63ème Groupe d'Études de Chimie Organique

Du 27 août au 1 septembre 2023

Kerjouanno - Morbihan

Conférenciers invités

Dr. Xavier Bantreil, IBMM, Montpellier
Prof. Marine Desage-El Murr, Université de Strasbourg
Dr Laure Haberkorn, Servier France
Dr Olivier Baslé, LCC, Toulouse
Prof. Véronique Michelet, Institut de Chimie de Nice
Prof. Sarah O'Connor, Max Planck Institute, Jena, Allemagne
Dr Grégory Pieters, CEA Saclay
Dr Adrien Quintard, DCM, Grenoble
Prof. Joost Reek, Amsterdam University
Prof. Peter Seeberger, Max Planck Institute, Potsdam, Allemagne
Dr Emmanuelle Schulz, ICMMO, Orsay
Prof. Mariola Tortosa, Université Autonome de Madrid

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GECO 63

Groupes d'Etudes de Chimie Organique

63ème Edition

Kerjouanno

27 aout au 1 septembre 2023

Chères participantes, chers participants,

C'est avec grand plaisir que nous vous accueillons pour ce 63ème GECO à Kerjouanno dans le golfe du Morbihan. Le comité d'organisation de ce GECO a été constitué autour des différents laboratoires de l'Université Paris Saclay, comme l'ICSN, l'ICMMO, l'ILV et BioCIS.

Le Groupe d'Études en Chimie Organique (GECO), créé en 1959, est une institution dont la tenue est un moment exceptionnel et privilégié de l'année pour la communauté des chimistes organiciens. Un principe fondamental du GECO est son déroulement dans une ambiance détendue et conviviale qui permet de favoriser au maximum les interactions entre participant(e)s, quel que soit leur statut.

Nous remercions particulièrement les 12 conférenciers/conférencières qui nous ont fait l'honneur d'accepter notre invitation et de vivre cette semaine avec nous. Ils sont issus de France et d'Europe et sont spécialisés dans différents domaines de la chimie organique. Ils/elles sont là pour vous toutes et tous, participant.e.s du GECO, qui nous avez rejoint nombreux. Ce congrès est pour vous ; tirez-en le maximum scientifiquement et humainement, notamment grâce à vos 42 impromptus qui nous promettent un riche programme scientifique ! Vous êtes nombreux/nombreuses à vivre votre premier GECO cette année et l'expérience montre que les participants du GECO reviennent volontiers régulièrement. Vous êtes donc toutes et tous le socle qui fera vivre le GECO pour les années à venir !

Le GECO ne peut se faire qu'avec le soutien financier de nombreux partenaires. A nouveau, les acteurs privés et institutions publiques qui gravitent autour de la « planète chimie organique » ont répondu présents ! Nous sommes très reconnaissants de l'implication et le support financier de tous, qui nous permettent d'être aujourd'hui ensemble.

Le GECO, c'est également plusieurs jours avec des exposants. Ceux-ci sont indispensables au GECO et font partie intégrante du congrès, que ce soit dans les temps scientifiques, les temps de pause et les moments plus récréatifs. Interagissez avec eux, discutez, allez les voir ; ils sont là pour nous, pour nous rencontrer et nous connaitre. Ils seront par la suite des partenaires privilégiés au cours de l'année pour accompagner nos besoins.

Nous vous souhaitons un excellent GECO !

Le Comité d'Organisation

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PROGRAMME SCIENTIFIQUE

Dimanche 27 août

16h00	Accueil des participants		
18h00	**Apéritif**		
18h50	Ouverture		
19h00	E. Schulz	Homogeneous supported (asymmetric) catalysis	ICMMO, Orsay
20h00	Pause		
20h15	Diner		

Lundi 28 août

8h30	J. Reek	Self-assembled molecular cages for transition metal catalysis and applications in living cells	University of Amsterdam
9h30	S. Antoniotti	From homogeneous to heterogeneous gold catalysis: practical advantages, new reactivity, or both?	ICN, Nice
9h45	L. Favereau	Persistent chiral mono- and diradicals with SOMO/HOMO inversion	ISCR, Rennes
10h00	Flash comms	Huber, ABCR, Anton-Paar	
10h15	Pause café		
10h45	P. Busca	Design and synthesis of saccharide-based molecular tools to probe DLODP and LOST orphan activities	LCBPT, Paris
11h00	C. Olivier	Design and Studies of Chiroptically-Active Molecular and Supramolecular Helical Systems	ISM, Bordeaux
11h15	C. Ghiazza	Dearomatisation of Pyridines through the Insertion of N-atom: Photochemical Skeletal Editing for the Synthesis of 1,2-Diazepines	ILV, Versailles
11h30	G. Blond	Syntheses of O, N, and S-Heterocycles through gold-mediated domino reactions	LIT, Strasbourg
11h45	Y. Ferrand	From Molecular Recognition to Catalysis: Designing an Artificial Decarboxylase	CBMN, Bordeaux
12h00	Flash comms	Vacuubrand, BLD, Biotage	

12h30	Déjeuner		
15h45	X. Bantreil	Mechanochemistry as an efficient tool for synthesis	IBMM, Montpellier
16h45	E. Leclerc	Fluorine-Activated Additive-Free Vitrimers	ICG, Montpellier
17h00	A. d.l. Torre	Double Allylic Substitutions of Alkenyl *vic*-Diols	ICMMO, Orsay
17h15	Pause café		
17h45	A. Specht	Towards biomedical applications of photolytic reactions	CAMB, Strasbourg
18h00	Flash Comms	Buchi, BTF, CEM	
18h15	M. Tortosa	Catalysis to increase complexity: stereoselective synthesis of sp3-rich building blocks	Madrid University
19h15	Pause		
20h15	Diner		

Mardi 29 août

8h30	V. Michelet	A Journey in Gold Catalysis Towards Diversity: from Heterocycles to Fragrances	ICN, Nice
9h30	J. Monot	Pd-S cooperativity: from stoichiometric activation of E–H bonds to catalytic hydroelementation	LHFA, Toulouse
9h45	P.-A. Bouit	Fluorescence switching with phosphorus-based multi-stage redox systems	ICSR, Rennes
10h00	Y. Coquerel	Severely twisted hexagon-based polycyclic aromatic hydrocarbons	iSm2, Marseille
10h15	Pause café		
10h45	B. Michelet	Leveraging long-lived arenium ions in superacid for meta-selective Friedel-Crafts methylation	IC2MP, Poitier
11h00	V. Mamane	Telluroniums Salts in Chalcogen Bonding Catalysis	ICS, Strasbourg
11h15	S. Vidal	Dynamic combinatorial libraries of glycoclusters: When glycoclusters go dynamic	ICSN, Gif
11h30	S. Prevost	Regioselective C-H functionalization of naphthalenes: new strategies for the synthesis of aromatic polyketides	ENSTA, Palaiseau
11h45	V. Patinec	Synthèse de bioconjugués à base de triazacyclononane pour le radiomarquage au [64Cu]Cu	LCEMCA, Brest
12h00	Flash Comms	TCI	
12h05	Pause		
12h30	Déjeuner		
15h45	O. Baslé	Bidentate NHC ligands for highly selective homogeneous transition metal-(photo)catalysis	LCC, Toulouse
16h45	Y. Trolez	Threading a linear molecule through a macrocycle thanks to boron	ICSR, Rennes
17h00	M. de Paolis	Enantioselective Ring Expansion	COBRA, Rouen
17h15	Pause café		
17h45	A. Goujon	Light-Frozen Dynamic Covalent Synthesis of Electron-Deficient Conjugated Materials	MOLTECH, Poitier

18h00	L. Lemiègre	Glycoboronates: Self-assembly and water-sensitive organogelators	ENSCR, Rennes
18h15	L. Haberkorn	Accelerating the Design-Make-Test-Analyse cycle, which technologies to use and for what purpose?	Servier, Gif-Sur-Yvette
19h15	Pause		
20h15	Diner		

Mercredi 30 août

9h00	P. Seeberger	Automated Glycan Assembly as Basis for Life and Material Science	Max Plank Institute, Potsdam
10h00	G. Audran	Alkoxyamines as therapeutic agents	ICR, Marseille
10h15	P. Peixoto	Asymmetric synthesis of allenes from simple alkynes using novel chiral diselenide reagents	ISM, Bordeaux
10h30	Pause café		
11h00	H. Clavier	A New Design of Chiral N-Heterocyclic Carbene (NHC)-Metal Complexes: Applications in Enantioselective Catalysis	iSm2, Marseille
11h15	A. Letort	Process Development of a Novel Route to Rilpivirine Hydrochloride – From Lab Scale to Pilot Scale	Minakem
11h30	D. Martin	Quel(s) mécanisme(s) pour les réactions radicalaires organocatalysées par des carbènes stables ?	DCM, Grenoble
11h45	J. Broggi	Concomitant Oxidative and Reductive Transformations with Breslow catalysts	ICR, Marseille
12h00	Déjeuner		
13h30	Activités extérieures au centre		
19h30	**Diner gala à l'extérieur**		

Jeudi 31 août

9h00	A. Quintard	From greener synthetic methodologies to chemically fueled supramolecular systems	DCM, Grenoble
10h00	M. Vayer	Propargylation of N-Heterocycles by Electrochemical Decarboxylation of Allenoic Acids	BioCIS, Orsay
10h15	Pause café		
10h45	P. Adler	Catalytic approach for amide coupling for the development of nucleic acid-supported catalysts	IBMM, Montpellier
11h00	A. Tessier	Cyclic Amidrazones: a new scaffold for drug-design in medicinal chemistry	CEISAM, Nantes

11h15	A. Panossian	Fluorosulfoxoniums – Easily accessible strong Lewis (or hidden Brønsted) acids	LIMA, Strasbourg
11h30	A. Amgoune	Nickel-Catalyzed Radical Cross Coupling of Amides	ICBMS, Lyon
11h45	M. Gingras	Asterisks, Dendrimers and Highly Distorted Helicene-Based Materials	CINaM, Marseille
12h00	Pause		
12h30	Déjeuner		
15h45	S. O'connor	Harnessing the natural product pathways of Nature	Max Plank Institute, Iéna
16h45	V. Magné	Controlled Reactivity of Sulfoxides on Surfaces.	LHFA, Toulouse
17h00	M. Schuler	Multivalent Chondroitin Sulfate Oligosaccharides as new tools to probe protein-CS interactions	ICOA, Orléans
17h15	Pause café		
17h45	V. Dalla	Dual Silyl – Gold catalysis : a flexible and powerful new concept for organic synthesis	URCOM, Le Havre
18h00	L. Evanno	Synthesis of *piper spp.* alkaloids by photocatalytic assemblies of piperine	BioCIS, Orsay
18h15	G. Pieters	Chiral Fluorophores: Design, structure/properties relationship and application	CEA, Saclay
19h15	Pause		
20h15	Diner		

Vendredi 1 septembre

9h00	M. Desage	Nature is the cure: reactivity blueprints for bioinspired catalysis and chemistry	ICS, Strasbourg
10h00	S. Coote	Broadening the scope of the Paternò-Büchi reaction	University of Bath
10h15	Pause café		
10h45	E. Roméro	High Throughput Experimentation as a technology enabling catalysis	CEA, Saclay
11h00	N. Nebra	Unusual RedOx Cycles for Trifluoromethylation Reactions	LHFA, Toulouse
11h15	S. Arseniyadis	Difluoro- and oxodifluoromethylation reactions under photoflow conditions using adaptable, low-cost, standardized 3D printed reactors	QMUL, London
11h30	Fin GECO 63		
	Presentation GECO64		
12h00	Déjeuner		

Planning flash comms exposants

lundi 28/08

10 h00:
Huber
ABCR
Anton-Paar

12 h00:
BLD
Biotage

18h00:
Buchi
BTF
CEM

Autre

TCI et Vacuubrand : mardi 12h00

Cloup: jeudi 10h15

Références

1. Titre. Initiale du prénom Nom1, Initiale du prénom Nom2, *Abréviation Journal* **année**, *volume*, page(s). DOI : XXX avec lien actif si possible
2.

Conférenciers

Homogeneous supported (asymmetric) catalysis

Emmanuelle SCHULZ

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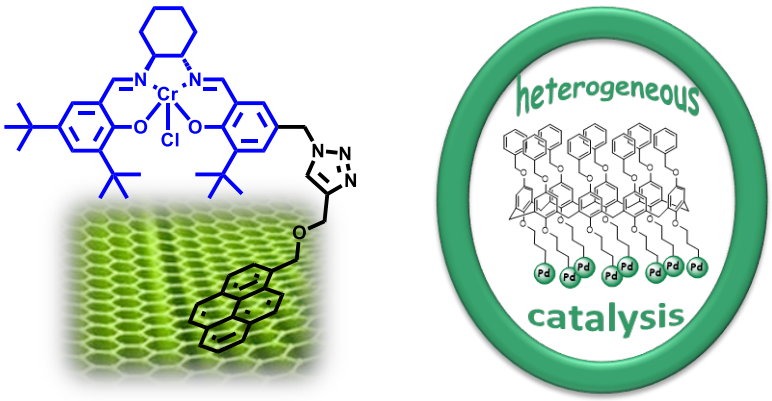
The role of organometallic catalysis allowing the targeted production of high value-added products no longer needs to be demonstrated, but the fine chemicals sector dedicated to health applications remains very demanding for innovative and sustainable synthesis routes.

On the one hand, the search for an efficient synthesis of enantioenriched functionalized molecules is still topical; Making precious chiral catalysts insoluble and therefore easily recoverable and reusable is an elegant way to answer the principles of green chemistry and sustainable development.

On the other hand, obtaining minimal residual traces of metal in the target products is another important objective; Most transition metals are indeed toxic species, and their presence in valuable chemicals is accurately regulated, depending on their mode of administration. Additionally, residual amounts of metals can interfere with subsequent synthetic steps of the process.

It is in this context that we work on the one hand on different modes of immobilization of chiral salen complexes and study their efficiency in the heterogeneous catalysis of enantioselective formation of C-C, C-O and C-N bonds.[1] Since cross-coupling reactions are prevalent tools in the fine chemical industry, we also propose the synthesis and the evaluation of the catalytic activity of Pd–NHC complexes covalently grafted on calix[8]arene supports in Suzuki-Miyaura[2] and Buchwald-Hartwig reactions.[3]



For some recent references

1. Calix[8]arene as new platform for Cobalt-Salen complexes immobilization and use in hydrolytic kinetic resolution of epoxides. I. Abdellah, C. Martini, A. Dos Santos, D. Dragoe, V. Guérineau, V. Huc, E. Schulz, *ChemCatChem* **2018**, *10*, 4761 ; DOI : 10.1002/cctc.201801164; Chiral Chromium Salen@rGO as Multipurpose and Recyclable Heterogeneous Catalyst. M. Abd El. Sater, M. Mellah, D. Dragoe, E. Kolodziej, N. Jaber, E. Schulz, *Chem. Eur. J.* **2021**, *27*, 9454; DOI: 10.1002/chem.202101003; Making Chiral Salen Complexes Work with Organocatalysts. Y. Yuan, M. Mellah, E. Schulz, Olivier R. P. David, *Chem. Rev.* **2022**, 122, 8841; DOI: 10.1021/acs.chemrev.1c00912
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3. Benzyloxycalix[8]arene supported Pd-NHC cinnamyl complexes for Buchwald-Hartwig C-N cross-couplings. S. Abi Fayssal, T. Naret, V. Huc, J. Buendia, C. Martini, E. Schulz, *Catal. Sci. Technol.* **2021**, *11*, 5223. DOI : 10.1039/D1CY00669J

Self-assembled molecular cages for transition metal catalysis and applications in living cells

Joost NH Reek

Homogeneous and supramolecular catalysis, van 't Hoff institute for molecular sciences, University of Amsterdam, The Netherlands E-Mail : j.n.h.reek@uva.nl

The interface between supramolecular chemistry and transition metal catalysis has received surprisingly little attention in contrast to the individual disciplines. It provides, however, novel and elegant strategies that lead to new tools for the search of effective catalysts, and as such this has been an important research theme in our laboratories.[1] In this context we have intensively explored the use of well defined nanospheres[2,3] that form by self-assembly in transition metal catalysis. These nanospheres create catalysts (and substrates) at high local concentration, just like in enzymes, higher reaction rates are observed for several reactions that operate via binuclear mechanism. Also, they provide new tools to control catalytic events in complex media. More recently we have translated the chemistry from the typical organic solvents to aqueous media and biorelevant conditions. This allows to use these nanostructure for new functions as gene delivery and nonnatural catalytic conversions in living cells.[4] In this lecture I will outline the strategies in catalysis and discuss the application in cells for potential cancer treatment and gene delivery, with a focus on the general concepts and most recent results.

