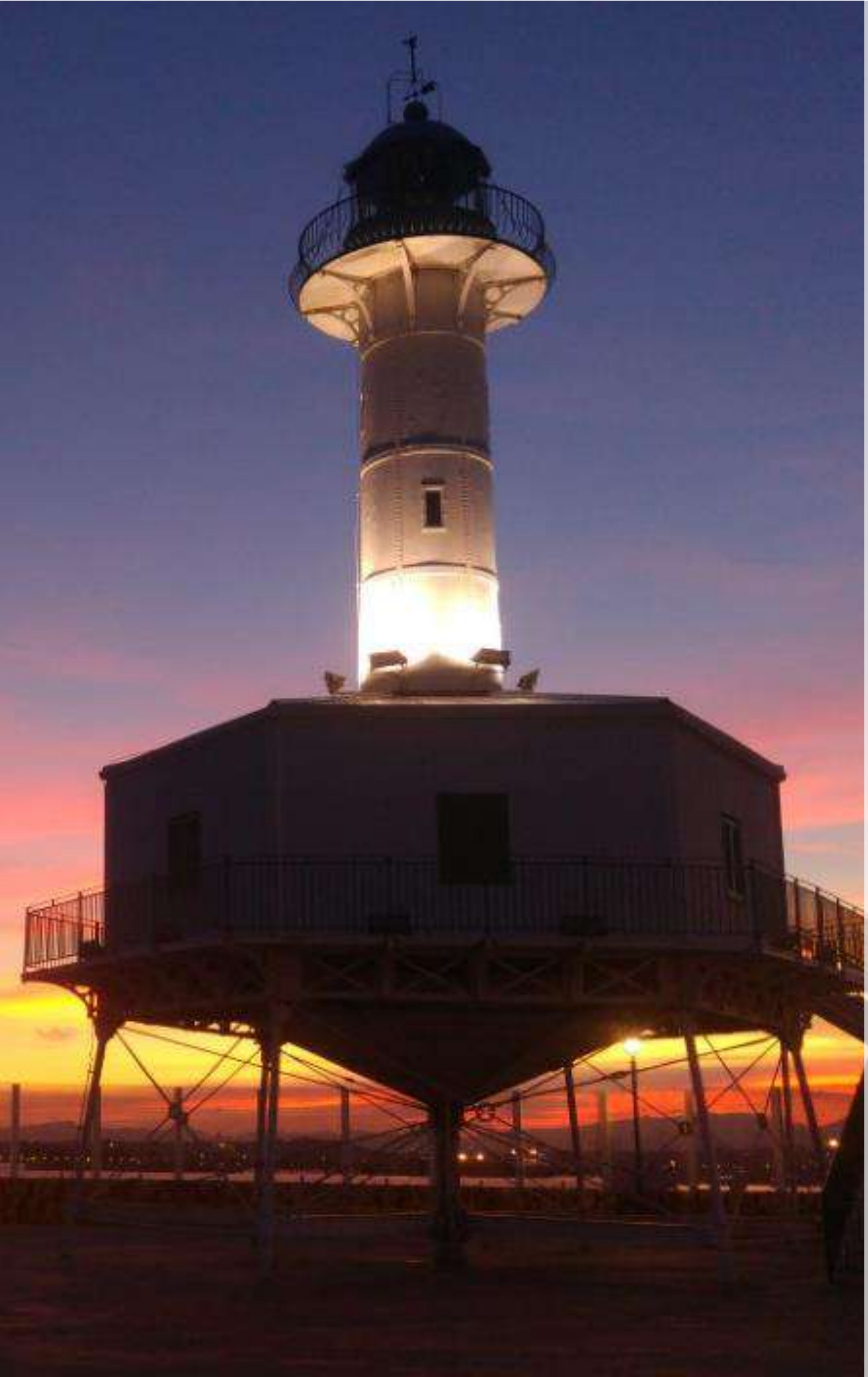

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KeyNotes

DIRECT ASYMMETRIC C-H TRANSFORMATIONS VIA ENOLATES: NEW REAGENTS AND CATALYSTS

M. Oiarbide

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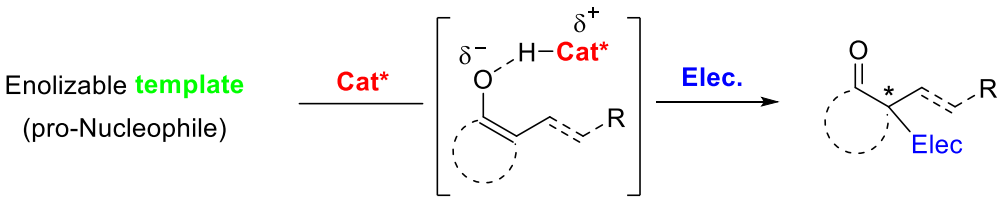
Construction of new carbon-carbon bonds at Cα of a carbonyl group is a classic transformation in organic synthesis and has resulted very versatile. Traditionally, this synthetic operation involves preformation of a stoichiometric enolate or equivalent species, which then is allowed to react with the proper electrophilic reagent. During the last two decades or so, various catalytic approaches have been developed to trigger this kind of transformations directly and enantioselectively, thus gaining in atom- and step-economy considerably. Among others, chiral catalysts featuring basic/H-bond donor bifunctional character have been shown competent in promoting various such transformations, constituting an invaluable resource of the modern synthetic toolbox.[1] In this context, our group has been interested in developing new templates (both nucleophilic and electrophilic) and catalysts aimed at overcoming some existing problems and limitations in this area, with the ultimate goal of making this technology more broadly applicable. Selected ideas along these efforts will be presented,[2] with a focus on methods that involve transiently generated di- and trienolates.[3]



Challenges: • reactivity • regioselectivity • enantiocontrol

Acknowledgements

We thank the University of the Basque Country UPV/EHU, Gobierno Vasco (IT1236-19), and Ministerio de Ciencia e Innovación (PID2019-109633GB-C21) for continuous support.

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KN-02

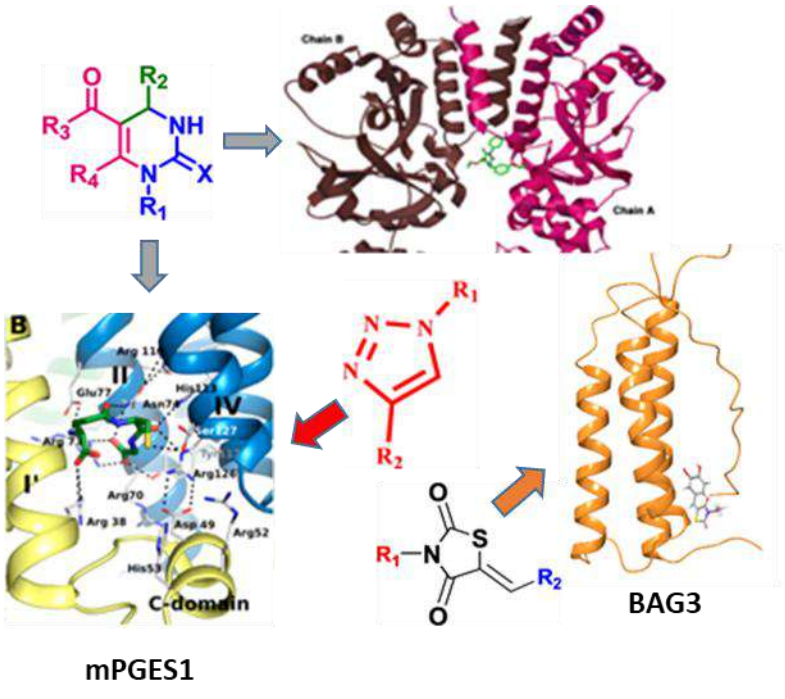
DISCOVERY OF NEW MOLECULAR PLATFORMS ABLE TO MODULATE SPECIFIC BIOLOGICAL TARGETS INVOLVED IN INFLAMMATION AND CANCER BASING ON *N*-HETEROCYCLIC PRIVILEGED STRUCTURES

Inés Bruno

The increasingly detailed knowledge of the mechanisms underlying pathological processes, the progress made in computational chemistry as well as the innovation in synthetic methodologies which can facilitate the construction of diverse and drug-like compound collections, gave a big boost to medicinal chemistry projects and changed the paradigm for the rapid and efficient discovery of new lead compounds by using integrated multifaceted approaches.

In this research area the use of privileged structure as validated starting points to develop potent and selective protein binders has become one of the most promising strategies in drug discovery processes. In this communication the results obtained using dihydropyrimidinone and 2,4-thiazolidinedione based molecules to explore three strategic targets deeply involved in inflammation and cancer, mPGES-1, HSP90 and BAG3 proteins, will be presented.

The multidisciplinary strategy involving computational techniques, organic synthesis as well as biophysical and biological methods will be detailed discussed.



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mPGES-1 inhibitors

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BAG3 inhibitors

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MECHANISTIC UNDERSTANDING-LED TRANSITION METAL CATALYZED C-H FUNCTIONALIZATION

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The development of greener and more efficient synthetic methodologies is essential for organic chemistry to reach its full potential in its application to many applied and fundamental scientific problems. Over the last two decades C-H activation has emerged as a powerful tool to streamline syntheses, functionalize complex scaffolds, while massively improving atom and step economy. However, several challenges are still to be addressed before C-H functionalization can be widely applied: 1) the development of mild reaction conditions with a broad scope, 2) the control of the regioselectivity of C–H activation, 3) the control of the selectivity of homo- versus cross-coupling in oxidative couplings, and 4) the development of conditions that can be safely used in industry.

Mechanistic understanding is a cornerstone for progress in organic chemistry. In this talk I will present some of our group's approaches in applying the knowledge derived from mechanistic studies into the design of more efficient processes and of novel catalysts and catalytic systems, such as the use of bimetallic Pd/Ag,[1] Pd/Cr[2] and Au/Ag[3] synergistic systems and the development of novel Ru-catalysts for late stage functionalization.[4,5]

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SYNTHESIS OF 2,6-DIMETHYLTYROSINE-LIKE AMINOACIDS

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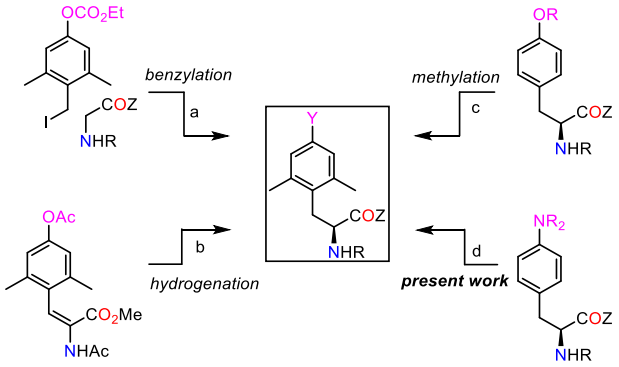
The aromatic moiety in the N-terminal message domain of opioid peptides, commonly represented by Tyr[1], Phe[1], and Phe[4], is fundamental in the binding and the activation processes of opioid receptors[1] In particular, 2,6-dimethyl-(L)-tyrosine (Dmt) has become one of the most popular non-natural amino acids to replace tyrosine in synthetic opioid peptides. The important role of Dmt is underlined by the number of reported syntheses of tyrosine derivatives carrying two symmetrically disposed methyl groups on the aromatic ring[2]. So far, three conceptually different approaches have been developed for preparing (*S*)-2,6-dimethyltyrosine and its derivatives. One approach is based on the enantio- or diastereoselective alkylation of glycine equivalents (Scheme 1, path a), while a second one is based on the asymmetric hydrogenation of Z-2-amido-3-(4-acetoxy-2,6-dimethylphenyl)-2-propenoates (path b). A third and more recent approach is based on the Pd-catalyzed dimethylation at positions 2 and 6 of the aromatic ring of tyrosine derivatives, as recently reported by Zhang and Ma[3] (path c)



Scheme 1

Inspired by the above works, we envisioned to extend the study of the Pd-catalyzed δ-*ortho* C(sp^2)–H activation strategy to differently 4-substituted (*L*)-phenylalanine picolinamides (path d), so as to obtain a small library of 2,6-dimethylated derivatives ready for incorporation in solid phase peptide synthesis (SPPS)[4].

Acknowledgements

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PALLADIUM CATALYZED COUPLING REACTIONS OF ARENES VIA METAL LIGAND COOPERATION

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Palladium-catalyzed C-C coupling reactions that directly functionalize C-H bonds have emerged as a powerful tool for C-C bond formation.[1] These reactions do not require a previous functionalization of every reaction partner and therefore conform to the principles of green chemistry, standing in a good position towards a more sustainable chemical synthesis. We have been looking closely at some of these transformations in order to better understand their mechanism and make them more efficient. In particular, we have been using chelating cooperating ligands such as 2,2'-bipyridin]-6(1H)-one (bipy-6-OH). Palladium complexes derived from this ligand are capable of accelerating C-H functionalization reactions of simple arenes (non-chelate assisted C-H activation).[2] Mechanistic studies show the cooperating effect of the ligand and its assistance in the C-H cleavage step by a concerted mechanism in the metal coordination sphere. In addition to the metal-ligand cooperation in the C-H activation, bipy-6-OH influences the product-forming step leading to chemoselective processes. The application of this type of ligands to direct arylations as well as aerobic oxidative Heck reactions of arenes will be discussed.

Acknowledgments

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HYDROXYSTEROID DEHYDROGENASES: AN ONGOING STORY

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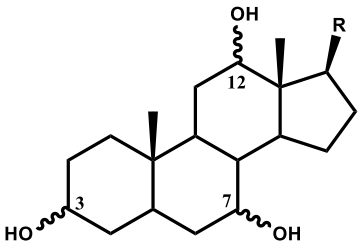
Bacterial hydroxysteroid dehydrogenases (HSDHs) are NAD(P)H-dependent enzymes that belong to the superfamily of short-chain dehydrogenases/reductases [1]. These enzymes catalyse the reversible regio- and stereoselective oxidoreduction of the hydroxyl/oxo moieties of steroidal compounds, displaying their high selectivity for oxygenated substituents at different positions of the steroidal skeleton (e.g., at C-3, C-7, and C-12) [2].

Exploiting HSDHs with same regioselectivity and opposite stereoselectivity it is possible to achieve Mitsunobu-like stereoinversions, as we have shown at position C-3 [3] and C-7 [4]. Moreover, using suitable cofactors regeneration systems, it is possible to run these enzymatic reactions in one-pot, avoiding the isolation of the ketonic intermediates [5, 6].

More recently, we have become interested in investigating the activity of these enzymes towards alcoholic or ketonic molecules that differ from steroids. Accordingly, the substrate promiscuity of a library of fifteen 7α-, 7β-, and 12α-HSDHs, either already known or obtained from a bioinformatic screening of in house or public available (meta)genomes, with a special focus for those from extreme environments, was tested for the stereoselective reduction of a panel of carbonyl substrates. [7].



Acknowledgments are gratefully due to the significant number of colleagues and students who have contributed to research in this area over the past 40 years.

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DESIGNING NEW SYNTHETIC CONCEPTS FOR IMPARTING MOLECULAR COMPLEXITY WITH C-1 SOURCES

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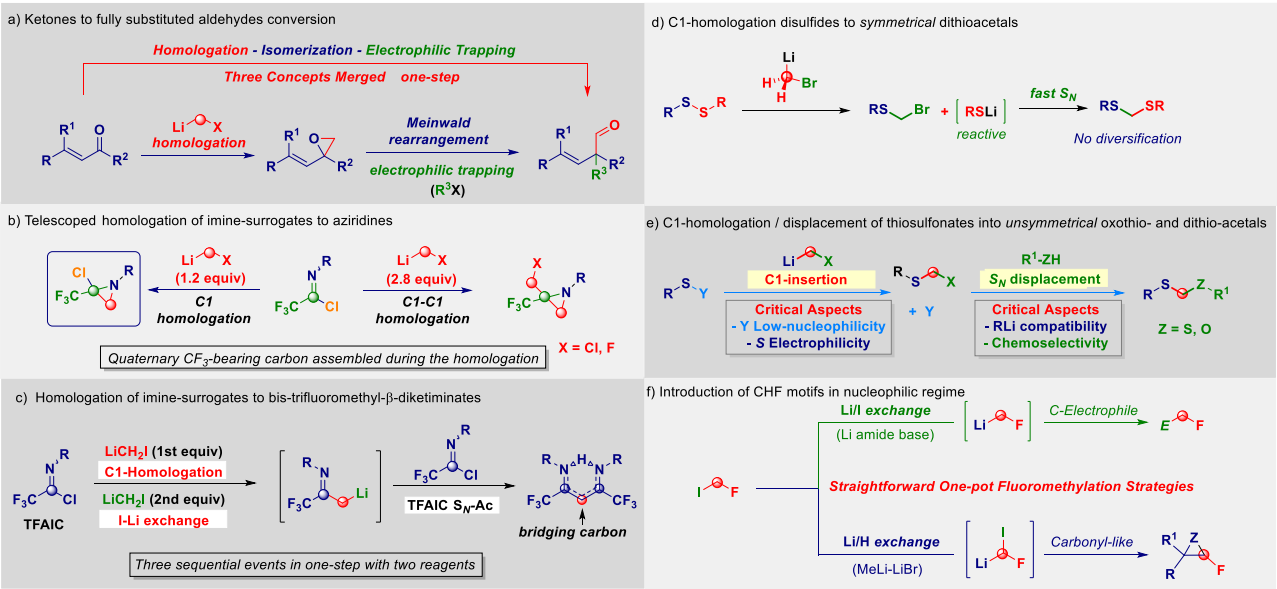
The direct transfer of a reactive nucleophilic CH_2X unit into an existing linkage enables the formal introduction of the moiety with the precisely defined degree of functionalization.[1] Upon the fine tuning of the reaction conditions governing the transformation, the initial homologation event can serve as the manifold for triggering unusual rearrangement sequences leading to complex architectures through a unique synthetic operation. The direct – full chemoselective - conversion of a ketone into the homologated all-carbon quaternary aldehyde (*via* a)[2], the telescoped homologation of imine-surrogates to quaternary aziridines (*via* b)[3] and bis-trifluoromethyl-β-diketiminates (*via* c) will illustrate these unprecedented concepts. Additionally, the homologation of disulfides and thiosulfonates will furnish symmetrical (*via* d) and unsymmetrical oxothio- and dithio-acetals (*via* e). The one-step mono-fluoromethylation of carbon electrophiles with extremely labile fluoromethyllithium reagents will provide a novel entry to valuable fluorinated building-blocks without the needing of using protecting elements for fluoro-containing carbanions (*via* f).[4] Moreover, novel strategies for introducing the difluoromethyl group through the proper activation of the commercially available $TMSCHF_2$ with an alkoxide will be discussed.[5]



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NEW OPPORTUNITIES IN CATALYTIC RUTHENIUM CARBENE/ALKYNE METATHESIS (CAM)

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Ruthenium vinyl carbenes derived from Cp/Cp*RuCl-based complexes have been routinely invoked as key intermediates in tandem reactions involving a carbene/alkyne metathesis (CAM).[1] These species are isoelectronic with the Grubbs-type family of catalysts, but their structural geometry and ligand properties make them more distinctive in catalytic reactions. The piano-stool arrangement of Cp*RuCl-vinylcarbenes favors a η^3-coordination mode which induces a deformation from planarity of the ruthenium carbene. Such distortion seems to increase the reactivity of the ruthenium vinyl carbene. In addition, the presence of the chloride ligand in an appropriate disposition acts as a Lewis base cocatalyst and promotes nucleophilic attacks to the ruthenium vinyl carbene (Figure 1).[2] The combination of these effects are directly related to the divergent behavior of these species.[3]

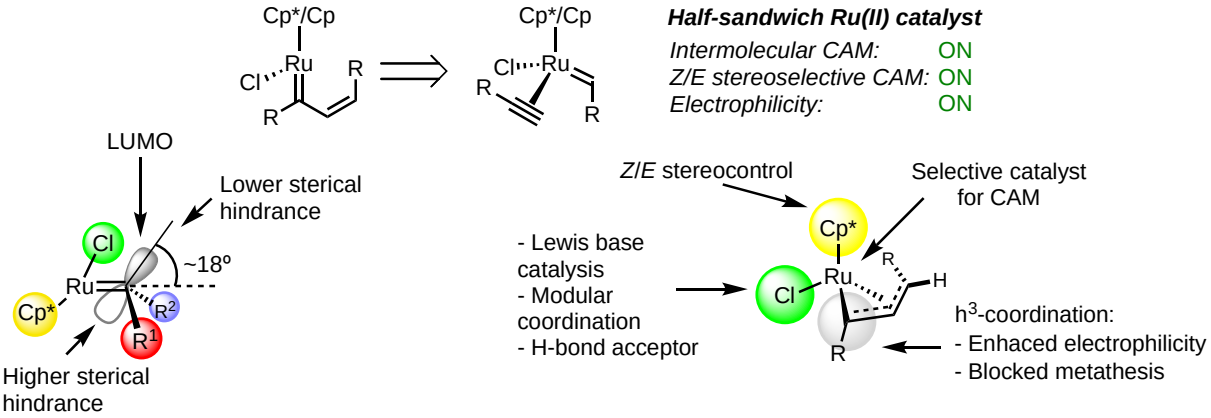

Figure 1. Reactivity and properties of ruthenium carbenes and their CAM-derived vinyl carbenes

Acknowledgements

This work has received financial support from MICINN (project PID-2020-118048GB-I00 and ORFEO-CINQA network RED2018-102387-T), the Xunta de Galicia (project ED431C 2018/04 and Centro singular de investigación de Galicia accreditation 2016-2019, ED431G/09) and the European Union (European Regional Development Fund – ERDF).

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KN-09

CONTINUOUS FLOW TECHNOLOGIES: A POWERFUL TOOL FOR THE STEREOSELECTIVE SYNTHESIS OF CHIRAL MOLECULES

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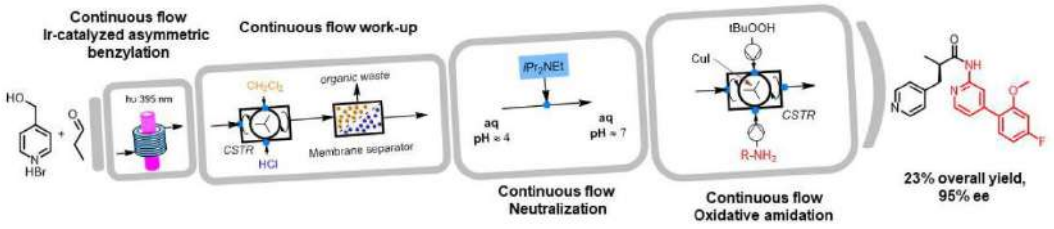
The use of enabling technologies and continuous-flow systems are becoming more and more important in the synthesis of chiral APIs (active pharmaceutical ingredients).

Organocatalytic reactions in (micro)-mesoreactors will be discussed, and compared with stereoselective catalytic in-flow reactions in 3D-printed reactors.

The combination of organocatalysis and photochemistry can give access to molecules in one step which would otherwise be difficult to attain. Examples of asymmetric organocatalyzed photochemical reactions translated into continuous flow are rare. An efficient continuous flow photoredox reactor, that was incorporated as one unit of operation into the first fully telescoped, continuous asymmetric catalytic synthesis of a privileged API will be presented.



A visible-light catalyzed cyclization of bis(enones) to afford enantiomerically enriched

cyclopentane rings and a continuous flow approach to access α-trifluoromethylthiolated esters and amides starting from commercially available arylacetic acids will be also described.

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Stereoselective Visible-Light Catalyzed Cyclization of Bis(enones): A Viable Approach to the Synthesis

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F. Herbrik , M. Sanz, A. Puglisi, S. Rossi, M. Benaglia

Enantioselective organophotocatalytic telescoped synthesis of a chiral privileged active

pharmaceutical ingredient

Chem. Eur. J. 2022, 28, accepted, https://doi.org/10.1002/chem.202200164

NEW NMR METHODS FOR STUDYING COMPLEX N-GLYCANS AND GLYCOPROTEINS

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Complex glycosylation patterns containing multiantennary N-glycans are typically found in mature glycoproteins. However, the structural characterization of these glycans is rather challenging. Usually, standard NMR and X-ray diffraction techniques fail to provide specific answers on the structure and molecular recognition features of these molecules due to intrinsic attributes of the glycan. As a promising approach, carbohydrates conjugated to lanthanide binding tags have revealed high potential toward this aim. This methodology has first been applied to the study of small oligosaccharides (di-, tri- and tetrasaccharides). [1] Proceeding from this experimental basis, we have extended this concept to the level of high degree branching and long chain N-glycans. [2] In addition, the molecular recognition properties of these complex glycans were characterized in detailed thanks to the unprecedented resolution obtained in the spectra.

On the other hand, we are also working on the development of new methods to characterize N-glycans in the context of intact glycoproteins. Recent works have shown the potency of NMR to deduce the glycosylation pattern of intact glycoproteins by using selective ^{13}C glycan labelled glycoproteins. [3] In this context, we are characterizing the glycosylation pattern of the D2 domain of the fibroblast growth factor receptor by using NMR since glycosylation seems to modulate the biological function of this protein.

Acknowledgements

Funding from “Ministerio de Ciencia e Innovación España”, project PID2019-105237GB-I00.

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PALLADIUM IODIDE CATALYZED OXIDATIVE CARBONYLATIONS IN THE SYNTHESIS OF FUNCTIONALIZED HETEROCYCLES

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In this lecture, I will present the recent achievements realized by my research group in the synthesis of functionalized heterocyclic derivatives by palladium iodide catalyzed oxidative carbonylation [1].

I will show how a simple catalytic system, consisting of PdI_2 in conjunction with an excess of KI and in the absence of additional ligands, is able to promote different oxidative carbonylation processes leading to a variety of carbonylated heterocycles.

Starting from CO and simple organic substrates (alkynes bearing a suitable placed nucleophilic group, in particular) as building blocks, these reactions have allowed obtaining functionalized furans, pyrroles, thiophenes, lactones, lactams, benzothiophenes, isoindolinones, isobenzofurans, and isocoumarins, between others, as well as fused heterocyclic derivatives, in one single synthetic step and under relatively mild conditions.

Acknowledgements

All the coauthors of the papers that I will refer to during my lecture are most gratefully acknowledged.

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ORGANOCATALYSIS IN THE EXCITED STATE
NEW AVENUES FOR ASYMMETRIC RADICAL PROCESSES

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The chemical reactivity of electronically excited molecules differs fundamentally from that in the ground state. This is the underlying reactivity concept of photochemistry,[1] which has traditionally allowed the development of unique chemical transformations not achievable via conventional ground-state pathways.[2] For example, an excited-state molecule is both a better electron-donor (i.e. a better reductant) and electron-acceptor (i.e. a better oxidant) than in the ground state. This explains why the light excitation of organic molecules can unlock unconventional reactivity manifolds. In this context, our laboratory has been exploring the potential of some organocatalytic intermediates to directly reach an electronically excited state upon visible-light absorption to then switch on novel catalytic functions that are unavailable to ground-state organocatalysis.[3] Studying the mechanism[4] of these photochemical approaches allowed us to expand the synthetic possibilities offered by the excited-state reactivity of organocatalytic intermediates and to develop enantioselective radical processes.[5]

Acknowledgements

MINECO (CTQ2016-75520-P) and the European Research Council (ERC 681840 - CATA-LUX) are thanked for financial support.

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IL

Invited Lectures

ANION RECOGNITION BY NEUTRAL CHALCOGEN BONDING RECEPTORS: EXPERIMENTAL AND THEORETICAL INVESTIGATION

Encarnación Navarro-García,[1] Bartomeu Galmés,[2] María D. Velasco,[1] Antonio Frontera[2] and Antonio Caballero[1]

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The utilization of neutral receptors for the molecular recognition of anions based on chalcogen bonding (ChB) is an undeveloped area of host–guest chemistry. In this communication, the synthesis of two new families of sulfur, selenium and tellurium-based ChB binding motifs are described. The stability of the thiophene, selenophene and tellurophene binding motifs has enabled the determination of association constants for ChB halide anion binding in the polar aprotic solvent THF by ^{1}H-, ^{77}Se- and ^{125}Te-NMR experiments. We have used two different aromatic cores and incorporated one or two Ch-binding motifs with the purpose to encapsulate the anion offering up to two concurrent chalcogen bonds. Theoretical calculations and NMR experiments reveal that, for S and Se receptors, hydrogen bonding interactions involving the acidic H-atom adjacent to the chalcogen atom are energetically favored over the ChB interaction. However, for the tellurophene binding motif, the σ-hole interaction is competitive and more favored than the H-bond.

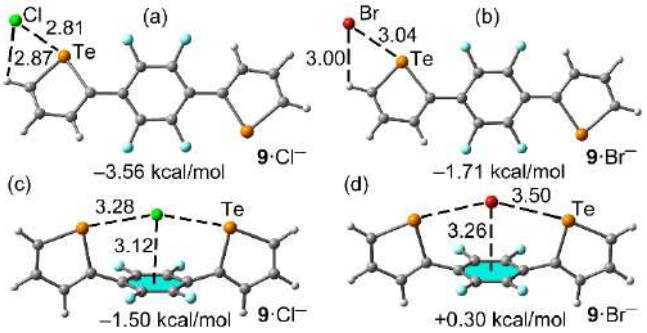

Figure 1. PBE0-D3/def2-TZVPP optimized geometries for two different binding modes in dipodal complexes with Cl^- (a,c) and Br^- (b,d). Distances in Å. BSSE-corrected energies in THF.

Acknowledgements

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FUNCTIONAL DYES FOR PHOTOVOLTAICS, GREEN PHOTONICS AND BIOLOGICAL APPLICATIONS

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In the last years, extensive efforts have been addressed to develop near-infrared (NIR) dyes both for biological and optoelectronic applications,[1] such as imaging, photodynamic therapy (PDT), solar cells and biological sensors. Among many, polymethine dyes must be considered as innovative photosensitizers due to the easy and low-cost synthesis along with remarkable absorption property in the far-red NIR region.[2] Squaraines and cyanines are characterized by high molar absorption coefficients, remarkable brightness, fluorescence and photostability, especially in organic media.

The present contribution focuses on the design and synthesis of various series of NIR absorbing polymethine dyes. A preliminary structure-properties relationship is presented to highlight the most relevant molecular moieties for the interactions with light and biomolecules. Among the different applications, results on their use as photosensitizers in Dye-Sensitized Solar Cells (DSSCs), PDT, and "turn-on" fluorogens for the quantitative detection of ct-DNA and proteins. Moreover, the encapsulation of these dyes in organic and inorganic nanomaterials to enhance their optical properties, photostability, biocompatibility and efficient cellular internalization will be discussed. Finally, the first application of these dyes as solid-state emissive materials in sustainable lighting based on emissive proteins will be presented.

Acknowledgements

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SYNTHESIS OF STEREODEFINED SKIPPED 1,4-DIENES FROM 1,1-DIBORYLALKENES

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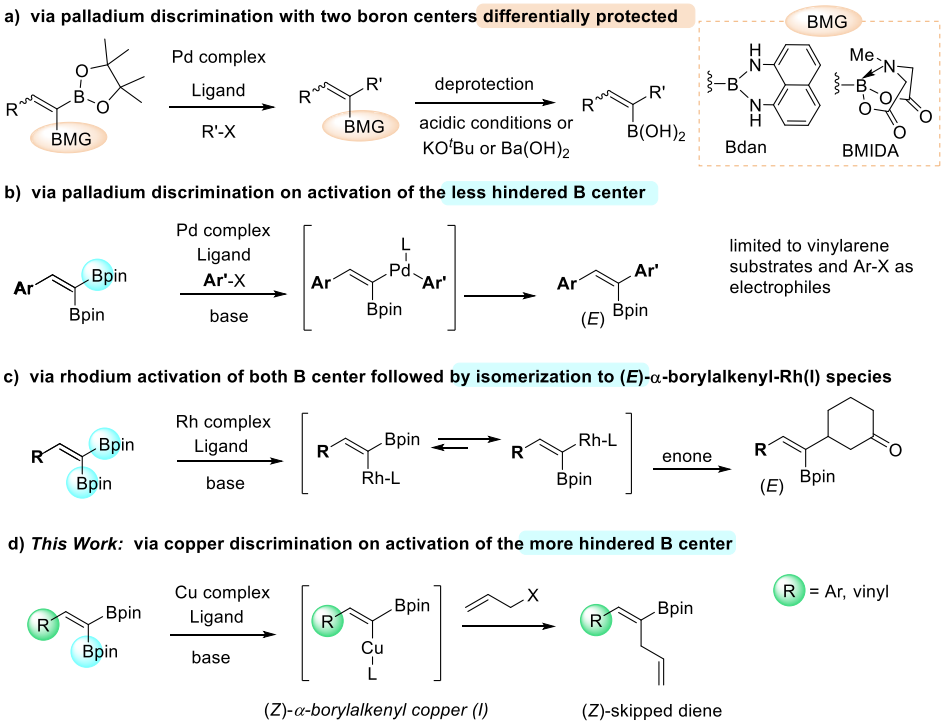
1,1-Diborylalkenes are emerging bifunctional building blocks applied in the modular synthesis of complex molecules, through boron-selective transformations.[1,2] When the two geminal boryl moieties on 1,1-diborylalkenes are different, the transformation in a stepwise manner occurs through the more reactive boryl group while the relatively inert boryl moiety (so-called boron masked group BMG) remains intact (Scheme 1a).[3] This would then require a deprotection sequence of the masked group to become a versatile boryl group.[4] However, when the geminal boryl moieties on 1,1-diborylalkenes are identical, the boron-selective reactions become a challenge. Palladium complexes have proved to interact with the Bpin group at the less hindered position of 1,1-di(pinacolboryl)alkenes, but only when an aryl group is present at the C_β position, to perform a Suzuki-Miyaura cross coupling with arylhalides (Scheme 1b).[5] Rhodium complexes have shown to activate non-selectively both C-Bpin moieties on substituted 1,1-diborylalkenes, although the (*Z*)-α-borylalkenyl Rh complex seems to isomerize towards (*E*)-α-borylalkenyl Rh complex which undergoes faster 1,4-addition to enones generating almost exclusively the (*E*) trisubstituted alkene (Scheme 1c).[6]



Scheme 1. Activation of *geminal* B-C(sp^2)-B towards selective coupling reactions

Since the key for a successful boron-selective reaction is to discriminate between the boryl groups, we describe here a new conceptual approach based on the generation of an α-borylalkenyl copper specie, activating the more hindered Bpin moiety of the 1,1-di(pinacolboryl)alkene, to promote a nucleophilic (Z)-selective Cu catalyzed reactivity with allyl bromides generating exclusively (Z)-skipped 1,4-dienes (Scheme 1d).

Acknowledgements

We thank Ministerio de Economía y Competitividad y por el Fondo Europeo de Desarrollo Regional FEDER through project PID2019-109674GB-I00. We thank AllyChem for the gift of diboron reagents

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KUQUINONES: FROM SERENDIPITY TO PHOTO(ELECTRO)CHEMICAL APPLICATIONS

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Ten years ago, in our laboratory, a new class of dyes, called KuQuinones (KuQs), has been discovered [1]. KuQuinones are pentacyclic, fully conjugated quinoid molecules, which exhibit a broad absorption band in the visible region, a low reduction potential as well as very interesting biochemical properties [2]. The peculiar spectroscopic and electrochemical features make them excellent candidates as photosensitizers in photoelectrochemical applications. Therefore, KuQs have been properly functionalized and anchored on different semiconductive metal oxides (ITO, NiO, SnO_2) to test their applications as photoactive materials in photoelectrochemical and photocatalytic devices [3,4].

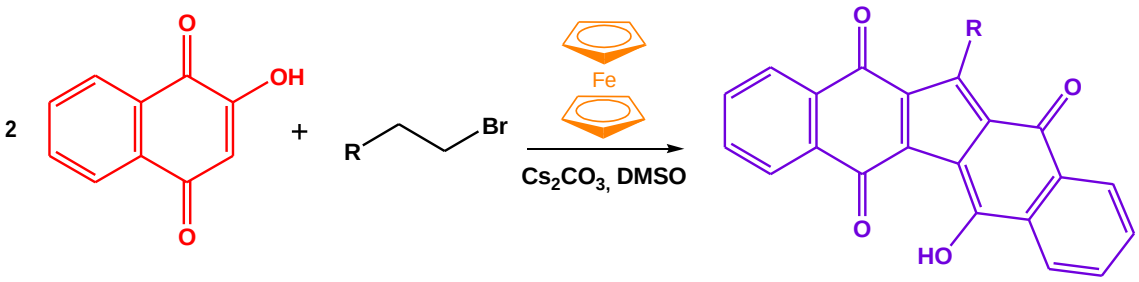

Figure 1. Synthesis of KuQuinones

In this communication an overview of our recent results of KuQs applications in photoelectrochemical system will be presented.

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EFFICIENT SYNTHESIS OF ORGANIC COMPOUNDS FOR SOLAR ENERGY CONVERSION BY DIRECT ARYLATION REACTIONS

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Organic compounds play pivotal roles in various devices for solar energy conversion, in which they may act as light-absorbing components, fluorescent emitters or charge-transporting materials. Clearly, development of sustainable protocols for the synthesis of such compounds will be crucial in favouring the future widespread diffusion of sunlight-harvesting technologies. In the last few years, we described several efficient routes for the preparation of organic photoactive compounds, such as sensitizers for dye-sensitized solar cells [1,2] or emitters for luminescent solar concentrators [3], in which most traditional cross-coupling reactions were replaced with direct arylation processes, leading to shorter synthetic sequences and reduced waste production (Fig. 1, top) [4]. More recently, we studied the use in such processes of biocompatible deep eutectic solvents (DES) in place of common organic volatile solvents, and compared the most relevant green chemistry metrics in the two cases (Fig. 1, bottom) [5].

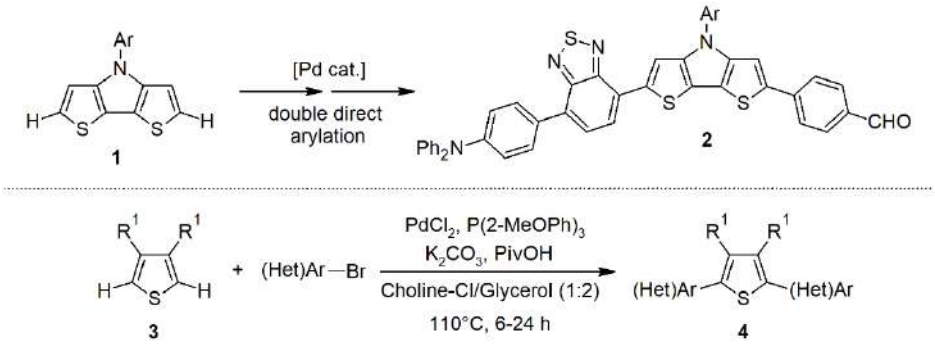

Figure 1. Direct arylations of thiophene derivatives.

