Journées de Chimie Organique

2, 3 and 4 november 2022
École polytechnique
Palaiseau, France

Société Chimique de France
Le réseau des chimistes

JCO 2022

Programme & Book of abstracts

www.jco2022.com

CONTENT

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As chairwoman of the Journées de Chimie Organique de la Société Chimique de France « JCO 2022 » and on behalf of the organizing committee, I am delighted to warmly welcome you all in Palaiseau for this major event held under the auspices of the Organic Chemistry Division of the French Chemical Society.

The JCO, organized every three years, bring together an international panel of world-renowned plenary speakers who will present cutting edge lectures in areas such as synthetic methodology, catalysis, total synthesis, medicinal chemistry, chemobiology, bioorganic chemistry, material science, supramolecular chemistry and sustainable chemistry, in front of an audience of more than 650 participants. Worthy of note are the lectures given by industrial scientists that should create a unique opportunity between the industrial and academic communities. 17 plenary and invited lectures will be complemented by the presentation of 60 oral communications given by young scientists, as well as more than 320 posters. In addition, 6 oral communication prizes and 10 poster prizes will be awarded. Our whole community should enjoy this meeting and discover new areas likely to create new synergies. You should know how happy we are to be able to receive you face-to-face in Palaiseau for all these scientific and friendly exchanges that we have deeply missed in recent years.

We have decided to keep the schedule chosen for the last edition of our JCO in 2019, allowing as many of you as possible to participate after a busy start of the academic year. We hope that this will once again contribute positively to maintaining the JCO as an unmissable chemistry event in our country.

We are very grateful to the École polytechnique for hosting us. We also warmly thank all the industrial and academic sponsors for their generosity.

All together, we hope that this conference will not only promote new discoveries but also the exchange of ideas for future collaborations and development. We therefore wish all participants to make the JCO 2022 a great rewarding and memorable event.

Emmanuelle Schulz
Symposium Chairwoman
President of the Organic Chemistry Division of the French Chemical Society

Organized by

Société Chimique de France
Le réseau des chimistes

DCO Division de Chimie Organique

Activation
Chemical Process Research & Catalysis

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Clémence ALLAIN

ENS Paris-Saclay
FRANCE

Luminescent mechano-responsive molecules and materials: from molecular engineering towards the elaboration of smart materials

Jean-Guy BOITEAU: Yves Chauvin Prize 2022

Nuvisan
FRANCE

Process Research and Development of API's: case studies

Margaret BRIMBLE

University of Auckland
NEW-ZEALAND

Natural Product Synthesis: A Crucible for New Method Development and Drug Discovery

Sukbok CHANG

Korea Advanced Institute of Science and Technology
KOREA

Development of C-H Amidation Reactions via Nitrenoid Transfer Pathway

Mélanie ETHEVE-QUELQUEJEU

Université Paris Cité
FRANCE

RNA conjugates: from the synthesis to applications

Nicolas GIUSEPPONE

Université de Strasbourg
FRANCE

Artificial molecular machines that work at all scales

Shū KOBAYASHI

University of Tokyo
JAPAN

Environment, Human Health, and Energy: Catalysts Play Key Roles Toward Sustainable Society

Eric MEGGERS

University of Marburg
GERMANY

Steering Asymmetric Catalysis with Metal-Centered Chirality

Véronique MICHELET: DCO Prize 2022

Institut de Chimie de Nice
FRANCE

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

Laurence MULARD

Institut Pasteur
FRANCE

Synthetic glycan-based vaccines to combat bacterial diseases: from concept to immunogenicity in human

Timothy NOEL
University of Amsterdam
THE NETHERLANDS

Innovation in HAT photocatalysis through use of flow

Monica PEREZ-TEMPRANO
Institut Català d'Investigació Química
SPAIN

Deciphering mechanims to design better catalytic reactions

Sarah REISMAN
California Institute of Technology
USA

Necessity is the Mother of Invention: Natural Products and the Chemistry They Inspire

Louis-Charles CAMPEAU

Merck
USA

Changing the World, One Reaction at a Time

Yohan GISBERT: Dina Surdin PhD Prize 2022

University of Groningen, THE NETHERLANDS
CEMES, FRANCE

Organometallic molecular motor derivatives for Single Molecule Force Spectroscopy experiments

Juliette MARTIN

Proteus
FRANCE

Biocatalysis: a Necessary Tool for Synthetic Chemist – a Focus on Industrial Applications

Thomas POISSON: Jean-Marie Lehn Prize 2022

COBRA INSA-Rouen
FRANCE

Photocatalytic and Electromediated Borylation and Silylation Reactions

WEDNESDAY 2 NOVEMBER		
08:00	Registration	Main Hall
09:00	Opening Ceremony	Amphithéâtre Poincaré
09:30	PL1 | Margaret BRIMBLE	Amphithéâtre Poincaré
10:15	IL1 | Louis-Charles CAMPEAU	Amphithéâtre Poincaré
10:45	Flash communication exhibitors 1	Amphithéâtre Poincaré
11:00	Coffee Break- *Sponsored by ACTIVATION*	Main Hall
11:30	PL2 | Mélanie ETHEVE-QUELQUEJEU	Amphithéâtre Poincaré
12:15	IL2 | Yohan GISBERT (Dina Surdin PhD award)	Amphithéâtre Poincaré
12:35	Flash communication exhibitors 2	Amphithéâtre Poincaré
12:50	Lunch	Main Hall
14:05	Oral Communications session #1a *Sponsored by CHARM$_3$AT*	Amphithéâtre Poincaré
	Oral Communications session #1b	Amphithéâtre Gay-Lussac
	Oral Communications session #1c	Amphithéâtre Pierre Faurre
16:20	EurJOC intervention	Amphithéâtre Poincaré
16:25	PL3 | Eric MEGGERS – *EurJOC WILEY Lecture*	Amphithéâtre Poincaré
17:10	Group Picture	Main Hall
17:15	Poster session #1 & Juice/Beer Break	Main Hall

THURSDAY 3 NOVEMBER		
09:00	PL4 | Shū KOBAYASHI	Amphithéâtre Poincaré
09:45	PL5 | Véronique MICHELET (DCO Prize)	Amphithéâtre Poincaré
10:30	Flash communication exhibitors 3	Amphithéâtre Poincaré
10:45	Coffee Break- *Sponsored by OXELTIS*	Main Hall
11:15	IL3 | Juliette MARTIN	Amphithéâtre Poincaré
11:45	IL4 | Thomas POISSON (J.M. Lehn Prize)	Amphithéâtre Poincaré
12:15	PL6 | Laurence MULARD	Amphithéâtre Poincaré
13:00	Lunch	Main Hall
14:15	Oral Communications session #2a *Sponsored by Syngenta*	Amphithéâtre Poincaré
	Oral Communications session #2b	Amphithéâtre Gay-Lussac
	Oral Communications session #2c	Amphithéâtre Pierre Faurre
16:30	PL8 | Sukbok CHANG	Amphithéâtre Poincaré
17:15	Poster session #2 & Juice/Beer Break	Main Hall

FRIDAY 4 NOVEMBER		
09:15	PL9 | Timothy NOEL – *SANOFI Lecture*	Amphithéâtre Poincaré
10:00	PL10 | Clémence ALLAIN	Amphithéâtre Poincaré
10:45	Coffee Break	Main Hall
11:15	PL11 | Jean-Guy BOITEAU (Yves Chauvin Prize)	Amphithéâtre Poincaré
12:00	PL12 | Monica PEREZ-TEMPRANO – *CHARM$_3$AT Lecture*	Amphithéâtre Poincaré
12:45	Lunch	Main Hall
14:00	PL7 | Nicolas GIUSEPPONE	Amphithéâtre Poincaré
14:45	PL13 | Sarah REISMAN – *MINAKEM Lecture*	Amphithéâtre Poincaré
15:30	Poster & oral communication awards	Amphithéâtre Poincaré
16:00	Closing ceremony	Amphithéâtre Poincaré

WEDNESDAY 2 NOVEMBER

08:00 Registration

09:00 - 09:30 Opening Ceremony
Emmanuelle SCHULZ, president of the DCO - Thierry GACOIN, president of the Chemistry Department of the École polytechnique
Jacques MADDALUNO, director of the Institut de Chimie du CNRS

09:30 - 10:15 *Chair: Emmanuelle SCHULZ*
PL1 | Margaret BRIMBLE - University of Auckland, NEW-ZEALAND
Natural Product Synthesis: A Crucible for New Method Development and Drug Discovery

10:15 - 10:45 IL1 | Louis-Charles CAMPEAU - Merck, USA
Changing the World, One Reaction at a Time

10:45 - 11:00 *Chair: Olivier BASLÉ*
Flash communication exhibitors 1

11:00 - 11:30 Coffee Break - *Sponsored by ACTIVATION*

11:30 - 12:15 *Chair: Kevin CARIOU*
PL2 | Mélanie ETHEVE-QUELQUEJEU - Université Paris Cité, FRANCE
RNA conjugates: from the synthesis to applications

12:15 - 12:35 IL2 | Yohan GISBERT (Dina Surdin PhD award) - University of Groningen, THE NETHERLANDS and CEMES, FRANCE
Organometallic molecular motor derivatives for Single Molecule Force Spectroscopy experiments

12:35 - 12:50 *Chair: Anis TLILI*
Flash communication exhibitors 2

12:50 - 14:05 Lunch

14:05 - 16:20 Oral Communications session #1

	ORAL COMMUNICATIONS SESSION #1A Sponsored by CHARM$_3$AT	ORAL COMMUNICATIONS SESSION #1B	ORAL COMMUNICATIONS SESSION #1C
	AMPHITHÉÂTRE POINCARÉ *Chair: Xavier GUINCHARD - Angélique FERRY*	AMPHITHÉÂTRE GAY-LUSSAC *Chair: Matthieu RAYNAL - Jean-Pierre DUTASTA*	AMPHITHÉÂTRE PIERRE FAURRE *Chair: Sandrine PIGUEL - Emmanuel GRAS*
14:05	OC01 Dorian DIDIER Electrocoupling- A Catalyst-free Alternative for C-C Bond Formation	OC11 Nicolas GILLAIZEAU-SIMONIAN Charge-Accelerated [3,3] Rearrangement of Vinyl Sulfoniums: Stereodivergent Access to γ-Lactones and γ-Lactams.	OC21 Antoine SIMONNEAU Revisiting N_2 Functionalization with Nucleophiles
14:18	OC02 Stéphane GOLLING 2-Amido-acroleins as a versatile platform for the synthesis of poly-functionalized silicon containing heterocycles	OC12 Cassandre BORIES Highly selective dearomatization of N-heteroarenes using well-defined low-valent cobalt hydrides	OC22 Floriane DOCHE Directed Palladium Catalyzed C-H (Ethoxycarbonyl) difluoromethylthiolation Reaction

14:31	OC03 **Ophélie MONTIEGE** First total synthesis of chaxalactin B	OC13 **Arona FALL** Diastereoselective addition of redox active esters to azomethine imines by electrosynthesis	OC23 **Catherine TAILLIER** Taming the reactivity of Phosphiranium ions: Recent progress in the development of selective C-centered ring-openings
14:44	OC04 **Nawel GOUAL** Bimetallic complexes of photoswitchable phosphines derived from nine-membered cyclic azobenzenes: synthesis, photochromic properties and uses in gold catalysis	OC14 **Erwan BRUNARD** Catalytic amination of unactivated C–H bonds in the presence of electronically activated sites	OC24 **Wei CAO** Total Synthesis of Ophiorrhine A, G and Ophiorrhiside E Featuring a Bioinspired Intramolecular Diels–Alder Cycloaddition
14:57	OC05 **Guillaume DAGOUSSET** Photoredox Generation of Oxygen-Centered Radicals: α-Alkoxylation and α-Trifluoromethoxylation of Carbonyl Compounds	OC15 **Mehdi ABDELLAOUI** Reactant-Induced Photoactivation of In Situ Generated Organogold Intermediates Leading to Alkynylated Indoles	OC25 **Expédite YEN-PON** Transition-metal-free multi-component difunctionalization of [1.1.1]propellane
15:10	OC06 **Xueyang LIU** Indirect Enantiocontrol of Tertiary Alcohols and Quaternary Centers by Acylative Organocatalytic Kinetic Resolution	OC16 **Nicolas DUGUET** Thermomorphic polyethylene-supported organocatalysts for the valorization of biomass and CO2	OC26 **Gaétan ARCHER** Photoredox generation of isothiouronyl radical cations: A new platform in covalent radical catalysis
15:23	OC07 **Max COEHLO** Excited State Intramolecular Proton Transfer based Fluorophores with Circularly Polarized Luminescence Emission	OC17 **Thomas-Xavier METRO** Unprecedented insight into the structure of fatty-acid based (nano)materials enabled by mechanochemical 17O-labeling schemes	OC27 **Eléonore TACKE** Late-stage functionalization of a fluorescent scaffold to afford a new generation of large Stokes shift red-emitting dyes with promising properties for biological imaging
15:36	OC08 **Saif Eddine CHERIF** Merging Grubbs' Second-Generation Catalyst with Photocatalysis Enables Z–Selective Metathesis of Olefins: Scope, Limitations, and Mechanism	OC18 **Carlotta FIGLIOLA** Investigation of new organic photosensitizing platforms for selective photodynamic therapy	OC28 **Clément CHAUVIER** Transition-Metal-Free Silylation of Unactivated C(sp2)–H Bonds with tert-Butyl-Substituted Silyldiazenes
15:49	OC09 **Guillaume LEFEVRE** Taming redox non-innocence of weak-field iron complexes: an opportunity in catalysis	OC19 **Rebecca CHURAMANI** Control of supramolecular architecture by structural variation of self-assembling cyclodextrins	OC29 **Fabien LUCAS** Simplified Green-emitting Single-Layer Phosphorescent Organic light-emitting diodes with an external quantum efficiency > 22%
16:02	OC34 **Sophie RODRIGUES** A Gallium-Catalyzed C–H Propargylation of Arenes	OC20 **Raphael LABRUERE** In-cell synthesis of cytotoxic phenanthridine through bioorthogonal cyclization: the "Cycl'in-Cell" strategy	OC30 **Kevin TATOUEIX** Hydrogen Isotope Exchange via in-situ generated catalytic rhodium nanoparticles

16:20 - 16:25 EurJOC intervention

16:25 - 17:10 *Chair: Jeanne CRASSOUS*

PL3 | Eric MEGGERS – *EurJOC WILEY Lecture* - University of Marburg, GERMANY

Steering Asymmetric Catalysis with Metal-Centered Chirality

17:10 - 17:15 Group Picture

17:15 Poster session #1 & Juice/Beer Break

THURSDAY 3 NOVEMBER

09:00 - 09:45 *Chair: Frédéric LAMATY*
PL4 | **Shū KOBAYASHI** - University of Tokyo, JAPAN
Environment, Human Health, and Energy: Catalysts Play Key Roles Toward Sustainable Society

09:45 - 10:30 PL5 | **Véronique MICHELET (DCO Prize)** - Institut de Chimie de Nice, FRANCE
A Journey in Gold Catalysis Towards Diversity: from Heterocycles to Fragrances

10:30 - 10:45 *Chair: Olivier BASLÉ - Anis TLILI*
Flash communication exhibitors 3

10:45 - 11:15 Coffee Break- *Sponsored by OXELTIS*

11:15 - 11:45 *Chair: Morgan DONNARD*
IL3 | **Juliette MARTIN** - Proteus, FRANCE
Biocatalysis: a Necessary Tool for Synthetic Chemist – a Focus on Industrial Applications

11:45 - 12:15 IL4 | **Thomas POISSON (J.M. Lehn Prize)** - COBRA INSA-Rouen, FRANCE
Photocatalytic and Electromediated Borylation and Silylation Reactions

12:15 - 13:00 PL6 | **Laurence MULARD** - Institut Pasteur, FRANCE
Synthetic glycan-based vaccines to combat bacterial diseases: from concept to immunogenicity in human

13:00 - 14:15 Lunch

14:15 - 16:30 Oral Communications session #2

	ORAL COMMUNICATIONS SESSION #2A Sponsored by SYNGENTA	**ORAL COMMUNICATIONS SESSION #2B**	**ORAL COMMUNICATIONS SESSION #2C**
	AMPHITHÉÂTRE POINCARÉ *Chair: Boris VAUZEILLES - Florence MAHUTEAU-BETZER*	AMPHITHÉÂTRE GAY-LUSSAC *Chair: Cyril OLLIVIER - Florian LUTTRINGER*	AMPHITHÉÂTRE PIERRE FAURRE *Chair: Stéphanie NORSIKIAN - Damien BONNE*
14:15	OC31 **Marie SCHULER** Design of protein-based platforms for sugars multivalency	OC41 Margaux BOSSUAT Bioinspired lipidic alkynylcarbinols as anticancer agents	OC51 **Pierre-Antoine BOUIT** Straightforward Access to Multifunctional pi-Conjugated P-Heterocycles Featuring an Internal Ylidic Bond
14:28	OC32 **Eric LECLERC** Fluorine-Activated Additive-Free Vitrimers	OC42 Guanghao HUANG Asymmetric Inverse-Electron-Demand Diels-Alder Cycloaddition between 2-Pyrones and Acyclic Enol Ethers: Gram-Scale Total Synthesis of (+)-Lucidumone	OC52 **Julie BROGGI** Photocatalysis with super organic electron donors

14:41	OC33 **Johnny HU** A Bis-Acridinium Macrocycle as Multi-Responsive Receptor and component of a Switchable [2] rotaxane	OC43 **Anne-Doriane MANICK** Synthesis, characterizations and applications of haloazaphosphatranes	OC53 **Laurent FERRIÉ** Synthesis, Reactivity, and Functionalization of Endoperoxides: Application in Total Synthesis
14:54	OC10 **Emmanuelle THINON** Identification of protein targets of an inhibitor of viral infection using an affinity-based probe	OC44 **Mathias REBOLI** Intramolecular hydrosilylation of alkynes by electro-reductive nickel catalysis	OC54 **Flavie RAMBAUD** Development of a new cycloaddition/fragmentation reaction sequence
15:07	OC35 **Ludivine DELFAU** Reassessment of the reducing power of Breslow-type derivatives in NHC-catalyzed reactions.	OC45 **Isabelle MARCHAND** Synthesis of aziridines and reactivity of ketenes in flow	OC55 **Kajetan BIJOUARD** Organocatalysts confined within the cavity of cyclodextrins
15:20	OC36 **Thomas ABEGG** Cascade [3,3]-sigmatropic rearrangements involving (cyclopropyl)vinyl azides: Synthesis of highly substituted seven-membered rings	OC46 **Thomas DEIS** Martin's Spirosilane-based Pentacoordinated Organosilicons: Synthesis, Optical Resolution & Configurational Stability	OC56 **Georgina KIRBY** Iron-Catalysed Intermolecular Oxyamination of Alkenes Using Hydroxylamine Derivatives as Clean Nitrogen Sources
15:33	OC37 **Nazarii SABAT** Chemoenzymatic synthesis of DNA and XNA oligonucleotides	OC47 **Marc DEVILLARD** Synthesis of photochromic siloles by Pd-catalyzed reaction between a silacyclopropene and terminal alkynes: scope and mechanistic insights	OC57 **Valentin DOROKHOV** Modular approach to substituted pyridoazepinones
15:46	OC38 **Arthur GAUCHERAND** Simultaneous Control of Central and Helical Stereogenic Elements on Small Molecules	OC48 **Grédy KIALA** Continuous Flow Chemistry Process for the catalytic Functionalization of Biomass Derivatives	OC58 **Nicolas PETRY** Mechanosynthesis of Iminosydnone-based APIs
15:59	OC39 **Stéphane MAISONNEUVE** Photoswitchable GlycoMacrocycles, from synthesis to their chiroptical properties and potential applications	OC49 **Rémi PELLETIER** Fluorogenic dimers as bright switchable probes for enhanced super-resolution imaging of cell membranes	OC59 **Antonio DEL VECCHIO** Development of Highly Efficient Cyclic(alkyl)(amino)carbene Ruthenium Complexes for Olefin Metathesis
16:12	OC40 **Daniela VERGA** Tracking G4 ligand distribution in cells by a guided immunofluorescence methodology	OC50 **Anaïs SCUILLER** Cycloadditions of π-Allylpalladium(II) intermediates towards Medium-Sized N-Heterocycles	OC60 **Mayssa ZAYENE** Site Selective Palladium(II)-Catalyzed C(sp3)–H Methylene Diarylation of a Tropane scaffold

16:30 - 17:15 *Chair: Samir MESSAOUDI*

PL8 | **Sukbok CHANG** - Korea Advanced Institute of Science and Technology, KOREA

Development of C-H Amidation Reactions via Nitrenoid Transfer Pathway

17:15 Poster session #2 & Juice/Beer Break

FRIDAY 4 NOVEMBER

09:15 - 10:00 *Chair: Anis TLILI*

PL9 | Timothy NOEL – *SANOFI Lecture* - University of Amsterdam, THE NETHERLANDS

Innovation in HAT photocatalysis through use of flow

10:00 - 10:45 PL10 | Clémence ALLAIN - ENS Paris-Saclay, FRANCE

Luminescent mechano-responsive molecules and materials: from molecular engineering towards the elaboration of smart materials

10:45 - 11:15 Coffee Break

11:15 - 12:00 *Chair: Angela MARINETTI*

PL11 | Jean-Guy BOITEAU (Yves Chauvin Prize) - Nuvisan, FRANCE

Process Research and Development of API's: case studies

12:00 - 12:45 PL12 | Monica PEREZ-TEMPRANO – *CHARM$_3$AT Lecture* - Institut Català d'Investigació Química, SPAIN

Deciphering mechanims to design better catalytic reactions

12:45 - 14:00 Lunch

14:00 - 14:45 *Chair: Matthieu SOLLOGOUB*

PL7 | Nicolas GIUSEPPONE - Université de Strasbourg, FRANCE

Artificial molecular machines that work at all scales

14:45 - 15:30 PL13 | Sarah REISMAN – *MINAKEM Lecture* - California Institute of Technology, USA

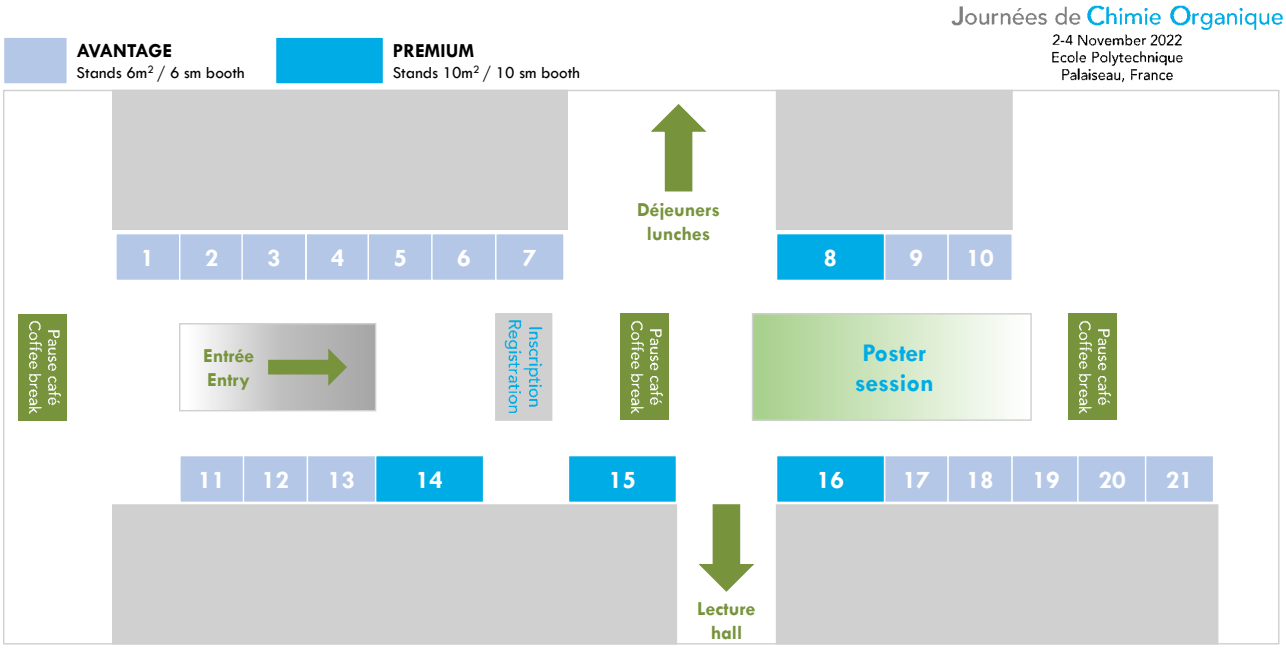
Necessity is the Mother of Invention: Natural Products and the Chemistry They Inspire

15:30 - 16:00 Poster & oral communication awards

16:00 Closing ceremony

OPENING HOUR OF THE EXHIBITION

Wednesday November 2nd: 9h00- 18h30
Thursday November 3rd: 9h00- 18h30
Friday November 4th: 9h00- 14h00



EXHIBITORS

1- TCI	2- MDPI MATERIALS/MOLECULES	3- MAGRITEK
4- THERMOFISHER	5- HUBER	6- CEM
7- KNF	8- ADVION INTERCHIM	9- JASCO
10- BIOTAGE	11- ABCR	12- CARLO ERBA
13- ANTON-PAAR	14- SERLABO	15- BÜCHI
16- CLOUP	17- NOVECAL	18- MBRAUN
19- VACUUBRAND	20- ELICITYL	21- ROSACHEM

The event will be held at the École polytechnique de Palaiseau.

COFFEE BREAKS

Coffee breaks will be served at the time scheduled in the programme in the main Hall of École polytechnique.

LUNCHES

Lunches could be taken at the restaurant of the École polytechnique. The amount of selected lunches will be added to the registration fees and tickets will be given to participants at the welcoming desk. Lunch tickets can be purchased on site from polytechnique vending machines or directly at the self.

ORAL SESSIONS

10 STRICT minutes for presentation, and up to 2 minutes for questions.
You must arrive 15 minutes before your session.
A laptop will be available in each lecture hall for the oral communications sessions. These laptops will also be available in the main hall (at the registration desk) every morning before each OC session to upload presentations.
Please use preferably PDF files. In the case of ppt or pptx files, do not overload with too many animations; slides size, big screen (16/9).

POSTER SESSIONS

There will be 2 sessions posters during the congress. The 1st one on Wednesday November 2nd and the second one on Thursday November 3rd.
You will find your reserved place by referring to the number assigned to you. Posters have to be installed on the same morning of the day of presentation, it must be removed from the billboard at the end of the day. Authors are asked to stand by their posters during the sessions allocated for this purpose, so that they can answer questions.

INTERNET

Wireless internet is available throughout the École polytechnique.

POLYTECHNIQUE APP «X CAMPUS»

The Polytechnique application for cellphones and tablets « X CAMPUS » is available for free download from the Apple App Store or the Android market. You will access to a lot of useful information such as general plan of the campus, schedule of the next buses to get to and from the campus, schedule of the next RER departure, etc.

Plenary lectures & Biographies

DISTINGUISHED PROFESSOR DAME MARGARET BRIMBLE FRS

University of Auckland
NEW-ZEALAND

BIOGRAPHY AND RESEARCH INTERESTS

Dame Margaret Brimble is a Distinguished Professor and Director of Medicinal Chemistry at the University of Auckland, New Zealand. She is an Associate Editor for Organic Letters, Deputy Director of the Maurice Wilkins Centre for Molecular Biodiscovery and Past-President of IUPAC Organic and Biomolecular Division III. She is a Fellow of the Royal Society London, Dame Companion of the New Zealand Order of Merit, has been inducted into the American Chemical Society Medicinal Chemistry Hall of Fame and received the Rutherford, Hector and MacDiarmid medals (Royal Society NZ), the Kiwinet BNZ Supreme award and Baldwins Research Entrepreneur 2019 commercialization awards and the Marsden medal (NZ Association of Scientists). She was awarded the Sosnovsky Award for Cancer Therapy and Natural Products award from the Royal Society of Chemistry. Her research focusses on the synthesis of novel bioactive natural products/antimicrobial peptides and the synthesis of lipopeptides for cancer vaccines and new biomaterials. She discovered the drug candidate trofinetide (NNZ2566) that was successful in phase 3 clinical trials for Rett Syndrome (Neuren Pharmaceuticals and Acadia Pharmaceuticals; FDA approval in 2022) and NNZ2591 (phase 2 clinical trials for Phelan-McDermid syndrome, Angelman syndrome and Pitt Hopkins syndrome). She is co-founder of the cancer immunotherapy company SapVax that has licensed her CLipPA peptide lipidation technology to develop self-adjuvanting peptide-based cancer vaccines. Her laboratory hosts NZ's only laboratory accredited by Medsafe NZ to manufacture peptides under cGMP for human clinical trial.

Twitter handle
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@Brimble_lab

Website
https://brimble.chem.auckland.ac.nz

PL1

Natural Product Synthesis: A Crucible for New Method Development and Drug Discovery

Margaret Brimble[1]

[1] *School of Chemical Sciences, 23 Symonds Street, Auckland 1142, New Zealand*

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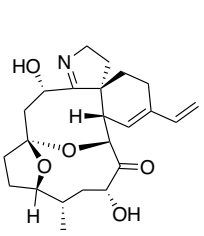
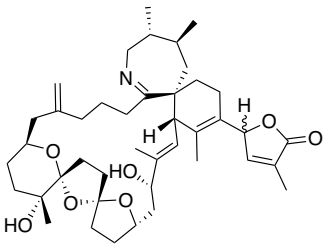
Natural products have long been regarded as "Nature's medicine chest" providing invaluable platforms for developing front-line drugs. The chemical structures of natural products have evolved over several millennia for a specific biochemical purpose and their molecular frameworks can be considered "privileged scaffolds." This lecture will showcase the synthesis of bioactive natural products and peptides from our own research as examples of underexplored novel structural chemotypes for drug discovery.

Due to the on-going global expansion of antimicrobial resistant (AMR) infections, and the declining proportion of FDA-approved antimicrobial drugs over the past three decades, AMR is now recognised worldwide as one of the greatest threats facing humankind in the 21st century. Antimicrobial peptides and proteins (AMPs) exist widely throughout nature and protect organisms from infection by destroying a broad range of pathogens. Due to the unique and non-specific bactericidal mechanism of action of AMPs, AMPs have a lower tendency to elicit antibiotic resistance than conventional antibiotics and are potentially useful therapeutic agents. The chemical synthesis and biological activity of several representative examples of antimicrobial peptides/proteins will be described.

Inspired by their complex architecture and potential as pharmaceutical lead compounds, the spirocyclic imine class of marine toxins (e.g. portimine and 13-desMe spirolide C) have attracted the attention of our research group.[1] The total syntheses of these natural products have challenged the repertoire of existing synthetic methods. Examples of new synthetic methods developed by our group whilst engaging in the total synthesis of these unique bioactive natural products will be highlighted.



portimine



13-desMe spirolide C

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MÉLANIE ETHEVE-QUELQUEJEU

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BIOGRAPHY AND RESEARCH INTERESTS

Mélanie Etheve-Quelquejeu is professor of chemistry and the head of the Master program “Frontiers in Chemistry” at the university of Paris. She leads the group “Chemistry of RNAs, Nucleosides, Peptides and Heterocycles”, in the laboratory “Chimie & Biochimie, Pharmacologiques et toxicologiques”, UMR 8601. She obtained her PhD at Sorbonne University in France in 1997. She conducted postdoctoral studies at Stanford University in California with Prof. J. Collman and then at the University California at Santa Barbara with Prof. B. Lipshutz. She works in the field of Chemical Biology of RNA and she developed chemical tools to explore the synthesis of cell wall of bacteria. These projects involve the chemistry of nucleotides and nucleic acids, the synthesis of peptides and β-lactam derivatives and methodological developments for post-functionalization of biomolecules. She is author of 70 publications, including J. Am. Chem. Soc., Angewandte. She co-organized « The XXII Roundtable on Nucleosides, Nucleotides and Nucleic Acids », at the Pasteur Institut, (Paris, July 2016). She was scientific officer at the Institut de Chimie du CNRS (section 16) between 2016 and 2021.

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PL2

RNA conjugates: from synthesis to application

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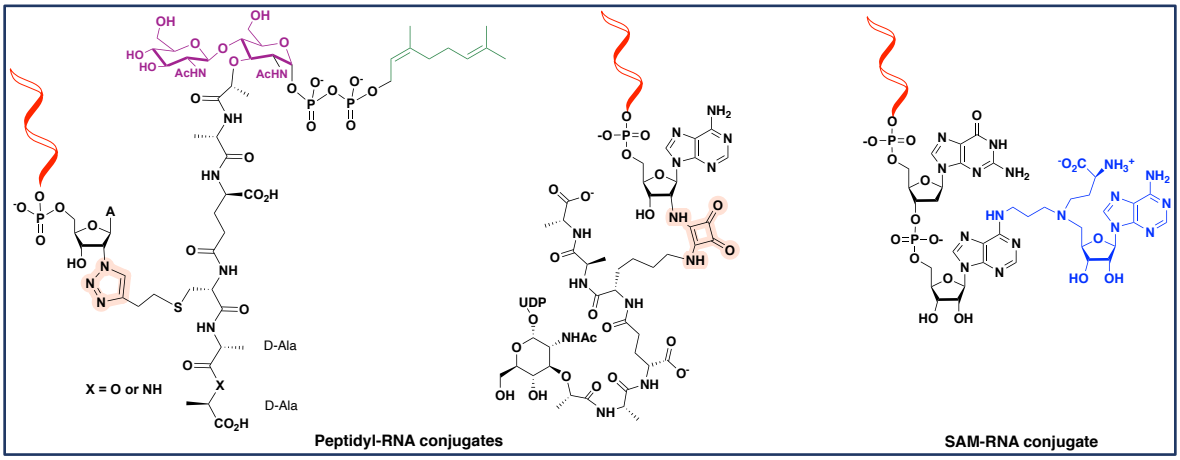
The investigation of the role of RNAs in cellular processes is one of the most dynamic areas in Biology. In addition to their key functions in protein synthesis, new RNA activities are constantly discovered. To study biological processes involving RNAs, in our team, we develop synthetic methodologies to obtain stable and reactive RNAs[1] or RNA-conjugates[2]. The use of nucleoside and nucleotides chemistry, solid phase support synthesis, enzymatic reactions, or post-functionalization methods[3] allowed us to obtain a large variety of RNAs-conjugates, which will be presented here. These RNA analogs were used for the study of aminoacyl transferases[1-3], a tRNA-dependent family of enzymes that catalyze an essential step in peptidoglycan synthesis of bacteria and for the study of m^{6}A-RNA methyltransferases[2] involved in important epigenetics events in humans, virus, or bacteria.



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BIOGRAPHY AND RESEARCH INTERESTS

Eric Meggers studied Chemistry at the University of Bonn (Germany) and received his Ph. D. degree from the University of Basel (Switzerland). After postdoctoral research at the Scripps Research Institute (USA) he started his independent career as Assistant Professor at the University of Pennsylvania (USA). Since 2007, Eric Meggers is Full Professor in the Department of Chemistry at the University of Marburg (Germany). He was holding a secondary appointment at the College of Chemistry and Chemical Engineering of Xiamen University (P. R. China) from 2012 to 2016. The Meggers laboratory is currently focused on the design and development of chiral-at-metal complexes for applications in asymmetric catalysis.

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PL3

Steering Asymmetric Catalysis with Metal-Centered Chirality

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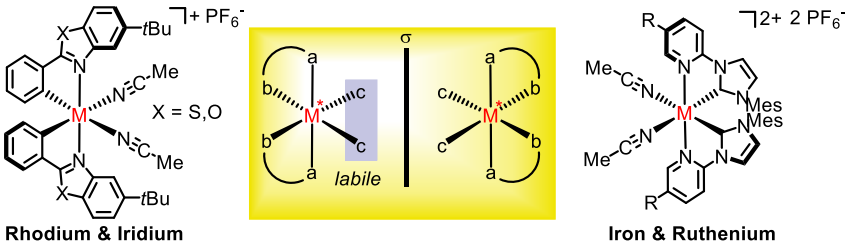
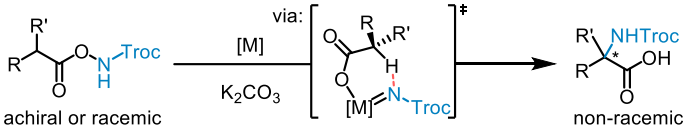
Over the past few years, our laboratory has advanced the design and application of a novel class of powerful asymmetric catalysts in which the required overall chirality originates solely from a stereogenic metal center.[1,2] Such chiral-at-metal catalysts are of interest due to their intrinsic structural simplicity (only achiral ligands) and provide untapped opportunities with respect to novel catalysts architectures and properties.

Our initial design consisted of bis-cyclometalated Ir(III)[3] or Rh(III)[4] complexes. More recently, we expanded the family of chiral-at-metal catalysts with Ru(II)[5] and Fe(II)[6] bis-(pyridyl-NHC) complexes. Most of these propeller-type complexes feature C_2-symmetry with either Λ- (left-handed screw) or Δ-configuration (right-handed screw).

The presentation will provide insight into the design, synthesis, and applications of such chiral-at-metal catalysts including asymmetric photocatalysis,[7,8,9] electrochemistry,[10] and enantioselective C(sp^3)-H aminations.[11]



Newest application: Expedite synthesis of α-amino acids



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SHU KOBAYASHI

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BIOGRAPHY AND RESEARCH INTERESTS

Shū Kobayashi studied at The University of Tokyo, receiving his Ph.D. in 1988 working under the direction of Professor T. Mukaiyama. Following an initial period as assistant professor, he was promoted to lecturer then associate professor at Science University of Tokyo (SUT). In 1998, he moved to the Graduate School of Pharmaceutical Sciences, The University of Tokyo, as full professor. In 2007, he was appointed to his current position as professor of organic chemistry in the Department of Chemistry, Faculty of Science, The University of Tokyo.

Professor Kobayashi held various visiting professorships, including the Universite Louis Pasteur, Strasbourg (1993), Kyoto University (1995), Nijmegen University (1996), Philipps-University of Marburg (1997), Paris-Sud (2010), and ESPCI (2016). Professor Kobayashi has wide-ranging research interests that include the development of new synthetic methods and novel catalysts, organic reactions in water, solid-phase and flow synthesis, total synthesis of biologically interesting compounds, and organometallic chemistry. He has held numerous named lectureships and is a recipient of many prestigious awards, including the Chemical Society of Japan Award for Young Chemists (1991), Springer Award in Organometallic Chemistry (1997), IBM Science Award (2001), Organic Reactions Lecturer (2002), Nagoya Silver Medal (2002), Mitsui Chemical Catalysis Science Award (2005), JSPS Prize (2005), the Arthur C. Cope Scholar Award from the American Chemical Society (2006), Howard Memorial Lecturer (2006), C.S. Hamilton Award (2006), Merck-Cambridge Lecturer (2007), Boehringer Ingelheim Lecturer (2009), Humboldt Research Award (2013), Green Chemistry Minister of Education Award (2013), Green Chemistry Minister of Education Award (2013), Honorary Professor, Wuhan Institute of Technology (2013), TUM-IAS Honorary Hans Fischer Senior Fellow (2013), Honorary Professor, Wuhan University of Technology (2014), Association for the Advancement of Science(AAAS) Fellow (2015), Toray Science and Technology Prize (2016), Honorary Professor, Hebei Engineering University (2016), Negishi Award (2018), Chemical Society of Japan Award (2019), The T.-Y. Luh Lectureship Award (2019), and The Medal of Honor with Purple Ribbon (2020 Autumn).