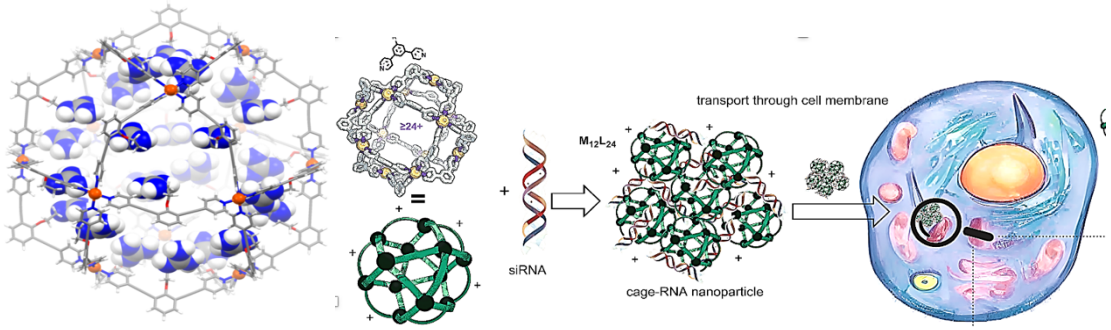

Figure 1: An example of a M12L24 nanosphere as scaffold to bind catalysts (left) and functionalized nanospheres for gene delivery (right)

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2. Pioneering work on nanospheres: Fujita, etal. a) *Angew. Chem. Int. Ed.* **2004,** *43*, 5621 b) *Science* **2010**, *328*, 1144 c) *Chem. Commun.* **2009**, *13*, 1638. d) J.P Stang et al. J. *Am. Chem. Soc.* **1999**, *121*, 10434.
3. For some of our work on nanospheres a) Reek et al., "*Nature Chemistry*, **2016** *8*, 225-230; b) Reek et al *Angew. Chem., Int. Ed.,* **2014,** *52,* 13380; c) Reek et al *Angew. Chem., Int. Ed.,* **2018,** *57,* 11247; d) Reek et al *Chem. Sci.,* **2019**,*10*, 1316. e) Reek et al *J. Am. Chem. Soc.* **2020,** *142* (19), 8837.f) Reek et al *J. Am. Chem. Soc.* **2022**, *144*, 15633
4. Reek et al *Chem* **2023**, in press https://doi.org/10.1016/j.chempr.2023.03.018

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Mechanochemistry as an efficient tool for synthesis

Xavier BANTREIL

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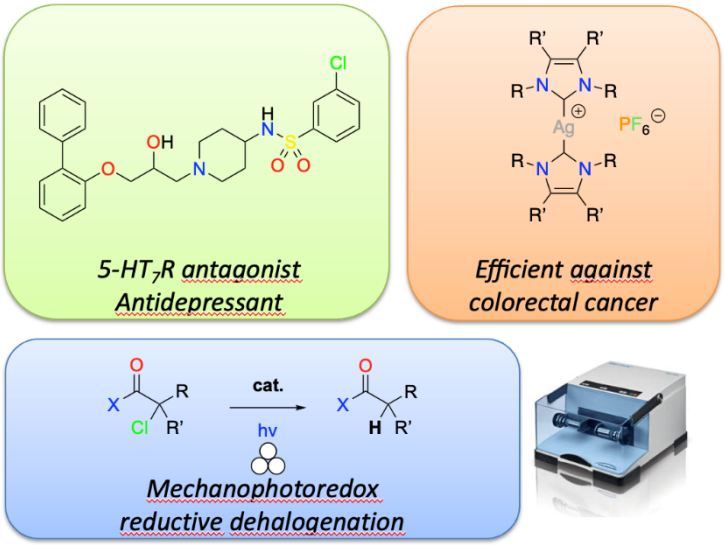
The first report of a mechanochemical reaction was made by Theophrastus of Eresus in 315 B.C. with the reduction of cinnabar into mercury thanks to grinding using a copper mortar and pestle in the presence of acetic acid. Despite this early discovery, mechanochemistry has only been recognized in 2019 by IUPAC as one of the ten technologies that could change our world.[1]

In the Green Chemistry and Enabling Technologies research group in Montpellier, we are using mechanochemistry, and more specifically ball-milling and twin-screw extrusion, to develop more sustainable methodologies for the synthesis of high value molecules.

In the past years, we developed our expertise in numerous domains, including Metal-Organic Frameworks (MOF) synthesis,[2] sustainable monomer preparation and catalyst synthesis for polymerization,[3] the synthesis of organic molecules potent against anxiety[4] and organometallic molecules featuring N-heterocyclic carbene ligands with high activity against colorectal cancer.[5] More recently, we have been focusing on merging ball-milling and photoredox chemistry for the catalytic reductive dehalogenation reaction.[6]



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1. Ten Chemical Innovations That Will Change Our World: IUPAC identifies emerging technologies in Chemistry with potential to make our planet more sustainable. F. Gomollon-Bel *Chem. Int.* **2019,** *41*, 12. DOI:10.1515/ci-2019-0203
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6. Unpublished results.

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Catalysis to increase complexity: stereoselective synthesis of sp^3-rich building blocks

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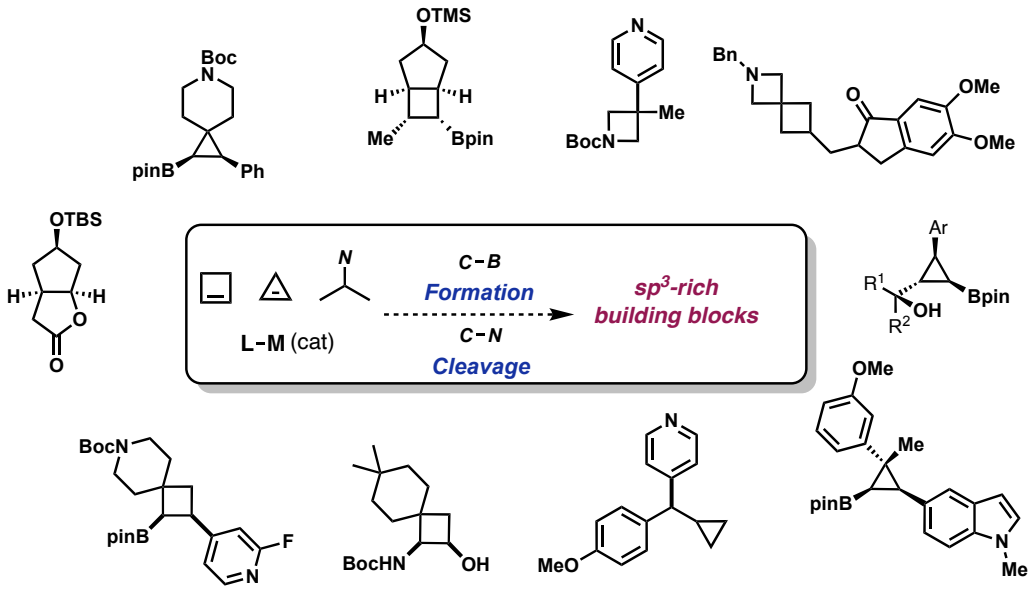
Transition metal catalysis is a powerful tool for the creation of stereocenters in organic molecules. Both, the use of a chiral catalyst or a chiral starting material, are valuable and complementary approaches to accomplish this goal. In our group, we have recently focused on the development of metal-catalyzed enantioselective and stereospecific transformations for the preparation of sp^3-rich building blocks, providing tools for stereodefined carbon-boron bond formation and selective carbon-nitrogen bond cleavage. These methods have allowed us to prepare a broad variety of useful synthetic intermediates, with special emphasis on the synthesis of functionalized small rings.[1] Some of these transformations will be presented in this talk.



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1. Selected references: a) Teresa, J.; Velado, M.; Fernández de la Pradilla, R.; Viso, A.; Lozano, B.; Tortosa, M. *Chem. Sci.* **2023**,*14*, 1575. (b) Nóvoa, L.; Trulli, L.; Parra, A.; Tortosa, M. *Org. Lett.* **2021**, *23*, 7434. (c) Nóvoa, L.; Trulli, L.; Parra, A.; Tortosa, M. *Angew. Chem. Int. Ed*. **2021**, *60*, 11763. (d) Amenós, L.; Trulli, L.; Nóvoa, L.; Parra, A.; Tortosa, M. *Angew. Chem. Int. Ed*. **2019**, *58*, 3188. (e) Guisan-Ceinos, M.; Parra, A.; Martin-Heras, V.; Tortosa, M. *Angew. Chem. Int. Ed*. **2016**, *55*, 6969

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A Journey in Gold Catalysis Towards Diversity: from Heterocycles to Fragrances

Véronique MICHELET

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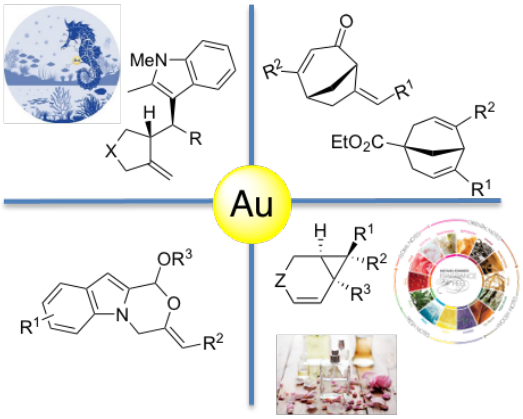
Over the past 20 years, significant research has been directed toward the development of new methodologies for synthetic efficiency and atom economy processes in the presence of gold complexes.[1] We have been initially engaged in a wide project dedicated to the development of catalytic methodologies for the synthesis of original and functionalized carbo- and heterocycles.[2,3,4] The synthesis and characterization of original NHC ligands based on an imidazo[1,5-a]pyridin-3-ylidene (IPy) scaffold has been described as well as their use as tunable ligands for efficient gold-catalyzed C-N, C-O and C-C bonds formations. High activity, regio-, chemo- and stereoselectivities were obtained for hydroelementation and domino processes.[4] We broadened the interest of heterocycles, by reacting specific enynes and enol ether alkynes and also by reacting aldehyde-ynes derivatives.[5] The preparation of functionalized polycyclic skeletons via a gold-mediated process of aldehyde-yne derivatives was also recently developed under racemic and asymmetric conditions.[5] We prepared low molecular weight enyne derivatives and optimized the reaction conditions allowing functionalized volatile oxa-bicyclo[4.1.0]-hept-4-ene in good to excellent isolated yields. The remarkable efficiency and selectivity of the gold catalyst was demonstrated on a 25 g scale with very low catalyst loadings. The synthetic interest of these low molecular weight bicyclic enols was further demonstrated by the unprecedented olfactory evaluation of the bicyclic derivatives fragrances.[6]
This presentation will show the latest results on the sustainable access to biomolecules as well as fragrances.



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Bidentate NHC ligands for highly selective homogeneous transition metal-(photo)catalysis

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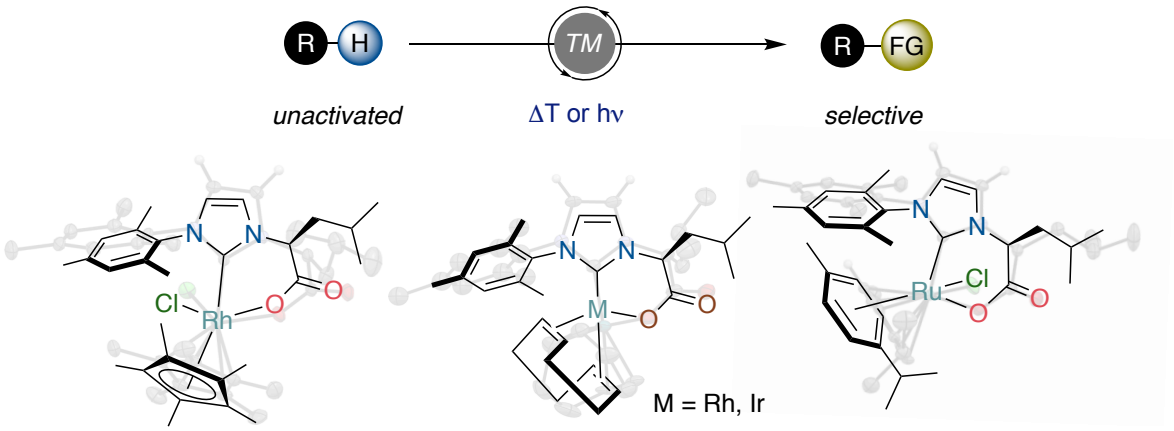
Au cours des dernières décennies, la fonctionnalisation directe des liaisons carbone-hydrogène s'est révélée comme une alternative de choix aux réactions de couplage croisé classiques nécessitant des substrats pré-fonctionnalisés. Par ailleurs, la photocatalyse offre la possibilité d'utiliser la lumière visible comme une source d'énergie sûre, abondante et renouvelable.

Sur la base de notre expertise dans la conception de catalyseurs de métaux de transitions (TM), nous avons récemment développé une nouvelle classe de ligands carbènes *N*-hétérocycliques (NHC) qui a démontré son utilité dans la préparation de photocatalyseurs (PC) d'Ir(III) particulièrement robustes,[1] ainsi que dans l'élaboration de catalyseurs efficaces à base de Rh(III) pour la borylation de liaisons C-H.[2] Plus récemment, nous avons découvert une fonctionnalisation C-H régiosélective induite par la lumière visible et catalysée à température ambiante par un complexe de Rh(I).[3] Dans la continuité de cette étude,[4] des complexes de Ru(II) et d'Ir(I) ont respectivement démontré des activités catalytiques intéressantes dans la réaction de borylation régiosélective des arylphosphines,[5] et en silylation déshydrogénante des arènes.[6]



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“ACCELERATING THE DESIGN-MAKE-TEST-ANALYSE CYCLE, WHICH TECHNOLOGIES TO USE AND FOR WHAT PURPOSE?”

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Today, the challenges inherent in the discovery of new medicines remain more complicated than ever.
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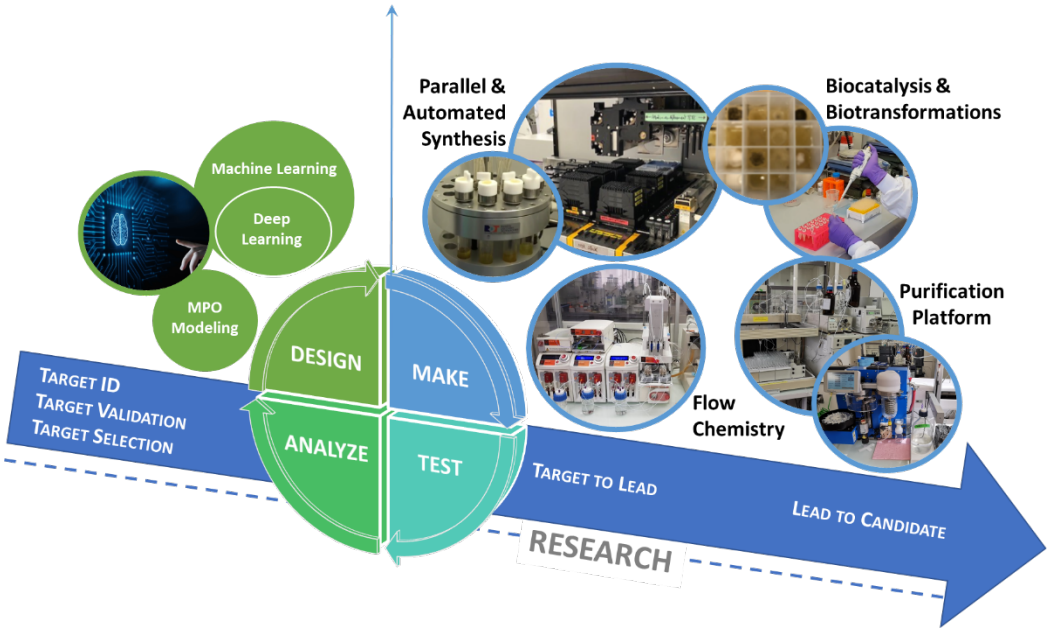
AI, Machine Learning & Deep Learning, Technological Platforms such as Parallel and Automated Synthesis, Flow chemistry, Biocatalysis, Biotransformations are all technologies that support projects and are expanding the Chemist's classical toolbox.



Although these technologies can undeniably have a great impact, their incorporation into existing workflows can be complicated.
We will discuss how these technologies can accelerate the discovery of new drugs but also the challenges that need to be overcome.

Automated Glycan Assembly as Basis for Life and Material Science

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Rapid preparation of polysaccharides by automated glycan assembly (AGA)[1] using a synthesizer[2] provides access to diverse glycans as large as 151-mers.[3] Accelerated microwave-assisted synthesis methods[4] are now used to prepare ever more complex glycans including cis-linked polysaccharides[5] are enabling fundamental investigations into the structure and function of polysaccharides.

Synthetic glycans in combination with single molecule imaging,[6] molecular modelling and other physical methods to characterize carbohydrate structure [7-9] allow us to address fundamental questions of carbohydrate structure, folding and material science. [10, 11] Recently, we described the design, synthesis, and characterization of the first stapled oligosaccharides with increased enzymatic stability and cell penetration. [12]

Synthetic glycans are the basis for the development of vaccines against different bacteria [13] that are currently in clinical evaluation. Monoclonal antibodies and nanobodies against glycans are the basis for a program aimed at developing novel diagnostics and therapeutics. [14]

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From greener synthetic methodologies to chemically fueled supramolecular systems

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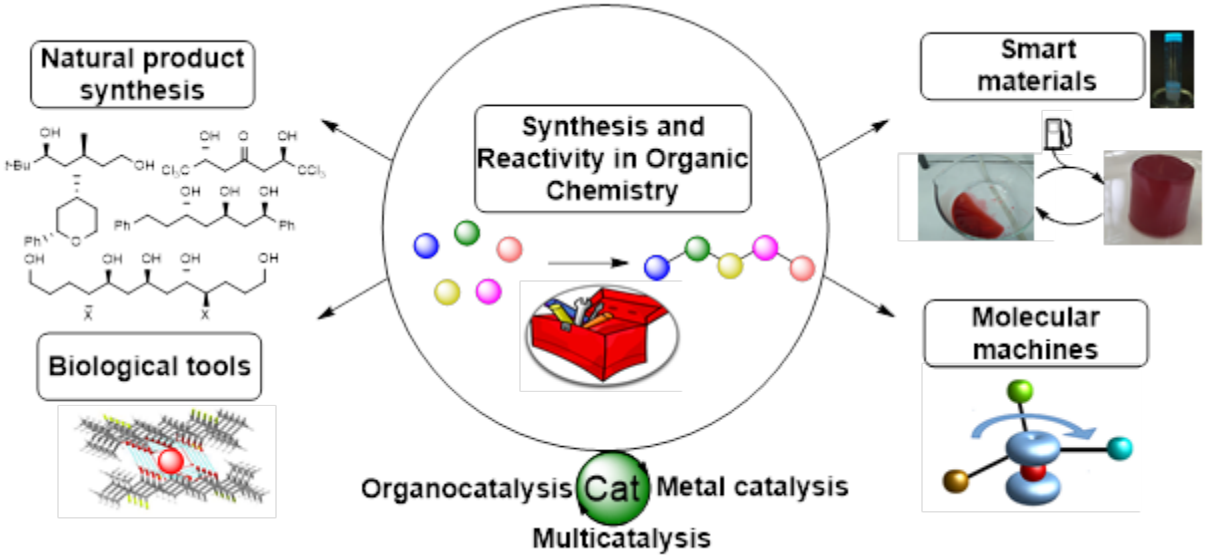
The presentation will highlight our recent success in the development of multi-catalytic transformations.[1,2] Based on the combinations between inexpensive iron or copper complexes with organocatalysts, they enable the rapid preparation of a broad range of molecules of interest. This was demonstrated in the context of natural products synthesis but also recently in the elaboration of new type of supramolecular objects.[3] Finally, transposition of the catalytic principles recently found implication in the design of smart materials or molecular machines.[4]



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Harnessing the natural product pathways of Nature

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Nature makes thousands of molecules– natural products– that have many applications. In fact, many are used as medicines. Plants in particular are an extremely important source of these molecules. Our group aims to discover the genes inside of plants that are responsible for doing the chemistry that creates these molecules from very simple starting materials. By discovering these genes, we can produce important natural products in greater quantities in ways that are environmentally friendly. We are developing new methods to find these genes. We can now look at single plant cells, and see which genes, and which natural products, are found in each individual cell. These methods allow us to find the genes that we are looking for much more quickly. Very often, important natural products are made by plants in very small quantities, or the natural plant producers are hard to grow. This means that it is hard to get enough natural product to use in the clinic. Once we discover the genes that are responsible for making a natural product- for example, the anti-cancer drug vinblastine- we can insert them into yeast or tobacco plants; then these yeast cultures or tobacco plants produce the natural product. We also look for examples in which Nature has made the same molecule twice. From these examples, we can compare and contrast two different chemical solutions that nature has evolved. We can then, in the laboratory, mix and match the two chemical pathways to design our own. For example, we showed that the insect repellent nepetalactone is made by both the catnip plant and aphids.