In this communication, we will describe our most significant findings, highlighting the reactions scope, the properties of the synthesized compounds and our efforts in expanding the range of metal-catalyzed reactions in the new environmentally-friendly reaction media.

Acknowledgements

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CATALYTIC CARBYNE TRANSFER IN ORGANIC SYNTHESIS

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The art of organic synthesis and reaction discovery relies on logic-guided thought processes that often involve hypovalent carbon reactive species and their corresponding stabilized equivalent forms. However, not all of the possible carbon reactive intermediates and their reactivity rules have attracted the same attention by the synthetic community. This is mainly because of the perception of the lack of synthetic utility and importantly, because of the challenges associated with controlling its extreme reactivity and lack of efficient sources.

In this lecture, I will show how the catalytic generation of conceptually-novel radical carbenoids, carbyne equivalents, and metal-carbynoids enabled the discovery of new carbon reactivity towards C–H and C–C bonds. The metal or photocatalytic activation of tailored sources revealed new reactivity rules at carbon that have been under-appreciated, not only in the design and discovery of new chemical reactions, but also in their use to build molecular complexity through unexplored disconnection approaches. Our catalytic carbyne transfer platform has demonstrated to be an effective and unique option in the construction of chiral centers with aryl C–H or by breaking C–C double bonds, and that has found applications in the late-stage functionalization of medically relevant agents. [1],[2],[3]

Acknowledgements

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RATIONALLY PREDICTING DISTAL ACTIVITY-ENHANCING MUTATIONS IN TRYPTOPHAN SYNTHASE

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Enzymes exist as an ensemble of conformational states, whose populations can be shifted by substrate binding, allosteric interactions, but also by introducing mutations to their sequence. Tuning the populations of the enzyme conformational states through mutation enables evolution towards novel activity.[1] A common feature observed in many laboratory-evolved enzymes, is the introduction of remote mutations from the catalytic center, which often have a profound effect in the enzyme catalytic activity. [2] As it happens in allosterically regulated enzymes, distal mutations regulate the enzyme activity by stabilizing pre-existing catalytically important conformational states.

In this talk, our new computational tools based on inter-residue correlations from microsecond time-scale Molecular Dynamics (MD) simulations and enhanced sampling techniques are applied in Tryptophan synthase (TrpS) complex. TrpS is composed of TrpA and TrpB subunits, which allosterically activate each other and have no activity when isolated. [3,4] We show how distal mutations introduced in TrpS resuscitate the allosterically-driven conformational regulation and alter the populations and rates of exchange between multiple conformational states, which are essential for the multistep reaction pathway of the enzyme.[3] The exploration of the conformational landscape of TrpS is key for identifying conformationally-relevant amino acid residues of TrpB and TrpA distal from the active site.[4] We predict positions crucial for shifting the inefficient conformational ensemble of the isolated TrpB and TrpA to a productive ensemble through intra-subunit allosteric effects. The experimental validation of the new conformationally-driven TrpB and TrpA design demonstrates their superior stand-alone activity in the absence of binding partner, comparable to those enhancements obtained after multiple rounds of experimental laboratory evolution. Our work evidences that the current challenge of distal active site prediction for enhanced function in computational enzyme design can be ultimately addressed.

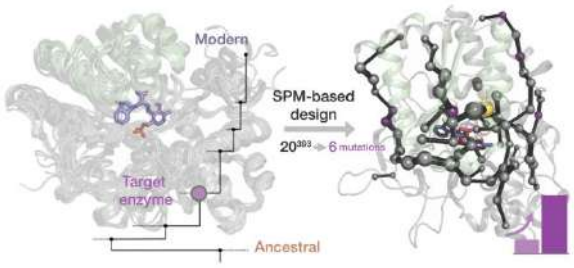

Figure 1. Scheme of the computational protocol used for the rational design of conformationally-driven stand-alone TrpB variants. Ancestral sequence reconstruction is combined with the correlation-based tool SPM.

Acknowledgements

We thank the Generalitat de Catalunya for the emerging group CompBioLab (2017 SGR-1707) and Spanish MINECO for project PGC2018-102192-B-I00. M. A. M. S. was supported by the Spanish MINECO for a PhD fellowship (BES-2015-074964) and by the National Research Foundation of Korea (NRF) under the Brain Pool Program (NRF-2021H1D3A2A02038434), J. I. F. was supported by the European Community for Marie Curie fellowship (H2020-MSCA-IF-2016-753045) and Juan de la Cierva-Incorporación fellowship (IJCI-2017-34129). S.O. is grateful to the funding from the European Research Council (ERC) under the European Union's Horizon 2020 research and innovation program (ERC-2015-StG-679001), and the Human Frontier Science Program (HFSP) for project grant RGP0054/2020.

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SYNTHETIC CARBOHYDRATE-BASED MATERIALS

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Polysaccharides are the most abundant organic materials in nature, yet correlations between their three-dimensional structures and macroscopic properties have not been established. With automated glycan assembly (AGA), we prepared well-defined oligo- and polysaccharides resembling natural as well as unnatural structures.[1] These synthetic glycans are ideal probes for the fundamental study of polysaccharides, shedding light on how the primary sequence affects the polysaccharide properties (*i.e.* solubility and crystallinity). Molecular dynamics simulations, NMR spectroscopy, and single molecule imaging allowed for the visualization of polysaccharides' conformation and revealed that some polymers form helices while others adopt rod-like structures.[2] Modifications in specific positions of the oligosaccharide chains permitted to tune the three-dimensional structures and solubility of such compounds.[3] These synthetic oligosaccharides self-assembled into nanostructures of varying morphologies.[4] Differences in chain length, monomer modification, and aggregation methods yielded glycomaterials with distinct shapes and properties, offering valuable models to study the aggregation of natural polysaccharides.

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CYCLOPROPENES: USEFUL REAGENTS FOR CARBENE CHEMISTRY

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Cyclopropenes are the smallest unsaturated carbocycles. In spite of the obvious high ring strain, a number of cyclopropenes are isolable and can be handle without special precautions. Cyclopropenes show a rich reactivity as it is the case for related unsaturated compounds as alkenes or alkynes; however, the particular structure of cyclopropenes provide additional reactivities unattainable for typical alkenes.[1] Among those reactions, cyclopropenes are particularly interesting as carbene precursors, supplementing other reagents capable of generating these valuable synthetic intermediates. In this invited lecture, an overview of the possibilities offered by cyclopropenes to generate vinyl carbene intermediates through metal-catalyzed rearrangements are presented.[2]

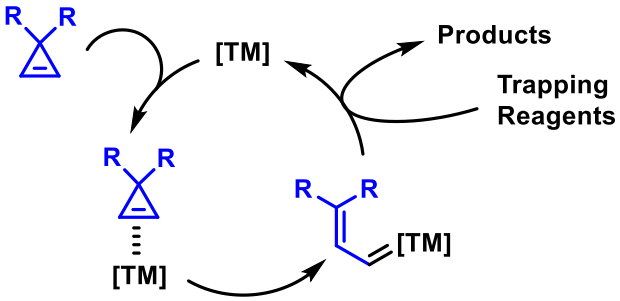

Figure 1. Metal-catalyzed generation of carbenes from cyclopropenes: Overall transformation.

Acknowledgements

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MOLECULAR RECOGNITION OF CARBOHYDRATES. A PREORGANIZED HYDROGEN-BONDING MOTIF

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Selective recognition of carbohydrates by several classes of proteins, such as lectins, is a key step in both physiological and pathological processes. [1] Biomimetic receptors are a class of synthetic small molecules developed to recognize saccharides by non-covalent interactions used by lectins, such as hydrogen bonds and hydrophobic interactions. Biomimetic receptors can be a useful tool to interfere with protein-carbohydrate recognition events, as well as to target specific carbohydrates for drug delivery and diagnostic purposes. Because carbohydrate recognition in nature occurs in aqueous media, water represents a challenge for artificial receptors in the recognition of polar species like carbohydrates. For this reason, biomimetic receptors effective in aqueous media are still sporadic in the literature.[2] In this lecture, we present a recently developed family of biomimetic receptors based on a highly preorganized diaminocarbazole hydrogen bonding unit,[3] which recognize mono- and disaccharides of biological relevance in water with affinities comparable to those of natural lectins.[4,5]

Figure 1. Schematic representation of receptor architectures based on diaminocabazole binding units.

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HIGHLY DISTORTED CHIRAL NANOGRAPHENES: SYNTHESIS AND PROPERTIES

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The controlled preparation of well-defined distorted nanographenes by a bottom-up approach based on organic synthesis allows the direct establishment of unprecedented structure-property relationships on carbon nanostructures. Simultaneous incorporation of different defects on nanographenes affords highly curved structures with novel photophysical properties, such as the combination of two-photon absorption (TPA) based upconversion and circularly polarized luminescence (CPL).[1,2] The combination of both non-linear and chiroptical properties in nanographenes opens up new possible future applications for distorted nanostructures. Novel highly twisted aromatic cores can be created by incorporating non-hexagonal rings together with chiral motifs, leading to highly rigid configurationally stable chiral molecular nanographenes.[3,4]

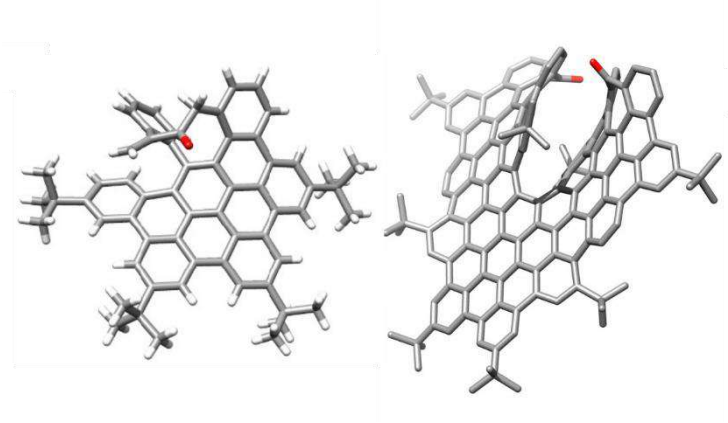

Figure 1. Helically chiral nanographenes

Acknowledgements

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SUPRAMOLECULAR GREEN CATALYSTS FROM SELF-ASSEMBLED SHORT PEPTIDES

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Self-assembling peptides are versatile building blocks for supramolecular catalysts [1]. Di- and tri-peptides are readily made on a large scale at low cost, and the Phe-Phe motif is convenient for molecules that self-organise in green solvents into diverse nanostructured materials, which do not persist in the environment [2]. Amino acid chirality offers means for stereocontrol at the microscopic scale too [3], and to tune biodegradation rates [4]. Of particular interest are supramolecular catalysts that can be switched on/off with assembly/disassembly (Figure 1), ideally to engineer synthetic cascades in the future.

In particular, combination of self-assembling Phe-Phe with histidine yields a heterochiral tripeptide that self-organises into nanotapes and gels in water at neutral pH. Only when assembled, it mimics a hydrolase [5]. Inclusion of further amino acids to mimic the catalytic triad (*e.g.*, His-Ser-Asp) was explored to enhance catalytic activity [6]. Furthermore, N- and C-termini modifications fine-tune assembly, catalysis, and can avoid side reactions [7,8].

We envisage wider scope of application, thanks to the wide array of natural and non-natural amino acids available, with diverse sidechains. For example, substitution of histidine with proline [8] yields supramolecular organocatalysts for Michael-type reactions in water [9]. We are now actively seeking collaborators keen on catalysis to adventure together in this field.

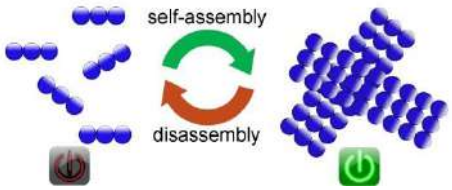

Figure 1. Tripeptides (blue) are ideal building blocks for switchable supramolecular catalysts.

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SHORT AND MODULAR SYNTHESES BASED ON [3,3]-SIGMATROPIC REARRANGEMENTS

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During the last years, we have been involved in the development of a diversity-oriented synthetic strategy aimed to transform simple, linear and densely functionalized molecular platforms into collections of topologically diverse scaffolds incorporating biologically relevant structural motives such as N- and O- heterocycles, multifunctionalized aromatic rings, fused macrocycles, etc.[1] Many of these transformation rely on the [3,3]-sigmatropic rearrangement of appropriate substrates, and during this presentation some examples will be presented.

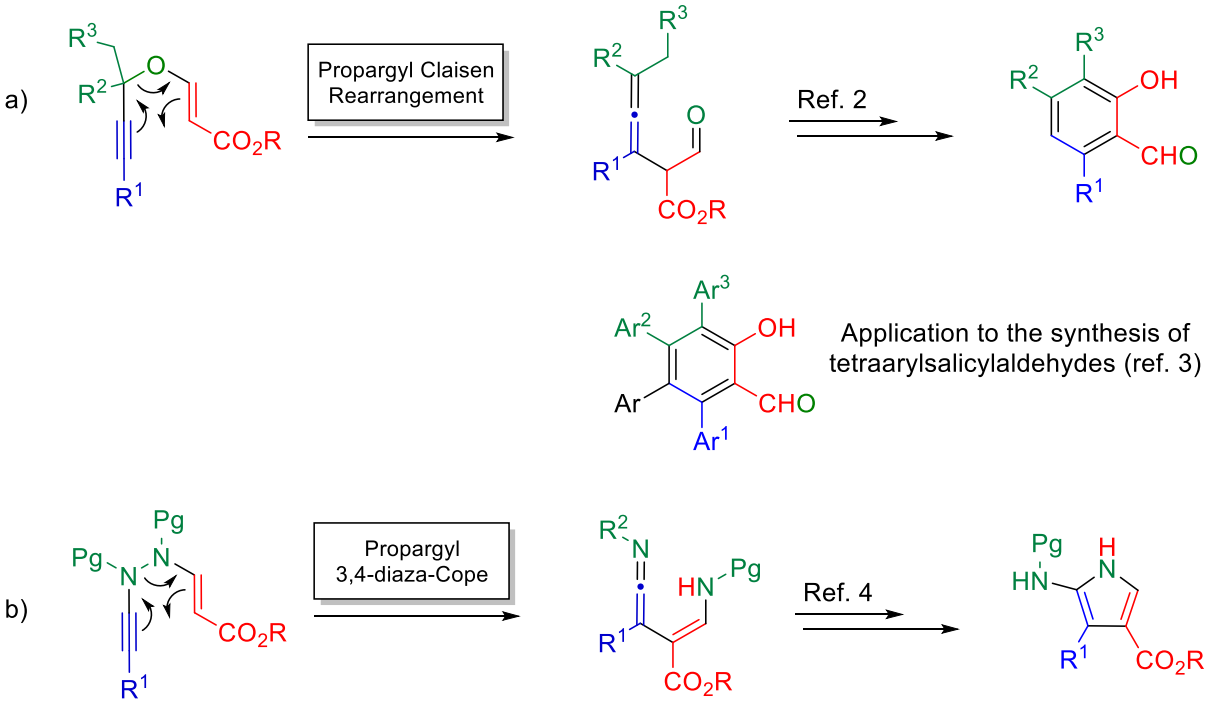

Figure 1. Examples of [3,3]-sigmatropic-triggered methodologies.

Acknowledgements

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BULKINESS AS A DEFINING FEATURE IN GOLD CHEMISTRY

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The chemistry of gold has witnessed a frenetic development over the last two decades due to the disclosure of a wide variety of catalytic applications under homogeneous conditions. However, fundamental information on bonding schemes and structural information of unconventional gold species, including key intermediates of mechanistic cycles, have evolved at a slower pace. To this end, the use of sterically congested ligands that confer kinetic stabilization has proved to be a highly convenient strategy. Following this approach, we have investigated a family of highly congested electrophilic Au(I) fragments stabilized by sterically hindered phosphine ligands containing a terphenyl (2,6-C_6H_3-Ar_2) substituent. With a strong focus on building gold-based bimetallic architectures, herein I will discuss some of these studies which permitted us to isolate unknown digold structures, study in detail unconventional reaction modes, such as C—B bond cleavage and C—C bond formation processes, design frustrated Lewis pairs entirely based on transition metals, trapping transient bimetallic intermediates or identify rare examples of weak interactions in gold-metalloids compounds.

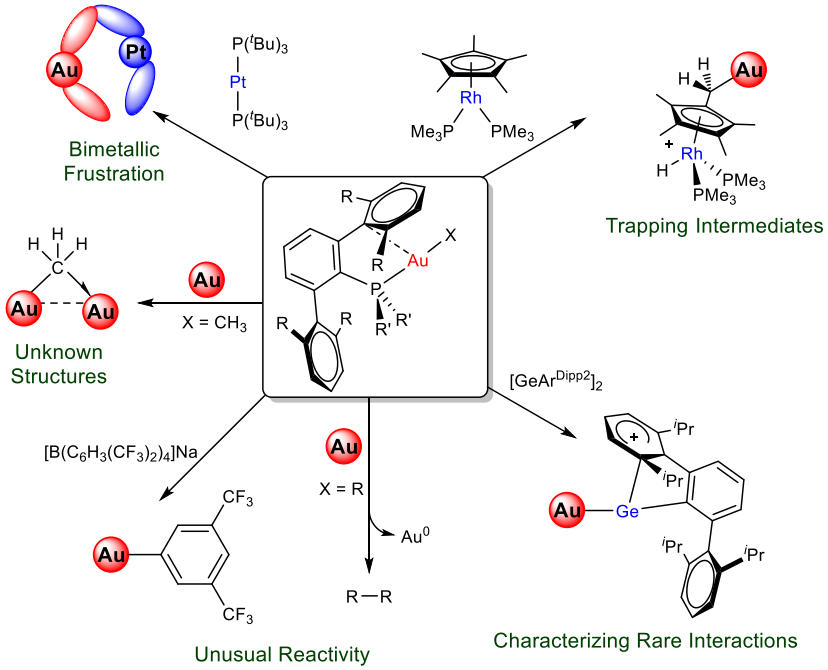

Figure 1. Unusual chemical outcomes from terphenyl phosphine gold complexes

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ADVENTURES IN CHEMICAL PROBING OF NATURAL PRODUCT BIOSYNTHESIS

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Natural products constitute an abundant and highly diverse source of bioactive compounds that ultimately can become important anticancer, antibiotic, antiviral, antiparasitic and anti-inflammatory agents. The detailed elucidation of 'old' and new biosynthetic pathways leading to natural products is therefore of the utmost importance towards novel bioactive product generation and diversification. In our lab we have been developing a range of chemical probes for the 'capture' and the elucidation of biosynthetic intermediates leading to natural product assembly *in vitro* and in live microorganisms. The probes mimic the building blocks utilised by natural product enzymatic assembly lines (*e.g*. polyketide synthases and nonribosomal peptide synthetases) and intercept biosynthetic intermediates throughout whole natural product formation, thereby unveiling unprecedented mechanistic details and novel opportunities for chemoenzymatic product diversification [1-5, and **Fig. 1**]. Herein I will present and discuss our latest probe development for the dissection of complex known natural product pathways [6-10] and the elucidation of cryptic pathways from under investigated microorganisms [11].

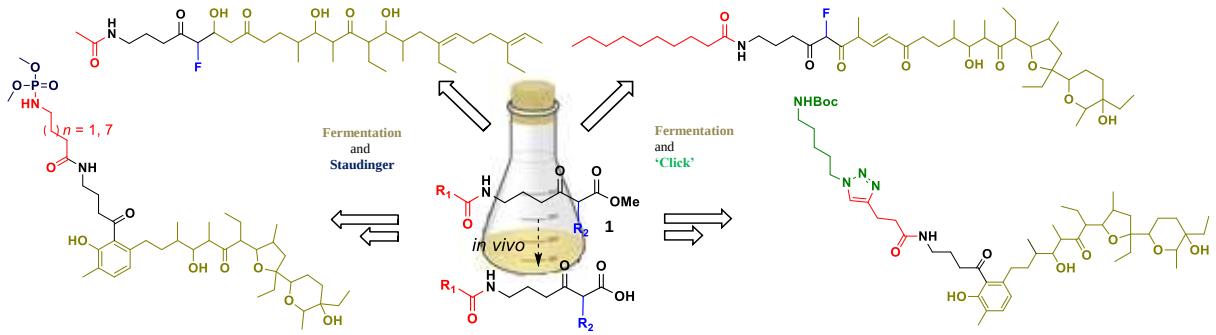

Figure 1. Chemical probes (**1**) capable of reacting with enzyme-bound biosynthetic intermediates (in gold) can be utilised for the investigation and the structural diversification of natural products.

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DEEP EUTECTIC SOLVENTS: FROM SUSTAINABLE REACTION MEDIA TO SUPRAMOLECULAR MATERIALS

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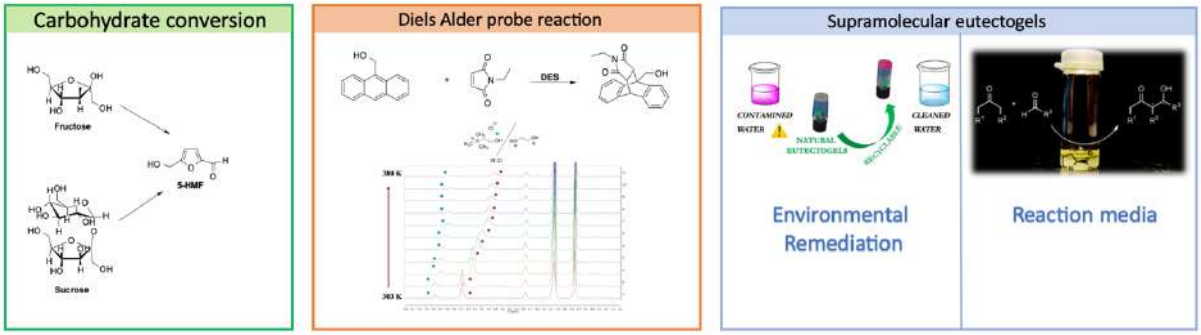
The pressing environmental challenges facing contemporary society, like depletion of fossil fuels and global warming, have geared research to minimize the environmental impact of chemical processes, following the methodological approach of Green Chemistry. A prominent concern of a chemical process is the solvent used, and for this reason, non-conventional, more environmentally compatible solvents have been introduced.[1] In this context, the latest development is constituted by Deep Eutectic Solvents (DES).[2] DES are mixtures of simple compound with a definite melting point, lower of any individual components and often liquid at room temperature. The components used are often cheap and readily available compounds. Due to their low volatility and flammability as well as distinct structural organization, DES could be applied both as sustainable reaction media and components of materials.
Under this light, we employed DES as reaction media and for obtaining supramolecular gels.



In the first case, we successfully used DES as solvent media for the conversion of carbohydrates into 5-hydroxymethylfurfural (5-HMF).[3] This reaction is important since it provides synthetic access to an industrially relevant product, like 5-HMF, from renewable sources. The reaction was carried out in the presence of Amberlyst 15 as catalyst, observing high yields and selectivity, as well as good recyclability of the solvent/catalyst system. To further investigate the properties of DES as solvent media, we studied a Diels Alder cycloaddition as a probe reaction. Temperature dependent NMR and Resonance light scattering allowed us to observe a relationship between reaction outcome and structural organization of the solvent.

We also employed DES to obtain supramolecular gels.[4,5] In particular, we characterized gels comprising L-aminoacids and the DES formed by choline chloride and phenylacetic acid.

These gels showed good rheological properties and proved to be efficient and recyclable sorbents for the removal of cationic dyes from water. Finally, supramolecular eutectogels proved efficient non-conventional reaction media for C-C forming reactions like aldol and Michael reactions.

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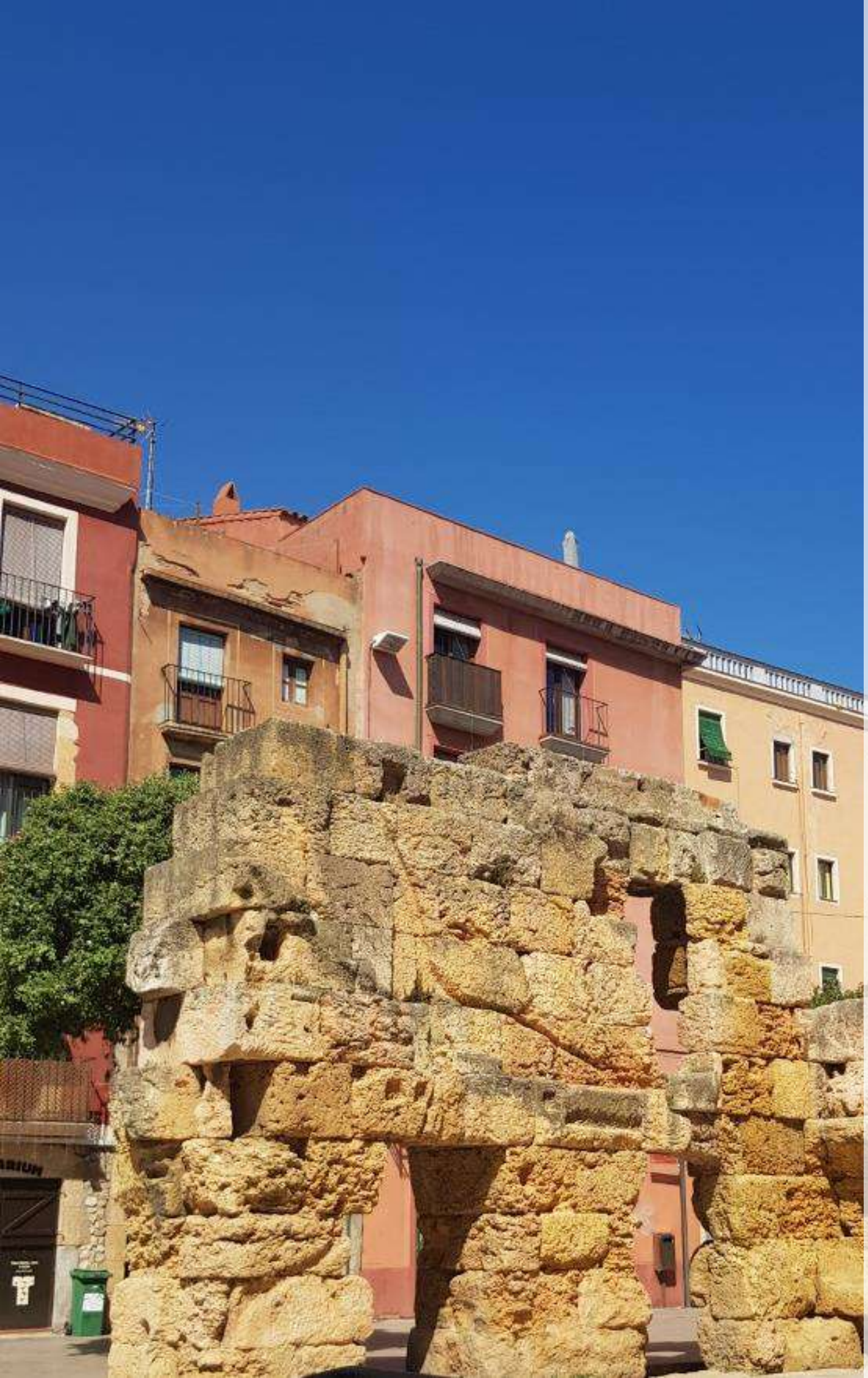

OC

Oral Communications

FUNCTIONALIZATION OF SP^3 C–H BONDS VIA INTERRUPTED NICKEL CHAIN-WALKING CATALYSIS

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While originally designed to control the topology of polymers, catalytic chain-walking reactions have recently offered new reaction pathways for forging carbon-carbon bonds at previously unfunctionalized *sp*^{3} C–H sites by formally translocating the metal catalyst throughout the alkyl side-chain.[1] Among multiple transition metals amenable for this strategy, nickel catalysts offer unique one- and two-electron manifolds to unravel novel retrosynthetic disconnections. Despite this advances, nickel-catalyzed chain-walking reactions are predominantly dictated by steric or electronic effects among the alkyl chain, with functionalization occurring either at its terminal position or adjacent to a stabilizing group.[2,3] Here, rather than using auxiliary augmented strategies,[4] a novel nickel-catalyzed site-selective functionalization is presented where simple amides are able to stop the chain-walking process via chelation to access functionalization at new *sp*^{3} C–H sites. Depending on the reaction conditions, a 5- or 6-membered ring nickelacycle can be favoured to forge C(*sp*^{3})-C(*sp*^{3}) bonds using activated alkylamines as electrophiles. This strategy, applicable to both terminal and internal alkenes, was found to be compatible with common organic functional groups, and overall pictures a distinct all-alkyl retrosynthetic disconnection difficult to access by other means.

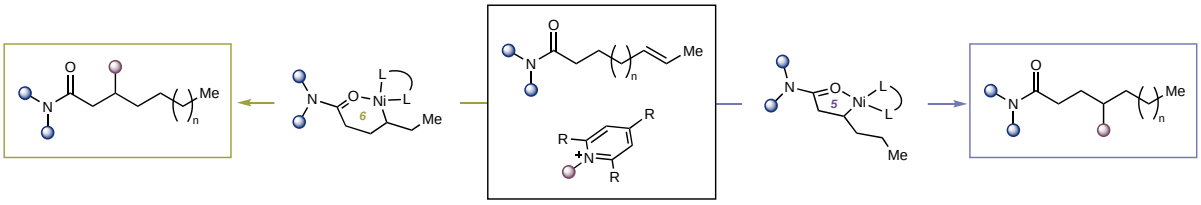

Figure 1. Site-selective alkylation of *sp*^{3} C–H bonds via nickel chain-walking catalysis

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COPPER PHOTO-CATALYZED GENERATION OF GLYCOSYL RADICALS FOR SELECTIVE ADDITION TO ELECTRON-POOR DOUBLE-BONDS; AN ACCESS TO C-GLYCOSYL AMINO ACIDS FOR GLYCOPEPTIDES SYNTHESIS

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Herein we present the selective addition of glycosyl radical to dehydroalanine analogues to afford high valuable C-glycosyl amino acids promoted by an affordable copper photocatalyst. C-Glycosyl peptides are well-known mimics of the native glycoproteins; they differs from these last ones for stable C-C linkages instead of O/N-C bonds, that make them more metabolically stable and suitable for therapeutical purposes[1]. C-Glycosyl amino acids can be employed in this regard to instal sugar fraction on the target peptides and proteins; thus, operational simple protocol to access these compounds is always welcomed. Inspired by literature on stoichiometric and catalytic generation of glycosyl radical to form C-C bond with electron-poor olefins[2,3], we envisaged the possibility to exploit photo-catalysis to generate the glycosyl radical which could be sequestered by electron-poor bis-BOC protected dehydroalanine derivates affording the resulting protected C-Glycosyl amino acids. We optimized the reaction condition screening different photocatalysts, solvents and reductants/additive. Cheap and easily to prepare Copper complex, shown in Scheme 1, has been found to afford the desired products in up to 100 % of yield (12 examples) in Water/EtOH mixture.

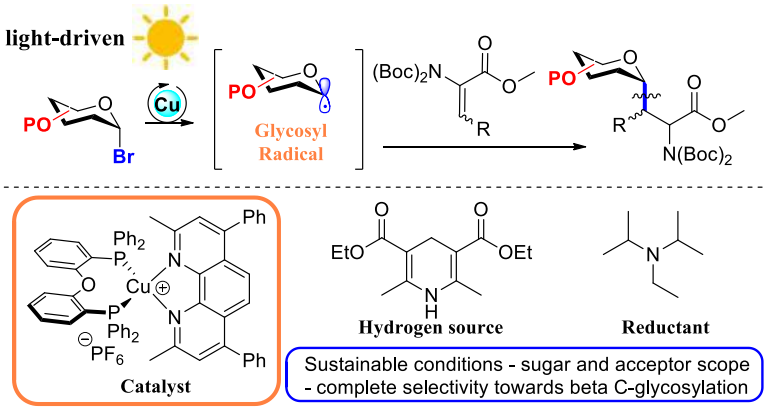

Figure 1. addition of glycosyl radical to dehydroalanine analogues promoted copper photocatalyst.

The scope extension has been investigated varying the sugars, protecting groups and the electrophile. Furthermore, photophysical measurements have been performed to investigate the redox quenching and the mechanism.

Acknowledgements

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ASSEMBLY OF DECALIN SKELETONS VIA GOLD(I)-CATALYZED POLYENYNE CYCLIZATION

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The potential of cascade polyenyne cyclization has been demonstrated to be an efficient way for the construction of molecular diversity.[1] Our group reported the gold(I)-catalyzed cyclization of polyenynes for the construction of up to four C–C bonds and applied it to the synthesis of steroid derivatives.[2] Now, we have focused on the development of a new methodology for the assembly of decalin skeletons via gold(I)-catalyzed dienyne cyclization of tetrasubstituted silyl enol ethers in a stereodefined manner. This methodology has led to the formation of building blocks for the synthesis of different natural products such as avarone and avarol, and related compounds.

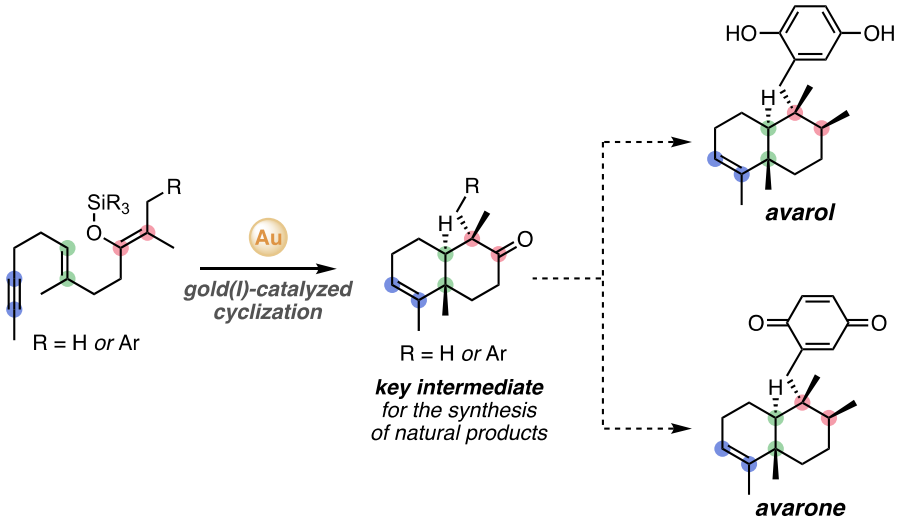

Figure 1. Construction of decalin derivatives by cyclization of dienynes.

Acknowledgements

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RADICAL CYCLOADDITION REACTIONS OF VINYLINDOLES UNDER VISIBLE LIGHT PHOTOREDOX CATALYSIS

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Transformation of simple indoles into (polycyclic) complex scaffolds has become the object of intensive studies in synthetic organic chemistry due to ubiquitous occurrence of indole core in the structure of relevant molecules.[1] In particular, catalytic-promoted manipulation of indoles have become an incomparable tool to increase indole structural complexity working under exceedingly mild conditions and in a regio- and stereo-controlled fashion.[2] In this context we reported in the last years the synthesis of complex carbazole and cyclohepta[b]indole derivatives through (4+2) and (4+3) cycloaddition reactions of vinylindoles under gold catalysis or metal-free conditions.[3] Taking into account these premises, this oral communication will deal with our recent achievements in the field of cycloaddition reactions involving vinylindoles as 4π systems. In particular, we have investigated a radical cation Diels-Alder reaction between vinylindoles and neutral alkenes that proceeds under visible light photoredox catalysis. The results obtained in this work will be discussed in the context of our investigations on catalytic manipulation of indole-based systems.

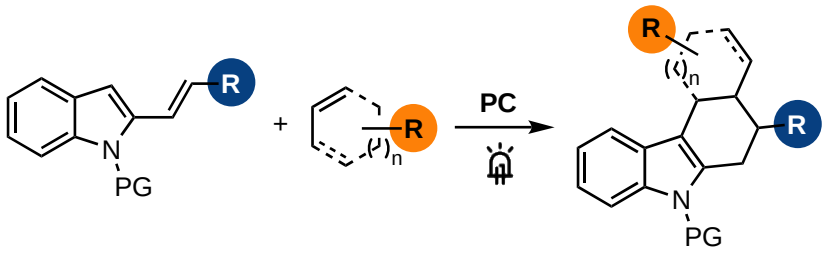

Figure 1.

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PD NANOPARTICLES SUPPORTED ONTO CATECHOL-FUNCTIONALIZED CARBON NANOTUBES: A RECYCLABLE CATALYTIC SYSTEM FOR THE HECK REACTION

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The well-known properties of carbon nanotubes (CNTs), such as high chemical and thermal stability, mechanical strength, and excellent electrical and thermal conductivity, are responsible for their widespread diffusion in a plethora of fields. However, the low processability of pristine CNTs, which are poorly dispersible in most media, is the first obstacle to overcome in order to enhance their potential of use. This lack of solubility/dispersibility can be circumvented by means of covalent functionalization of CNTs or their noncovalent interactions with various functional molecules/polymers.[1] Although the latter method guarantees the retention of the π-conjugated system of CNTs while safeguarding their native properties, the weak interactions involved could give rise to nanocomposites that suffer from poor stability. Therefore, the covalent functionalization method represents the suitable alternative to enhance the stability of CNTs-based hybrids. However, among the non-destructive functionalization methods, self-polymerization of dopamine (2-(3,4-dihydroxyphenyl)ethylamine) to generate a polydopamine (PDA)[2] coating onto the surface of CNTs represents a very powerful approach to considerably expand their application fields. The strong adhesion properties of dopamine arise from the presence of catechol moieties that under oxidative conditions can generate *o*-quinone derivatives, which in addition to the self-polymerization process, can undergo to further reaction with various functional groups, i.e. amines or thiols, by means of Michael addition or Schiff base reaction.[3] Given the great research interest aroused by CNTs-based composites, herein the direct introduction of catechol moieties, which can serve as anchoring points of further functionalities, onto the CNTs sidewalls is reported.[4] This approach could represent a valuable alternative to PDA coating, paving the way to further applications of such hybrid materials in other fields such as heterogeneous catalysis.[5] The reaction of multi-walled carbon nanotubes (MWCNTs) with an *in situ* generated diazonium salt,[6] arising from the reaction between 4-aminocatechol and

isoamyl nitrite, was chosen as convenient and highly efficient method for the functionalization of MWCNTs. The as-prepared MWCNT-catechol hybrid showed a good dispersibility in water and other polar solvents such as methanol, ethanol, and *N*,*N*-dimethylformamide, proving the enhanced hydrophilicity upon functionalization. MWCNT-catechol hybrid was used as support to deposit Pd(II) ions exploiting the metal ion binding ability of the catechol moieties.[7] The subsequent reduction with $NaBH_4$ gave rise to the formation of Pd nanoparticles (NPs). The so-obtained MWCNTs-catechol-Pd material was used as recyclable catalyst (up to 9 cycles) in the Heck reactions between methyl acrylate/styrene and aryl iodides (**Figure 1**).