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PL4

Environment, Human Health, and Energy: Catalysts Play Key Roles Toward Sustainable Society

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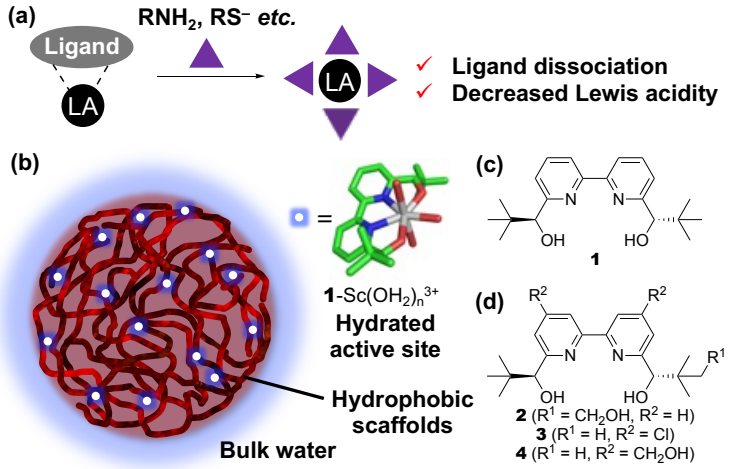
Synthetic organic chemistry has contributed a lot to modern society. Towards future sustainable society, we have been investigating on environment, human health, and energy issues from viewpoints of synthetic organic chemistry. In this lecture, the use of water in place of organic solvents in organic transformations, continuous-flow synthesis, and hydrogen storage and transport for a new energy in future society will be discussed. In these works, novel catalyst systems play key roles.

For catalytic organic reactions in water, the bioinspired supramolecular architectures were used to compartmentalize highly charged aqua scandium ions into chiral hydrophobic scaffolds. The recycling without significant loss in catalytic performance has been considered a formidable task, especially for Lewis acid-catalyzed reactions. This is because Lewis basic impurities derived from starting materials, products, and water are highly competitive ligands for both substrate binding and metal complexation, poisoning the Lewis acids and leading to their leaching. Notwithstanding the use of basic aniline, the optimal architecture allowed for effective suppression of Sc^{3+} leaching and for reuse of solvent–catalyst couples without mortiferous deactivation in asymmetric ring-opening reactions. A proof-of-concept application to asymmetric thia-Michael addition and hydroxymethylation was also demonstrated. The successful recycling in highly Lewis basic environments underpins the exceptionally high robustness of the chiral Lewis acid catalyst.[1]

In this lecture, other topics on flow chemistry for drug synthesis and heterogeneous catalysts for hydrogen storage and transport will be also discussed.[2,3]



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VÉRONIQUE MICHELET: DCO Prize 2022

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BIOGRAPHY AND RESEARCH INTERESTS

Véronique Michelet completed her graduate studies at Ecole Nationale Supérieure de Chimie de Paris (ChimieParisTech, France) and received her PhD degree in 1996 from Sorbonne University in the group of Pr. J.-P. Genêt. After post-doctoral research in the groups of Pr. J.D. Winkler (University of Pennsylvania, USA) and A.G.M. Barrett (Imperial College, UK), she was appointed at ChimieParisTech as CNRS Associate Researcher in 1998, promoted Director of Research in 2007 and obtained a Professor position at the Institut de Chimie de Nice, Université Côte d'Azur in 2017. Her research interests combine fondamental and applied aspects of catalysis for the development of new synthetic methodologies for carbon-carbon and carbon-heteroatom formations. They involve asymmetric catalysis, and the development of novel catalytic systems for atom- and step-economical reactions such as cycloisomerization reactions and domino processes. Gold catalysis is one of her favorite research topics.

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PL5

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

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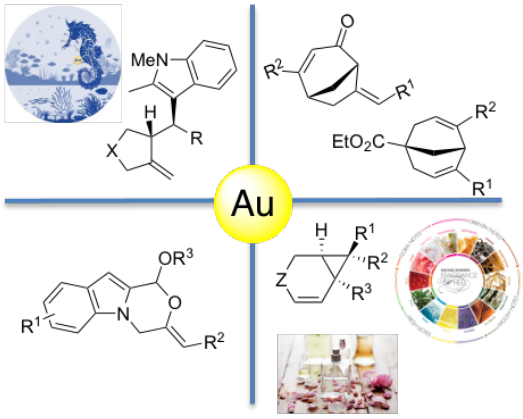
Over the past 20 years, significant research has been directed toward the development of new methodologies for synthetic efficiency and atom economy processes in the presence of gold complexes.[1] We have been initially engaged in a wide project dedicated to the development of catalytic methodologies for the synthesis of original and functionalized carbo- and heterocycles.[2,3] 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 indole skeletons via a gold-mediated cycloisomerization/alkoxylation process of 1,7-aldehyde-yne 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.[4]

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BIOGRAPHY AND RESEARCH INTERESTS

Laurence A. Mulard graduated as an engineer from the ESPCI in Paris (France). She received a M.S. and Ph.D. in Chemistry from the UPMC in Paris. After three postdoctoral years at the NIH in Bethesda (MD, USA), she returned to Paris to join the Institut Pasteur. Since 2008, she is Director of the Chemistry of Biomolecules laboratory. Starting mid-2015, she served as Deputy Director of the Structural Biology and Chemistry department for four years. Research in her group spans a broad range of topics from peptide science to the chemistry and biology of carbohydrates. Her main interests are on microbial polysaccharides and the use of synthetic surrogates thereof for developing carbohydrate-based probes, diagnostic tools, therapeutic agents and vaccines. Focus has been on combating diarrheal diseases with emphasis set to advance vaccine development against pathogenic bacteria.

Following the identification of surface exposed glycoepitopes and the demonstration that conjugates featuring short synthetic glycans induced protection against Shigella in animal models, the first-in-human Shigella synthetic oligosaccharide-based vaccine candidate that was developed in her laboratory entered clinical trials in 2016.

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PL6

Synthetic glycan-based vaccines to combat bacterial diseases: from concept to immunogenicity in human

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Pathogens often express unique surface glycans, which contribute to their survival in the host and represent potential targets for vaccine development. Several polysaccharides and polysaccharide-protein conjugates are now licensed for routine vaccination and others are being developed. Besides, synthetic glycan-based conjugate vaccines are gaining increasing interest as attractive substitutes to the use of polysaccharide antigens of biological origin.[1]

Shigellosis, or bacillary dysentery, caused by the enteroinvasive bacteria *Shigella*, was identified as one of the main diarrheal diseases in children under five.[2] Species/serotype diversity and geographical distribution strongly support the need for a multivalent vaccine.

Using the *Shigella* context and the need for a highly immunogenic vaccine able to generate protective immunity in young children, we will address cutting-edge strategies for the design of the next generation glycoconjugate vaccines against infectious diseases.[3]

Interfacing chemical biology and structure-based vaccinology, we have developed vaccine candidates consisting of synthetic fragments of selected *Shigella* surface polysaccharides (Figure) covalently linked *via* single point attachment to protein carriers. SF2a-TT15,[4] a conjugate featuring a 15mer oligosaccharide hapten was shown to be strongly immunogenic in human volunteers. With SF2a-TT15 as a model, the presentation will discuss oligosaccharide selection, vaccine design, synthesis, and properties thereof.

Shedding light on the input of organic chemistry in the context of vaccine development, the path forward to a broad coverage *Shigella* vaccine will also be exemplified for *S. flexneri* 3a and *S. sonnei*, two other prevalent *Shigella* serotypes. Emphasis will be on the importance of site-selective *O*-acetylation and on the challenge of zwitterionic oligosaccharide synthesis.

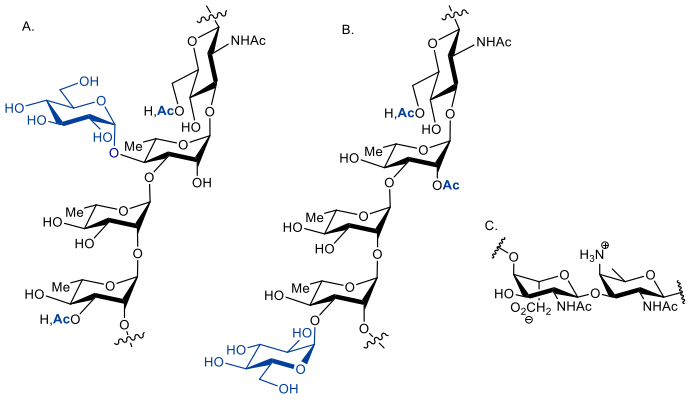

Figure: Repeating unit of the specific polysaccharides from *S. flexneri* 2a (A), *S. flexneri* 3a (B) and *S. sonnei* (C).

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BIOGRAPHY AND RESEARCH INTERESTS

Nicolas Giuseppone is director of the Research Federation on Materials and Nanosciences of the Grand Est Region, and deputy director of the Institut Charles Sadron in Strasbourg. He received his PhD in asymmetric catalysis from the University of Orsay, France, performed a post-doctoral research in total synthesis at The Scripps Research Institute, California, USA, and entered the field of supramolecular chemistry as a CNRS researcher (laboratory of Prof. J.-M. Lehn, University of Strasbourg). In 2008 he started his own research group, and was awarded an ERC Starting Grant from the European Research Council in 2010. In 2013 he was nominated as a junior member of the Institut Universitaire de France (IUF), and promoted Distinguished Professor at the University of Strasbourg in 2016. His research interests are focused on supramolecular chemistry and supramolecular polymers, molecular machines, and functional materials.

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PL7

Artificial molecular machines that work at all scales

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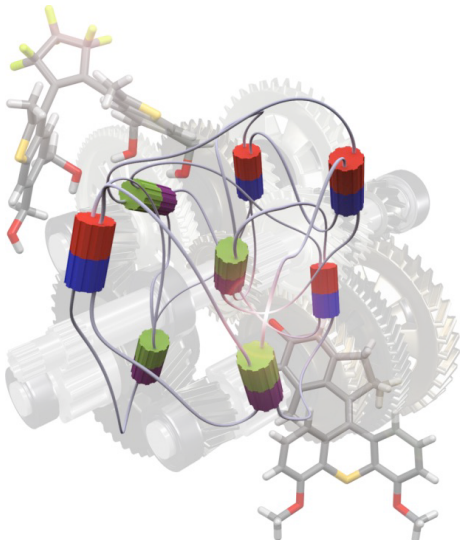
Making molecular machines that can be useful in our macroscopic world is a challenging long-term goal of nanoscience. Inspired by the protein machinery found in biological systems, and based on the theoretical understanding of the physics of motion at nanoscale, organic chemists have developed a number of molecules that can produce work when triggered by various external chemical or physical stimuli.[1] In particular, basic molecular switches that commute between (meta)stable states, and more advanced molecular motors that produce unidirectional cyclic motions out-of-equilibrium when fueled with external energy, have been reported. However, the integration of individual molecular motors in a continuous mechanical process that can have measurable effects at various length scales and up to the macroscale remains an important objective. We will discuss advances developed by our group on artificial molecular machines, which involve their mechanical coupling with polymer systems. We will show how it becomes possible to integrate them and to make use of their mechanical work going from individual molecular devices to macroscopic materials.



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BIOGRAPHY AND RESEARCH INTERESTS

Sukbok Chang received his Doctor degree (1996) from Harvard University under the supervision of Professor Eric N. Jacobsen. After a postdoctoral work at Caltech with Professor Robert H. Grubbs, he joined Ewha Womans University (Seoul) as an assistant professor in 1998, and moved to KAIST in 2002. Since 2013, he has been additionally appointed as a director at Institute for Basic Science (IBS) to lead the Center for Catalytic Hydrocarbon Functionalizations. He received Young Chemist Award (Korean Chemical Society: KCS sponsored by WILEY) in 2002, and was selected as a Star Faculty (Korea Research Foundation) in 2008. He was also awarded the Korean Chemical Society Academic Award in 2010, Korean Science Prize (President of Korea) in 2013. He was selected as a Member of the Korean Academy of Science & Technology in 2014, and recognized by the Clarivate as a Highly Cited Researcher since 2015. He is an Associate Editor of ACS Catalysis (2015-). His research interests reside in the development, mechanistic understanding of transition metal catalysis and their synthetic applications.

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PL8

Development of C-H Amidation Reactions via Nitrenoid Transfer Pathway

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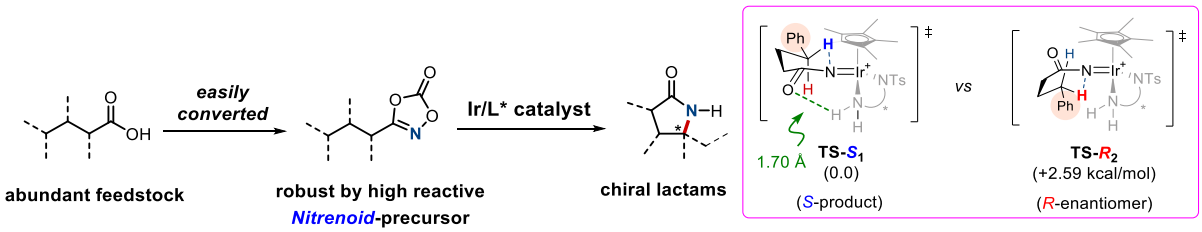
Direct amidation of C–H bonds is a highly desirable reaction considering high utility of amidated products in total synthesis, medicinal chemistry and materials science. Although tremendous research efforts have been made especially in recent years, the current status enabling such C–H reactions in excellent stereoselectivity and high efficiency is still rather limited. In this context, we have developed a novel methodology that employs tailor-made Ir-based catalysts in combination with dioxazolone substrates to access a short-lived metal-nitrenoid intermediate, thereby eventually leading to a construction of γ-lactams via an outer-sphere C–H insertion pathway. The scope was found to be broad and a range of carboxylic acids could be readily utilized for the lactam formation. Indeed, the power of this new method was demonstrated in the successful late-stage functionalization of bio-active molecules to produce molecules that are highly sought after for pharmaceutical applications.

More recently, we have successfully introduced an iridium-based catalyst system for asymmetric C–H amidation that enables facile construction of chiral γ-lactams starting from commodity chemicals. Various types of secondary C–H bonds, such as being positioned at the benzylic, unactivated aliphatic, propargylic, and allylic sites, were all smoothly reacted in a regio- and stereoselective manner. The present approach will find broad applications in medicinal chemistry, and the mechanistic insights may provoke further developments in related asymmetric catalysis.



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TIMOTHY NOËL

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BIOGRAPHY AND RESEARCH INTERESTS

Timothy Noël received in 2004 his MSc degree (Industrial Chemical Engineering). He then moved to Ghent University to obtain a PhD in synthetic organic chemistry (2005-2009). Next, he crossed the ocean to work at the Massachusetts Institute of Technology (MIT) as a Fulbright Postdoctoral Fellow with Professor Stephen L. Buchwald. Returning to Europe, he became assistant professor in 2012 and associate professor in 2017 at Eindhoven University of Technology. In 2020, he was promoted to Full Professor at the University of Amsterdam where he is the Chair of Flow Chemistry. His research interests are synthetic organic chemistry and technology, and especially the delicate synergy between these two fields. His research on flow chemistry was recognized with several awards, including the DECHEMA award (2017), the Hoogewerff Jongerenprijs (2019), the IUPAC-ThalesNano Flow Chemistry Award (2020) and the KNCV Gold Medal (2021). He is the editor in chief of Journal of Flow Chemistry.

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PL9

Innovation in HAT photocatalysis through use of flow

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Until recently, many reactions have been exclusively performed in conventional batch LabWare. With the advent of microreactor technology, significant effort has been devoted to develop a wide variety of continuous-flow techniques to facilitate organic synthesis. Microreactor technology offers several advantages compared to traditional batch reactors, such as, enhanced heat- and mass-transfer, improved irradiation, safety of operation and the possibility to integrate several reaction steps and subsequent separations in a single streamlined process.

My group has taken a great interest in assisting chemists by developing automated and flow-based reaction technologies capable of reducing manual labor, increasing the reproducibility of the results and accelerating reaction discovery. This further allows the chemists to explore uncharted chemical space.

In this presentation, we will give an overview of our synthetic methodology development, exemplified by Hydrogen Atom Transfer (HAT) photocatalysis, and how these synthetic methods were impacted by continuous-flow microreactor technology. Furthermore, we will discuss the developed technology and reaction models in detail.

CLÉMENCE ALLAIN

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BIOGRAPHY AND RESEARCH INTERESTS

Clémence Allain received her PhD from Sorbonne Université in 2006 under the supervision of Dr. Marie-Paule Teulade-Fichou. Her PhD work dealt with the synthesis and study of fluorescent probes to label DNA. From 2007 to 2009, she worked as a post-doctoral fellow, first in the group of Prof. Bernold Hasenknopf (Sorbonne Université) to develop porphyrin-polyoxometallate hybrids then in the group of Prof. Stephen Faulkner (Oxford University) to develop heterometallic lanthanides complexes. In 2010, she was appointed as a CNRS researcher to work in PPSM laboratory in ENS Paris-Saclay in the team led by Prof. Pierre Audebert. There, she prepared and studied molecules and materials based on the s-tetrazine scaffold. In 2014, she started a new research project on the development of mechano-responsive fluorescent materials, in close collaboration with Dr. Rémi Métivier in PPSM, for which she has been awarded an ERC Starting grant in 2017. She received the CNRS Bronze Medal in 2017 and was promoted Directrice de Recherches CNRS in 2021.

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PL10

Luminescent mechano-responsive molecules and materials: from molecular engineering towards the elaboration of smart materials

Clémence Allain[1], Marine Louis[2], Benjamin Poggi[1], Iulia Turcas[1], Joy Ann Panis[1,2], Laurence Bodelot[3], Tsuyoshi Kawai[2], Arnaud Brosseau[1], Rémi Métivier[1]

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Fluorescent materials are able to signal different stimuli with a high sensitivity. In particular, a material is called "mechanofluorochromic" when its fluorescence emission changes upon mechanical stimulation (pressure, shearing force…). Mechanofluorochromic compounds have attracted a rapidly growing interest for the last ten years and several series of new molecules have been synthesized.[1] We aim at relating the molecular structure of a mechanofluorochromic dye to its sensitivity to different mechanical stimuli, and at quantifying their fluorescence response to such stimuli, with the ultimate goal of developing force sensors based on these fluorescent probes.

We have studied various series of mechanofluorochromic compounds,[2] amongst which difluoroboron β-diketonate derivatives (figure 1), that gather appealing photophysical properties (bright luminescence in the solid state together with a marked change in fluorescence emission colour after mechanical stimulation) and versatile synthesis.[3] Our strategies to quantify their mechanofluorochromic responses[4] as well as our on-going efforts to develop compounds that combine mechanofluorochromism with Circularly Polarized Luminescence (CPL) emission will be presented.[5]

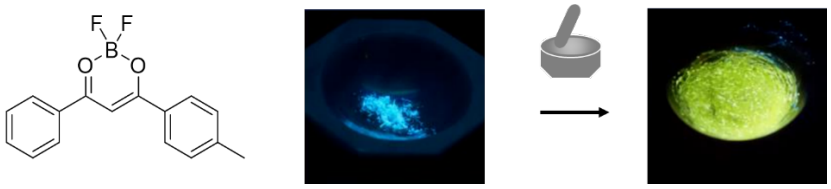

Figure 1: example of a mechanofluorochromic difluoroboron β-diketonate together with photographs (exc 365nm) of crystalline powder and grounds ample.

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JEAN-GUY BOITEAU
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BIOGRAPHY AND RESEARCH INTERESTS

Jean-Guy Boiteau studied Chemistry at the Ecole Nationale Superieure de chimie de Mulhouse. He received his Ph.D. degree in 2001 under the guidance of Prof. J. Eustache on the total synthesis of (-)-fumagillol. Following this, he performed his postdoctoral research with Prof. B. L. Feringa (Chemistry Nobel Prize 2016, Rijksuniversiteit, Groningen, The Netherlands) on asymmetric catalysis. Jean-Guy Boiteau began his career in 2003 as a medicinal chemist at Galderma R&D, Sophia-Antipolis, France. In 2010 he became Head of Process Research & Development and in 2018 he joined the Nuvisan Group as Head of Chemical Development, Sophia-Antipolis, France.

He his author or co-author of 27 scientific papers and inventor of 43 patents.

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PL11

Process Research and Development of API's : case studies

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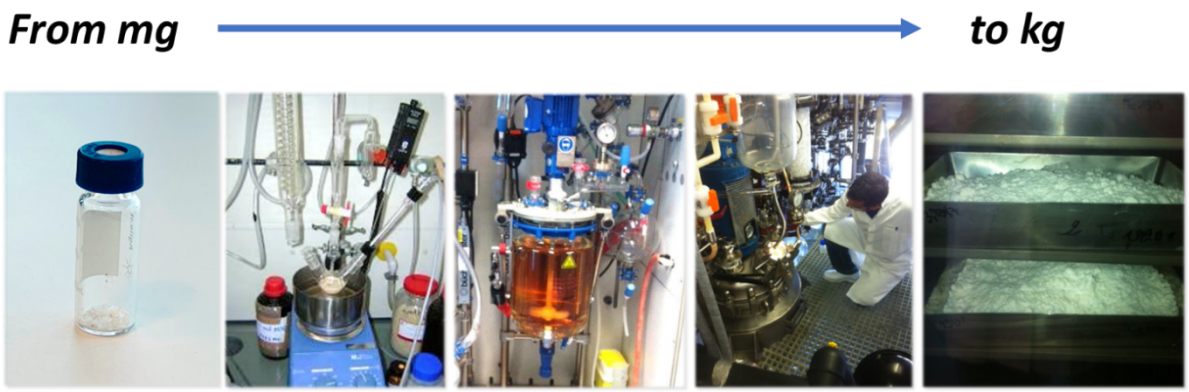
Numerous molecules are identified in medicinal chemistry and the evaluation of their pharmacological properties in humans requires the manufacture of several kilograms of active ingredient, notably to cover toxicology studies and Phase I clinical trials. In general, at the end of medicinal chemistry work, the candidate selected for human testing has only been synthesized on a scale of a few hundred milligrams, so scaling up by a factor of several million is an important step in drug development. Chemical development is a discipline that is rarely learned in school and is therefore largely acquired through experience, it lies at the crossroads of chemistry, physics, engineering, thermodynamics, and regulatory aspects. Let's have a look at this discipline through some examples. [1]



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MÓNICA PÉREZ TEMPRANO

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BIOGRAPHY AND RESEARCH INTERESTS

Mónica H. Pérez-Temprano obtained her PhD in 2011 at the University of Valladolid (Spain) under the supervision of Prof. Espinet and Prof. Casares. In 2012, she joined the research group of Prof. Melanie Sanford at the University of Michigan. In 2015, she began her independent career as Junior Group Leader at Institute of Chemical Research of Catalonia (ICIQ).

At ICIQ, the Pérez-Temprano group is focused on using mechanisms as a priori tool for developing innovative and more sustainable first-row metal-catalyzed transformations. Her research career has been recognized with different awards and honors including the JSP Fellowship (Bürgenstock Conference 2018), her selection as one of the "Talented 12" of 2018 by Chemical & Engineering News (C&EN), or the 2020 Young Investigator Group Leader Award by the Spanish Royal Society of Chemistry. In addition, she is member of the International Advisory Board of Organometallics, Chem Catalysis and the Early Career Advisory Board of Chemistry – A European Journal.

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PL12
Deciphering Mechanisms to Design Better Catalytic Reactions

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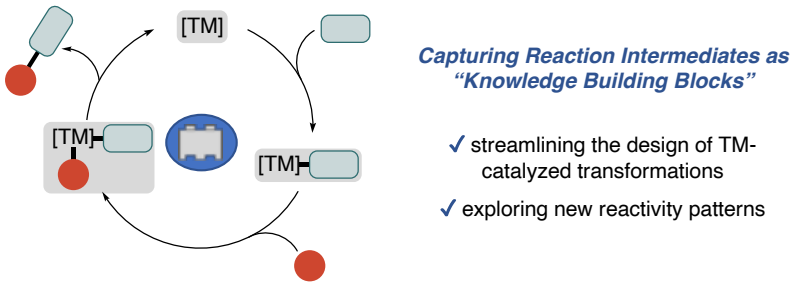
Most reactions set-up in the lab fail.[1] This is one of the biggest problems chemists face when designing transition metal-catalyzed transformations.[2] Moreover, the translation of scientifically well-established reactions to "real-world" applications often does not lead to the desired products.[3] This striking situation prompts two key questions: Why do reactions fail? Can failed reactions be used to trigger a paradigm-shift in reaction design?
Our group aims to answer these questions placing fundamental understanding at the center of process design. We use mechanistic studies as a powerful tool to facilitate the bottom-up design of more efficient chemical processes.[4] Our research program is based on simple, yet usually overlooked, concept: chemical reactions rely on the performance of the reactive intermediates within the catalytic cycles. By capturing these transient species and using them as "knowledge building blocks" (KBBs), we expose the obstacles hindering transition metal-catalyzed transformations efficiency (Scheme 1) and capitalize on the gathered fundamental knowledge to streamline more resource-efficient transformations.[5]



Scheme 1.

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SARAH REISMAN

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BIOGRAPHY AND RESEARCH INTERESTS

Professor Sarah Reisman earned a BA in Chemistry from Connecticut College in New London, CT and her Ph.D. in chemistry from Yale University, conducting research with Prof. John L. Wood in the area of natural product total synthesis. As an NIH post-doctoral fellow, Sarah pursued studies in the field of asymmetric catalysis working with Prof. Eric Jacobsen at Harvard University. In 2008, Sarah joined the faculty at the California Institute of Technology where she is now the Bren Professor of Chemistry. Research in the Reisman laboratory seeks to advance the science of chemical synthesis, through synergistic contributions in both strategy design for natural product synthesis and reaction development. Reisman is recognized as a leader in the area of natural product synthesis, where her group has contributed new strategy-driven approaches a number of complex highly oxidized natural products. In addition to her program in natural product synthesis, Reisman has made impactful contributions to the rapidly advancing field of Ni-catalysis, with an emphasis on asymmetric reductive cross-coupling reactions. Reisman is an editorial board member at Organic Syntheses and an associate editor for the Journal of the American Chemical Society. Reisman has been recognized with a number of awards for teaching and research, including an Alfred P. Sloan Research Fellowship, a Cottrell Scholar Award, the Arthur C. Cope Scholar Award, the Tetrahedron Young Investigator Award, the Margaret Faul Women in Chemistry award, and the ACS Elias J. Corey Award.

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PL13

Necessity is the Mother of Invention: Natural Products and the Chemistry They Inspire

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The chemical synthesis of natural products provides an exciting platform from which to conduct fundamental research in chemistry and biology. Our group is currently pursuing the synthesis of several structurally complex natural products, with a particular focus on the development of new convergent fragment coupling strategies. The densely packed arrays of heteroatoms and stereogenic centers that constitute these polycyclic targets challenge the limits of current technology and inspire the development of new synthetic strategies and tactics. This seminar will describe the latest progress in our target-directed synthesis endeavors.

Invited lectures & Biographies

LOUIS-CHARLES CAMPEAU

Merck
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BIOGRAPHY AND RESEARCH INTERESTS

Louis-Charles (aka L.-C.) Campeau is currently Associate Vice President and the Head of Small Molecule Process Research & Development at Merck (known as MSD in France). His team is responsible for all active pharmaceutical ingredient supply for the pre-clinical and clinical for the entire small molecule Merck portfolio as well as establishing world-class manufacturing process for new Merck products. L.-C. is French Canadian, originally from Cornwall in Eastern Ontario. After completing all of his undergraduate research in French, he joined Merck after completing his Ph. D. studies in 2007 with the late Professor Keith Fagnou at the University of Ottawa in Canada. In 2016, he was awarded the inaugural Young Alumni Awards of Excellence by the University. At Merck, he was a key contributor to the discovery and early development of Doravirine a non-nucleoside reverse transcriptase inhibitor approved by the FDA in 2018. Over his tenure at Merck, L.-C. and his team have made important contributions to >40 clinical candidates and 6 more commercial products, including molnupiravir for the treatment of COVID-19. Active on social media (@DrLCSquare), L.-C. uses his platform to advocate for equity, diversity, and inclusion, started the #ChemistsWhoCook movement and was a co-founder of #SocialIsolationSocial with Stuart Cantrill during the pandemic helping bring together the world's scientist virtually since March 2020.

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IL1

Changing the World, One Reaction at a Time

L.-C. Campeau[1]

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Biocatalysis and the advent of direct evolution have transformed the way chemists make molecules. In our journey to develop green and sustainable manufacturing processes for the new medicines of tomorrow, we have redefined our expectations of what is possible by judicious introduction of biocatalytic reactions. This presentation will outline impacts across many families of molecules from nucleoside analogues which are critical components of life-saving therapies used in the treatment of viral disease and cancer, to non-canonical amino acids which are the basis of novel macrocyclic peptides for the treatment of atherosclerosis. Despite their ubiquity in pharma and commercial value, the state-of-the-art methods for the preparation of these motifs in drug discovery, drug development and eventual commercialization are lacking and remain a poorly solved problem in organic synthesis. Our work has culminated in aspirational syntheses from commodity chemicals using a biocatalytic in-vitro cascades.

YOHAN GISBERT:
Dina Surdin PhD Prize 2022

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CEMES, FRANCE

BIOGRAPHY AND RESEARCH INTERESTS

Yohan studied Chemistry at the Université Paul Sabatier (Toulouse, France). After internships in Prof. Nitschke's group at Cambridge University working on supramolecular cages and in Prof. Veige's group at the University of Florida (Gainesville) synthesizing new supramolecular polymers, he joined the CEMES-CNRS (Toulouse) under the supervision of Dr. Claire Kammerer and Prof. Gwénaël Rapenne for his masters and PhD thesis in the field of nanotechnologies. His research involved the design and synthesis of new molecular machines derived from an electrical molecular motor, allowing to increase its functionality or to measure its output force at the single molecule scale. In parallel, more fundamental studies were also undertaken with, for instance, the development of a cyclopentadiene hexaarylation reaction. In 2022, Yohan joined Ben Feringa's research group at the Rijksuniversiteit Groningen (Netherlands) to study new molecular switches and motors designed to produce a coupled motion, allowing the preparation of new molecular systems displaying a controlled dynamic chirality. This project will continue until 2024 in the context of a Marie Skłodowska-Curie Actions Postdoctoral Fellowship. His research interest includes the multistep synthesis of challenging organic and organometallic compounds and their study within stimuli-responsive molecular and supramolecular systems with a particular focus on transdisciplinary collaborative projects.

IL2

Organometallic molecular motor derivatives for Single Molecule Force Spectroscopy experiments

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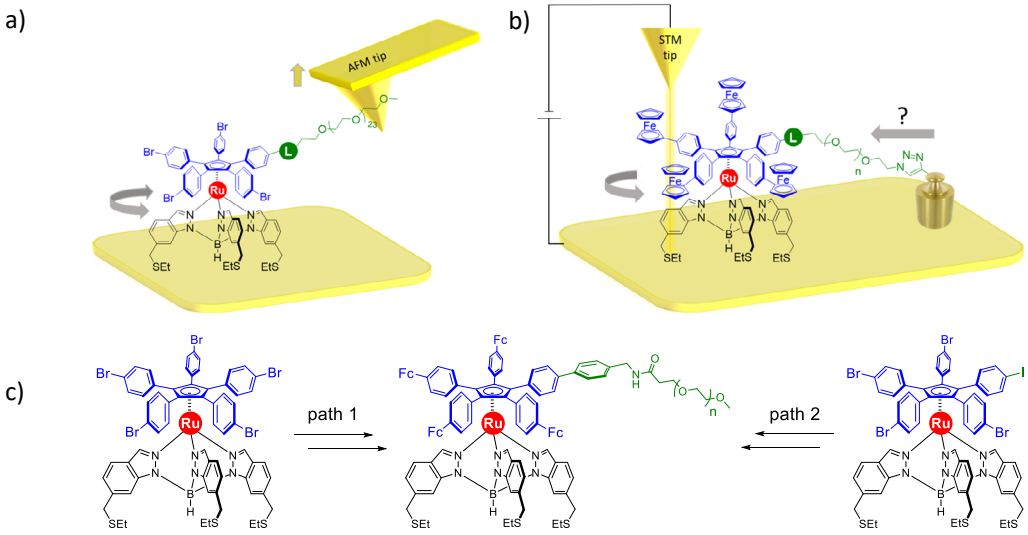
Our group reported in 2013 the synthesis of an electron-fueled ruthenium-based molecular motor able to provide unidirectional rotation when stimulated by the tip of a Scanning Tunneling Microscope.[1] This motor has been designed to be studied at the single-molecule scale on metallic surface, following a bottom-up building approach.
To estimate the motive power of this motor, two strategies have been devised, both involving the functionalization of the motor with a single polyethylene glycol (PEG) chain (in green), connected to the rotor (in blue) by a linker (L). When terminated by a methoxy group, this PEG tether is allowing for direct force measurements by AFM-based Single Molecule Force Spectroscopy experiments[2] in solution and at room temperature (a). Further functionalization of the PEG chain with a molecular load,[3] to be dragged on surface upon STM tunneling-current-induced actuation of the motor enables indirect force measurements with the ruthenium complex acting as a molecular winch at low temperature (b).
To obtain the target molecular winches, two synthetic strategies were explored (c): a statistical approach involving the non-directed monofunctionalization of the symmetric penta(bromophenyl)cyclopentadienyl ruthenium complex (path 1) and a directed approach which discriminates one position of the cyclopentadienyl precursor (path 2).[4] Both synthetic routes will be presented as well as force measurements results and current developments.



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JULIETTE MARTIN, Ph.D.
R&D Partnerships Manager at Seqens

Proteus
FRANCE

BIOGRAPHY AND RESEARCH INTERESTS

After completing her Ph.D. in Organic Synthesis at the University of Caen (France), Juliette conducted an Industrial Post-doctoral fellowship in Asymmetric Chemocatalysis at Zeneca Life Science Molecules in UK. In 1999, she joined Avecia (UK) as R&D Team Manager focusingon New Technology Platforms involving chemo- and bio-catalysis.

In 2006, she joined Seqens once the newly joint-venture was created with the industrial biotechnology company Protéus (France).

In 2009, she became R&D Manager focusing on some 'Key Technologies' process development. She then became Head of Biocatalysis for Pharma Synthesis.

In 2012, she was appointed General Manager of Protéus.
Today, she values her 25 years' experience in the field of chemistry & biocatalysis to leverage R&D Paternerships

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IL3

"Biocatalysis : a Necessary Tool for Synthetic Chemist – a Focus on Industrial Applications"

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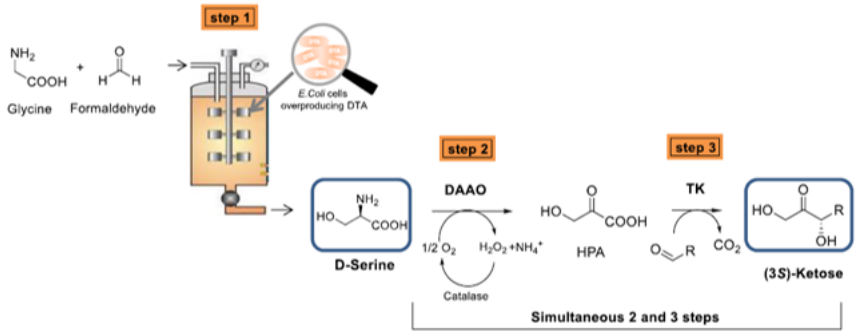
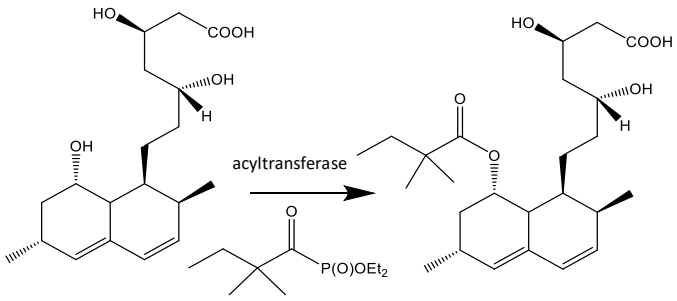
Protéus by SEQENS is a pioneer in biotechnology field, specialized in the discovery, engineering and production of enzymes for industrial applications, as well as in the development of innovative bioprocesses involving these enzymes. Protéus by SEQENS is part of the SEQENS Group, an integrated global leader in pharmaceutical solutions and specialty ingredients producing high-value complex molecules.
Enzymes enable unique and specific functionalization difficult to achieve by conventional chemical processes within competitiveness. Taking advantage of this attribute, we will demonstrate their potential through several examples showing the high selectivity and specificity of these enzymes as well as their potential industrial applications. For instance, non-natural aminoacids synthesis[1] without protection/deprotection steps, we will also present an example of regioselective acylation within high specificity[2]. Finally, biocatalysis can be a true alternative for precious metal replacement.





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THOMAS POISSON: Jean-Marie Lehn Prize 2022

COBRA INSA-Rouen
FRANCE

BIOGRAPHY AND RESEARCH INTERESTS

Thomas Poisson received his PhD (Rouen Univ.) in 2008 under the mentorship of Dr. Vincent Levacher, working on the new catalytic enantioselective protonation reactions. Afterwards, he joined the group of Prof. Shu Kobayashi (Tokyo Univ.) as a JSPS fellow, working on asymmetric catalysis using alkaline earth metal complexes. Then, he joined the group of Prof. Magnus Rueping (RWTH-Aachen), working on new photocatalyzed reactions. In 2011, he was appointed as an Associate Professor at INSA Rouen Normandie and he defended his habilitation in 2015. The same year, he was elected Distinguished Junior Fellow of the French Chemical Society (SCF). In 2016, he received the "prix jeune enseignant-chercheur" from the Organic Chemistry Division of the SCF and in 2017 he was recipient of the Thieme Chemistry Journal award, the JSP Fellowship of the 52nd Bürgenstock Conference and was nominated as a Junior Member of the "Institut Universitaire de France". In 2022, he received the Jean-Marie Lehn award from the Organic Chemistry Division of the SCF. Thomas Poisson has also strong partnerships with companies and is from 2018 deputy director of IDECHEM a joint laboratory with Oril Industrie. In 2020, he co-founded with Prof. P. Jubault and Dr. Legros NormandyFlowChem, a platform dedicated to Continuous Flow Synthesis thanks to the support of the Normandy Region and the French Government. Since 2018, Thomas Poisson is Full Professor of Chemistry at INSA Rouen Normandie.