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Chiral Fluorophores: Design, structure/properties relationship and application

Grégory PIETERS

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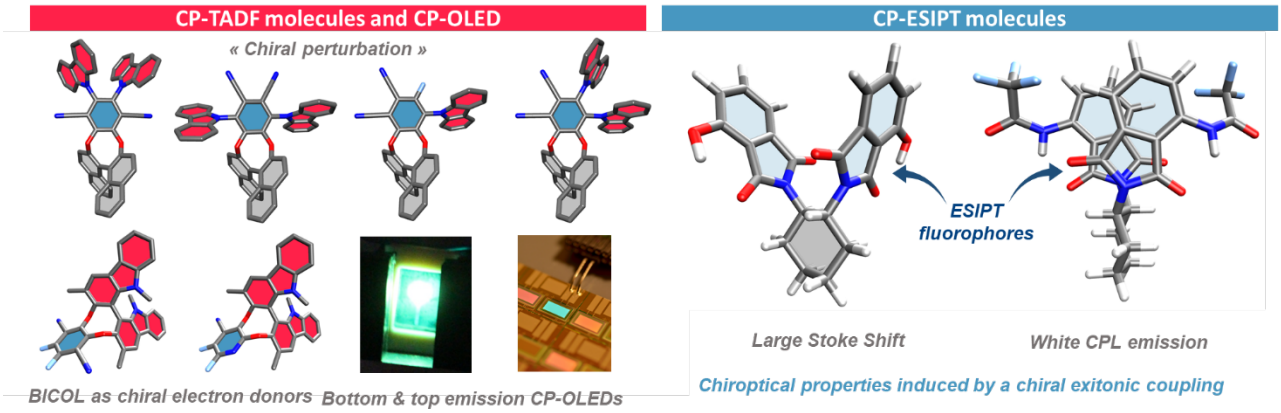
The study of small organic molecules displaying circularly polarized luminescence (CPL) emission is nowadays a very active field of research due to the numerous potential applications of such chiral compounds in nanomaterials, optoelectronic and photonic devices, molecular recognition systems and switches. In regard to displays application, the uses of CPL active fluorophores as emissive dopants in circularly polarized organic light emitting diodes (CP-OLEDs) recently appears as an appealing approach to limit the impact of anti-glare filters on the brightness and therefore the power consumption of such devices.[1]

In this talk, our recent efforts to design and optimize the performances of chiral emitters merging thermally activated delayed fluorescence (TADF) properties and CPL emission and their application as emissive dopants in bottom and top emission CP-OLED devices will be first summarized.[2-4] In a second part of this talk, the first CPL active molecules based on excited state proton transfer (ESIPT)[5] fluorescence and the possibility to design CPL emitters by the control of the dynamic chirality of helical donor-acceptor active fluorophores will be discussed.



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Nature is the cure: reactivity blueprints for bioinspired catalysis and chemistry

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The exquisite and unrivalled efficiency of biological systems relies on the use of reactivity-enhancing tools to perform chemical reactions.[1] Among these tools, redox cofactors situated near metalloenzymatic active sites provide electron storage and release to assist the neighboring metal center in performing the reactions.

Emulating such systems, the development of catalysts bearing redox-active ligands is a blossoming research field.[2] Our contributions to this field include transfer of CF_3 groups[3], stabilization of masked high-valent metallic oxidation states[4], and transfer of nitrene and carbene moieties by redox-active copper complexes ligands. From a broader point of view, our efforts aim at cross-fertilizing the field of bioinspired catalysis with other reactivity-enhancing strategies such as spin catalysis[5], entatic state reactivity[6] and ligand design[7,8].

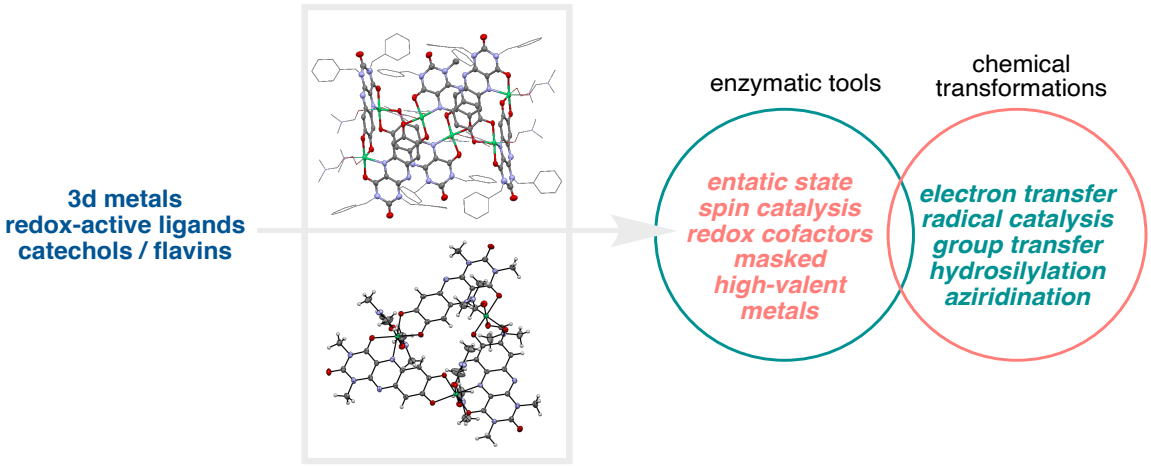

Figure 1. Combining bioinspired strategies for redox catalysis

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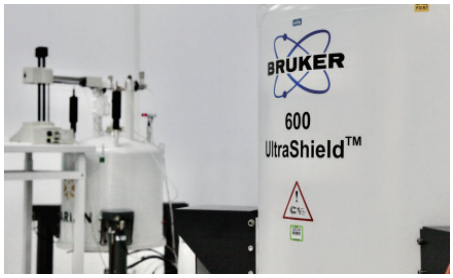

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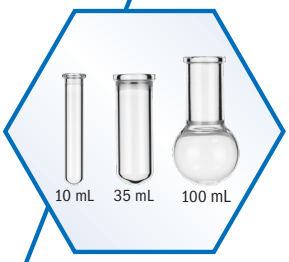

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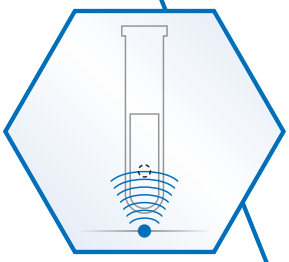

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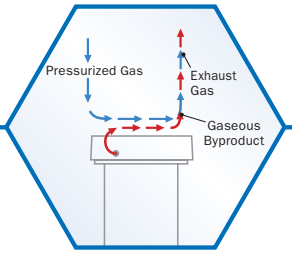

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From homogeneous to heterogeneous gold catalysis: practical advantages, new reactivity, or both?

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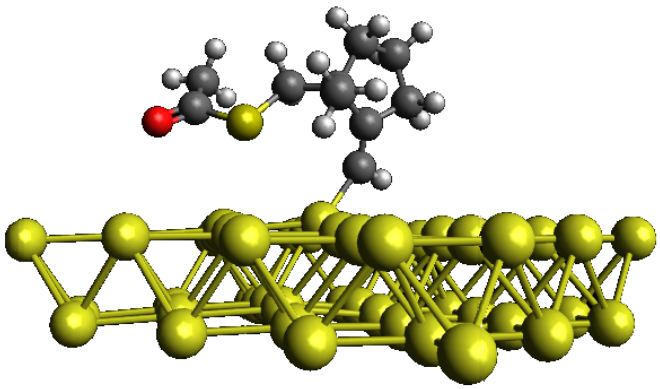
Although early reports on the use of gold in catalysis by Hutchings and Haruta were describing the use of finely divided gold particles[1,2], the gold rush observed these last two decades mostly focused on homogeneous gold catalysis.[3] More recently, heterogeneous gold catalysis, either by heterogeneisation of gold complexes through immobilization techniques or by using gold nanoparticles as catalysts, has emerged.[4,5]

Looking back at some reactions studied in our group, and considering current research we carry out on the topic, we will present some elements to evaluated whether heterogeneous approaches should only be seen as bringing practical advantages (e.g. recyclability, flow chemistry, …) or allow the discovery of new reactivity, or both.



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Persistent chiral mono- and diradicals with SOMO/HOMO inversion

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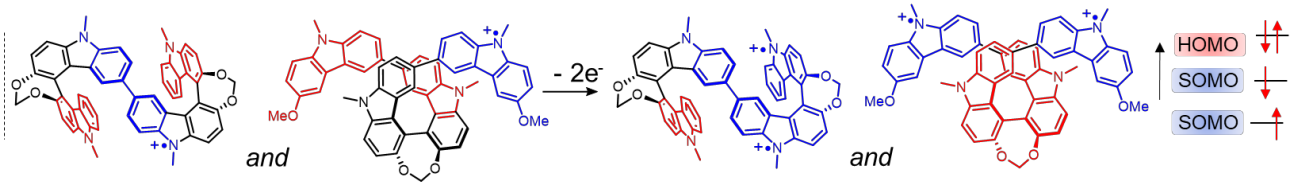
Chiral π-conjugated materials have recently emerged as a promising direction in material science due to their specific interaction with CP-light and the potential of the latter in several domains of applications such as organic light-emitting diodes (OLEDs), organic field-effect transistors (OFETs) and magnets.[1] While extensive researches have been focusing on organic closed-shell chiral dyes, a few attention has been given to their open-shell counterparts due to their low configurational stability and high chemical reactivity.[2] This presentation will illustrate our last experimental and theoretical results regarding the design of persistent organic chiral mono- and diradicals in which the energy of the singly occupied molecular orbital (SOMO) is below the highest doubly occupied molecular orbital (HOMO) level.[3] The peculiar orbital energetics of these SOMO–HOMO inversion (SHI) organic radicals set their electronic properties apart from the more common situation where the SOMO is the highest occupied orbital of the system. Our objective is to establish molecular guidelines for designing this type of radical, and to showcase the potential of SHI radicals in organic spintronics as well as for the development of more stable luminescent radicals for OLED applications (Figure 1).



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Design and synthesis of saccharide-based molecular tools to probe DLODP and LOST orphan activities

Michaël BOSCO[1], Haïfei GAO[1], Younès BOUZIDI[2], Su-Jin PAIK[2], Isabelle CHANTRET[2], Sébastien FORT[3], Stuart E. H. MOORE[2], Christine GRAVIER-PELLETIER[1], Patricia BUSCA[1]

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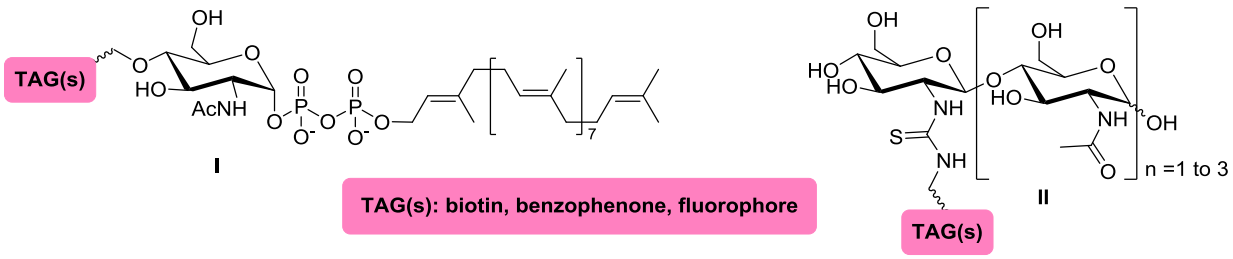
Free oligosaccharides (fOS) have been shown to be proinflammatory (fOSp) and contribute to certain rare inherited inflammatory diseases [1]. These fOS can be generated during protein N-glycosylation and two key players are likely to be involved in their production and/or regulation: Dolichol-Linked Oligosaccharide Diphosphatase (DLODP) in the endoplasmic reticulum, and Lysosomal Oligosaccharide Transporter (LOST) in the lysosome. While these activities were characterized at the biochemical level, the corresponding genes are still unknown [2].

In order to study, isolate and identify DLODP and LOST associated proteins, affinity based probes corresponding to general structures **I** and **II** were designed and synthesized [3]. These saccharide-based molecular tools are bearing one or two tags such as biotin, a photoreactive group and/or a fluorophore in order to visualize and/or purify the targeted proteins.



In this communication, we will disclose our latest results regarding the synthesis and use of these probes.

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3. We gratefully acknowledge FRM (DCM 20181039551) and ANR (ANR-18-CE44-0007) for financial support.

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Design and Studies of Chiroptically-Active Molecular and Supramolecular Helical Systems

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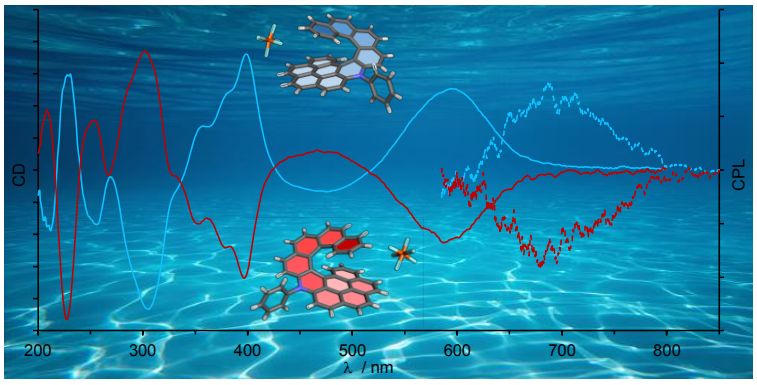
The generation and modulation of circularly-polarized luminescence (CPL) arising from chiral photoluminescent systems has drawn much attention in the last years as various applications emerge such as circularly-polarized electroluminescent devices, optical information encoding or processing, and chemical or biological chirality sensing.
In this context, fascinating chiroptically-active materials have emerged, based on various structural approaches to precisely control the arrangement of building blocks and enhance the chiroptical activity. Additionally, the extensive variety of molecular designs offered by discrete chiral organic molecules provides chemists with a wide array of practical tools to modulate the chiroptical effects.
This presentation will provide an overview of our recent contribution to the field by designing and synthesizing original helically folded structures of different types that are functional oligoamide foldamers[1,2] and azahelicene derivatives[3] which chiroptical activity was assessed both in organic and aqueous media.



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Dearomatisation of Pyridines through the Insertion of N-atom: Photochemical Skeletal Editing for the Synthesis of 1,2-Diazepines

Clément GHIAZZA

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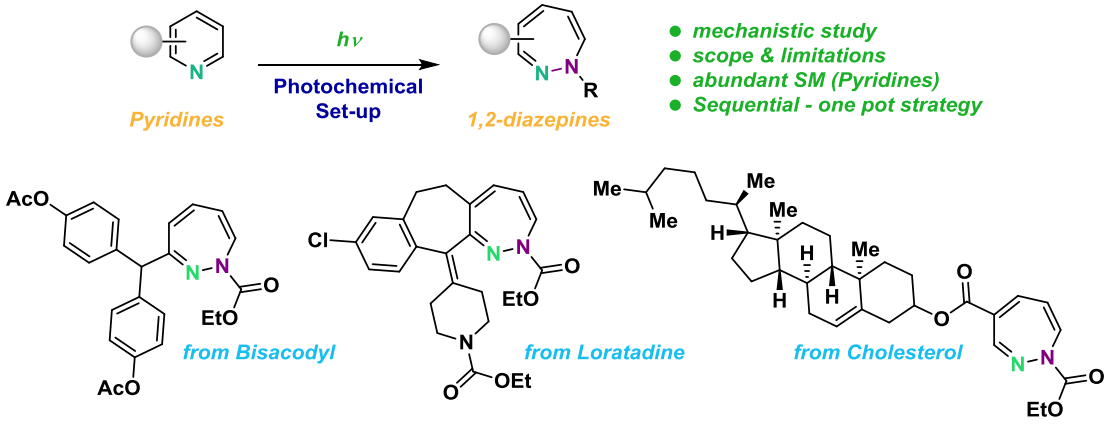
Pyridines are ubiquitous in bio-relevant compounds and are particularly coveted in drug design as they confer selectivity towards specific receptors and valuable physico-chemical properties.[1] The vast representation in pharmaceuticals is essentially due to the availability of pyridine moieties. In fact, many efficient methods describe the preparation of such aromatic core from cheap and abundant materials. In contrast, 7-membered-ring azaheterocycles like 1,2-diazepines are far less accessible, resultiung in a handful of bio-active compounds bearing this scaffold.[2] Indeed, the main synthetic route consists in a double condensation between a well-designed 1,5-dielectrophile and hydrazine as the N – N bond formation remains a challenge.

Interestingly, 1,2-diazepines and pyridines only differ by 1 additional N atom within the ring. Nevertheless, this seemingly simple change breaks the aromaticity and disrupts the planarity of the ring offering advantages in terms of selectivity of a tridimensional architecture. Therefore, swapping from pyridines to 1,2-diazepines can be very interesting if one wants to modulate the physico-chemical properties as well as the geometry of a targeted compound without significantly impacting the size of a substrate.