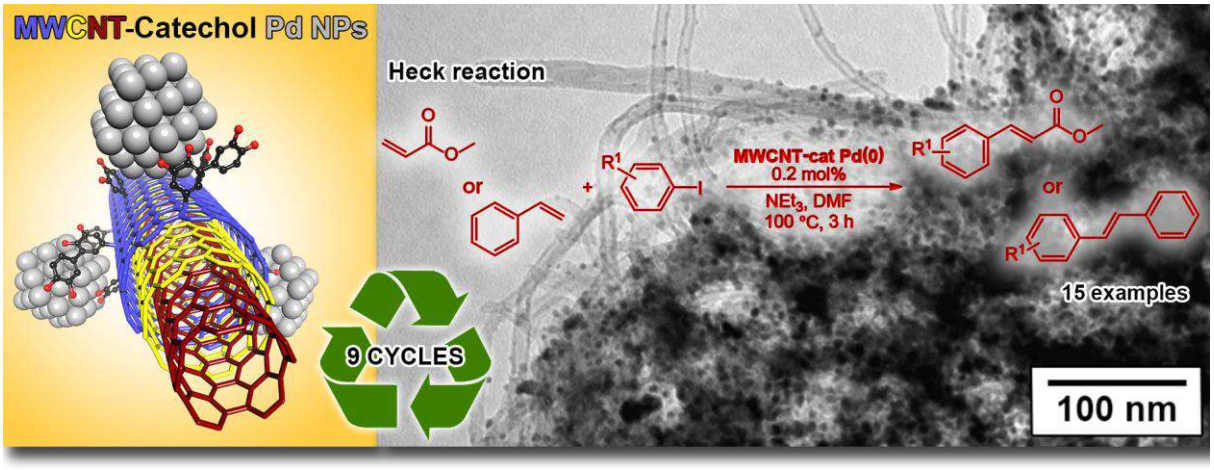

Figure 1. Graphic illustration of the prepared catalytic system (MWCNTs-catechol-Pd) and its use in the Heck reaction.

Acknowledgements

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ANTIBACTERIAL ACTIVITY CONTROL USING VISIBLE LIGHT

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Antibiotic resistance is an increasing concern worldwide. Accumulation of antibiotics in the environment increases the evolutionary pressure on microorganisms, which evolve and adapt at a great pace. Moreover, the number of new antibiotic classes entering the pipeline has been alarmingly low during the last decades.[1] Although new antimicrobials are still needed, a change of paradigm on how we fight bacterial infections is on high demand as new drugs are bound to suffer from the emergence of resistances as well.[2] On this regard, gaining the ability to switch drugs ON and OFF offers a unique opportunity to avoid the release of active drugs into the environment, thus reducing the chances of resistance arising and disseminating. In particular, visible light can be used as a clean and harmless stimulus to modulate the shape of a molecule and thus, its biological profile.

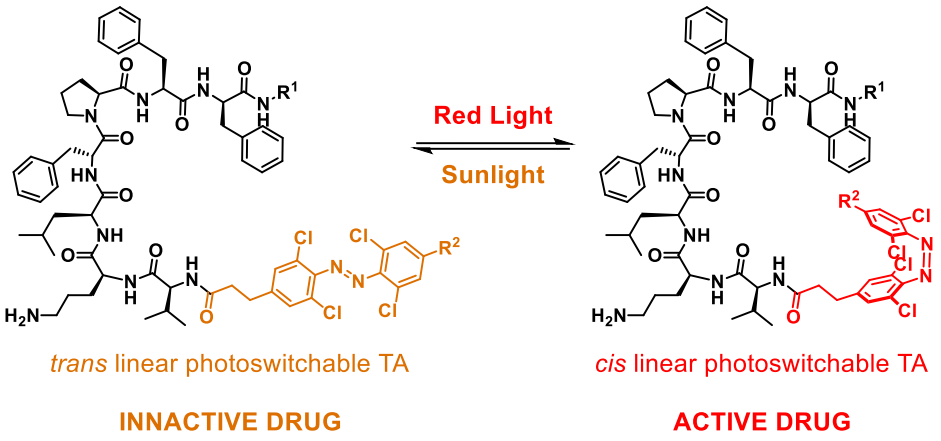

Figure 1. Visible light-photoswitchable linear tyricidine A analogues.

The introduction of a novel tetra-*ortho*-chloroazobenzene amino acid (CEBA) has allowed us to modulate the antimicrobial activity of tyrocidine A analogues using exclusively visible light, granting spatiotemporal control under benign conditions (Figure 1).[3] Compounds bearing this photoswitchable amino acid become active upon irradiation with red light, but quickly turn off upon exposure to other visible light wavelengths. Critically, sunlight quickly triggers isomerisation of the red light-activated compounds into their original *trans* isomer, offering an ideal platform for self-deactivation upon release into the environment. We found that linear analogues of tyrocidine A provide the best photocontrol of their antimicrobial activity, leading to compounds active against *Acinetobacter baumannii* or *Streptococcus pyogenes* only upon isomerisation.

Acknowledgements

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FLOW MICROREATOR TECHONOLOGY AS UNIQUE TOOL FOR THE GENERATION AND USE OF (HIGHLY) REACTIVE ORGANOLITHIUM REAGENTS

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The advent of flow chemistry represented a tremendous novelty in the way of thinking and performing transformations in organic synthesis.[1] Flow microreactor technology allowed the refining of various synthetic methodologies offering the possibility to explore transformations impossible to run using batch methods.[2] In this contribution, our recent efforts on the use of flow microreactor technology for the genesis and use of short-lived organometallic intermediates will be described. Specific attention will be attributed to the development of new fluoroalkylation strategies exploiting fluorinated lithium carbenoids [3, 4, 5]. Indeed, we, recently, merged our long-lasting interests in fluorine chemistry and flow microreactor technology reporting an external quenching method based on flow microreactors which allows the generation and use of short-lived fluoro-substituted methyllithium species, such as fluoromethyllithium, fluoroiodomethyllithium, and fluoroiodostannylmethyllithium.[6] In this report, we further demonstrated the potential of flow microreactor technology in fluoroalkylation chemistry by reporting the generation and use of secondary Li/F carbenoids. A detailed study on the stability and reactivity of these unprecedented highly reactive intermediates will be reported. Furthermore, the advantages of flow microreactor technology in taming other lithiated short-lived intermediates will be reported. [8, 9, 10]

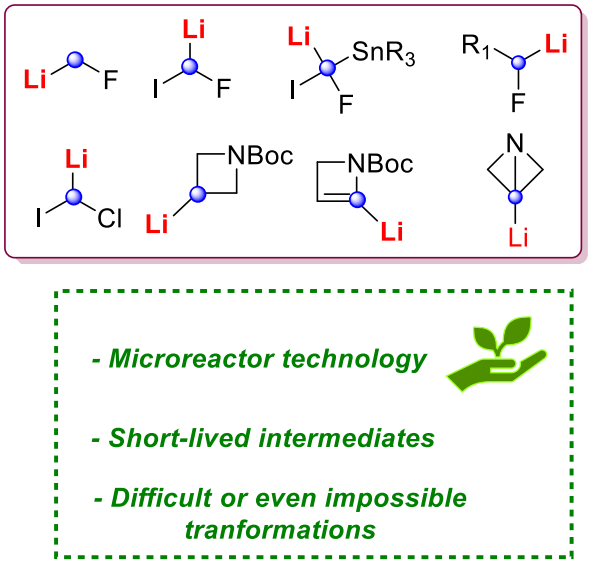

Figure 1. Flow microreator technology for the genesis and use of short-lived organolithium reagents.

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BRØNSTED ACID CATALYZED ENANTIOSELECTIVE TRANSANNULAR (3+2) CYCLOADDITION OF CYCLOALKENONE HYDRAZONES

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Highly functionalized 1,3-diamine fragments have demonstrated to be useful in medicinal chemistry not only because they are important structural motifs present in many natural products, but also because they serve as linkers and binding elements.[1] Moreover, these compounds are mostly constituted by polycyclic scaffolds, whose synthesis has always remained as a big challenge for synthetic organic chemists. For this reason, several transannular approaches have been recently developed as an alternative to the commonly used cyclization or cycloaddition reactions, showing in all cases an efficient control on the generated stereocenters.[2]

Therefore, we present herein the use of cycloalkenone hydrazones, derived from the corresponding cycloalkenones, as model substrates that can undergo enantioselective transannular (3+2) cycloaddition under BINOL-based chiral Brønsted acid catalysis. This methodology provides tricyclic scaffolds with a bridging hydrazine moiety, which can be easily converted into stereodefined decalin- or octahydro-1*H*-indene derived 1,3-diamines through reductive N-N cleavage and therefore, showing to be an efficient and straightforward manner to access *cis*-1,3-diamine-substituted bicyclic motifs (Figure 1).[3]

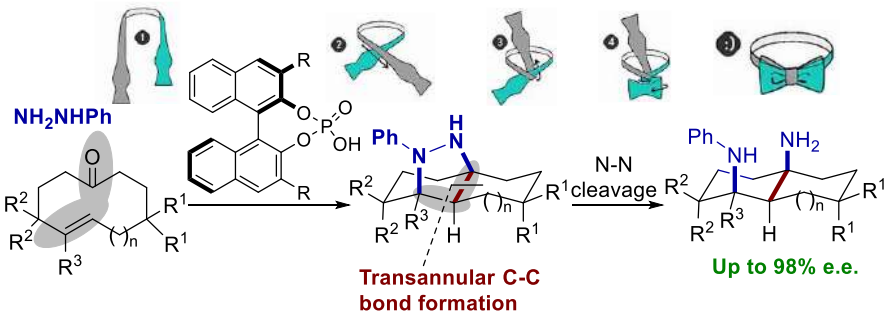

Figure 1. Enantioselective transannular (3+2) cycloaddition reaction.

Acknowledgements

This research was supported by the Spanish Ministerio de Ciencia, Innovación y Universidades (MCIU) through projects FEDER-PID2020-118422-GB-I00, FEDER-PID2019-109674-GB-I00 and FPI fellowship to J.S. and by the Basque Government (IT908-16). J.S. acknowledges the Spanish MCIU for an FPI fellowship.

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Flash Communications

STAPLED *o*-OPEs AS VERSATILE SCAFFOLDS FOR SINGLE-MOLECULE AND SPIN POTENTIOMETERS

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Development of increasingly miniaturized electronic devices is a growing area as it opens the possibility of studying nanoscale electronic circuits. In this context, molecular electronics is the field of science that studies the electron transport phenomena at the scale of one individual molecule. A wide variety of molecular bridges have been recently described and they can be useful as different electronic components such as wires, transistors, switches, etc.[1] However, few examples of molecular potentiometers have been reported and, up to now, most of them have low or moderated modulation factors. On the other hand, spintronics is a field focused on the design of compounds capable of working as spin filters. In this way, the electron spin could be used as an additional variable in electron transport control, improving information storage, processing and even encryption. At molecular scale, when the filtering process happens through a chiral organic compound is based on the *chiral-induced spin selectivity* (CISS) effect.[2] Keeping all of these in mind, here we show a new family of stapled foldamers based on *ortho*-oligophenylenethynylenes (*o*-OPEs). These compounds show good electronic properties as potentiometers, improving the features of similar structures found in literature.[3] It is due to the staple, which allows the helix to be stretched but without completely losing its folding. In addition, the use of a chiral staple allows the synthesis of an enantiopure helix, thus making it a spin potentiometer. In this case, we can control not only the intensity of current depending on distance, but also its spin, opening the door to a new and interesting research field.

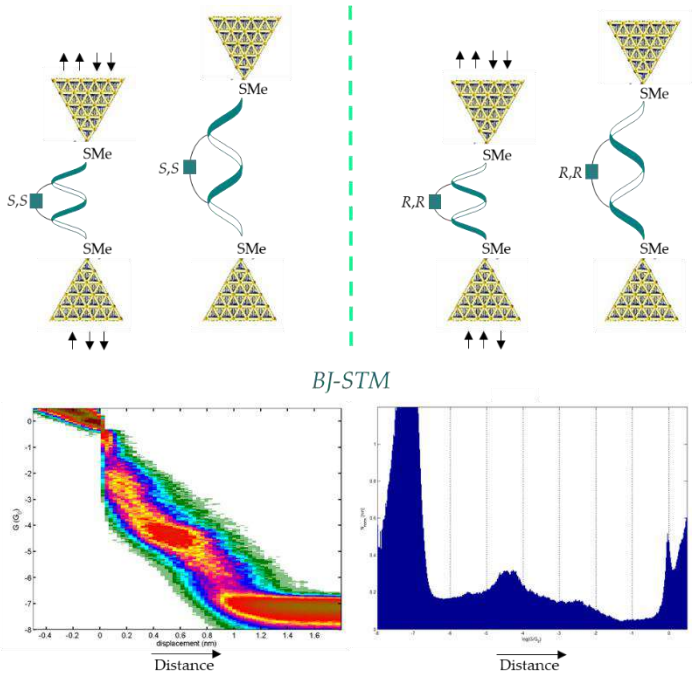

Figure 1. Measurement scheme of both enantiomers by *Break Junction*-STM.

Acknowledgments

We thank the Spanish MINECO for the “María de Maeztu” Programme for Units of Excellence in R&D (grant No. CEX2018-000805-M). L.A.Z. thanks financial support from the Universidad Autónoma de Madrid and the Comunidad de Madrid (grant No. SI3/PJI/2021-00191). J. J. P. acknowledges financial support from Spanish MICINN through Grant No. PID2019- 109539GB-C43, the Comunidad Autónoma de Madrid through the Nanomag COST-CM Program (Grant No. S2018/NMT-4321), and the Generalitat Valenciana through Programa Prometeo/2021/01. We also thank the Ministerio de Ciencia en Innovación (PID2020-113059GB-C21), Junta de Andalucía (P20_00162) and University of Granada (Visiting Scholar Program) for funding and A. O. G. also for her FPU contract. The authors thankfully acknowledge the computer resources, technical expertise, and assistance provided by the Centro de Computación of Universidad Autónoma de Madrid and the high performance computing (HPC) facility at Unisa.

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SELECTIVE OXIDATION OF THIOETHERS TO SULFOXIDES PROMOTED BY KUQUINONE ORGANO-PHOTOCATALYST

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Sulfoxides are bioactive molecules [1] and key intermediates in several organic processes.[2] Their synthesis was classically carried out through oxidation of the corresponding thioethers using strong oxidizing agents.[3] However, selectivity is limited, being over-oxidation products, namely sulfones, obtained often as by-products. More recently, the use of green oxidants, i.e. H_2O_2 or O_2 easily available and safe reagents, has been preferred.[4] Nevertheless, the possibility of using an organic photocatalyst represents a viable strategy to promote sustainable processes. In this work, the use of 1-hexylKuQuinone (KuQ) as metal-free photocatalyst for the selective thioethers oxidation to sulfoxides is proposed (Fig. 1). The broad and intense absorption spectrum in the visible range and the low reduction potential constitute suitable features for photocatalytic applications of KuQ.[5]

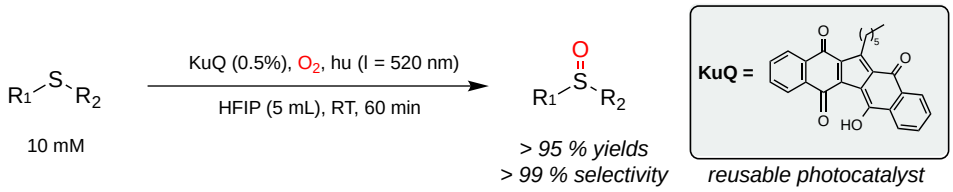

Figure 1. Thioethers photooxidation promoted by KuQ metal-free photocatalyst.

The light-induced oxidation process is promoted by visible light (green LED, λ = 520 nm). Reactions performed in 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP), using O_2 as oxidizing reagent, at room temperature, with 0.5 % KuQ lead to complete thioethers selective oxidation to sulfoxide in 60 minutes. Remarkably, the system can be recharged and recycled without loss of activity and selectivity, reaching turn-over number (TON) higher than 4000.

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KINETICALLY CONTROLLED CARBOXYLATION OF SECONDARY ALKYL BROMIDES THROUGH DUAL PHOTOREDOX AND NICKEL CATALYSIS

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Synthesizing aliphatic carboxylic acids has undergone substantial synthetic innovation from early methods requiring stochiometric amounts of harsh, organometallic reagents. Modern methods of metal-catalyzed reductive carboxylation reactions of organic halides with carbon dioxide feedstocks have shown to be particularly desirable as they offer mild and site-selective methods to these precursors [1]. Beyond their improved compatibility, these reactions offer new synthetic design strategies to forge motifs which are abundant in pharmaceutically relevant molecules. Notable advances have been made in nickel-catalyzed reactions with alkyl halides and carbon dioxide that functionalize the aliphatic chain at the site where nickel is most thermodynamically stable, irrespective of the initial site of the alkyl halide. These methodologies have been developed by mean of both stoichiometric heterogenous and photocatalytic homogeneous reductants. “Chain-walking” type mechanism explains the results obtained in such reports [2,3].

As elegant as those methodologies are, there is to this day still a lack of possibilities when it comes to internal functionalization of unactivated aliphatic sites, standing as the “last missing piece” of the alkyl halide carboxylation arena. Therefore, in realizing such a goal, we investigated a protocol that allows for the *ipso*-carboxylation of unactivated alkyl bromides (Figure 1). The ligand choice and homogeneous environment proved critical for the success of this method.

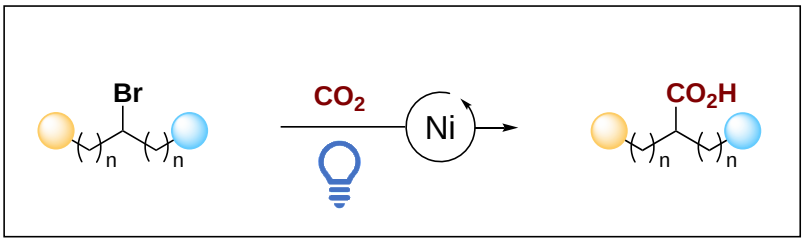

Figure 1. General Scheme of the Method.

Acknowledgments

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SYNTHESIS OF PHOTORESPONSIVE CALIX[6]ARENE-BASED ORIENTED ROTAXANES

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This work had the aim to disclose a new strategy for developing novel devices and materials endowed with programmable photoresponsive properties. Recently, stilbazolium salts were explored as a new class of photoresponsive components for the synthesis of oriented pseudorotaxanes. In a previous work, it was evidenced that a calix[6]arene-based wheel[1] can bind, in non-polar media, a stilbazolium salt to yield a mixture of pseudorotaxane orientational isomers.[2] The ratio of these isomers is not fixed, and it can be reversibly tuned by changing the temperature and the solvent. The two orientational isomers experienced spectroscopic properties depending on the orientation of the axle inside of the non-palindromic wheel.

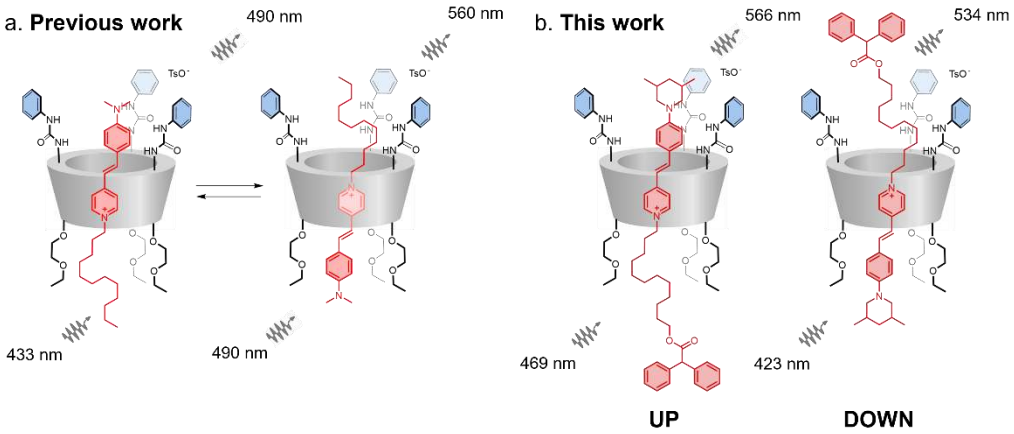

Figure 1. a. calix[6]arene-based orientational pseudorotaxanes;[2] b. rotaxane orientational isomers **UP**, and **DOWN**.

The synthesis and the spectroscopic studies of two oriented rotaxanes will be reported (**DOWN** and **UP** in Figure 1). Our results demonstrate that not only the confinement of a guest but also its orientation inside the host can be employed as tools to tune the spectroscopic properties.

Acknowledgements

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NEW COBALT CATALYSTS FOR CYCLIZATION REACTIONS

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Sustainability, availability, and economical concerns have made first row transition metal catalysts an increasing field of research.[1] These first-row transition metals are less reactive than their second and third row counterparts and require an important investment in ligand design to achieve competitive efficiency. Here we present a new family of tripodal ancillary ligands (Figure 1) that assist the catalytic power of cobalt, a highly abundant first row transition metal. These ligands present for the first time both encumbering and electron withdrawing properties. This design increases the stability of low oxidation states once the ligand is coordinated to cobalt.

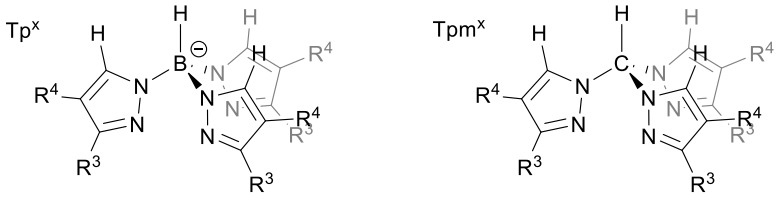

Figure 1. New ligands prepared

Here we demonstrate the usefulness of these new catalysts in cyclization reactions.[2] The cyclization reactions assayed occur with an excellent performance using low catalyst loading and small amounts of reducing agent.

Acknowledgements

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LEVERAGING AMINOALKYL RADICALS FOR THE MODULAR ENGAGEMENT OF ORGANIC HALIDES IN REDOX CHEMISTRY

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The emergence of (photo)redox catalysis has enabled the development of new methodologies that generate highly reactive radicals under mild conditions [1]. Notwithstanding, the general and reliable generation of carbon radicals from inactivated alkyl and aryl halides remains an unsolved problem in redox chemistry, in view of their often inaccessible SET reduction potentials (E_{red} < –2 V vs SCE) [2]. In fact, nowadays synthetic chemists still rely on the same systems based on halogen-atom transfer (XAT) developed more than 40 years ago to engage organic halides in radical transformations, sometimes underutilized due to the acute toxicity (e.g. tributyltin hydride) or hazards (e.g. explosive initiators) associated to the reagents employed. We have recently demonstrated how simple amines (e.g. triethylamine), some of the cheapest and most common reagents present in any synthetic lab, can be used as surrogates of tributyltin hydride for the homolytic activation of carbon-halogen bonds [3-4]. Aminoalkyl radicals, easily generated under thermal or photochemical conditions from amines, can be engaged in kinetically-favored polarized XAT processes providing effective access to alkyl and aryl radicals. The utility of this strategy has been showcased in a wide range of redox transformations allowing the construction, with high chemoselectivity, of sp^3–sp^3, sp^3–sp^2 and sp^2–sp^2 carbon–carbon and Csp^3–N bonds under mild conditions, opening a new gateway for the modular use of alkyl and aryl halides in (photo)redox and radical chemistry.

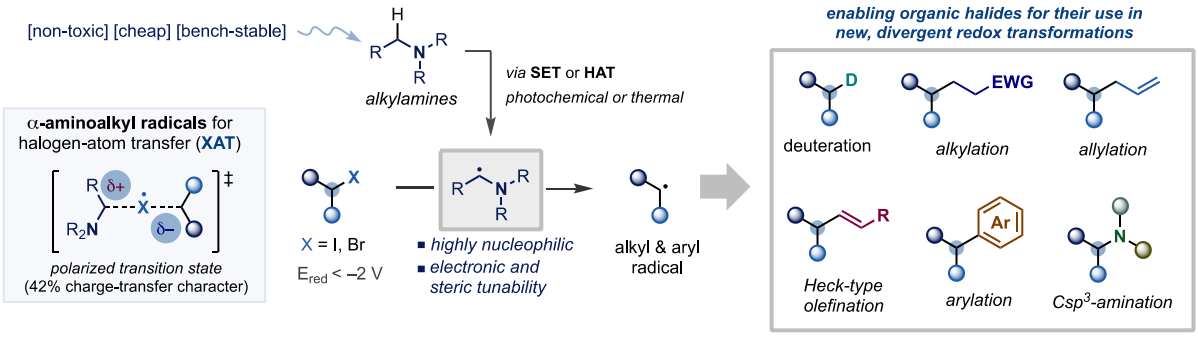

Figure 1. XAT with aminoalkyl radicals for the utilization of organic halides in redox settings

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FC-07

TOTAL SYNTHESIS OF DAUCANE NATURAL PRODUCTS

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Our group recently reported a gold(I)-catalyzed approach for the synthesis of complex hydroazulenes,[1] which are related to the daucane family of sesquiterpenes and related natural products. Taking advantage of this new methodology, the gold(I)-catalyzed cycloisomerization/cycloaddition cascade gives rise to a common intermediate 5/7-bicyclic skeleton, which can be later converted into different naturally-occurring compounds such aspterric acid, penigracid A and schisanwilsonene A (Figure 1).[2] Progress towards these synthetic goals will be presented.

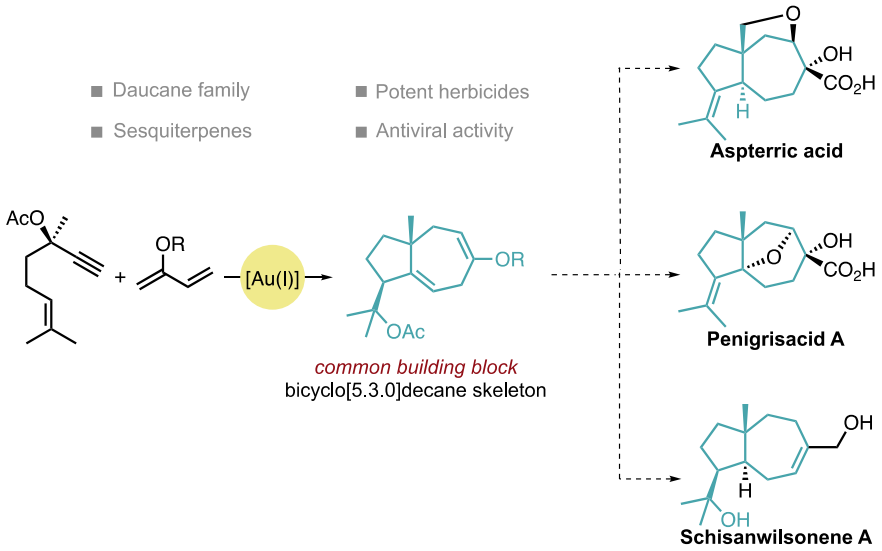

Figure 1. Gold(I)-catalyzed cycloisomerization/cycloaddition cascade for the synthesis of the common building block

Acknowledgements

We thank the MCIN/AEI/10.13039/501100011033 (PID2019-104815GB-I00, CEX2019-000925-S), Horizon 2020 Marie Skłodowska-Curie COFUND grant agreement (No 801474), the ERC (Adv. Grant 835080), the AGAUR (2017 SGR 1257), and CERCA Program/Generalitat de Catalunya for financial support.

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Pd-CATALYZED CARBONYLATION FOR THE SYNTHESIS OF FUROTHIENOPYRANDIONE DERIVATIVES

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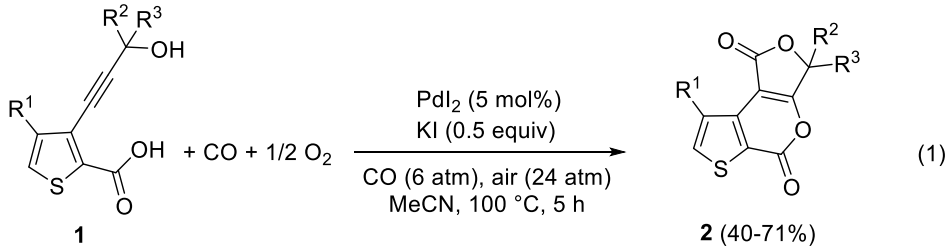
Molecules containing the thiophene core find application in several different fields, in particular as pharmaceutic agents (with antimicrobial,[1] anti-inflammatory,[2] and anticancer activities[3]), as well as key components in materials with optoelectronic properties.[4]

In this contribution, we present a new method for the synthesis of tricyclic heterocycles bearing the thiophene core, as shown in equation 1. The process, which starts from readily available 3-(3-hydroxyprop-1-yn-1-yl)thiophene-2-carboxylic acids **1**, is promoted by the PdI_2/KI catalytic system[5] and corresponds to an oxidative carbonylative double cyclization reaction.



1 **2** (40-71%) (1)

The high value added 1*H*-furo[3,4-*b*]thieno[3,2-*d*]pyran-1,5(3*H*)-dione derivatives **2** were obtained in good yield in one step and in a multicomponent fashion, working under relatively mild conditions (100 °C in MeCN for 5 h, under 30 atm of a 4:1 mixture of CO-air).

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MODIFIED PHOSPHOLIPIDS SUITABLE FOR INCORPORATION INTO LIPOSOMES FOR TREATMENT IN NEUROLOGICAL DISORDERS

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Current treatments of some brain disorders are suboptimal, due to limited access of biologically active compounds through the blood-brain barrier (BBB). Searching for more efficient therapies for Alzheimer's disease and Glioblastoma, our aim focused onto the rational design of innovative constructs to be included in suitable nanovectors for drug delivery to the brain [1], as well as to the construction of imaging-friendly liposomes suitable for diagnostics [2].

More specifically, matrix metalloprotease (MMPs) enzymes are over-expressed in several types of brain cancer, where their ability to degrade the extracellular matrix leads to metastasis; and are causative factors in the progression of some neurodegenerative diseases [3]. Thus, hybrid constructs (HYB) made of a phospholipid and a lipopeptide sequence recognised by MMP2 and/ or MMP9 were evaluated for their ability to self-assemble with natural phospholipids and cholesterol; then, assembled HYB-containing liposomes loaded with neuroactive drugs were tested for their bioavailability and disassembly in absence and presence of MMPs. As a result, we confirmed their nature as enzyme-triggered liposomes.

Furthermore, the insertion of a triple bond on the polar head of phospholipids led, after its characterization and assembly into liposomes, to nanoobjects suitable for diagnostics via a click chemistry approach – liposome functionalization with PET reagents, fluorescent molecules, etc [4].

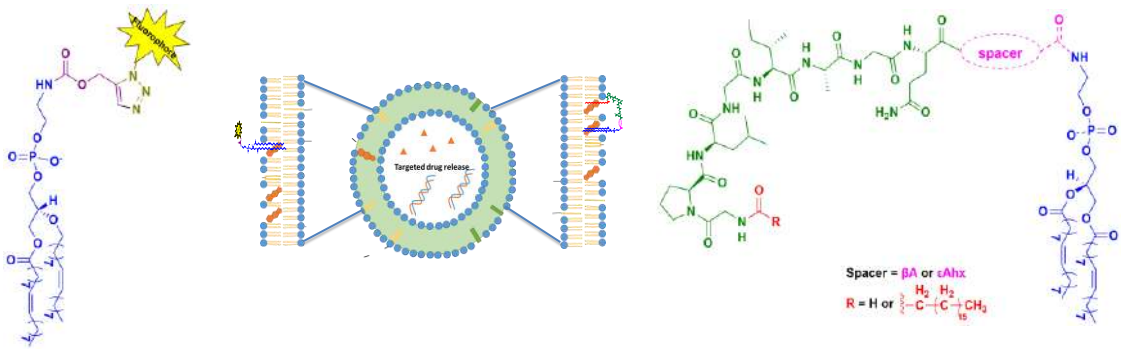

Figure 1. General structures of diagnostic-targeted phospholipids (left) and DOPE-MMP2/9-specific phospholipid-peptide hybrids (right).

Acknowledgements

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ENANTIOSELECTIVE MICHAEL ADDITIONS TO A,B-UNSATURATED ALDEHYDES

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The stereoselective formation of carbon-carbon bonds represents an important challenge in the field of Organic Synthesis. In this context, Michael additions hold a prominent position amongst the few reactions that allow these types of transformations although the regioselectivity of such reactions with α,β-unsaturated carbonylic compounds (1,2 vs 1,4 additions) becomes a serious hurdle in the development of new procedures, to the point that there are hardly examples of stereoselective Michael additions to α,β-unsaturated aldehydes. [1-2].

Therefore, the regioselectivity as well as stereochemical control on Michael additions to α,β-unsaturated aldehydes are remarkable concerns of these transformations. Regarding all the possible ways to control the stereochemical outcome, the asymmetric catalysis has recently become the preferred option since it allows the obtention of the chiral product avoiding the use of stoichiometric chiral reagents, which enhances the atom economy of the process.

Keeping in mind all the ideas, we have striven to develop a methodology for enantioselective Michael reactions from *N*-acyl thiazinanethiones with activated α,β-unsaturated aldehydes catalysed by chiral Ni(II) complexes [3]. Facing the above-mentioned challenges, we have successfully obtained exclusively the 1,4-addition adduct with both *syn* and *anti* configurations with high diastereoselectivities and excellent enantioselectivities. In addition, we have demonstrated that this methodology accepts a wide variety of aromatic α,β-unsaturated aldehydes as well as shows a good tolerance to functional groups such as esters and alkynes (Figure 1).

In summary, we have developed a highly regioselective, chemoselective, and stereoselective Michael additions that give access to the four potential stereoisomers in an enantiomerically pure form in high yields.

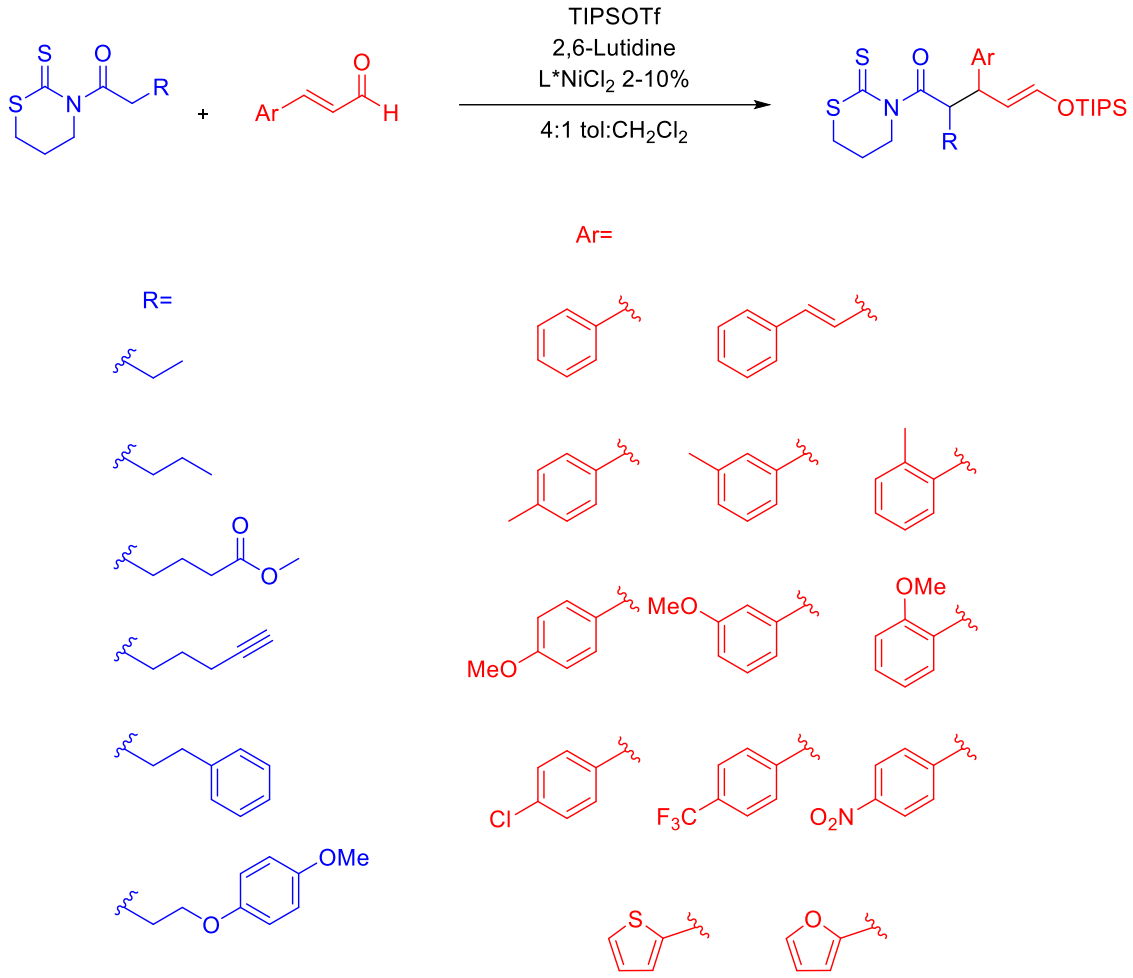

Figure 1. Enantioselective Michael addition

Acknowledgements

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COPPER(II) TRIFLATE AS AN EFFICIENT CATALYST FOR ARYLATION/HYDROAMINATION OF ALLYL ALCOHOLS

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In the last years, hydroamination procedures of non-activated carbon-carbon double bonds have received significant attentions to access fine chemicals or building blocks in organic synthesis. Among the various transition-metal catalysts usually employed to achieve C-N bond formation, copper(II) salts and complexes - such as copper(II) triflate - were proven to be highly performing.[1] Moreover, recent studies have shown that metal triflates can be used also for the *in situ* generation of triflic acid which could be exploited in reactions involving carbocation intermediates.[2]

Following our interest toward hydroamination procedures,[3] we developed a copper(II) triflate-promoted decarboxylative arylation/hydroamination of *O*-allyl *N*-tosyl carbamates in the presence of aromatic compounds providing 1-arylpropan-2-amines.[4] Recently, we investigated a more efficient method to synthesize the same kind of products by treatment of easy accessible allyl alcohols as C3 synthons, sulfonamides, and aromatic partners with $Cu(OTf)_2$ in catalytic amount (Figure 1). The copper-catalyzed process is greatly enhanced by the presence of a phosphine ligand which makes milder the reaction conditions.