His research interests focus on the development of new methodologies, metal-catalyzed reactions, with an emphasis on copper chemistry, electron transfer based reactions using photocatalysis and electrosynthesis, asymmetric catalysis and fluorinated molecules.

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IL4
Photocatalytic and Electromediated Borylation and Silylation Reactions

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As part of the Organic Chemistry, radical chemistry is an important research area as the reactivity of radicals is complementary to the ones of the two electrons and polar manifolds. In this regard, the recent advent of photocatalysis[1] and the renewal of electrochemistry[2] offer interesting approaches to broaden the current know-how of the community.
Besides, organoboron species and organosilicon species are linchpins in organic synthesis. Organoborons are widely used in Suzuki cross-coupling reaction, allylation or Cham-Lam-Evans cross-coupling reactions, while organosilicon species found application in allylation or Brook rearrangement, for instance.
Herein, we will disclose our efforts to develop photocatalytic and electrochemical borylation and silylation reactions involving single electron transfer.[3]

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Oral Communications

OC01
Electrocoupling
A Catalyst-free Alternative for C-C Bond Formation

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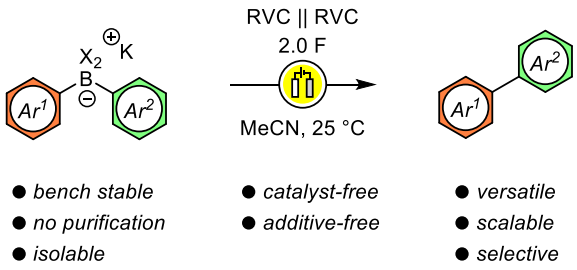
Our efforts toward sustainable C-C bond formation have led us to investigate alternative catalyst-free coupling reactions. Having previously demonstrated that organoboron reagents can serve as templates in Zweifel olefinations[1,2] and strained ring functionalization,[3,4,5] we set out to develop a conceptual approach for hetero-coupling reactions.

As many methods for the formation of hetero-biaryls require expensive and/or environmentally challenging transition-metal catalysts as well as inert and dry conditions, we envisioned that bench-stable, hetero-substituted arylborate salts could undergo formation of (hetero)biaryls, triggering the key 1,2-metallate rearrangement step under electrochemical oxidation.[6,7,8]



First, a novel and practically simple access to tetraarylborates will be described, providing a new library of heterosubstituted structures.

Second, the chemoselectivity of the electrocoupling reaction will be discussed, as well as its currents applicability and limitations.[9,10,11]

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OC02

2-Amido-acroleins as a versatile platform for the synthesis of poly-functionalized silicon containing heterocycles

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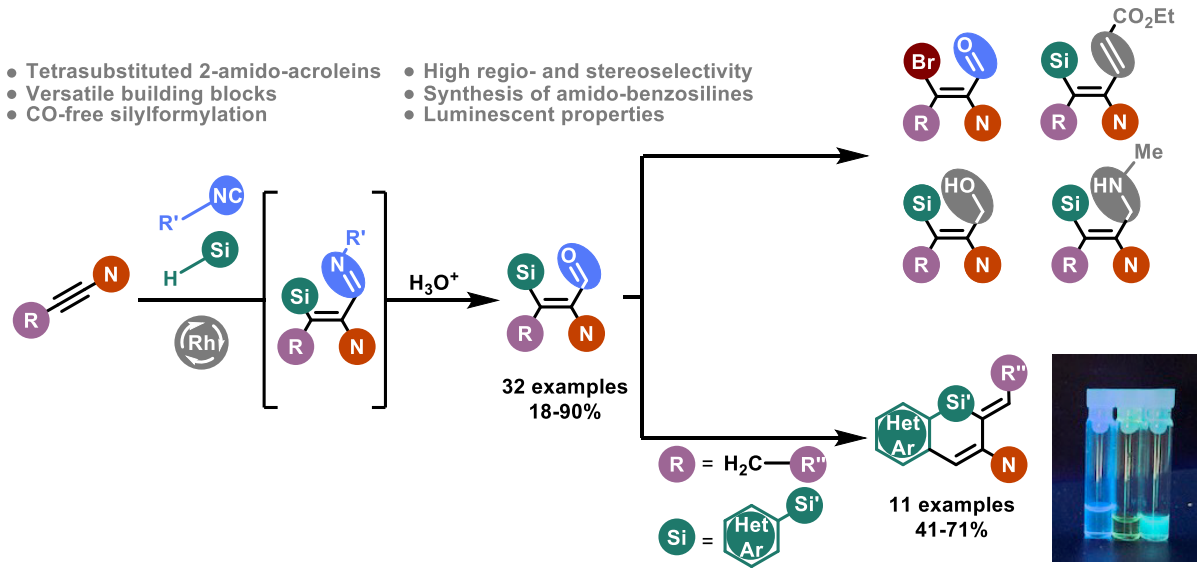
2-Amino-acroleins are valuable building blocks that have not been sufficiently studied due to the lack of efficient, selective, and versatile synthetic methods, especially when tetrasubstituted ones are targeted.

In this context and inspired by a previous work reported by Fukumoto,[1] we have recently developed the first rhodium-catalyzed silylformylation applied to ynamides. To make this approach practically easy to implement in any laboratory, isocyanides were used as a substitute of carbon monoxide. After optimization, we demonstrated that this reaction is fully regioselective towards 2-amido-acroleins and almost always stereoselective for the *syn*-addition product (isomer *E*). Different functional groups on the ynamide, silane and isocyanide are tolerated leading to a high degree of diversity on the final compound. These products can be easily converted to vinyl bromide, allylic alcohol, amine and diene.[2] As part of our interest in the synthesis of sila-heterocycles,[3] we subjected these 2-amido-acroleins to an intramolecular Friedel-Crafts reaction leading to the formation of poly-functionalized amido-benzosilines.[4] These molecules are analogs of sila-rhodamines and they exhibit interesting luminescent properties that can be easily tuned by changing the electronic nature of the different substituents on the 2-amido-acroleins.



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[4] *Unpublished results.*

OC03

First Total Synthesis Of Chaxalactin B

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[1] *Institut des Molécules et Matériaux du Mans, IMMM UMR 6283 CNRS, Le Mans Université, Avenue Olivier Messiaen, 72085 Le Mans CEDEX 9, France*

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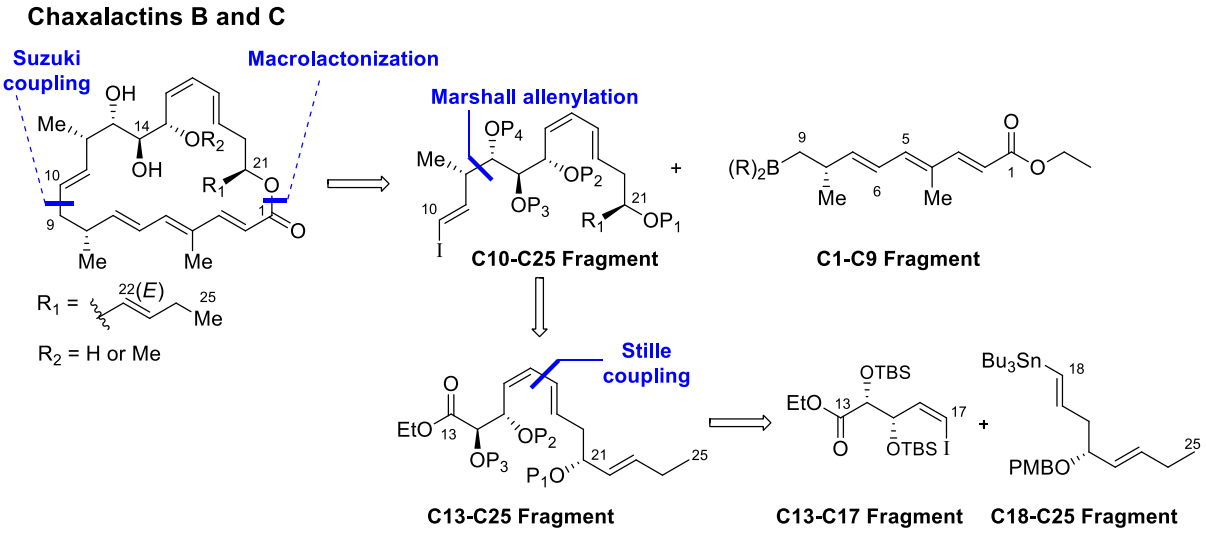
Chaxalactins A, B and C are 22-membered macrolactones isolated in 2011 from a strain called *Streptomyces sp. C34*, collected in hyper-arid Atacama Desert (North of Chili).[1] The complex structure of these molecules coupled with their interesting antibiotic and potential antitumor activities makes this family of molecules synthetically challenging important targets. Despite their interest, no total synthesis of these compounds has been reported so far. The aim of this project is to synthesise for the first time chaxalactins A, B and C and related analogues. Chaxalactins could be obtained by a Suzuki coupling between the C1-C9 and C10-C25 fragments, followed by a macrolactonization reaction. The C10-C25 fragment could be prepared from the C13-C25 fragment using a Marshall allenylation key step to introduce and control the C12, C13 stereocenters. The C13-C25 fragment could in turn be obtained by a Stille coupling between the C13-C17 and C18-C25 fragments.



In this communication, we will report the first total synthesis of chaxalactin B and the synthesis of an advanced intermediate of chaxalactin A. The first biological evaluation will also be presented.

[1] M. E. Rateb, W. E. Houssen, W. T. A. Harrison, H. Deng, C. K. Okoro, J. A. Asenjo, B. A. Andrews, A. T. Bull, M. Goodfellow, R. Ebel, M. Jaspars, *J. Nat. Prod.* **2011**, 74, 1965.

OC04

Bimetallic complexes of photoswitchable phosphines derived from nine-membered cyclic azobenzenes : synthesis, photochromic properties and uses in gold catalysis

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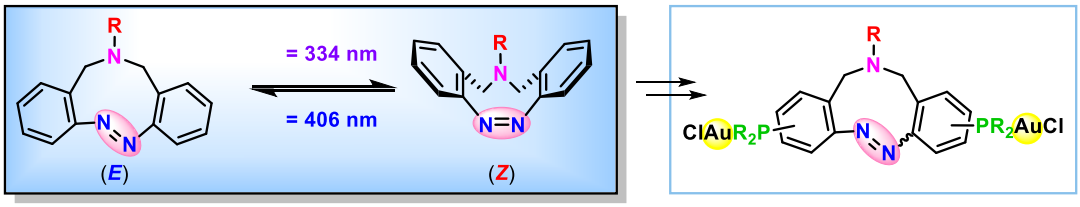
Azobenzene photoswitches are widely used to tune the properties of biomolecules, catalysts or materials, using light as an external stimulus.[1] Especially, the range of structural and photophysical properties of azobenzene photoswitches could be extended significantly with the development of cyclic species. For example, eight-membered ring azobenzenes called diazocines have been extensively studied the past decade.[2] Nevertheless, only two studies have reported the synthesis of nine-membered cyclic azobenzenes.[3]

In this context, we have developed a new family of cyclic, C2-symmetric photoswitchable molecules, the 13-dihydro-11*H*-dibenzo[*c*,*h*][1,2,6]triazonines. These nine-membered cyclic azobenzenes display a nitrogen function in the saturated ring chain. Their properties, i.e. *E*-preference combined with bistability over a large temperature range, nicely complement the properties of the known acyclic azobenzenes and diazocines. The specific features of these compounds are (*i*) a preferred *E*-configuration, (*ii*) nearly quantitative bi-directional photoswitching, (*iii*) high thermal stability of both *E*- and *Z*-forms.[4]



We used this new backbone to synthesize the corresponding diphosphines and bimetallic gold (I) complexes. These new photoswichable catalysts, which retain the intrinsic properties of the triazonine backbone, have been used in selected reactions to evaluate their catalytic activities.

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OC05

Photoredox Generation of Oxygen-Centered Radicals: α-Alkoxylation and α-Trifluoromethoxylation of Carbonyl Compounds

Camille Banoun[1], Thibaut Duhail[1], Flavien Bourdreux[1], Tommaso Bortolato[2], Javier Mateos[2], Elsa Anselmi[1,3], Benson Jelier[4], Antonio Togni[4], Emmanuel Magnier[1], Luca Dell'Amico[2], Guillaume Dagousset[1]

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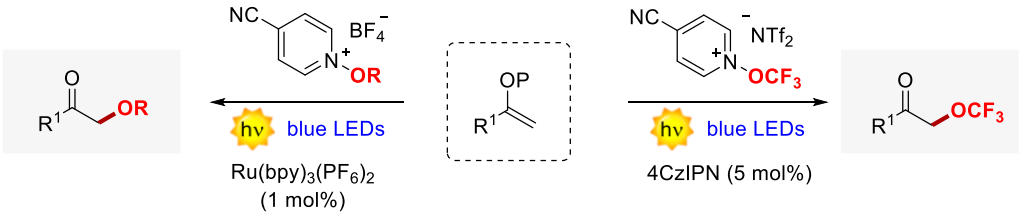
O-centered radicals play a central role in many natural processes, from atmospheric chemistry to biology.[1] In organic synthesis, by contrast with their C-centered analogs, they are regarded as highly reactive intermediates, which are essentially prone to undergo β-scission or HAT processes, furnishing eventually a more stable C-centered radical. Recently, our group has been interested in new alkoxylation reactions, by trapping these O-centered radical species with efficient radical acceptors in order to create new C-O bonds.[2] In particular, we were able to synthesize a wide range of new α-alkoxylated ketones and amides which are otherwise difficult to access (Scheme 1, left).[3] In addition, in collaboration with the groups of Pr. A. Togni (ETH Zurich) and Dr. L. Dell'Amico (University of Padova), a methodology to prepare α-trifluoromethoxylated carbonyls could also be successfully developed (Scheme 1, right).[4] Although quite similar, in-depth mechanistic studies showed a quite distinct mechanism between both protocols, which will be presented herein together with their scope and limitations.



- *48 examples, up to 89% yield*
- *One-pot process from carbonyls*
- *Photocatalyzed mechanism*
- *Compatible with complex alkoxy groups*

- *29 examples, up to 52% yield*
- *Mild metal-free method, in batch or flow*
- *Radical chain mechanism*
- *Applicable to biorelevant molecules*

Scheme 1

[1] Suárez, E.; Rodriguez, M. S. *Radicals in Organic Synthesis*; Renaud, P.; Sibi, M. P.; Wiley-VCH: Weinheim, **2001**.

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[3] Banoun, C; Bourdreux, F; Magnier, E; Dagousset, G. *Org. Lett.* **2021**, *23*, 8926.

[4] Duhail, T.; Bortolato, T.; Mateos, J.; Anselmi, E.; Jelier, B.; Togni, A.; Magnier, E.; Dagousset, G.; Dell'Amico, L. *Org. Lett.* **2021**, *23*, 7088.

OC06

Indirect Enantiocontrol of Tertiary Alcohols and Quaternary Centers by Acylative Organocatalytic Kinetic Resolution

Xueyang Liu, Titouan Desrues, Jean-marc Pons, Valérie Monnier, Jean-arthur Amalian, Laurence Charles, Adrien Quintard, Cyril Bressy

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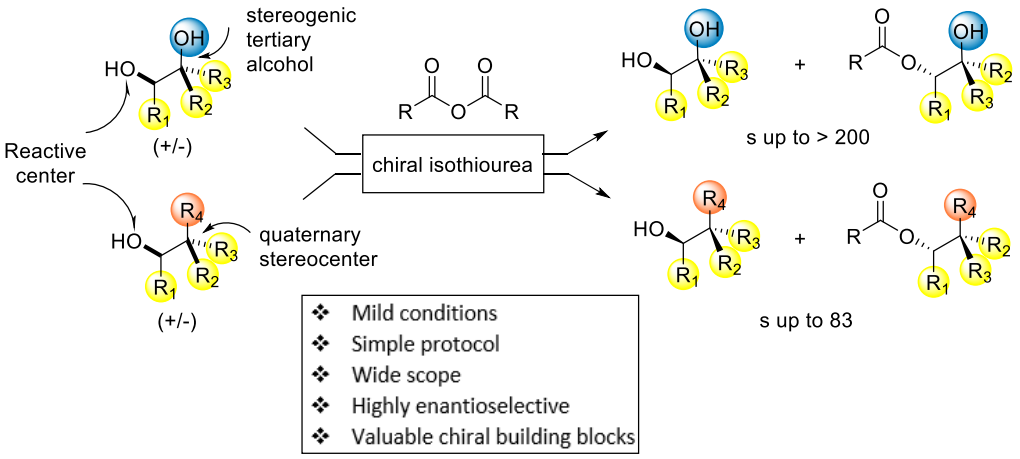
The stereocontrol of chiral tertiary alcohols and quaternary stereocenters represent a recurrent challenges in organic synthesis. In our laboratory, we elaborated a simple, efficient, and indirect strategy to enantioselectively prepare both of these challenging targets through a chiral isothiourea* catalyzed selective acylation of adjacent secondary alcohols. This transformation enables the kinetic resolution (KR) of easily prepared racemic diastereoenriched precursors. In the first challenge, secondary/tertiary diols provided both monoesters and starting diols in highly enantioenriched forms (s-value>200).[1]
In the second challenge, this indirect method was also used to control the quaternary centers, providing desired product with s value up to 185.[2]



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[2] Liu, X.; Pons, J.-M.; Monnier, V.; Charles, L.; Quintard, A.; Bressy, C. Enantiocontrol over Acyclic Quaternary Stereocenters by Acylative Organocatalyzed Kinetic Resolution. *Eur. J. Org. Chem*, **2022**, e202101475.

OC07

Excited State Intramolecular Proton Transfer based Fluorophores with Circularly Polarized Luminescence Emission

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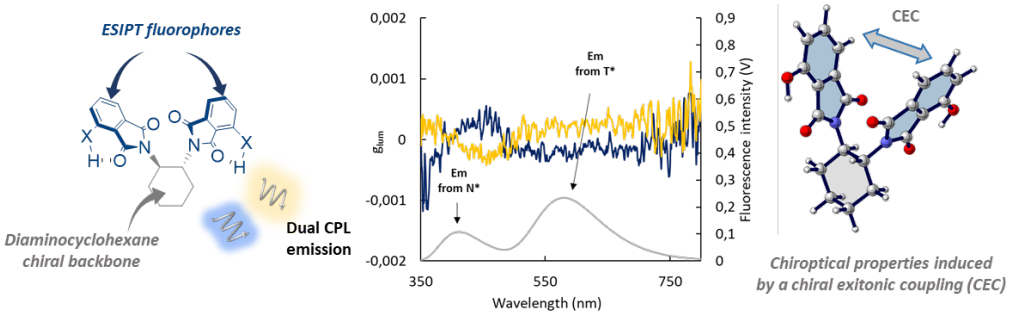
The design and study of small organic molecules exhibiting circularly polarized luminescence emission (CPL-SOMs) has recently gained momentum, notably because such chiral molecules have a wide variety of potential applications in photonic and optical devices. These last five years, important efforts have been made in order to merge CPL emission properties with other particular photophysical phenomenon. Indeed, such a combination is mandatory to unlock the potential of CPL emitters in terms of application. Hence, CPL-SOMs displaying phosphorescence or aggregation induced emission properties has been recently developed. In this context, our group has pioneered the development of Chiral TADF materials, which is today the subject of numerous research works [1]. Despite all the recent advances in this active domain of investigation, no molecular design allowing to combine CPL and Excited State Intramolecular Proton Transfer (ESIPT) fluorescence has been described until recently. ESIPT fluorophores display numerous interesting properties, such as large Stoke-shift or dual emission properties. Due to these particular characteristics, ESIPT fluorophores have found applications in a large number of domains such as Biology for sensing purposes or in Material Science as emissive dopants in OLED [2]. In this presentation, I will describe the first molecular design allowing to gain access to ESIPT fluorophores with CPL emission [3]. In this new class of emitters, the chiroptical activity originates from a chiral excitonic coupling induced by the tethering of two ESIPT fluorophores via a readily accessible 1,2-transdiaminocyclohexane scaffold. Using this approach has notably allowed to synthesize in one step a CPL molecule displaying very large Stoke shifts (up to 222 nm in toluene solution) and one of the rare example of CPL active dual-emission materials.



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OC08

Merging Grubbs' Second-Generation Catalyst with Photocatalysis Enables Z–Selective Metathesis of Olefins: Scope, Limitations, and Mechanism

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Olefin cross metathesis is one of the most powerful and convenient approaches for the forming of carbon-carbon double bonds. The stereoselectivity of the alkenes are mainly governed by the structure of the catalyst.[1] For instance, benzylidene-[1,3-bis(2,4,6-trimethylphenyl)imidazolidin-2-ylidene]-dichloro-ruthenium (**1**), commonly known as Grubbs second generation catalyst, is known to lead to the exclusive formation of *E*-alkenes (Figure 1). In this communication, we show that the challenging contra-thermodynamic *Z*-isomers can easily be obtained by simply combining the metathesis catalyst (**1**) with a well-designed photocatalyst under blue light irradiation. The scope and limitations of this unprecedented approach are discussed based on both computational and experimental mechanistic experiments (Figure 2).[2]

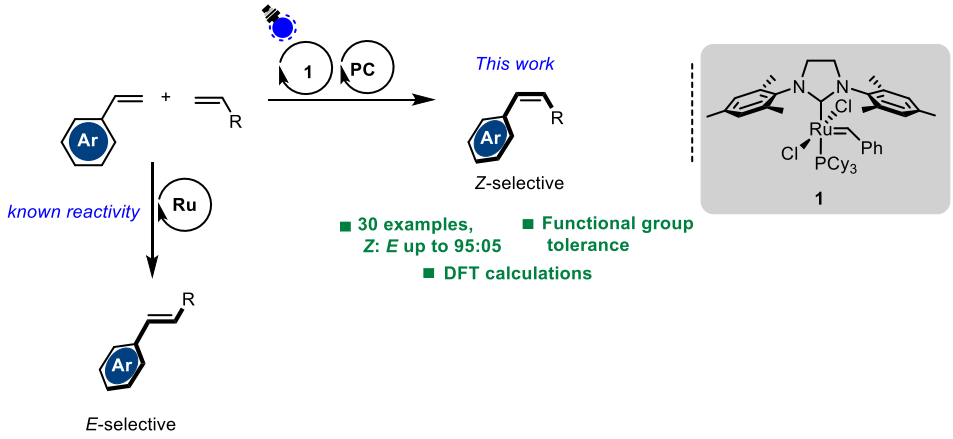

Figure1.

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OC09

Taming redox non-innocence of weak-field iron complexes : an opportunity in catalysis

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Weak-field N-based ligands such as 1,10-phenanthrolines or 2,2'-bipyridines are ubiquitous in iron coordination chemistry, yielding well-known Fe^{II} and Fe^{III} complexes. However, much less is known regarding the coordination chemistry of analogous complexes with similar ligands associated to lower oxidation states, e.g. Fe^{0} or Fe^{I}. The related complexes are highly unstable, the non-innocence of those weak-field ligands allowing easy electron-transfer processes within the ligand (Figure 1, top) leading to decomposition paths.[1] In this work, we demonstrate that the use of modified phenanthrolines (N,N) involving sterically hindered groups at the C_4 and C_7 positions strongly stabilizes new neutral complexes $(N,N)_2Fe$, which were structurally characterized. A thorough investigation by Mössbauer spectroscopy, SQUID magnetometry and Magnetic Circular Dichroism (MCD) clearly shows a non-innocent behavior of the (N,N) ligand, the steric pressure at the C_4 / C_7 positions protecting the excess of electronic density brought by iron-to-ligand backbonding (Figure 1, bottom). A remarkable consequence of this steric blocking is the subsequent enhanced thermal and temporal stabilities of $(N,N)_2Fe$ in solution. Catalytic applications will be discussed, including promising performances of this complex as a cheap and non-toxic catalyst for [2+2+2] alkyne cyclotrimerization.[2]

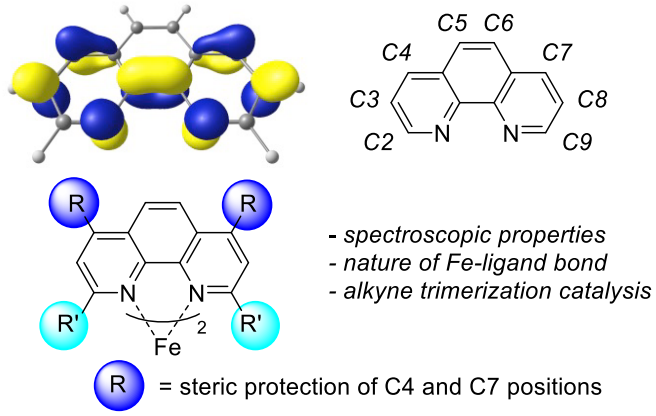

Figure 1. (top) LUMO+1 level of 1,10-phen; (bottom) steric protection of electron transfer in new $(N,N)_2Fe$ species discussed in this work.

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OC10
Identification of protein targets of an inhibitor of viral infection using an affinity-based probe

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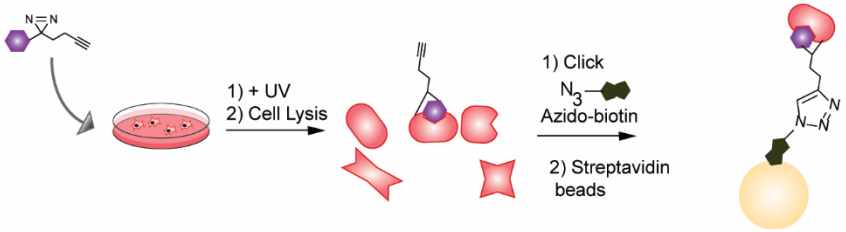
The characterization of cellular pathways that regulate virus internalization and pathogenesis in host human cells is essential for the discovery of exploitable cellular drug targets. Flaviviruses (Denv, Zika, etc) and Influenza A virus remain a serious threat to human health. These viruses typically enter cells through a common pathway, endocytosis, and rely on the acidification of the endosome to fuse with the endosomal membrane and release their RNA genome into the cytoplasm, which then allows the replication of the virus and further infection. Interestingly, the natural product nanchangmycin was shown to inhibit the endocytosis of these viruses and viral infection, however, the mechanism of action is unknown.[1]

To identify the molecular(s) target(s) of nanchangmycin, we applied an affinity-based proteome profiling approach that has been extensively used to identify cellular targets of bioactive molecules. The method is based on a photoaffinity probe able to crosslink and label with an alkyne tag the protein target(s) of nanchangmycin. The alkyne tag can be used to add an azido-biotin via Copper-catalyzed azide-alkyne cycloaddition (“click”) and further enrich nanchangmycin targets on streptavidin beads to facilitate their identification by mass-spectrometry based proteomics.
We will describe the synthesis and validation of this probe, as well as its use in quantitative proteomic experiments to map the protein targets of nanchangmycin in a human cell line. We will particularly study how the target(s) of nanchangmycin are linked to endocytosis and viral infection. These results will allow us to decipher the mode of action of nanchangmycin and might reveal novel antiviral drug targets.



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OC11

Charge-Accelerated [3,3] Rearrangement of Vinyl Sulfoniums: Stereodivergent Access to γ-Lactones and γ-Lactams

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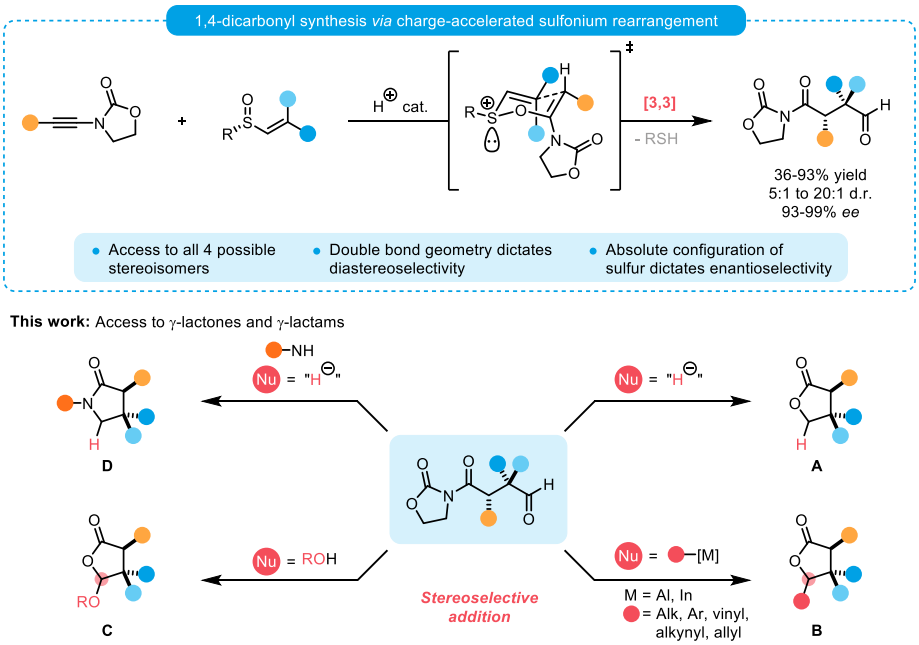
γ-Lactones and γ-lactams are very common structural motifs in bioactive natural products, however, their stereoselective synthesis are scarce, especially when highly substituted.[1] In 2018, our group disclosed an acid-catalysed, stereodivergent approach for the synthesis of 1,4-dicarbonyls from ynamides and vinyl sulfoxides via [3,3]-sigmatropic rearrangement.[2,3] All four possible stereoisomers can be obtained using this method. Whereas the geometry of the double bond of the vinyl sulfoxide dictates the relative configuration of the two stereocenters formed in the reaction, the absolute configuration of the sulfur atom is responsible for the enantioselectivity.

With an easy access to well stereodefined 1,4-dicarbonyl in hand, we anticipated that stereoselective addition of a nucleophile would trigger a cyclisation, leading to valuable γ-lactones. We developed methods to introduce various nucleophiles such as hydride (**A**), carbon nucleophile (**B**) and alkoxy (**C**). Alternatively, pre-treatment of a 1,4-dicarbonyl with an amine followed by nucleophile addition of a nucleophile led to the formation of γ-lactams (**D**). Overall, highly decorated γ-lactones and γ-lactams were obtained in good to excellent yields and with high stereoselectivities, hence tackling a major synthetic challenge.



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OC12

Highly selective dearomatization of *N*-heteroarenes using well-defined low-valent cobalt hydrides

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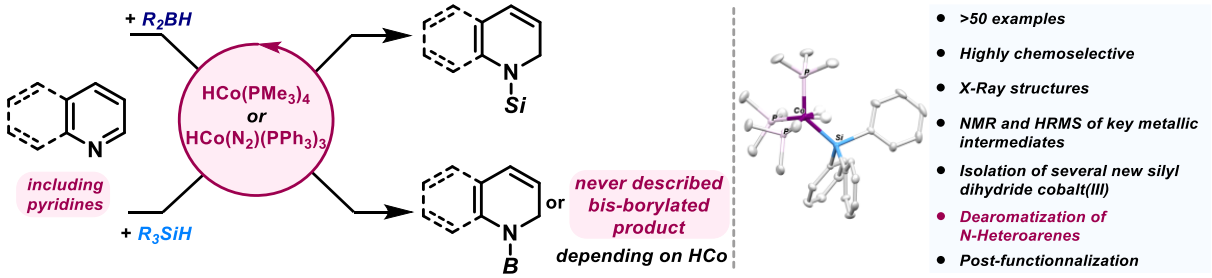
Metal hydrides are usually very reactive key intermediates in catalytic cycles.[1] Our group has been working on well-defined low-valent cobalt hydride complexes bearing simple trimethylphosphine ligands. We have shown that these types of complexes are very efficient for various reactions such as C—H bonds activation,[2] alkynes hydrosilylation and hydroboration[3] and more recently imines hydrosilylation.[4] In this communication, we will show that these robust catalytic conditions, that tolerate a various range of protecting groups and silanes, can be extended to *N*-heteroarenes.[5] In the literature few examples of selective 1,2-hydroboration have been reported, even less for hydrosilylation, and scarce are using non-noble metals.[6] To the best of our knowledge, this is the first example of selective dearomatization of quinolines and pyridines catalyzed by cobalt complexes.



The difference of catalytic activity between two cobalt hydrides will be discussed when using either hydrosilane or hydroborane that lead to two distinct products. New bis-borylated substrates were obtained and post-transformations were carried out in order to demonstrate their synthetic applications.[7] Mechanistic insights have also been conducted and we will present the synthesis and isolation of diverse new silyl dihydride cobalt (III) complexes whose structure have been confirmed by X-Ray analysis. In addition, stoichiometric experiments, characterization of key metallic intermediates and NMR monitoring have been carried out to go further.

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[7] Unpublished results.

OC13
Diastereoselective addition of redox active esters to azomethine imines by electrosynthesis

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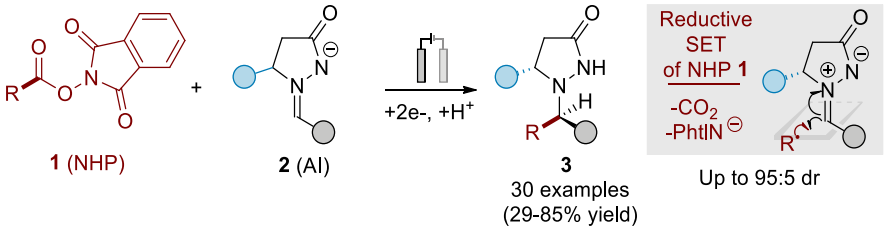
Azomethine imines (**AI**) are versatile dipoles historically involved into cycloadditions and nucleophilic addition reactions of anionic species, towards the construction of valuable cyclic-hydrazine derived products.[1] However, radical-based transformations of Dorn-Otto type azomethine imines **2** were only recently explored by visible-light photoredox catalysis.[2,3] In that context, few examples of a chiral C5-substituted azomethine imines were reported and low or undefined diastereoisomeric ratios were described.



Diastereoselectives radical addition to azomethine imine by electrosynthesis.

We envisaged an alternative approach to provide original pyrazolidinones **3** with high diastereoisomeric ratios from chiral azomethine imines **2** using electrochemical conditions. Our strategy consists in the use of *N*-(acyloxy)phthalimides (NHPs) **1** as versatile radical precursors upon a decarboxylative cathodic reductive SET event.[4] Thereby, an efficient addition reaction of various alkyl radicals to such dipoles (up to 85% yield) in a stereoselective fashion (up to 95:5 dr) will be presented.[5]

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OC14

Catalytic amination of unactivated C–H bonds in the presence of electronically activated sites

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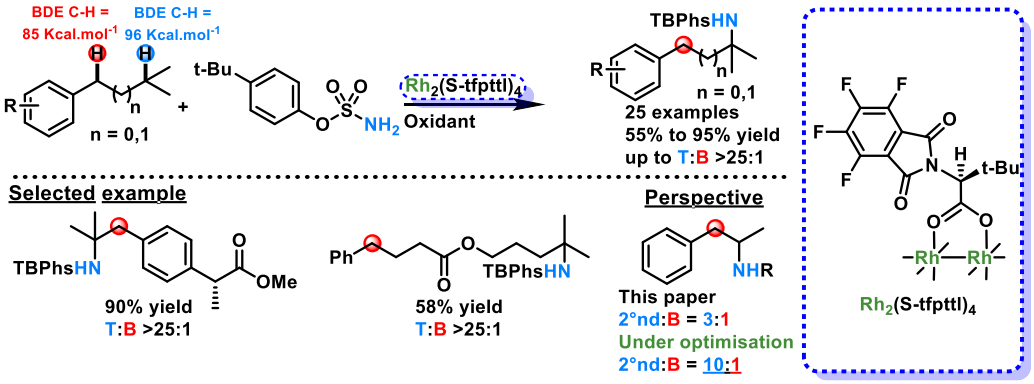
The design of site-selective C(sp^3)–H functionalization reactions is a great challenge with important applications in synthesis and medicinal chemistry.[1] A first approach to meet this goal relies on directed functionalization reactions through the use of coordinating groups or intramolecular reactions. By contrast, in the case of undirected C(sp^3)–H functionalization reactions, the site-selectivity is often governed by the innate reactivity of the substrate, particularly by the C–H bond dissociation energies (BDEs).[2] Despite their efficiency, both strategies suffer from limitations with many C-H bonds remaining inaccessible.

Catalyst-controlled site-selective C(sp^3)–H functionalization reactions is a third strategy that has recently emerged to go beyond the limitations of substrate-controlled reactions.[3] In this context, our group recently initiated studies to address the issue of the selective intermolecular amination of unactivated tertiary C(sp^3)–H bonds (BDE of 96 kcal·mol^{-1}) bonds in the presence of an activated benzylic site (BDE of 85 kcal·mol^{-1}) through the search for new reagents and catalysts. In this communication, we thus will describe the discovery of a highly discriminating rhodium-bound nitrene species resulting from the synergistic combination of a dirhodium(II) complex and a sulfamate.[4] These reagents allow to go beyond the BDE-driven reactivity of C-H bonds and convert selectively tertiary C(sp^3)–H bonds to afford α,α,α-trisubstituted amides in high yields. The scope of the reaction, its application to the late-stage amination of complex products, and its possible extension to the more challenging selective functionalization of linear alkyl chains will be reported.



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OC15

Reactant-Induced Photoactivation of In Situ Generated Organogold Intermediates Leading to Alkynylated Indoles

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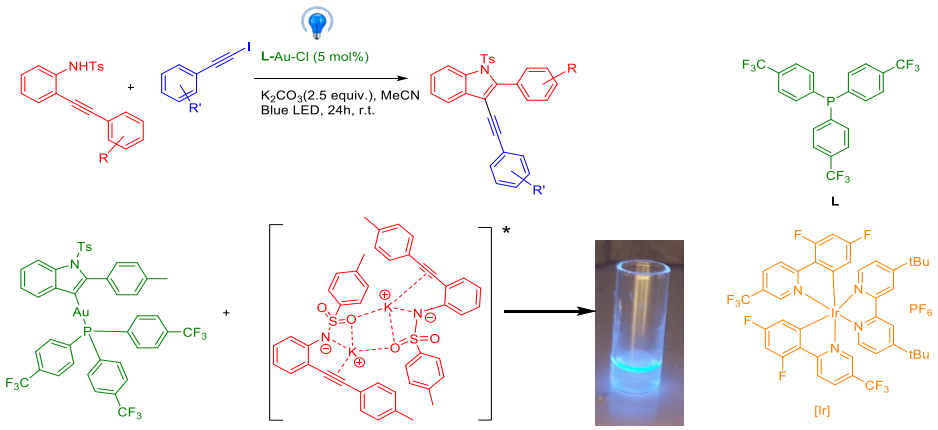
Gold(I) complexes can hardly perform oxidative additions with alkynyl and aryl halides in cross-coupling reactions due to a high Au(I)/Au(III) redox potential[1]. To address this issue, some strategies have been considered, including the use of an external strong oxidant[2] or a set of bidentate hemilabile ligands[3], likely to enhance the bi-electron oxidation. However, this issue remains challenging nowadays and, in this context, the photoactivation of a metallic centre represents an elegant solution[4]. Therefore, our team developed in 2019 an iridium photocatalyzed alkylynative cyclization of *o*-ethynyl-phenol to form branched benzofurans[5]. Recently, to explore the scope of this reactivity, we approached the behavior of *o*-ethynyl-tosylanilines in similar conditions[6]. Surprisingly, we discovered that, for this substrate, the photosensitization of the intermediate vinylgold(I) occurs without exogenous photocatalyst but through a photoactive reactant formed by the smooth deprotonation of the aniline. The related salt can form a photosensitive aggregate likely to absorb the light of the blue LEDs and promote the gold(I) complex into an excited state able to achieve the oxidative addition with the alkyne iodine.