In recent years, skeletal editing of aromatic compounds has emerged as a powerful shortcut saving practitioners from extensive and time-consuming retrosynthetic analysis.[3] Thus, atoms were inserted, deleted or even substituted in order to modify the nature of an aromatic ring in few steps. In this context, we have recently elaborated a user-friendly protocol enabling the rapid conversion of pyridines into 1,2-diazepines in a single flask operation. The method has been successfully applied to real life pharmaceuticals. Ultimately, this strategy aims to accelerate the discovery and design of new drugs in R&D programs.



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Syntheses of *O*, *N*, and *S*-Heterocycles through gold-mediated domino reactions

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Heterocycles represent structural architectures frequently found in biologically active natural and unnatural compounds, drugs, and agrochemicals. Significant advances toward the synthesis of heterocyclic compounds have been achieved in homogeneous gold catalysis. Besides, over the past decade, homogeneous gold catalysis as part of domino processes has been the subject of intense research because of its potential to rapidly build molecular complexity. Prompted by the above considerations, we have developed versatile methodologies leading to *O*, *N* and *S*-heterocycles such as furopyrans (**2**, **3**), benzothiophenes (**4**) and benzoazepines (**5**), in a highly efficient and straightforward manner through gold-mediated domino reactions.[1-5]

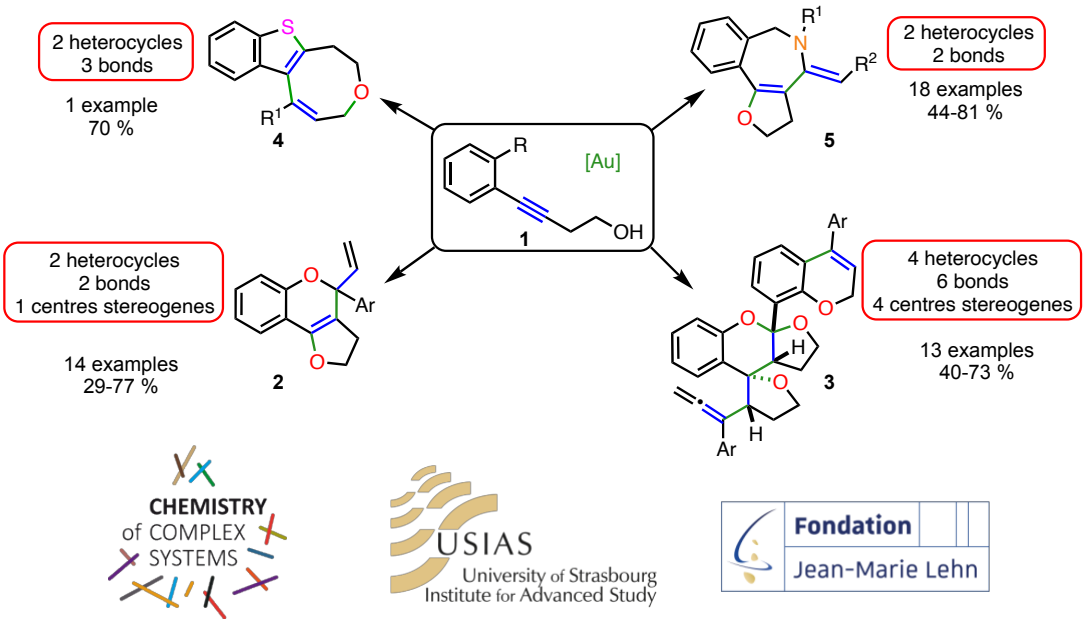

Fig. 1 Gold-mediated domino reactions for the syntheses of *O*, *N* and *S*-heterocycles

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From Molecular Recognition to Catalysis: Designing an Artificial Decarboxylase

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Aromatic oligoamides present all the required features to act as efficient scaffolds for the molecular recognition of chiral polar guests. Their oligomeric nature offers unmatched modularity in that each and every monomer may be varied in order to tune the structure, the dynamics and host-guest properties. Helices with variable inner diameters can be used as capsules that can totally isolate a substrate from the external medium (Fig. 1, left). While catalysis using foldamers is a rapidly developing area, there has been no account on catalysis within foldamer containers making use of their recognition properties.

Recent efforts in our group have focused on the design of capsule shaped catalysts for the decarboxylations of perfluorosuccinic acid (Fig. 1). The functionalization of a capsule with electron donating morpholine moieties allowed the deprotonation of the dicarboxylic acid guest and its subsequent double decarboxylations. Surprisingly, the CO_2 molecules generated during the reaction could be trapped in the foldamer cavity and the resulting gas-foldamer complex could be characterized in solution and in the solid state. Alternatively, heating of the capsule in the presence of an excess of diacid allows for catalysis to proceed.

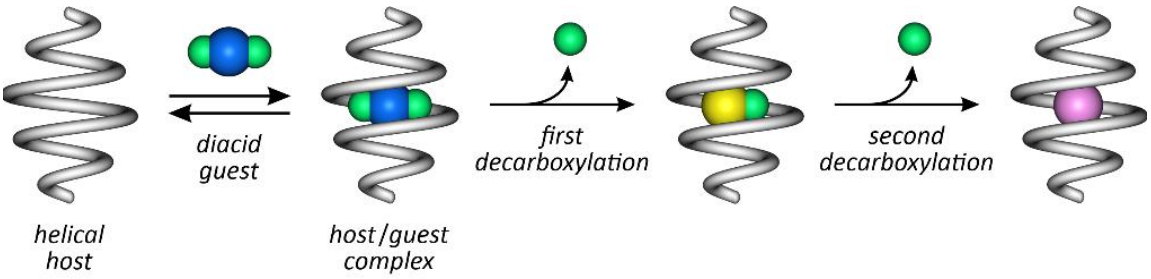

Figure 1. Schematic representation of the host/guest complex formation followed by two consecutive decarboxylation reactions of a diacid guest.

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Fluorine-Activated Additive-Free Vitrimers

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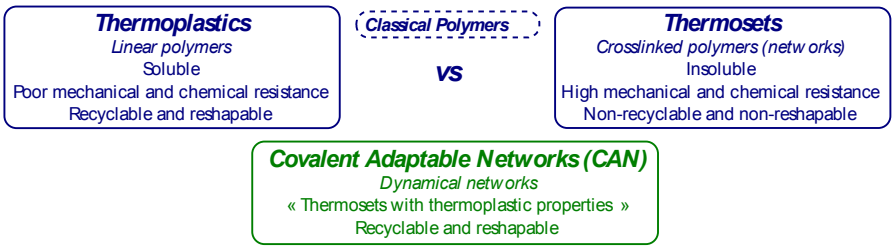
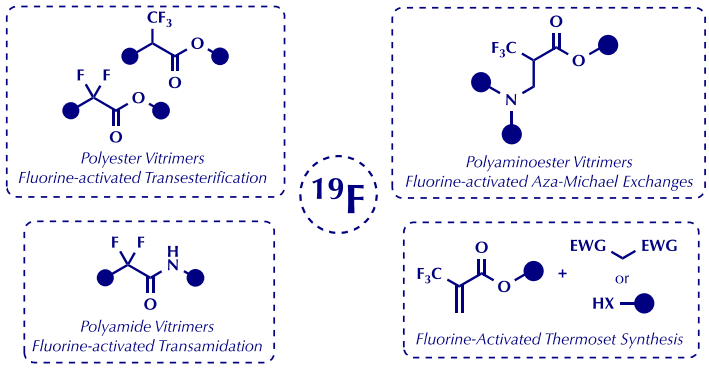
For almost two decades, the frontier between the two traditional categories of polymers, namely thermoplastics and thermosets, has been blurred by the development of vitrimers, a particular class of covalent adaptable networks (CANs).[1] This new breed of organic materials indeed gathers the mechanical and chemical resistance of permanent 3D networks and, to some extent, the reprocessability and recyclability of linear polymers.[2] The peculiar properties of CANs rely on the following simple strategy: the 3D network is composed of **covalent links that can be exchanged with other functions or similar links** elsewhere in the network upon application of a stimulus (heat or light).[3]



However, long reprocessing times, high temperatures and, in most cases, **high catalyst loadings** are often required, still limit the applicability of such materials through ageing or catalyst leaching. The development of **catalyst-free vitrimers** and CANs that can be easily reprocessed at reasonable temperatures is therefore an exciting challenge. Our own contribution to this field is based on **the use fluorinated groups to accelerate exchange reactions in the network** (transesterification, transamidation, aza-Michael) that allowed the preparation of efficient catalyst-free vitrimers.[4] The different strategies that were developed on this topic, as well as the molecular studies to support them, will be discussed.



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Double Allylic Substitutions of Alkenyl *vic*-Diols

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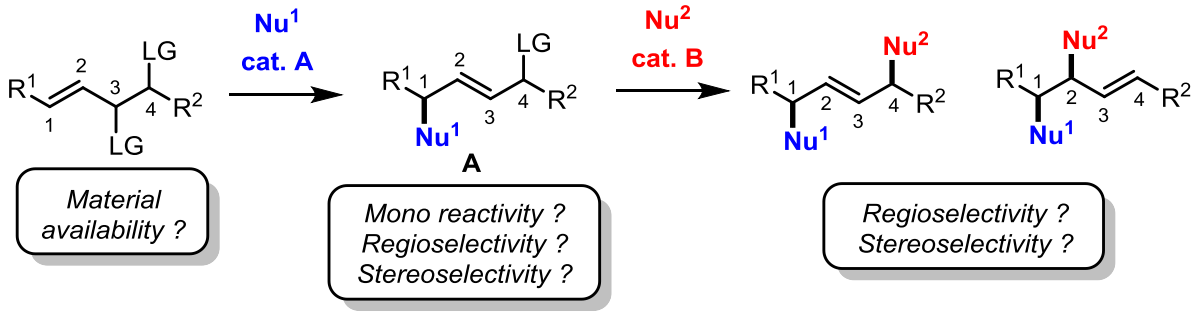
Allylic substitution is arguably one of the most powerful tools for the creation of C-C and C-heteroatom bonds in organic synthesis.[1] The best example is the venerable Tsuji-Trost reaction, which is commonly employed as a regio- and stereoselective method for the creation of C-C, C-O, C-N and C-S bonds. On the other hand, double allylic substitution sequences are surprisingly scarce given the level of molecular complexity that could be reached through this kind of one-pot approach.[2] Indeed, the successive allylic alkylation of 3,4-difunctionalized but-1-ene derivatives presents many challenges (Scheme 1). First, the regioselective introduction of two nucleophiles implies differentiating between electrophilic positions 1 and 3 for the first substitution, and positions 2 and 4 for the second one. In addition, the fact that compound **A** resulting from a first allylic alkylation is also a substrate for a second allylic alkylation poses chemoselectivity issues, if one wants to introduce two different nucleophiles (Nu^1 could react again on substrate A). The final product displays two new stereogenic centers, which raises the question of stereoselectivity in this sequence. Finally, for this transformation to be of interest for the community of synthetic chemists, it needs to depend on easily accessible precursors.

Herein, we propose a novel strategy based on multicatalysis for the regioselective double allylic substitution of easily accessible alkenyl *vic*-diol derivatives. This approach allows the introduction of two different nucleophiles, opening the door to molecular diversity from simple allylic diol derivatives.



Scheme 1 : Challenges of a regioselective double allylic substitution

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TOWARDS BIOMEDICAL APPLICATIONS OF PHOTOLYTIC REACTIONS.

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The use of photolabile protecting groups (PPGs) has been growing in emphasis for decades, and they nowadays enable cutting-edge results in numerous fields ranging from organic synthesis to various field of biology.[1-2] PPGs are chemical entities that can be conjugated to a biological effector to hide its biological activity, forming a stable so called "caged compound". This conjugate can be simply cleaved by light and therefore, the functionality of the biological effector is restored with the formation of a PPG by-product. The use of UV irradiation (normally within power density between 10^{-1} and 10^{-3} W.cm^{-2}) to manipulate the functions of biomolecules or mediate on-demand drug release in living systems *via* effective photoactivation with very high spatial and temporal control is a remarkable, well-developed and reviewed technique.[2] During the last two decades, the challenge was to overcome the difficulty that only high energy light (i.e. UV, the one damaging biological tissues) can induce photochemical reactions. One strategy to lower phototoxicity within the domain of one-photon excitation process is based on tailoring the caging groups with extended π-conjugation and introducing heteroatoms and functional groups in the ring system so that larger dipole change can be generated upon excitation. Therefore, blue light-sensitive photoremovable groups have been reported in the coumarin,[3] *o*-nitrobenzyl,[4] and *o*-nitrophenethyl series.[5] This later strategies enable new biomedical applications in particular for the treatment of proliferative retinopathy. Therefore, the development of blue light sensitive caged small gene inducers[6] will be presented in this context.

For more general biomedical applications the development of Red to NIR sensitive systems is highly sought after. In this context, we will also present our recent development emissive upconversion nanoparticles systems using the TTA-UC strategy[7] (for Red or NIR to blue light upconversion). And we will present how we have been able to further functionalize those nanoparticles with blue light-sensitive photocleavable linkers in order to trigger drugs releases using red light.

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Pd-S cooperativity: from stoichiometric activation of E–H bonds to catalytic hydroelementation

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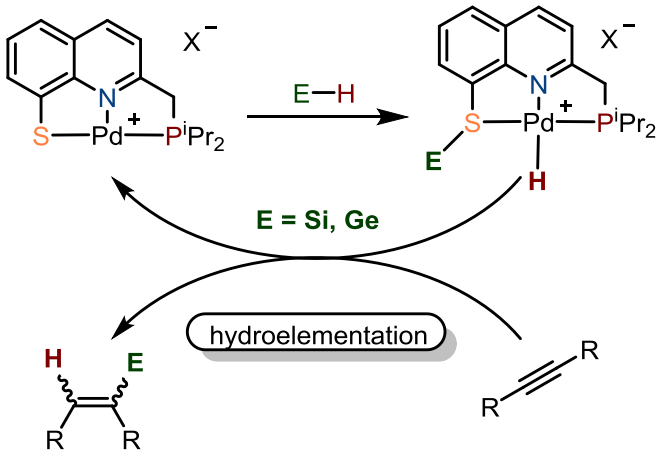
Thanks to the synergy between two different catalytic sites, extraordinary improvements in efficiency and selectivity can be achieved. In this context, metal/ligand cooperation (MLC), in which one of the ligands participates actively to the activation of the substrates, can be highlighted.[1] In this domain, pincer complexes of transition metals play an important role. One of the most representative models was reported by Milstein[1], based on an aromatization/dearomatization process of a pyridine based pincer.

Although group 10 metals are widely used in catalysis, they are less studied in MLC than metals of group 8 and 9.[2] Ten years ago, our group has reported indenediide Palladium complexes bearing an electron rich backbone.[3] Remarkable results have been obtained in catalytic cyclisation processes involving C-O/C-N & C-C bonds formation.

To further develop MLC with group 10 metals, we recently developed a new platform deriving from the quinoline moiety that can combine two types of non-innocent behavior: via aromatization/dearomatization of the quinoline moiety, or via polar M-S bond.[4] Catalytic applications of this new Pd complex will be introduced for the hydrosilylation and hydrogermylation of alkynes in parallel to the use of the obtained vinylgermanes/silanes for orthogonal derivatization.



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Fluorescence switching with phosphorus-based multi-stage redox systems

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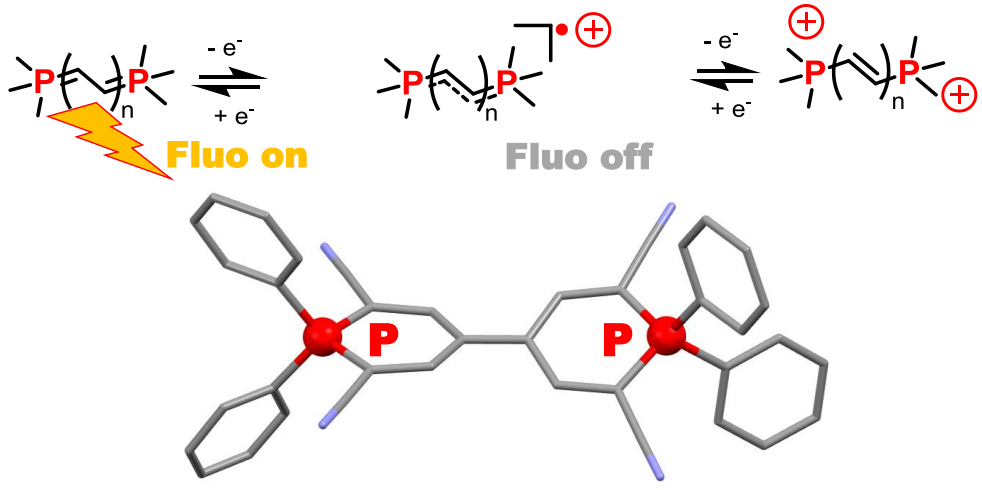
Organic multi-stage redox systems are key component in many technological fields ranging from organic electronic to spintronic. Among the strategies used to design such compounds, one approach consists in linking two cationic heteroatoms through a π-conjugated backbone featuring an even number of *sp*^{2} C-atoms.[1] This led to the preparation of "Weitz type" derivatives with three stable redox states including a stable radical cation intermediate. Methyl-Viologens (MV) are probably the most emblematic electron acceptors of this family.[2] Although Hünig *et al.* mentioned the applicability of this strategy to systems in which P is the unique heteroatom (see Fig.), such derivatives were not described before 2020, despite the wide literature on organophosphorus based π-systems and switches. To tackle this challenge, we took advantage of the possibility to convert a cationic $\sigma^4\lambda^4$ P$^+$-atom into a neutral ylidic $\sigma^4\lambda^5$ P (Fig.). We reported the straightforward synthesis of a family of dicationic P-containing Polycyclic Aromatic Hydrocarbons. (Spectro)electrochemical studies proved that these compounds possess three stable redox states and we demonstrated that these novel acceptors possess a "viologens-like" redox behaviour. Electrochemical modulation of fluorescence highlighted the potential of these intrinsically switchable electroactive fluorophores.[3] In order to prepare similar fluorophores which properties could be addressed upon oxidation (rather than reduction), a stable bis-ylide linked by an even number of *sp*^{2} C has to be prepared. We thus decided to prepare λ^5-biphosphinines linked through their 4,4'-position. In this "impromptu", we will discuss the synthesis, optical and redox properties of this new generation of intrinsically switchable electroactive fluorophores.