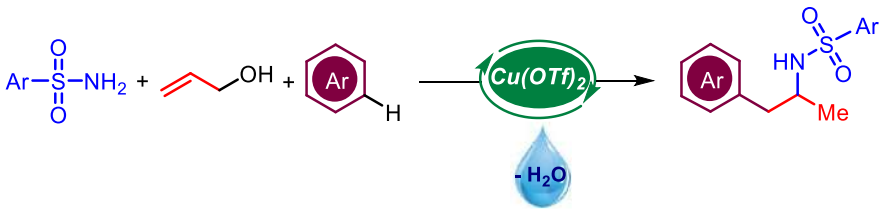

Figure 1. Copper(II) triflate catalysed arylation/hydroamination procedure

The detailed mechanism for this C-H based cascade reaction will be discussed in the communication.

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MAPPING THE ELECTRONIC STRUCTURE AND THE REACTIVITY TRENDS FOR STABILIZED α-BORYL CARBANIONS

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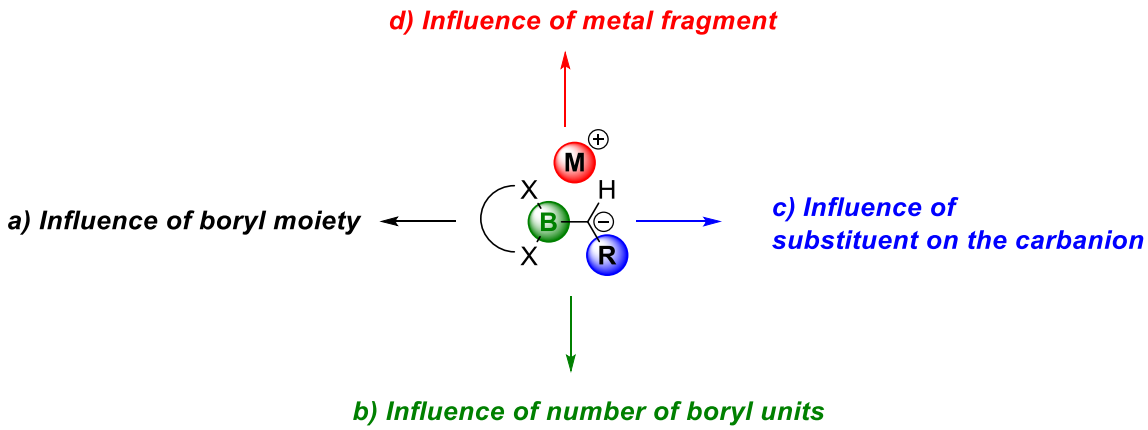
The chemistry of stabilized α-boryl carbanions show a remarkable diversity, and can enable many different synthetic routes towards efficient C-C bond formation.[1] The electron-deficient, trivalent boron center stabilizes the carbanion facilitating its generation and tunning its reactivity. We describe here the electronic structure and the reactivity trends of a large dataset of α-boryl carbanions. We use DFT-derived parameters for capturing their electronic and steric properties, computational reactivity towards model substrates, and crystallographic analysis within the Cambridge Structural Dataset. This study maps the reactivity space by systematically varying the nature of the boryl moiety (Scheme 1a), number of α-boryl motifs (Scheme 1b), the substituents of the carbanionic carbon (Scheme 1c), and the metal countercation (Scheme 1d). This trend map aids the selection of the appropriate reactive synthon depending on the sought reactivity.[2]



Scheme 1. Analysis of structural features influencing the nature of the α-boryl carbanions

Acknowledgements

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FC-14

GLYCOCONJUGATES RECOGNITION BY HUMAN LECTINS

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Lectins occur ubiquitously in nature and are a broad group of non-immunoglobulin proteins with high affinity for carbohydrates but display no enzymatic activity.[1] It is well known that lectins have an important role in the innate immune system, being involved in cell-cell communication, cellular trafficking and regulation of the immune cell functions,[2] thus, making them potential therapeutic agents.

During the last decades the interest focused on bacterial glycoconjugates due to their thigh involvement with the immune system. MAMPs (microbe-associated molecular patters trigger the immune response, being lipopolysaccharides (LPS) one example of MAMP involved in the physical binding between host proteins and microbe.[3] LPS is a heat stable amphiphilic molecule known for being the major component of Gram-negative bacteria outer membrane external leaflet. In its smooth form, LPS is constituted by three different motifs: the lipid A, the core and the O-antigen. Instead, its rough form, also known as lipooligosaccharide (LOS) is characterized by the absence of the O-chain. Historically known as “bad guys” due to the endotoxicity and pathogenic activity of the lipid A, recent studies unveiled the possibility of LPS to act as weak agonists or antagonists, positioning the LPS as an interesting potential drug to target dysregulated intestinal immune response.[4][5]

However, despite the growing interest in investigating the association between host receptor lectins and exogenous glycan ligands, the molecular mechanisms underlying bacterial recognition by human lectins are still not fully understood. For example, we focused our attention on a C-type lectin such as dendritic cell-specific intracellular adhesion molecules (ICAM)-3 grabbing non-integrin (DC-SIGN) and we investigated it in the interaction with different bacterial-derived glycans. Furthermore, insights on glycans recognition by galectins have also been studied, in particular the interaction between Galectin-1 and Galectin-3 and two different synthetically prepared glycoconjugates (Figure 1).

Therefore, here we tackle the important question of host-glycan interaction by using the ligand-based NMR methods like saturation transfer difference NMR (STD NMR) or transferred NOESY (tr-NOESY) among others,[6] combined with other biophysical techniques and computational studies. The combination of such studies allowed to design the epitope mapping of the interaction and the bioactive conformation of the

ligand to porpoise a 3D complex of the interaction between different ligands from synthetic and bacterial origin and lectins.

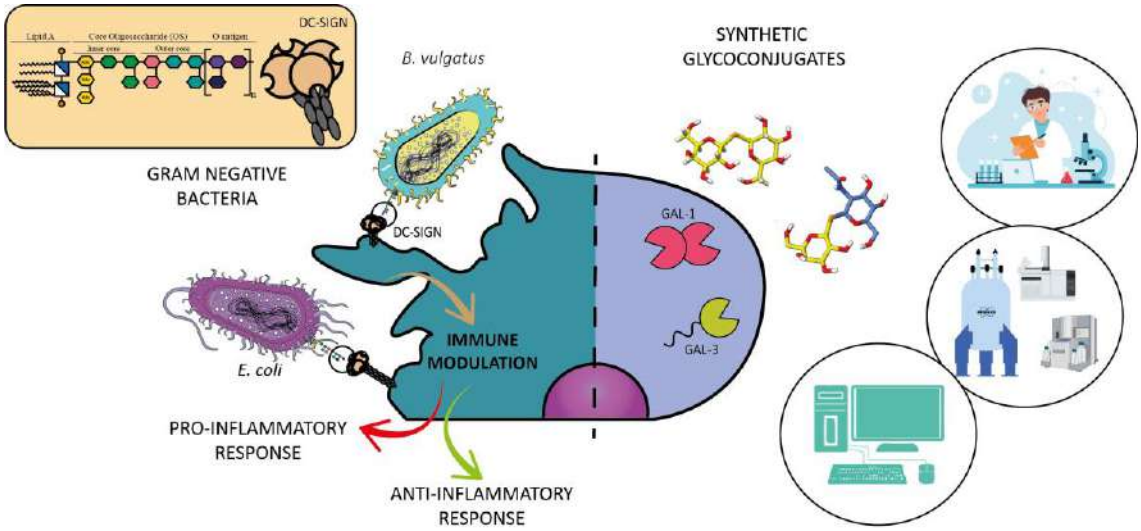

Figure 1. Schematic representation of the recognition of bacterial and synthetic glycoconjugates by lectins being the combination of NMR and other biophysical techniques, the wet lab and the computational calculations the bases of the interaction studies.

Acknowledgements

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CATALYTIC SUSTAINABLE AND SELECTIVE ALLYLATION OF ANILINES BY CARBOXY-IMIDAZOLIUM HALIDES

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Chemists should face the sustainable development that society is demanding, providing the suitable chemical processes. Catalysis, among the 'Green Chemistry' principles [1], must play a key role in this advancement. Aware of that, our research group has focused on the development of catalytic organic syntheses, in the absence of solvents. Thus, metal-organic frameworks (MOF) have been employed, as heterogeneous catalysts under solvent-free conditions, to carry out the synthesis of amides by oxidative coupling [2], and the synthesis of quinoline derivatives [3]. Moreover, catalytic amounts of iron-based imidazolium salts have been employed, under neat conditions, in the preparation of thioamides [4], and in the selective synthesis of quinolines, 2- and 4-allylanilines starting from the same reagents [5]. Moreover, carboxy-functionalized imidazolium halides can be employed as components in the preparation of low transition temperature mixtures (LTTM) in combination with urea [6]. In addition, bis(carboxy)-functionalized halides, which are ionic organic solids (IOS), have been explored as heterogeneous catalysts, being possible to perform reactions without solvents. Indeed, the presence of the functional groups and the counterion proved to be relevant during the catalysis, in the preparation of quinoline and acridine derivatives [7]. These moieties facilitate the interaction between the reactants, allowing the reaction to take place under solventless conditions [8]. In this communication, we present our findings in the development of metal-free catalytic systems for the regioselective allylic substitution of alcohols with anilines. The catalytic systems are based on 1,3-bis(carboxymethyl)imidazolium halides, which are IOS. These organic salts can be easily separated from the reaction mixture by simple filtration, reusing them efficiently afterwards. The study has revealed that the imidazolium counterion plays a crucial role in the regioselectivity of the process, the different salts being complementary in terms of regioselectivity for the allylic substitution of alcohols with anilines (Figure 1). Thus, imidazolium chloride selectively produces the *N*-substitute anilines (21 examples), after 2 h at 80 ºC. The bromide imidazolium provides selectively 2-allylanilines (11 examples), after 24 h at 100 ºC. Finally, the iodide salt forms exclusively the 4-allylaniline regioisomers (16 examples), after 6 h at 80 ºC. Moreover, the alcohol melting thermal event, measured with differential scanning calorimetry (DSC) is modified by the presence of the IOS, due to the favorable interactions.

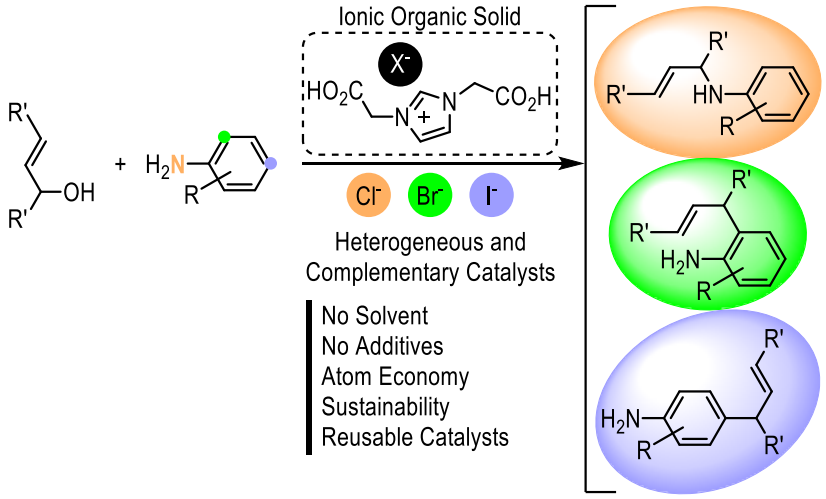

Figure 1. Selective allylation of anilines based on anion-dependent imidazolium catalyst

Acknowledgements

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STRUCTURE AND FUNCTION OF THE ADHESION COMPLEX OF *MYCOPLASMA GENITALIUM* AND *MYCOPLASMA PNEUMONIAE*: TOWARDS THE DEVELOPMENT OF ANTI-ADHESION DRUGS

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Mycoplasma pneumoniae (*Mpn*) is a human pathogen responsible for upper and lower respiratory tract infections [1]. It is estimated that this bacterium is responsible for up to 40% of community-acquired pneumonias in persons of all ages. Remarkably, in contrast to other important respiratory pathogens, a vaccine for *Mpn* is not yet available. On the other hand, *Mycoplasma genitalium* (*Mge*) is a sexually transmitted bacterium that has been implicated in several urogenital pathologies such as urethritis in men and cervicitis and pelvic inflammatory disease in women [2]. Additionally, *Mge* has been associated with preterm birth, spontaneous abortion and HIV acquisition. These two closely related pathogens express cytoadhesins that mediate attachment to sialylated glycan receptors. Recently, we solved the crystal structures of the main cytoadhesins of *Mge* and *Mpn*, both isolated and as complexes with sialylated oligosaccharides [3-5]. This finding allowed us to pinpoint the binding pocket for the neuraminic acid moiety. Molecular recognition knowledge at atomic level is pivotal in the development of new drug design approaches toward new anti-adhesive compounds. NMR spectroscopy is one of the most widely used techniques to detect and characterize at atomic level transient ligand-receptor interactions in solution. In particular, Saturation Transfer Difference NMR (STD-NMR), WaterLOGSY, diffusion- and relaxation-based experiments, together with transferred NOE (tr-NOE) techniques allow, indeed, to investigate the ligand behaviour when bound to a receptor, determining, among others, the epitope map of the ligand and its bioactive conformation [6-8]. In this project, we use different biophysical techniques and computational methods, to establish the molecular basis for sialoglycan recognition and ligand specificity of these bacterial cytoadhesins. The information obtained could be used to identify competitive

binding inhibitors. In this context, the rapid emergence of antibiotic resistance documented in both, *Mpn* and *Mge*, emphasizes the urgency for the development of alternative therapeutic strategies.

Acknowledgements

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SYNTHESES OF HETEROCYCLE-CONTAINING CERAMIDE ANALOGS AND THEIR BIOLOGICAL EVALUATION AS DES1 INHIBITORS

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The view on dihydroceramides (dhCer), generally regarded to be innocuous, changed after the revelation that they might have regulatory roles in biology.[1] In this scenario, dihydroceramide desaturase (Des1) stands out as a new therapeutic target. It catalyzes the formation of a double bond in dhCer to convert it to ceramide (Cer) in the *de novo* synthesis of this sphingolipid. Inhibition of Des1 is expected to cause an accumulation of dhCer, which has been related to cell growth arrest and apoptosis.[2] GT11 is the first, and still the most effective, sphingolipid analogue Des1 inhibitor sphingolipid analog reported to date (Figure 1).[3] The limited number of Des1 inhibitors described until now, as well as the lack of a crystalline structure of the enzyme, has hampered the understanding of their inhibition mechanism. For this reason, the synthesis of new inhibitors is necessary to shed light on this field.

In this communication we will present the syntheses of different ceramide analogues (Figure 1) that maintain all the structural requirements described to date for Des1 inhibition,[4] but incorporating a structurally rigid heterocycle that can stablish additional interactions with the enzyme biding site. Thus, in the proposed compounds, the double bond of ceramide has been formally replaced by a triazole ring (both 1,4 and 1,5-disubstituted regioisomers); a 2,4-disbustituted furan ring, a 2,3-disubstituted cyclopropenone or their derivatives having a shorter *N*-acyl chain to ensure good cell permeability. The evaluation results of these ceramide analogues as Des1 inhibitors will be presented and discussed in the light of docking studies.

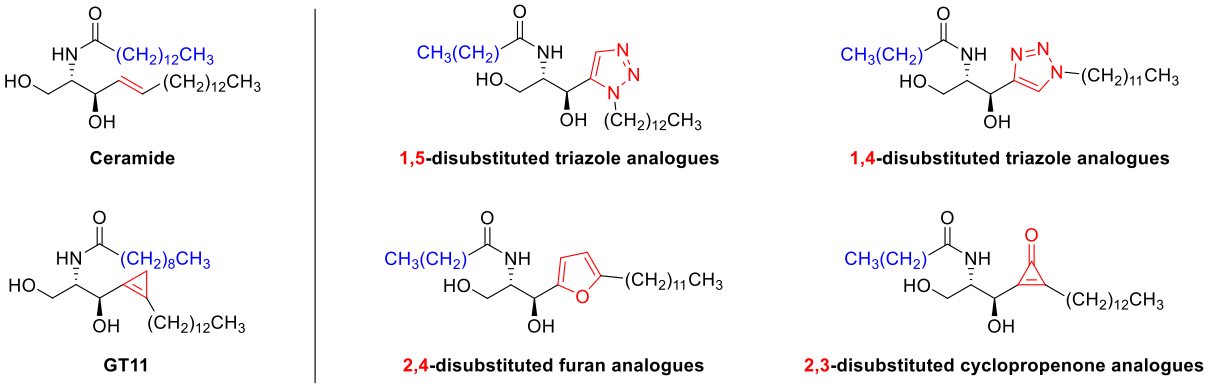

Figure 1. Structure of Ceramide, GT11 and synthesized analogues.

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NON-NATURAL AMINO ACIDS WITH MORPHOLINE CORE AS ORGANOCATALYSTS FOR 1,4 ADDITION REACTION BETWEEN ALDEHYDES AND NITROOLEFINS

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The use of small organic molecules as organocatalysts has been known for more than a century, but only in the past decade has become a thriving area of general concepts and widely application for asymmetric reactions. These substances present many advantages, such as less toxicity, less pollution and more economically viability than the organometallic catalysts that dominated asymmetric synthesis since the early 2000[1]. The success of organocatalysis in the past decade has been the identification of catalyst-mode of activation and reactivity. In particular, many studies have demonstrated how pyrrolidine ring results more reactive than the corrispective piperidine or morpholine analogue[2]. The less reactivity of Morpholino-enamine is explainable by the presence of the oxygen in position 4 of the ring instead of a CH_2 group[3]. Here, we present a new class of organocatalysts with morpholine core, showing excellent selectivity and specificity in 1,4-addition reaction between aldehydes and nitroolefins.
Theoretical computational studies disclosed the transition state of the reaction, explaining why, despite of all the limitations of morpholine core for enamine catalysis, our proposed catalysts actually work affording the desired products in good to exquisite selectivity.

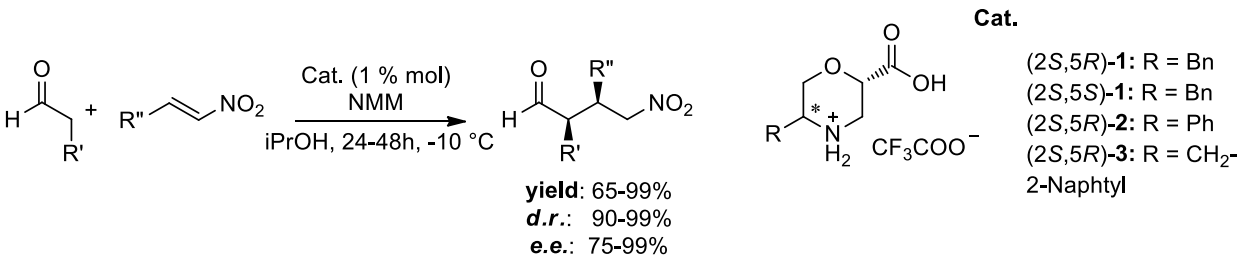

Figure 1. Proposed reaction and chemical structure of the proposed catalysts (2*S*,5*R*)-**1**, (2*S*,5*S*)-**1**, (2*S*,5*R*)-**2**, (2*S*,5*R*)-**3**

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LITHIUM AMIDES PROMOTED CHEMO- AND REGIOSELECTIVE ANIONIC FRIES REARRANGEMENT UNDER AEROBIC CONDITIONS IN SUSTAINABLE REACTION MEDIA

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The anionic *ortho*-Fries rearrangement (A*o*F) represents an interesting protocol for the preparation of salicylamide derivatives. This process arises from the directed *ortho*-metalation (D*o*M) of *O*-aryl carbamates promoted by organolithiums and proceeds in the absence of an external electrophile upon slow warming to room temperature.[1] Strictly reaction conditions, such as low temperatures, dry ethereal solvents and inert atmosphere, are typically required for this transformation. However, the use of Deep Eutectic Solvents (DESs) and cyclopentyl methyl ether (CPME) as sustainable reaction media under simple experimental conditions (room temperature, open air) has been recently reported for organometallics-promoted transformations.[2] Building upon these findings, we have investigated the possibility to promote the A*o*F rearrangement of *O*-aryl carbamates using alkyllithiums and lithium amides under aerobic conditions in CPME and DESs as sustainable reaction media.

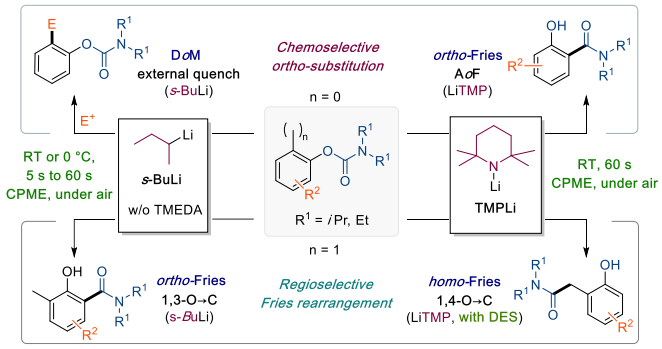

Figure 1. Chemo- and regioselective *O*-aryl carbamate manipulation under aerobic conditions.

Acknowledgements

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SOLUTION-PROCESSABLE OLEDs BASED ON PHOSPHORESCENT K^3-(N^C^C)-GOLD(III) COMPLEXES

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Efficient OLED devices have been fabricated using organometallic complexes of platinum group metals.[1] Still, the high material cost and low stability represent central challenges for their application in commercial display technologies. Based on its innate stability, gold (III) complexes are emerging as promising phosphorescent emitters for high-efficiency OLEDs. However, despite recent advances in the coordination and organometallic chemistry of gold, only few compounds have been successful in high-performance devices. A series of alkynyl-, N-heterocyclic carbene (NHC)- and aryl-gold(III) complexes stabilized by a k^3-(N^C^C) template have been prepared and their photophysical properties have been characterized in detail.[2,3]. These complexes could be accessed easily via ligand exchange or transmetalation reactions from the corresponding gold(III)-halides. Most of the studies compounds exhibit good photoluminescence quantum efficiency (η_{PL}) of up to 33%. The PL emission can be tuned from sky-blue to yellowish green colors by variations on both the ancillary ligands as well as on the pincer template. Further, solution-processable OLED devices based on some of these complexes display remarkable emissive properties (η_{CE} 46.6 $cd \cdot A^{-1}$ and η_{ext} 14.0 %), thus showcasing the potential of these motifs for the low-cost fabrication of display and illumination technologies.

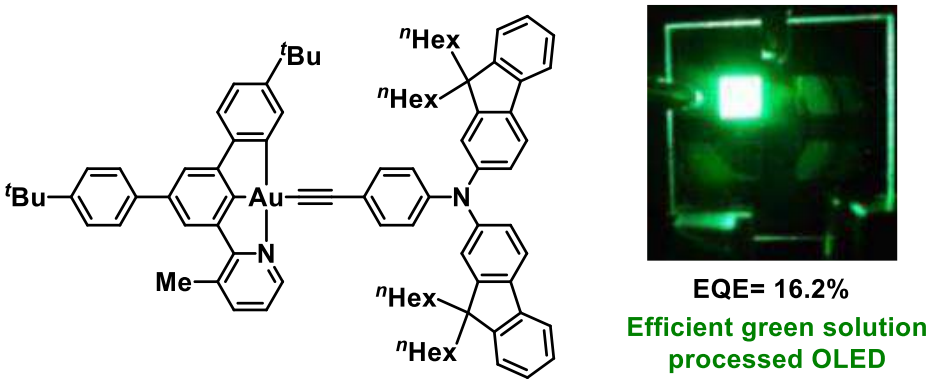

Figure 1. Structure of κ^3-(N^C^C)-aminophenylalkynyl-N,N′-bisfluorenyl-Au(III) complex

Acknowledgements

C.N. thank the European Research Council (ERC Starting grant agreement no. 307948) and the Swiss National Science Foundation (SNF) (200020-146853), for financial support. C.J.S. is grateful for the financial support from SNF (200021-178944) and ETH Zurich.

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MOLECULAR DYNAMIC SIMULATION ANALYSIS OF SIGLEC 7 – GLYCAN COMPLEXES

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Sialoglycans modulate many immune responses across infectious diseases and cancers.[1] These responses are based on Siglec (sialic acid-binding immunoglobulin-like lectin) and 'Siglec-like' proteins interacting with endogenous or exogenous ligands. Recently, Siglec-7 has been shown to mediate immunomodulation by interacting with the lipopolysaccharides (LPS) and the outer membrane vesicles (OMVs) of colorectal cancer (CRC) associated *Fusobacterium nucleatum* strains.[2]

Here we report the molecular and structural investigations of the interactions occurring between Siglec-7 and the LPS O-antigen structure from *F. nucleatum* 51191[3] and 25586[4] strains. We used a Molecular Dynamic Simulations approach to decipher at the atomic level, the key aspects of the ligands' recognition by Siglec-7. These findings can be used for future inhibitor design and novel therapeutic approaches to attenuate CRC progression.

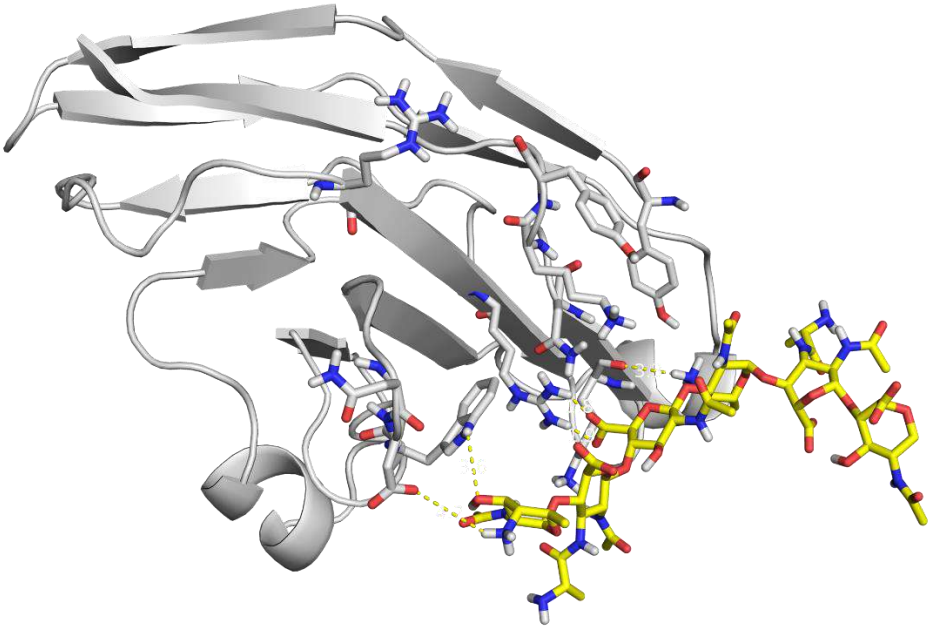

Figure 1. Cluster from a Molecular Dynamic Simulation on Siglec 7 and the OPS from *F. nucleatum* 51191.

Acknowledgements

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APPLICATION OF RENEWABLE THIOLS IN THE PREPARATION OF POLY(THIOURETHANE) COVALENT ADAPTABLE NETWORKS

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One of the industries most dependent on fossil fuels is the polymer industry: over 99% of polymer production uses monomers derived from oil and gas. For this reason, polymers derived from biomass (biopolymers) are widely developed. Different monomers derived from biomass have been proposed in the last decades: lignin, saccharides, vegetable oils, and terpenes, among others. [1]

On the other hand, thermosetting polymers are advantageous in a broad range of industrial applications due to their chemical and thermal resistance and excellent mechanical performance [2]. However, once finished their useful life, due to the impossibility of being recycled, they become an environmental problem, being incineration or landfill the only solutions.

A new family of polymeric materials is being developed to solve thermosetting recycling issues, starting from renewable materials. They present a covalent adaptable network structure (vitrimeric materials) whose topology can be changed by thermally activated reversible chemical processes. These reversible reactions allow this type of cross-linked polymers' reprocessing and recycling and exhibit other excellent characteristics such as self-healing or self-welding properties [3].

In this work, two different terpenes (squalene and limonene) have been converted into thiols using a two-step process previously reported [4] (see Figure 1) consisting of a thiol-ene photochemical reaction followed by saponification. Combinations of these two thiols in different proportions have been reacted with hexamethylene diisocyanate (HDI) by using two different kinds of catalyst (a Lewis acid as dibutyltin dilaurate, DBTDL, and a thermal base generator as 1,5-diazabicyclo[4.3.0]non-5-ene tetraphenylborate, BGDBU), to obtain different poly(thiourethane) covalent adaptable networks. Then, the mechanical and vitrimeric properties of these materials were tested.

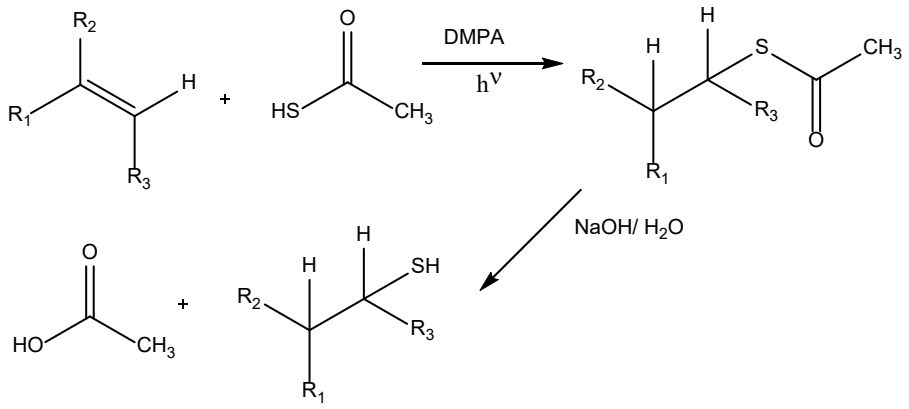

Figure 1. Schematic preparation of thiol from alkene

From the results, it can be observed that on increasing the proportion of hexathiolated squalene, the temperatures obtained from the peak of tan δ evolution increase, whereas, on increasing the proportion of dithiolated limonene, the relaxation times decrease. In this way, we can tailor the characteristics of the materials. Moreover, using an organic catalyst such as BGDBU, reduces relaxation times and increases tan δ temperatures simultaneously. The results are summarized in Table 1.

Table 1. Main data extracted from DMA analysis

Sample (SQLM)	$T_{tan\delta}$ (ºC)	t_{37} (s) at 180 ºC
SQLM 2575 acid	86	165
SQLM 5050 acid	95	342
SQLM 7525 acid	107	2232
SQLM 2575 base	91	10
SQLM 5050 base	101	36
SQLM 7525 base	107	109

Acknowledgments

This work is part of the R&D projects PID2020-115102RB-C21 and PID2020-115102RB-C22 funded by MCINAEI/ 10.13039/501100011033. We acknowledge these grants and the Generalitat de Catalunya (2017-SGR-77 and BASE3D).

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CATALYTIC HYDRODIFLUOROALKYLATION OF UNACTIVATED OLEFINS

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Difluorinated alkyl compounds represent important building blocks in the drug discovery pipeline due to their role as bioisosters of ethereal oxygen fragments and the ability to influence both the reactivity of adjacent functional groups and the 3D-conformation of hydrocarbon side-chains. At present, existing protocols for incorporating difluorinated alkyl moieties rely traditionally on functional group interconversion with harsh and toxic reagents (DAST, HF, BF_3-OEt_2) while modern methodologies have leveraged various classes of activated substrates, thus restricting the general exploration of difluoroalkyl-containing molecules with untapped potential in agrochemicals or pharmaceuticals. Here, we report a general and modular catalytic technique that streamlines the preparation of *gem*-difluoroalkanes from simple precursors. We show how abundant unactivated olefins can be converted to difluoroalkyl motifs, and expand the protocol to include structurally complex compounds and light olefin feedstocks such as ethylene or propene, thus enabling access to synthetically versatile difluorinated alkyl architectures. Our approach is enabled by a cooperative interplay of halogen-atom transfer and hydrogen-atom transfer, thus offering a new entry point for accessing biologically relevant difluorinated molecules.

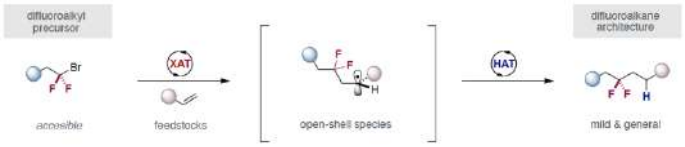

Figure 1. A synthetic pathway to streamline the access to difluoroalkyl architectures

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TRANSBORYLATION BETWEEN DIBORON REAGENTS AND ALKENYLBORANES

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Over the last decades, alkenylboranes have been considered powerful intermediates for the functionalization of alkenes.[1] In particular, *E*-alkenylboranes have become essential building blocks for the elaboration of functionalized alkenyl groups with retention of the stereoselectivity. Transborylation reactions, performed so far, have in common that the R group are transferred from very reactive boryl motifs to pinacolborane via C–BR_2 / H–Bpin cross-metathesis.[2-4] Herein, we describe the exchange of boryl moieties between alkenylboranes and diboron reagents as a stereospecific cross-metathesis pathway with concomitant formation of mixed diboron reagents via C(sp^2)–Bpin / B'–B' exchange. The stereo control of the sequence is guaranteed throughout the robustness of the new type of transborylation methodology. Additionally, the synthesis and characterization of different types of transborylated products have been accomplished for alkenylboranes with *Z*- and *E*-configuration containing chiral boryl units (Figure 1).

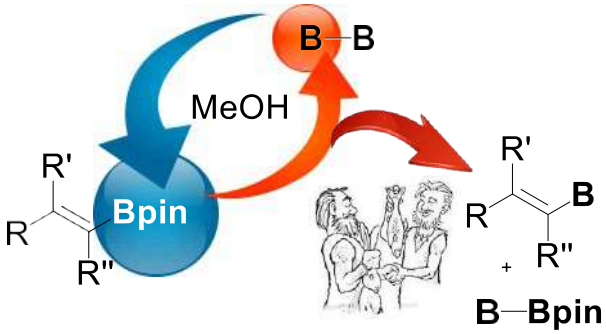

Figure 1.

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ORGANOCATALYTIC DIASTEREO- AND ENANTIOSELECTIVE VINYLOGOUS ADDITION OF ALKYLIDENEPYRAZOLONES TO DIFFERENT ELECTROPHILES

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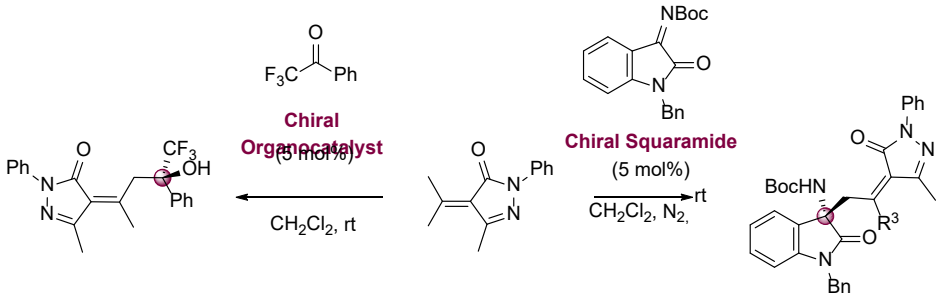
The direct catalytic asymmetric vinylogous reaction represents a powerful tool in synthetic organic chemistry to introduce stereocenters at the γ-position or even more remote positions of the functional groups in organic compounds in an atom-economical and efficient way.[1] On the other hand, pyrazolone scaffold is an important class of nitrogen heterocycle that is present in a wide range of drugs, agrochemicals and biological active compounds.[2] Therefore, the development of methodologies for the stereoselective synthesis of this class of compounds is significant for organic chemistry.[3] In the research area of vinylogous reactions, the asymmetric nucleophilic γ-addition of α,β-unsaturated pyrazolone bearing γ-hydrogen atoms to electrophiles has been explored for the construction of chiral pyrazolones. Herein, we present our results using alkylidenepyrazolones as nucleophiles in an organocatalytic vinylogous Mannich[4] reaction and in an organocatalytic vinylogous aldol[5] reaction.



Scheme 1. Organocatalytic stereoselective vinylogous addition of alkylidenepyrazolones

Acknowledgements

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AN ELECTROCHEMICAL AND COMPUTATIONAL CROSS STUDY ON KUQUINONE REDOX SPECIES

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Quinone-based molecules fill a key role in biological processes, in energy storage and in CO_2 reduction devices thanks mainly to their highly tunable redox chemistry. The study of their electrochemical features has become a fascinating topic in chemistry. Our interest in quinone chemistry started in 2012, when we synthesised a new highly conjugated quinone-based compound, called KuQuinone (KuQ). The peculiarity of such molecules is the presence in the structure of two condensed naphthoquinone units, which implies the possibility to undergo multiple one-electron reduction processes. In this contribution, a detailed electrochemical investigation of KuQuinone will be presented.[1] Electrochemistry has been examined changing solvent, supporting electrolyte, and adding different additives. In particular, additions of 2,2,2-trifluoroethanol (TFE) as hydrogen-bond donor and Scandium triflate as Lewis acid led to an important positive shift of reductions processes likely due to the interaction with KuQ carbonyl moieties. DFT calculations and UV-vis-NIR spectroelectrochemistry will be also presented to give a further insight on the KuQ's reduced species.