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OC16

Thermomorphic polyethylene-supported organocatalysts for the valorization of biomass and CO_2

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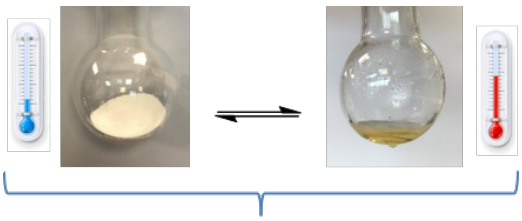
Organic cyclic carbonates are currently the subject of intense research due to their interesting applications in polymers, electrolytes, building-blocks and solvents.[1] One of the most direct ways to prepare organic cyclic carbonates is through the reaction of epoxides and CO_2, giving the desired species with 100% atom economy. A lot of catalytic systems were reported for this reaction, including homogeneous or heterogeneous, organic or organometallic species, which all have inherent advantages and drawbacks.[2]

In this context, we have developed original thermomorphic polyethylene-supported organocatalysts. The thermomorphic support allows the organocatalyst to combine the advantages of homogeneous (high catalytic activity, low loading) and heterogeneous (easy purification, recyclability) catalysis.



thermomorphic polyethylene-supported organocatalyst (ThermoPESO)

These organocatalysts were successfully applied to the preparation of carbonates from epoxides and CO_2,[3] including vegetable oil derivatives.[4] More recently, they were also used to prepare vinylene carbonates from benzoins/acyloins using diphenyl carbonate as a carbonyl source.[5] In this case, the thermomorphic catalyst was recycled over 5 runs to prepare +30 g of product showing its interest on the preparative scale.

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OC17

Unprecedented insight into the structure of fatty-acid based (nano)materials enabled by mechanochemical ^{17}O-labeling schemes

Jessica Špačková[1], Charlyn Fabra[1], Sébastien Mittelette[1], Emeline Gaillard[1], Chia-Hsin Chen[1], Ieva Goldberga[1], Guillaume Cazals[2], Aurélien Lebrun[2], Marie Hubert-Roux[3], Isabelle Schmitz-Afonso[3], Saad Sene[1], Dorothée Berthomieu[1], Kuizhi Chen[4], Zhehong Gan[4], Christel Gervais[5], Thomas-Xavier Métro[1], Danielle Laurencin[1]

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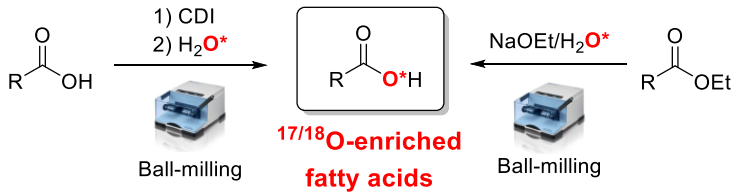
Fatty acids are omnipresent in biological systems, with applications in the fields of lipidomics and metabolomics, as well as in human nutrition research. They are also widely used in the production of materials, for example as surfactants in nanoparticles syntheses. Yet, several questions regarding their structure and reactivity remain, including their mode of binding to some metal cations or their mode of interaction at the surface of (nano)materials.

^{17}O isotopic labeling is a potentially powerful approach to access this type of information using NMR, yet, until recently,^{17}O NMR spectroscopy had not yet been used for studying complex fatty-acid systems. Indeed, previously described ^{17}O labeling protocols were not only rare and costly, but also suffered from long reaction times, experimental constraints and/or poor experimental description. As an answer to this situation, we have developed user-friendly and cost-efficient protocols for the labeling of fatty acids using mechanochemistry.[1] Here, ball milling enabled to introduce ^{17}O into fatty acids using minimal amounts of costly ^{17}O-labeled water. This labeling strategy was then used to reach unprecedented insight into the structure of ^{17}O-enriched fatty-acid based (nano)materials.[2]



✓ Low-cost (µL amounts of H_2*O)
✓ High yield & enrichment
✓ Applicable to EPA & DHA

⇨ New information on (nano)materials structure & reactivity via ^{17}O NMR

[1] Špačková, J.; Fabra, C.; Cazals, G.; Hubert-Roux, M.; Schmitz-Afonso, I.; Goldberga, I.; Berthomieu, D.; Lebrun, A.; Métro, T.-X.; Laurencin, D. Cost-efficient and user-friendly ^{17}O/^{18}O labeling procedures of fatty acids using mechanochemistry. *Chem. Commun.* **2021**, *57*, 6812-6815, 10.1039/d1cc02165f.

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OC18

Investigation of new organic photosensitizing platforms for selective photodynamic therapy

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Photodynamic therapy (PDT) is a medical treatment using the light in combination with a photosensitizer (PS) and molecular oxygen ($^3O_2$) against cancers and microbial infections.[1,2] The therapeutic effects of PDT derive from the absorption of light by the PS, which, reacting with $^3O_2$, produces singlet oxygen ($^1O_2$) and other reactive oxygen species (ROS) causing cell death, vessel damage and an inflammatory and immune response.[1],[2] Nowadays, although its minimal systematic invasiveness and toxicity, PDT is used as complementary to other established therapeutic solutions, such as radiotherapy, chemotherapy or surgery.[3]As part of the laboratory's interest in developing new dyes for biological, material and medical applications,[4] we propose the development of new photosensitizing platforms 1) synthetically versatile, 2) toxic only in response to specific intracellular stimuli or to targeted biomolecules and 3) able to absorb simultaneously two photons.[5] Previous investigations on the use of the pyrrolyldipyrrin scaffold for breast cancer-targeted PDT[6] will be presented as well as the current research on new difluoroboron-based fluorophores as potential organic PS.

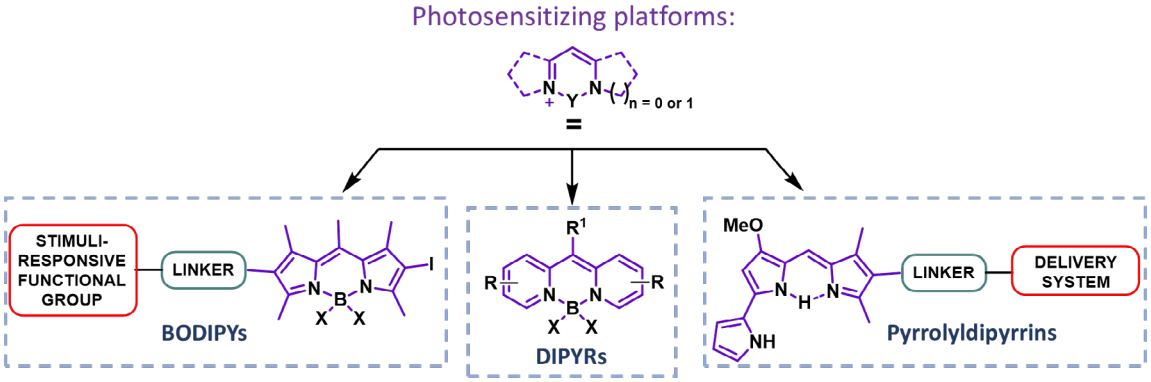

Figure 1. Selected platforms for the development of PS for targeted PDT.

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OC19

Control of supramolecular architecture by structural variation of self-assembling cyclodextrins

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Gene therapy is a crucial scientific field we must further develop, and the Covid-19 crisis only confirms it. Viruses are known to be highly effective genetic material vectors. Among them, the *tobacco mosaic virus* (TMV) whose coat proteins can self-assemble in a cooperative hierarchical co-assembly with RNA, inspired our group to design a synthetic artificial virus based on cyclodextrins (CD).

We synthesized adamantyl-functionalized CD 1 and demonstrated its ability to self-assemble into a supramolecular polymer. We then showed that CD 1 could induce transfection of nucleic acids (NA).[1] To understand its mode of assembly we studied the CD 1/DNA mixture by CryoEM. To our surprise and delight, we found that very long thin fibers were formed. We further proved that they contain many copies of double stranded DNA 18-mer, which are surrounded by self-assembled CD 1 a structure highly reminiscent of TMV.

Amazingly, a slight change of structure of CD 1 into CD 2, where the adamantyl group is positioned in the center of the cavity induces a drastic modification of the assembly: tubes were obtained instead of fibers. (Fig 1) Now, we are studying this system and other CD variations with mRNA/DNA in terms of shape and size to optimize transfection of mRNA.

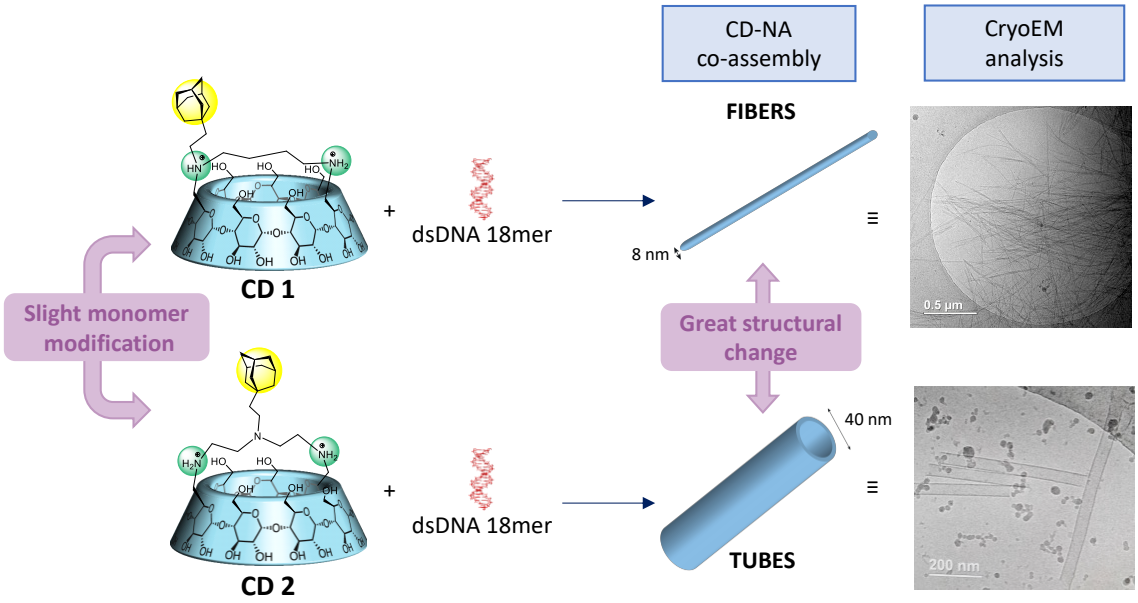

Fig 1 : Control of the hierarchical co-assembly architecture built from different CD and double stranded DNA 18-mer

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OC20

In-cell synthesis of cytotoxic phenanthridine through bioorthogonal cyclization: the "Cycl'in-Cell" strategy

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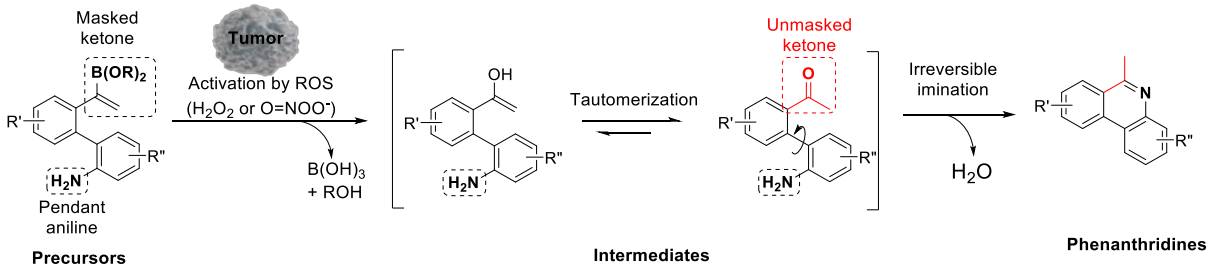
Pharmacological inactivation of antitumor drugs toward healthy cells is a critical factor in prodrug development. Typically, pharmaceutical chemists graft temporary moieties to existing antitumor drugs to reduce their pharmacological activity as much as possible.[1,2,3] Here, we report a platform where the structure of the prodrug excludes the preexisting antitumor drug motif and is based on an inactive synthetic precursor able to generate the cytotoxic agent by bioorthogonal cyclization within a tumor environment. Using phenanthridines as cytotoxic model compounds, we designed ring-opened biaryl precursors that generated the phenanthridines through bioorthogonal irreversible imination. This reaction was triggered by reactive oxygen species, commonly overproduced in cancer cells,[4] able to convert a vinyl boronate ester function into a ketone that subsequently reacted with a pendant aniline. An inactive precursor was shown to engender a cytotoxic phenanthridine against KB cancer cells. Moreover, the kinetic of cyclization of this prodrug was extremely rapid (< 10 ms) inside living cells of KB cancer spheroids so as to circumvent drug action.[5] The synthesis and in cellulo results of the phenanthridines and precursors will be described in this presentation.



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OC21

Revisiting N_2 Functionalization with Nucleophiles

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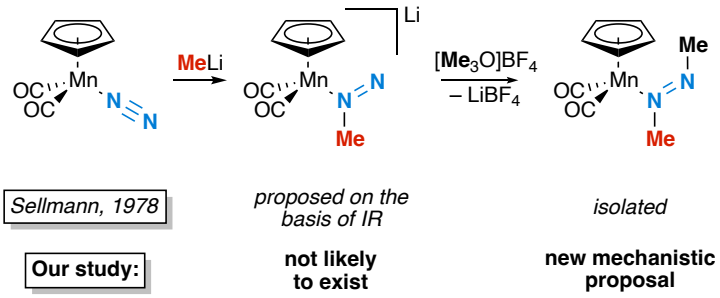
Coordination to a transition metal is the way elected by Nature to achieve the transformation of the abundant but inert N_2 molecule: within the active site of the nitrogenases, an FeS cluster binds N_2 and allows its reduction to NH_3.[1] Inspired by the nitrogenase, chemists have been able to activate N_2 within coordination complexes, eventually achieving catalytic reduction of N_2 to NH_3 under ambient conditions.[2] N_2-complexes have also shown reactivity going beyond NH_3 synthesis, with the production of N-containing organic molecules (amines, nitriles, N-heterocycles) from N_2 through its activation to a metallic center.[3] In these transformations, the N–C bond is almost exclusively built by the reaction of coordinated N_2 with a C-electrophile. Yet, a unique example of functionalization by a C-nucleophile (an organolithium reagent) has been proposed, involving the complex $[CpMn(N_2)(CO)_2]$,[4] leading to N_2-derived azo compounds. Intrigued by this peculiar reactivity, we have carried out a mechanistic study combining experiment and DFT. We have devised a previously undetected intermediate that seems crucial for obtaining an N-containing compound. Besides, our data suggest that the direct attack of the C-nucleophile (RLi) on coordinated N_2, initially proposed as a key step for N_2 functionalization,[4] is not likely to take place.[5]



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OC22
Directed Palladium Catalyzed C-H (Ethoxycarbonyl)difluoromethylthiolation Reaction

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Over the years, fluorine-containing compounds have become essential in pharmaceuticals, agrochemicals and material sciences.[1] Due to the remarkable properties of the fluorine atom or fluorinated groups, their incorporation onto molecules will modulate their physico-chemical and biological properties, resulting in promising applications for new drug discovery for instance.[2] In the past decade, particular attention was given to new sulfur-containing fluorinated groups for their unique features, such as an interesting lipophilicity and a strong withdrawing character.[3a,b] More recently, a strong interest has been shown on original fluoroalkylthiolated groups SCF_2FG (FG = functional group).[3b-g] Although transition metal catalyzed direct C–H bond functionalization appeared to be a powerful tool for C-C, C-N or C-O bond formation,[4] the direct formation of a C(sp^2)-SRf bond remains a challenging transformation. In this context, key players in the field have already developed methodologies for trifluoromethylthiolation and more recently difluoromethylthiolation of various classes of compounds.[5] In this context, an original method for the direct regioselective C-H (ethoxycarbonyl)difluoromethylthiolation of 2-phenylpyridine and 2-vinylpyridine derivatives has been developed in our group.[6]

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OC23

Taming the reactivity of Phosphiranium ions : Recent progress in the development of selective C-centered ring-openings

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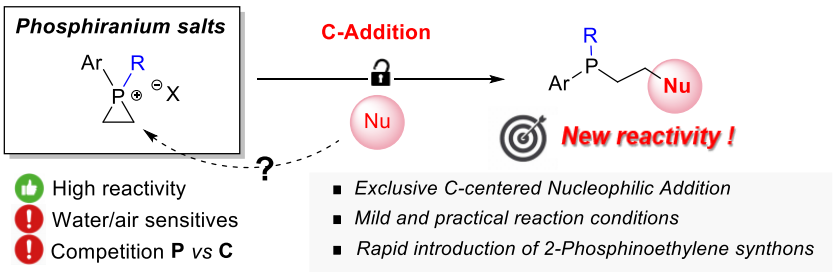
Despite the prominence of phosphorus chemistry in modern science, phosphiranium salts remain elusive species although these strained rings constitute interesting building blocks with high synthetic potential for the direct incorporation of phosphino ethylene units in molecules. For long, these strained cyclic cationic species were only occasionally postulated as transient intermediates[1] and even today, only a limited number of isolated and fully characterized phosphiranium salts is described.[2] Their ring-opening has not been studied further with only a few examples of nucleophilic attack occurring exclusively on phosphorus.[3]

Herein, we report our recent efforts to unveil the chemistry of these species, ranging from the preparation of new phosphiranium salts displaying an extended spectrum of reactivity to the development of unprecedented C-centered ring openings with nucleophiles.[4]



Acknowledgements: We gratefully acknowledge financial supports from the French National Research Agency (**ANR-19-CE07-0047-01**), the Region Normandie and the University Le Havre Normandie.

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OC24

Total Synthesis of Ophiorrhine A, G and Ophiorrhiside E Featuring a Bioinspired Intramolecular Diels–Alder Cycloaddition

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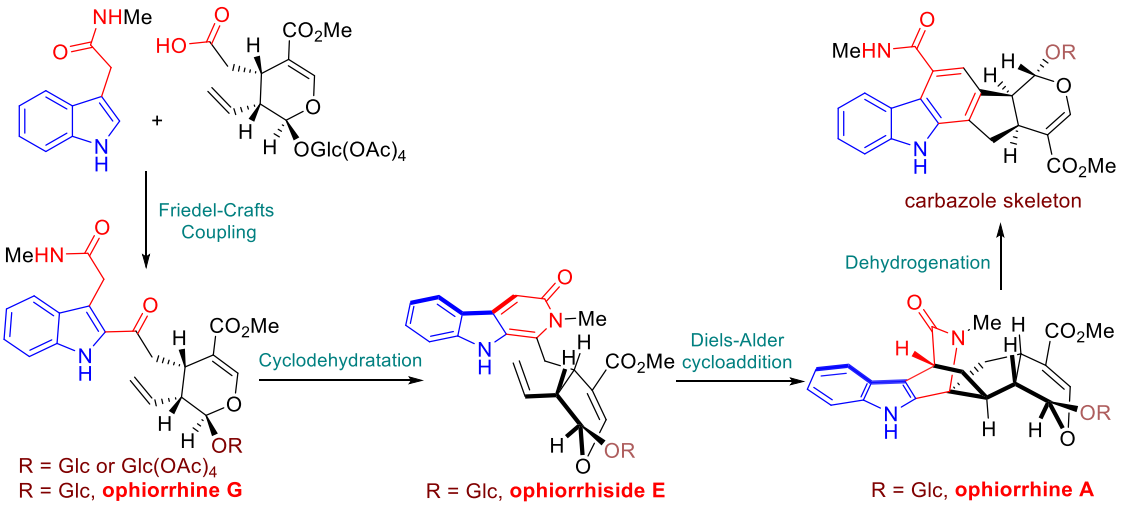
Monoterpene indole alkaloids (MIAs) are an important family of natural products due to their structural diversity and prominent pharmacological activities. [1] Ophiorrhine A, [2] G [3] and Ophiorrhiside E [4] are monoterpene indole alkaloids which were isolated from the plant Ophiorrhiza japonica and trichocarpon. Ophiorrhine A displays an intriguing complex spirocyclic moiety and exhibits significant inhibition specifically against the LPS-induced proliferation of B lymphocyte cells with IC_{50} value 18.6 µM. [2]

We achieved the first total synthesis of ophiorrhine A, G and ophiorrhiside E. Several strategies were investigated to construct the indolopyridone moiety of ophiorrhiside E, the postulated biosynthetic precursor of ophiorrhine A. Eventually, the Friedel-Crafts-type coupling of indolyl-acetamide with secologanin-derived acid chloride delivered ophiorrhine G. Cyclodehydratation of a protected form of the latter was followed by the desired spontaneous intramolecular Diels-Alder cycloaddition of protected ophiorrhiside E leading to ophiorrhine A, which cloud transfer to an undiscovered natural product candidate carbazole skeleton. [5]



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OC25

Transition-metal-free multi-component difunctionalization of [1.1.1]propellane

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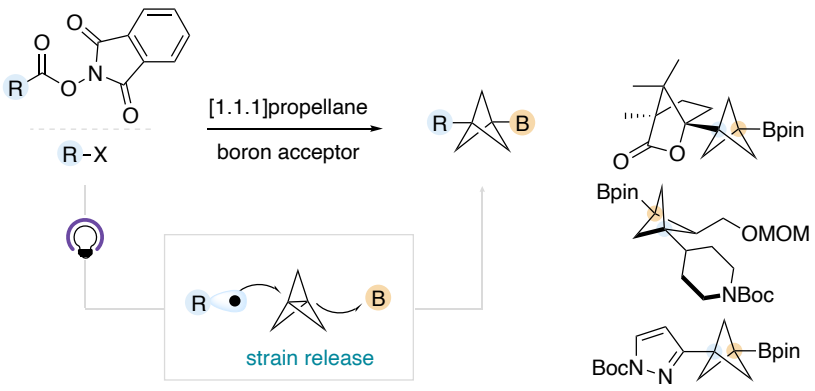
Strained bicyclic substructures are increasingly relevant in medicinal chemistry discovery research because of their role as bioisosteres.[1] Over the last decade, the successful use of bicyclo[1.1.1]pentane (BCP) as a para-disubstituted benzene replacement has made it a highly valuable pharmacophore.[2] However, various challenges, including limited and lengthy access to useful BCP building blocks, are hampering early discovery research. We reported a single-step transition-metal-free multi-component approach to synthetically versatile BCP boronates.[3] Radicals derived from commonly available carboxylic acids and organohalides perform additions onto [1.1.1]propellane to afford BCP radicals, which then engage in polarity-matched borylation. A wide array of alkyl-, aryl- and alkenyl-functionalized BCP boronates were easily prepared. Late-stage functionalization performed on natural products and approved drugs proceeded with good efficiency to generate the corresponding BCP conjugates. By taking advantage of BCP trifluoroborate salts derived from the BCP boronates, we were able to perform various photoredox transformations forging C–C and C–N bonds.



□ *Unexpensive and abundant feedstocks* □ *Versatile* □ *Broad scope*

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OC26

Photoredox generation of isothiouronyl radical cations: A new platform in covalent radical catalysis

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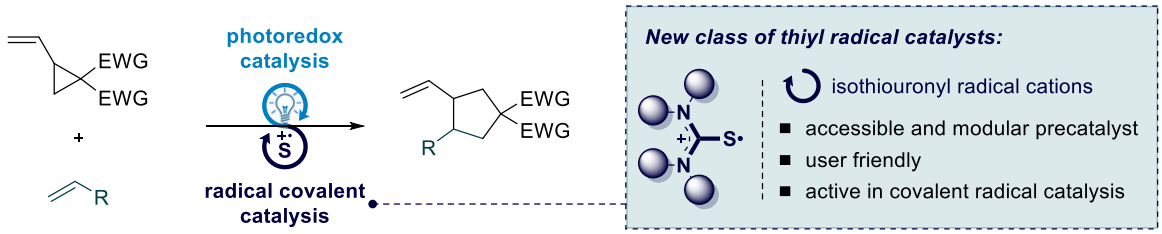

Scheme 1 Isothiouronyl radical cation: A photoredox-generated radical covalent catalyst for vinyl cyclopropanes (3+2) cyclization cascade with olefins

Thiyl radicals are well-known for their ability to reversibly add onto C-C multiple bonds.[1] This reactivity has been used to trigger radical cascades in the field of covalent radical organocatalysis.[2] Although this was first demonstrated more than 30 years ago by independent works of Oshima[3] and Feldman,[4] radical covalent catalysis has known a confidential development in comparison to other fields of organocatalysis. Indeed, the use of neutral thiyl radicals to catalyze radical cascade from alkenes conveys several practical issues for organic chemists, including their generation *in situ* under harsh conditions from malodorous thiols or disulfides, a fast deactivation by dimerization and a low structural diversity leading to arduous modulation of their reactivity. In this context, our group has recently investigated new strategies to perform thiyl-based radical covalent catalysis under simple, practical, and efficient conditions. We thus designed a double catalytic system involving the photoredox-catalyzed generation of isothiouronyl radical cations directly from readily accessible thioureas.[5] Mechanistic investigations have revealed the key formation of dicationic dimer. The original catalytic system was finally applied to a formal (3+2) radical cycloaddition between various vinyl cyclopropanes and alkenes.

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OC27

Late-stage functionalization of a fluorescent scaffold to afford a new generation of large Stokes shift red-emitting dyes with promising properties for biological imaging

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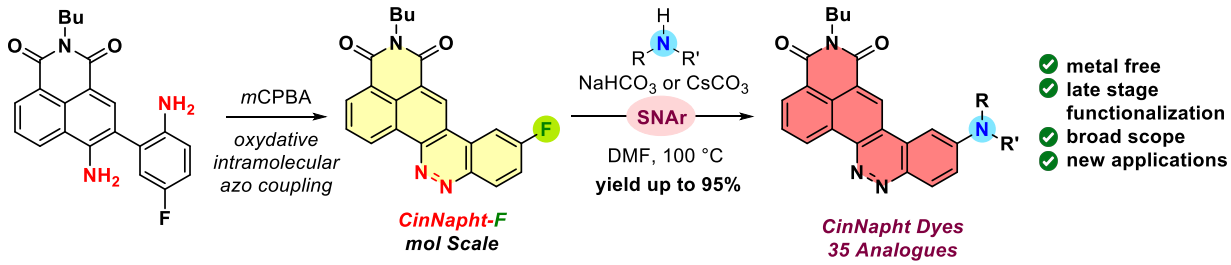
With the increasing interest of optical molecular imaging in medicine, fluorescence microscopy has seen constant development contributing to the emergence of new technologies and probes without discontinuity for the past decades. Fluorogenic probes are now considered as critical tools for the study of biological environments.[1] Therefore, there is definite interest in creating a new easily tunable chemical scaffold exhibiting fluorescent behavior that could later be used for the design of such probes. In this context, our group has investigated the synthesis of a fused ring cinnoline/naphthalimide hybrid here called "CinNapht" dyes.[2] The first generation of these new fluorophores exhibits original and promising properties in conventional fluorescence: a red emission, a large Stoke Shift, a strong solvatochromism, high chemo- and photostability and biocompatibility.[3] Here we present a an easy access to numerous analogues of CinNapht dyes by late-stage functionalization and a study of their photophysical properties. We have re-designed the synthesis via a fluorinated CinNapht-F intermediate that can react with a wide variety of amines in a SNAr type reaction. The reaction conditions and its scope have been investigated. We have now an easy access to new fluorophores with improved photophysical properties associated with a true utility for cell imaging applications such as organelle imaging.



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OC28

Transition-Metal-Free Silylation of Unactivated C(sp²)–H Bonds with *tert*-Butyl-Substituted Silyldiazenes

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Aromatic organosilanes bearing C(sp²)–Si bonds have found increasing applications across the chemical science and have traditionally been synthesized from the corresponding arylhalides (bromide or iodide). The direct intermolecular silylation of C(sp²)–H bonds represents an atom-economical alternative as it bypasses the substrate pre-functionalization step, yet poses significant reactivity and selectivity challenges. In this respect, the most common strategy still relies on stoichiometric C–H metalation/silylation sequences mediated by organolithium (RLi) or Grignard reagents (RMgX), which nonetheless generate large amount of metallic wastes and display limited scope of application.

Catalytic protocols, mostly using hydrosilanes (R_3SiH) as silicon sources, have also been described,[1] but they display unfavorable thermodynamics and are typically based on expensive catalytic systems, often derived from noble metals, or lack generality.[2] In this communication, we will introduce the use of an alternative silicon source, namely the *tert*-butyl-substituted silyldiazenes (*t*Bu–N=N–SiR_3), that are readily accessible from commercially available precursors and structure of which enables the C(sp²)–H bond silylation of unactivated heteroaryl and aryl compounds under ambient, transition-metal-free catalytic conditions.[3] Conceptual implications as well as mechanistic considerations will be discussed along with the synthetic potential of this new methodology.

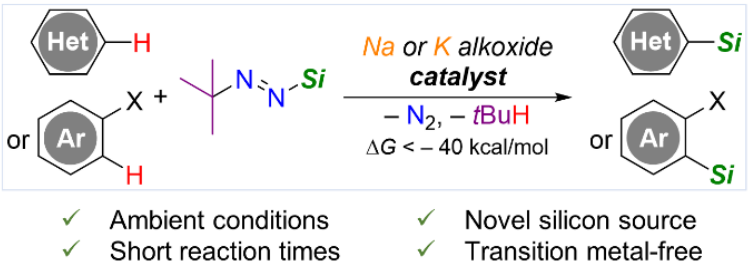

Figure 2: Silylation of unactivated C(sp²)–H Bonds with tert-butyl-substituted silyldiazenes catalyzed by potassium or sodium alkoxides.

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OC29

Simplified Green-emitting Single-Layer Phosphorescent Organic light-emitting diodes with an external quantum efficiency > 22%

Fabien Lucas[1], Clément Brouillac[2], Sadiara Fall[3], Nicolas Zimmerman[3], Denis Tondelier[1], Bernard Geffroy[1,4], Nicolas Leclerc[5], Thomas Heiser[3], Christophe Lebreton[6], Emmanuel Jacques[6], Cassandre Quinton[2], Joëlle Rault-Berthelot[2], Cyril Poriel[2]

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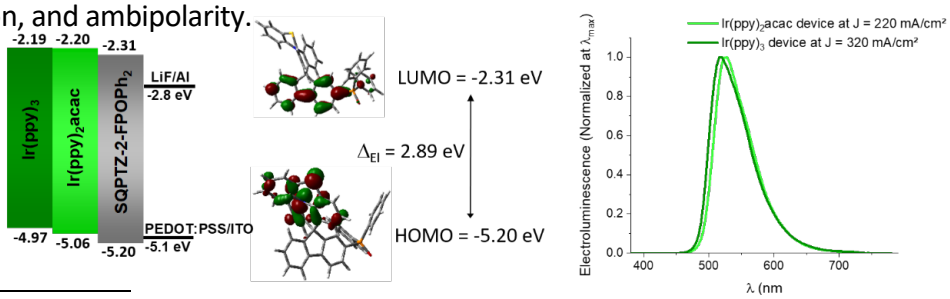
The development of new π-conjugated systems has led to the emergence of new devices such as organic light-emitting diodes (OLEDs), which are the cornerstone of next-generation display screens. In these display screens, pixels fabricated from phosphorescent OLEDs (PhOLEDs)[1] are multilayer architectures composed of injection, transport, blocking and emissive layers (EML). In order to develop a more virtuous technology (more sustainable and less expensive), simplification of the devices architecture is mandatory. The ideal devices are the single-layer PhOLEDs (SL-PhOLEDs), with a very simple stack only constituted of the electrodes and the EML. These devices can hence significantly decrease their environmental footprint and cost. Nevertheless, removing the functional layers of an OLED drastically decreases the performances and there is, so far, only a few examples of high-performance SL-PhOLEDs.[2,3,4] Thus, in SL-PhOLEDs, the role of the functional layer should be performed by the EML and more precisely by the organic semi-conductor (OSC), which should allow an excellent injection/transport/recombination of charges. In this work, thanks to a rational design of the OSC, we report a green-emitting SL-PhOLED, displaying a very high external quantum efficiency of 22.7%. This performance is, to the best of our knowledge, the highest reported for SL-PhOLEDs (all colours considered). The EML of this device is constructed on the barely studied $Ir(ppy)_2acac$ phosphor and a high efficiency host material possessing a Donor-spiro-Acceptor design obtained through a quick and efficient synthesis route. Through a structure/property/device performance relationship study combining morphological (AFM), photophysical (time-resolved spectroscopy) and charge transport studies, we show that the EML presents all the required characteristics such as smooth surface, quick radiative deactivation, and ambipolarity.



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OC30

Hydrogen Isotope Exchange via in-situ generated catalytic rhodium nanoparticles

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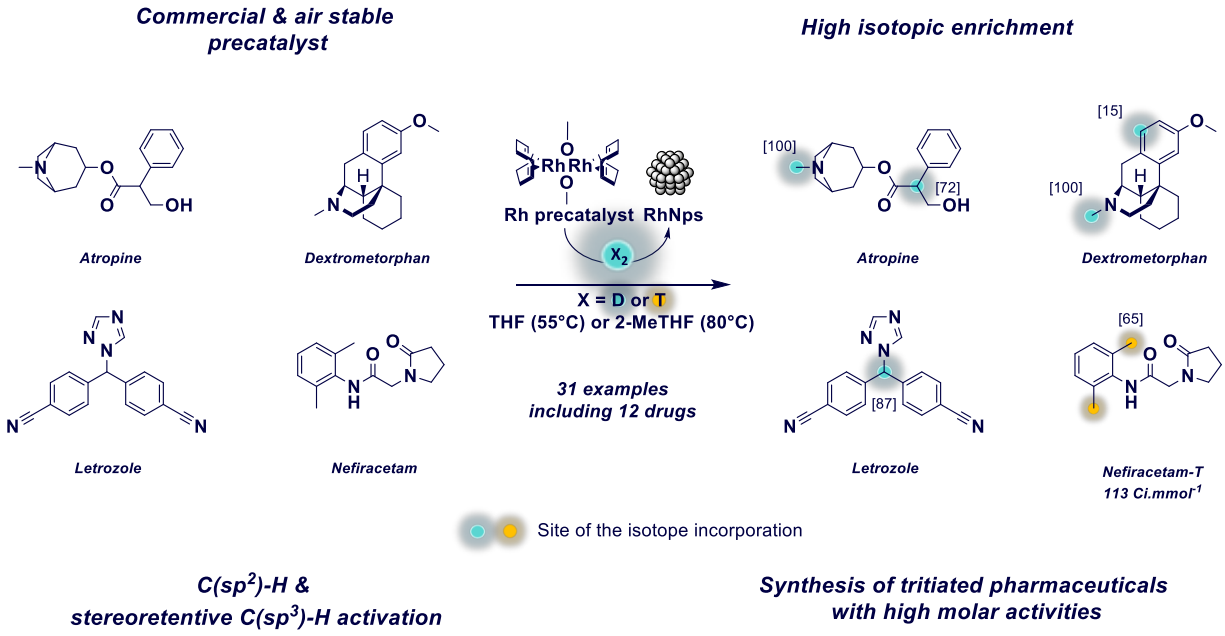
The growing demand for deuterated and tritiated compounds in numerous applications (ADME studies, Imaging, Omics, Materials for instance) implies the development of more efficient, and broadly applicable synthetic methodologies.[1] In this context, we describe an easy-to-implement method for the late-stage labeling of complex pharmaceuticals by generating the catalytic nanoparticles directly in the reaction media from a commercial precursor and using the substrate itself as a stabilizing agent.[2]



This method was applied to single-step late stage deuteration/tritiation of various pharmaceuticals containing *N*-heterocycles, amines and benzylic scaffolds. This strategy affords high deuterium atoms incorporation and very high molar activities in the context of tritium labeling. The morphology and size of the particles were investigated using TEM experiments establishing no particular correlation between the size of the particles generated and the substrate of the reaction. Finally, recycling experiments were conducted to demonstrate the potency and robustness of the catalytic system and process.

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OC31

Design of protein-based platforms for sugars multivalency

Marie Schuler[1], Josip Tomas[1], Léa Latour[1], Giuliano Cutolo[1], Pierre Buisson[1], Ludovic Landemarre[2], Chrystel Lopin-Bon[1], Pierre Lafite[1], Arnaud Tatibouët[1]

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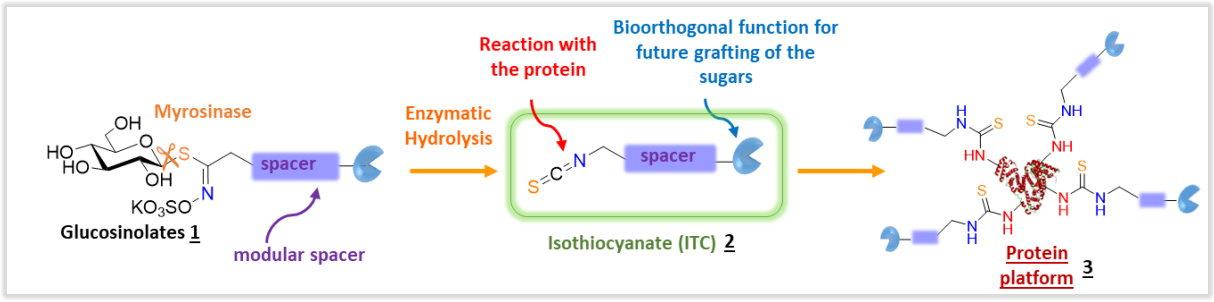
Multivalency, widely observed in Nature in glycan-proteins recognition, counterbalances the rather weak association constants of carbohydrate ligands with their receptors (lectins for example). This effect has been explored by chemists to design and synthesize novel efficient carbohydrate-based ligands, as it 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.[1]

The central platform, from which multiple carbohydrate elements are displayed, influences the size and the shape of the multivalent ligand. Proteins, which have the advantages of being water-soluble, are commonly used as carriers for the multivalent presentation of glycans with valencies around 15 to 20. The resulting (semi)synthetic ligands are called neoglycoproteins with respect to naturally occurring glycoproteins and have been used for many years as probes for carbohydrate-proteins interactions.[2] We have recently developed a safe and biocompatible isothiocyanate-based conjugation process that relies on the *in situ* enzymatic generation of a reactive isothiocyanate species **2** after hydrolysis of stable water-soluble synthetic glucosinolates precursors **1** with myrosinase, a highly specific β-thioglucoside hydrolase.[3] We would like to present here our recent results around the chemical modification of native proteins using this enzymatically triggered bioconjugation process.