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Severely twisted hexagon-based polycyclic aromatic hydrocarbons

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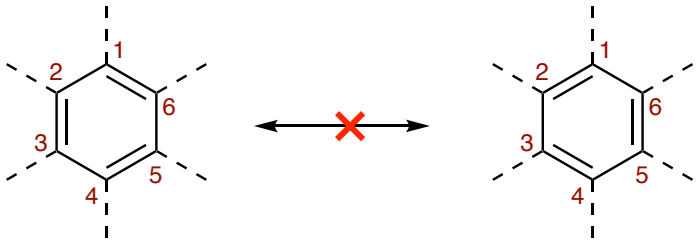
In a series of papers published in 1865 – 1866, Prof. Friedrich August Kekulé (1829 – 1896), a Professor of Chemistry at the University of Ghent in years 1858 – 1867, proposed a cyclic structure for benzene based on his theory of the tetratomicity of carbon. In 1872, he refined his proposal with now a *fully symmetric* structure for benzene with D_{6h} symmetry: he postulated that the structure of benzene is the average between two isomers of hexagonal 1,3,5-cyclohexatriene.[1] Note this was six decades before the introduction of the resonance structures theory and the concept of mesomery by Linus Pauling,[2] and the introduction of the Hückel (4n+2) rule of aromaticity for monocyclic conjugated systems.[3]

In this lecture, I will discuss the synthesis and some properties of contorted large polycyclic aromatic hydrocarbons prepared recently in our group. Notably, these molecules are composed of hexagonal rings only, some of which exhibit a severe torsion and a marked non-alternant 1,3,5-cyclohexatriene character.[4]



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Leveraging long-lived arenium ions in superacid for *meta*-selective Friedel-Crafts methylation

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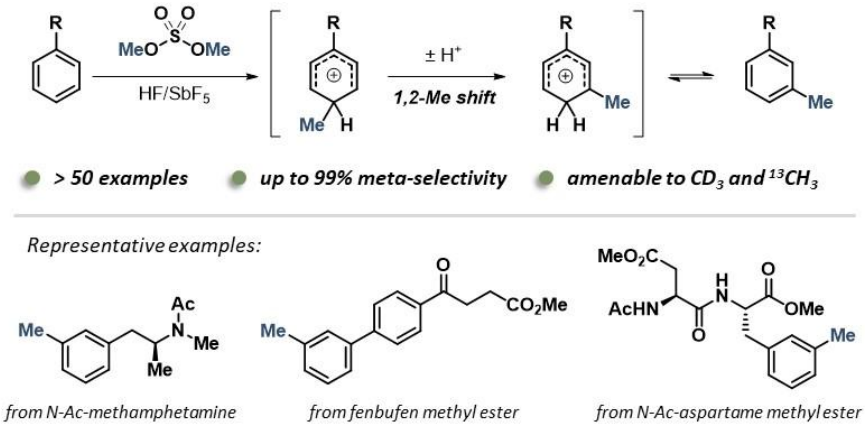
Electrophilic aromatic substitution (S_EAr) is an essential transformation in many large-scale industrial processes with applications spanning from polymer chemistry to the production of feedstock chemicals. Such transformation has also an evident relevance in drug discovery which relies extensively on benzenoid rings.[1] The regioselectivity of S_EAr transformations can be directly correlated to the relative stability of the σ-complex intermediates which is influenced by electronic and steric factors, mostly favoring the para position to the electron-donating group in the simpler case of monosubstituted arenes. However, the selective access to intrinsically-disfavored positions still remains a highly challenging task and mostly restricted to directed metal-catalyzed C–H activation strategies.[2] Herein, we describe a broadly-applicable Friedel-Crafts methylation with non-natural site selectivity.[3] The key to the reactivity is the use of superacidic conditions which allows to favor the controlled isomerization of σ-complex intermediates.



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Telluroniums Salts in Chalcogen Bonding Catalysis

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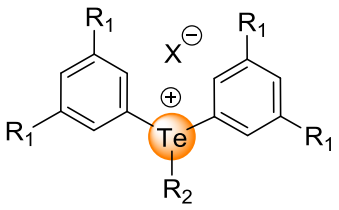
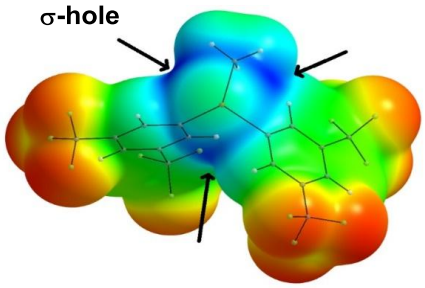
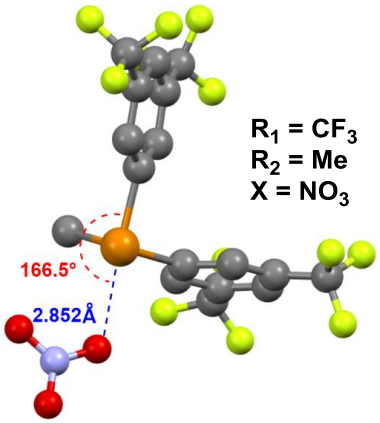
The chalcogen bond (ChB) is a non-covalent interaction analogous to the halogen bond (XB). These two interactions are due to the attraction between a nucleophilic entity (Lewis base) and an electrophilic region, called σ-hole, present on the halogen or chalcogen atoms. The number of σ-holes on an atom generally depends on its valence. Thus, a monovalent halogen has one σ-hole while divalent chalcogen atoms have two σ-holes. Although comparable to hydrogen bonding (HB) in terms of strength, XB and ChB on the other hand are highly directional. This interesting property has recently allowed the exploitation of ChB in many applications and more particularly in organocatalysis. As with XB, the strength of ChB depends on the polarizability of the chalcogen atom (S<Se<Te) and therefore chalcogen interactions involving tellurium are the strongest. Tellurium derivatives are therefore very promising for applications based on σ-hole interactions. This presentation will focus on the latest results from our laboratory involving cationic derivatives of tellurium, the telluroniums, which have three σ-holes and which have proven to be very effective in many catalytic reactions.[1,2]







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Dynamic combinatorial libraries of glycoclusters: When glycoclusters go dynamic

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Pseudomonas aeruginosa is a well-known pathogen responsible for pulmonary infections among others. It is most notably found in hospitals as a cause for nosocomial infection. Anti-adhesive strategies are inhibiting the adhesion of bacteria to the host cells. Two soluble tetrameric lectins (LecA and LecB) have been identified in this process. LecA is known for its affinity for β-galactosides while LecB exhibit an affinity for α-fucosides. We have designed multivalent glycoclusters to inhibit these lectins with applications *in vivo* as potential therapeutic anti-infectious agents.[1] The calix[4]arene-based glycocluster (Figure 1) displayed nanomolar affinity for LecA and provided protection against pulmonary infection in animal.[2]

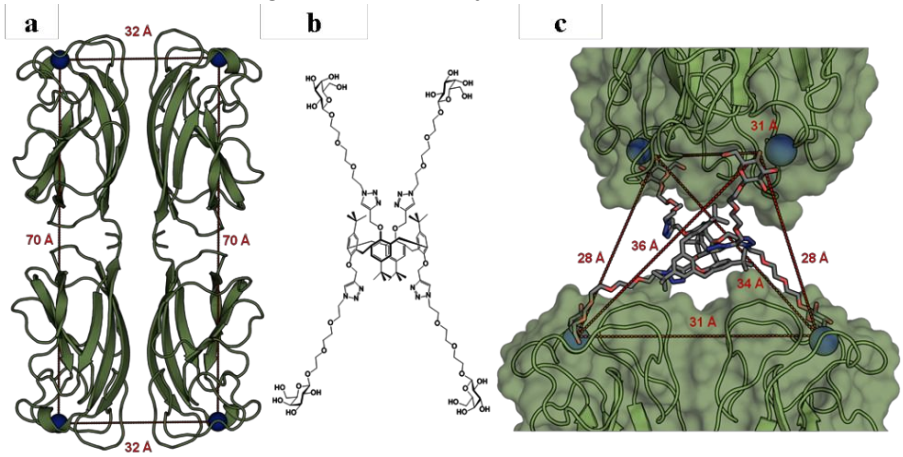

Figure 1: (a) Three-dimensional structure of lectin LecA. (b) Galactosylated 1,3-alternate calix[4]arene-based glycocluster. (c) Molecular modeling pictures of aggregative chelate arrangement between LecA and the ligand.

We have now developed self-assembling glycoclusters based on the concept of dynamic combinatorial chemistry (Figure 2).[3] The building block is composed of an aromatic core, a spacer and a carbohydrate and will self-assemble in solution through disulfide bonds to generate a dynamic combinatorial library of glycoclusters. In this communication, we will detail the synthesis of the building blocks and the results obtained during the dynamic combinatorial libraries.

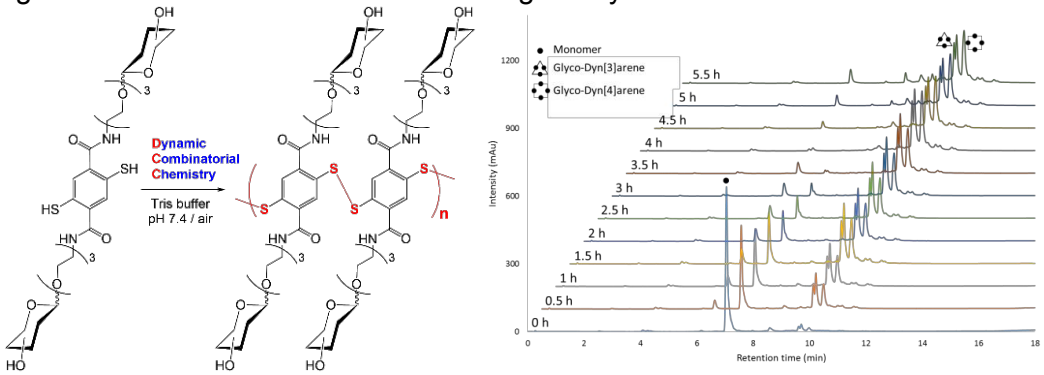

Figure 2: (left) Equilibration of glycosylated dithiphenol building blocks. (right) HPLC kinetic analysis of the equilibrium toward dyn[3]- and dyn[4]arene-based glycoclusters.

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Groupe d'Etudes en Chimie Organique
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Regioselective C–H functionalization of naphthalenes: new strategies for the synthesis of aromatic polyketides

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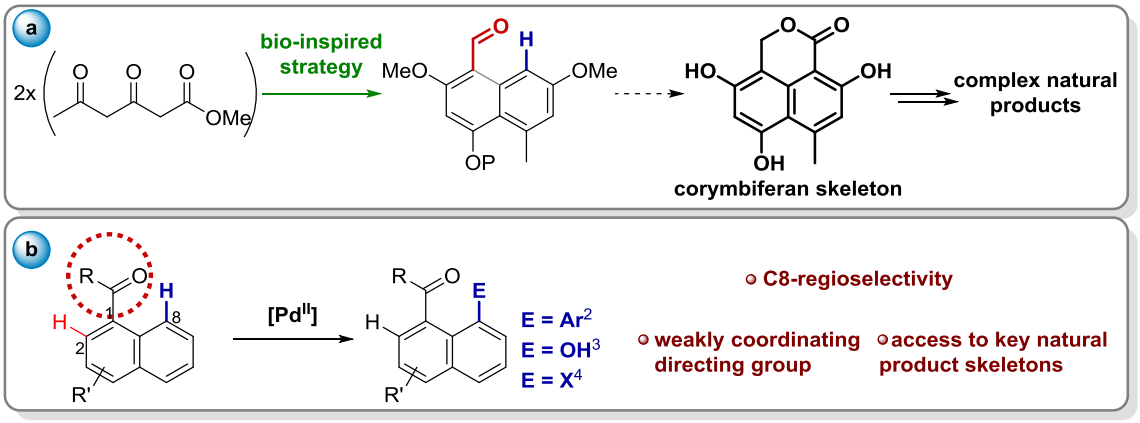
Polyketides are an important class of highly biologically active secondary metabolites. Among them, corymbiferans are aromatic fungal polyketides bearing a characteristic naphthol ring annulated with a 6-membered lactone, which is a commonly found skeleton, as monomeric or dimeric natural products exhibiting remarkable biological properties.[1]

Our work is mainly driven by the development of new methodologies related to aromatic polyketide synthesis. Based on their biosynthesis, we have designed a synthetic strategy relying on a polyketone analogue cyclization to obtain the corymbiferan skeleton, a key intermediate for the synthesis of complex natural products (*Fig.a*). During this approach, we had to focus on C8-functionalization of naphthalene derivatives. Our objective was to selectively functionalize the position 8 of naphthalene thanks to carbonyl derivative as directing group in order to apply our strategy in natural product synthesis. In this context, a palladium catalyzed C8-arylation of naphthalenes was developed,[2] as well as a C8-oxygenation which allows a direct access to the naphtholactone skeleton.[3] In addition, in order to access many natural product skeletons, regioselective halogenation reactions of 1-naphthaldehydes was recently disclosed (*Fig. b*).[4] Based on these C-H activation methodologies, research in natural product synthesis is currently ongoing in the laboratory.



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Synthèse de bioconjugués à base de triazacyclononane pour le radiomarquage au [^{64}Cu]Cu

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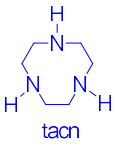
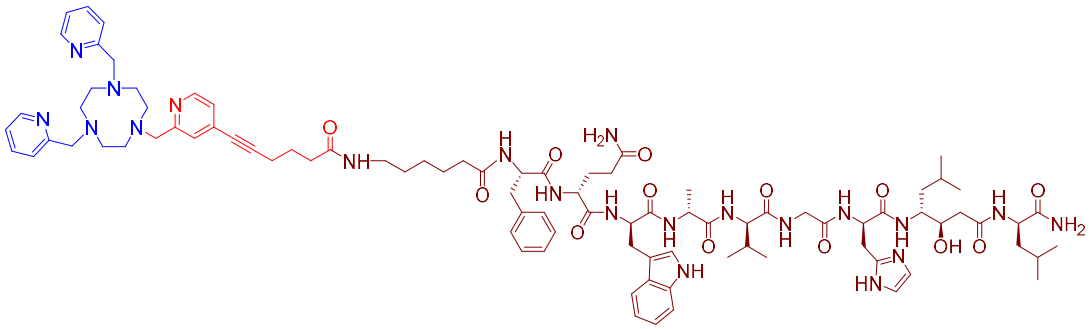
L'imagerie TEP (Tomographie par émission de positons) est une technique d'imagerie des cancers basée sur l'utilisation de radioisotopes émetteurs β^+ incorporés dans des radiopharmaceutiques. Quand le radionucléide est un cation métallique, il est encapsulé dans un chélateur organique, lui-même conjugué, via un linker, à un biovecteur spécifique du marqueur tumoral ciblé. Parmi les émetteurs β^+ cationiques disponibles, le ^{64}Cu est particulièrement intéressant de par ses caractéristiques intrinsèques (temps de demi-vie, énergie d'ionisation), mais également par la formation possible d'une paire théranostique de radionucléides avec son radioisotope parent ^{67}Cu, émetteur β^-, susceptible d'être utilisé en radiothérapie.

Les polyamines cycliques telles que le tacn (triazacyclononane) sont reconnues pour leurs très bonnes propriétés complexantes vis-à-vis des cations des métaux de transition et des lanthanides, ce qui en fait des chélateurs très appréciés pour la synthèse de nouveaux radiopharmaceutiques performants. Notre groupe est ainsi spécialisé dans la conception de nouveaux dérivés de polyamines cycliques pour des applications en imagerie et en thérapie.



Dans cette communication, la synthèse de quelques radiopharmaceutiques potentiels basés sur le macrocycle tacn et visant particulièrement le cancer de la prostate sera présentée. Les différentes étapes incluant la synthèse des chélateurs bifonctionnels, leur bioconjugaison au vecteur peptidique d'intérêt dérivé de la bombésine et les résultats de radiomarquage au ^{64}Cu seront détaillés.



Exemple d'un bioconjugué pour le radiomarquage au [^{64}Cu]Cu synthétisé au laboratoire

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Groupe d'Etudes en Chimie Organique
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Threading a linear molecule through a macrocycle thanks to boron

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While boron has extensively been used to assemble complex assemblies like cages,[1] it has never been used to thread a linear molecule through a macrocycle.

In this presentation, we will show it is in fact possible to use boron to thread BODIPYs and other species through macrocycles designed on purpose.[2] These new assemblies were unambiguously characterized by NMR spectroscopy as well as by X-ray diffraction for some of them (figure 1).

Interestingly, fluorescent threaded species show higher quantum yields (up to 91%) than their non-threaded counterparts as well as a better photostability.