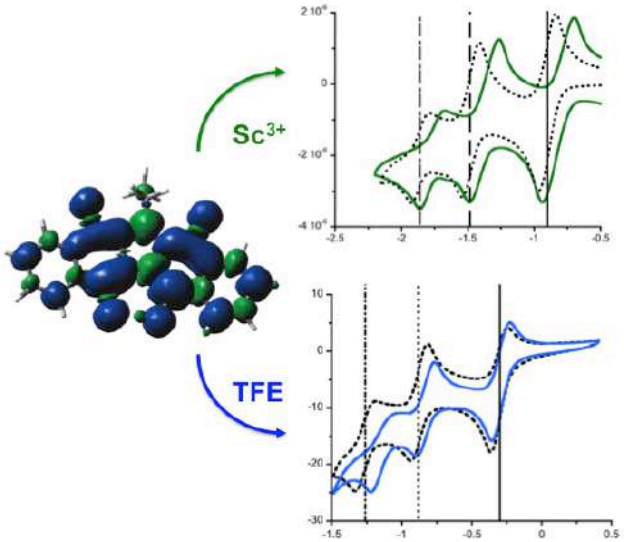

Figure 1. KuQ's reduction processes with (top_green line) Scandium ions and (bottom_blue line) TFE.

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ENANTIOSELECTIVE FORMATION OF 2H/4H-CHROMENES DERIVATES VIA TANDEM GOLD(I)-CATALYZED REACTION WITH ACETYLENE GAS

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Interest in homogeneus gold catalysis has undergone a marked increase giving rise to the discovery of new cationic gold(I) complexes as catalysts for diverse transformations of alkenes, alkynes and allenes.[1] In parallel, the development of efficient asymmetric variants of these reactions is required in order to take full advantage of their potential. In this context, our group has recently reported the use of acetylene gas in the gold(I)-catalyzed reaction with *trans*-stilbene for the selective synthesis of (*Z*, *Z*)-1,3-dienes, and the formation of their corresponding oligomers by formal insertion of C_2 units.[2]

A novel approach for the development of enantioselective chromene products (widely present in natural products and pharmacologically active compounds) is presented through a combination of an intermolecular reaction of phenol derivates with acetylene gas, followed by an intramolecular alkoxycyclization. The reaction takes place with acetylene gas, which can be easily generated in situ, through an intermediate cyclopropyl gold(I) carbene that undergoes a nucleophilic attack leading to the desired products bearing the common chromene skeleton. The reaction has also been performed in an enantioselective manner with chiral gold(I) complexes.

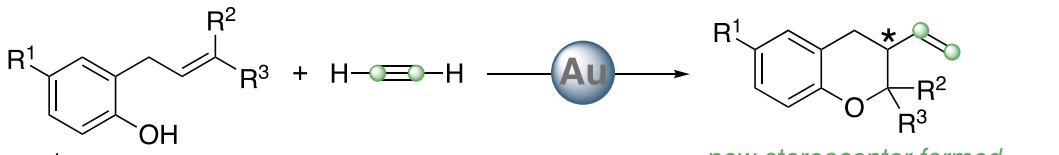

Figure 1. Gold(I)-catalyzed tandem cyclization with acetylene gas

Acknowledgements

We thank the MCIN/AEI/10.13039/501100011033 (PID2019-104815GB-I00, CEX2019-000925-S, and FPI to T.Medina-Gil), the ERC (Adv. Grant 835080), and CERCA Program/Generalitat de Catalunya for financial support.

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NATURAL DEEP EUTECTIC SOLVENTS AS EFFICIENT AND REUSABLE PROMOTERS FOR ACETALIZATION REACTIONS UNDER MILD CONDITIONS

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Carbonyl compounds are among the most synthetically important classes of organic substrates due to their ubiquitous and versatile chemical reactivity.[1] Aldehydes and ketones, however, requires protection to survive multi-step chemical processes frequently found in modern laboratory and industrial syntheses.[1] Acetals are one of the most popular protecting groups for the carbonyl functionality and can also behave as excellent intermediates in organic synthesis.[1] Common synthetic strategies, where either the use of metal catalysts or large excess of reagents and volatile organic solvents, raise many disadvantages and potential environmental problems, such as reflux conditions, long reaction times and usually poor selectivity.[2] Natural Deep Eutectic Solvents (NaDESs) have emerged as alternative eco-friendly solvents for an increasing number of synthetic transformations. Remarkably, in some cases one (or more) components of the NaDESs plays an active role in the reaction mechanism and directly participates as a catalyst.[3] With the aim to address these issues and comply with the principles of green and sustainable chemistry we tested several NaDESs, in which one of the components is a carboxylic acid, as medium to promote acetalization procedures. The reaction conditions were optimized and the scope widely investigated on substituted carbonyl substrates. To assess the full sustainability of the proposed approach, the recyclability and scalability of the process were investigated, thus proving that multi-grams preparations are possible with complete recycle of the medium.

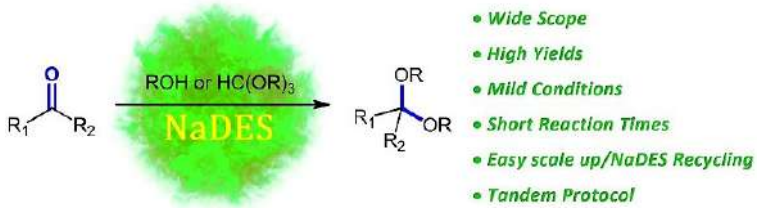

Figure 1. Natural deep eutectic solvents promoted acetalization reactions.

Acknowledgements

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H-BONDED COUNTERION-DIRECTED ENANTIOSELECTIVE AU(I) CATALYSIS[1]

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Gold(I) complexes usually present a linear dicoordinated geometry, which places the ligand on the opposite site of the substrate hindering the transmission of the stereochemical information from the chiral ligand to the reaction center. Furthermore, both the ligand–Au and substrate–Au bonds present free rotation, and the nucleophilic addition generally occurs with an outer-sphere mechanism. A novel approach for the achievement of enantioselective transition-metal catalysis is presented, where a hydrogen-bond donor placed on a ligand of a cationic gold(I) complex precisely positions a chiral counterion responsible of transferring the stereochemical information (Figure 1). This strategy has been, for the first time, successfully applied in the activation of challenging alkynes in the 5-exo-dig and 6-endo-dig cyclizations of 1,6-enynes, with and without the addition of nucleophiles, combining an achiral phosphinourea Au(I) chloride complex with a BINOL-derived phosphoramidate Ag(I) salt. ^{1}H NMR titrations experiments, detailed kinetic studies, nonlinear effects and solvent studies are provided to prove the key H-bond interaction of the catalytic system. This work provides a starting point for the development of supramolecularly assembled chiral metal complexes.

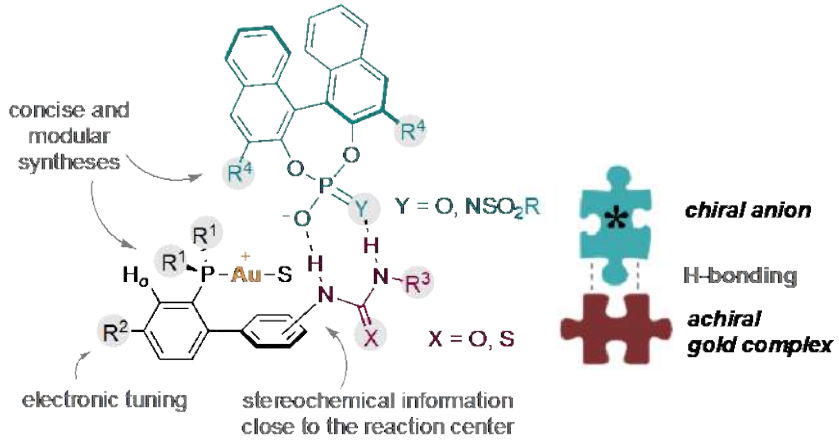

Figure 1. Design for asymmetric H-bonded counterion directed gold (I) catalysis

Acknowledgements

We thank the MCIN/AEI/10.13039/501100011033 (PID2019-104815GB-I00, CEX2019-000925-S, and FPU to À.M.), the European Union (Horizon 2020 MSC COFUND to A.F.), the ERC (Adv. Grant 835080), the AGAUR (2017 SGR 1257), and CERCA Program/Generalitat de Catalunya for financial support.

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PHYTOTOXINS ISOLATED FROM PATHOGENIC FUNGI OF FOREST TREES IN MEDITERRANEAN BASIN

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The main causes of forest plant diseases are pathogenic fungi, which are able to produce phytotoxins, i.e. secondary metabolites, which are virulence factors and are involved at different stages of pathogenesis.[1] Forest plant diseases in the Mediterranean area are a public interest issue, considering the resulting huge losses to the wood industry and landscape. The European ash (*Fraxinus excelsior* L.) epidemic disease, known as “ash dieback”, is caused principally by an invasive pathogen *Hymenoscyphus fraxineus*. A new toxin has been isolated, together with four known furanoditerpenoids, from the organic extract of fungal culture filtrate.[2] *Diplodia olivarum* is a canker agent of various plant hosts in Italy, as carob tree, wild olive and lentisk. The fungus was grown on two media and from the corresponding organic extracts a new cleistanthane nor-diterpenoid together with other diterpenoids and an isocoumarin have been isolated.[3] Recently, *Diplodia sapinea* recognized in Tunisia as causal agent of branch canker and dieback of maritime pine. Two new trisubstituted furanones have been isolated from the organic extract of its culture filtrate.[4]
This oral communication will be focused on the chemical and biological characterizations of the phytotoxins produced by these three pathogenic fungi.

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ENANTIOSELECTIVE SYNTHESIS OF SULFONIC ACIDS BEARING A QUATERNARY STEREOGENIC CENTER

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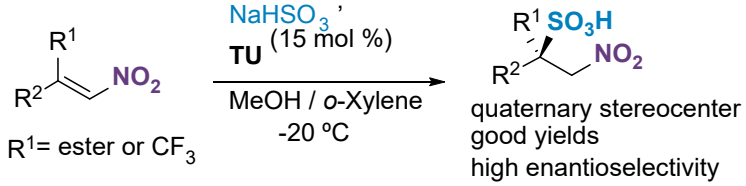
Chiral sulfonic acids and their derivatives have remarkable significance and application in natural product and pharmaceutical chemistry [1]. As a result, the pursuit of new catalytic strategies that enable the effective synthesis of sulfur-containing organic molecules with the introduction of chiral information is an important goal in modern synthetic organic chemistry. In this context, enantioselective nucleophilic addition of cheap and readily available sodium bisulfite has been used for the direct synthesis of sulfonic acids and their salts upon addition to electrophilic double bonds [2]. Recently, our group and others have described the organocatalytic addition of sodium bisulfite to nitroalkenes as a convenient approach to chiral sulfonic acids and taurine derivatives bearing a tertiary stereogenic center [3].

Herein, we present our preliminary results on the extension of this methodology to β,β-disubstituted nitroalkenes to obtain sulfonic acids featuring a quaternary sterogenic center [4]. Bifunctional thioureas catalyze the conjugate addition of sodium bisulfite to β,β-disubstituted nitroalkenes bearing a trifluoromethyl group or an ester group to give the corresponding nitrosulfonic acids with good yields and enantiomeric excesses.



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1,2-DICARBOFUNCTIONALIZATION OF 1,1-ARYLBORYLALKENES

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Multicomponent reactions (MCRs), wherein three compounds intermolecularly combine in a sequential manner, are revealed as ideal strategies in diversity-oriented synthesis. Here, we describe a new protocol for 1,2-dicarbofunctionalization of vinyl boronates forming new vicinal C(sp^3)–C(sp^3) bonds. Additionally, this reaction has been achieved using neither a metal catalyst, additives, photocatalysts, nor a radical initiator.[1-3] By the regioselective nucleophilic addition of C(sp^3) to 1,1-phenylboryl alkene, a borataalkene intermediate is formed during the process, which has been demonstrated by using ^{11}B NMR spectroscopy. The following step is the nucleophilic attack of the alpha-boryl carbanion intermediate to C(sp^3) electrophiles, at room temperature, through a S_N2 nucleophilic substitution with primary and secondary aliphatic C(sp^3) halides (Scheme 1). This MCRs guarantees that the new tetrasubstitued carbon formed retains all the C atoms from the three starting materials involved in the assembly.

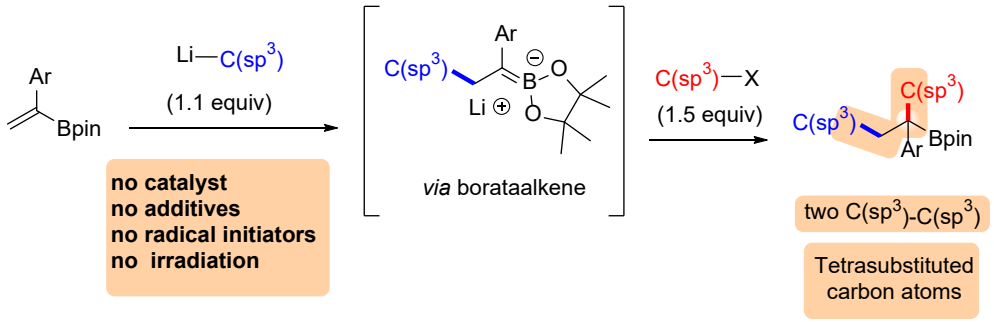

Figure 1.

Acknowledges

We thank Ministerio de Economía y Competitividad y por el Fondo Europeo de Desarrollo Regional FEDER through project PID2019-109674GB-I00.

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GOLD(I)-CATALYZED STEREOSELECTIVE CYCLIZATIONS: A CHIRAL AUXILIARY APPROACH

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Our group reported the gold(I)-catalyzed cyclization of polyenynes by the activation of terminal alkynes or bromoalkynes.[1] Now, through the use of the commercially available Oppolzer's sultam or Evans oxazolidinone chiral auxiliaries, the stereoselective gold(I)-catalyzed spirocyclization of polyenynes and alkoxycyclization of 1,6-enynes has been achieved. Despite the broad application of chiral auxiliaries in asymmetric synthesis, only one isolated example had been reported in gold catalysis.[2] Our work represents the first case where this methodology can be applied to a broad range of substrates resulting in good yields and stereoselectivities.

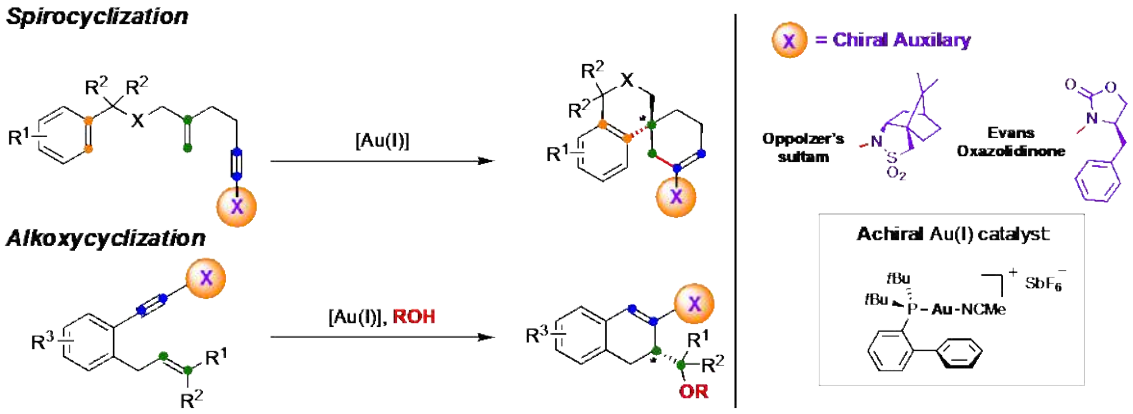

Figure 1. Au(I)-catalyzed diastereoselective spyrocyclization and alkoxycyclization of 1,6-enynes

Acknowledgments

We thank the MCIN/AEI/10.13039/501100011033 (PID2019-104815GB-I00, CEX2019-000925-S), the ERC (Adv. Grant 835080), the AGAUR (2017 SGR 1257), and CERCA Program/Generalitat de Catalunya for financial support.

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HIGHLY DIASTEREOSELECTIVE MULTICOMPONENT ACCESS TO SPIROCYCLOPROPYL OXINDOLES ENABLED BY NON-CHIRAL RARE-EARTH METAL SALTS

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Rare earth metals (REMs) have been largely used in organic synthesis in last years, mainly thanks to their versatility and stability in different solvents [1]. Their eco-compatibility, united to their unique features as Lewis acids, prompted their implementation allowing to access numerous highly-valued compounds [2]. Multicomponent reactions (MCRs) likewise arose as a modern approach in fine synthesis, furnishing a useful and simpler tool for the realization of complex frameworks, saving time and solvents [3]. In this work, we propose a protocol that merge the above-cited advantages for the preparation of spirocyclopropyl oxindoles, a family of compounds known for their spendability in medicinal chemistry [4]. Such approach (**Figure 1**) allowed to obtain polysubstituted spirooxindole derivatives in short time, good yields and excellent diastereoselectivity (up to 19:1:0:0). This last unexpected feature, *a fortiori* in absence of any chirality inductor, has been deepened with the help of a series of QM-DFT calculations.

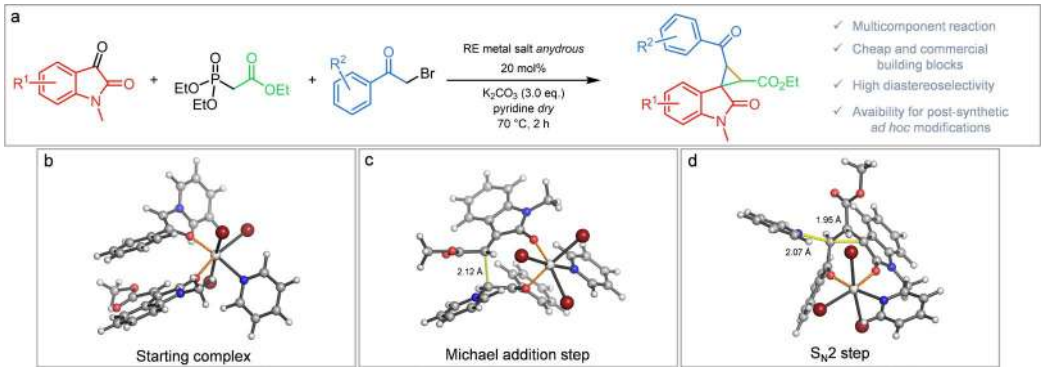

Figure 1. Reaction scheme (a) and minimum energy starting complex (b) and transition states (c-d)

Acknowledgements

We thank the Ministry of University and Research (MUR) for a doctoral grant and for the financial support through SI.F.I.PA.CRO.DE project - PON ARS01_00568 - CUP: B29C20000360005.

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NEW CHIRAL FERROCENYL LIGANDS FOR ASYMMETRIC GOLD (I) CATALYSIS

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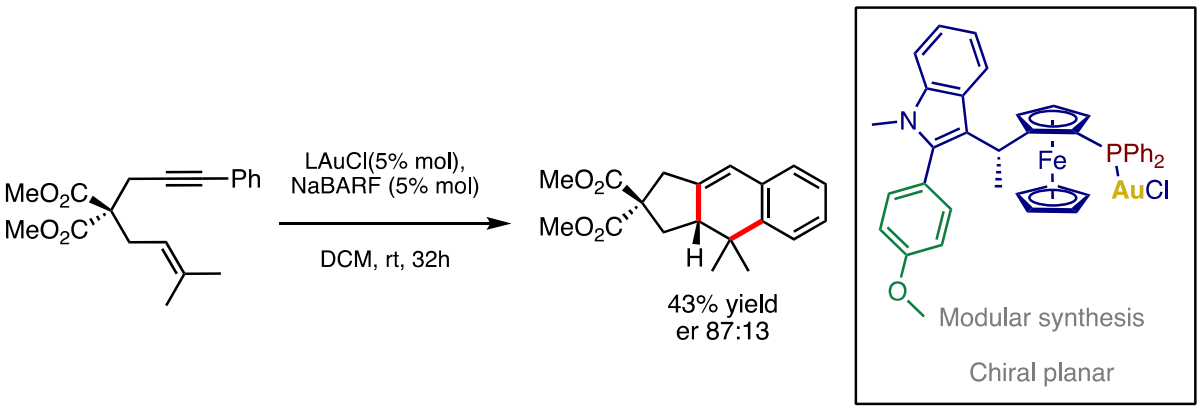
Following up the recent work of our group in enantioselective gold (I) catalysis[1,2], we report the modular synthesis of a novel class of chiral-planar gold (I) complexes supported by 1,2-disubstiuted monophosphino ferrocenyl ligands. The synthesis of these new complexes was achieved in a concise and simple manner which enabled fast development and optimization leading to a small library. Those gold(I)-complexes, when armed with 2-aryl indoles as substituents, give good enantioselectivities in the cyclization of 1,6-enynes. The application of these new complexes and related catalysts in enantioselective gold (I)-catalyzed



transformations will be disclosed.

Acknowledgements: We thank MCIN/AEI/10.13039/501100011033 (PID2019-104815GB-I00, CEX2019-000925-S), the ERC (Adv. Grant 835080), the AGAUR (2017 SGR 1257), and CERCA Program/Generalitat de Catalunya for financial support.

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GOLD(I)-CATALYZED 1,3,5-CYCLOTRIMERIZATION OF TERMINAL ALKYNES

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The metal-catalysed cyclotrimerization of alkynes to give trisubstituted benzenes has generally been found to be selective for the formation of asymmetric 1,2,4-trisubstituted products. Only few examples have shown selectivity towards 1,3,5 substitution patterns and mainly for propargylic alkynes.[1,2,3] We have found the cyclotrimerization of alkynes catalysed by Au(I) complexes with a hitherto unprecedented 1,3,5-selectivity. A computational study of the mechanism suggests that the selectivity arises from the strict head-to-tail oligomerisation and the involvement of Dewar benzene intermediates in productive pathways.

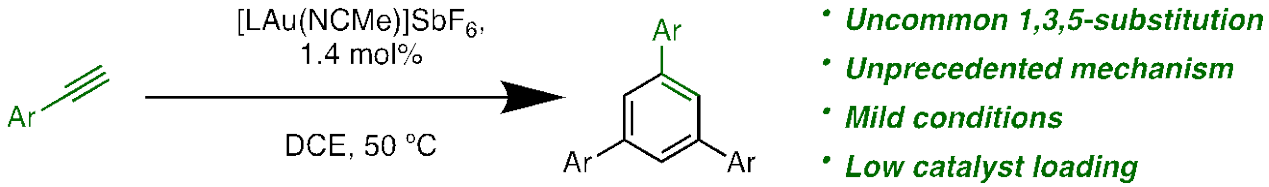

Figure 1. Gold(I)-catalysed cyclotrimerization of alkynes.

Acknowledgments

We thank the MCIN/AEI/10.13039/501100011033 (PID2019-104815GB-I00, CEX2019-000925-S), the ERC (Adv. Grant 835080), the AGAUR (2017 SGR 1257), and CERCA Program/Generalitat de Catalunya for financial support.

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ON THE NATURE OF GOLD(I) VINYLIDENES

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Gold(I) vinylidenes have been proposed as potential intermediates in some gold-catalyzed transformations [1]. However, their high reactivity has hampered their direct study [2]. Only one gold(I) vinylidene highly stabilized by two silyl groups has been characterized by NMR, although its structure is very different from species proposed as genuine catalytic intermediates [3]. Our group had recently synthesized highly reactive gold(I) carbenes, formed from stable gold(I) carbenoids [4]. Now, we have developed a method to generate gold(I) vinylidenoids from simple gold(I) chloride complexes, which, by reaction with $GaCl_3$ at -90ºC, give rise to (η^2-diarylacetylene)gold(I) complexes via 1,2-aryl migration (Figure 1).

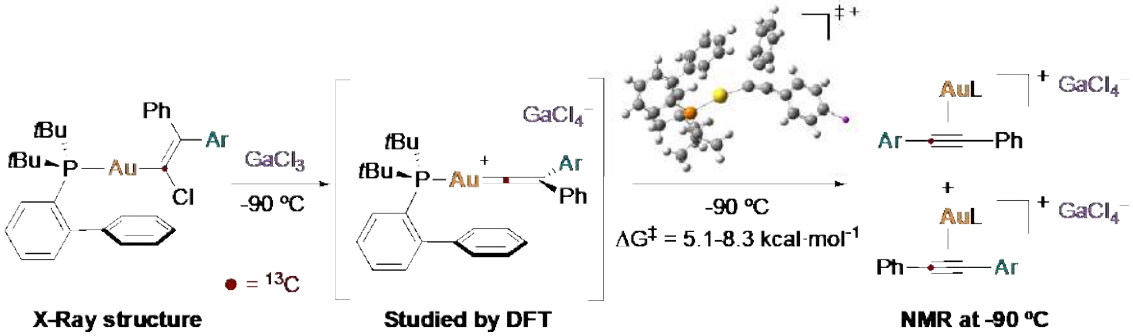

Figure 1. Present study.

The NMR study of this reaction with ^{13}C labelled gold(I) vinylidenoid complexes, combined with DFT studies, allowed us to investigate the mechanism of this transformation.

Acknowledgements

We thank MCIN/AEI/10.13039/501100011033 (PID2019-104815GB-I00, CEX2019-000925-S, and FPU to A.H.P.), the ERC (Adv. Grant 835080), the AGAUR (2017 SGR 1257), and CERCA Program/Generalitat de Catalunya for financial support.

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A CARBYNE TRANSFER PLATFORM FOR THE CATALYTIC GENERATION OF FISCHER-TYPE CARBENES

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Fischer carbene complexes are some of the most versatile organometallic reagents in the construction of complex architectures due to their broad and diverse reactivity.[1] However, catalytic processes capable of generating such carbenes are rare.[2–5] In 2019, our group reported a new carbyne transfer platform involving the catalytic generation of Rh(II)-carbynoids as $I^{(III)}$-substituted Rh(II)-carbenes. We demonstrated that Rh-carbynoids were able to emulate the carbene/carbocation behavior of a monovalent cationic carbyne (:$^{+}$C–R), and provide access to allyl cations via alkene C(sp^2)–C(sp^2) bond cleavage.[6,7] Recently, we wondered whether Rh-carbynoids could intercept alkene-substituted carboxylic acids and generate, upon elimination of the hypervalent iodine leaving group, a Fischer-type Rh(II)-carbene able to undergo intramolecular cyclopropanation. In this communication, we would like to share the successful development of this idea and its application in the stereoselective synthesis of complex cyclopropane-fused lactones.

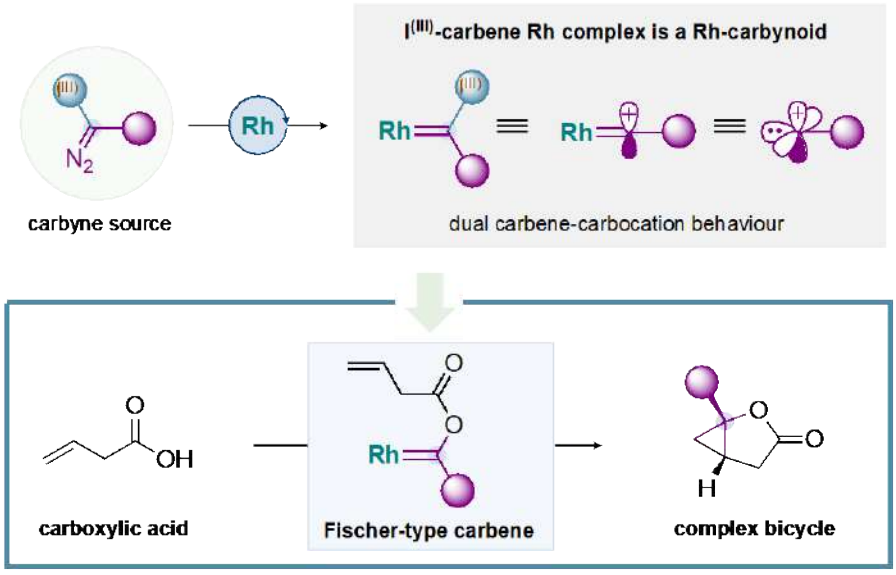

Figure 1.

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SYNTHESIS OF 2,6-DIMETHYLTYROSINE-LIKE AMINO ACIDS THROUGH PICOLINAMIDE-ENABLED C–H DIMETHYLATION OF 4-DIBENZYLAMINO PHENYLALANINE

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The aromatic moiety in the N-terminal message domain of opioid peptides, commonly represented by Tyr[1], Phe[1], and Phe[4], has been proved to be fundamental in binding and activation processes of opioid receptors. In particular, 2,6-dimethyl-(*L*)-tyrosine (Dmt) has become one of the most popular non-natural amino acids to be inserted in synthetic opioid peptides.[1] Peptides incorporating Dmt instead of Tyr in the message domain led to mixed NOP/OP agonist profiles, in addition to increased biological activity and stability.[2]

Since an interesting non-racemizing C–H activation Pd-catalyzed recent approach has been reported to obtain Dmt through dimethylation in positions 2 and 6 of the aromatic ring of tyrosine derivatives,[3] it was possible to extend the study of Pd-catalyzed δ-*ortho* C(sp^2)–H activation strategy to obtain differently 4-substituted *L*-phenylalanine picolinamides, starting from 4-NO_2-phenylalanine. Indeed, working on the 4-*N*-dibenzylamino-phenylalanine it was possible to obtain a small library of 2,6-Dmt-like derivatives, characterized by diverse electronic/steric properties in position 4 of the aromatic ring due to the presence of a variety of EWG, EDG and bulky functional groups. (Fig. 1).[4]

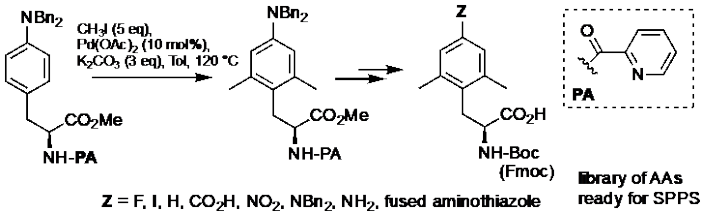

Figure 1. Synthetical approach to a small library of *p*-substituted Fmoc/Boc protected Dmt-like non-natural amino acids

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GOLD(I)-CATALYZED CONVERGENT SYNTHESIS OF LINEAR ACENES

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Our group developed a novel strategy for the synthesis of partially saturated higher acenes and related compounds based on successive Sonogashira couplings between 1,7-enynes and diiodinated arenes followed by gold(I)-catalyzed [4+2] cycloadditions, which are robust transformations that proceed under mild conditions.[1-4] Now a more convergent methodology has been developed that enables the acquisition of higher members of the acene series, starting from tridecacene-H8, whose structure can be visualized by high-resolution STM and non-contact AFM imaging.

Figure 1. General synthesis of higher hydroacenes, starting from tridecacene-H8.

Acknowledgements

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MECHANISTIC INSIGHTS ON THE ENANTIOSELECTIVE GOLD(I)-CATALYZED [4+2] CYCLOADDITION OF 1,6-ENYNES

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Newly developed chiral gold(I) catalysts by our group give good enantioselectivities in the cyclization of 1,6-enynes.[1] Recently we have prepared a new generation of more active catalysts that has been also applied for atroposelective cyclizations. A detailed kinetic study has been performed in order to get a better understanding of the working mode of our complexes as compared to JohnPhosAu(MeCN)SbF_6.[2] The use of silver salts to activate the gold(I) complex has been avoided by using isolated cationic gold(I) catalysts (*R,R*)-**A** and (*R,R*)-**B**. A set of experiments has been designed to study the single steps involved in the catalytic cycle; among which are the determination of the reaction rate equation by variable time normalization analysis[3] and initial rates, kinetic isotopic effect studies, determination of thermodynamic parameters of activation by Eyring analysis.

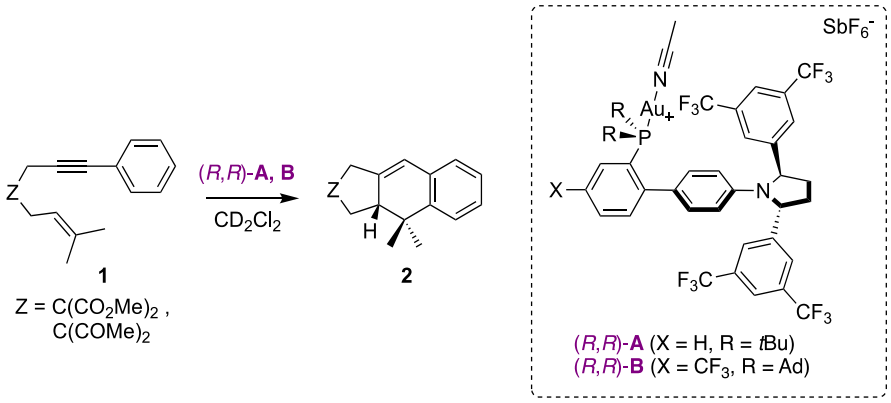

Figure 1. General scheme of the studied reaction

Acknowledgements

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NOVEL GOLD(I)-CAVITAND CATALYSTS

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Encapsulation of metal centers in supramolecular cages has been used for enhancing the selectivity of metal catalysts as an approach for mimicking the behavior of enzymes.[1] Our group has recently reported the synthesis of a family of achiral and chiral gold(I)-cavitand complexes from resorcin[4]arenes for the new selectivity in the cyclization of dienynes and the enantioselective alkoxycyclization of 1,6-enynes, respectively.[2]

Now, a new generation of gold(I)-cavitand catalysts has been designed to achieve new selectivities. First, employing bulkier walls (W) to force a constrained conformation for substrates to fit in the cavity pocket. Then, efforts towards the synthesis of new chiral gold(I) cavitands as asymmetric catalysts will also be presented.

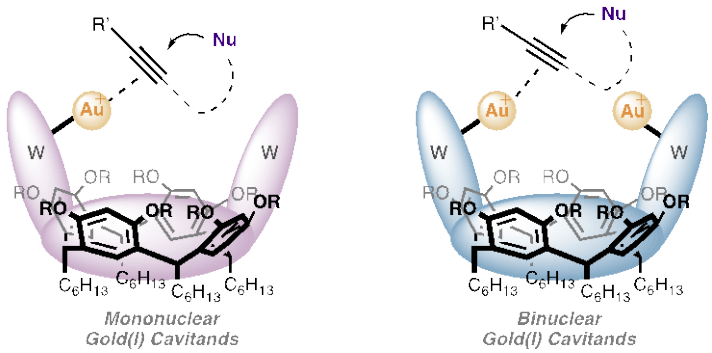

Figure 1. Mononuclear and Binuclear Gold(I) Cavitands

Acknowledgements

We thank the MCIN/AEI/10.13039/501100011033 (PID2019-104815GB-I00, CEX2019-000925-S), the ERC (Adv. Grant 835080), the AGAUR (2017 SGR 1257), and CERCA Program/Generalitat de Catalunya for financial support.

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ALTERNATIVE SYNTHESIS OF L-DOPA METHYL ESTER AND ANALOGUES.

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A short and alternative synthesis of L-3,4-dihydroxyphenylalanine methyl ester (L-DOPA methyl ester) starting from L-3-nitrotyrosine in few steps, without the use of enzymes or bacteria as it is known in literature, but through the formation of the diazonium salt that allows the entry of a second phenol moiety. The only cons of this reaction step is the low yield.

The idea of synthetizing the L-DOPA arises from our recent published paper[1] where we synthetized a small library of N-Boc or N-Fmoc 2,6-dimethylated phenylalanine derivatives with different functional groups in position 4, through the palladium-catalysis directed C-H functionalization described by Wang[2] in 2017. Consequently, instead of dimethylated tyrosine or phenylalanine derivatives, we thought to synthetize the L-2-methyltyrosine starting from L-3-nitrotyrosine with the same methodology. In this context we decided also to synthetize L-2-methyl-DOPA methyl ester and to reach this goal we identified two different pathways.

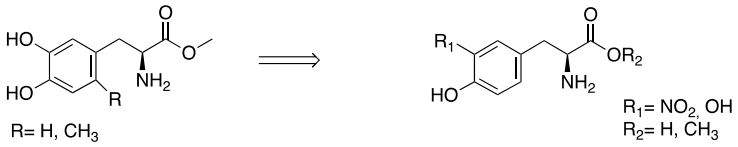

Figure 1. Synthesis of L-DOPA methyl ester and L-2-methyl-DOPA methyl ester.

Both approaches follow the Pd-catalysis strategy used by our group, the differences lie in the starting substrate.

The first synthetic way starts from L-DOPA methyl ester (previously synthetized or commercial one) passing through the step of catalysis of the picolinamide catechol (protected as dioxol) intermediate.

The second synthesis starts from the 3-nitrotyrosine to obtain the 3-dibenzylamino-tyrosine phenol-protected that allows the obtainment of the methylation of the position 2, molecule that will be converted to the catechol moiety and to the L-2-methyl-DOPA methyl ester.

Acknowledgements

University of Ferrara, FAR 2021, A.F.

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STEREOPREDICTION OF SECONDARY PROPARGYLAMINES DERIVED FROM A^3 REACTION PROMOTED BY Ce/Cu SYSTEM

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Propargylamines are precursors for synthesis of heterocyclic scaffolds employed in drugs, and in recent years their treatment of neurodegenerative diseases has been of particular interest.[1] Secondary propragylamines obtained by A^3 coupling reaction promoted by Ce/Cu based Lewis acids were previously investigated by us.[2] Given that the synthesis of proparglyamines from primary amines is much less investigated,[3] we studied our strategy to obtain propargylamines from *(R)-(+)-phenylethylamine*. This study is aimed to predict and find relative configuration of the newly formed stereogenic centres.