Those modified proteins will then serve as scaffolds to anchor well-defined monosaccharides or synthetic oligosaccharides fragments to build high valency neoglycoproteins[4] with a specific macromolecular architecture.

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OC32

Fluorine-Activated Additive-Free Vitrimers

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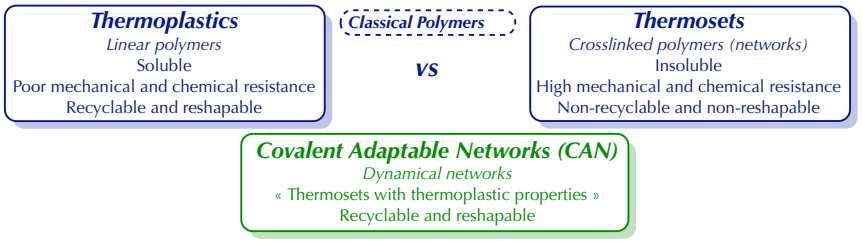
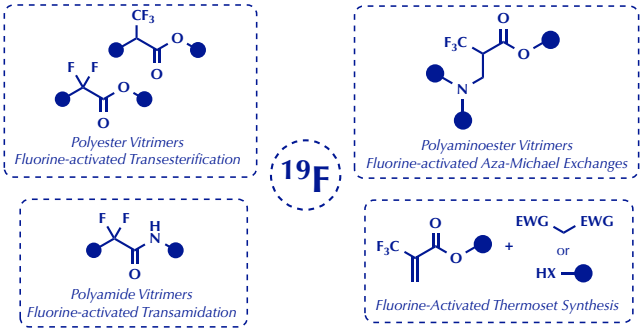
For almost two decades, the frontier between the two traditional categories of polymers, namely thermoplastics and thermosets, has been blurred by the development of vitrimers, a particular class of covalent adaptable networks (CANs).[1] This new breed of organic materials indeed gathers the mechanical 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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OC33

A Bis-Acridinium Macrocycle as Multi-Responsive Receptor and component of a Switchable [2]rotaxane

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The acridinium core is a building block with a great potential in supramolecular chemistry. Indeed, it is an electron-deficient polyaromatic unit (presence of a positive charge) able to interact with electron rich polyaromatic guests through π-donor/π-acceptor interactions.[1-2] In addition, acridinium units have chemiochromic, electrochromic and photochromic properties.[3-4-5] Despite this unique multi-responsive behavior, the acridinium core was not intensively used in supramolecular chemistry and was barely incorporated in MIMs.

A bis-acridinium cyclophane incorporating switchable acridinium moieties with a 3,5-dipyridylanisole spacer was successfully synthesized (**Figure 1**)[6] and was studied as a multi-responsive host for polycyclic aromatic hydrocarbon guests. Moreover, the dicationic host was also easily switched between organic and perfluorocarbon phases for applications related to the enrichment of perylene from a mixture of polycyclic aromatic hydrocarbons. It was also incorporated in a [2]rotaxane responsive to orthogonal stimuli (chemical and redox) leading to two distinct mechanical responses.

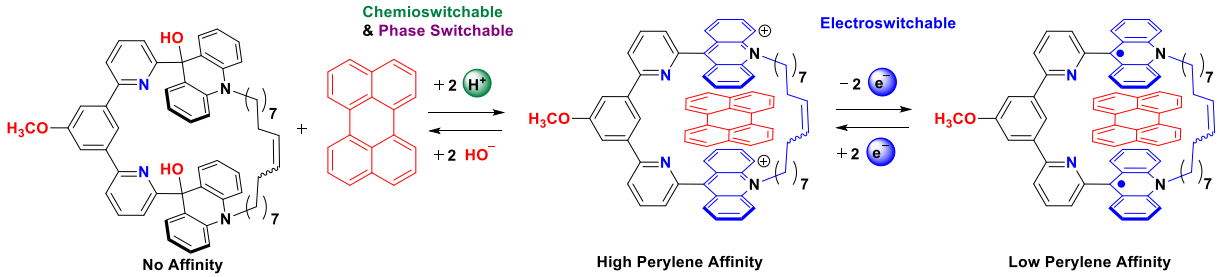

Figure 1 - Chemiochromic and electrochromic properties of the bis-acridinium macrocycle

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OC34

A Gallium-Catalyzed C–H Propargylation of Arenes

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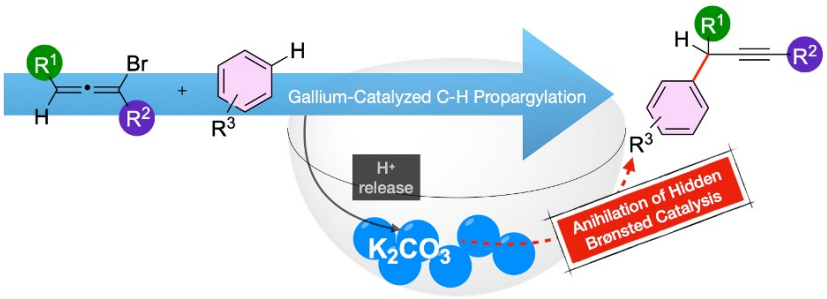
Organic synthesis greatly relies on catalytic processes, a large part of which involving Lewis acids. This covers a wide range of transformations, including industrially relevant ones such as aldol, Friedel-Crafts, Mannich, coupling reactions, etc. The field of Lewis-acid catalyzed homogeneous transformations is still a thriving area of research in which progress is frequently reported.

The C–H propargylation of arenes is a reaction of great interest, allowing the direct introduction of an easily transformable alkyne moiety through the formation of a Csp^2–Csp^3 bond.[1] In contrast with C–H allylations, which have been reported under various transition metal-catalyzed conditions and others,[2] the C–H propargylation of arenes has been much less studied. In most cases, the coupling partner is a propargylic alcohol, or an alkyne exhibiting a leaving group at the propargylic position but avoiding the S_N2' process leading to an allene[3] instead of the alkyne has been rarely achieved.[4] Interestingly, Glorius and co-workers have recently shown that bromoallenes could be used for the direct C–H propargylation of arenes under manganese(I)/Lewis acid co-catalysis.[5] While efficient, this method is limited to 2-pyridylindoles and 2-pyridylpyrroles as arene partners.

To shed light on the mechanism of this C–H propargylation process, several experiments were performed. Herein, we disclose our findings regarding the in-depth study on this reaction[6] based on a kinetic study, as well as its applicability to a wide range of substrates in a very efficient way. The unexpected compatibility of K_2CO_3 with $GaCl_3$ represents a great opportunity to develop new and truly gallium-catalyzed transformations.



selective C-H propargylation with Gallium
valuable allenes, chemoselective
detailed mechanisitic studies: kinetics, computations

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OC35

Reassessment of the reducing power of Breslow-type derivatives in NHC-catalyzed reactions

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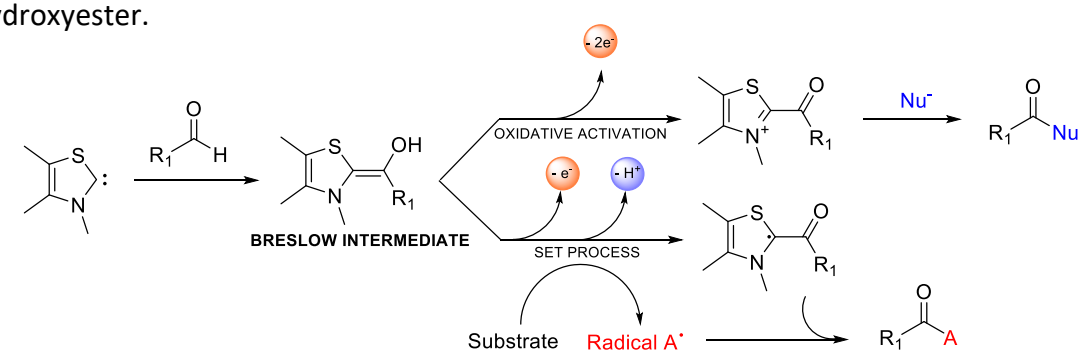
Thiamine is a necessary cofactor in the acetylation mechanism of coenzyme A, a key component in the citric acid cycle. In the late 1950s, Breslow[1] postulated that the deprotonation of thiamine led to the formation of a stabilised carbene: a thiazolylidene. Since then, interest in *N*-heterocyclic carbenes (NHC) in organocatalysis[2] has grown steadily. NHC allow the formation of functionalized ketones from aldehydes through the formation of enaminols, so called Breslow intermediates. Oxidative reactions using a two-electron pathway is one of the most popular transformations. Reactions through radical pathways *via* single electron transfer (SET) has emerged based on Studer's[3] work and followed by Rovis[4] and Chi[5] with enantioselective radical reactions catalysed by NHC, such as transformations of enals into *β*-hydroxyester.



For these reactions, it is known that the key step in the catalytic cycle is not a SET from Breslow intermediate to a mild one-electron oxidant but *via* its deprotonated form[6]. We show that mechanistic assumptions, which were previously considered to be well established, are in fact biased[7] based on our results concerning the understanding of the electrochemical processes involved.

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OC36

Cascade [3,3]-sigmatropic rearrangements involving (cyclopropyl)vinyl azides: Synthesis of highly substituted seven-membered rings

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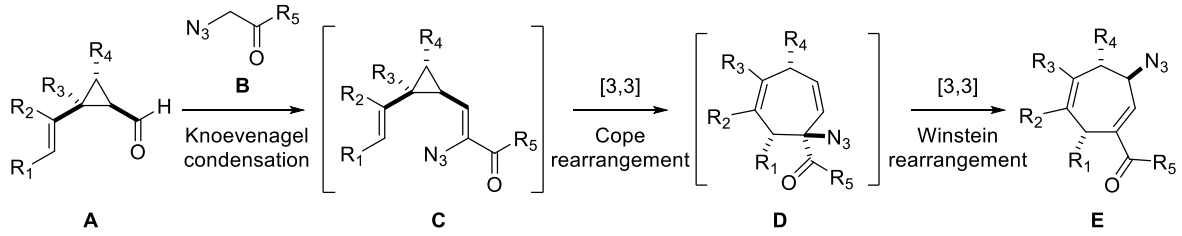
Azides are useful compounds in organic synthesis which can be used as amine precursors or be involved in bioorthogonal ligation reactions.[1] Despite the potential hazards associated with the use of such compounds, vinyl azides have recently emerged as a particularly valuable class of hetero-substituted alkenes owing to their versatile reactivity.[2] To date, to the best of our knowledge, sigmatropic rearrangements constitute one class in which vinyl azides have not been involved, despite their synthetic potential to access other classes of functionalized aliphatic azides.[3]

Herein, we present our results on the development of cascade [3,3]-sigmatropic rearrangements involving (cyclopropyl)vinyl azides. Diversely substituted 2-vinyl-cyclopropanecarbaldehydes **A** were involved in a Knoevenagel condensation with α-azido ketones **B**.[4] The resulting *cis*-dialkenylcyclopropanes **C** evolve by a Cope rearrangement which is followed by an allylic transposition of the tertiary azides **D**, known as the Winstein rearrangement,[5] leading to the azido-cycloheptadienes **E**, incorporating up to three stereocenters.



Post-functionalization reactions of the azido-cycloheptadienes **E** allow access to highly substituted seven-membered rings which are less encountered than five- and six-membered carbocycles in drugs[6] but are currently eliciting a growing interest in medicinal chemistry.[7]

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OC37

Chemoenzymatic synthesis of DNA & XNA oligonucleotides

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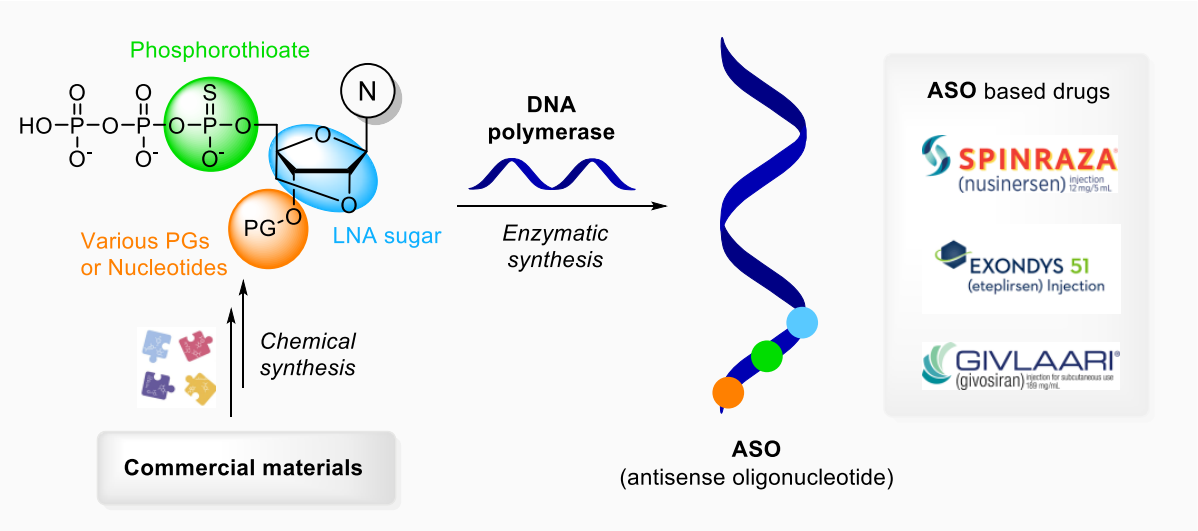
Recent advances of mRNA-based vaccines[1] and FDA-approval of various antisense oligonucleotides (ASO)[2] clearly demonstrates the importance of therapeutic oligonucleotides. There is a high and steadily increasing demand for the synthesis of chemically modified oligonucleotides. Antisense oligonucleotides (ASO) as an efficient therapeutics require the introduction of different chemical modifications in order to improve their biological stability, pharmacokinetic properties and drug delivery efficiency. In this context, sugar (locked nucleic acids, LNA) and phosphate backbone (phosphorothioate) are the most favored sites for the modifications. Controlled chemoenzymatic synthesis of DNA and XNA (xeno nucleic acid) is a highly emerging alternative that circumvents the limitations of traditional solid-phase synthesis.

Scheme



Herein, we report the chemical synthesis of variously modified nucleoside triphosphates (dN*TPs) containing phosphorothioate (PS),[3] locked sugar (LNA),[3] 3'-protecting groups (phosphate, Bz, Piv, Mesitoyl, Piv, allyl, Me, CH_2N_3)[4,5] as well as 3'-prolonged trinucleotides. Thereafter, we tested these dN*TPs as substrates for the controlled enzymatic synthesis of DNA and XNA oligonucleotides using TdT and PEX reactions with diverse DNA polymerases. As a result, moderate to high levels of incorporations into DNA and XNA were achieved.

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OC38

Simultaneous Control of Central and Helical Stereogenic Elements on Small Molecules

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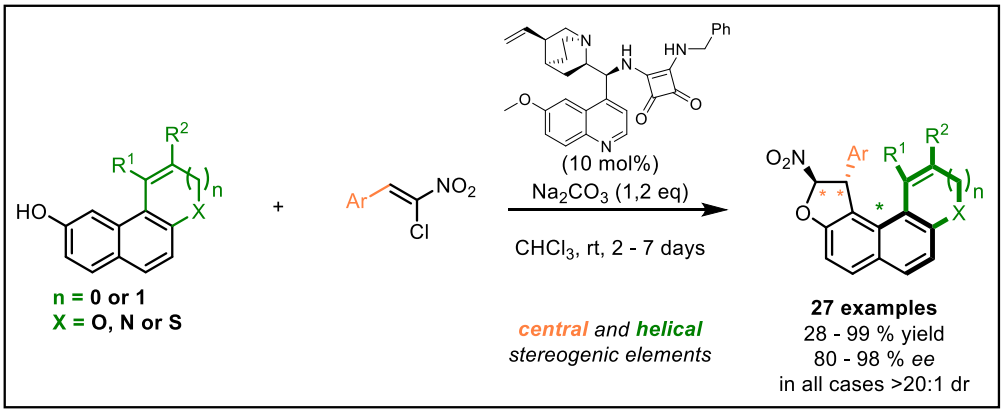
Small molecules featuring different types of stereogenic elements are very challenging synthetic targets, especially when displaying configurationally labile helical chirality. Previously, we developed a method to access enantiomerically enriched atropoisomers[1] and dioxa[6]helicenes[2] via centrally chiral dihydrofurans formation. Herein, based on these works, we propose an enantioselective organocatalytic approach for the synthesis of small molecules bearing both central and helical stereogenic elements, starting from achiral substrates. Products were obtained with excellent enantioselectivity in most cases with simultaneous control of the helicity and two stereogenic centers. Such obtained products could handle post-functionalization with good retention of enantiopurity.



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OC39

Photoswitchable GlycoMacrocycles, from synthesis to their chiroptical properties and potential applications

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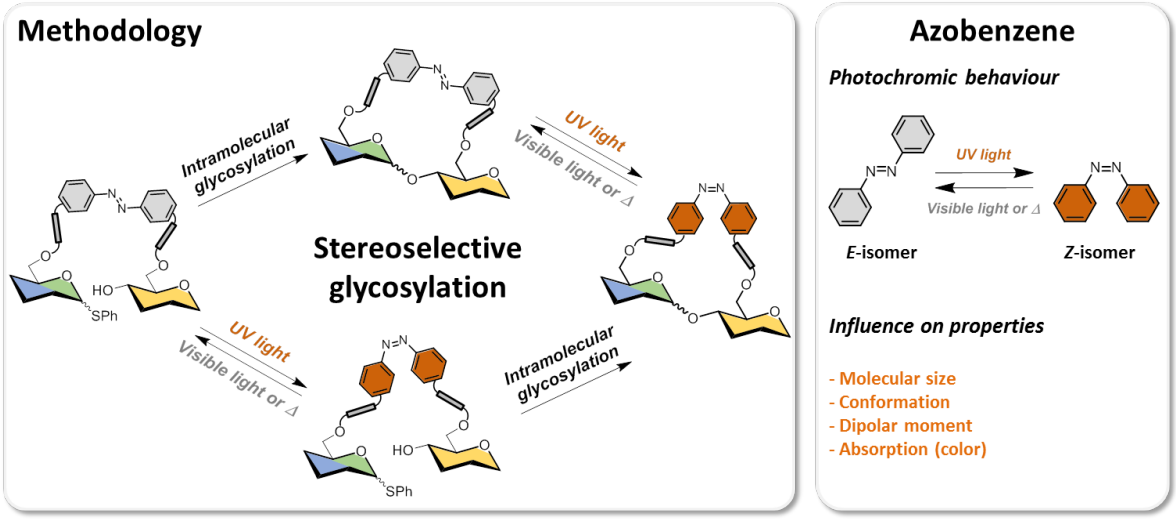
Photochromic molecules and materials attract a considerable interest in different fields because they offer great opportunities for the reversible photomodulation of chemical, biological and pharmacological activities with potential applications in various domains like optical materials, photopharmacology and photocatalysis.[1]

Since several years our group is developping new photoswitchable glycomacrocycles (P-GM) containing an azobenzene unit for the modulation of chiroptical properties through E/Z photoisomerization. Our approach is to combine in a same molecular architecture the advantages of a sugar-based macrocyclic compound to the photochromism.[2,3,4,5] These 'smart' glycomacrocycles display very interesting properties like chirality transfer and supramolecular chirality, photocontrolled molecular shape or solubility, and multistimuli-responsive gelation ability in organic solvents. Furthermore, synthesis of macrocyclic compounds is still a challenging task. For this purpose, we have also developed a methodolodgy and realized the proof of concept of using azobenzene as template to obtain glycomacroclactones *via* an intramolecular glycosylation in good yields with high stereoselectivity.

An overview of their synthesis, photochemical and chiroptical properties, as well as their application as chiral dopants in liquid crystals will be presented.



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OC40

Tracking G4 ligand distribution *in cells* by a guided immunofluorescence methodology

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Repetitive guanine-rich DNA and RNA sequences can form compact nucleic acid secondary structures known as G-quadruplexes (G4s). The large body of data acquired from bioinformatics analysis and biophysical, biochemical and cell-based assays unequivocably suggests that small synthetic molecules selective for G4 structures represent highly valuable chemical biology tools necessary to unveil G4 biological functions.[1] This is why strong effort has been focused on the design and synthesis of selective G4 ligands that can be used as G4 probes. The development of imaging techniques combined with G4 selective fluorescent tools are required to support these studies. Therefore, several imaging methods have been devised for tracking G4 ligand distribution *in cells*.[2] However, two of the most selective G4 ligands developed so far, PDS and PhenDC3, are not fluorescent or are characterized by a very low intrinsic fluorescence. Thus, several labelling approaches based on both *ex situ* and *in situ* synthesis of fluorescent-tagged G4 ligands have been proposed.[2b,3] In spite important developments, fluorescent tag functionalization did not overcome the issues associated to the spatial resolution of fluorescent microscopy; hence, signal amplification is required to allow G4 imaging with higher precision.

In this study, we proposed the development of a new visualization strategy called G4 ligand Guided Immunofluorescence Staining (G4-GIS) based both on specific recognition by small molecule and antibody signal amplification properties. By using PDC core as selective G4 ligand, we synthesized a series of immuno-tag (5-BrdU) modified PDC derivatives from PDC CuAAC precursors which selectively bind G4 structures with high affinity as confirmed by biophysical assays. *In situ* functionalization efficiency was tested *in vitro* and antibody recognition of the ligands bound to G4 structures was validated using a modified ELISA. Afterwards, both *ex situ* and *in situ* functionalized G4 ligands were incubated *in cells* and the new immunostaining method established. The latter allowed not only the comparison of G4 ligand distribution after and prior 5-BrdU functionalization, but also to point out regions of weak ligand accumulation, hardly visible by direct fluorophore functionalization, providing a new useful approach of high sensitivity for G4 ligand target detection.[4]

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OC41

Bioinspired lipidic alkynylcarbinols as anticancer agents

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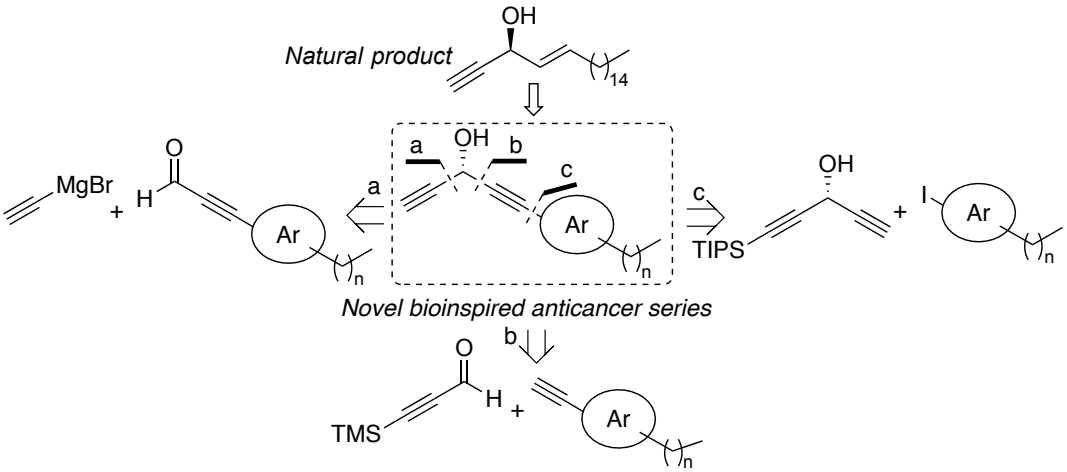
Cytotoxic natural acetylenic lipids embedding a chiral alkynyl carbinol unit at the terminal position of a linear aliphatic skeleton represent a potential source of anticancer agents.[1] We showed that chemistry-driven evolution of such lipidic alkynyl carbinols (LACs) could lead to an up to 1000-fold increase in potency for enantioenriched synthetic analogues.[2] We also recently demonstrated that cytotoxic LACs behave as prodrugs upon *in situ* enantiospecific oxidation by SDR enzymes (Short-chain Dehydrogenases/Reductases): the resulting ynones react as Michael acceptors with multiple proteins, including a proteasome subunit, thus inducing apoptosis.[3]



A new series of anticancer molecules will be described, in which the alkynylcarbinol pharmacophore is conjugated with an (hetero)aromatic ring, itself bearing the lipophilic chain.[4] In order to ensure optimal efficiency and flexibility, 3 complementary synthesis routes were studied. More than 30 synthetic analogues, as well as *in cellulo*-clickable probes, were obtained under racemic or enantioenriched form. Biological data of cytotoxicity, cell imaging and modification of cellular proteins using clickable probes show that this potent anticancer series displays the same mechanism of action as the one recently uncovered for related non-aromatic LACs,[3] thus confirming their pharmacological potential.

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OC42

Asymmetric Inverse-Electron-Demand Diels-Alder Cycloaddition between 2-Pyrones and Acyclic Enol Ethers: Gram-Scale Total Synthesis of (+)-Lucidumone

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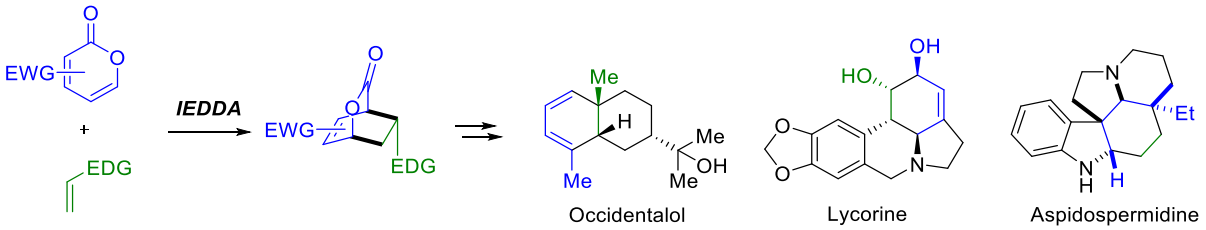
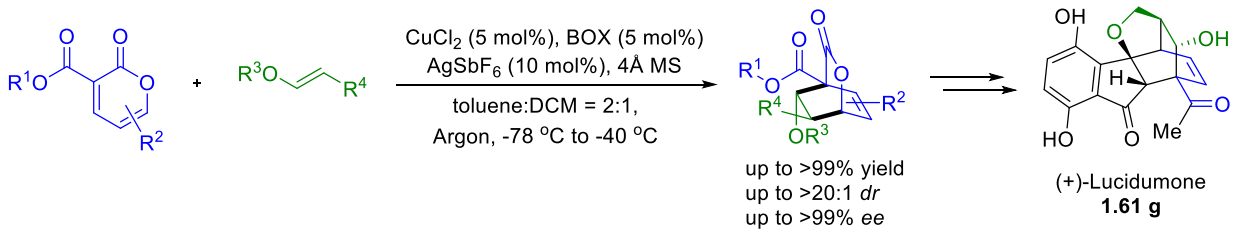
The inverse-electron-demand Diels–Alder (IEDDA) cycloaddition of electron-poor 2-pyrones as electrophilic dienes has been extensively studied in the past fifty years. The reaction provides an efficient access to bridged bicyclic lactones and their derivatives, such as densely functionalized 1,3-cyclohexadienes after CO_2 extrusion and polysubstituted aromatic compounds through elimination. Thus, the IEDDA cycloaddition has been used for the synthesis of many biologically active natural products and drug candidates.[1]



Herein we reported a broadly applicable diastereo- and enantioselective inverse-electron-demand Diels-Alder reaction of 2-pyrones and acyclic enol ethers. Using a copper(II)-BOX catalytic system, bridged bicyclic lactones are obtained in very high yields (up to 99% yield) and enantioselectivities (up to 99% ee) from diversely substituted 2-pyrones and acyclic enol ethers. Mechanistic experiments as well as DFT calculations indicate the occurrence of a stepwise mechanism. The synthetic potential of the bridged bicyclic lactones is showcased by the enantioselective total synthesis of (+)-Lucidumone on a gram scale.[2]



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OC43

Synthesis, characterizations and applications of haloazaphosphatranes

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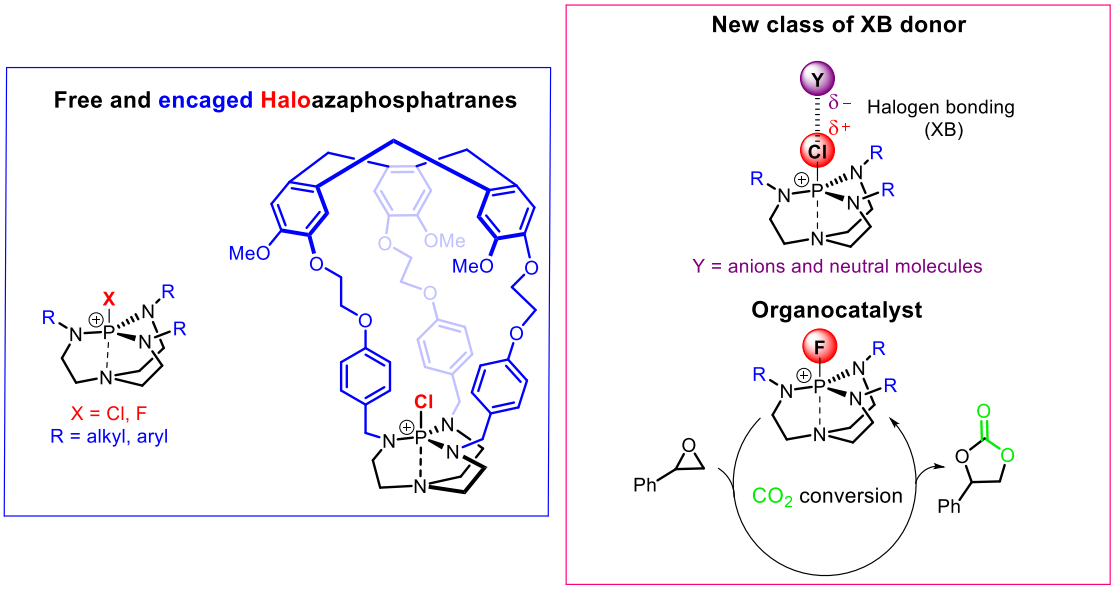
Proazaphosphatranes, also known as Verkade's superbases, are non-ionic highly basic phosphorus derivatives.[1] This class of compounds has found numerous applications from basic and nucleophilic catalysts, ligands for transition metals, to Lewis bases in frustrated Lewis pair (FLP) systems.[2] Their conjugated acids, the azaphosphatranes have been also used as organocatalysts.[3] Although their first synthesis was reported in 1989, the haloazaphosphatranes, the halogenated parents of proazaphosphatranes, were much less studied.

In this context, we successfully developed simple and convenient routes to readily access to various fluoro-, and chloroazaphosphatrane derivatives.[4] With these compounds in hand, we investigated their properties especially as a new class of halogen bond (XB) donors for anions recognitions or as catalytic systems for CO_2 conversion. So as to build more efficient and selective receptors for anion or neutral molecules, we decided to include chlororazaphosphatrane as XB donor moiety in a molecular container as the hemicryptophane.



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OC44

Intramolecular hydrosilylation of alkynes by electro-reductive nickel catalysis

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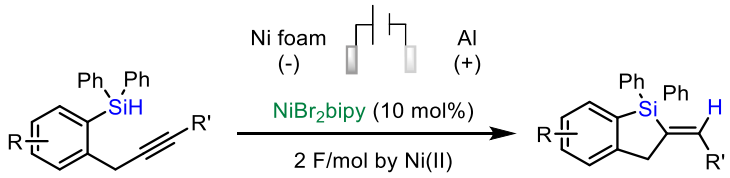
Carbon and silicon atoms have similar properties in molecules (valency, geometry…), however, the difference in the covalent radius gives organosilicon compounds distinct physical, chemical, optical, and biological properties.[1] For example, organosilicon compounds have many advantages for medicinal applications, such as enhanced lipophilicity, higher OH acidity, alternative metabolic pathways, and distinct upfield NMR signals, giving organosilicons a strong added value over carbon in some cases.[2]
A common way to access these silylated compounds is through hydrosilylation. This reaction consists of the addition of a hydrogen-silyl function on a sp^2 or sp carbon. Usually, these hydrosilylation reactions use expensive noble metals such as rhodium or platinum.[3] In this work, we have developed a simple and efficient method to access new silylated heterocycles without using noble metals. This method relies on the use of a stable and low-cost pre-catalyst, $NiBr_2bipy$, which is reduced to Ni(0) by electrochemistry to perform an intramolecular hydrosilylation reaction on an alkyne (fig 1). This methodology is fully regio- and stereoselective with moderate to good yields.

Figure 3 : Nickel-catalyzed electrochemical intramolecular hydrosilylation reaction



- ✓ Up to 93% of yield
- ✓ easy to handle and air stable nickel
- ✓ 100% regioselective
- ✓ 100% stereoselective

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OC45

Synthesis of aziridines and reactivity of ketenes in flow

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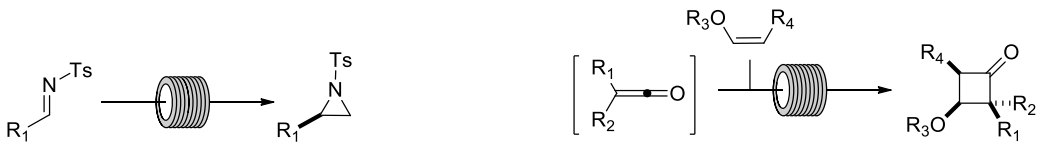
With years of experience working on ketenes[1] and total synthesis of natural products,[2] the SeRCO team recently discovered a formal (3+2) cycloaddition of ketenes with aziridines,[3] affording in very good yields a direct synthetic pathway to γ-lactams, a very common motif in natural products.

To bring additional diversity in this process, we decided to study this reaction using flow chemistry, and especially the generation of ketenes.[4] Flow chemistry often solves problems of efficiency and safety, offering a more robust and reliable way to synthesise and manipulate reactive species and hazardous or toxic compounds. The generation of ketenes perfectly encompass these problems, but the flow generation of ketene is so far limited to nucleophilic addition.

In this work, we have studied the flow generation of ketenes in [2+2] cycloaddition affording crucial information on the overall process (solvent compatibility, kinetic of the cycloaddition, base to be used…). In addition, aiming at developing the overall (3+2) cycloaddition process using flow techniques, the arduous, non-reliable, thus problematic aziridine batch synthesis was also studied using flow chemistry.



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OC46

Martin's Spirosilane-based Pentacoordinated Organosilicons: Synthesis, Optical Resolution & Configurational Stability

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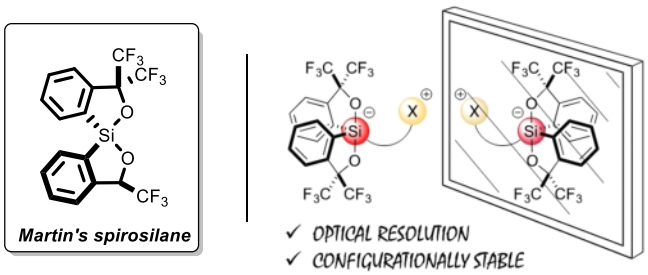
Conversely to carbon, silicon has the ability to form hypercoordinated compounds. Since the emergence of such species in the 1980s,[1] a large number of stable pentacoordinated organosilicons were reported and some have found applications in synthetic transformations.[2] Martin's spirosilane, which is based on two dilithiated hexafluorocumyl alcohol moieties that are appended to a silicon center, is a suitable precursor for the synthesis of pentacoordinated silicon species owing to the intrinsic properties of its C,O-bidentate ligands.[3] Furthermore, not only Martin's spirosilane is well-suited to reach pentacoordination, but also to face configurational stability which is one the biggest challenge of hypercoordinated silicon. In constrast to tetravalent derivatives,[4] pentacoordinate species are prone to Berry pseudo-rotations, a fast substituents permutation, ending in racemization.[5] By combining Martin's spirosilane rigidity to a judicious choice of the fifth substituent, our group recently reported the first examples of resolution of pentacoordinated silicon species displaying high configurational stability.[6] DFT study provided insights about the enantiomerization pathways and ligands' influence on the involved transition states within such species.



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OC47

Synthesis of photochromic siloles by Pd-catalyzed reaction between a silacyclopropene and terminal alkynes: scope and mechanistic insights

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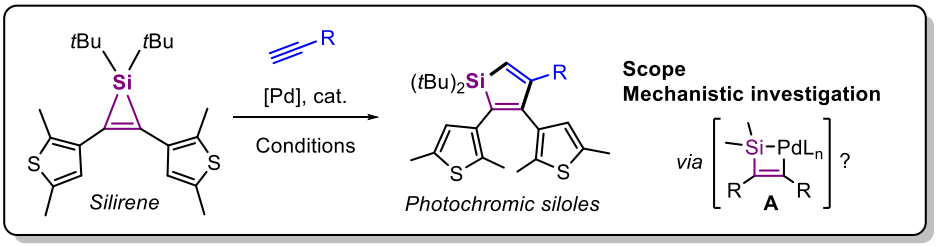
As part of our research program aimed at developing new synthetic methodologies in main-group chemistry, we have been recently focused on the synthetic potential of tight silicon rings as precursor to higher heterocyclic structures. Inspired by seminal findings of Seyferth[1] and others,[2] we have developed a facile route to photochromic siloles based on the 1,2-dithienylethene backbone (see figure).[3] The synthesis is based on the reaction of a decorated silacyclopropene (silirene) and terminal alkynes in the presence of a catalytic amount of palladium. The results obtained in that direction, including the scope and limitations of the reaction, will be presented. In addition, our efforts to unveil its mechanism and more particularly to address the issue of **A**-type palladasilacycles will be discussed.