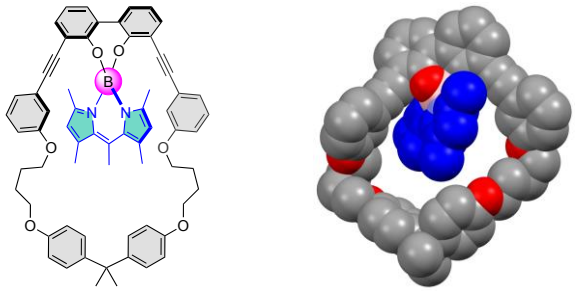

Figure 1. *Threaded BODIPY through a macrocycle and its X-ray structure.*

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Groupe d'Etudes en Chimie Organique
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Enantioselective Ring Expansion

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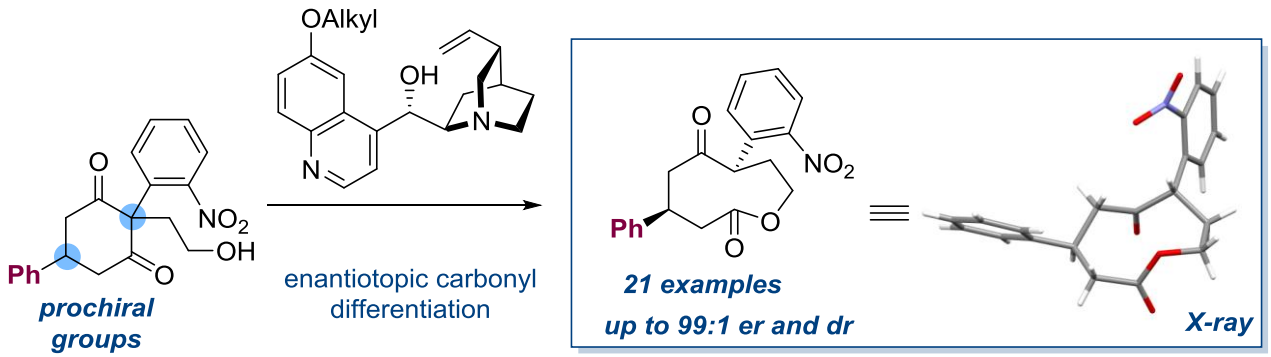
The lactonization of 2-(2-nitrophenyl)-1,3-cyclohexanediones containing an alcohol side chain and up to three distant prochiral elements was developed by isomerization under the mediation of simple organocatalysts such as quinidine.[1] Through a process of ring expansion, strained nonalactones and decalactone are produced with up to three stereocenters in high er and dr (up to 99:1). Alkyl, aryl, carboxylate and carboxamide moieties were examined as substituents of the 1,3-cyclohexanedione motif, leading to functionalized nonalactones after ring expansion.



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Groupe d'Etudes en Chimie Organique
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Light-Frozen Dynamic Covalent Synthesis of Electron-Deficient Conjugated Materials

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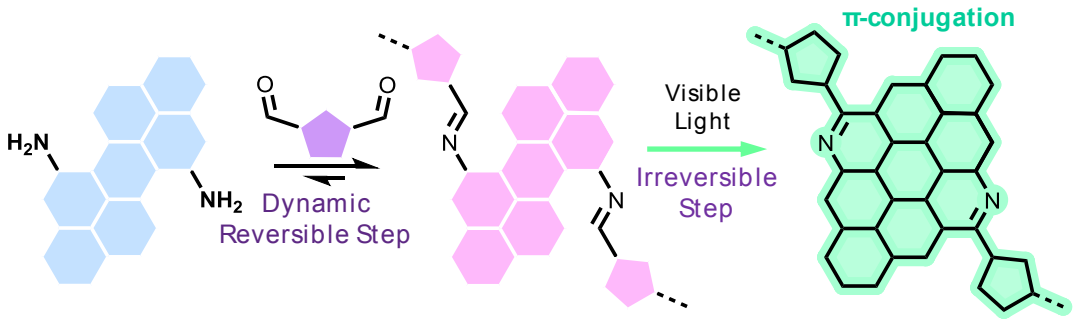
Organic electronics devices are now all around us and the chemistry of organic semiconductors of various optical and electronic properties is blooming. If the development of p-type (holes transporting, electron-rich) organic semiconductors has seen the synthesis of a wide variety of high-performing new materials, the preparation of their n-type (electron-transporting, electron-poor) equivalents is still lagging behind. This is mainly due to the difficulty to selectively and efficiently introduce electro-attracting group on conjugated molecules and to the low variety of electron-poor scaffolds available.

We present here an alternative way to prepare AzaBenzannulated PeryleneDiimides (AzaBPDIs) that proceeds in three steps in one pot: an imine condensation by reaction between an amino-PDI derivative and an aldehyde, followed by a visible-light induced photocyclization and re-aromatization. This class of materials has been so far underexploited in organic electronics as previous strategies relied on poorly efficient acid-catalysed cyclization. This light-mediated method allows us to prepare bay-extended perylenoïd materials without the need for a precious metal catalyst and the tedious preliminary bromination of the PDI core.

Multimeric and heteroatoms doped materials prepared with various aromatic side-groups showed good n-type semiconducting properties and performed as modest non-fullerene acceptors in organic solar cells exhibiting high open-circuit voltages. Interestingly, the reversible and dynamic covalent character of the first step of the reaction opens a new route for the synthesis of organic semiconducting polymers, by preparing size-defined oligomers and polymers at thermodynamic equilibrium, subsequently locked by exposure to visible light into kinetically inert materials.



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Groupe d'Etudes en Chimie Organique
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Glycoboronates: Self-assembly and water-sensitive organogelators

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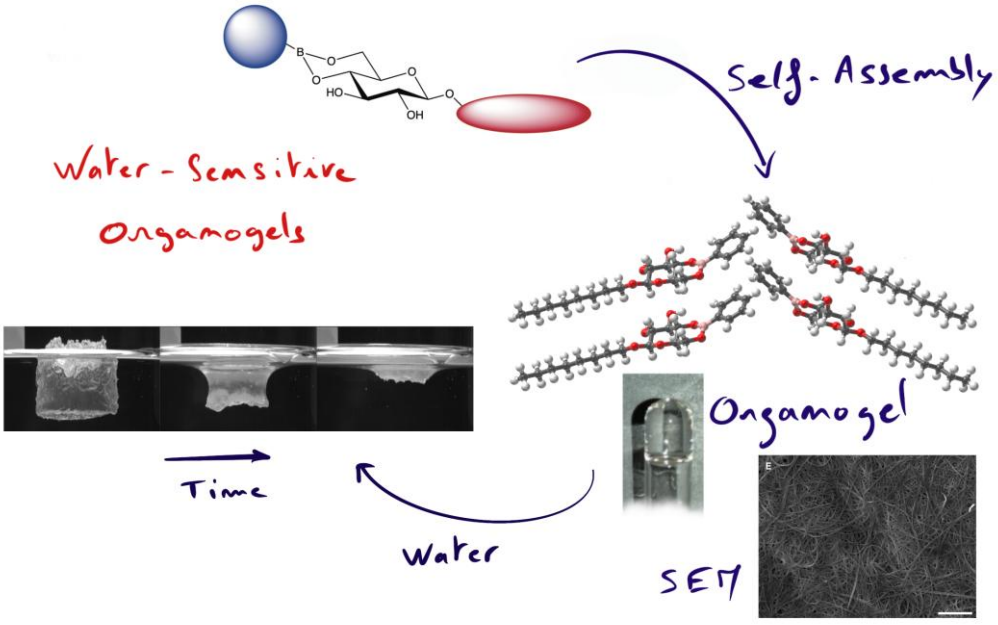
The preparation of gels with low-molecular-weight gelators is based on the formation of a 3D-network responsible for the immobilisation of a solvent. The corresponding fibers are obtained through the self-assembly of those gelators thanks to van der Waals interactions, π–π interactions, hydrogen bonding or electrostatic interactions.[1] It turns then aqueous or organic solutions into hydrogels or organogels, respectively. Sugar-based derivatives are already known for their potential as remarkable organogelators.[2] Recently, we described an easy synthesis of a new class of organogelators obtained by esterification of a glucoside with aromatic or aliphatic boronic acids.[3] These sugar-boronate derivatives permitted to investigate the impact of both the alkyl chain and the aromatic part on the gelation properties. Several organogels were obtained in various solvents. We fully characterized those gels by rheometry, electron microscopy (SEM) and X-ray diffraction to understand as much as possible the type of self-assembly involved during the formation of the organogels. The boronate function offers new properties to those gels. Indeed, our organogels demonstrated a remarkable water-sensitivity which can be tuned through variations on the chemical structure of the gelators.



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Alkoxyamines as therapeutic agents

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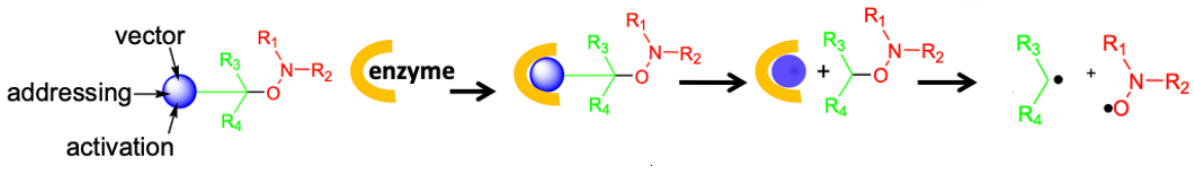
Many diseases such as cancer, malaria, various infectious diseases constitute a major problem in our societies, and this situation will become critical during the next decade. It is therefore necessary to develop very active drugs that are not toxic for healthy tissues.

Our strategy will deliver alkyl radicals or reactive oxygen species (ROS) only in the right place. This strategy is promising as it relies on the generation of highly reactive and non-selective radical species, which makes drug-resistance highly challenging. Thus, we prepared very stable pro-drugs which then be transformed into toxic radical species by the action of a specific enzyme, which is only active near a pathology.[1] Thus, we develop families of drugs (alkoxyamines) activatable by specific proteases overexpressed during a pathology.

For *Plasmodium*, the target protease will be plasmepsine.[2] For glioma, the protease will be neutrophil elastase.[3] For bacteria, we aim noxious and drug-resistant bacteria exhibiting a highly specific enzymatic activity as *Staphylococcus aureus* that secretes Glu-C V8 protease.

The most significant results concerning alkoxyamines and their biological applications will be presented.



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Asymmetric synthesis of allenes from simple alkynes using novel chiral diselenide reagents

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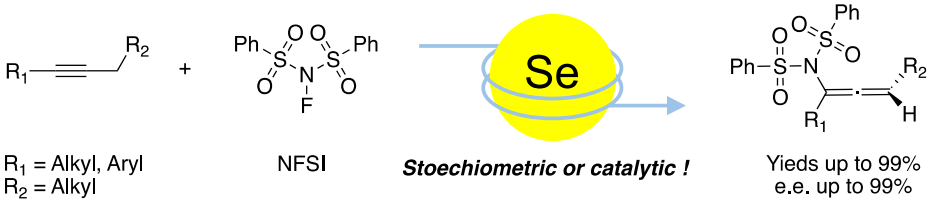
Allene chemistry has experienced remarkable developments in the past few decades. This is most certainly due to their synthetic potential in regio- and stereoselective C–C and C–X bond-forming transformations, as well as their occurrence in a variety of natural products and pharmacologically active compounds.[1] Most of the classical chemical reactions (additions, eliminations, substitutions or rearrangements) have been used toward their synthesis,[2] and have led to an important number of methods. Despite this large variety of methodologies to access allenes, the asymmetric synthesis of such motifs based non-metal-mediated processes is still in its infancy.[3]

To address this question, we have recently developed efficient novel chiral diselenides that can promote the stereoselective formation of allenes from simple non-activated alkynes in presence of N-fluorinated sulfonimide.[4] The results of our efforts will be here presented, and will disclose the use of either stoichiometric or catalytic loadings of the chiral diselenides to generate a wide scope of trisubstituted allenes in both excellent yields (51 - 99 %) and enantiometric excesses (up to 99 %).



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A New Design of Chiral N-Heterocyclic Carbene (NHC)-Metal Complexes: Applications in Enantioselective Catalysis

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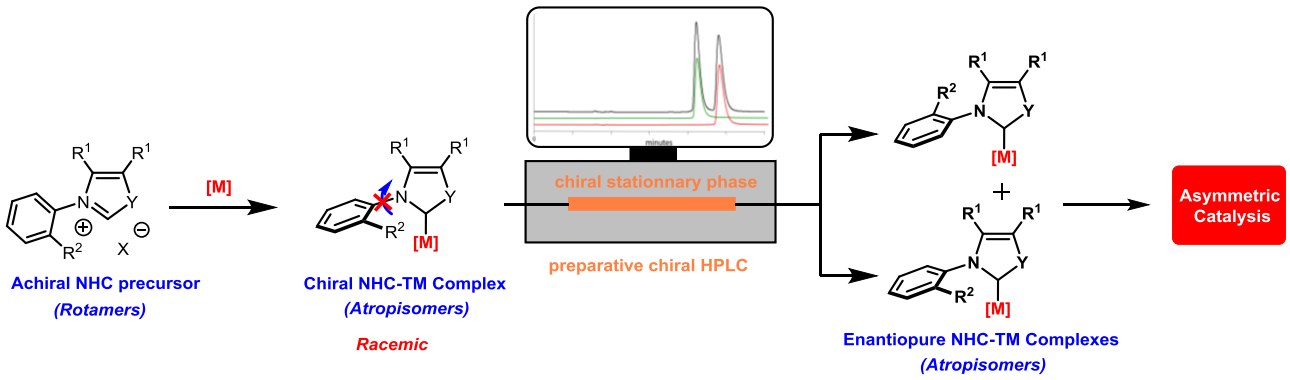
In enantioselective transition-metal catalysis, chiral ligands are key players. The success of N-heterocyclic carbenes (NHCs) as stable electron-rich neutral ligands in homogeneous catalysis led to the development of a wide array of chiral NHCs as stereodirecting ancillary ligands for various asymmetric reactions.[1]
Recently, we devised a new design of chiral NHC-metal complexes based on restricted rotations of dissymmetric aryl groups as *N*-substituents of the NHC ligands.[2] Advantageously, this design does not require the use of chiral synthons since the axis of chirality is created during the metalation step. However, NHC-metal complexes are formed as racemic. Thanks to the high chemical stability of most of NHC-metal complexes, a resolution by chiral HPLC at preparative scale enabled to obtain both enantiomers with high yields and excellent enantioselectivities.



Details concerning the syntheses, configurational stabilities and the values of the rotational barriers will be presented.[3,4] Series of chiral palladium-, copper-, gold- and ruthenium-NHC complexes have been prepared and their application in enantioselective catalysis allowed to reach high level of enantioselectivities.[2-6]

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Process Development of a Novel Route to Rilpivirine Hydrochloride – From Lab Scale to Pilot Scale

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Rilpivirine hydrochloride is a Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI). Known since the early 2000's, it is now used as an active pharmaceutical ingredient for the treatment of HIV infection. This approved drug substance can either be used alone or in combination with other active substances.

An industrial process of this active ingredient was developed and Rilpivirine Hydrochloride could be produced on a 10 kg scale.[1,2]

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Quel(s) mécanisme(s) pour les réactions radicalaires organocatalysées par des carbènes stables ?

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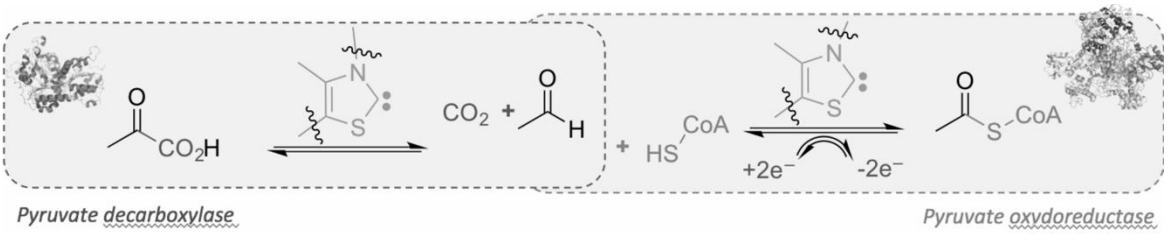
Il y a plus de 70 ans, il a été postulé que la forme active de la thiamine était sa base conjuguée, portant formellement un motif carbénique.[1] Cette hypothèse, confirmée récemment,[2] a été à l'origine du développement spectaculaire des carbènes stables en tant que catalyseurs organiques.[3] Ces approches se sont longtemps focalisées sur des réactions « ioniques », typiquement catalysées par les nucléophiles et bio-inspirées des pyruvate-décarboxylases (Figure ci-dessous, à gauche). Très récemment, plusieurs équipes se sont inspirées des pyruvates oxydoreductases[4] (Figure ci-dessous, à droite) et ont montré que des transformations radicalaires organo-catalysées étaient possibles en conditions oxydantes.[5]



Dans cet exposé nous présenterons nos résultats les plus récents concernant la compréhension des processus électrochimiques en jeu et la nature des intermédiaires radicalaires. Nous montrerons notamment que des hypothèses mécanistiques, dont la validité était jusqu'alors considérée comme bien établie, sont en fait incorrectes.[6]

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Concomitant Oxidative and Reductive Transformations with Breslow catalysts

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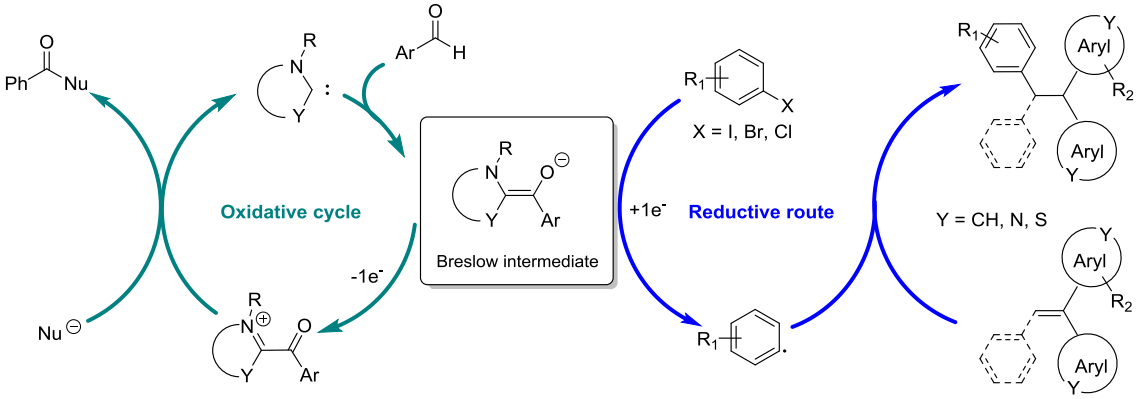
The last decade, a multitude of organocatalyzed transformations of carbonyl derivatives took advantage of the oxidation of Breslow intermediates, arising from the reaction of carbonyl substrates with stable *N*-Heterocyclic Carbenes (NHCs). However, valorization of the electrons lost during these oxidative transformations had not been addressed until recently. In 2021, Ohmiya and Bertrand independently demonstrated that these Breslow intermediates can also be used as formal reductants.[1] NHC-organocatalyzed arylacylations of diverse alkenes were thus performed upon reduction of iodoaryl derivatives into radical species. In their reaction, the aldehyde used to generate the Breslow enaminol was also integrated in the final addition product.