Cu-based promoting systems as $CuSO_4$/NaI and CuI/$CeCl_3 \cdot 7H_2O$ were employed, both characterized by ease of use, low toxicity, and cost (**Figure1**). For each propargylamine structure of most stable conformer was determined by DFT calculations and corresponding ^{1}H-NMR was simulated and compared with the experimental data collected.[4]

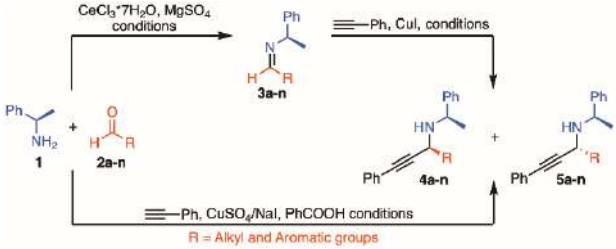

Figure 1. Two-step and multicomponent synthesis of secondary proparglyamines.

Products are obtained in good yields and diastereomers were isolated in most cases and characterized by ^{1}H-NMR and polarimetric analysis. Shielding and deshielding effects obtained by ^{1}H-NMR analysis are in very good accordance with the computational calculations. Considered the overall collected data, the relative configuration of new chiral center can be assigned.

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SPECIALIZED METABOLITES AS STIMULANT AND/OR INHIBITORS OF PARASITIC WEED GERMINATION AND SEEDLING GROWTH

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Broomrapes (*Orobanche* and *Phelipanche* spp.) and dodders (*Cuscuta* spp.) are parasitic weeds infesting a large number of important crops causing severe yield losses. Current control relies on the use of synthetic herbicides causing environmental pollution and can affect human health. Considering that seed germination and seedling growth towards the host are key phases for parasitic weed infection, an alternative approach proposed for the management of these weeds has been to use plant metabolites to stimulate suicidal germination in absence of the host, or to inhibit host-induced parasitic germination and/or seedling growth towards the host. Therein, the identification of compounds with these parasitic weed-specific mechanisms of herbicidal action can provide control alternatives. The roots of eighteen autotrophic weeds were investigated as allelopathy donors using chromatographic and spectroscopic methods, in order to find metabolites that could be used as model molecules for the synthesis of new bioherbicides [1]. Recently, a mixture of glycosidic acids isolated from *Convolvulus arvensis* inhibited the radicle growth of broomrapes [2] and, an acetylenic furanone produced by *Conyza bonariensis* inhibited the seedling growth of dodder. This communication will illustrate the results obtained in the isolation and chemical characterization of metabolites as stimulants of suicidal germination and/or inhibitors of parasitic weed infection. Future perspectives will consist in the development of synthetic methods of the active compounds, their analogues or mimics, and their incorporation into appropriate polymers for practical applications.

Acknowledgment

Gabriele Soriano holds a PhD scholarship funded by INPS (Istituto Nazionale Previdenza Sociale). Additional support funded by CSIC and Córdoba University: RYC-2015-18961 to Monica Fernandez-Aparicio, PRAEMS grant to Pilar Carretero and JAEIntro-2021-2-IAS-02 to Lilibeth Torres-Elizalde.

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DISSECTING ELECTRONIC AND STERIC EFFECTS IN CHIRAL GOLD(I) CATALYSTS

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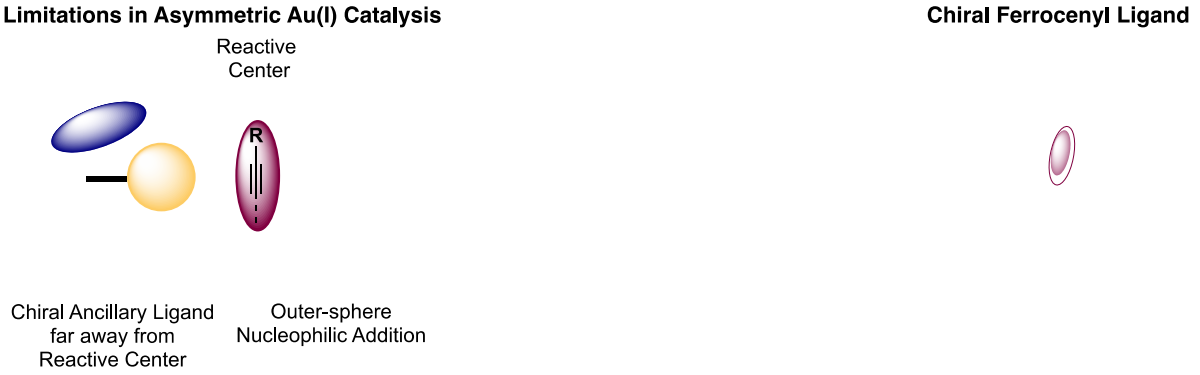
Gold(I) complexes were well established as a general tool for the C-C multiple bonds activation to build up complex molecular architectures. Despite, the development of broad scope enantioselective transformations has been slower, which can be attributed to the linear coordination geometry adopted by Au(I).[1] Recently, new imaginative ligand designs have been proposed in enantioselective gold(I) catalysis. We have prepared a new class of chiral gold(I) catalysts containing remote C_2-symmetric 2,5-disubstituted pyrrolidines[2] and unprecedented gold(I) complexes with planar chiral monodentate ferrocene-based ligands from ferrocenyl sulfoxide.[3] Both complexes promote enantioselective cyclizations in good to excellent enantiomeric ratios. Computational studies allowed for the dissecting of their electronic and steric effects and the elucidation of their modes of action. As revealed by NCI plots, non-covalent interactions between the different substrates and ligands are responsible of the selective folding of substrates in the chiral pocket of the new gold(I) catalysts.



Acknowledgements

We thank the MCIN/AEI/10.13039/501100011033 (PID2019-104815GB-I00, CEX2019-000925-S), the ERC (Adv. Grant 835080), the AGAUR (2017 SGR 1257), and CERCA Program/Generalitat de Catalunya for financial support.

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NEW N-HETEROCYCLIC CARBENE GOLD(I) COMPLEXES FOR ENANTIOSELECTIVE GOLD(I) CATALYSIS

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Since the first example of N-heterocyclic carbene (NHC) gold(I) complexes reported in 2007,[1] many other NHC-gold(I) complexes have been reported.[2] Inspired from recent developments in enantioselective gold(I) catalysis reported by our group,[3] we have now developed a new family of modular chiral NHC gold(I) catalysts bearing a C_2-chiral 2,5-diarylpyrrolidine group. Applications of these new chiral gold(I) catalysts in asymmetric catalysis will be presented.

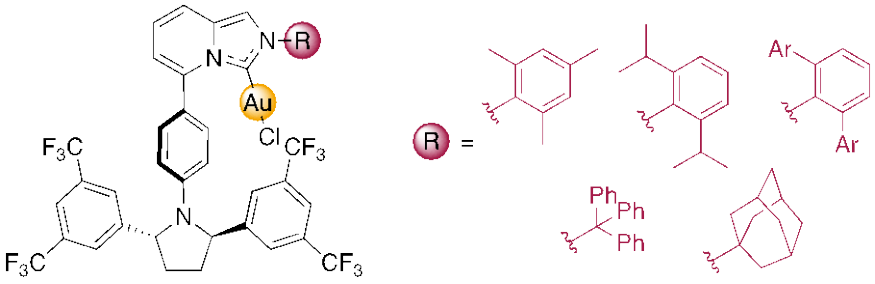

Figure 1. Results in enantioselective gold(I) catalysis with these new complexes will be reported.

Acknowledgements: We thank the MCIN/AEI/10.13039/501100011033 (PID2019-104815GB-I00, CEX2019-000925-S), the ERC (Adv. Grant 835080), the AGAUR (2017 SGR 1257), and CERCA Program/Generalitat de Catalunya for financial support.

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NATURAL COMPOUNDS WITH ANTIMICROBIAL ACTIVITY AGAINST MULTIDRUG-RESISTANT AND BIOFILM-FORMING GRAM-POSITIVE PATHOGENS

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Antimicrobial resistance is a phenomenon that seriously endangers the control of diseases around the world with a consequent increase in mortality associated with infection. Furthermore, about 80% of microbial infections are associated with the formation of biofilm, a film formed by bacteria enclosed in a self-produced extracellular polymeric matrix, adhered to biotic and abiotic surfaces such as those of implantable materials (prostheses, cardiac devices or dental implants). One of the sources of new antibiotics that have original carbon skeleton to overcome antibiotic resistance are the plants. They produce a plethora of bioactive specialized metabolites used as defense against pathogens and are involved in many physiological processes [1,2].

A screening on endemic plants collected in different regions of the Mediterranean basin was aimed to find new antibiotics. The organic extract obtained from the aerial part of *Cotula cinerea* demonstrated antibiotic activity against *Enterococcus faecalis* and was fractionated by bioguided purification procedures yielding five sesquiterpene lactones. They were identified by spectroscopic methods as the guaiantrienolides 6-acetoxy-1β-, 6-acetoxy-1α-, and 6-acetoxy-10-β-hydroxyguaiantrienolide and the germacranolides haagenolide and 1,10–epoxyhaagenolide. This communication reports the isolation, complete spectroscopic properties and the absolute stereochemistry of these compounds and their specific antibiotic and antibiofilm activity against the clinical and reference isolates of *E. faecalis* [3].

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SYNTHESIS OF BENZOTHIOPHENE DERIVATIVES IN DEEP EUTECTIC SOLVENTS

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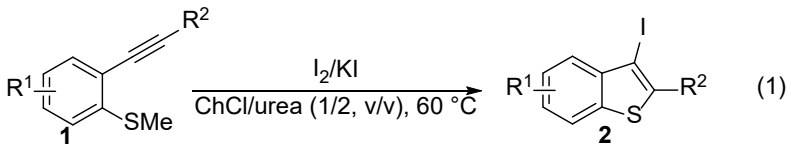
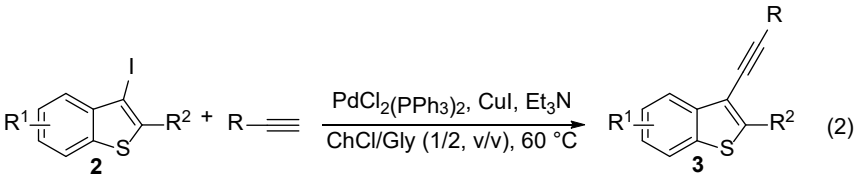
3-Iodobenzothiophenes are very important benzothiophene derivatives. In fact, they are useful precursors for the formation of biologically relevant compounds[1] and as cross-coupling partners for the synthesis of functionalized benzothiophene derivatives and complex molecular architectures.[2] We report here the first example of iodocyclization of readily available 2-methylthiophenylacetylenes **1** in a deep eutectic solvent (ChCl/urea, 1/2 v/v) as recyclable and more sustainable solvent with respect to the classical VOCs employed so far (Eq. 1).



(1)

The 3-iodothiophenes **2** were successfully employed for performing representative Sonogashira (Eq. 2) and Suzuki cross-coupling reactions (Eq. 3) also in deep eutectic solvent (ChCl/Gly, 1/2 v/v). The solvent-catalyst system could be conveniently recycled several times without any loss of activity in both coupling processes, thus further demonstrating the practical usefulness of our approach.



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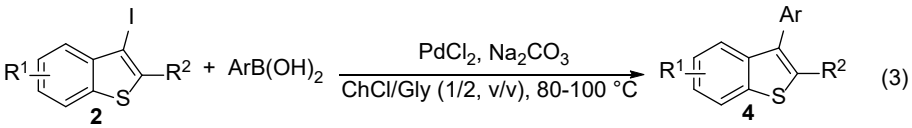

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SELECTIVE LIQUID-PHASE HYDROGENATION OF FLAVONOIDS: NOVEL STRATEGIES FOR SUSTAINABLE CHEMICAL DEVELOPMENT

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Flavonoids are a family of polyphenolic metabolites that can be naturally found in a wide range of plants and fruits. [1] Given the natural abundance of flavonoids, there is an increasing interest in their use as renewable feedstocks in chemical synthesis. Flavonoids can be extracted agro-waste, so the development of processes to convert them to high-value-added products are of paramount importance from the point of view of bio-circular economy. [2]

Selective catalytic hydrogenation is a clean and atom economic transformation used in a wide range of industrial applications and one of the most valuable processes for the sustainable synthesis of food products and pharmaceuticals. In this regard, the hydrogenation of flavonoids under mild conditions in a green solvent certainly meets the demand for environmentally friendly chemical processes. [3]

We have developed strategies for the sustainable and selective synthesis of reduced flavonoids of chemical/œbiological interest based on the liquid-phase catalytic hydrogenation of chalcones and flavanones controlled by the solvent, catalyst and/or substrate.

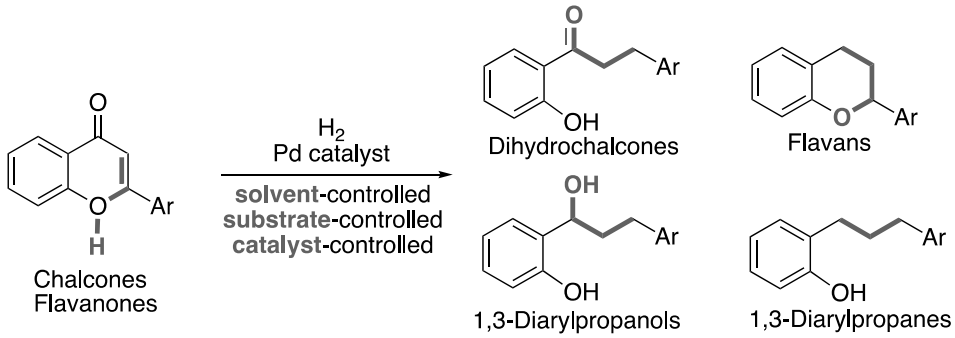

Figure 1. Selective catalytic hydrogenation of chalcones and flavanones

Acknowledgements

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DEEP EUTECTIC SOLVENTS AS SUSTAINABLE MEDIA FOR ORGANIC TRANSFORMATIONS

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In the last few years, the development of new sustainable synthetic methods is oriented toward new pathways that include the employment of environmental friendly solvents, such as the Deep Eutectic Solvents (DESs).[1] Deep Eutectic Solvents represent an innovative class of solvents related to the category of ionic liquids and they are a eutectic mixture of a hydrogen bond donor and a hydrogen bond acceptor. Thanks to their composition and features, DESs are employed in a variety of chemical transformations not only as "innocent" solvents but also as "active" participants in the reaction.[2]

Herein, we report our recent results in the development of multicomponent reactions and intra- and intermolecular cyclization approaches promoted by the presence of DESs (fig 1). In particular, we will disclose the A^3 coupling reaction[3] and a couple of cyclization reactions involving arylalkynes with a reactive group in the *ortho* position promoted by carefully selected DES as "active" solvents.[4]

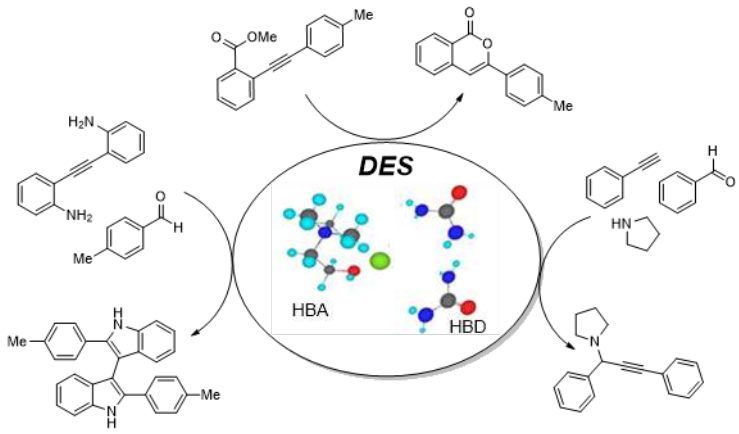

Figure 1

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DEVELOPMENT OF NEW AND SELECTIVE BINDERS OF THE EPIGENETIC READER BRD9

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Epigenetic dysregulation is often linked to several human pathologies, including inflammatory, cardiovascular diseases, and more clearly cancer. Abnormal epigenetics is considered a critical hallmark of human cancers and histone modifying proteins have emerged as novel promising targets for anticancer therapy. Epigenetic modifications are governed by three groups of epigenetic modulators: “writers”, “erasers”, and “readers”. Among the protein reader modules, Bromodomain-containing proteins (BRDs) have recently been receiving growing interest from the scientific community due to their relation to different malignancies and their crucial role in oncogenesis [1,2]. In this context, Bromodomain-containing protein 9 (BRD9) is overexpressed in many human cancers, such as acute myeloid leukemia and human squamous cell lung cancer and has become an attractive therapeutic target for cancer treatment. Therefore, the discovery of new potent and selective BRD9 ligands could be useful for elucidating the biological and pharmacological role of this reader module and for corroborating its therapeutic potential. [3] On the other hand, the discovery of small molecules, endowed with high affinity and selectivity within the BRDs families, represents a significant challenge since bromodomains show a highly conserved overall fold.[4,5] Thanks to the aid of structure-based 3D BRD9 pharmacophore models, recently developed by our research group, herein we describe the design and the synthesis of a new tri-fused heterocyclic scaffold. [6] This represents the chemical core for the synthesis of a wide range of structural derivatives obtained through a quick and high-yielding synthetic approach. Moreover, biophysical screenings and preliminary biological investigations of these new BRD9 modulators are reported.

Acknowledges

The research leading to these results has received funding from AIRC under MFAG 2017 - ID. 20160 project – P.I. Lauro Gianluigi.

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ENANTIOSELECTIVE FORMAL SYNTHESIS OF THE MARINE MACROLIDE (-)-CALLYSPONGIOLIDE

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The isolation of the new macrolide polyketide (**–**)-callyspongiolide from the marine sponge *Callyspongia* sp. collected off the coast of Indonesia was reported by Proksch in 2014.[1] The captivating architecture of (**–**)-callyspongiolide along with its high *in vitro* cytotoxicity and low natural abundance make (**–**)-callyspongiolide an attractive and challenging synthetic target.[2]

Our synthetic approach is based on the construction of two fragments, the macrocyclic core (Fragment **A**) and the side chain (Fragment **B**), which will be joined in the last stages of the synthesis by a Sonogashira coupling reaction. For the assembly of the macrocyclic ring (Fragment **A**), we envisaged a Mitsunobu esterification of carboxylic acid **1** (C_1-C_{10}) with an alcohol **2** (C_{11}-C_{15}) and a subsequent ring-closing metathesis (RCM) reaction leading to the *E*-configurated C_{10}-C_{11} double bond. Starting from an easily accessible aldehyde **3** (C_3-C_7) bearing the first stereocenter (C-5), the preparation of **1** involves the successive formation of the C_7-C_8 bond by a homocrotylboration reaction, and the C_2-C_3 bond by a Still-Gennari olefination.

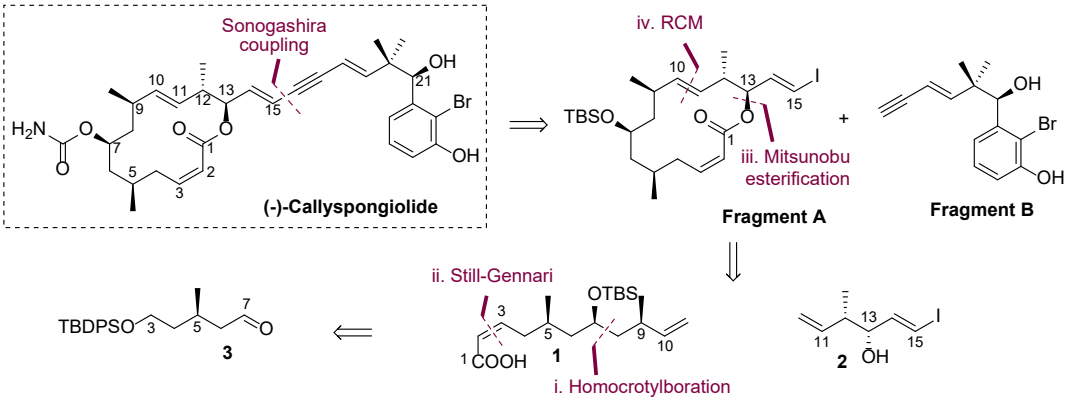

Figure 1. (–)-Callyspongiolide synthetic strategy

Our results in the synthesis of the macrocyclic Fragment **A**, which constitutes an enantioselective formal synthesis of (–)-callyspongiolide, will be presented.[3]

Acknowledgments: Financial support from MICIN/FEDER (RTI2018-093974-B-I00).

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OLEFINATION REACTION BETWEEN ALDEHYDES AND DIBORYLSILYLMETHIDE LITHIUM SALTS

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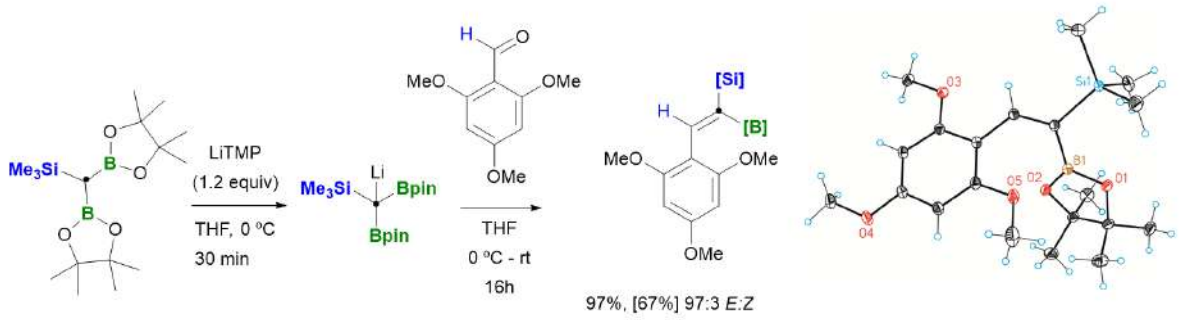
We became interested to launch a systematic study on the olefination of aromatic and aliphatic aldehydes in the presence of the reagent $LiC[B]_2[Si]$ ([B]= Bpin or Bhex, [Si]= $SiMe_3$, $SiMe_2{}^tBu$, $SiPh_2{}^tBu$) with the aim to get densely functionalised 1,1-silylborylated trisubstituted alkenes. The introduction of silyl groups in the polyborylated reagent can be used as an alternative strategy to control the stereoselectivity on the boron-Wittig reaction (Scheme 1).[1] We have found that picolinaldehyde, thiophene-2-carbaldehyde and furan-2-carbaldehyde could be involved in stereodetermining intermediates via intramolecular interaction of N, S or O with B. The condensation of diborylsilylmethide lithium salts with α,β-unsaturated aldehydes provides a direct pathway to synthesize 1,1,-silylborylated conjugated dienes and diynes.



Scheme 1. Boron-Wittig reaction of aldehydes with $LiC(Bpin)_2(SiMe_3)$ for stereoselective trisubstituted alkene synthesis.

Acknowledges

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ASYMMETRIC TANDEM CYCLOAROMATIZATION-INTRAMOLECULAR PICTET SPENGLER REACTION

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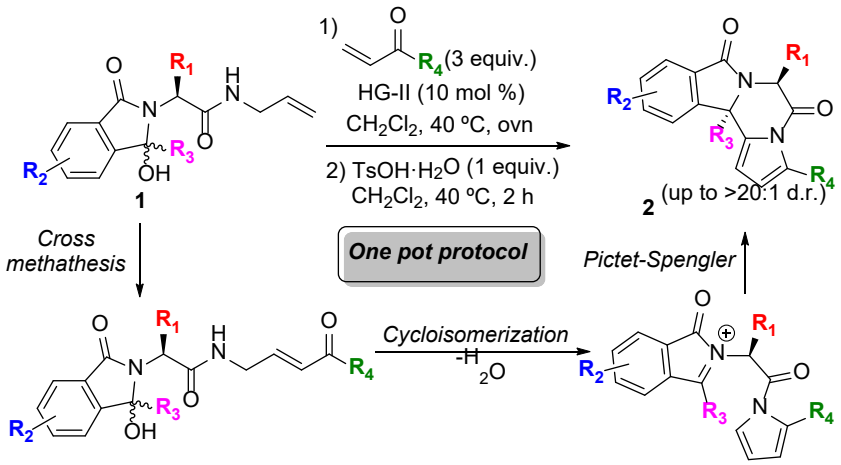
Substituted pyrroles, either in monocyclic form or embedded in polycyclic scaffolds, are structural motifs frequently encountered in many biologically active natural products and therapeutic agents.[1] Therefore, this interesting framework has attracted high interest in synthetic organic chemistry.[2]

The asymmetric synthesis of tetracyclic pyrroles **2** bearing two stereocenters, one of them quaternary, has been devised. The process, that was performed in a one-pot protocol, involved a cross metathesis/ cycloisomerization/ Pictet Spengler-type sequence of substrates **1**, in turn prepared by condensation of the corresponding allyl amide-derived α-amino acids and ortho-acyl benzoic acids.[3]

The overall sequence took place in generally good yields in the presence of second generation Hoveyda-Grubbs catalyst and TsOH, providing the best results in terms of diastereoselectivity with starting materials derived from isoleucine. A wide variety of substitution is allowed at the conjugated ketone, the quaternary stereocenter and the aromatic ring. Those compounds could be considered as Pictet-Spengler conjugates of natural amino acids.

Scheme 1. Synthetic strategy towards polycyclic pyrroles **1**



Acknowledges

We gratefully thank the Spanish Ministerio de Ciencia e Innovación (PID2020-115294GB-I00 to C. P) for financial support. M. E. and D. G. thank the Spanish Ministerio de Educación, Cultura y Deporte for predoctoral fellowships (FPU16/04533 and FPU18/02750).

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TRIFLUOROMETHYLATION OF STRUCTURALLY DIVERSE FEEDSTOCKS VIA SP³ C-C BOND CLEAVAGE

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Trifluoromethyl (CF_3) functional groups have found increasing involvement in the drug discovery pipeline of pharmaceuticals and agrochemicals due to their ability to impart favorable pharmacological properties. The unique steric and electronic properties of the CF_3 group can enhance the pharmacokinetic properties of compounds through improved permeability, lipophilicity and metabolic stability. Targeting this motif, multiple synthetic methods have been developed to assemble C(sp^2)- and C(sp^3)-CF_3 containing molecules via nucleophilic, electrophilic or radical based protocols. Typical substrates amenable to C(sp^3)-CF_3 functionalization leverage the reactivity at unsaturated precursors, preinstalled functionality such as organic halides or activated C(sp^3)-H sites

Looking to diversify molecular building blocks to C(sp^3)-CF_3 scaffolds, we noticed that while carbonyl electrophiles have been heavily explored by direct nucleophilic and electrophilic activation of ketones, more sophisticated approaches at C-C bond functionalization remained unreported. We envisioned that this C-C bond cleavage event may act as a mild and general bond activation to furnish a nucleophilic open-shelled alkyl radical that would be intercepted by an electrophilic CF_3 source.

Herein we disclose a general protocol for C(sp^3) trifluoromethylation of aliphatic carbonyl or alkene precursors via sp^3 C-C bond cleavage. The reaction proceeds under visible-light mediated copper catalyzed or promoted conditions, which offers an operationally simple and scalable protocol to aliphatic trifluoromethylated products.

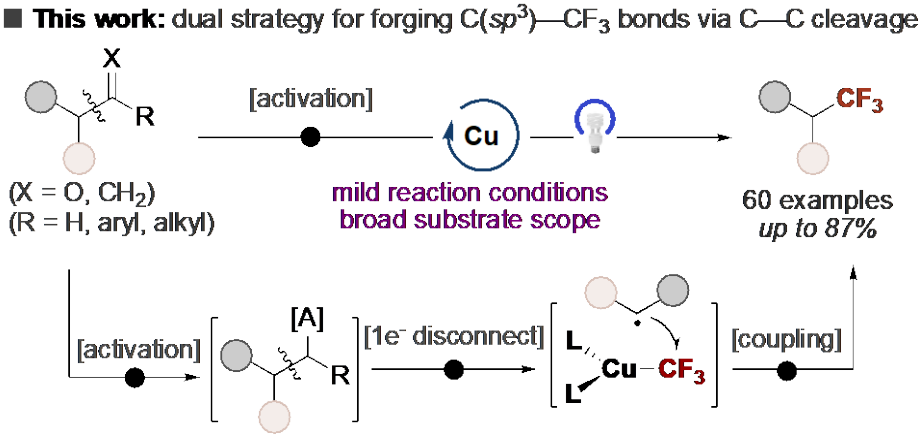

Figure 1. Alkyl trifluoromethylation from unsaturated moieties

In summary, we have developed an efficient protocol for the conversion of structurally diverse feedstocks containing ketones, aldehydes, or alkenes to the corresponding trifluoromethylated analogues by inert sp^3 C–C cleavage. This technology offers an unconventional manifold for enabling trifluoromethylation events with an excellent and diverse chemoselectivity and application profile under mild conditions, even within the context of late-stage functionalization of advanced intermediates. We believe this process will complement current trifluoromethylation methods and would be of considerable value to chemical industry and academia.

Acknowledges

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FIRST TOTAL SYNTHESIS OF (–)-SCHOBERINE B

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(–)-Schoberine B is a tetracyclic alkaloid possessing a 5-carbon exogenous straight side chain. It has been recently isolated from the aerial parts of *Myrioneuron faberi* in People's Republic of China.[1] Since its total synthesis has not yet been described, its structure has not been confirmed and its biological properties remain mostly unknown.

In this presentation, our results in the total synthesis of (–)-schoberine B will be disclosed. Starting from a stereoisomeric mixture of ketoacid **1**, a cyclocondensation reaction with (1*S*,2*R*)-*cis*-aminoindanol is performed leading stereoselectively to lactams **2a** and **2b**, which differ in the absolute configuration of the four stereocenters on the decahydroquinoline moiety. The reductive removal of the chiral inductor from lactam **2a** and the oxidation of the silyl to a hydroxymethyl substituent, allowed the obtention of the enantiopure *cis*-decahydroquinoline **3a** which was transformed into the desired alkaloid (–)-schoberine B. Starting from lactam **2b**, and following the same synthetic sequence, the total synthesis of the enantiomeric (+)-schoberine B was also achieved.

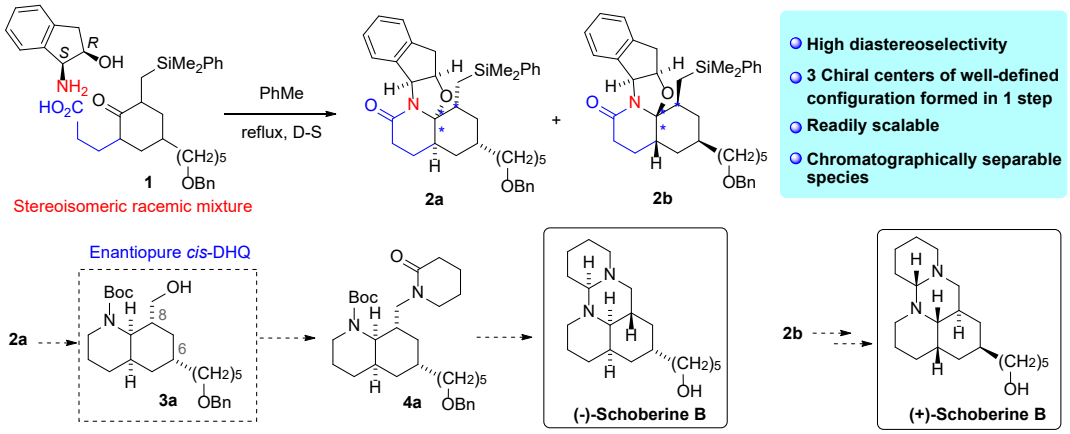

Figure 1. Total synthesis of (–)-schoberine B and (+)-schoberine B

Acknowledges

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COPPER CATALYZED STEREOSELECTIVE CROSS COUPLING OF *GEM*-DIBORYLALKENES

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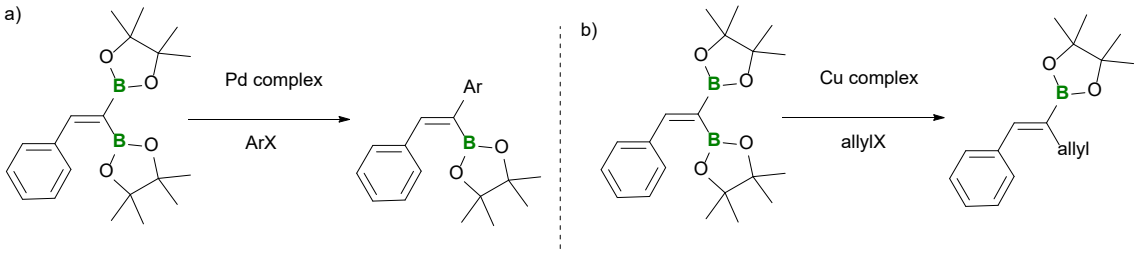
Gem-diborylalkenes have emerged as efficient reagents for selective cross-coupling reactions.[1] Since the two geminal boryl substitutents of the gem-diborylalkenes can be differentiated and transformed in a stepwise manner, palladium complexes demonstrated to catalyse stereoselective cross-coupling with aryl iodides to afford (*E*)-alkenylboronates as single isomers (Scheme 1a).[2] However, despite the fact that copper salts are known to catalyse the coupling between aryl boronate esters with aryl halides,[3] there is no precedents on the coupling with gem-diborylalkenes. Here we disclose the efficient copper catalysed stereoselective cross-coupling of gem-diborylalkenes with allyl halides to afford (*Z*)-alkenylboronates as exclusive isomers (Scheme 1b). [3]



Scheme 1. *Gem*- diborylalkenes cross-coupling using a) palladium complexes vs b) copper complexes.

Acknowledges

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TRIFLUOROMETHYL-DIRECTED GLYCOSYLATION

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Fluorinated carbohydrates are appreciated molecular fragments in chemical (glyco)biology and diagnostics.[1] Available synthetic protocols are mainly restricted to the preparation of mono-fluorinated sugars,[2] whereas trifluoromethyl congeners remain virtually underdeveloped. Other easily accessible trifluoroacetamides and trifluoroacetoxy groups have been reported which are the closest-art in the CF_3-containing glycosides.[3] Herein we present a protocol for accessing a series of previously uncharted 2-deoxy-2-trifluoromethylpyranosides from parent glycals. Exploration of the stereoselective outcome of the glycosylation step revealed a pronounced substrate control rendering 1,2-*trans*-glycosides that arises from the configuration of the CF_3 moiety. The synthetic utility of this approach was further demonstrated with the preparation of CF_3-modified natural glycoside analogs, including disaccharides, steroidal aglycones, amino acids and sphingosine analogs.

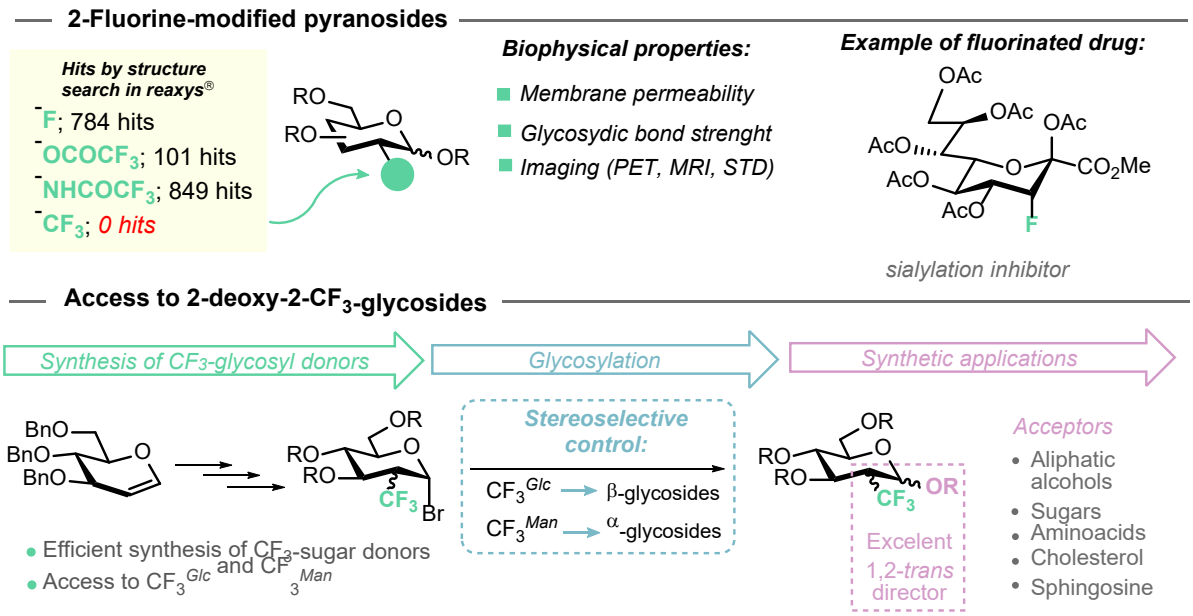

Figure 1. Reported 2-deoxypyranosides bearing fluorinated groups at C-2 position and improved properties of fluorinated sugars (top). Methodology applied for the synthesis of 2-CF_3-glycosides, stereo-chemical outcome of the glycosylation reaction and application of the method using natural analogues (bottom).

Acknowledgments

We thank the Spanish Government-MCIU and the national agency of investigation-AEI (CTQ2017-90088-R, PID2020-120584RB-I00 to O.B., FPI grant PRE2018-085730 to I.B.) and the Universitat Rovira i Virgili (2012BPURV-67 to J.M.) for financial support.