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OC48

Study of direct C-H arylation of biomass derivatives by heterogeneous palladium catalysis and its application in Continuous Flow Chemistry

Grédy Kiala, PhD advisor(s): Prof. G. Poli, Dr. J. Oble, Dr. M. Roy (IPCM); Dr. J. Blanchard and the Dr. C. Louis (LRS)

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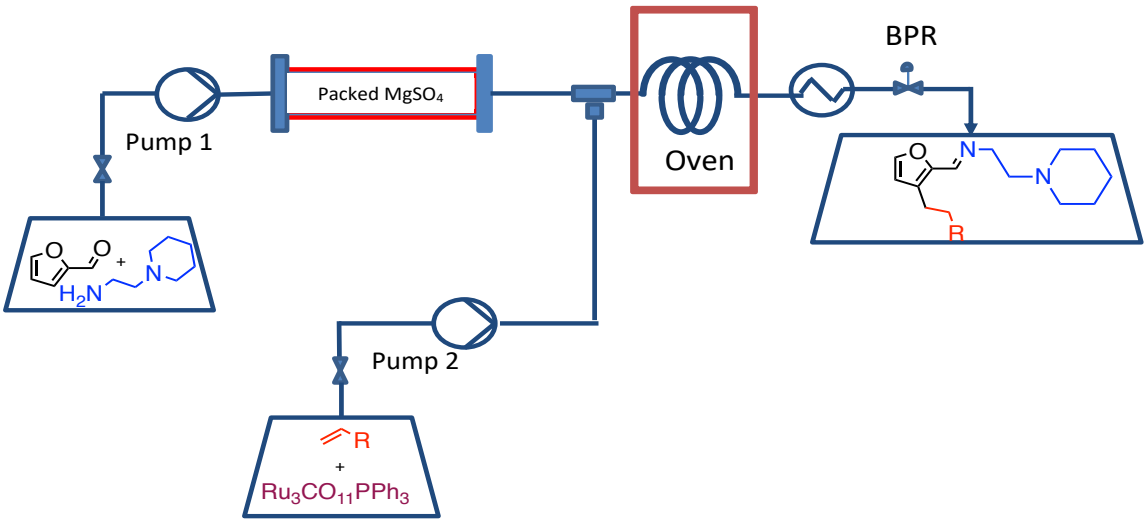
Furfural is one of the most promising bio-based products and is obtained by dehydration of lignocellulosic biomass from both agricultural residues and dedicated crops[1]. It has a strong potential as a renewable platform for the sustainable production of fine chemicals[2]. In particular, the direct functionalization of furfural by C-H activation is an emerging area that is the focus of many research efforts.

Our group has recently developed methods for the functionalization of furfural-derived imines at the C-3-position by alkylation, arylation and alkenylation [3,4]. These processes are based on the use of ruthenium catalyst at high temperatures (130-150 °C).

To make this reaction cleaner and safer, we have developed a **continuous flow chemistry** process, which is an important tool for synthetic organic chemists [5]. This process allowed us to achieve better efficiency, better yield and an easy scale up of the reaction.



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OC49

Fluorogenic dimers as bright switchable probes for enhanced super-resolution imaging of cell membrane

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Super-resolution fluorescence imaging based on single-molecule localization microscopy (SMLM) enables visualizing cellular structures with nanometric precision. However, its spatial and temporal resolution largely relies on the brightness of ON/OFF switchable fluorescent dyes. Moreover, in cell plasma membranes the single-molecule localization is hampered by the fast lateral diffusion of membrane probes. Here, to address these two fundamental problems, we propose a concept of ON/OFF switchable probes for SMLM based on fluorogenic dimers of bright cyanine dyes. In these probes, the two cyanine units connected with a linker were modified at their extremities with low-affinity membrane anchors (figure 1). Being self-quenched in water due to intramolecular dye H-aggregation, they displayed light up in apolar and viscous media, including lipid membranes. Charged group in the linker further decreased the probe affinity to the lipid membranes, thus accelerating its dynamic reversible ON/OFF switching. The concept was validated on red cyanine 3 and far-red cyanine 5 dyes. SMLM of live cells revealed that the new probes provided higher brightness and ~10-fold slower diffusion at the cell surface, compared to reference probes Nile Red and DiD, which boosted axial resolution of biomembrane imaging >3-fold down to 31 nm. The new probe allowed unprecedented observation of nanoscale fibrous protrusions on plasma membranes of live cells with 40-s time resolution, revealing their fast dynamics. Thus, going beyond the brightness limit of single switchable dyes, using cooperative de-quenching in fluorogenic dimers, and slowing down probe diffusion in biomembranes open the route to significant enhancement of super-resolution fluorescence microscopy of live cells.

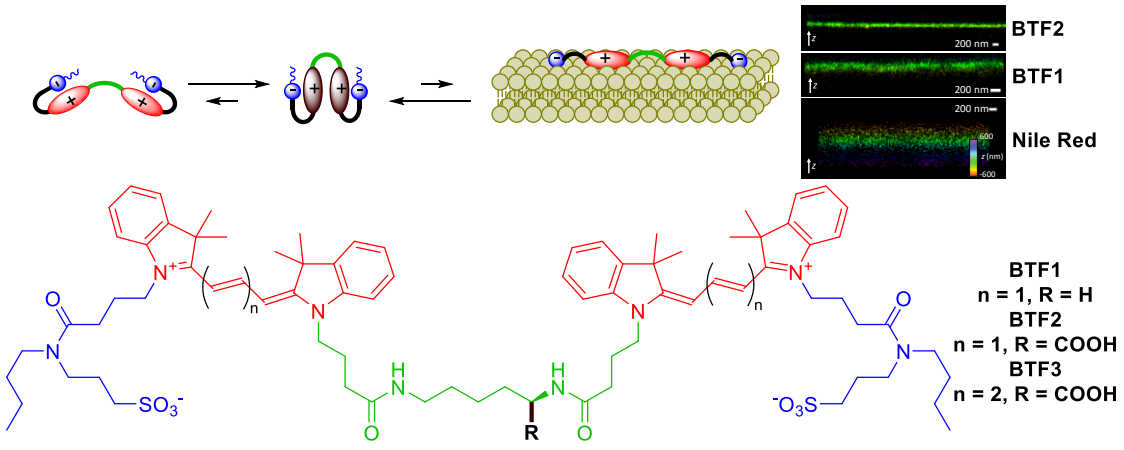

Figure 1: Prinple of designed BTF probes and their chemical structures

OC50

Cycloadditions of π-Allylpalladium(II) Intermediates towards Medium-Sized *N*-Heterocycles

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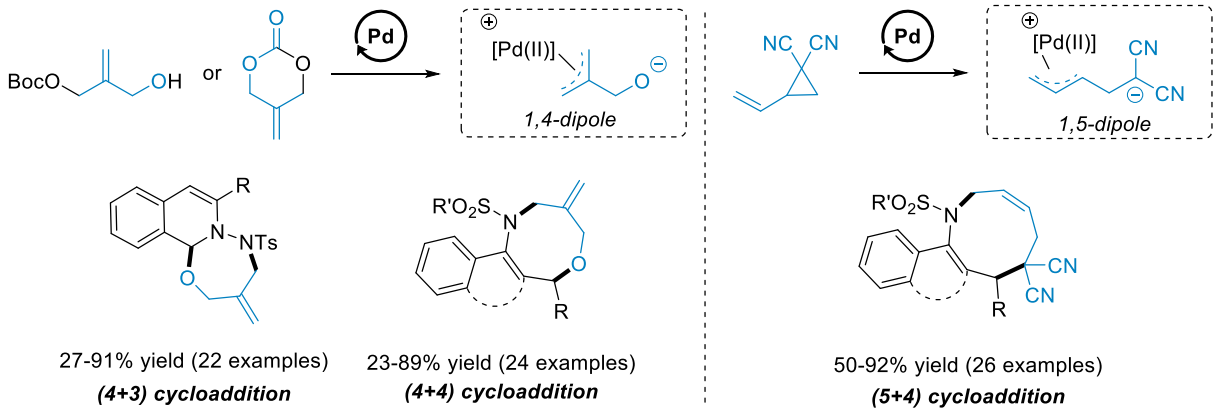
Medium-sized *N*-heterocycles are scaffolds of high importance in medicinal chemistry and are widely encountered in biologically active molecules.[1] While numerous synthetic strategies focus on the preparation of five- or six-membered rings, the need for efficient methodologies towards polysubstituted and stereodefined medium-sized *N*-heterocycles remains an important challenge for organic chemists.

π-Allylpalladium(II) zwitterionic intermediates, which can be obtained from various precursors after oxidative addition by a palladium(0) catalyst, have emerged as versatile precursors for the preparation of a wide variety of carbo- and heterocycles.[2] Our research group recognized their remarkable synthetic potential for the preparation of medium-sized *N*-heterocycles. A 1,4-oxygenated-dipole allowed the efficient preparation of seven-membered oxadiazepines, using *in situ* formed azomethine imines from hydrazones *via* a sequential silver(I)/palladium(0) catalysis. This dipole is also suitable for (4+4) cycloadditions towards eight-membered oxazocines. Nine-membered azonanes were also prepared thanks to the discovery of a reactivity switch of vinylcyclopropane under a palladium(0) catalysis, as they react as an all-carbon 1,5-dipole.[3]



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OC51

Straightforward Access to Multifunctional π-Conjugated P-Heterocycles Featuring an Internal Ylidic Bond

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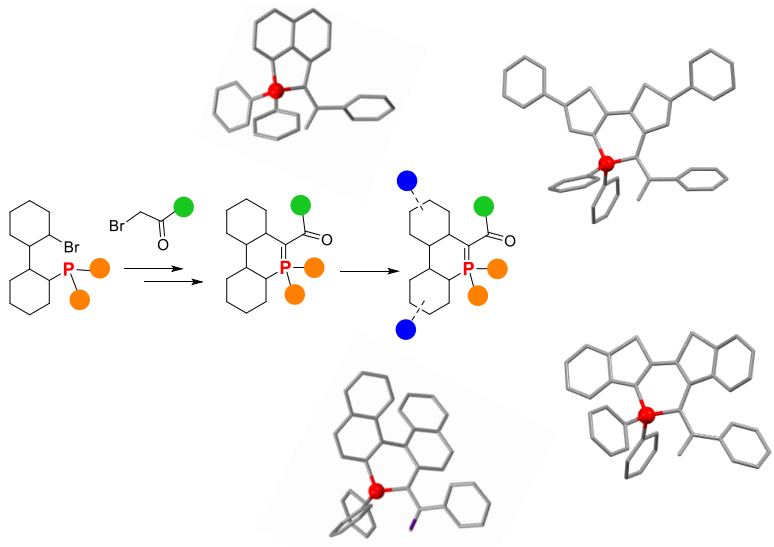
In the field of molecular materials based on phosphorus-containing π-systems, little attention was devoted to phosphacycles featuring an internal P-ylide.[1] Hence, this bond was supposed to be too reactive. Actually, organic chemists use this reactivity since decades to create C-C bond with the Wittig reaction. In the present work, we report the straightforward one-pot synthesis of novel 5 or 6-membered P-heterocycles featuring an internal ylidic bond (see Fig.). The stability of the compounds tolerates post-functionalization through direct arylation to introduce electron-rich/poor substituents and the synthetic strategy is also compatible with the preparation of more elaborated polyaromatic scaffolds such acenes and helicenes (see Fig.). Using a joint experimental (X-ray analysis, optical and redox properties) and theoretical approach, we perform a full structure-property relationships study on these new platforms. In particular, we show that molecular engineering allows not only tuning their absorption/emission on the entire visible range but also endowing them with chiroptical or non-linear optical properties, making them valuable dyes for a large panel of photonic or opto-electronic applications.[2]



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OC52
Photocatalysis with super organic electron donors

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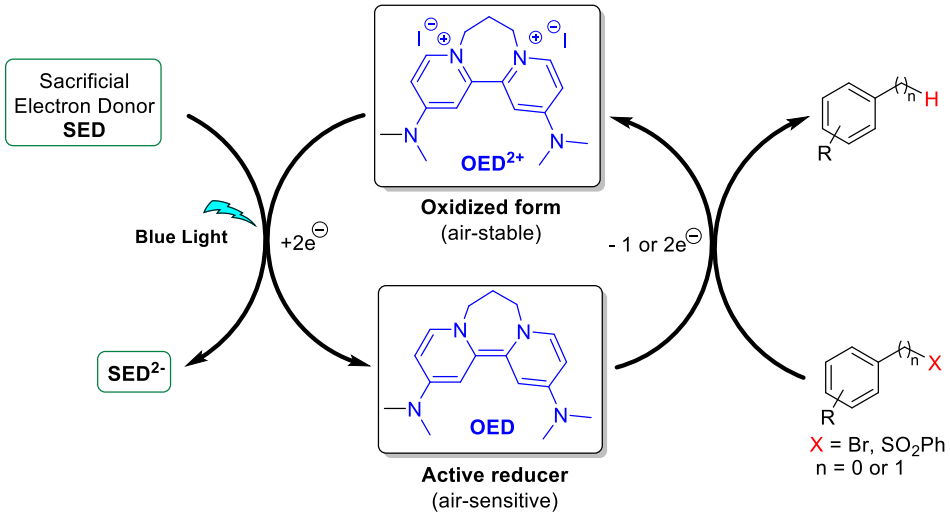
Photocatalyzed reductive methodologies have emerged as a powerful strategy for the generation of original radical species under mild conditions.[1] Among the different photocatalysts explored, organic dyes have been used as an attractive alternative to transition metal complexes.[2] However, most of them present modest reduction potentials limiting their reactivity to the generation of radical intermediates from strong electron-deficient acceptors. In the quest for innovative and selective reduction methodologies, super organic electron donors (OEDs) represent ideal eco-compatible and powerful reducing agents for the generation of radical or anionic species by single or double electrons transfers.[3,4] Nevertheless, OEDs were used in a stoichiometric amount. Therefore, we developed an OED-photocatalyzed reduction methodology where the active reducer **OED** is regenerated by electron transfers to its oxidized form **OED^{2+}** using a sacrificial electron donor. This new photoredox catalytic system was applied to the reduction of functionals groups with low reduction potentials (sulfone, aryl halide and triflate) into radical or anionic intermediates. This photocatalytic system represents an unprecedented way to catalytically generate carbanions, including aryl anions.



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OC53
Synthesis, Reactivity, and Functionalization of Endoperoxides: Application in Total Synthesis

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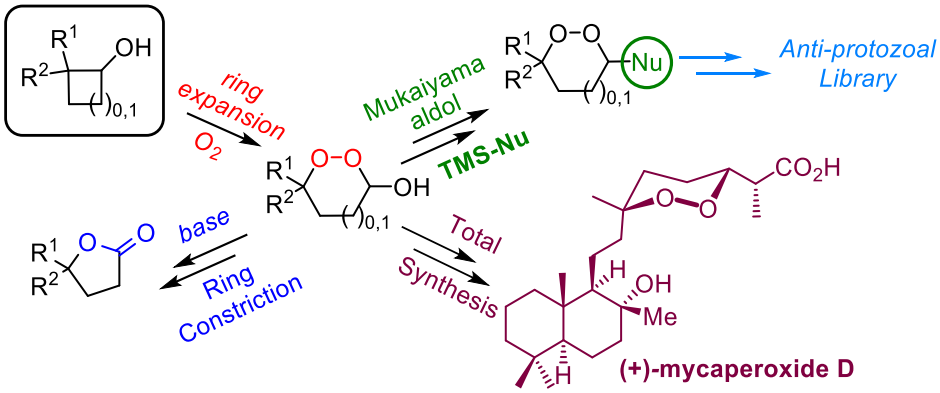
1,2-Dioxolanes and 1,2-dioxanes are examples of endoperoxides, which can be found in many natural substances, but also have many perspectives in medicinal chemistry. Despite many reported methods, their syntheses are still challenging to incorporate the peroxy bond in polyfunctionalized molecules.[1] These last years, we focused on developing strategies to access these reactive patterns to attain the construction of bioactive molecules and original natural products. Thus, we developed methods to build 5- or 6-membered endoperoxide using ring-expansion of strain cycloalkanols.[2] We then studied the reactivity of endoperoxide to obtain functionalized substances through Mukaiyama aldol reaction[3,4] or to undergo original ring-constriction.[5] The application of this work culminated in elaborating a medicinal chemistry library[6] and accomplishing the total synthesis of marine natural products.[7]



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OC54

Development of a new cycloaddition/fragmentation reaction sequence

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Diels-Alder cycloaddition reactions have been commonly used by organic chemists to synthesize substituted cyclic systems. Heterocycloadditions like nitroso Diels-Alder have also already been reported to form 3,6-dihydro-*2H*-oxazines in which the NO bond could be cleaved.[1]

In 2018, our team have reported a new entry into highly functionalized cyclohexane derivatives by a sequence involving a nitroso Diels-Alder cycloaddition with benzene oxide, followed by a base-mediated fragmentation, with complete control of relative configuration of every stereogenic centers.[2]

These results showed an interesting synthetic potential, which prompted us to undergo further studies on the scope and application of this sequence.

We first chose to focus on the use of benzene oxide for Diels-Alder cycloadditions in order to assess the synthetic potential of these reactions with this diene, for which few reactions are known.[3] We have extended it, not only to different nitroso derivatives, but also to other hetero-dienophiles (**Fig. 1**).

We have also studied the fragmentation of these cycloadducts using a variety of bases to form a diversity of functionalized cyclohexene oxide derivatives. The role of the cycloadduct double bond during this fragmentation has been investigated. Moreover, a new type of fragmentation has been discovered showing an unexpected reactivity of *tert*-butyllithium base. We will present our latest results about this reaction sequence and the molecular diversity it induces.

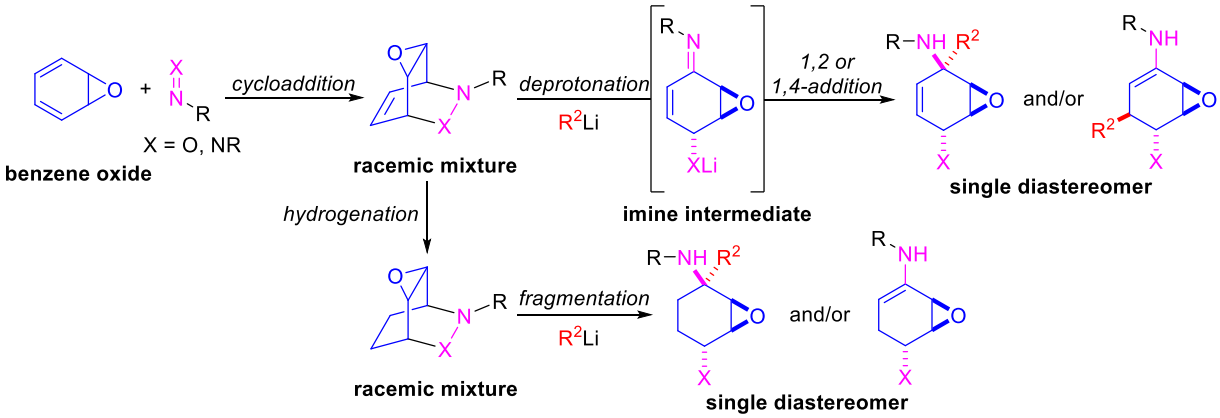

Fig. 1 Cycloaddition/fragmentation reaction sequence

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OC55

Organocatalysts confined within the cavity of cyclodextrins

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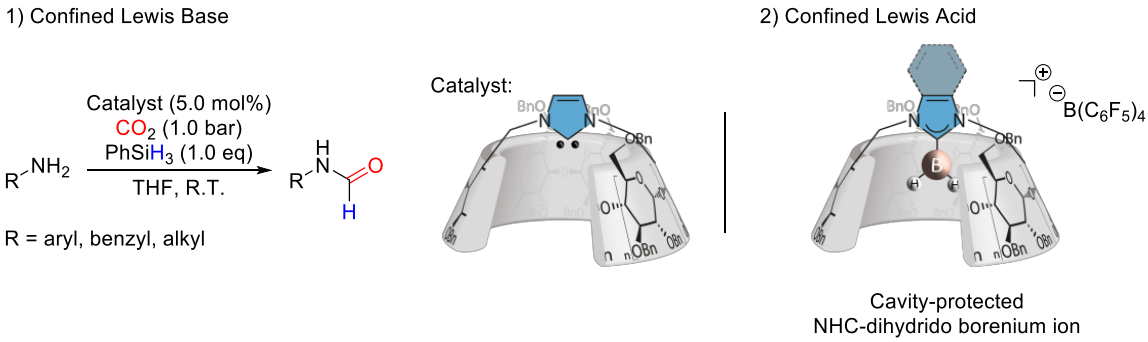
Cyclodextrins (CDs) have been studied as platforms for selective catalytic reactions. The bridging of CDs with a *N*-heterocyclic carbene (NHC) ligand led to a rigidification and a deformation of their cavities, conferring them a helicoidal chirality.[1] The presence of the NHC moiety allowed the formation of diverse metallic complexes pointing inside the cavity. Reactions involving coinage metals (Cu, Ag, Au) have been described and showed great regio- or enantioselectivities towards hydroboration, cycloisomerization and alkoxycyclization reactions.[2]

We recently turned our interest towards the confinement of reactive carbenes and borenium ions to study the influence of the cavity in metal-free reactions.

We have used the free NHCs as Lewis bases in catalysis. The confined carbenes showcase an enhanced cavity influence regarding the formylation of amines *via* CO_2 hydrosilylation.[3] The presence of a cavity prevents over-formylation reactions with aniline and slows the formylation of sterically hindered amines, inducing chemoselectivity.

We have also synthesized NHC-boranes, precursors to strongly Lewis acidic borenium ions, to first study their structural features. The protection brought by the cavity of the CD allows us to form the elusive NHC–BH_2^+ borenium ion that was thought to be non-isolable.[4] This borenium ion is also active towards catalysis for the hydrosilylation of ketones and shows different selectivities in function of the cavity size.



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OC56

Iron-Catalysed Intermolecular Oxyamination of Alkenes Using Hydroxylamine Derivatives as Clean Nitrogen Sources

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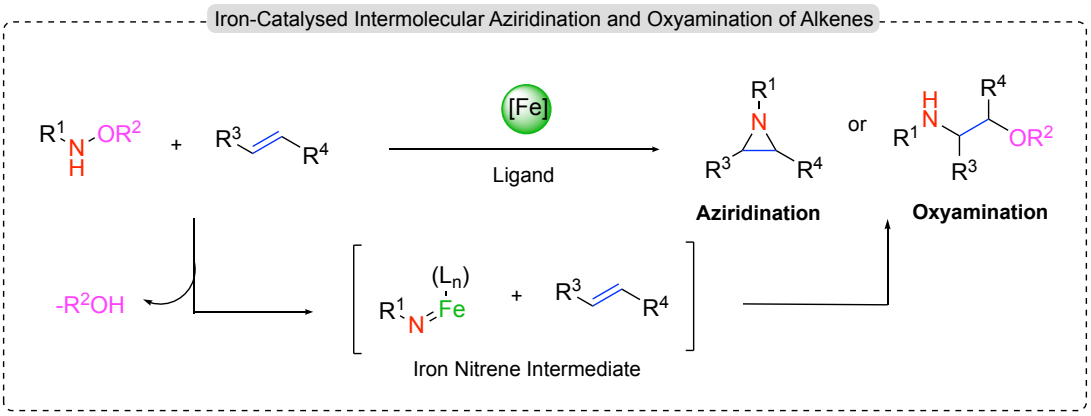
Nitrogen-containing molecules are incredibly valuable in organic synthesis and are used as chiral ligands, synthetic intermediates, and pharmaceuticals. There has thus been an ongoing effort into the development of new, efficient, and robust methodologies for C-N bond formation.

Metallonitrenes are a powerful tool for the formation of C-N bonds and have led to the development of efficient processes such as aziridination, alkene difunctionalisation and C-H amination.[1] However, most of these developed processes are poorly atom economical, due to them requiring external oxidants, and are also based on the use of non-sustainable materials such as rare and expensive transition metals (Rh, Pd, etc.). Hydroxylamine derivatives, in the presence of a transition-metal, can form a metallonitrene intermediate avoiding the requirement for external oxidants, since the presence of the N–O bond acts as an endogenous oxidant.[2] Surprisingly, the generation of metal nitrenes from hydroxylamine derivatives and cheap, abundant, and non-toxic iron sources has been scarcely studied.[3]

Following our previous studies[4] on the reactivity of iron-nitrenes deriving from hydroxylamine derivatives, we will present our recently developed intermolecular iron-catalysed oxyamination of alkenes hydroxylamine derivatives as a nitrogen source. This sustainable process allows for efficient access to both a new C-N bond and a new C-O bond in one step, yielding protect 1,2 amino-alcohols in good-to-excellent yields. Mechanistic studies into this iron-catalysed nitrene transfer processes are currently ongoing within our group.



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OC57

Modular approach to substituted pyridoazepinones

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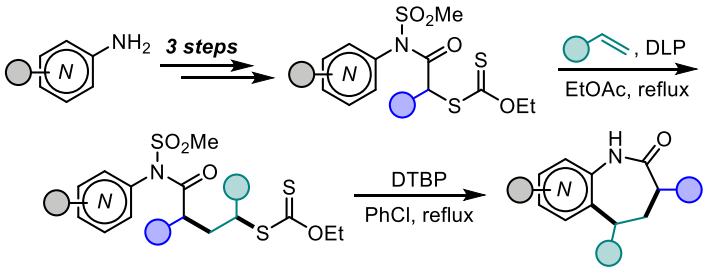
Pyridoazepinones are a pyridine-containing scaffold present in natural products and synthetic medicinally-relevant compounds.[1] It also may serve as a classical isostere of the benzazepinone motif, which is a part of various biologically active substances. However, no general method for the preparation of pyridoazepinones has been described until these days, and the existing strategies suffer from low functional group tolerance and harsh conditions.

The proposed strategy toward pyridoazepinones is based on the radical chemistry of xanthates and uses commercially available aminopyridines as starting materials. It features the construction of the seven-membered ring by C-C bond formation via the xanthate addition-transfer process to non-activated alkenes, followed by radical cyclization and re-aromatization of the pyridine ring, enabled by homolytic cleavage of the sulfonamide bond.[2]

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



Synthesis of [3,2-b], [4,3-b] and [2,3-b] isomers • 24 examples • Derivatization • One-pot and gram-scale synthesis

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OC58
Mechanosynthesis of Iminosydnone-based APIs

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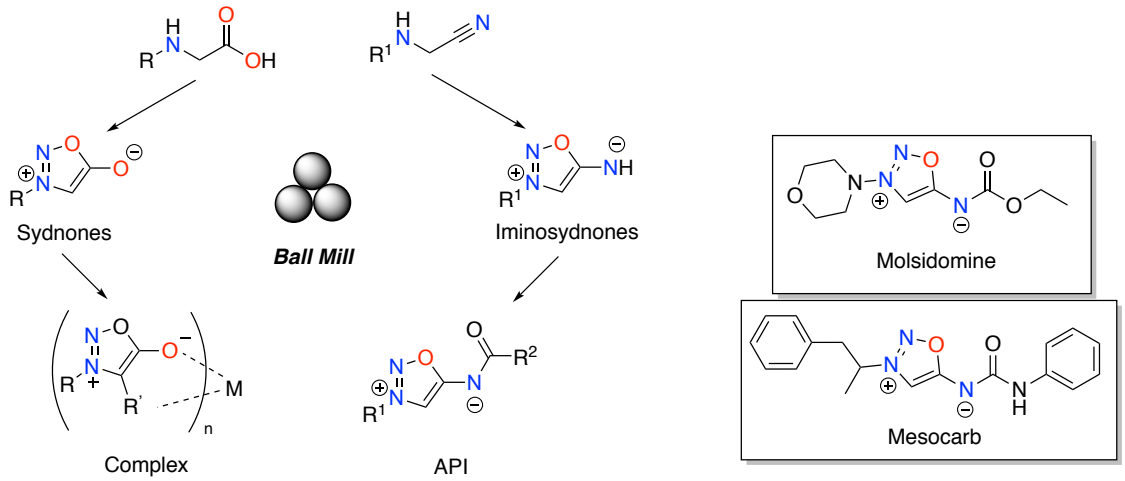
Mesoionic compounds like sydnones, iminosydnones and münchnones are dipolar five-membered heterocycles displaying noteworthy chemical properties and biological activities. For instance, functionnalized sydnones and iminosydnones are key structures for bioconjugation applications via 1,3-dipolar cycloadditions.[1] Besides, several substituted iminosydnones are commercialized for decades as drugs, especially in the cardiovascular field.[2] Mechanochemistry, i.e. inducing chemical reactions through mechanical forces, for instance in ball mills, was recognized in 2019 by IUPAc as one of the "10 chemical innovations that will change the world".[3] Hence solventless syntheses of organic molecules have developed dramatically in the last years, providing "green" and efficient methods to access bioactive molecules.[4] As our team recently designed the mechanosynthsesis of sydnones and of relative coordination complexes,[5] we tackled the development of a mechanochemical method to access several bioactive iminosydnones.[6] So, in this communication we will present our last results on the synthesis of iminosydnone-based Active Pharmaceutical Ingredients (API) such as Molsidomine and Mesocarb via ball milling.



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OC59

Development of Highly Efficient Cyclic(alkyl)(amino)carbene Ruthenium Complexes for Olefin Metathesis

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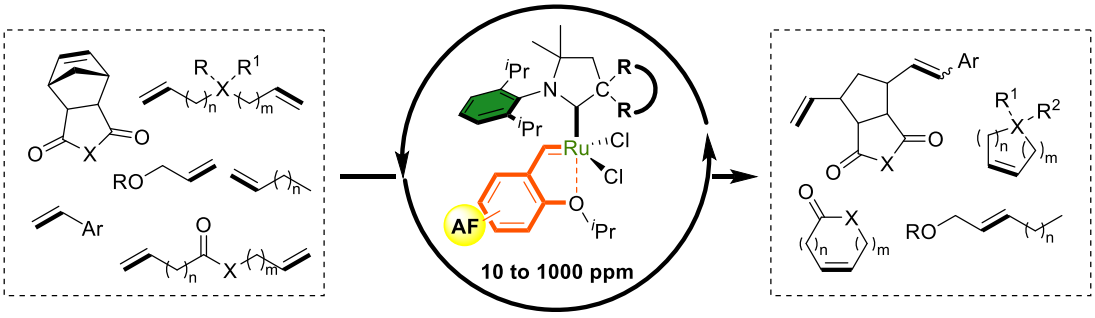
The versatility of Olefin Metathesis (OM) is evident from its successful application to natural product synthesis, to pharmaceutical and crop science, the valorization of renewable feedstocks or the preparation of new materials.[1] N-Heterocyclic-Carbene (NHC) ruthenium complexes are recognized for their high catalytic efficiency. However, they face stability issues in presence of ethylene, a common byproduct for OM.[2,3] Cyclic(alkyl)(amino)carbene (CAAC) ruthenium complexes do not undergo the common degradation path, being more stable but at the same time less reactive.[4] Herein we report on the synthesis and the catalytic activity of a new series of bench-stable CAAC-Ru catalyst bearing stabilizing bulkier substituents on the heterocyclic moiety and a strategic activating functionalization (AF) on the styrenyl fragment. These complexes revealed to be highly competent for Ring-Closing Metathesis (RCM), Cross-Metathesis and Macrocyclization also at low to very low catalytic loading (10-1000 ppm).



Ring-Closing Metathesis - Cross-Metathesis - Macrocyclization - Ring-Opening-Cross Metathesis

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OC60

Site Selective Palladium(II)-Catalyzed C(sp^3)–H Methylene Diarylation of a Tropane Scaffold

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Tropane alkaloids are relevant compounds in the field of therapeutic research particularly the arylated tropane class of derivatives (Figure 1A). For instance, compound **1b** was reported as a narcotic antagonist while **1b** was shown to lower circulating blood glucose levels by 60-80% and possesses an analgesic activity similar to codeine. Moreover, 2,3-aryltropanes (such **1c**), compounds that have been scarcely described to date, were found to be highly selective ligands for the dopamine transporter (DAT) at the nanomolar level.

As part of our ongoing interest in functionalization of tropane motifs combined with our aim to identify new biological activities, we sought to design a new C(sp^3)–H activation approach to synthesize unknown arylated tropanes in a site-selective manner. Herein (Figure 1B), we report the first pallado-catalyzed double C(sp^3)–H arylation of the tropane skeleton in positions 2 and 4 driven by the aminoquinoline (AQ) directing group positioned in the C3 position.[1] The reaction is site-selective delivering 2,4-β-*cis*-diaryl tropanes. Preliminary biological evaluations showed that this series of compounds displays premising antiproliferative activities against colon cancer cell lines.

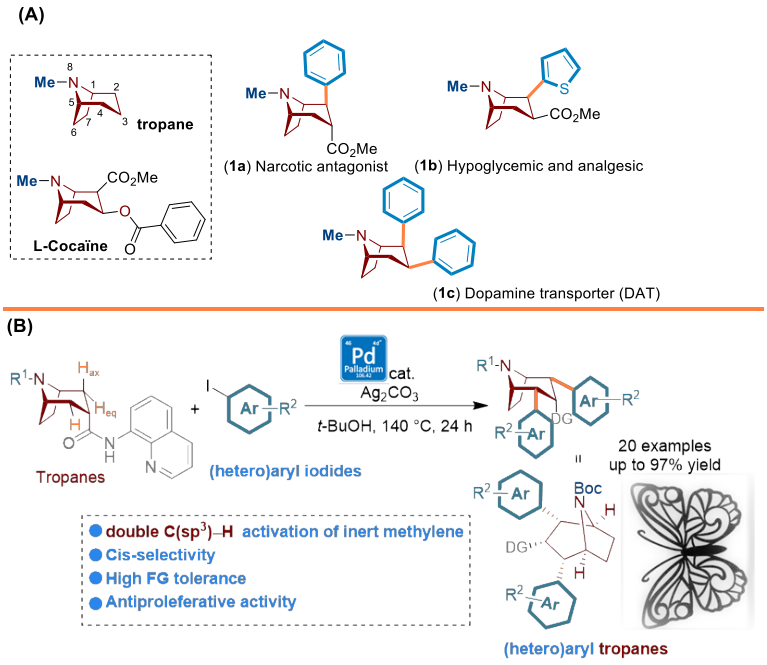

Figure 1.

[1] Mayssa Zayene *et al*. **2022**, submitted.

Posters

P A001
Electrocoupling
A Catalyst-free Alternative for C-C Bond Formation

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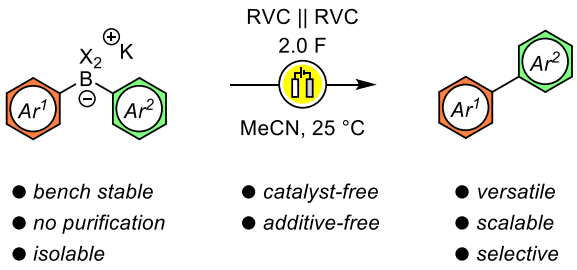
Our efforts toward sustainable C-C bond formation have led us to investigate alternative catalyst-free coupling reactions. Having previously demonstrated that organoboron reagents can serve as templates in Zweifel olefinations[1,2] and strained ring functionalization,[3,4,5] we set out to develop a conceptual approach for hetero-coupling reactions.

As many methods for the formation of hetero-biaryls require expensive and/or environmentally challenging transition-metal catalysts as well as inert and dry conditions, we envisioned that bench-stable, hetero-substituted arylborate salts could undergo formation of (hetero)biaryls, triggering the key 1,2-metallate rearrangement step under electrochemical oxidation.[6,7,8]



First, a novel and practically simple access to tetraarylborates will be described, providing a new library of heterosubstituted structures.

Second, the chemoselectivity of the electrocoupling reaction will be discussed, as well as its currents applicability and limitations.[9,10,11]

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P A002

Bioinspired lipidic alkynylcarbinols as anticancer agents

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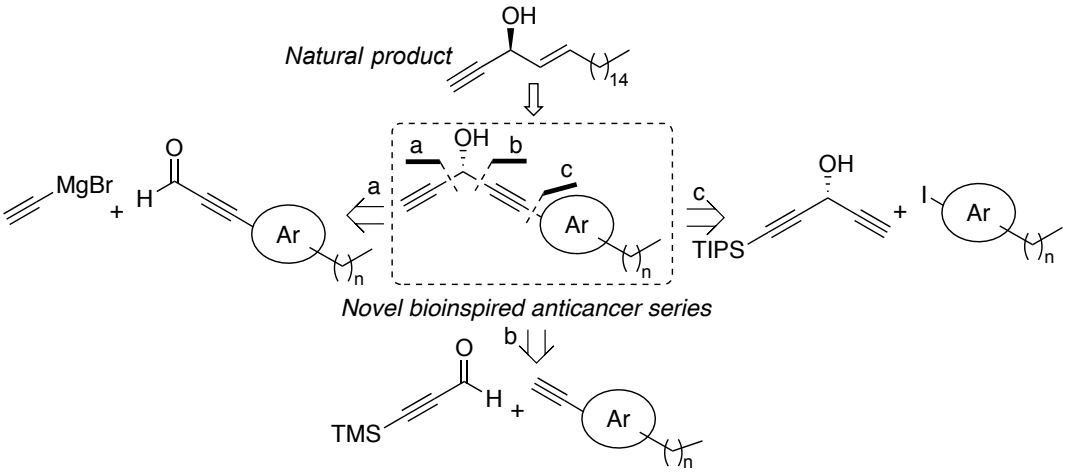
Cytotoxic natural acetylenic lipids embedding a chiral alkynyl carbinol unit at the terminal position of a linear aliphatic skeleton represent a potential source of anticancer agents.[1] We showed that chemistry-driven evolution of such lipidic alkynyl carbinols (LACs) could lead to an up to 1000-fold increase in potency for enantioenriched synthetic analogues.[2] We also recently demonstrated that cytotoxic LACs behave as prodrugs upon *in situ* enantiospecific oxidation by SDR enzymes (Short-chain Dehydrogenases/Reductases): the resulting ynones react as Michael acceptors with multiple proteins, including a proteasome subunit, thus inducing apoptosis.[3]



A new series of anticancer molecules will be described, in which the alkynylcarbinol pharmacophore is conjugated with an (hetero)aromatic ring, itself bearing the lipophilic chain.[4] In order to ensure optimal efficiency and flexibility, 3 complementary synthesis routes were studied. More than 30 synthetic analogues, as well as *in cellulo*-clickable probes, were obtained under racemic or enantioenriched form. Biological data of cytotoxicity, cell imaging and modification of cellular proteins using clickable probes show that this potent anticancer series displays the same mechanism of action as the one recently uncovered for related non-aromatic LACs,[3] thus confirming their pharmacological potential.