Our project was to develop a strategy where the Breslow enolate catalyst both serves as an electron source for challenging reductive transformations and as key intermediate for the valorization of aldehydes through oxidative transformations. This thus allows the interdependent formation of two distinct products through concomitant oxidative and reductive transformations. For this purpose, novel sources of NHCs and aldehydes were explored to generate more powerful organic reducers.[2] Imidazolylidene-based enaminols proved to be powerful donors for the single-electron transfer reduction of various challenging substrates. The generated radical intermediates were further exploited in arylations of alkenes while the sacrificial aldehydes were valorized through oxidation reactions.[3]



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Propargylation of *N*-Heterocycles by Electrochemical Decarboxylation of Allenoic Acids

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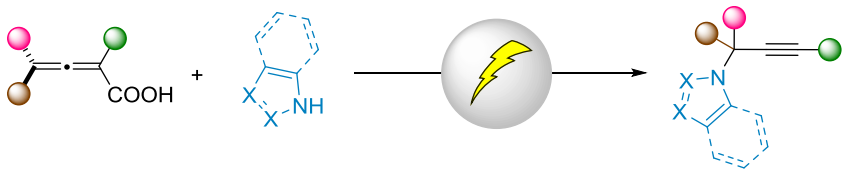
Nitrogen-based heterocyclic compounds can be found in numerous categories of therapeutic agents with diverse biological activities such as antimicrobial, anticancer, analgesic, anti-inflammatory, etc…[1] Due to synthetic importance and various bioactivities showed by azole derivatives, a major synthetic effort have been dedicated into generating libraries of these compounds. Among those strategies, the C−N bond formation have attracted much attention and innovative processes from easily available starting materials under mild conditions have been developed. In particular, electrochemical decarboxylative cross-coupling of C(sp^3)–N bonds have recently been reported to functionalize azoles.[2] In sharp contrast, the propargylation of azoles is much less developed and only a limited number of methods were reported.[3]

In that context, we aim to developpe an efficient strategy to access densely functionalized *N*-propargylated azoles from allenoic acids using electrochemistry (Scheme 1). This method provides an unprecedented access to quaternary centers containing a *N*-heterocycle and an alkyne.



Scheme 1. Propargylation of *N*-Heterocycles by Electrochemical Decarboxylation of Allenoic Acids.

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Catalytic approach for amide coupling for the development of nucleic acid-supported catalysts

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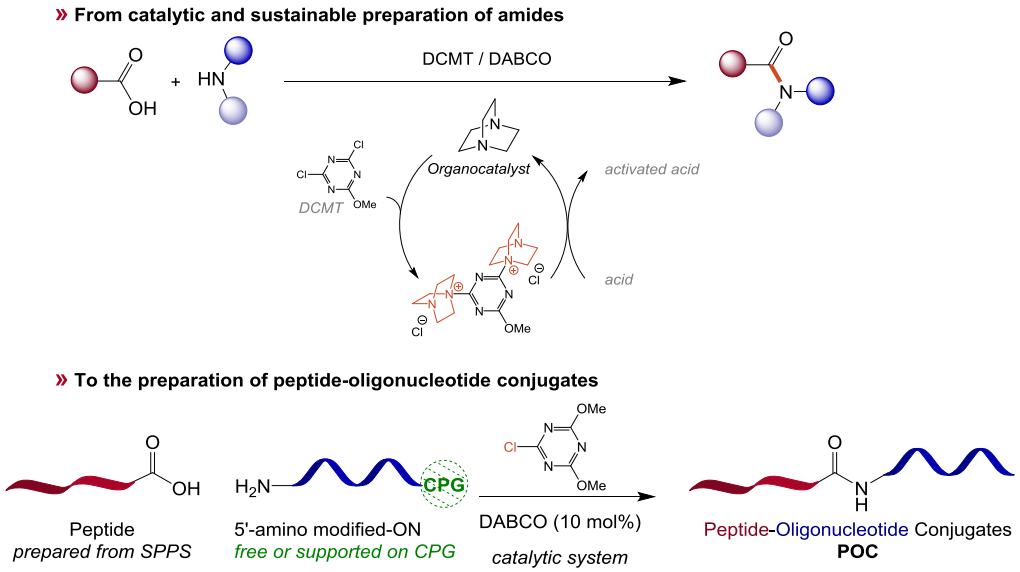
Amides are one of the most important functional groups in organic chemistry and play essential roles in both the pharmaceutical industry and life sciences. However, due to the natural reactivity of carboxylic acids and amines, their direct coupling is challenging and often leads to reactions that are not atom-economic and produce large amounts of nonrecoverable by-products. Despite the impressive number of coupling reagents available, sustainable methods for amide bond formation are still needed. To address this challenge, we developed a new catalytic approach for the direct preparation of amides from carboxylic acids and amines. This method has been applied with good efficiency on a wide range of substrates, without epimerization of chiral stereocenters and on SPPS.[2]

The method was then extended to the chemistry of oligonucleotides for the preparation of peptide – oligonucleotide conjugates (POC) using an amide linker. POC are widely used as biologically relevant compounds: oligonucleotide serves as the therapeutic substance (anti-sense RNA, siRNA etc) while the peptide helps for cell penetration (amongst other applications).[3] In this context, our method was adapted both in aqueous solution and on CPG solid support.

These new POC will be further evaluated as organocatalysts.



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Cyclic Amidrazones: a new scaffold for drug-design in medicinal chemistry

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Omnipresent both in nature and in synthetic chemistry, heterocycles constitute essential molecular units that are found in natural products, in medicinal chemistry, in materials, in catalysis, etc... Their structural characteristics directly influence the physicochemical properties of the molecules that contain these heterocyclic units (conformation, solubility, electronic density, etc.), thus justifying their role and their attractiveness in each of these areas. Within this chemical space, nitrogenous heterocycles hold a primordial place, as for example in pharmaceutical chemistry, where nearly 60% of drugs approved by the FDA are composed of at least one nitrogenous heterocycle (Figure 1), with a clear predominance of piperidine, pyridine or piperazine units.[1]

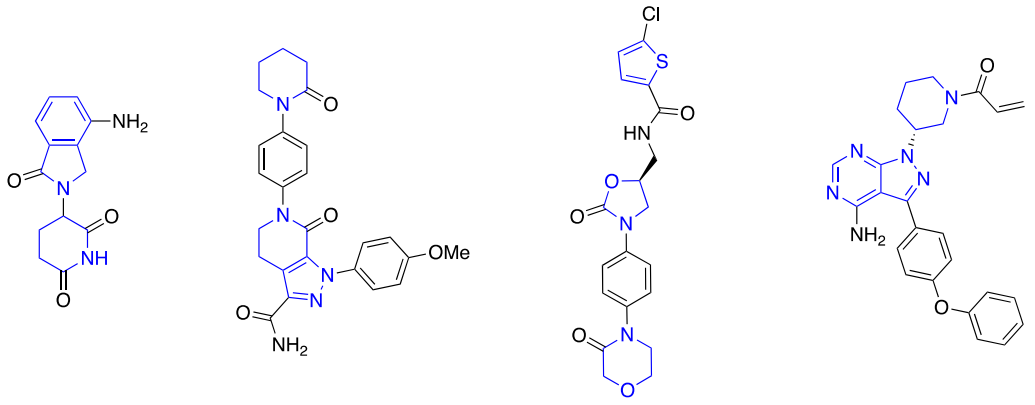

Figure 1. Recent big pharma's blockbusters featuring key aza-heterocyclic componds.

This communication will present the preparation of cyclic amidrazones as new non-aromatic aza-heterocyclic structures by original synthetic methodologies implemented within our research team.[2] The synthetic developments of these aza-heterocycles aim to integrate new functionalities on original heterocyclic units, and to access new families of functionalized heterocycles. Given the strong predominance of nitrogen heterocycles in medicinal chemistry, the exploitation of these original aza-heterocyclic structures will contribute to pave the way of new bioisosteric scaffolds within the drug space of pharma blockbusters.

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Fluorosulfoxoniums – Easily accessible strong Lewis (or hidden Brønsted) acids

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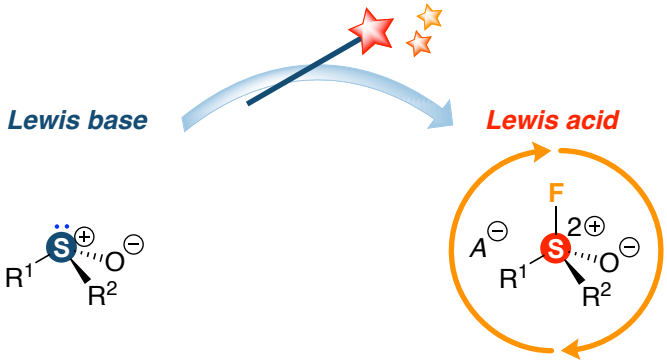
Non-metal strong Lewis acids are continuously being developed for catalytic applications, especially since the advent of Frustrated Lewis Pair (FLP) catalysis as a complement or alternative to transition metal catalysis. However, FLPs often involve a highly electron-deficient borane as Lewis acidic component, whose synthesis and handling can be delicate.

A possible way to address this issue is the use of fluoro-oniums as strong Lewis acids obtained easily from phosphines or sulfoxides. Whereas fluorophosphoniums have been intensely investigated as potent catalysts,[1] fluorosulfoxoniums have been neglected, with only 4 examples including the polymerization of THF.[2] Our contribution to the field of fluorosulfoxonium chemistry consisted in the improvement of their synthesis, unlocking the access to highly Lewis acidic ones, and in their evaluation in catalytic reactions.[3]



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Nickel-Catalyzed Radical Cross Coupling of Amides

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Resonance destabilized amides have recently emerged as new potent, bench-stable acyl electrophiles in transition metal-catalyzed cross-coupling reactions to forge C(acyl)-C(sp^2) bonds via C-N bond activation, thereby allowing the efficient preparation of aryl ketones.[1] However, while the remarkable properties of nickel catalysts unlocked the development of challenging cross-coupling reactions with C(sp^3)-hybridized substrates, methods enabling the conversion of amides to valuable alkyl ketones via C(acyl)-C(sp^3) bond formation remain extremely rare.

Our group is interested in the development and understanding of innovative catalytic approaches merging rational design of nickel-based catalysts with the use of photochemical and electrochemical approaches to convert readily available feedstock chemicals efficiently and sustainably to high added value organic scaffold.[1] Within this context, we have recently developed and investigated two complementary nickel-catalyzed processes enabling the cross-electrophile coupling of N-acyl-imides with alkyl halides (as alkyl radical precursors) under mild conditions. The first strategy is based on cooperative nickel and photoredox catalysis and relies on a silyl radical-mediated photocatalytic process to activate the alkyl bromide through halogen abstraction.[2] The second strategy relies on electrochemical steps for the generation of the alkyl radical. This method proved suitable for the synthesis of valuable linear alkyl ketones. Mechanistic studies including cyclic voltammetry, stoichiometric reactions, and isolation of catalytic intermediates provided a set of fundamental insights into monovalent (bpy)nickel-mediated single-electron oxidation of alkyl halides and C-N bond oxidative addition of alkyl amides.[3] The concept, scope, and limitations of both approaches, as well as mechanistic investigation will be discussed during the presentation.

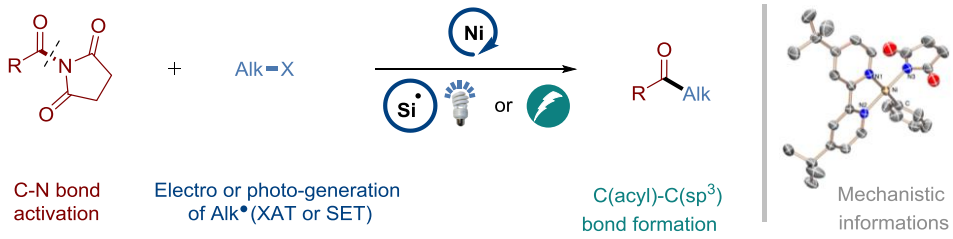

Figure 1. Ni catalyzed cross-electrophile coupling of amides with alkyl halides: development and mechanistic investigations.

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Asterisks, Dendrimers and Highly Distorted Helicene-Based Materials

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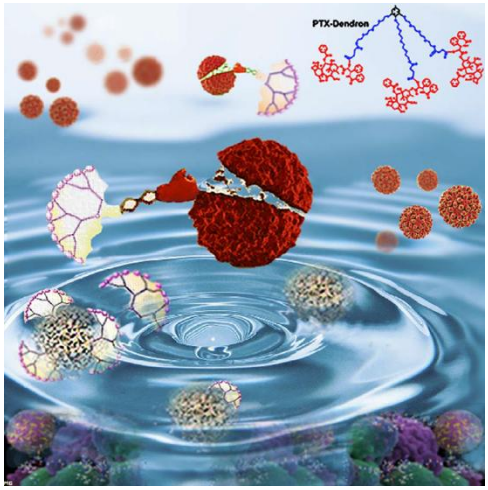

A selection of polyfunctionalized, polysulfurated and multivalent molecular architectures of various topologies will be presented, along with their synthesis and a brief survey of some applications in materials and life sciences. They comprise asterisks, dendrimers and distorted molecules (helicenes and multihelicenes), which often incorporate sulfur and arene units,[1] leading to multifunctional and luminescent (phosphorescent and fluorescent) nano-objects.[2] They represent an underexploited class of macromolecules with attractive features, rich supramolecular interactions, chiroptical and electronic properties, which could be modulated by some metal interactions,[3-4] by some cation-π interactions and by some π-π complexes. Selected applications of these asterisks, dendrimers and distorted helicenic architectures[12,13] will be presented as basic nanomaterials in various applications.[5 -11]

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Controlled Reactivity of Sulfoxides on Surfaces.

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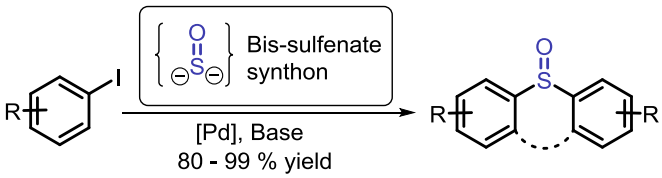
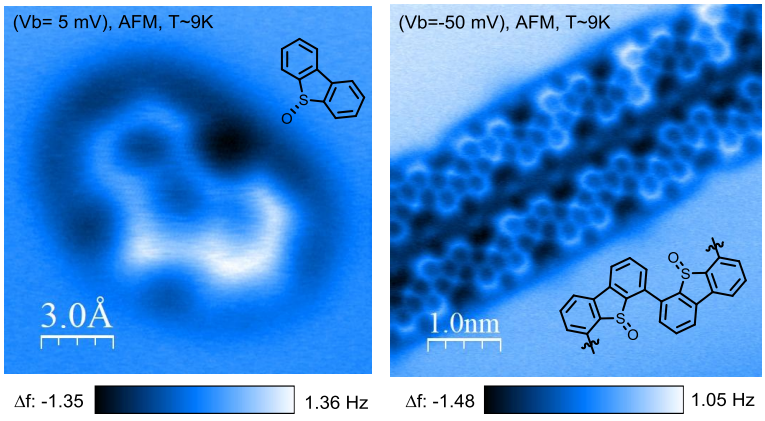
The analysis of chemical reactions on surface using scanning probe microscopy with subatomic resolution is a blooming research field.[1] Indeed, this tool allows the manipulation and observation of potentially highly reactive species, and thus, to gain unprecedented structural information and/or the elucidation of mechanistic pathways. For such investigations, the molecules studied must be specifically designed, presenting a good adsorption on the surface of choice whilst keeping the desired reactivity. Our approach focuses on the use of arylsulfoxides, allowing a good surface adsorption through π-interactions from the aryl moieties as well as polar interactions from the strong dipolar sulfoxide moiety. Moreover, these molecules exhibit intriguing photoreactivity, undergoing either the deoxygenation[2] or the loss of their SO moiety under light irradiation.[3]

The synthesis of biarylsufoxides typically involves the oxidation of the parent thioether, but we envisioned to use the more straightforward double pallado-catalyzed coupling of aryl halides with the bis-sulfenate synthon. Noteworthy, this approach avoids the thioether oxidation step and thus allows using sensitive substrates. We will describe two new bis-sulfenate precursors, which are used to afford a large variety of biarylsulfoxides, including potential candidates for on-surface studies.



To this end, in collaboration with the CEMES-Toulouse and the IM2NP-Marseille we are studying the reactivity and photochemistry of sulfoxides in solution, as well as on surface by means of Scanning Tunneling (STM) and non-contact Atomic Force (nc-AFM) Microscopies. In our first experiments, we studied the adsorption of different dibenzothiophene-*S*-oxides on metallic and insulating surfaces. We subsequently investigated an Ullmann-type reactivity from a brominated derivative on Au(111) and shown that long polymeric chains could be obtained upon annealing. Finally, preliminary results on the light irradiation of dibenzothiophene-*S*-oxides suggest a reactivity that remains to unravel.



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Multivalent Chondroitin Sulfate Oligosaccharides as new tools to probe protein-CS interactions

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Chondroitin sulfates (CS) are heteropolysaccharides that belong to a family of complex, polyanionic polymers called glycosaminoglycans (GAGs). They consist of a repeating disaccharide unit composed of a D-glucuronic acid (D-GlcA) and a 2-acetamido-2-deoxy-D-galactose (D-GalNAc) and contain, on average, one sulfate group per disaccharide unit.[1] The most commonly sulfated positions are positions 4 (CS-A) and/or 6 (CS-E and CS-C, respectively) of the D-GalNAc moiety. Due to their rich structural diversity and to their various sulfation patterns, CS play an important role in numerous biological processes such as neuronal development, morphogenesis or cell-cell recognition by their ability to bind with various proteins.[2] CS also play a structural role and are naturally abundant in all mammalian connective tissues especially in cartilage, skin and bone.[3] Multivalency is widely observed in Nature for glycan-proteins recognition mainly to counterbalance the rather weak association constants of carbohydrate ligands with their receptors (lectins for example). Indeed, multivalency offers significant enhancements in terms of affinity and selectivity and can induce specific supramolecular arrangement on the cell surface since proper presentation of the ligand is critical for recognition.[4] To date, only scarce examples of multivalent CS have been reported so far.[5]

We present here our recent results about the synthesis of well-defined sulfated CS fragments[6] and their anchoring onto various platforms to promote multivalency. Those innovative glycoconjugates will be used as new tools to probe protein-CS interactions.