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A NEW SYNTHETIC ROUTE TOWARD THE ENANTIOSELECTIVE CONSTRUCTION OF THE SPIRO[INDOLIZIDINE-1,3′-OXINDOLE] FRAMEWORK

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The spiro[pyrrolidine-3,3′-oxindole] ring system is a structural moiety present in oxindole alkaloids, which constitute a large group of monoterpenoid alkaloids with interesting pharmacological properties. These tetracyclic oxindole alkaloids differ structurally in the functionalized substituent at C-15 and the two-carbon substituent at C-20 and in the configuration at the C-3, C-7, C-15, and C-20 stereocenters (biogenetic numbering). The access to *E*-ethylidene-bearing spiro[indolizidine-1,3′-oxindoles] with a *cis* H-3/H-15 stereochemistry has been little explored. The alkaloid 7(*S*)-geissoschizol oxindole alkaloid was isolated in 2009 from *Tabernaemontana corymbosa*, a Malaysian plant belonging to the Apocynaceae family, which also constitutes the source of several other alkaloids with significant cytotoxic activities. No total synthesis of 7(*S*)-geissoschizol has been reported so far. As an extension of our work on the use of (*S*)-tryptophanol-derived bicyclic lactams for the enantioselective synthesis of indole alkaloids,[1] we have developed an efficient methodology for the generation of spiroindoline[2] and spirooxindole compounds.[3] In this context, we report here a synthetic route for the enantioselective construction of the spiro[indolizidine-1,3′-oxindole] with a *cis* H-3/H-15 stereochemistry, a functionalized two-carbon substituent at C-15, and an *E*-ethylidene substituent at C-20, which is the immediate precursor of the alkaloid 7(*S*)-geissoschizol. The key steps of our synthetic approach are: (i) the preparation of an enantiopure tryptophanol-derived oxazolopiperidone lactam by a stereoselective cyclocondensation reaction with an oxoester derivative, (ii) a highly stereoselective spirocyclization, (iii) the removal of the hydroxymethyl chain, and (iv) the incorporation of an ethylidene side chain on the piperidine ring. Following this route, the 21-oxo derivative of the alkaloid 7(*S*)-geissoschizol oxindole has been prepared.[4]

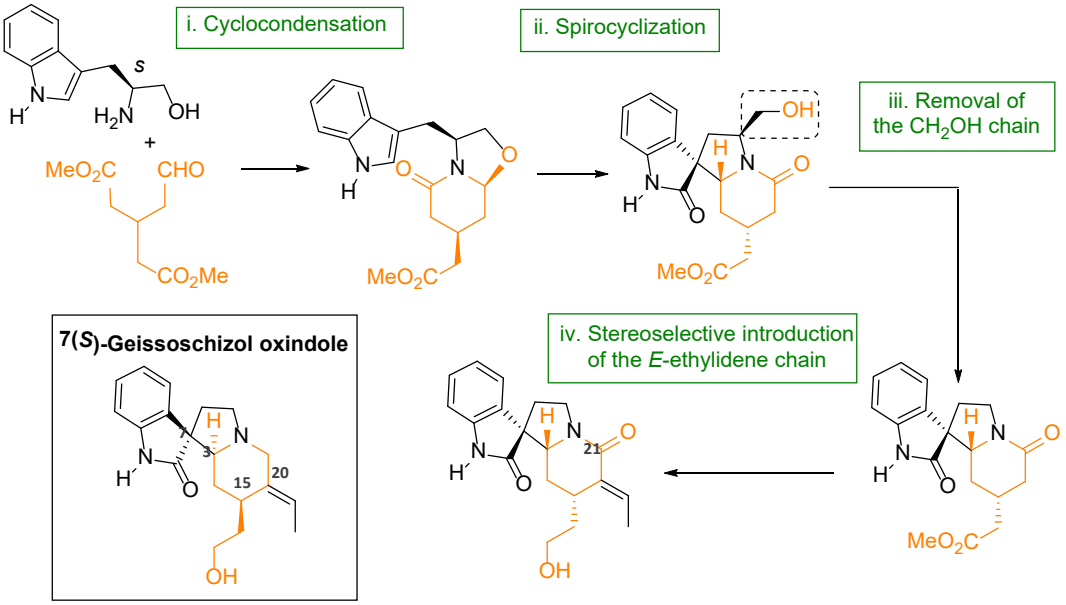

Figure 1.

Acknowledgements:

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GAINING INSIGHT ON THE I(III)-MEDIATED FLUOROAMINATION REACTION OF ALLYL CARBAMATES

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Sphingolipids play a central role in cancer processes. The dynamic balance between Ceramide and Sphingosine-1-phosphate determines cancer cell fate. The inhibition of Sphingosine Kinase 1 (SphK1) by sphingosine analogues has been reported to promote cell apoptosis, thus creating new opportunities for cancer treatment.[1] With the rise of vicinal fluoroamino moieties in anti-tumoral drugs,[2] we envisioned that the synthesis of C3-fluorinated sphingosine analogues might lead to potential SphK inhibitors. A simple way to obtain this vicinal fluoroamino motif is through the I(III)-promoted fluoroamination of an alkene substrate featured with a nitrogen functional group. [3,4]

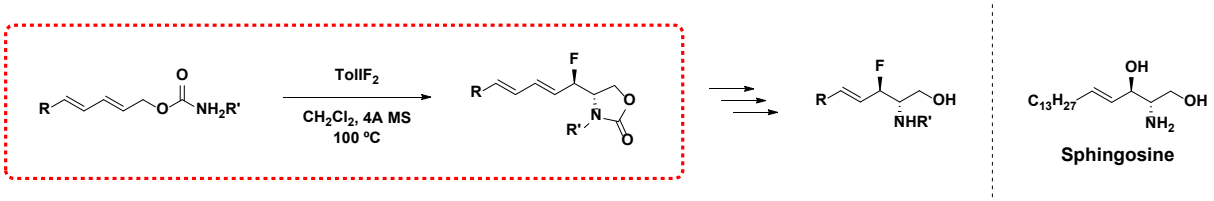

Figure 1. Fluoroamination of allyl carbamates with hypervalent iodine as the key step for the preparation of C3-fluorinated sphingosine analogues.

In this work we will describe the results obtained on the mechanism and reaction scope of the hypervalent I(III)-mediated aminofluorination reaction of model allyl carbamates. An emphasis will be made in studying the effect of the substitution and acidity of the carbamate and the configuration of the double bond on the efficiency and the stereoselectivity of the process. For dienyl carbamates, regioselectivity will be also studied.

Acknowledges

Mineco, Spain (CTQ2017-89750-R); URV for a predoctoral Martí Franquès fellowship (2018PMF-PIPF-26).

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LEWIS ACID CATAYZED EFFICENT THIONATION OF AMIDES BY AN UNCONVENTIONAL S SOURCE

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Over the past years, thioamide derivatives have received special attention by the synthetic community. A part from being useful synthons for preparing sulfur and nitrogen containing heterocycles,[1] thioamides also serve as synthetic isosteres for amides in peptide backbones. Indeed , thioamides are known to improve the thermal and proteolytic stability of amide containing compounds as well as their pharmacokinetic properties.[2] Different pharmaceutical compounds, such as propylthiouracil, thioacetazone or the androgen receptor agonist enzalutamide, derive their activity to the presence of this significant fragment.[3] Despite being rare in biology, this moeity is also present in ribosomally synthesized peptides as well as in known proteins. [4] The current-state-of-the-art for synthesizing this valuable synthon involves elemental sulfur or organic compound bearing a P=S or a C=S bond. Due to the increasing biological relevance and synthetic applicability of thioamides, methods *"[…] for the introduction of the sulphur atom without nasty smelling, functional group compatibility of reagents, easier ways to isolate the resulting thioamides, and lesser amounts of by-products, which have to be frequently handled as wastes, are the key issues to be addressed in the future development of synthetic methods".*[5]

Here we report an innovative methodology for the synthesis of thioamides from the corresponding amide derivative by using an unusual sulphur source (**Figure 1**). This methodology allow the formation of the desired product with the complete absence of organic byproducts. Moreover, the inorganic S source is completely odourless and exhibits a high functional group compatibility. Aromatic and aliphatic amides as well as acetanilides are well tolerated and result in full conversion to the desired thioamide in most of the cases.

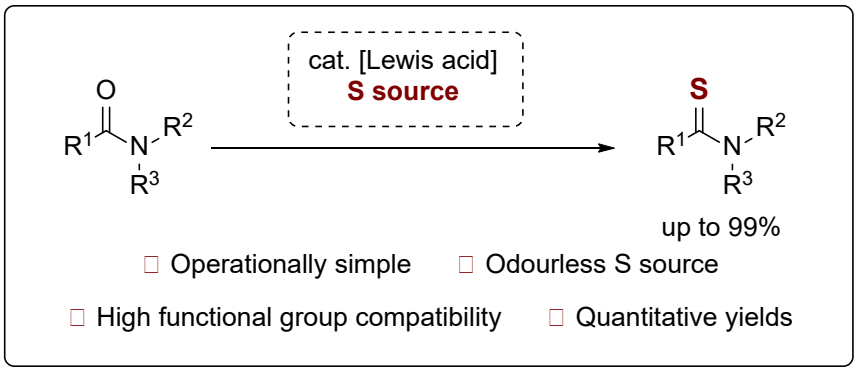

Figure 1. Lewis acid catalyzed thionation of amides.

Acknowledges

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FULL CHARACTERIZATION OF BACTERIAL SIALYLATED ENVELOPE COMPOUNDS

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Pathogenic microbes have evolved the ability to protect their envelope glycans with self-ligands, dampening host immune responses.[1] Various human pathogens, including viruses and bacteria (*Campylobacter*, *Helicobacter*, *Neisseria*, etc.) have evolved the ability to coat cell surfaces with sialic acid-containing ligands, mimicking host glycans. In this way, pathogens can be recognized by inhibitory Siglecs and elude host immune responses, promoting successful bacterial colonization and tolerance [2,3]. Siglecs (sialic acid-binding immunoglobulin-like lectins) represent essential components of the immune system. Because of their ability to preferentially recognize and bind to exposed sialylated glycans on cell surfaces, they act as regulators of a variety of critical cellular mechanisms, including cell-to-cell communication, immunomodulation, and inflammation.[4]

Understanding the role of Glycans and glycosylation in immunity is critical to understanding the etiology and progression of immune-related diseases.[5] Therefore, the structure and function of components of the bacterial sialylated envelope will be presented, to open a route for the design of new glycomimetics for the therapeutic tuning of the Siglecs – sialylated glycans axis.[6]

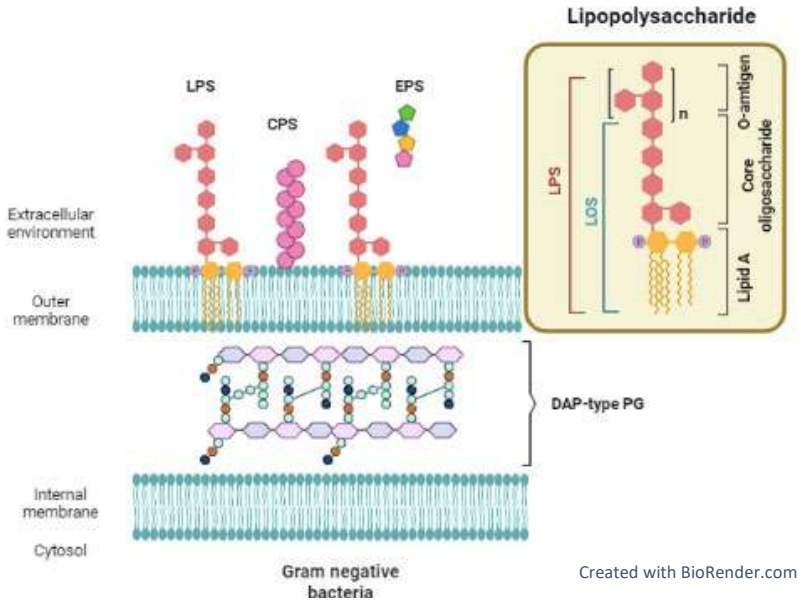

Figure 1. Gram-negative bacteria cell envelope

Acknowledges

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NEW BIO-BASED POLY(ACYLHYDRAZONE) VITRIMERS: SYNTHESIS AND CHARACTERIZATION

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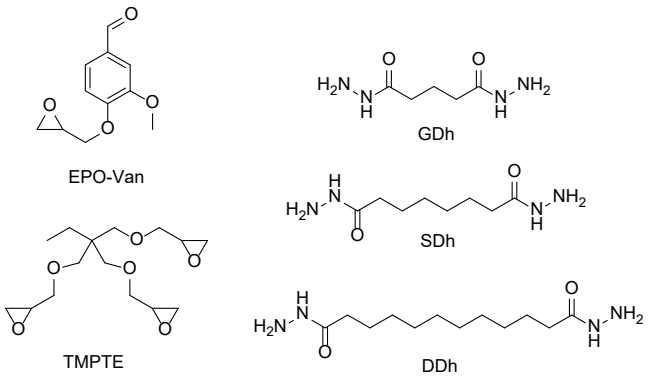
In recent years, products derived from renewable resources have attracted huge interest in materials science to reduce the use of petrochemical compounds as well as to find greener synthetic routes to avoid the depletion of fossil resources. Vanillin is very interesting as a starting compound due to its phenolic and aldehyde groups that can be further modified to get suitable functionality. Moreover, the rigid structure due to the aromatic ring provides high thermal and mechanical properties to the obtained materials. In the present work, we describe the synthesis and characterization of a series of new bio-based poly(acylhydrazone) vitrimers. Three different dihydrazides derived from biobased glutaric, suberic, and dodecandioic acids were obtained in high yields via two-step synthesis as well as the glycidyl derivate of vanillin (EPO-Van).



Scheme 1. Structure of the starting monomers to prepare the poly(acylhydrazone) networks

In 2004, Lehn and co-workers reported the ability of acylhydrazone dynamic bonds to produce dynamers [1]. They stated that the reversibility of these linear polymers relies on the imine group of the acylhydrazone while the amide group provides hydrogen bonding like in polyamides. They demonstrated the exchangeable behaviour of these bonds upon heating by combining poly(acylhydrazone)s with different aldehydes or dihydrazides. However, the interchange reaction between acylhydrazones in thermosets by imine metathesis has never been reported. In our study, it has been confirmed by the use of model compounds and GC

analysis. This process does not require any excess of dihydrazide or the presence of any catalyst.

Dihydrazides were prepared by Fischer esterification of dicarboxylic acids and further reaction with hydrazine hydrate [2]. Dihydrazides and EPO-Van monomers were condensed to get vitrimers containing acylhydrazone dynamic covalent bonds. To increase flexibility trimethylolpropane triglycidyl ether (TMPTE) was added. Since EPO-Van has epoxy and aldehyde reactive groups, in this curing system, before the epoxy-amine reaction, aldehydes react with -NH_2 of dihydrazides due to the latent character of these compounds as epoxy curing agents [3]. The dihydrazides were added in stoichiometric proportions, with an EPO-Van/TMPTE molar relation 3:1. Cross-linked materials were successfully obtained as thin red films with high transparency. They were characterized by FTIR to confirm the complete reaction and then, they were characterized by TGA and DMTA.

To confirm the vitrimeric nature of the networked poly(acylhydrazone)s, the time temperature-dependent relaxation behaviour was investigated. The stress relaxation curves revealed that these materials were capable of rapidly relaxing stress, by reaching the reference relaxation value of 63% (σ/σ_0 = 0.37) in less than one minute at 185 °C for poly(GDH), in 1.5 min at 170 °C for poly(SDH) and in almost 3 min for poly(DDH) at 160 °C. From these experiments, it can also be calculated the time for almost total relaxation of the networks, which is reached in nearly 3.5, 5, and 10 min, respectively at 190 °C.

The recyclability of the materials prepared was also investigated. The temperature of recycling was set to 190 °C to avoid degradation. The material before and after recycling showed similar DMTA curves, proving the possibility of recycling. The thermosetting nature of these materials was proved by heating in dichlorobenzene at reflux for 12h. The 98.5 % in weight was recovered. However, on treating them with a 2M HCl solution/THF 8:2 mixture for 24 h at 70 °C, the starting dicarboxylic acids could be recovered, indicating that these thermosets can be hydrolysed in acidic conditions.

Acknowledgments

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SIDEROPHORES AGAINST *PYRICULARIA ORYZAE*

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Rice *(Oryza sativa L.)* is the major staple food for more than 50% of world's population, providing approximately 19% of the daily calories consumed. Italy is one of the major producers and exporters within the EU with an average production of 1.3 million metric tons. The most destructive rice pathogen worldwide is *Pyricularia oryzae*, causing globally 30% yield losses, with an enormous economic impact. The management of the rice blast disease requires a massive application of fungicides, which accounts for more than 8% of total fungicide market.[1]

During the years, diverse fungicide classes have been used against *P. oryzae*.[2,3] In Italy, only two classes of fungicides are currently approved for *P. oryzae* treatment: strobilurins and demethylation inhibitors (DMI).[4] Despite their great potential, both fungicide classes have a single-site mode of action, which makes them prone to resistance development in fungal pathogen populations.

Considering the above mentioned drawbacks, the discovery and validation of new targets and/or new scaffolds are urgently needed. In this scenario, the modulation of ferroptosis, a newly defined form of iron-dependent cell death, has recently emerges as a potential new strategy to control fungal pathogenesis. In *P. oryzae* ferroptosis takes part to the conidial cell death during the infection of the fungus. It starts in the terminal conidial cell, and then progresses to the other two cells during the appressorium formation and maturation, and this ferroptotic cell death is required for the infection. For the initiation of ferroptosis in the pathogen, ferric ions (Fe^{3+}) and not ferrous ions (Fe^{2+}) are responsible.[5]

Herein, we present the synthesis and biological activity evaluation of novel iron chelators (siderophores) designed to suppress ferroptosis. In particular, natural and nature-inspired compounds containing the catecholamide or the hydroxamate moiety, and hybrid molecules having the siderophore scaffold linked to the pharmacophore of active antifungal compounds were prepared and tested against *P. oryzae*.

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DEVELOPMENT OF NEW AZOBENZENE C-H ACTIVATION REACTIONS

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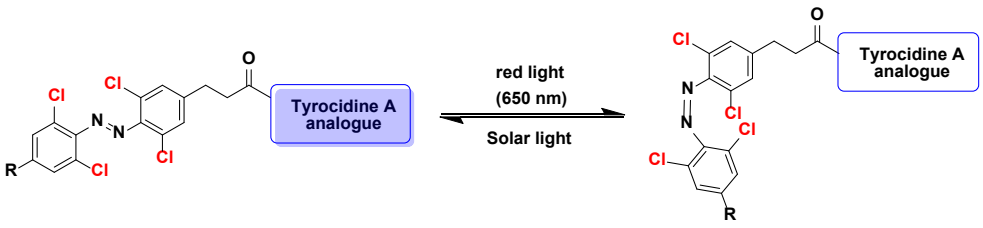
The increase of antimicrobial resistances is already showing worrying damaging effects and it is set to be one of the biggest challenges humanity is facing.[1] In recent years, some approaches have been tackled which employ light to combat this issue. Photopharmacology has been applied to a great variety of targets due to the orthogonality and great spatiotemporal control light offers .[2] As such, various precedents have appeared showing how antimicrobial resistance can be tackled using molecular photoswitches.

Within this context lie our group's interests. Recently, we reported photoswitchable tyrocidine A analogues, which by introduction of tetra-*ortho*-chloro-substituted azobenzenes accomplish the isomerization, and corresponding activation via red light of their antibiotic properties. Subsequent exposure to solar or white light led to their deactivation. These photoswitches allowed for the activation of the antibiotic in a controlled manner using benign visible light and once the antibiotics are excreted and enter in contact with solar or ambient white light, they are isomerised back to their inactive form.



In this work, we aim to develop a methodology to synthesize *tetra*-ortho-methoxylated azobenzene amino acids as photoswitchable building blocks. These azobenzenes can be also isomerized using red light instead of harmful UV light and are more robust towards nucleophilic aromatic substitution, thus broadening their scope of application.[4]

Here we present our main advances in the development of these C-H activation methodologies for azobenzene moieties.

Acknowledges

We acknowledge Prof. Mercedes Amat Tusón for their support of this work and our group.

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P2-13

BYPASSING *PYRICULARIA ORYZAE* RESISTANCE BY NOVEL ANTIFUNGAL AGENTS TARGETING CYTOCHROME BC1 COMPLEX

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Phytopathogenic fungi are responsible for huge crop losses every year, with consequent economic damage. *Pyricularia oryzae* represents the most dangerous fungal phytopathogen being the cause of rice blast, a highly destructive disease widely distributed across the world.[1] In this context, the spread of fungicide resistance, which is hampering the use of commercially available agrochemicals (e.g. strobilurins, benzimidazoles, dithiocarbonates and azoles), constitutes an additional global threat.[2], [3] An example is given by the G143A mutation in the *cytochrome b* of *P. oryzae*, responsible for the loss of efficacy of strobilurins. Thus, the identification and development of novel lead compounds for crop disease management are of utmost importance these days. In this work, two libraries of commercially available compounds (Agrochem and Biodesign) were screened employing a three-dimensional model of *P. oryzae* cytochrome *bc1* complex.[4] Compounds with the best glide score and whose binding mode was characterized by the presence of relevant interactions (**Figure 1**), were selected as a starting point for the synthesis of a small collection of molecules including: 6-phenylpyridazin3(*2H*)-ones, aryl-amides, aryl esters and hydrazones. The obtained compounds were

tested on a panel of eight phytopathogenic fungi including a wild-type and a strobilurin-resistant strain of *P. oryzae*. Compound **1b** (**Figure 1**) displayed the most interesting results, showing a promising inhibitory activity towards both the wild-type and the strobilurin-resistant strains of *P. oryzae.*

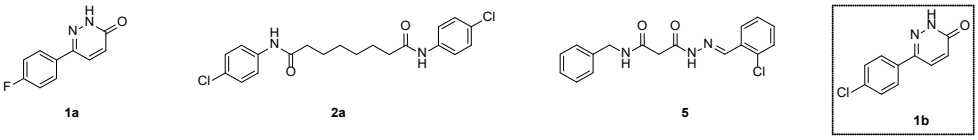

Figure 1. Chemical structures of the top scoring molecules; compound **1b**.

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CHEMICAL APPROACHES TO TARGET TUBULIN/MICROTUBULES DYNAMICS

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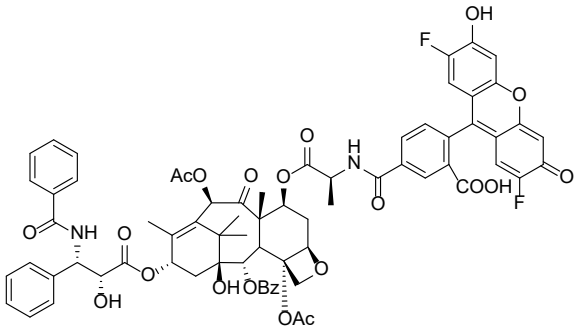
The sheer abundance and variety of microtubule(MT)-targeting agents (MTAs) still continues to inspire the scientific community, even after decades of their successful application as chemotherapeutics (e.g., paclitaxel, maytansine). One of the new horizons of tubulin modulation is the employment of MTAs in the symptomatic treatment of neurodegenerative pathologies, a class of diseases characterized by axonal transport deficiencies. The impairment of neuronal transport has been linked to axonal MT instability and to a progressive loss of MT mass in neurons, features that could potentially benefit of the use of microtubule-stabilizing agents (MSAs). In parallel, new insights on the structural modifications exerted by MTAs on the MT lattice are needed, aiming to understand their effect on cellular transport. As a part of European ITN network TubInTrain, our research focuses on these aspects in two complementary ways: through the chemical modification of known MSAs, and the rational design and synthesis of novel MTAs.

Chemical modifications of known MSAs:

The chemical modification of paclitaxel, the progenitor of the broad anti-cancer taxane class, sparked from an observation: fiber diffraction experiments revealed that Flutax-2 (Figure 1), a fluorescent taxane bearing a bulky substituent in position C7, expands the microtubule lattice – in contrast with the behaviour of other taxanes. It can even compact intrinsically expanded lattice models [unpublished data].

Figure 1



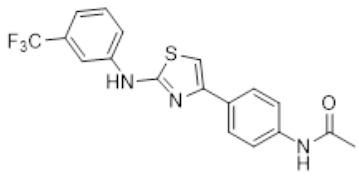
Flutax-2 chemical structure.

To further investigate this interesting result, we planned the synthesis of a series of derivatives of paclitaxel presenting bulky substituents in position 7, aiming to understand which is the steric requirement that produces the inversion of the expansion behaviour. After computational validation, the synthesis of two of the initially proposed fifty structures has been carried out.

Rational design of new MTAs:

Traditionally the binding sites on tubulin are regarded as six, but in the last year the research groups composing our ITN Network published the discovery of a new completely characterized binding site[1], and 11 smaller ones identified via a comprehensive crystallographic fragment screen[2]. Furthermore, a follow-up publication demonstrated that it is possible to “grow” a fragment binding to a novel site, dubbed the Todalam site (Figure 3), located at the inter-dimer interface into fully active tubulin targeting agents, able to modulate MT dynamics.[3]

Figure 2



Todalam chemical structure.

We planned the synthesis of a series of (a) paclitaxel derivatives presenting bulky substituents in position 7 (Flutax-like) and (b) Todalam inspired molecules. Their interaction with tubulin/microtubules has been studied by fiber diffraction and X-ray crystallography experiments. In my presentation I will report the latest developments of this project.

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DIRECT AND ENANTIOSELECTIVE REACTIONS CATALYSED BY CHIRAL Ni(II) COMPLEXES

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The stereocontrolled construction of carbon-carbon bonds is one of the most challenging tasks for the synthesis of chiral natural products and other bioactive compounds with relevant therapeutic properties. In this context, transformations based on the reaction of metal enolates play a prominent role among the synthetic methods employed for obtaining those molecules of interest.[1]

For many years, the stereochemistry of these enolate-based reactions has been controlled by chiral auxiliaries,[2] but the continuing demand for increasingly more efficient procedures in accordance with the atom economy[3] has given rise to the emergence of a vast number of catalytic transformations for the asymmetric construction of carbon-carbon bonds,[4] paying special attention to those methods that underlined the benefits of using easily removable scaffolds attached to the carboxylic moiety.[5]

Inspired by such precedents and after studying the synthesis of one single stereocentre,[6] the group has been focused on developing direct and enantioselective reactions on *N*-acyl thioimides catalysed by chiral Ni(II) complexes with *in situ* activated electrophiles derived from aldehydes that lead to the asymmetric formation of two chiral centres simultaneously through an open transition state.

First developed methodology allows the synthesis of silyl-protected *anti*-aldols with remarkable yield and diastereoselectivities and excellent enantioselectivities from a wide array of *N*-acyl groups and aromatic aldehydes,[7] providing enantiomerically pure intermediates of high synthetic interest when the achiral platform is removed properly. XIII Spanish-Italian Symposium on Organic Chemistry

Similarly, an analogous reaction using aromatic acetals as electrophiles has been studied, allowing the construction of the corresponding *syn* product instead also in high yields, good diastereoselectivities and excellent enantiocontrol.

Hence, both *syn* and *anti* adducts are available using either of the two methodologies, just being aware of using the correct combination of scaffold, catalyst and activated electrophile, as well as removing the carboxylic moiety properly to obtain the required intermediate.

Acknowledgements

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TRIPODAL LIGANDS FOR FIRST-ROW TRANSITION METALS AS POTENTIAL CATALYSTS

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Activation reactions of highly inert substrates, as are saturated hydrocarbons, require highly electrophilic metal catalysts. Traditionally, these processes have been developed using late second or third row transition metals such as palladium, platinum, or iridium.[1] The application of first row transition metals on these processes is gaining importance in our days. These less reactive first row metal centers need more sophisticated ancillary ligands to achieve efficient transformations. However, their development is worthy due to the undoubted benefits derived from economic and environmental issues.

Ancillary ligands that present small catalytic pocket and electron releasing character could facilitate the coordination of the metal centers with the highly inert C-C and C-H bonds.[2] In our approach polypyrazolyl ligands have been selected due to the possibility of fine tuning of their electronic and steric properties by modifying the number and position of substituents on the pyrazolyl rings, which allows fine-tuning of the open-coordination site and the coordination ability.[3]. This strategy allows the synthesis of ligands with both low electron density and small catalytic pocket (Figure 1).

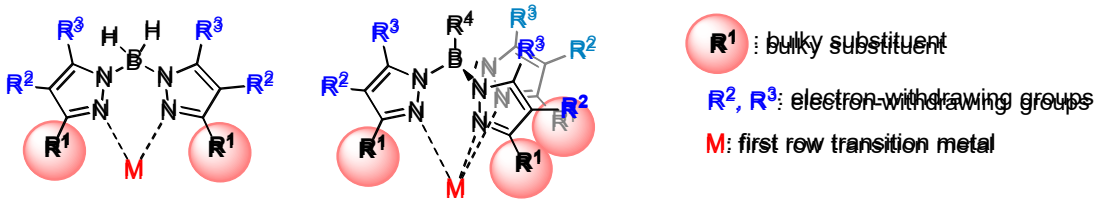

Figure 1.

Here we present the use of these new ligands in the synthesis of first row metals complexes. The k^3-coordination of the metal by the scorpionate,[4] the presence of bulky substituents in R^1 and the reduced basicity of the coordinating nitrogen atoms is traduced in an electronic stabilization of low oxidation states of the metal centers. This special stabilization is being exploited in several catalytic processes.

Structural determination of the coordination mode in the new metal complexes is carried out by single crystal X ray diffraction (Figure 2).

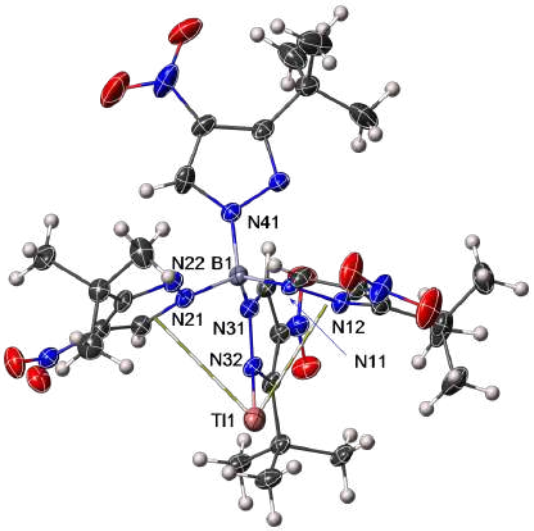

Figure 2.

Acknowledgements

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DIHYDROQUINAZOLINONES AS ADAPTATIVE C(SP^3) HANDLES IN ARYLATIONS AND ALKYLATIONS BY DUAL CATALYTIC C–C BOND-FUNCTIONALIZATION

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Transition-metal-catalyzed cross-coupling reactions are convenient technologies for the rapid construction of carbon-carbon bonds. These approaches have been widely applied to the preparation of biologically relevant molecules and functional materials, by academic and industrial institutions alike.[1,2] Consequently, there is continual interest in methods that can render traditionally inert functionality as cross-coupling partners, included in this are ketones which are widely available commodity chemicals and easy to install synthetic handles.

Synthetic manipulations of ketones generally rely on their latent polarity, specifically the electrophilicity of C=O bonds[3] and nucleophilicity of enolate[4] related structures. In contrast, the selective and catalytic cleavage of ketone *α* C−C bonds as a platform for installing chemical functionality remains challenging.[5,6] However, such techniques hold promise for creating conceptually new disconnections during retrosynthetic analysis.

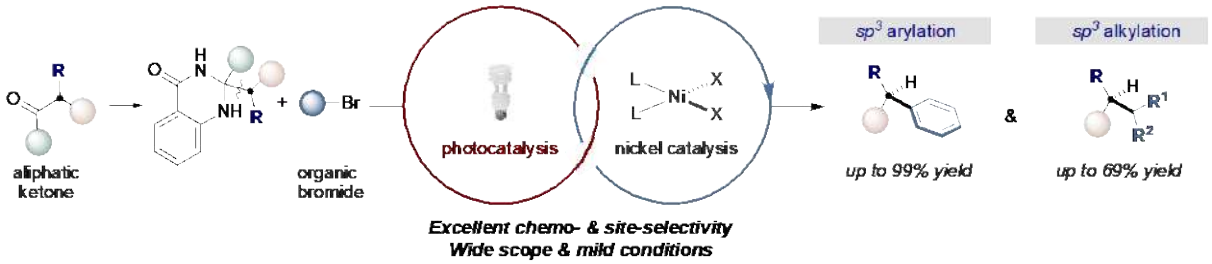

Figure 1. Metallaphotoredox approach for using ketones as cross-coupling synthons.

We have developed a dual catalytic strategy that utilizes dihydroquinazolinones derived from ketone congeners as adaptative one-electron handles for forging C(sp^3) architectures via *α* C–C cleavage with aryl and alkyl bromides.[7] This method is distinguished by its wide scope and broad application profile, providing a catalytic technique complementary to existing C(sp^3) cross-coupling reactions that operates within the C–C bond-functionalization arena. Mechanistic experiments were conducted, all of which are consistent with the operation of a reductive quenching photoredox cycle, beginning with single-electron oxidation of dihydroquinazolinones by excited-state photocatalyst resulting in radical fragmentation driven by formation of an aromatic by-product.

Acknowledges

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DIRECT PREPARATION OF α-CHLOROIMINES AND CHLOROENAMINES USING GOLD(I) CATALYSIS

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α-Monohalogenated imines and enamines are highly reactive invaluable intermediates in the synthesis of nitrogen-containing heterocycles and α-haloamines due to the presence of two contiguous electrophilic positions.[1] These versatile building-blocks have been prepared through the halogenation of a previously formed imine or enamine [2] or through condensation of the corresponding α-chloroketone.[3] Both processes have severe limitations due to the use of high excess of reagents or the formation of secondary products. The special instability of chlorimines and chlorenamines against hydrolysis introduces an additional drawback during their purification (Figure 1).

Previous work

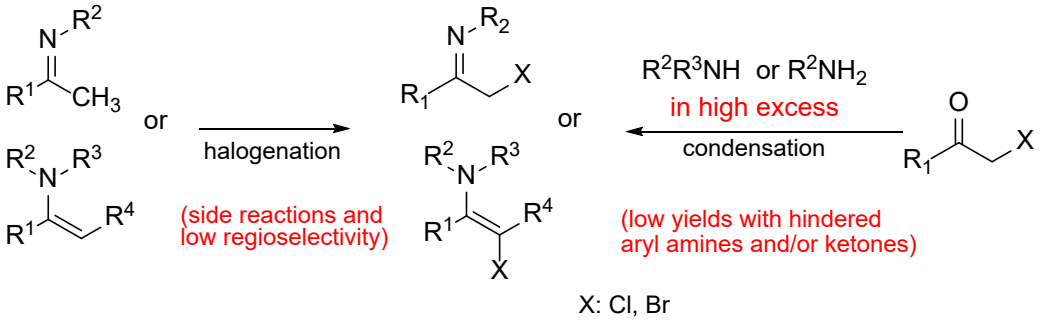

Figure 1.

Intermolecular hydroamination of alkynes has recently been highlighted as one of the best alternatives for the synthesis of imines and enamines. Here we present a new preparation of chloromethylketimines and chloroenamines through the gold(I)-catalyzed hydroamination of chloroalkynes with primary and secondary aromatic amines (Figure 2). The reaction proceeds with clean, direct and complete conversion, total selectivity, and atom economy using equimolar amounts of reagents and 1 mol % of commercially available IPrAuCl, activated with NaBArF, as catalyst. These results open a way to the synthesis of a new family of aromatic chloroenamines not accessible up to date and the preparation of versatile building-blocks as chloromethylketimines, precursors of indoles and β-chloroamines, among others, through one-pot two step procedures using this new strategy.

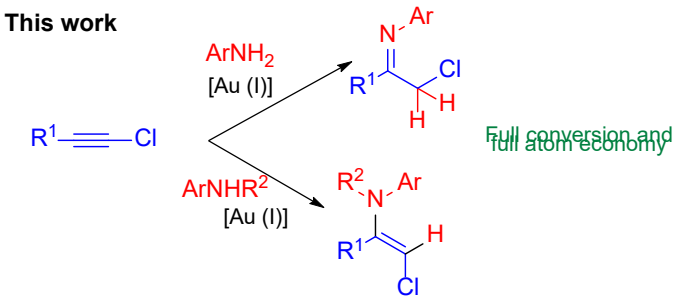

Figure 2.

Acknowledges

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SMARTPHONE BASED SENSING OF STRESS BIOMARKERS BY OPTICAL ARRAY

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The development of sensors that can quantitatively measure stress biomarkers in our fluids, such as blood, urine, saliva, sweat, and tears, have a significant impact on the field of medical diagnosis.[1] The release of neurotransmitters and hormone by the nervous and endocrine systems, respectively, is one of the essential reactions of our body to stress exposure. Therefore, primary stress markers include small-biomolecules and neurotransmitters, such as catecholamines and hormones, including dopamine (DA) and cortisol, respectively.[2]

Our target is to develop sensoristic devices to detect stress biomarkers in harsh and adverse environments, such as space missions.[3] We have chosen to exploit the Array technology for the realization of the sensor device, due to its peculiar characteristics: *i*) easy to use, *ii*) extremely selective, *iii*) sensitive; *iv*) easily implementable.[4]

Array was designed considering an optical output. In particular, we selected and synthetized some organic fluorophores (probes) considering two important features: 1) spectral properties of the transductor, in particular due to the absorption/emission range of the probe; 2) interactions with the analyte by non-covalent interactions, such as hydrogen bonds, ion-dipole interactions, dipole-dipole and π–π interactions.

Taking into account these considerations, the selected and synthetized fluorescent probes are bodipys, naphtalimides, rodhamines, macrocyclic receptors (Figure 1).

The interaction between each probe and the stress marker has been tested previously in solution, then the Array response has been analyzed by using a commercial smartphone as detector. The ability to analyze optical data using a common smartphone (equipped with a high-resolution camera) is an added value compared to common (and traditional) optical and analytical techniques, such as UV-Vis, fluorescence and chromatography.[5] The use of a smartphone for this purpose opens up the possibility of being able to perform quick analyzes in the field.

These features avoid a complicated sampling and the necessity to have highly specialized staff.