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P A003

2-Amido-acroleins as a versatile platform for the synthesis of poly-functionalized silicon containing heterocycles

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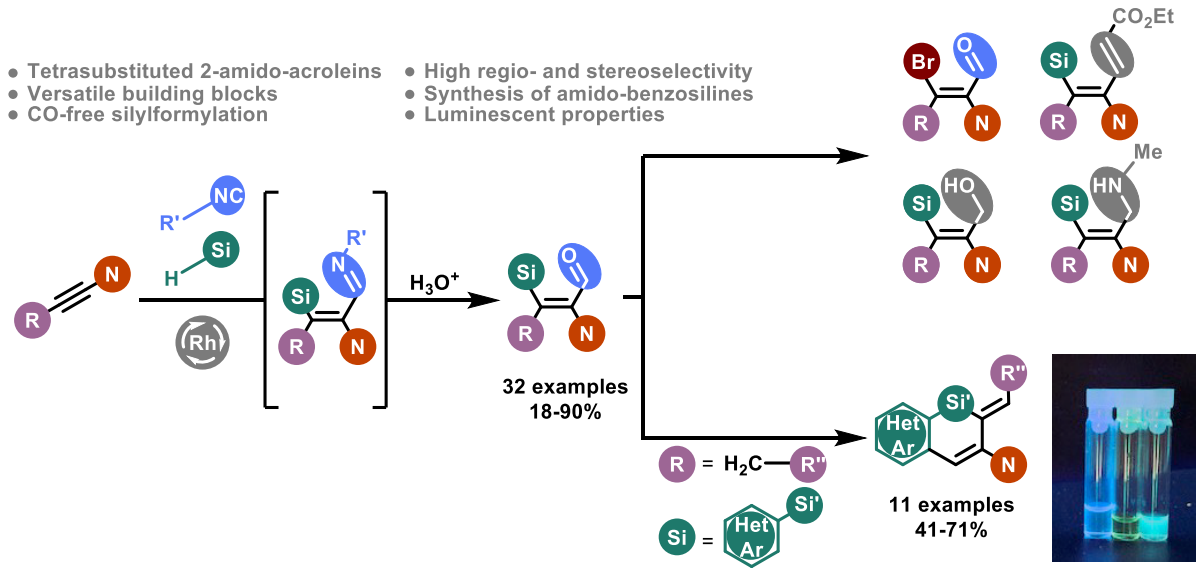
2-Amino-acroleins are valuable building blocks that have not been sufficiently studied due to the lack of efficient, selective, and versatile synthetic methods, especially when tetrasubstituted ones are targeted.

In this context and inspired by a previous work reported by Fukumoto,[1] we have recently developed the first rhodium-catalyzed silylformylation applied to ynamides. To make this approach practically easy to implement in any laboratory, isocyanides were used as a substitute of carbon monoxide. After optimization, we demonstrated that this reaction is fully regioselective towards 2-amido-acroleins and almost always stereoselective for the *syn*-addition product (isomer *E*). Different functional groups on the ynamide, silane and isocyanide are tolerated leading to a high degree of diversity on the final compound. These products can be easily converted to vinyl bromide, allylic alcohol, amine and diene.[2] As part of our interest in the synthesis of sila-heterocycles,[3] we subjected these 2-amido-acroleins to an intramolecular Friedel-Crafts reaction leading to the formation of poly-functionalized amido-benzosilines.[4] These molecules are analogs of sila-rhodamines and they exhibit interesting luminescent properties that can be easily tuned by changing the electronic nature of the different substituents on the 2-amido-acroleins.



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P A004

Diastereoselective addition of redox active esters to azomethine imines by electrosynthesis

Ludovic Leleu, Thomas Martzel, Arona Fall,
Vincent Levacher, Sylvain Oudeyer, Jean-François Brière
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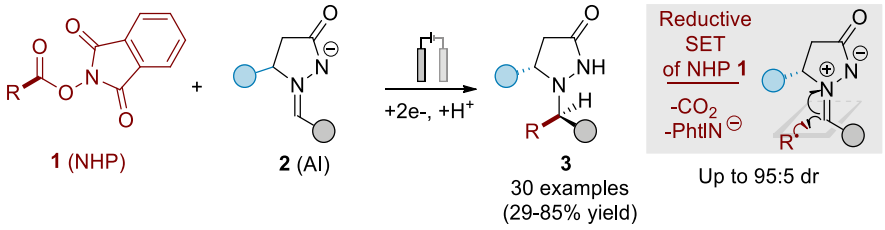
Azomethine imines (**AI**) are versatile dipoles historically involved into cycloadditions and nucleophilic addition reactions of anionic species, towards the construction of valuable cyclic-hydrazine derived products.[1] However, radical-based transformations of Dorn-Otto type azomethine imines **2** were only recently explored by visible-light photoredox catalysis.[2,3] In that context, few examples of a chiral C5-substituted azomethine imines were reported and low or undefined diastereoisomeric ratios were described.



Diastereoselectives radical addition to azomethine imine by electrosynthesis.

We envisaged an alternative approach to provide original pyrazolidinones **3** with high diastereoisomeric ratios from chiral azomethine imines **2** using electrochemical conditions. Our strategy consists in the use of *N*-(acyloxy)phthalimides (NHPs) **1** as versatile radical precursors upon a decarboxylative cathodic reductive SET event.[4] Thereby, an efficient addition reaction of various alkyl radicals to such dipoles (up to 85% yield) in a stereoselective fashion (up to 95:5 dr) will be presented.[5]

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P A005

Catalytic amination of unactivated C–H bonds in the presence of electronically activated sites

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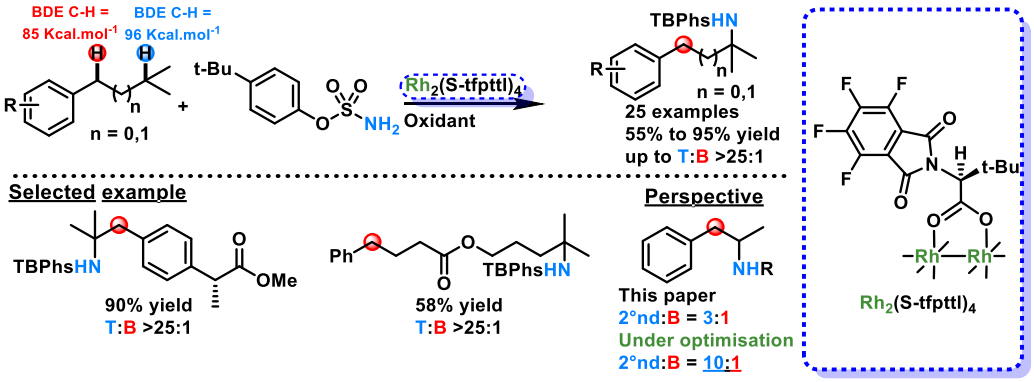
The design of site-selective C(sp^3)–H functionalization reactions is a great challenge with important applications in synthesis and medicinal chemistry.[1] A first approach to meet this goal relies on directed functionalization reactions through the use of coordinating groups or intramolecular reactions. By contrast, in the case of undirected C(sp^3)–H functionalization reactions, the site-selectivity is often governed by the innate reactivity of the substrate, particularly by the C–H bond dissociation energies (BDEs).[2] Despite their efficiency, both strategies suffer from limitations with many C-H bonds remaining inaccessible.

Catalyst-controlled site-selective C(sp^3)–H functionalization reactions is a third strategy that has recently emerged to go beyond the limitations of substrate-controlled reactions.[3] In this context, our group recently initiated studies to address the issue of the selective intermolecular amination of unactivated tertiary C(sp^3)–H bonds (BDE of 96 kcal·mol^{-1}) bonds in the presence of an activated benzylic site (BDE of 85 kcal·mol^{-1}) through the search for new reagents and catalysts. In this communication, we thus will describe the discovery of a highly discriminating rhodium-bound nitrene species resulting from the synergistic combination of a dirhodium(II) complex and a sulfamate.[4] These reagents allow to go beyond the BDE-driven reactivity of C-H bonds and convert selectively tertiary C(sp^3)–H bonds to afford α,α,α-trisubstituted amides in high yields. The scope of the reaction, its application to the late-stage amination of complex products, and its possible extension to the more challenging selective functionalization of linear alkyl chains will be reported.



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P A006

Synthesis, characterizations and applications of haloazaphosphatranes

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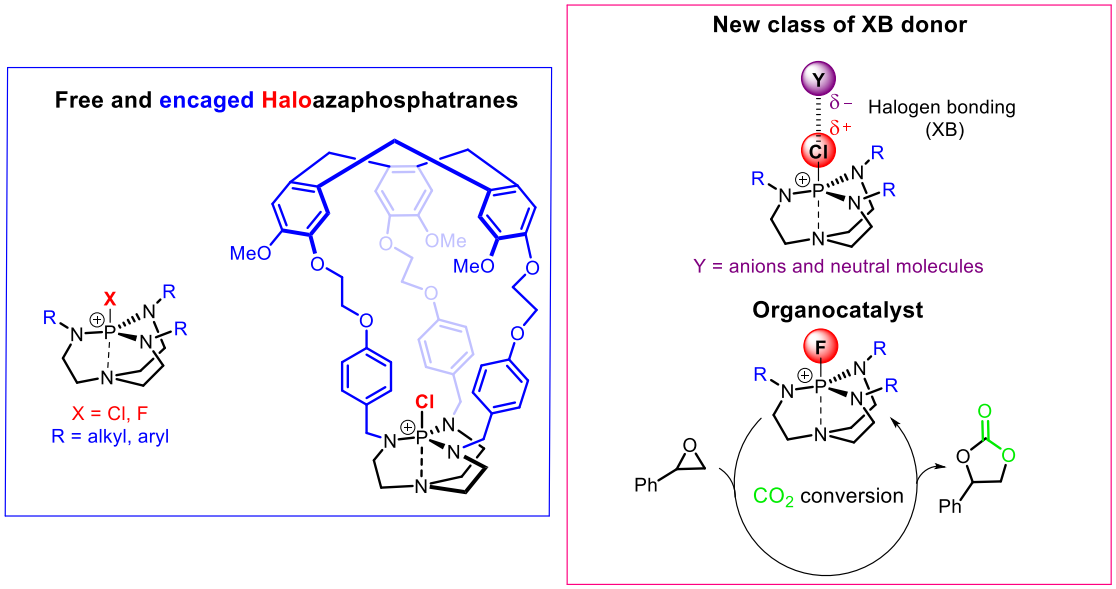
Proazaphosphatranes, also known as Verkade's superbases, are non-ionic highly basic phosphorus derivatives.[1] This class of compounds has found numerous applications from basic and nucleophilic catalysts, ligands for transition metals, to Lewis bases in frustrated Lewis pair (FLP) systems.[2] Their conjugated acids, the azaphosphatranes have been also used as organocatalysts.[3] Although their first synthesis was reported in 1989, the haloazaphosphatranes, the halogenated parents of proazaphosphatranes, were much less studied.

In this context, we successfully developed simple and convenient routes to readily access to various fluoro-, and chloroazaphosphatrane derivatives.[4] With these compounds in hand, we investigated their properties especially as a new class of halogen bond (XB) donors for anions recognitions or as catalytic systems for CO_2 conversion. So as to build more efficient and selective receptors for anion or neutral molecules, we decided to include chlororazaphosphatrane as XB donor moiety in a molecular container as the hemicryptophane.



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P A007

Revisiting N_2 Functionalization with Nucleophiles

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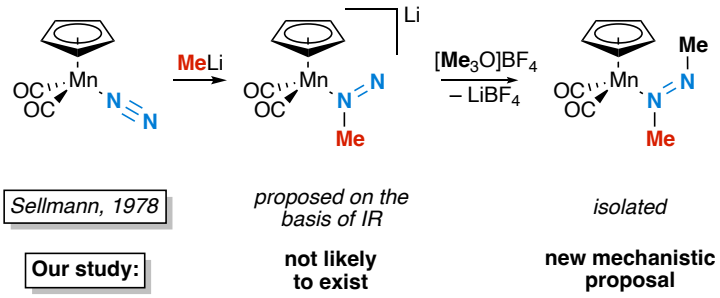
Coordination to a transition metal is the way elected by Nature to achieve the transformation of the abundant but inert N_2 molecule: within the active site of the nitrogenases, an FeS cluster binds N_2 and allows its reduction to NH_3.[1] Inspired by the nitrogenase, chemists have been able to activate N_2 within coordination complexes, eventually achieving catalytic reduction of N_2 to NH_3 under ambient conditions.[2] N_2-complexes have also shown reactivity going beyond NH_3 synthesis, with the production of N-containing organic molecules (amines, nitriles, N-heterocycles) from N_2 through its activation to a metallic center.[3] In these transformations, the N–C bond is almost exclusively built by the reaction of coordinated N_2 with a C-electrophile. Yet, a unique example of functionalization by a C-nucleophile (an organolithium reagent) has been proposed, involving the complex $[CpMn(N_2)(CO)_2]$,[4] leading to N_2-derived azo compounds. Intrigued by this peculiar reactivity, we have carried out a mechanistic study combining experiment and DFT. We have devised a previously undetected intermediate that seems crucial for obtaining an N-containing compound. Besides, our data suggest that the direct attack of the C-nucleophile (RLi) on coordinated N_2, initially proposed as a key step for N_2 functionalization,[4] is not likely to take place.[5]



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P A008

Directed Palladium Catalyzed C-H (Ethoxycarbonyl)difluoromethylthiolation Reaction

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Over the years, fluorine-containing compounds have become essential in pharmaceuticals, agrochemicals and material sciences.[1] Due to the remarkable properties of the fluorine atom or fluorinated groups, their incorporation onto molecules will modulate their physico-chemical and biological properties, resulting in promising applications for new drug discovery for instance.[2] In the past decade, particular attention was given to new sulfur-containing fluorinated groups for their unique features, such as an interesting lipophilicity and a strong withdrawing character.[3a,b] More recently, a strong interest has been shown on original fluoroalkylthiolated groups SCF_2FG (FG = functional group).[3b-g] Although transition metal catalyzed direct C–H bond functionalization appeared to be a powerful tool for C-C, C-N or C-O bond formation,[4] the direct formation of a C(sp^2)-SRf bond remains a challenging transformation. In this context, key players in the field have already developed methodologies for trifluoromethylthiolation and more recently difluoromethylthiolation of various classes of compounds.[5] In this context, an original method for the direct regioselective C-H (ethoxycarbonyl)difluoromethylthiolation of 2-phenylpyridine and 2-vinylpyridine derivatives has been developed in our group.[6]

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P A009

Asymmetric Inverse-Electron-Demand Diels-Alder Cycloaddition between 2-Pyrones and Acyclic Enol Ethers: Gram-Scale Total Synthesis of (+)-Lucidumone

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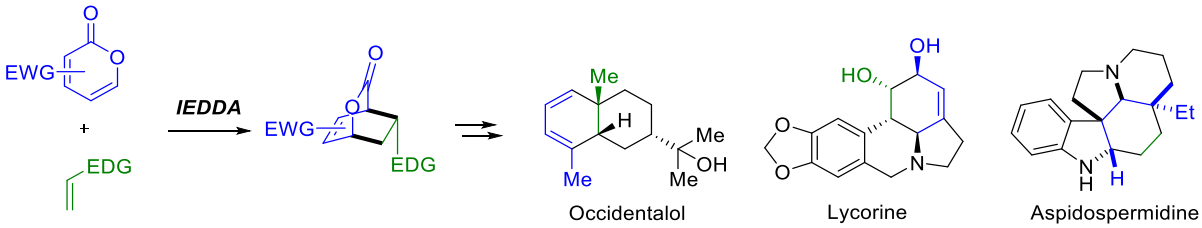
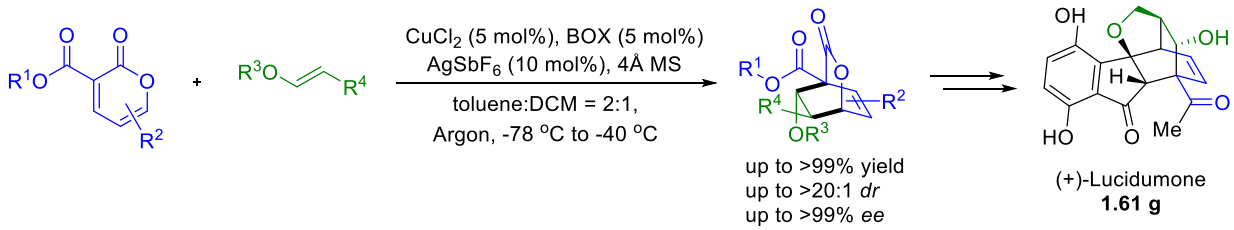
The inverse-electron-demand Diels–Alder (IEDDA) cycloaddition of electron-poor 2-pyrones as electrophilic dienes has been extensively studied in the past fifty years. The reaction provides an efficient access to bridged bicyclic lactones and their derivatives, such as densely functionalized 1,3-cyclohexadienes after CO_2 extrusion and polysubstituted aromatic compounds through elimination. Thus, the IEDDA cycloaddition has been used for the synthesis of many biologically active natural products and drug candidates.[1]



Herein we reported a broadly applicable diastereo- and enantioselective inverse-electron-demand Diels-Alder reaction of 2-pyrones and acyclic enol ethers. Using a copper(II)-BOX catalytic system, bridged bicyclic lactones are obtained in very high yields (up to 99% yield) and enantioselectivities (up to 99% ee) from diversely substituted 2-pyrones and acyclic enol ethers. Mechanistic experiments as well as DFT calculations indicate the occurrence of a stepwise mechanism. The synthetic potential of the bridged bicyclic lactones is showcased by the enantioselective total synthesis of (+)-Lucidumone on a gram scale.[2]



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P A010

First Total Synthesis Of Chaxalactin B

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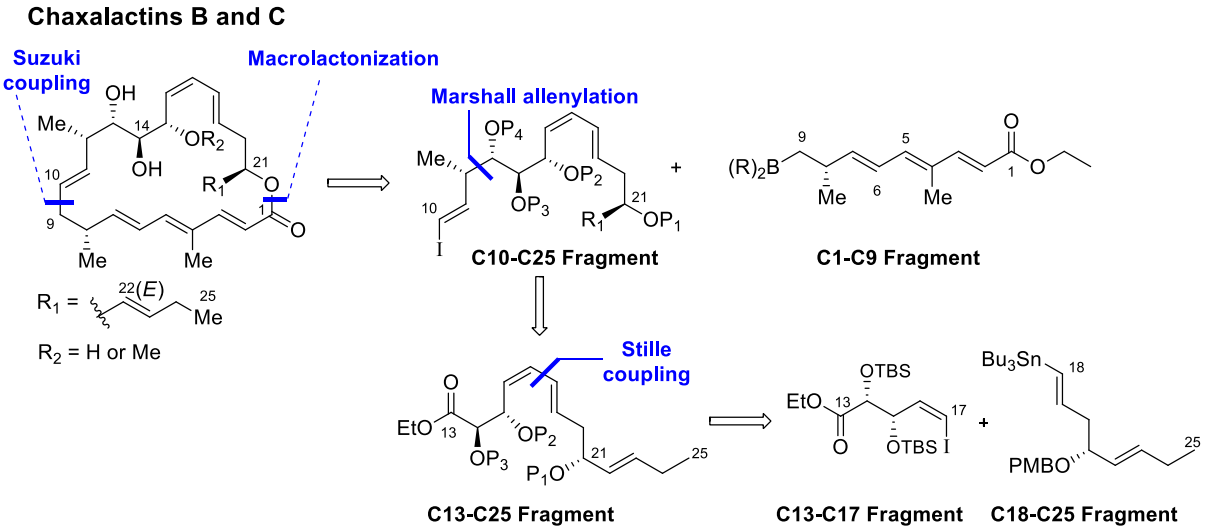
Chaxalactins A, B and C are 22-membered macrolactones isolated in 2011 from a strain called *Streptomyces sp. C34*, collected in hyper-arid Atacama Desert (North of Chili).[1] The complex structure of these molecules coupled with their interesting antibiotic and potential antitumor activities makes this family of molecules synthetically challenging important targets. Despite their interest, no total synthesis of these compounds has been reported so far. The aim of this project is to synthesise for the first time chaxalactins A, B and C and related analogues. Chaxalactins could be obtained by a Suzuki coupling between the C1-C9 and C10-C25 fragments, followed by a macrolactonization reaction. The C10-C25 fragment could be prepared from the C13-C25 fragment using a Marshall allenylation key step to introduce and control the C12, C13 stereocenters. The C13-C25 fragment could in turn be obtained by a Stille coupling between the C13-C17 and C18-C25 fragments.



In this communication, we will report the first total synthesis of chaxalactin B and the synthesis of an advanced intermediate of chaxalactin A. The first biological evaluation will also be presented.

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P A011

Unprecedented insight into the structure of fatty-acid based (nano)materials enabled by mechanochemical ^{17}O-labeling schemes

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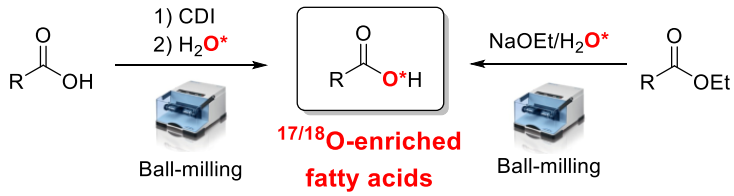
Fatty acids are omnipresent in biological systems, with applications in the fields of lipidomics and metabolomics, as well as in human nutrition research. They are also widely used in the production of materials, for example as surfactants in nanoparticles syntheses. Yet, several questions regarding their structure and reactivity remain, including their mode of binding to some metal cations or their mode of interaction at the surface of (nano)materials.

^{17}O isotopic labeling is a potentially powerful approach to access this type of information using NMR, yet, until recently,^{17}O NMR spectroscopy had not yet been used for studying complex fatty-acid systems. Indeed, previously described ^{17}O labeling protocols were not only rare and costly, but also suffered from long reaction times, experimental constraints and/or poor experimental description. As an answer to this situation, we have developed user-friendly and cost-efficient protocols for the labeling of fatty acids using mechanochemistry.[1] Here, ball milling enabled to introduce ^{17}O into fatty acids using minimal amounts of costly ^{17}O-labeled water. This labeling strategy was then used to reach unprecedented insight into the structure of ^{17}O-enriched fatty-acid based (nano)materials.[2]



✓ Low-cost (µL amounts of H_2*O)
✓ High yield & enrichment
✓ Applicable to EPA & DHA

⇨ New information on (nano)materials structure & reactivity via ^{17}O NMR

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P A012

Bimetallic complexes of photoswitchable phosphines derived from nine-membered cyclic azobenzenes : synthesis, photochromic properties and uses in gold catalysis

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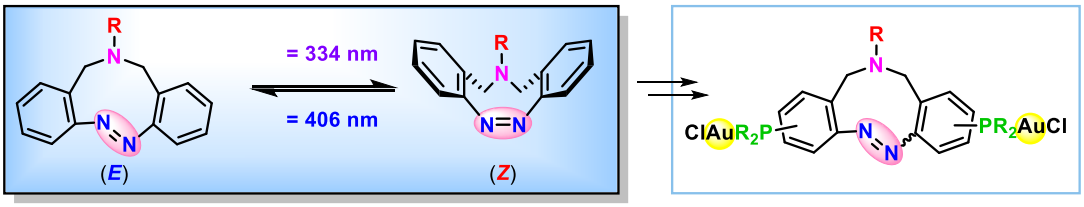
Azobenzene photoswitches are widely used to tune the properties of biomolecules, catalysts or materials, using light as an external stimulus.[1] Especially, the range of structural and photophysical properties of azobenzene photoswitches could be extended significantly with the development of cyclic species. For example, eight-membered ring azobenzenes called diazocines have been extensively studied the past decade.[2] Nevertheless, only two studies have reported the synthesis of nine-membered cyclic azobenzenes.[3]

In this context, we have developed a new family of cyclic, C2-symmetric photoswitchable molecules, the 13-dihydro-11*H*-dibenzo[*c*,*h*][1,2,6]triazonines. These nine-membered cyclic azobenzenes display a nitrogen function in the saturated ring chain. Their properties, i.e. *E*-preference combined with bistability over a large temperature range, nicely complement the properties of the known acyclic azobenzenes and diazocines. The specific features of these compounds are (*i*) a preferred *E*-configuration, (*ii*) nearly quantitative bi-directional photoswitching, (*iii*) high thermal stability of both *E*- and *Z*-forms.[4]



We used this new backbone to synthesize the corresponding diphosphines and bimetallic gold (I) complexes. These new photoswichable catalysts, which retain the intrinsic properties of the triazonine backbone, have been used in selected reactions to evaluate their catalytic activities.

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P A013

Late-stage functionalization of a fluorescent scaffold to afford a new generation of large Stokes shift red-emitting dyes with promising properties for biological imaging

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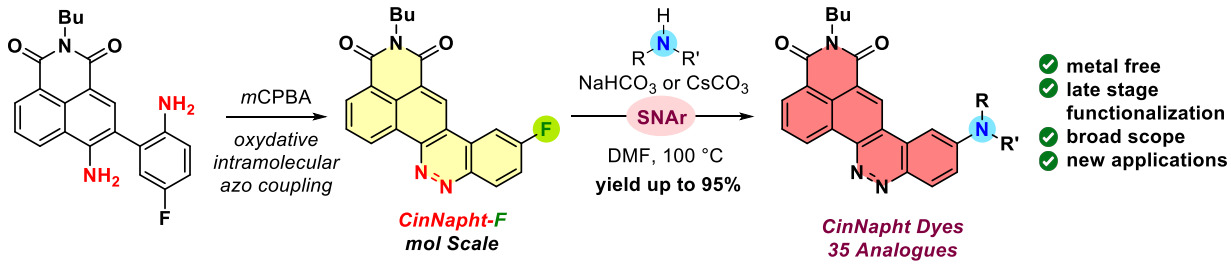
With the increasing interest of optical molecular imaging in medicine, fluorescence microscopy has seen constant development contributing to the emergence of new technologies and probes without discontinuity for the past decades. Fluorogenic probes are now considered as critical tools for the study of biological environments.[1] Therefore, there is definite interest in creating a new easily tunable chemical scaffold exhibiting fluorescent behavior that could later be used for the design of such probes. In this context, our group has investigated the synthesis of a fused ring cinnoline/naphthalimide hybrid here called "CinNapht" dyes.[2] The first generation of these new fluorophores exhibits original and promising properties in conventional fluorescence: a red emission, a large Stoke Shift, a strong solvatochromism, high chemo- and photostability and biocompatibility.[3] Here we present a an easy access to numerous analogues of CinNapht dyes by late-stage functionalization and a study of their photophysical properties. We have re-designed the synthesis via a fluorinated CinNapht-F intermediate that can react with a wide variety of amines in a SNAr type reaction. The reaction conditions and its scope have been investigated. We have now an easy access to new fluorophores with improved photophysical properties associated with a true utility for cell imaging applications such as organelle imaging.



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P A014

Photoredox Generation of Oxygen-Centered Radicals: α-Alkoxylation and α-Trifluoromethoxylation of Carbonyl Compounds

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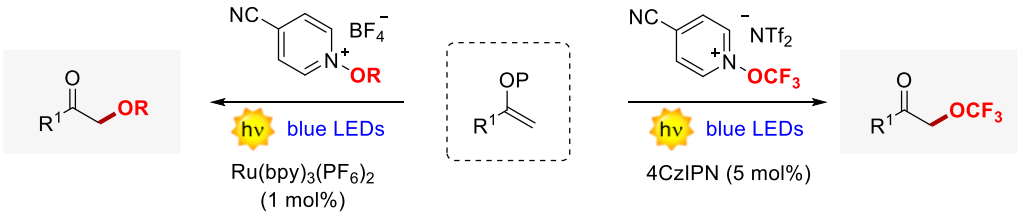
O-centered radicals play a central role in many natural processes, from atmospheric chemistry to biology.[1] In organic synthesis, by contrast with their C-centered analogs, they are regarded as highly reactive intermediates, which are essentially prone to undergo β-scission or HAT processes, furnishing eventually a more stable C-centered radical. Recently, our group has been interested in new alkoxylation reactions, by trapping these O-centered radical species with efficient radical acceptors in order to create new C-O bonds.[2] In particular, we were able to synthesize a wide range of new α-alkoxylated ketones and amides which are otherwise difficult to access (Scheme 1, left).[3] In addition, in collaboration with the groups of Pr. A. Togni (ETH Zurich) and Dr. L. Dell'Amico (University of Padova), a methodology to prepare α-trifluoromethoxylated carbonyls could also be successfully developed (Scheme 1, right).[4] Although quite similar, in-depth mechanistic studies showed a quite distinct mechanism between both protocols, which will be presented herein together with their scope and limitations.



- *48 examples, up to 89% yield*
- *One-pot process from carbonyls*
- *Photocatalyzed mechanism*
- *Compatible with complex alkoxy groups*

- *29 examples, up to 52% yield*
- *Mild metal-free method, in batch or flow*
- *Radical chain mechanism*
- *Applicable to biorelevant molecules*

Scheme 1

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P A015

Synthesis of aziridines and reactivity of ketenes in flow

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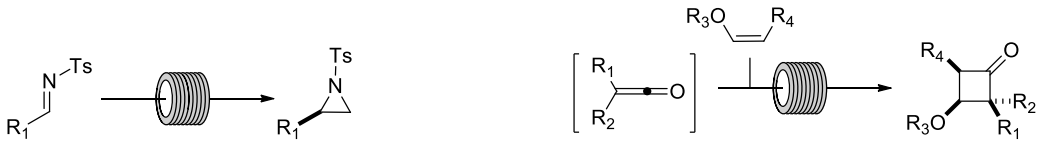
With years of experience working on ketenes[1] and total synthesis of natural products,[2] the SeRCO team recently discovered a formal (3+2) cycloaddition of ketenes with aziridines,[3] affording in very good yields a direct synthetic pathway to γ-lactams, a very common motif in natural products.

To bring additional diversity in this process, we decided to study this reaction using flow chemistry, and especially the generation of ketenes.[4] Flow chemistry often solves problems of efficiency and safety, offering a more robust and reliable way to synthesise and manipulate reactive species and hazardous or toxic compounds. The generation of ketenes perfectly encompass these problems, but the flow generation of ketene is so far limited to nucleophilic addition.

In this work, we have studied the flow generation of ketenes in [2+2] cycloaddition affording crucial information on the overall process (solvent compatibility, kinetic of the cycloaddition, base to be used…). In addition, aiming at developing the overall (3+2) cycloaddition process using flow techniques, the arduous, non-reliable, thus problematic aziridine batch synthesis was also studied using flow chemistry.



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P A016

Modular approach to substituted pyridoazepinones

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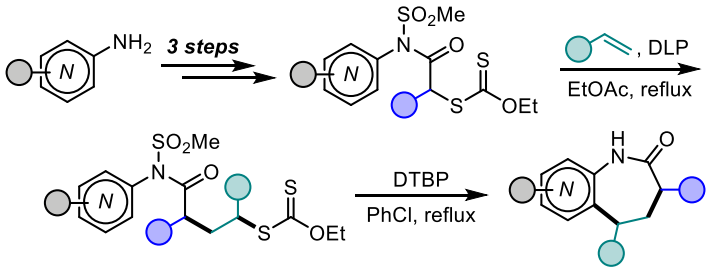
Pyridoazepinones are a pyridine-containing scaffold present in natural products and synthetic medicinally-relevant compounds.[1] It also may serve as a classical isostere of the benzazepinone motif, which is a part of various biologically active substances. However, no general method for the preparation of pyridoazepinones has been described until these days, and the existing strategies suffer from low functional group tolerance and harsh conditions.

The proposed strategy toward pyridoazepinones is based on the radical chemistry of xanthates and uses commercially available aminopyridines as starting materials. It features the construction of the seven-membered ring by C-C bond formation via the xanthate addition-transfer process to non-activated alkenes, followed by radical cyclization and re-aromatization of the pyridine ring, enabled by homolytic cleavage of the sulfonamide bond.[2]

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



Synthesis of [3,2-b], [4,3-b] and [2,3-b] isomers • 24 examples • Derivatization • One-pot and gram-scale synthesis

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P A017

Indirect Enantiocontrol of Tertiary Alcohols and Quaternary Centers by Acylative Organocatalytic Kinetic Resolution

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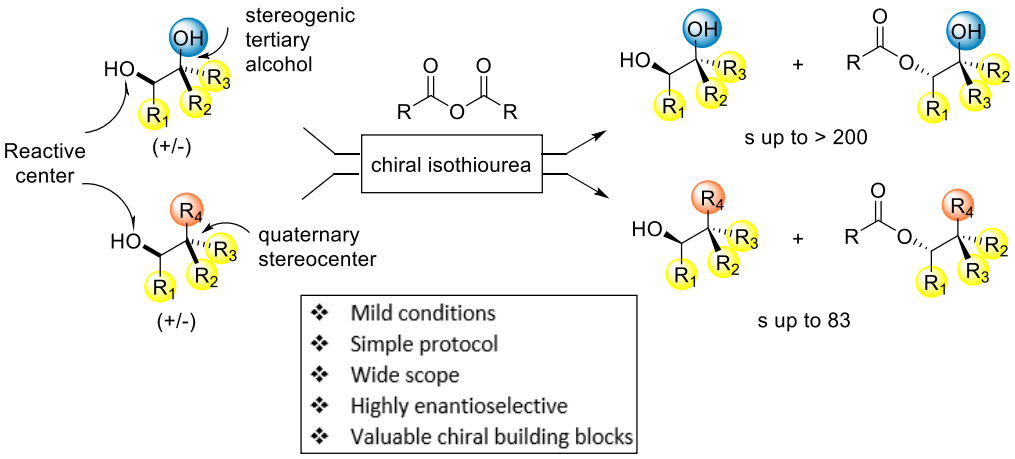
The stereocontrol of chiral tertiary alcohols and quaternary stereocenters represent a recurrent challenges in organic synthesis. In our laboratory, we elaborated a simple, efficient, and indirect strategy to enantioselectively prepare both of these challenging targets through a chiral isothiourea* catalyzed selective acylation of adjacent secondary alcohols. This transformation enables the kinetic resolution (KR) of easily prepared racemic diastereoenriched precursors. In the first challenge, secondary/tertiary diols provided both monoesters and starting diols in highly enantioenriched forms (s-value>200).[1]
In the second challenge, this indirect method was also used to control the quaternary centers, providing desired product with s value up to 185.[2]



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P A018

Mechanosynthesis of Iminosydnone-based APIs

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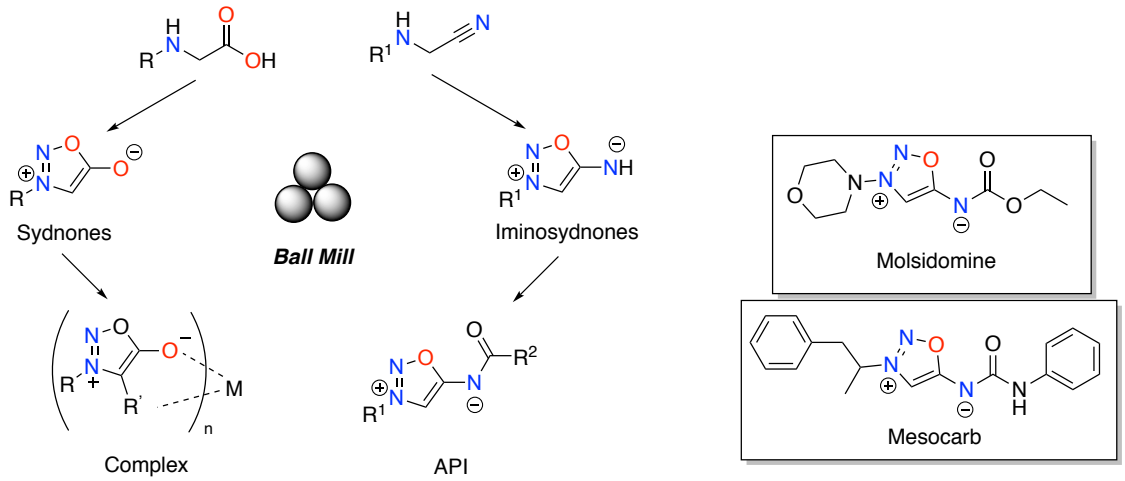
Mesoionic compounds like sydnones, iminosydnones and münchnones are dipolar five-membered heterocycles displaying noteworthy chemical properties and biological activities. For instance, functionnalized sydnones and iminosydnones are key structures for bioconjugation applications via 1,3-dipolar cycloadditions.[1] Besides, several substituted iminosydnones are commercialized for decades as drugs, especially in the cardiovascular field.[2] Mechanochemistry, i.e. inducing chemical reactions through mechanical forces, for instance in ball mills, was recognized in 2019 by IUPAc as one of the "10 chemical innovations that will change the world".[3] Hence solventless syntheses of organic molecules have developed dramatically in the last years, providing "green" and efficient methods to access bioactive molecules.[4] As our team recently designed the mechanosynthsesis of sydnones and of relative coordination complexes,[5] we tackled the development of a mechanochemical method to access several bioactive iminosydnones.[6] So, in this communication we will present our last results on the synthesis of iminosydnone-based Active Pharmaceutical Ingredients (API) such as Molsidomine and Mesocarb via ball milling.



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P A019

Chemoenzymatic synthesis of DNA & XNA oligonucleotides

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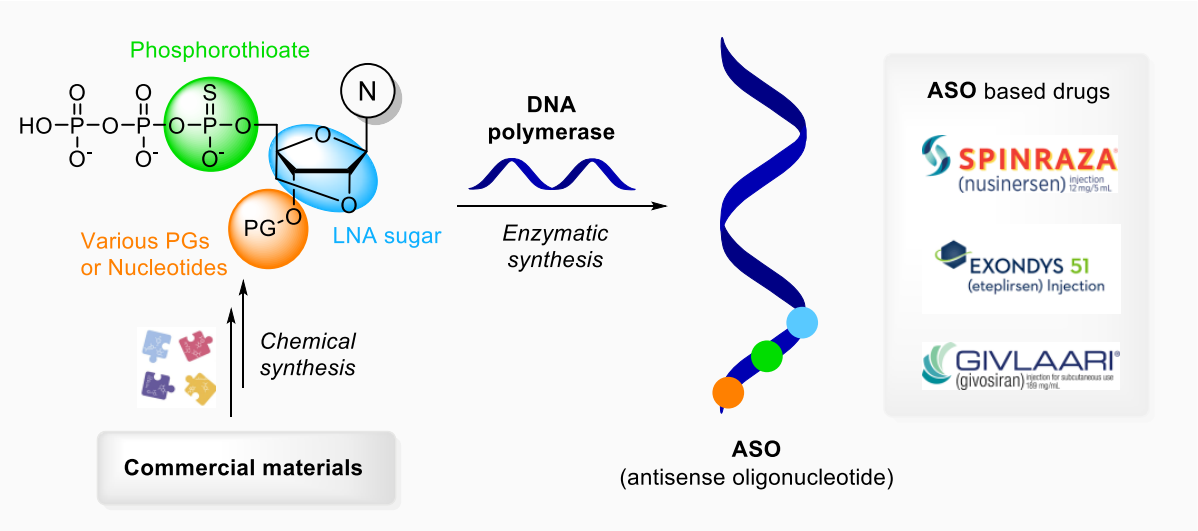
Recent advances of mRNA-based vaccines[1] and FDA-approval of various antisense oligonucleotides (ASO)[2] clearly demonstrates the importance of therapeutic oligonucleotides. There is a high and steadily increasing demand for the synthesis of chemically modified oligonucleotides. Antisense oligonucleotides (ASO) as an efficient therapeutics require the introduction of different chemical modifications in order to improve their biological stability, pharmacokinetic properties and drug delivery efficiency. In this context, sugar (locked nucleic acids, LNA) and phosphate backbone (phosphorothioate) are the most favored sites for the modifications. Controlled chemoenzymatic synthesis of DNA and XNA (xeno nucleic acid) is a highly emerging alternative that circumvents the limitations of traditional solid-phase synthesis.