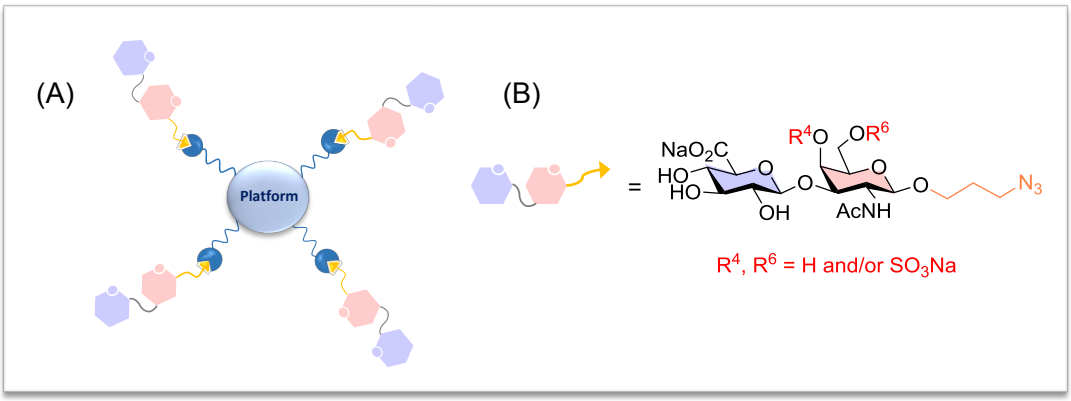

Figure 1: (A) Multivalent CS oligosaccharides; (B) Structure of CS disaccharide

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Dual Silyl – Gold catalysis : a flexible and powerful new concept for organic synthesis

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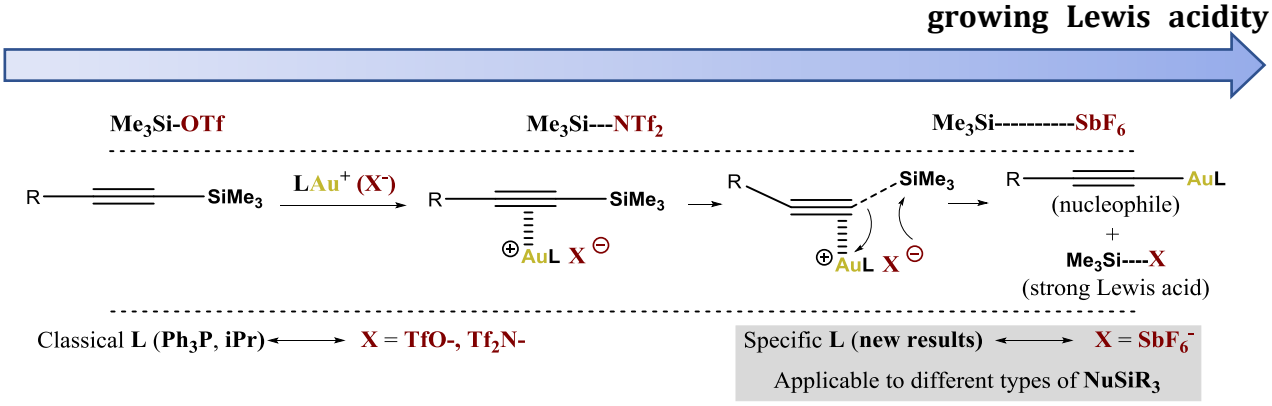
Some years ago, our group has developed an unprecedented dual silicon – gold approach which is based on the propensity of gold(I) carbophilic complexes with specific counteranions (**LAuX** – **X = triflate** or **triflimidate**) to efficiently activate and desilylate **trimethylsilylalkynes**, thereby mediating the *in situ* formation of equal and catalytic quantities of a nucleophilic gold(I) acetylide and a silyl Lewis acid (**TMSX**) of ***tunable strength***. This unprecedented manifold indeed brings in action the concept of Silicon – Gold metathesis and opens avenues for developing synergistic silyl-gold(I)-catalyzed alkynylation strategies of diverse pro-electrophiles which were heretofore unattainable.[1] A notable feature of our system is its flexibility, which indeed manifests with the possibility to modulate the strength of the ancillary silyl Lewis acid – **TMSOTf** *versus* **TMS---NTf$_2$** – by the proper selection of the gold counter ion, which offers an adjustment parameter to meet the specific reactivity requirements of a particular pro-electrophile.
The observation of a powerful effect of the ligand supporting the gold center has recently allowed us to extend our method beyond the **triflate** and **triflimidate** counterions, and by this way to introduce a "*high performance* ***trimethylsilylium hexafluoroantimonate [Me$_3$Si$^+$] (SbF$_6^-$]*** *catalysis*" hitherto unknown in silyl Lewis acid chemistry.[2] The power of this new system is first manifested in its ability to surpass catalytic performances of many alkynylations previously conveyed by triflimidate anion, which most likely results from a significant stronger Lewis acidity expressed by ***[Me$_3$Si$^+$] (SbF$_6^-$]***.[2,3] More importantly, it also has an extensive and unprecedented scope of application, which is manifested in an effective dual activation capability of various organosilanes other than TMSalkynes, and therefore offers a new versatile platform for synergic silicon-gold catalysis.



Our method therefore now spans the continuum of triflate, triflimidate and hexafluoroantimonate counterions, and in fact is becoming extremely flexible and of potential wide usage in organic synthesis. Through the description of new results that will highlight the interest and specificity of each of our three anionic systems, this communication will illustrate all the versatility of the method.

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Synthesis of *piper spp*. alkaloids by photocatalytic assemblies of piperine.

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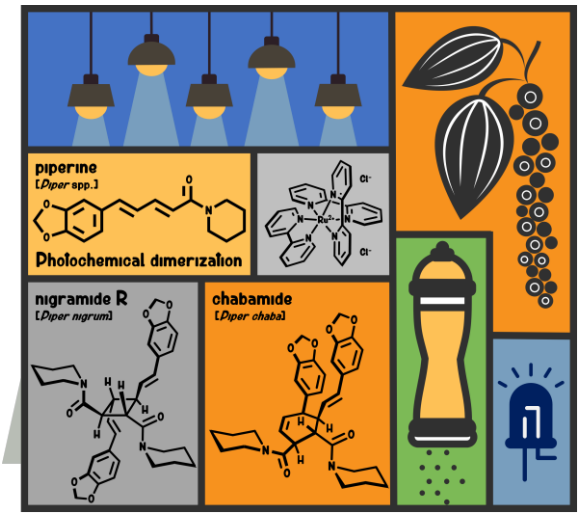

Piper spp. constitute a family of lianas cultivated for their edible berries used as spices. The most popular one is *Piper nigrum* which is universally consumed as the green, white and black peppers. Its pungent taste is due to piperine isolated in 1819 by Ørsted. Since 2001, several dimeric structures were isolated from *P. nigrum* and *P. chaba* (dipiperamides, nigramides, chabamides, and piperchabamides). Two dimeric patterns are encountered: i) the vinylcyclobutanes from [2+2] assemblies; ii) the cyclohexenes from [4+2] assemblies. In the vinylcyclobutane group, six molecules originates from the dimerization of piperine [dipiperamides A, B, E, F and G and nigramide R], while the other related compounds [diperamides C and D, nigramides P, Q and S, piperchabamide H] originate from cross-assemblies [mainly piperine, piperettine and ilepcimide]. In the cyclohexene group more structural diversity is encountered. Only two compounds originate from the [4+2] assemblies of piperine [chabamide and nigramide B], while others are from cross assemblies of related precursors, bearing variation on the amide function, the substitution of the polyene and the number of double bonds.

To realize the synthesis of these dimers, we decided to carry out [2+2] and/or [4+2] cycloadditions directly on piperine. To perform regioselective and diastereoselective assemblies, we turned to photocatalysis. Conditions adapted to a reductive photocatalytic cycle allowed us to exclusively activate the **α-β** double bond of piperine and to selectively obtain a set of natural products depending on the catalysts and adjuvants used.

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Broadening the Scope of the Paternò-Büchi Reaction

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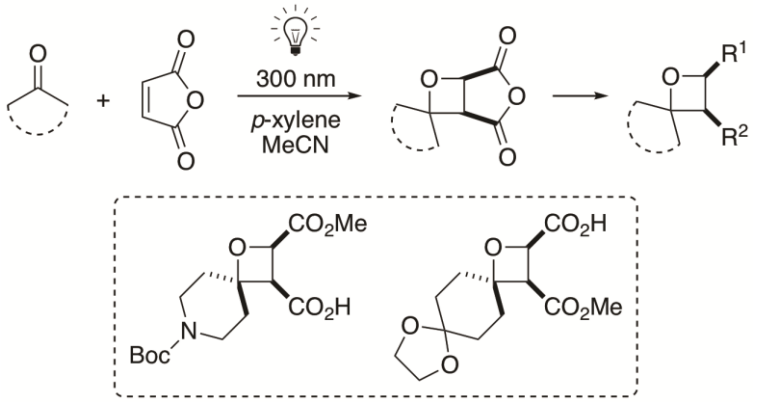
Oxetanes (four-membered cyclic ethers) are of considerable interest within drug discovery and are also valuable synthetic intermediates. However, the synthesis of oxetanes is not always straightforward, particularly when particular substitution patterns are required.[1]

The Paternò-Büchi reaction (a [2+2] photocycloaddition between an alkene and an aldehyde/ketone) is arguably the most "direct" way to form an oxetane ring, but is usually limited to aromatic aldehydes/ketones and electron-rich alkenes. We have developed[2] a telescoped approach to functionalized spirocyclic oxetanes, involving a Paternò-Büchi reaction between maleic anhydride and a cyclic ketone, followed by ring opening of the resulting anhydride with a nucleophile, which takes place with complete regioselectivity. The resulting spirocyclic oxetanes are versatile building blocks that bear various sites for further diversification, and their conversion to a wide range of novel derivatives will be presented.



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High-Throughput Experimentation as a technology enabling catalysis

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High-Throughput Experimentation (HTE) allows for general reactions to be run at 1/8th (10 µmol) or 1/32th (2.5 µmol) normal reaction scale, cutting down the amount of substrates needed to find the optimum conditions. It also allows a high number of reaction conditions to be tested in parallel, and helps researchers to map the chemical space of a specific reaction. In the same time, HTE can be a rapid and cost-effective way to synthesize chemical libraries.[1]

Inspired by the most important academic HTE center at UPenn, Philadelphia, the CEA has recently assembled a state-of-the-art academic laboratory designed to aid in the development of novel synthetic methodologies and solve challenges in difficult chemical transformations and embrace direct-to-biology approaches in drug discovery.[2]

With this new technology in hand, the SCBM is empowering its research in the field of catalysis and medicinal chemistry.

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Unusual RedOx Cycles for Trifluoromethylation Reactions

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Fluorine atoms drastically affect the biological properties of organic synthons.[1] Amongst the most common perfluorinated groups, the CF_3 moiety occupies a preferential place in drug discovery and agrochemical design. Creating C–CF_3 bonds *via* cross-coupling reactions is an appealing strategy to build molecular complexity. However, unfortunately, the C–CF_3 bond formation *via* reductive elimination (R.E.) from [C–M–CF_3] fragments represents a challenging task. An original approach to favor the key R.E. step resides in the preparation of high-valent organometallics. In this communication, the utility of high oxidation state $M^{III}CF_3$ compounds (M = Cu, Ag) to enable the selective trifluoromethylation of different scaffolds will be disseminated (**Figure 1**). In particular, significant advances on the synthesis and characterization of $Cu^{III}CF_3$ and $Ag^{III}CF_3$ species,[2-4] alongside their crucial role in trifluoromethylation reactions[3,4] taking place through uncommon redox shuttles, will be presented.

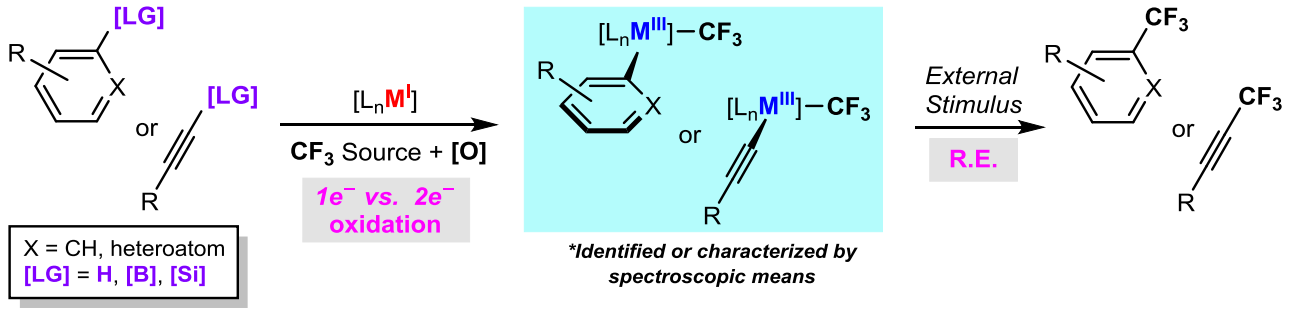

Figure 1. Guiding principle of this talk: Synthesis of high oxidation state $M^{III}CF_3$ complexes (M = Cu, Ag) *via* $2e^-$ oxidation step and subsequent use for synthetic purposes (trifluoromethylation).

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Difluoro- and oxodifluoromethylation reactions under photoflow conditions using adaptable, low-cost, standardized 3D printed reactors

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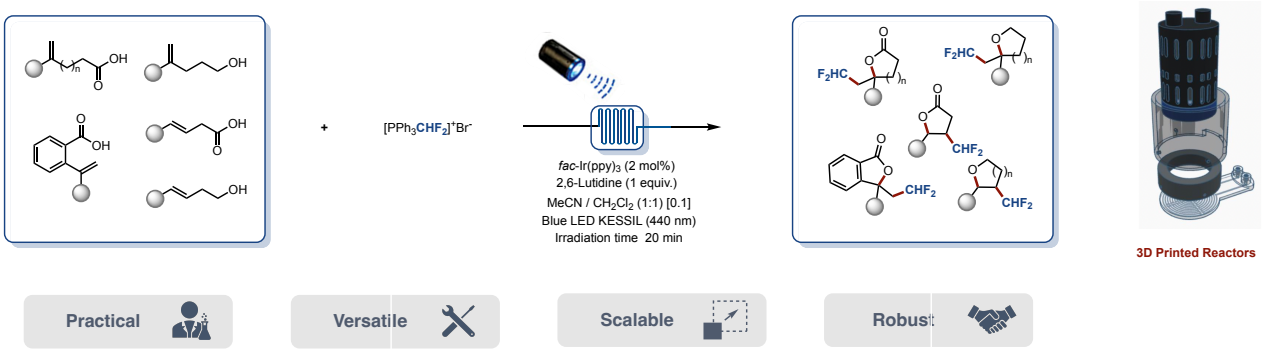
In recent years, there has been a significant increase in the scientific community's interest in photochemical reactions. In this context, flow chemistry has emerged as a powerful technique for conducting such transformations as, in contrast to batch reactions, flow chemistry enables the use of a larger surface area-to-volume ratio, resulting in better light penetration and higher catalytic efficiency. Here, we report a series of difluoro- and oxodifluoromethylation reactions under photoflow conditions, which allow a straightforward and scalable access to CHF_2-containing compounds using adaptable low-cost standardized 3D printed reactors.[1-3]



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Dimanche 27		Lundi 28		Mardi 29		Mercredi 30		Jeudi 31		Vendredi 1	
		8h30	J. Reek	8h30	V. Michelet						
		9h30	S. Antoniotti	9h30	J. Monot						
		9h45	L. Favereau	9h45	P.-A. Bouit	9h00	P. Seeberger	9h00	A. Quintard	9h00	M. Desage
		10h00	Flash comms	10h00	Y. Coquerel	10h00	G. Audran	10h00	M. Vayer	10h00	S. Coote
		10 h15	Pause café	10 h15	Pause café	10h15	P. Peixoto	10h15	Pause café	10h15	Pause café
		10h45	P. Busca	10h45	B. Michelet	10h30	Pause café	10h45	P. Adler	10h45	E. Roméro
		11h00	C. Olivier	11h00	V. Mamane	11h00	H. Clavier	11h00	A. Tessier	11h00	N. Nebra
		11h15	C. Ghiazza	11h15	S. Vidal	11h15	A. Letort	11h15	A. Panossian	11h15	S. Arseniyadis
		11h30	G. Blond	11h30	S. Prevost	11h30	D. Martin	11h30	A. Amgoune	11h30	Fin GECO 63
		11h45	Y. Ferrand	11h45	V. Patinec	11h45	J. Broggi	11h45	M. Gingras		Pres.GECO64
		12h00	Flash comms	12h00	Pause	12h00	Déjeuner	12h00	Pause	12h00	Déjeuner
		12h30	Déjeuner	12h30	Déjeuner	13h30		12h30	Déjeuner		
16h00	Accueil des participants	15h45	X. Bantreil	15h45	O. Baslé			15h45	S. O'connor		
		16h45	E. Leclerc	16h45	Y. Trolez			16h45	V. Magné		
		17h00	A. d.l. Torre	17h00	M. de Paolis		Activités extérieures au centre	17h00	M. Schuler		
		17h15	Pause café	17h15	Pause café			17h15	Pause café		
18h	**Apéritif**	17h45	A. Specht	17h45	A. Goujon			17h45	V. Dalla		
18h50	Ouverture	18h00	Flash Comms	18h00	L. Lemiègre			18h00	L. Evanno		
19h00	E. Schulz	18h15	M. Tortosa	18h15	L. Haberkorn			18h15	G. Pieters		
20h00	Pause	19h15	Pause	19h15	Pause		**Diner gala**	19h15	Pause		
20h15	Diner	20h15	Diner	20h15	Diner	19h30	**à l'extérieur**	20h15	Diner		