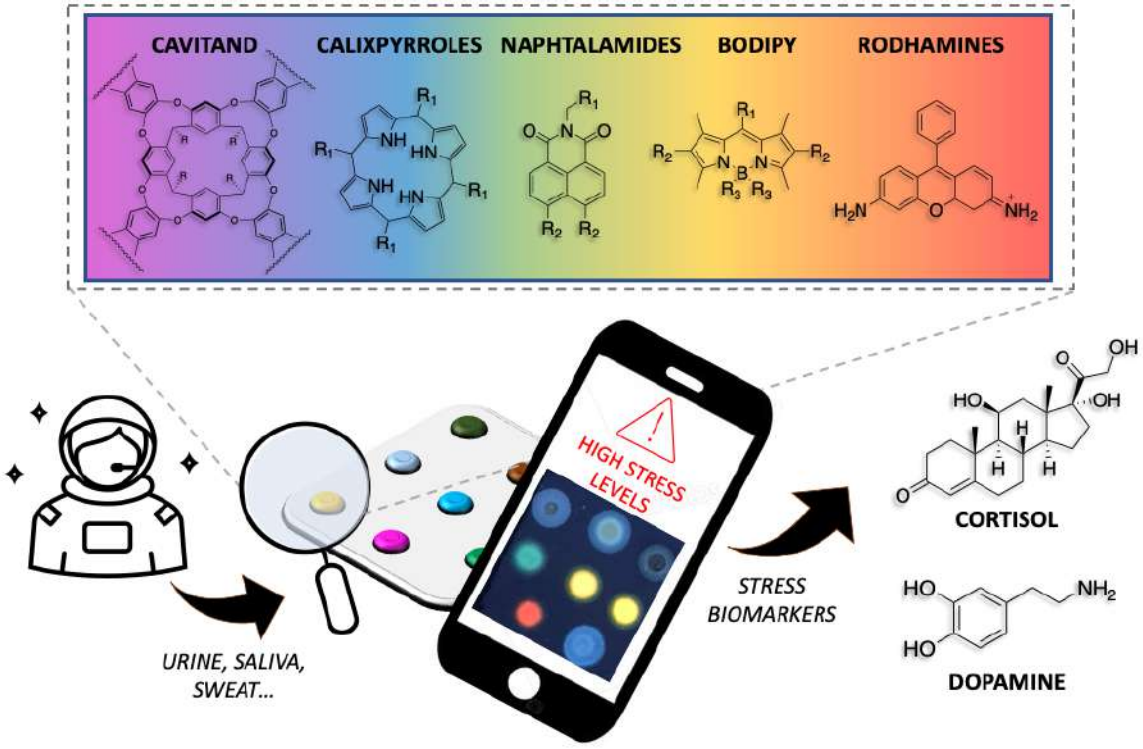

Figure 1. Real sample of the sensoristic device.

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SENSING OF CHEMICAL WARFARE AGENTS: A SUPRAMOLECULAR APPROACH

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The use of toxic chemical compounds, also called Chemical Warfare Agents (CWAs),[1] previously used also as pesticides, is still current, as demonstrated by the recent international scenario.[2] Detection of CWAs can be performed by instrumental techniques, which show excellent sensibility and selectivity, however they are expensive in term of cost time-analysis, and size, thus precluding the real application. In the last decade, a new sensing method based on the supramolecular interactions between a sensor and CWAs has been developed.[3,4] This strategy, named as “Supramolecular Approach”, shows some advantages respect to the covalent sensing. In particular, Supramolecular Approach leads to the possibility *i*) to reuse the sensor, *ii*) to improve the affinity for the CWAs by an appropriate design of the receptor/sensor and *iii*) avoid false-positive response due to the possibility to establish multiple interactions between sensor and analyte (Multi-Topic Approach). In this contribution we report our results in the supramolecular recognition of CWAs exploiting different strategies:

i) Acid-Base interactions, due to the interaction between CWA and a Acid-Lewis metal center;[5]

ii) H-bonds formation, due to the ability of ethanolmine moiety to recognize CWA molecule by hydrogen bonds;[6]

iii) and Multi-Topic approach, in which different non-covalent interactions occur simultaneously with the analyte, thus leading to higher affinity and selectivity.[7]

We demonstrated that efficiency and selectivity in the CWAs recognition can be modulated by the appropriate design of the receptor. In addition, detection of CWAs by fluorescent supramolecular receptors can be performed also by using a smartphone as detector, leading to a smart use in real fields.[8]

Figure 1.

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SYNTHESIS OF MMPS-RESPONSIVE LIPOPEPTIDES FOR TREATMENT OF NEURODEGENERATIVE DISEASES

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Central nervous system (CNS) disorders and brain cancers are some of the most devastating and yet poorly treated diseases, that are increasing in prevalence due also to our extended lifespan. In the last decades, efforts to design innovative therapeutics have failed to generate the desired outcomes, and the inability of putative drugs to cross the Blood Brain Barrier (BBB) is among the main reasons of such failures. [1]

Alzheimer ‘s disease and Glioblastoma are characterized by upregulation of matrix metalloproteases (MMPs), in particular MMP2 and MMP9, involved in the degradation of extracellular matrix. [2]

Their pathological activity can be exploited as a stimulus to trigger a responsive drug release from MMP-sensitive, BBB-permeable liposomes. [3]

Thus, we rationally designed and targeted synthetically some metalloprotease (MMPs)-responsive peptide-fatty acid chimeras, and we assessed their compatibility with liposome assembly; such nanovectors (Figure 1) were checked for their instability / ability to locally release their payloads in response to increased MMP2 and MMP9 levels. Controlled drug release was achieved through chemically modified lipidic components that respond to internal or external stimuli; their synthesis will be detailed in my presentation.

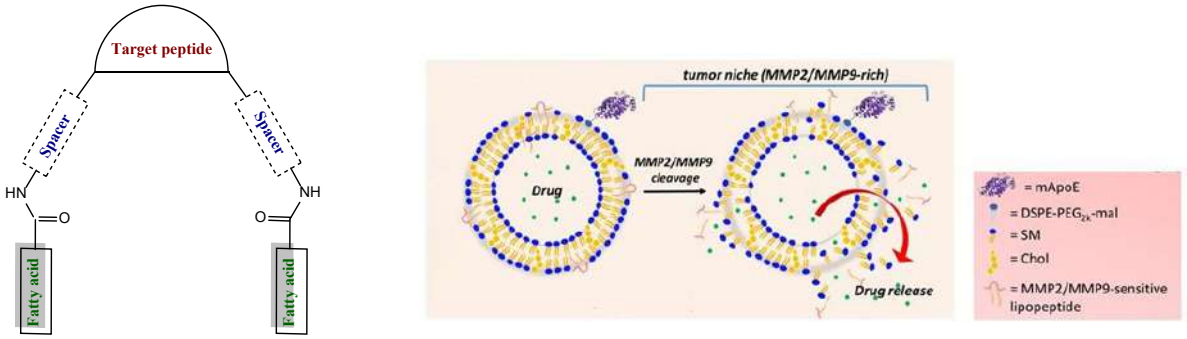

Figure 1. General structures of MMP2/9-specific peptide-fatty acid hybrids (left) and representative scheme of targeted-delivery of drugs to tumor cells (right).

Acknowledges

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NICKEL-CATALYZED HYDROALKENYLATION OF AZIRIDINES

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In 2002 Hillhouse demonstrated that Ni(0) and Ni(II) complexes can react with aziridines forming a so-called azanickellacyclobutanes (Figure 1, center).[1] Based on this investigation, many catalytical processes involving these metallacycles have been developed during last decade.[2] Recently, in the group of prof. Martin we expanded a scope of known coupling partners in the reaction with aziridines on CO_2 and developed an elegant protocol for β-amino acids synthesis (Figure 1, left).[3]

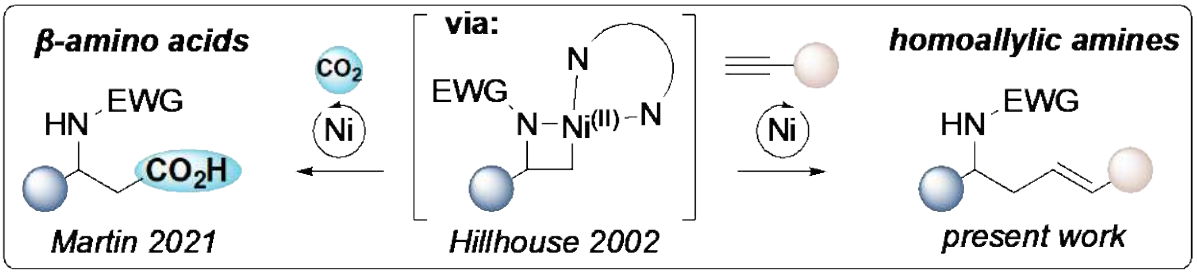

Figure 1. Aziridines as a synthetic platform

Following our interest in the further investigation of reactivity of such metallacycles, herein we report our recent progress in Ni-catalyzed hydroalkenylation of aziridines (Figure 1, right). Developed reaction shows and absolute regioselectivity, demonstrates a high functional group tolerance and allows to achieve homoallylic amines with good yields under mild reaction conditions.

Acknowledges

D.P. Zimin thanks European Union's Horizon 2020 for an ITN fellowship 859910.

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ALKENE ELECTROPHILIC CYCLIZATION MEDIATED BY A CATIONIC CARBYNE EQUIVALENT

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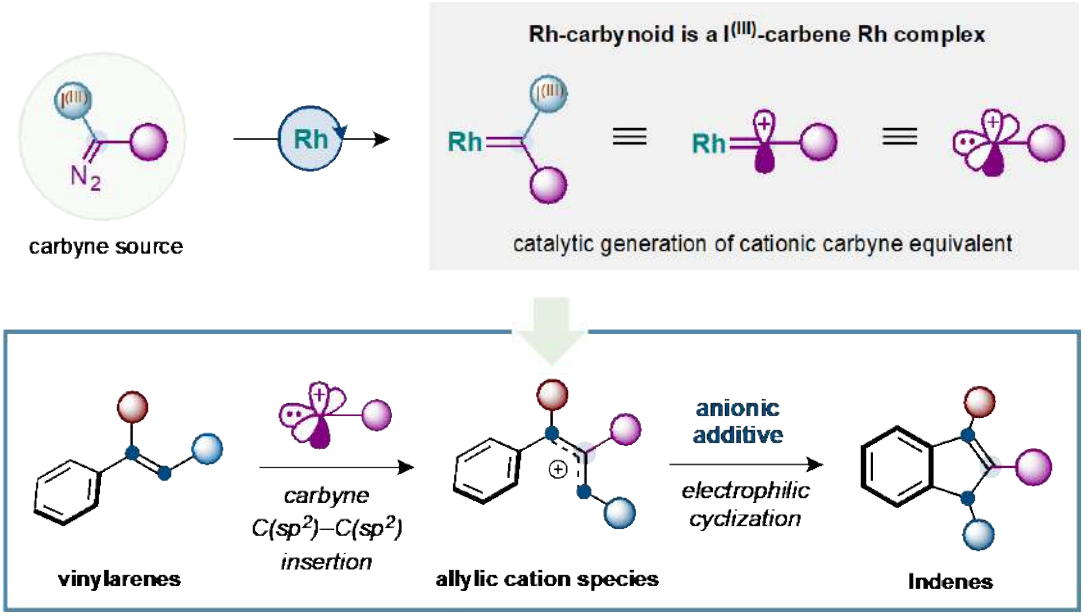
Organic reactions involving the cationic 4π-electrocyclic ring closure has been heavily employed in the synthesis of cyclic compounds.[1–3] In this regard, prevalent synthetic approaches to pharmaceutical and material relevant compounds with indene skeleton inevitably goes through such electrophilic cyclization methods.[4] However, the need for complex prefunctionalization to access electrophilic partners in strong Lewis acidic or harsh conditions, limits the scope and utility of such methodologies.[5] Our group reported the first catalytic generation of Rh-carbynoids as cationic carbyne equivalents from diazo-containing hypervalent iodine reagents.[6] We found that our Rh-carbyne equivalents provoke C–C bond scission by inserting the cationic monovalent carbon unit between both sp^2-hybridized carbons. This skeletal remodelling process accesses synthetically useful allyl cation intermediates that conduct to valuable allylic building blocks upon nucleophile attack.[7,8] Recently, we wondered whether we could selectively control cationic 4π-electrocyclic ring closure of allyl cations, thus providing streamline access to valuable indenes from readily available vinylarenes. In this communication, we would like to show the successful development of this idea, the scope and limitations as well as mechanistic insights on the key role of anionic additives to control the cyclization versus elimination reactions.



Acknowledgement

We thank the European Research Council (ERC-CoG 2019, 865554), Agencia Estatal de Investigación (AEI) of the Ministerio de Ciencia e Innovación (EUR2019-103814; PID2019-104101GB- I00; Severo Ochoa Excellence Accredi- tation 2020–2023 -CEX2019-000925-S) and the European Union for Marie Skłodowska-Curie Individual Fellowship (101028657) for the funding support.

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RATIONAL DESIGN AND SYNTHESIS OF A BODIPY-BASED PROBE SELECTIVE FOR TAU TANGLES

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Despite the numerous studies to elucidate the pathogenetic mechanisms underlying Alzheimer's disease (AD), to date there is still no effective therapy to treat AD or to significantly block the progression of symptoms.[1] Consequently, in order to develop a therapeutic strategy capable of preventing AD, the scientific research has focused on the study of accurate and specific diagnostic methods.[2] Recent studies have clearly demonstrated a strong correlation between the number of neurofibrillary tangles (NFTs) of tau protein and disease progression,[3] suggesting the NFTs as a biomarker of choice in the clinical diagnosis of AD.[4] Recently, the elucidation of the crystallographic structures of the PHF6 hexapeptide fragment by cryoEM microscopy, which plays a pivotal role in the propensity of tau protein to form self-assembled structures, have been reported.[5] In addiction, the construction of the computational model *6-mer* of the PHF6 fragment of the most conserved channel have been evaluated for the realization of Tau-specific fluorophores.[6] In this regard, although several fluorescent probes for the identification of AD biomarkers have been described in literature and/or have been patented, only a limited number of these have been found to be highly selective *in vivo* for the tau tangles and, to date, tau-selective fluorophores are still not commercially available. Based on these findings, a small-size focused library of BODIPY probes, namely BT1-8, has been rationally designed by extending the conjugation of position 3 of the BODIPY *core* with a highly conjugated systems ending with an aliphatic amine. The distance between the electron donor portion and the acceptor relies in the range of 13-19Å. The interaction with the model *6-mer* has been evaluated in terms of molecular docking and, among all, BT1 compound has been selected as the most promising selective P-tau probe in terms of *in silico* theoretical affinity, binding conformation and polarity. Accordingly, an efficient, versatile and cost-effective two-step synthetic strategy was developed. (**Figure 1**). The probe has been tested *in vitro* onto human iPSC-derived NGN2-induced neuronal cell cultures and has shown excellent photophysical properties and high selectivity for detecting NFTs on cell cultures of cortical neurons derived from human stem cells, confirming *in*

silico studies. Accordingly, given the chemical versatility of the BODIPY scaffold, owning to their relative ease of substitution and generally highly fluorescent nature, our findings offer new directions into the structural optimization of specific compounds for different target proteins [7].

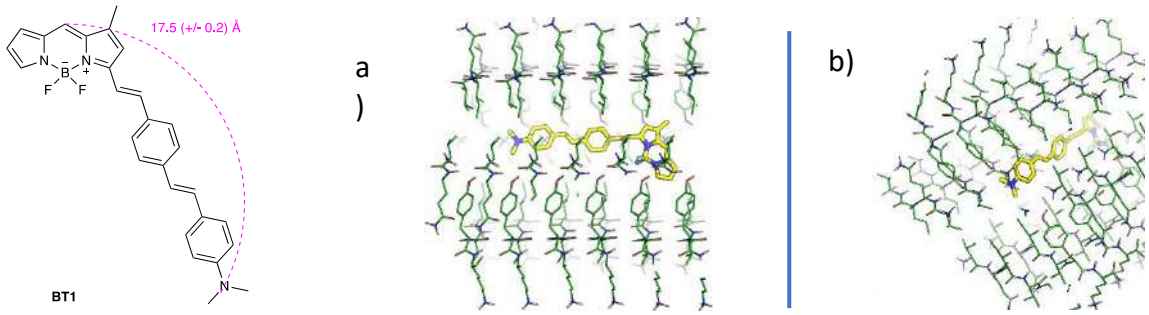

Figure 1: Chemical structure and molecular docking of **BT1** against the crystallographic structure of the PHF6 fragment. (a) Side view of the molecule in the protein tunnel. (b) Diagonal view of the molecule in the protein tunnel.

Acknowledges

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CHIRAL AND EXTREMELY DISTORTED NEW FAMILIES OF HEXA-PERI-HEXABENZOCORONENE DERIVATIVES

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These days, there is a special interest in the synthesis of chiral non-planar nanographenes thanks to their unique properties in comparison with their planar counterparts. One of their greatest attractions is their chiroptical properties, which might be implemented in organic electronics providing these molecules are stereochemically rigid with high configurational stability. Additionally, if they are doped with nitrogen atoms, they will take advantage of the ability of the nitrogen to coordinate with metals, be sensitive to pH and its redox modulation. Thus, it may allow the development of novel applications.

Here, we present three new families of hexa-peri-hexabenzocoronene (HBC)-based helical nanographenes incorporating π-extended carbo[5]helicenes. The first family bears octagonal carbocycles,[1] the second one shows nonagonal carbocycles[2] and the last one exhibits N-doped octagonal carbocycles. For the first time, the mentioned rings become a constituent of both a carbo[5]helicene and a HBC where their negative curvature is responsible for twisting both units. The inclusion of larger membered rings (n > 7) into these kinds of systems is an unexplored area where their presence induces remarkable high distortion and rigidity. Thus, it allowed us to study their chiroptical properties. In addition, the incorporation of nitrogen atoms has let us analyse the mentioned abilities of the nitrogen in distorted nanographenes.

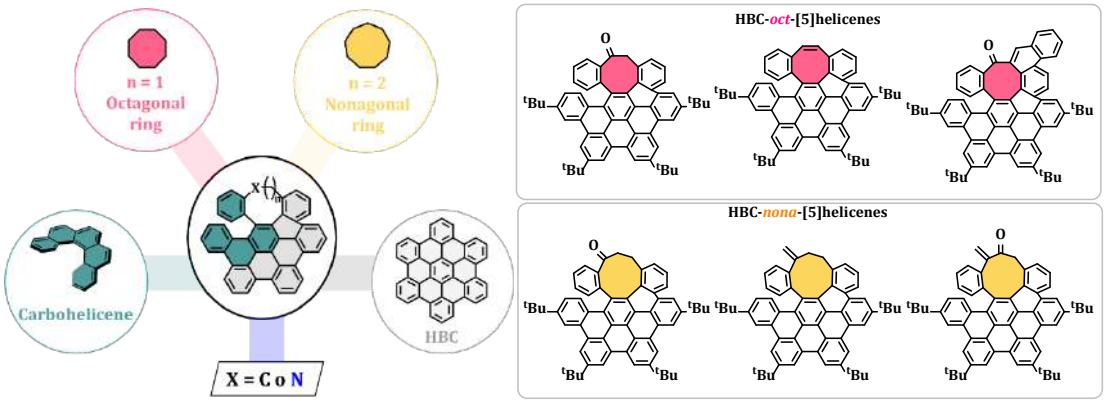

Figure 1. Schematic representation of the three families of distorted nanographenes.

Acknowledges

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GOLD(I)-CATALYZED REACTIVITY OF FURAN-YNES WITH *N*-OXIDES

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Furans represent a privileged scaffold for gold-catalyzed synthetic methodologies, as their nucleophilicity makes them valuable partners for reactions with alkynes, allenes and alkenes activated through gold coordination.[1] Moreover, the furan ring is prone to undergo ring opening in the reaction mechanism, thus offering unique pathways that have been studied since the first report on the gold-catalyzed intramolecular reaction of furan-tethered alkynes ("furan-ynes") in 2000.[2] More recently, furans have also been reacted with gold(I) carbenes, generated from propargyl acetates, 1,6-enynes and *retro*-Buchner reaction.[3] On this ground, we wanted to explore the reactivity of furan-ynes **1** under oxidative gold(I)-catalyzed conditions, through the use of *N*-*O* oxidants, which are known to generate reactive α-oxo gold(I) carbene species.[4] Our result show that three different heterocyclic scaffolds can be obtained: dihydropyridinone **2**, dihydropyrrole **3** and furan **4** (Figure 1). We investigated the effect of the ligand and the oxidant on the reaction outcome, thus disclosing the selective synthesis of two out of three possible products. In particular, the synthesis of dihydropyridinones was extended to a broad scope of substituents, giving access to a densely substituted heterocyclic molecular framework, whose synthetic value was underlined by further manipulations.[5]

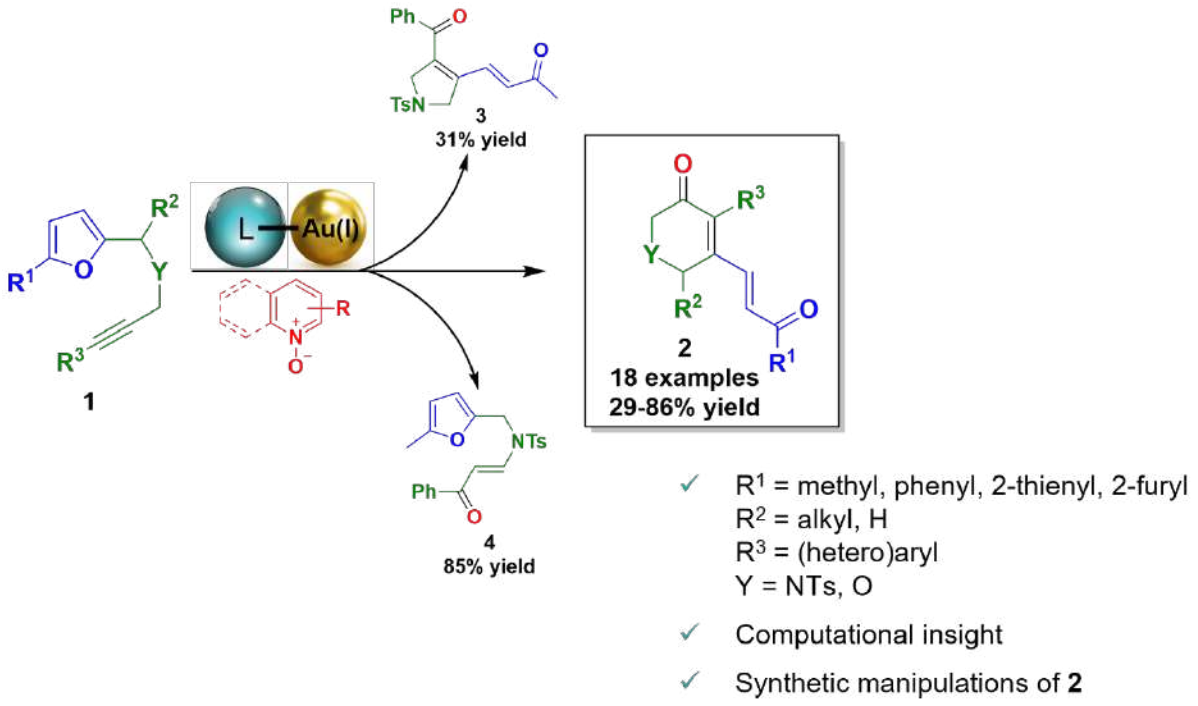

Figure 1. Possible outcomes in the gold(I)-catalyzed reaction of furan-ynes with *N*-oxides.

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DESIGN, SYNTHESIS AND EVALUATION OF NOVEL GLYCOMIMETICS AS LIGAND FOR LECTIN FROM *BURKHOLDERIA CENOCEPACIA*

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Over the years, antibacterial drug resistance has been recognized as an increasing problem for public health all over the world. Multi-drug resistant (MDR) bacteria emerged to be associated with severe nosocomial infections, representing a serious complication in the hospital settings.

Burkholderia cenocepacia is an opportunistic Gram-negative bacterium, which causes infections in immuno-compromised individuals, mainly in cystic fibrosis patients. Several MDR *B. cenocepacia* strains were found to be insensitive to many classes of antibiotics, making the treatment of related diseases very difficult [1].

The establishment of an infection by *B. cenocepacia* requires adhesion to host cells through carbohydrate/protein interactions. The lectins BC2L, sugar-binding proteins, mediate this process, representing potential targets for the antimicrobial therapy. Indeed, the inhibition of these interactions could prevent microbial adhesion and hinder the infective process. Four soluble lectins from *B. cenocepacia* have been identified (BC2L A-D), all containing a *C*-terminal dimeric domain which recognises mannose [2]. BC2L-C also presents an *N*-terminal trimeric domain, which demonstrates a fucose-binding activity. Thus, BC2L-C represents a novel type of *superlectin* with dual sugar recognition ability towards both mannose and fucose [3].

Glycomimetics have demonstrated to be reliable disruptors of carbohydrate/lectin interactions, since they were designed to emulate carbohydrate structures, with improved physicochemical and pharmacokinetic properties. This work aims at developing novel glycomimetics able to interfere with the carbohydrate–lectin recognition of BC2L-C. A modular fragment-based library of *C*- and *N*-glycomimetics has been designed and synthesized. Firstly, virtual screening of a fragment library allowed to select hit structures predicted to bind a site in BCL-C *N*-terminal domain, which is vicinal to the fucose binding pocket. These fragments were validated [4] and used to generate new bifunctional ligands. The general structure of the new molecules is composed by a sugar core connected to selected fragments through linkers of similar length (4-5 Å). The synthesized compounds were tested for their affinity towards BC2L-C N-terminal

domain through different biophysical techniques, including saturation transfer difference NMR spectroscopy (STD-NMR), differential scanning calorimetry (DSC) and isothermal titration calorimetry (ITC). This study allowed to identify hit compounds with increased affinity compared to the monosaccharide parent structure, up to one order of magnitude. Moreover, the first crystal structures of BC2L-C-Nt complexes with synthetic ligands have been solved, leading to the validation of computational and experimental studies. Starting from a preliminary structure-activity relationships (SAR), a second generation of new ligands is being planned.

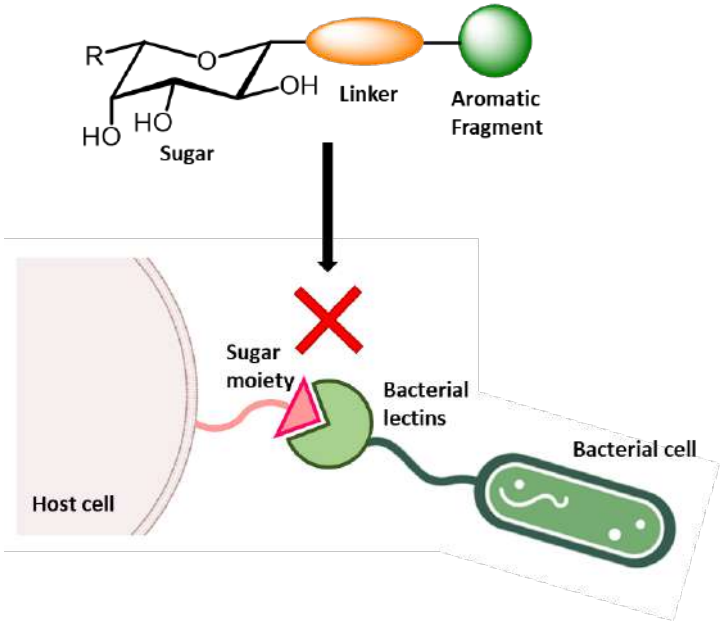

Figure 1. General structure of new BC2L-C antagonists.

Acknowledgements

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SELECTIVE SYNTHESIS OF DEACTIVATED 3-BENZOYLBENZOFURANS BY ONE-POT TANDEM ACYLATION/THERMAL CYCLIZATION OF *O*-[(BENZOYLOXY)BENZYL]TRIPHENYLPHOSPHORANES DERIVATIVES

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3-Benzoylbenzofurans are present in the structural cores of many bioactive molecules in current pharmaceutical use and development.[1] Numerous approaches towards the synthesis of 3-acylbenzofurans have been disclosed in the literature, most are only suitable for the preparation of derivatives bearing electron-donating groups.[2]

Electron-withdrawing groups such as nitro, ciano and trifluoromethyl, are widely used not only in organic chemistry, but also in pharmaceuticals as they improve metabolic stability, selectivity and lipophilicity of bioactive compounds.[3]

In a previous study, we have described the preparation of 3-benzoyl-2-phenylbenzofurans under Wittig reaction. The method shows to be effective for the synthesis of deactivated derivatives, however, it was limited to the preparation of benzofurans carrying identical substituents on the 2-phenyl and on the 3-benzoyl rings [4,5]

More recently, we unexpectedly observed that *o*-[(benzoyloxy)benzyl]triphenyl-phosphonium salts, react with benzoyl chlorides and triethylamine in toluene to afford, beside the corresponding 2-phenylbenzofuran, a mixture of two isomeric deactivated 3-acylbenzofurans. Herein we report a further optimization of the reaction conditions which allowed to obtain selectively a unique 3-acyl isomer with a simple, efficient, and economical synthetic procedure (Figure 1).

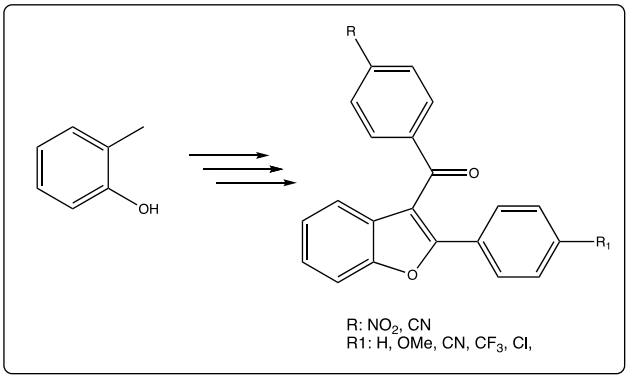

Figure 1

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EFFICIENT $TiCl_4$-ASSISTED SYNTESIS OF DIPEPTIDES USING MICROWAVE IRRADIATION

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The activation of amino acid carboxylic function is a key step in peptide synthesis. It is generally performed through the conversion of *N*-terminal amino acids into reactive acylating intermediates (acyl chlorides, anhydrides, activated esters) using activating reagents [1,2]. The importance of peptides has promoted the development of alternative methods for peptide bond formation [3]. Over the years, there was a growing interest in the use of metal catalysts for the synthesis of molecules containing the amide functional group [4].

Recently, a new solution method for the formation of peptide bond, by employing titanium tetrachloride ($TiCl_4$) as condensing agent in a pyridine-buffered medium at 40 °C, has been proposed [5,6].

In the present study the applicability of microwave irradiation for the $TiCl_4$-mediated formation of dipeptide systems has been investigated.

The developed methodology is based on the microwave-assisted activation of the carboxylic function of the *N*-terminal α-aminoacid (1 mmol) through the formation of an adduct with $TiCl_4$ (1 mmol) in the presence of pyridine that acts both as solvent and base.

A series of *N*-Fmoc, *N*-Boc, and *N*-Z-dipeptides were obtained in short times (50 minutes) and high yields (79-88%) keeping unchanged the acid-sensitive groups under the adopted reaction conditions.

The procedure was also extended successfully to the solid phase synthesis of dipeptides and *N*-Fmoc-protected dipeptides using Wang resin as solid support.

The application of microwave irradiation to both solution and solid-phase $TiCl_4$-mediated synthesis of dipeptide systems increased product purity and reduced drastically reaction times compared to the synthesis performed with conventional heating [7].

The recovery of the products has been standardized and allowed to obtain highly pure peptides. The investigation of the stereochemistry of the obtained dipeptide systems showed the almost complete retention of stereochemical integrity of the chiral centres of the precursors.

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MACROCYCLIC TRIAZOLOPEPTOIDS: A NEW CLASS OF EXTENDED CYCLIC PEPTOIDS

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Peptoids (oligomeric *N*-substituted glycines) are α-peptide "regioisomers" in which side chains are attached to the backbone amide nitrogen instead of the α-carbon (**Figure 1**.). Cyclic peptoids, macrocycles derived from the cyclization of linear peptoids are an attractive scaffold for several applications. They are stable and easily accessible by the so called submonomer approach on solid-phase and subsequent cyclization in solution in high dilution conditions.[1][2]

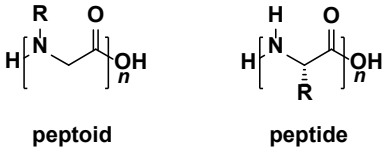

Figure 1. Comparison of peptoid and α-peptide structures.

In this communication, the synthesis and the properties of a new class of "extended"[3] macrocyclic peptoids, in which the peptoid backbone is enriched by the presence of 1,2,3-triazole moieties, will be described. The disubstituted 1,2,3-triazoles are an important tool in the peptidomimetic chemistry as they can mimic amide bond in terms of size, planarity and hydrogen bond properties.[4]

The cyclic triazolopeptoids (**Figure 2.**) are constructed on solid support *via* alkyne–azide cycloadditions in a submonomer approach[5] and subjected to the cyclization. This modular approach allows the incorporation of a wide variety of side chains (including the chiral ones) and thus renders cyclic triazolopeptoids very adaptable and promising candidates for both organocatalysis and supramolecular chemistry applications.

Figure 2. Representative structures of the new macrocyclic systems.

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OXYANION-HOLE MIMICS IN CATALYSIS AND SUPRAMOLECULAR RECEPTORS: CREATING NEW ARTIFICIAL HYDROLASES

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Enzymes are essential catalysts in many important industrial processes [1] despite some drawbacks, such as its high price, sensitivity to a narrow interval of pH, temperature or ionic strength, and the restriction for most of them to work in aqueous media. Therefore, the development of stable small organic catalysts which can reproduce the high selectivity and activity of hydrolytic enzymes is both timely and interesting from an industrial and academic point of view.

To mimic a particular enzyme mechanism is essential to understand how enzymes work. Pauling [2] suggests that the catalytic activity is caused by a larger association constant with the substrate in the transition state than in the ground state. Hydrolases, such as chymotrypsin and N-terminal hydrolases, are able to catalyse hydrolytic reactions by using a nucleophilic hydroxyl or thiol group, a basic nitrogen and an oxyanion hole. Key in this process is the oxyanion-hole motif, in which two backbone NHs stablish two hydrogen bonds with the negatively-charged oxygen of the transition-state intermediate.

Due to the difficult synthesis of a whole enzyme, emulation of the active site, specifically the oxyanion hole, is a good strategy to mimic hydrolases catalytic activity and association properties. [3] In our group we have studied the X-ray structure of hydrolases to mimic their active center with small synthetic organic molecules which contain the catalytic groups as well as the oxyanion-hole motif with a similar geometry to the enzyme catalytic center.

In this work we present the applications of these enzyme mimics in the transesterification of non-activated esters under neutral conditions [4] as well as the molecular recognition of carboxylates, the chiral discrimination of amino acids, [5] and the complexation of esters and alcohols. [6]

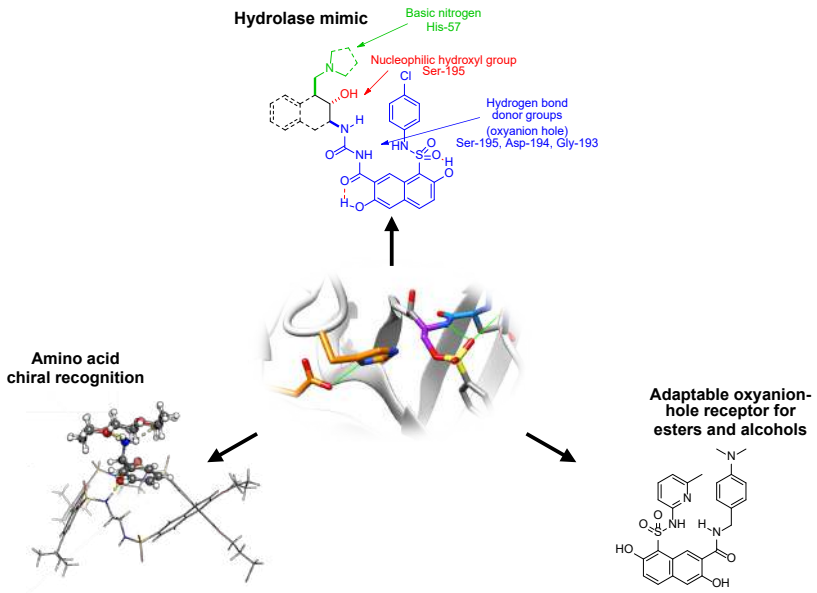

Figure 1. Enzyme mimics for transesterification reactions and supramolecular receptors for molecular recognition based on hydrolases' active center.

Acknowledges

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ELECTROPHILIC REAGENTS FOR THE DIRECT INCORPORATION OF SCF_2CF_2H AND SCF_2CF_3 MOTIFS

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The introduction of fluoroalkylthioether groups (SR_F) has attracted the attention of the drug discovery community given the special physicochemical and pharmacokinetic features they confer to bioactive compounds.[1] Synthetic advances in the field have been capitalized by methods to incorporate -SCF_3 and -SCF_2H motifs,[2] however, longer and synthetically more challenging polyfluoroethyl chains are still underdeveloped. Here, two saccharin-based reagents have been disclosed as optimal electrophilic reagents for the introduction of SCF_2CF_2H and SCF_2CF_3 motifs. The reactivity performance has been thoroughly investigated within a variety of nucleophiles, including heteroatoms, activated heterocycles, aromatic compounds, organometallic species as well as biologically relevant natural products and pharmaceutical drugs. Finally, multigram scale preparation and divergent derivatization has been explored from the unprecedented SCF_2CF_2H group.

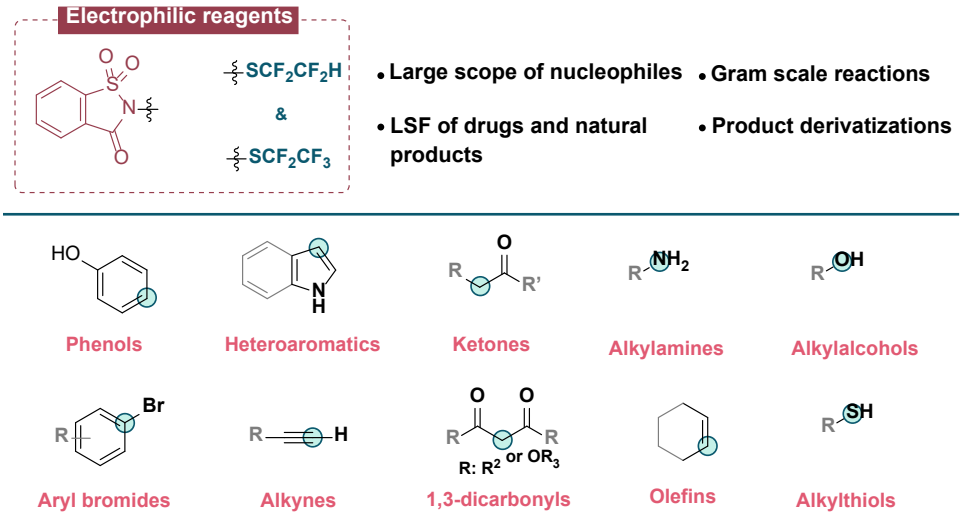

Figure 1. Electrophilic reagents for the incorporation of -SCF_2CF_2H and -SCF_2CF_3 motifs and scope of nucleophiles.

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