Scheme



Herein, we report the chemical synthesis of variously modified nucleoside triphosphates (dN*TPs) containing phosphorothioate (PS),[3] locked sugar (LNA),[3] 3'-protecting groups (phosphate, Bz, Piv, Mesitoyl, Piv, allyl, Me, CH_2N_3)[4,5] as well as 3'-prolonged trinucleotides. Thereafter, we tested these dN*TPs as substrates for the controlled enzymatic synthesis of DNA and XNA oligonucleotides using TdT and PEX reactions with diverse DNA polymerases. As a result, moderate to high levels of incorporations into DNA and XNA were achieved.

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P A020

Excited State Intramolecular Proton Transfer based Fluorophores with Circularly Polarized Luminescence Emission

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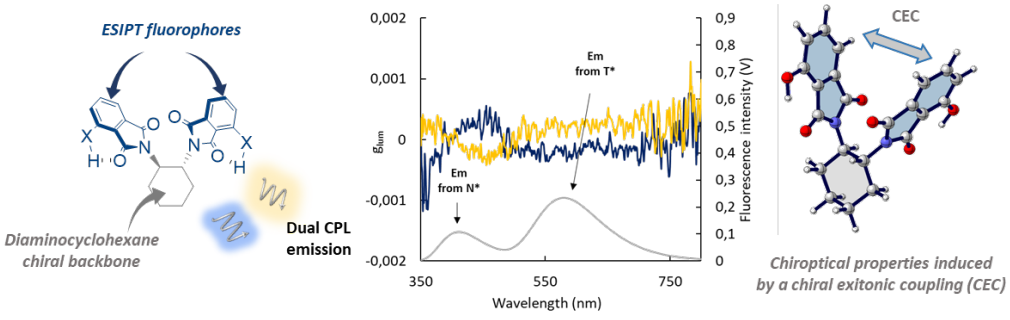
The design and study of small organic molecules exhibiting circularly polarized luminescence emission (CPL-SOMs) has recently gained momentum, notably because such chiral molecules have a wide variety of potential applications in photonic and optical devices. These last five years, important efforts have been made in order to merge CPL emission properties with other particular photophysical phenomenon. Indeed, such a combination is mandatory to unlock the potential of CPL emitters in terms of application. Hence, CPL-SOMs displaying phosphorescence or aggregation induced emission properties has been recently developed. In this context, our group has pioneered the development of Chiral TADF materials, which is today the subject of numerous research works [1]. Despite all the recent advances in this active domain of investigation, no molecular design allowing to combine CPL and Excited State Intramolecular Proton Transfer (ESIPT) fluorescence has been described until recently. ESIPT fluorophores display numerous interesting properties, such as large Stoke-shift or dual emission properties. Due to these particular characteristics, ESIPT fluorophores have found applications in a large number of domains such as Biology for sensing purposes or in Material Science as emissive dopants in OLED [2]. In this presentation, I will describe the first molecular design allowing to gain access to ESIPT fluorophores with CPL emission [3]. In this new class of emitters, the chiroptical activity originates from a chiral excitonic coupling induced by the tethering of two ESIPT fluorophores via a readily accessible 1,2-transdiaminocyclohexane scaffold. Using this approach has notably allowed to synthesize in one step a CPL molecule displaying very large Stoke shifts (up to 222 nm in toluene solution) and one of the rare example of CPL active dual-emission materials.



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P A021

Development of Highly Efficient Cyclic(alkyl)(amino)carbene Ruthenium Complexes for Olefin Metathesis

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[3] *UCSD-CNRS Joint Research Laboratory (IRL 3555), Department of Chemistry and Biochemistry, University of California, San Diego, La Jolla, California, 92093, United States*

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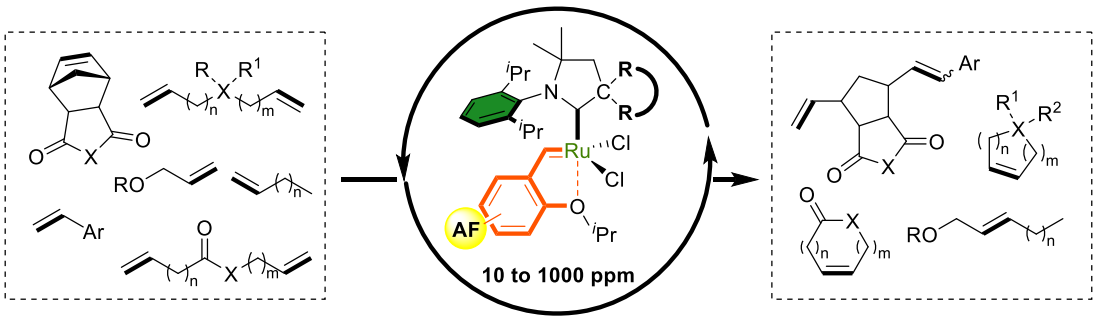
The versatility of Olefin Metathesis (OM) is evident from its successful application to natural product synthesis, to pharmaceutical and crop science, the valorization of renewable feedstocks or the preparation of new materials.[1] N-Heterocyclic-Carbene (NHC) ruthenium complexes are recognized for their high catalytic efficiency. However, they face stability issues in presence of ethylene, a common byproduct for OM.[2,3] Cyclic(alkyl)(amino)carbene (CAAC) ruthenium complexes do not undergo the common degradation path, being more stable but at the same time less reactive.[4] Herein we report on the synthesis and the catalytic activity of a new series of bench-stable CAAC-Ru catalyst bearing stabilizing bulkier substituents on the heterocyclic moiety and a strategic activating functionalization (AF) on the styrenyl fragment. These complexes revealed to be highly competent for Ring-Closing Metathesis (RCM), Cross-Metathesis and Macrocyclization also at low to very low catalytic loading (10-1000 ppm).



Ring-Closing Metathesis - Cross-Metathesis - Macrocyclization - Ring-Opening-Cross Metathesis

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P A022

Fluorogenic dimers as bright switchable probes for enhanced super-resolution imaging of cell membrane

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Super-resolution fluorescence imaging based on single-molecule localization microscopy (SMLM) enables visualizing cellular structures with nanometric precision. However, its spatial and temporal resolution largely relies on the brightness of ON/OFF switchable fluorescent dyes. Moreover, in cell plasma membranes the single-molecule localization is hampered by the fast lateral diffusion of membrane probes. Here, to address these two fundamental problems, we propose a concept of ON/OFF switchable probes for SMLM based on fluorogenic dimers of bright cyanine dyes. In these probes, the two cyanine units connected with a linker were modified at their extremities with low-affinity membrane anchors (figure 1). Being self-quenched in water due to intramolecular dye H-aggregation, they displayed light up in apolar and viscous media, including lipid membranes. Charged group in the linker further decreased the probe affinity to the lipid membranes, thus accelerating its dynamic reversible ON/OFF switching. The concept was validated on red cyanine 3 and far-red cyanine 5 dyes. SMLM of live cells revealed that the new probes provided higher brightness and ~10-fold slower diffusion at the cell surface, compared to reference probes Nile Red and DiD, which boosted axial resolution of biomembrane imaging >3-fold down to 31 nm. The new probe allowed unprecedented observation of nanoscale fibrous protrusions on plasma membranes of live cells with 40-s time resolution, revealing their fast dynamics. Thus, going beyond the brightness limit of single switchable dyes, using cooperative de-quenching in fluorogenic dimers, and slowing down probe diffusion in biomembranes open the route to significant enhancement of super-resolution fluorescence microscopy of live cells.

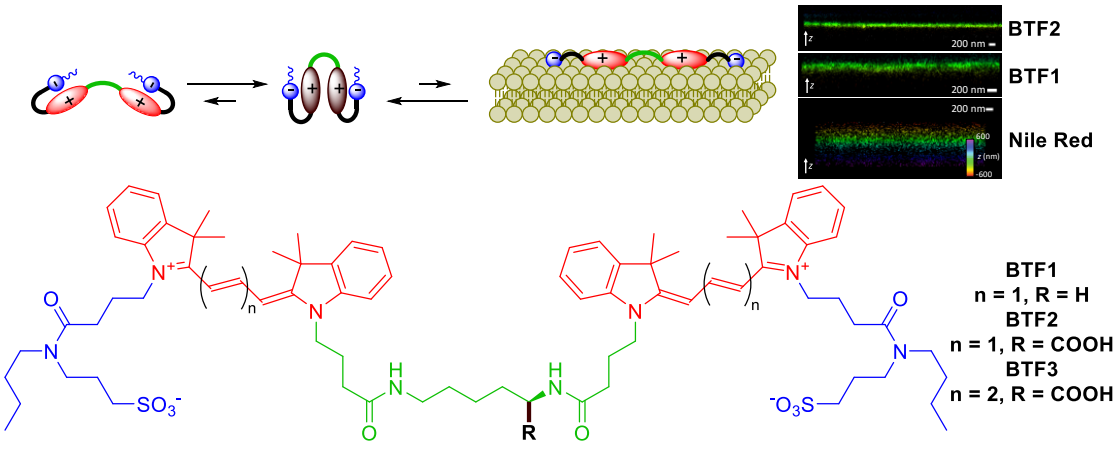

Figure 1: Prinple of designed BTF probes and their chemical structures

P A023

Cycloadditions of π-Allylpalladium(II) Intermediates towards Medium-Sized *N*-Heterocycles

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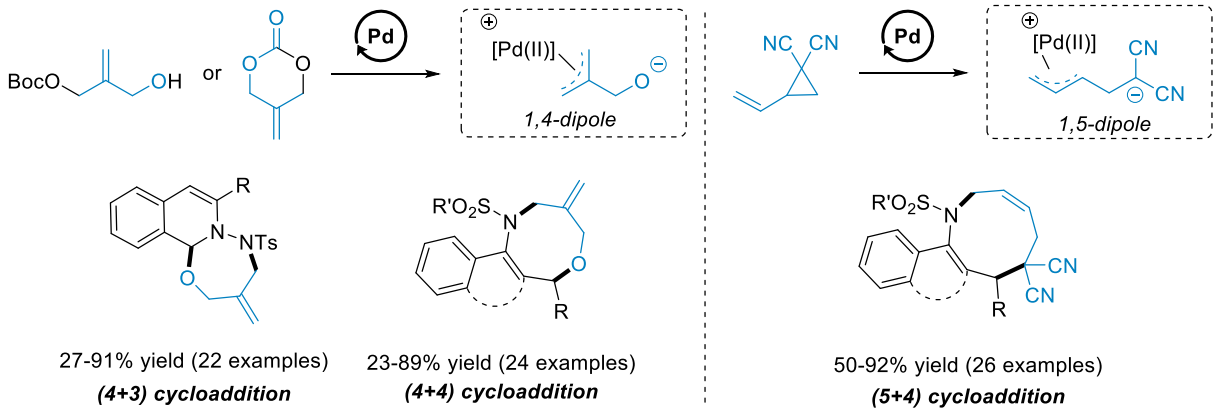
Medium-sized *N*-heterocycles are scaffolds of high importance in medicinal chemistry and are widely encountered in biologically active molecules.[1] While numerous synthetic strategies focus on the preparation of five- or six-membered rings, the need for efficient methodologies towards polysubstituted and stereodefined medium-sized *N*-heterocycles remains an important challenge for organic chemists.

π-Allylpalladium(II) zwitterionic intermediates, which can be obtained from various precursors after oxidative addition by a palladium(0) catalyst, have emerged as versatile precursors for the preparation of a wide variety of carbo- and heterocycles.[2] Our research group recognized their remarkable synthetic potential for the preparation of medium-sized *N*-heterocycles. A 1,4-oxygenated-dipole allowed the efficient preparation of seven-membered oxadiazepines, using *in situ* formed azomethine imines from hydrazones *via* a sequential silver(I)/palladium(0) catalysis. This dipole is also suitable for (4+4) cycloadditions towards eight-membered oxazocines. Nine-membered azonanes were also prepared thanks to the discovery of a reactivity switch of vinylcyclopropane under a palladium(0) catalysis, as they react as an all-carbon 1,5-dipole.[3]



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P A024

Rhodium(II)-catalyzed aromatic cyclopropanation

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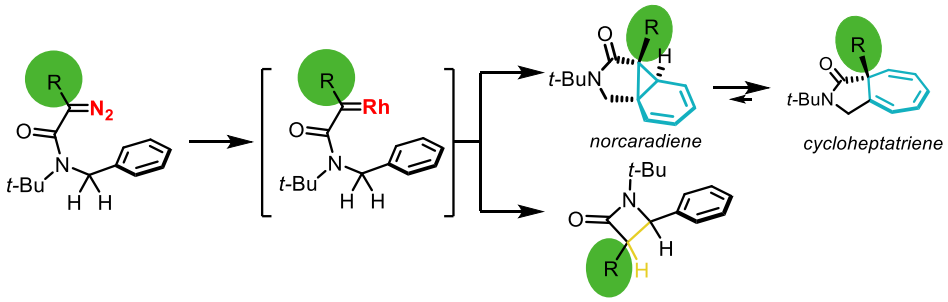
Carbenes are important synthetic species used in diverse types of reactions.[1] Among them, the cyclopropanation between a carbene and an aromatic ring, namely the Buchner reaction is a powerful method to build polycyclic systems.

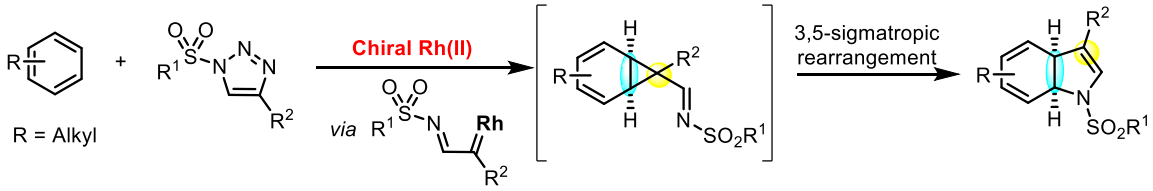
The development of organometallic catalysis has allowed major advances in carbene chemistry. Indeed, the formation of metallocarbene intermediate allow this transformation occurs in a much more efficient and selective way.[2,3]Among them, asymmetric intramolecular Buchner reaction was found as an efficient strategy to prepare enantioenriched seven-membered carbocycle-containing bicyclic compounds.[4] However, the competitive C-H insertion reactions are frequently observed in these transformations, although the factors responsible for this competition remain unclear.

Firstly, we decided to study the chemoselectivity of the intramolecular carbene insertion catalyzed by dirhodium(II) catalysts. This study has revealed some factors influencing the C-H insertion versus the cyclopropanation.



Scheme 1. Metallo-carbene insertion pathways

In parallel, we studied the intermolecular cyclopropanation with unactivated arene, which has little be studied due to the formation of many side products.[5] We then explored an asymmetric intermolecular cyclopropanation of α-imino rhodium(II) carbene complexes generated from *N*-sulfonyl-1,2,3-triazoles with aromatic rings. In this case, the cyclopropanation is followed directly by a sigmatropic rearrangement yielding dihydroindoles.



Scheme 2. Tandem Cyclopropanation/Sigmatropic rearrangement of N-sulfonyl-1,2,3-triazoles

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P A025

Radical Addition of SF_5Cl to Cyclopropenes: Synthesis of (Pentafluorosulfanyl)cyclopropanes

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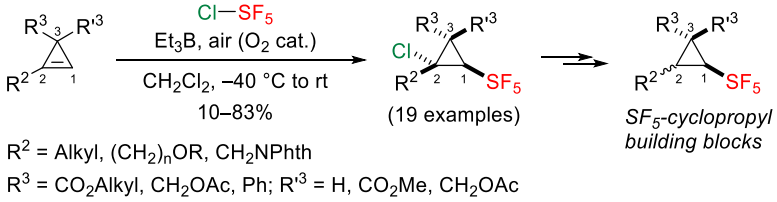
The cyclopropyl fragment appears in the top ten of the most encountered ring systems in drugs.[1] Fluorine or fluorinated groups are frequently used to improve the potency, the selectivity and the pharmacokinetic properties of a lead compound and are found in nearly a third of marketed pharmaceuticals and agrochemicals.[2] As a consequence, the development of cyclopropanes bearing fluorinated groups, which combine both these latter structural elements, has attracted significant interest. [3]

With the goal of accessing cyclopropanes bearing the "emerging" pentafluorosulfanyl substituent (SF_5),[4,5] the radical addition of SF_5Cl to cyclopropenes was investigated. Addition of the SF_5 radical, generated from SF_5Cl by initiation with Et_3B,[6] occurs regioselectively at the less substituted carbon of the cyclopropenes and *trans* to the most hindered substituent at C3, while chlorine atom transfer (at C2) proceeds with moderate to high levels of diastereocontrol. The carbon-chlorine bond in the resulting adducts can undergo subsequent radical reduction or be involved in a radical cyclization.



This transformation enables access to diversely substituted building blocks incorporating a (pentafluorosulfanyl)cyclopropyl moiety.[7]

Acknowledgment: Financial support from the ANR (DEFIS project, ANR-17-CE07-0008) is gratefully acknowledged.

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P A026

Synthesis of 4-phosphonyl-pyrrolidin-3-ones via [3+2] cycloaddition of nitrones with phosphonylallenes

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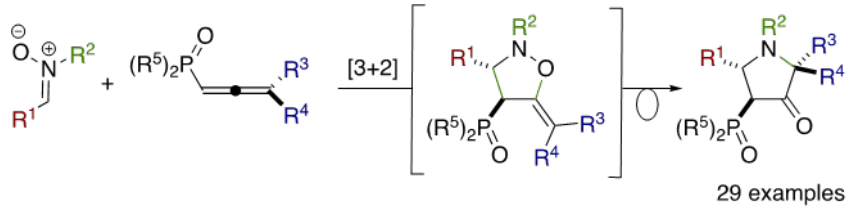
The 1,3-dipolar cycloaddition is an efficient method for the preparation of various five-membered heterocycles, often in high yields and with excellent stereocontrol. Cycloadditions of nitrones with alkenes and alkynes are well studied and lead, depending on the nature of the substrates and the operating conditions, to isoxazolidines, isoxazolines, acylaziridines, or β-lactams.[1] Compared to these well-documented examples, only a few 1,3-dipolar cycloadditions of nitrones with allenes have been reported, usually bearing electron-withdrawing groups.[2]

In this context, we report the 1,3-dipolar cycloaddition reaction of nitrones with phosphonylallenes, leading to a new family of pyrrolidine-3-ones. The optimal operating conditions were evaluated according to several parameters (solvents, temperature: classical heating or microwave irradiation, influence of Lewis acids...). A series of 4-phosphonylpyrrolidine-3-ones was obtained in good to excellent yields and with very good diastereoselectivities (Scheme 1). Some insights into the mechanism were found using DFT calculations.



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P A027

Sterically Hindered Pyridines Derived from 1-azatriptycene

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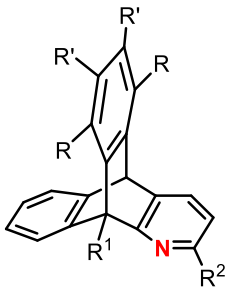
Azatriptycenes such as 1-azatriptycene belong to an unexplored class of fused pyridines to a triptycene core.[1]

Based on the unique three-dimensional rigid structure of triptycene scaffold, the 1-azatriptycene derivatives may result in unprecedented types of pyridines with quaternary stereogenic carbon center at the ortho position of the nitrogen atom which can be used as nucleophilic catalysts for asymmetric reactions process or as ligands for the design of transition metal complexes.[2,3]

The structural properties of the 1-azatriptycene could be modulated by introducing alkyl and aryl groups to increase the steric hindrance around the nitrogen in order to be used as Lewis base in frustrated Lewis pairs chemistry for the hydrogenation of unsaturated compounds.[4,5]



1-azatriptycene

Synthesis
X-ray analysis
Buried Volume
Basicity
Reactivity

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P A028
The added-value of chirality in molecular materials

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Exploring how chirality can improve functions in molecular materials have recently emerged as a promising direction in material science, due to the specific interaction of a chiral molecule with a circularly polarized (CP) light and its ability to filter the spin of electron upon charges conduction.[1] In this communication, I will illustrate our contributions in this research area with our last results regarding: *-1)* **The design of chiral luminophores for making CP-OLED**,[2] which can emit polarized electroluminescence and maximize the autonomy and contrast performances of conventional displays (Figure 1a); and *-2)* **The synthesis and characterization of innovative chiral open-shell molecular systems**,[3] showing an uncommon energetic inversion of their SOMO and HOMO levels (Figure 1b).

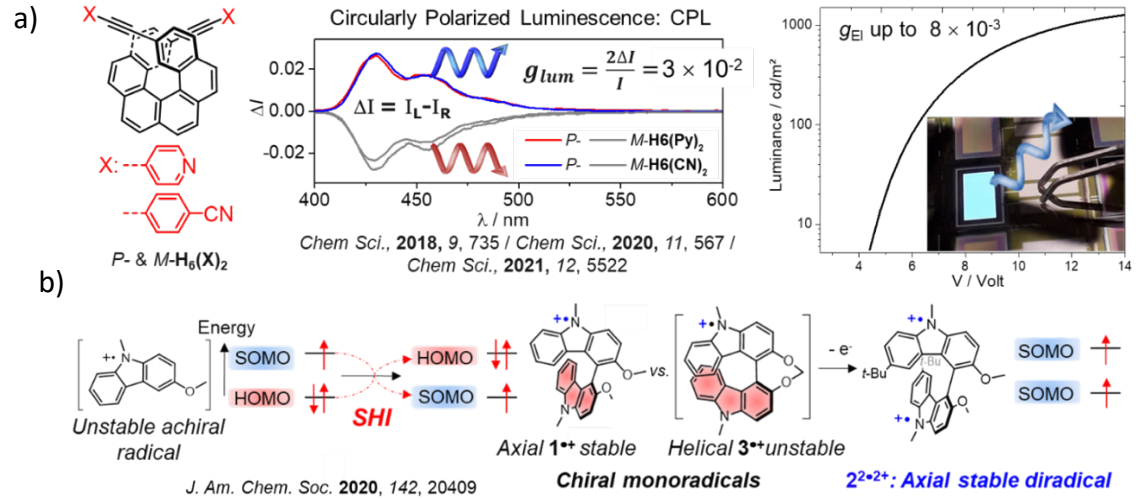

Figure 1: a) Chemical structures of helicene-based CPL emitters with the corresponding CP luminescence and electroluminescence spectra; b) Illustration of the SOMO-HOMO inversion (SHI) process found in organic radical chiral bicarbazole systems.

I hope that these examples will further highlight the importance of considering the property of chirality in material science, and may offer new opportunities for designing innovative chiral closed- and open-shell molecular materials.

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P A029

Electrocatalytic Oxidation of Alcohols towards added-value products using Acceptor-less Dehydrogenation Catalysts

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The development of energy and atom efficiency processes is thought to play an important role for a sustainable chemical industry of the future.[1] One opportunity could be the electrification of thermal processes to benefit from the inherent advantages of electrochemistry, such as safety, scalability, a cheap and traceless redox agent (electrons), and the possibility to directly control the energy input of a given reaction via the applied potential. One elegant example of modern redox chemistry is the alcohol oxidation *via* acceptor-less alcohol dehydrogenation (AAD) catalysts. Although this reaction class provides high atom efficiency, it requires in general a high thermal input and prolonged reaction times.[2] With the effort towards the electrification of such systems in mind, we have recently shown that a Milstein-type AAD catalyst can be activated electrochemically for the generation of ethyl acetate from ethanol under preparative conditions.[3] In this presentation, we show that the electrification of alcohol oxidation processes with AAD catalysts can be extended to produce molecular diversity and to generate added-value products from simple building blocks. We hope that the successful electrification of such atom-efficient systems can contribute to a more energy efficient organic redox chemistry.

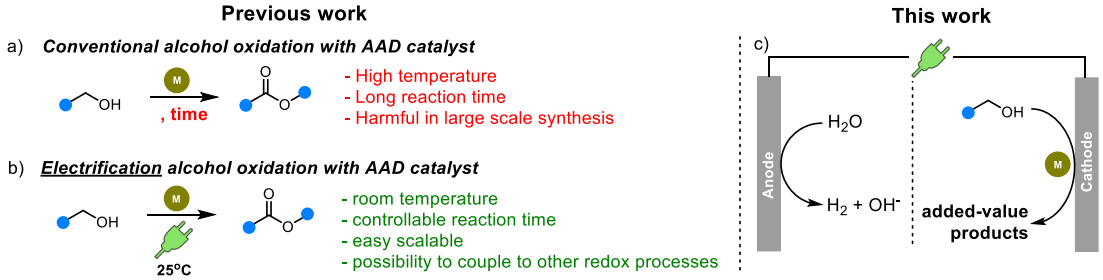

Figure 1. a) Conventional synthetic approach for alcohol oxidation with acceptor-less alcohol dehydrogenation (AAD) catalyst *vs.* b) electrifying approach. c) Schematic represent the production of added-value product with a possibility to electrifying the couple redox process (such as hydrogen evolution reaction).

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P A030

Exploring a new chemical space of RNA binders

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Proteins account for 1.5 % of the human genome but represent 90 % of the drugs targets. Whereas RNAs account for 90 % of human DNA but less then 5 % of the drugs targets. Thus, by targeting proteins, the chances of finding new cures are really narrowed. However, today, more evidences are demonstrated that targeting RNA is possible: In 2020, Risdiplam was the first RNA targeting drug FDA approved.

In our group, we established that combining an aromatic ring with a diamine can generate binders good affinity,[1] but selectivity is still a major issue. In the literature, few examples highlighted that 3D scaffolds can target particular secondary structures of RNA. [2]

In this context, this work focuses on the development of new RNA ligands bearing three parts: a spiro scaffold to target precise RNA structures, as well as an aromatic and diamine moieties for the affinity towards RNA. The chemical sequence relies on the following chemistry: Starting from a substituted cyclopentadiene, an azo-Diels-Alder yields a precursor of cis-diamine. After cyclisation through an unexampled Buchwald-Hartwig reaction and hydrogenolysis, spiro compounds are obtained. This method provides a variety of unprecedented scaffolds in a few steps. They are useful tools in the quest of selective RNA ligands and probes and expands the chemical space of the aromatic diamino compounds previously reported by our group.

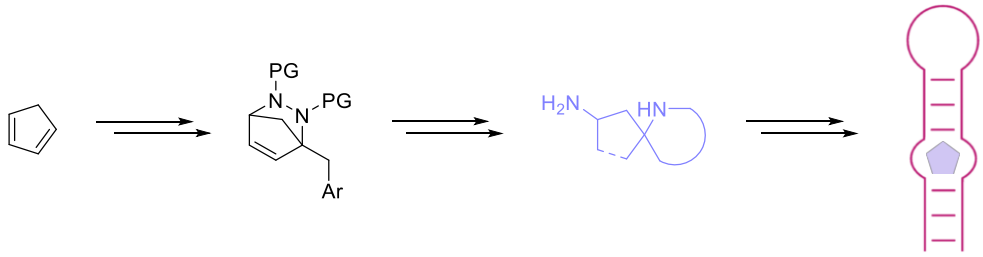

Figure 1.Synthesis of 3D RNA binders

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P A031

Synthesis and applications of planar chiral [2.2]paracyclophanes

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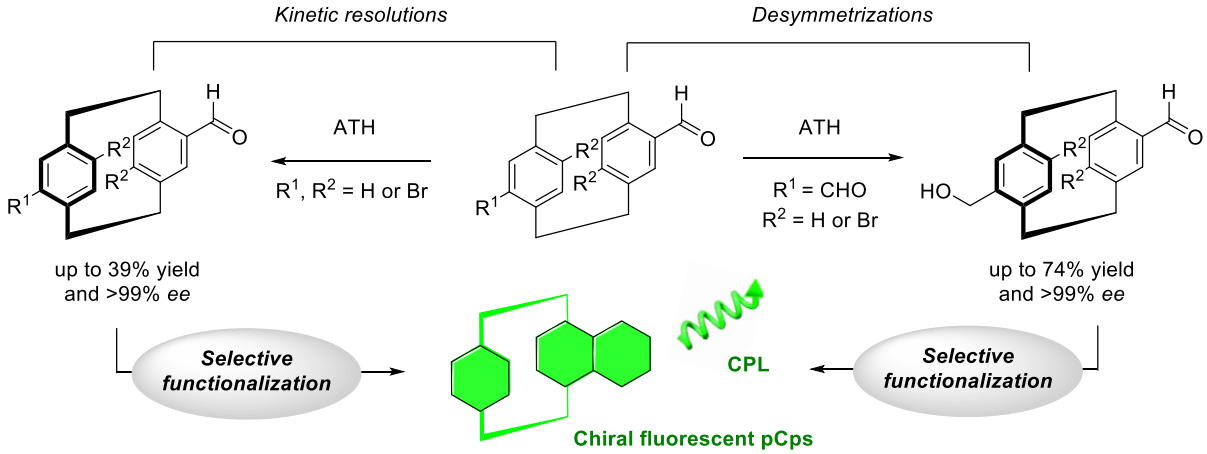
Originally discovered in a serendipitous fashion by vapor phase pyrolysis of *p*-xylene,[1] [2.2]paracyclophane (pCp) and its derivatives have rapidly gained in popularity amongst chemists due to their unique three-dimensional architecture[2] that can give rise to planar chirality.[3] Despite their broad range of applications, optically active paracyclophanes are still mainly obtained through enantiomer separation by chromatography on chiral stationary phases. The optimization of new asymmetric processes providing a practical access to chiral pCps can therefore be considered as a priority in modern cyclophane chemistry.
We have developed a general approach based on asymmetric transfer hydrogenations (ATH) for controlling the planar chirality of a range of substituted [2.2]paracyclophanes. Our strategy enables us to perform both the kinetic resolution of racemic compounds,[4] and the desymmetrization of centrosymmetric *meso* derivatives[5] on synthetically useful scales. The obtained enantioenriched derivatives, which incorporate different reactive groups on each ring of the pCp core, can be used as key intermediates for the preparation of new circularly polarized light (CPL) emitting dyes,[6] and RNA ligands.[7] Based on its broad applicability, our method should reveal to be an extremely useful tool to rapidly access complex planar chiral [2.2]paracyclophanes in their enantiopure form.



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P A032

Regio- and Stereoselective Addition to *gem*-Difluorinated Ene-Ynamides: Access to Stereodefined Fluorinated Dienes

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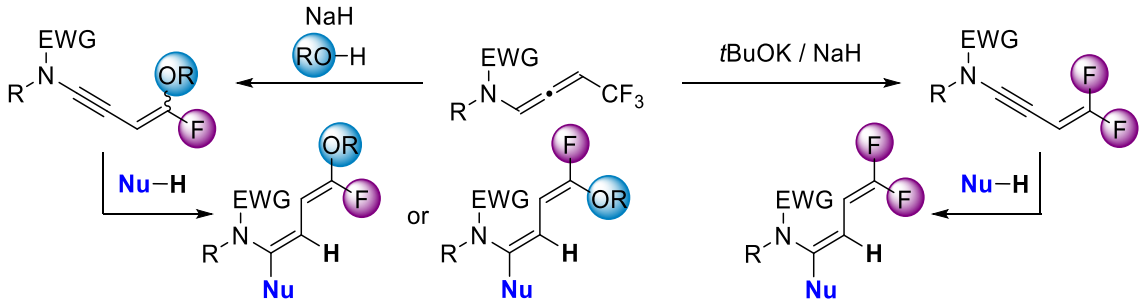
Organofluorine compounds play a pivotal role in life science and agrochemistry. The introduction of fluorine atoms into organic molecules has become a fast and growing research field. *Gem*-difluorinated alkenes are bioisostere of carbonyl compounds[1] whereas monofluorinated alkenes serve as peptides or enol mimics.[2]

N-allenamides can be seen are privileged building blocks due to their interesting balance between stability and reactivity.[3] In particular, trifluoromethylated *N*-allenamides could be obtained through copper-catalyzed addition of diazo compounds on terminal Ynamides.[4]
The first synthesis of gem-difluorinated ene-ynamides will be presented *via* deprotonation of trifluoromethylated *N*-allenamides and δ extrusion of fluorine. These highly reactive species, owing to their dual functional groups, offer a unique entry to difluorinated dienes and to stereodefined mono-fluoro-substituted dienes. Stereoselective addition on the ynamide moiety led to functionalized difluorinated dienes, whereas addition of *in situ* generated alkoxides, generated mono-fluorinated ene-ynamides through domino δ elimination followed by an addition/elimination sequence. The design of custom monofluorinated dienes could be achieved through hydrocarboxylation and hydrochlorination reactions.[5]



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P A033

Directed C-H functionalization of pseudo-anomeric position of glycal substrates by metal-catalyzed processes

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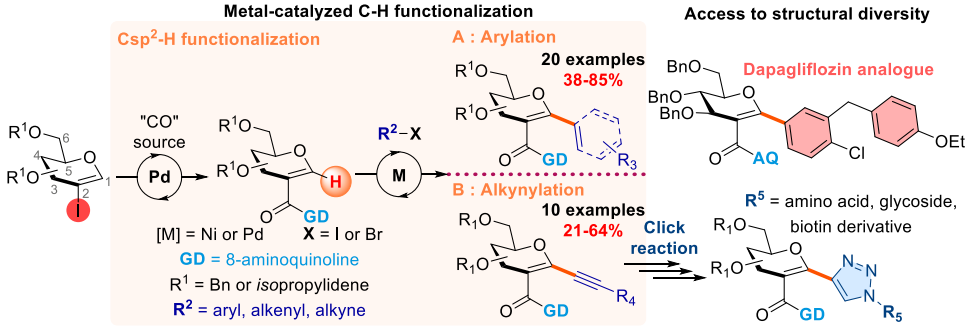
Current synthetic routes for *C*-arylglycosides involve multiple steps via prefunctionalized intermediates and frequently use strong bases. In recent years, C-H bond functionalization has become emerging in synthetic chemistry. To overcome the regioselectivity issues inherent in activating a specific C-H bond in complex substrates, the use of strategically placed directing groups (DG), has proven to be an effective strategy. However, examples of metal-catalyzed C-H functionalization (MCF) on sugars are still rare.[1] MCF of Csp^2-H bonds remains more developed in the literature examples than that of Csp^3-H, thus making glycals ideal partners to build C-C bonds at the pseudo-anomeric position (position 1). Nevertheless, without DG, MCF on glycals occur almost exclusively at its position 2. In order to functionalize the pseudo-anomeric position, it was considered to place a DG at the position 2 of the glycal. The bidentate 8-amidoquinoline DG is very popular in directed MCF examples and can be introduced in C2 via a pallado-catalyzed aminocarbonylation methodology previously developed in the laboratory. Thus, a directed pallado-catalyzed C-H arylation in the pseudo-anomeric position was set up from these C2-amidoglycals (***Erreur ! Source du renvoi introuvable.***, **A**).[2] Through the use of different glycals and iodinated partners, various *C*-aryl/alkenylglycoside structures were synthesized. This allowed the synthesis of glycosylated amino acids and of a Dapagliflozin analogue in excellent yields. Inspired by this arylation, a nickel-catalyzed C-H alkynylation reaction was performed on the same pseudo-anomeric position of the glycal, using the same DG (***Erreur ! Source du renvoi introuvable.***, **B**).[3] This alkynylation gives access to *C*-alkynylglycosides by using various glycals and alkyne bromides. Subsequently, a Huisgen cycloaddition reaction in the presence of copper could be performed, allowing the synthesis of various glycoconjugates in good yields. In particular, a lysine and a biotin derivative were introduced by this route.



Scheme 1: Developed access to C-arylglycosides via directed FCM and molecules of interest

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P A034

Exploiting σ-Hole Interactions in Solution: Chalcogen Bonding Organocatalysis

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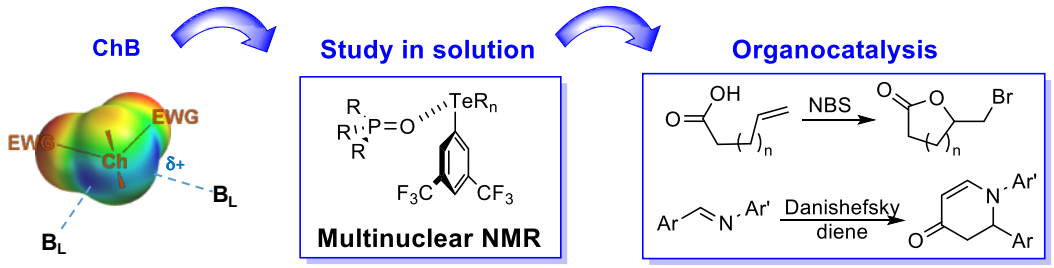
A chalcogen bond (ChB) describes the inter- or intra-molecular noncovalent interaction (NCI) occurring between a Lewis base and a chalcogen atom (Ch = S, Se, Te) acting as Lewis acid. Such NCI is very similar to the more common halogen bond (XB). Both are now understood through the concept of σ-hole, resulting of anisotropic electronic densities within covalently-bonded atoms.[1] Regions of lower density lying on the extension of a σ bond are called σ-holes. Associated with positive electrostatic surface potentials, σ-holes can induce attractive interactions with negative sites (lone pairs, anions, π-electrons) (See Figure, left). ChB has been mostly investigated in solid state, has been identified in biological systems and is currently raising increasing interest in organic chemistry, especially in anion recognition, anion transport and organocatalysis.[2] However, the latter aspects require exploiting and controlling ChB in solution.

The present communication covers our recent results regarding the synthesis of tellurium-based derivatives, the experimental investigations of their ChB in solution (Figure, middle) and their potentiality in the field of noncovalent organocatalysis (Figure, right).[3]



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P A035

Dynamic Combinatorial Libraries of peptides for the identification of protein inhibitors

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Small peptides are an ideal class of therapeutics to target protein-protein interactions (PPIs) considering their low toxicity and ability to mimic the large interacting domain of a protein. Nevertheless, they remain underexplored compared to traditional small drug-like compounds due to intrinsic limitations: relative low stability in the living organism, as well as difficulty to adopt a highly ordered bioactive conformation.[1] To overcome those limitations, two different approaches are well established for engineering PPIs peptidic inhibitors: 1) grafting residues, called “hotspots”, strongly interacting with a targeted protein onto a stable 3D structured scaffold; 2) introducing a covalent conformational constraint through macrocyclization, for instance by cross-linking two side-chains, so-called “stapling”, onto the peptidic hotspot-containing backbone. In our group, we are developing biocompatible protocols enable to generate libraries of potent peptidic PPI inhibitors based on Protein-Directed Dynamic Combinatorial Chemistry (P-D DCC).[2] This method allows the creation of peptidic libraries under thermodynamic control which, upon addition of the biological target, can be re-equilibrated and lead to the amplification of the best inhibitor; thus bypassing expensive and time-consuming parallel synthesis and screening of large library of peptides. Recently, we described a new strategy based on thioester exchange reactions, to dynamically graft amino acids side-chains onto a structurally ordered peptidic β-hairpin scaffold,[3] and we are currently working on dynamic stapling of unstructured peptide for targeting α-helix involved PPIs (Figure).

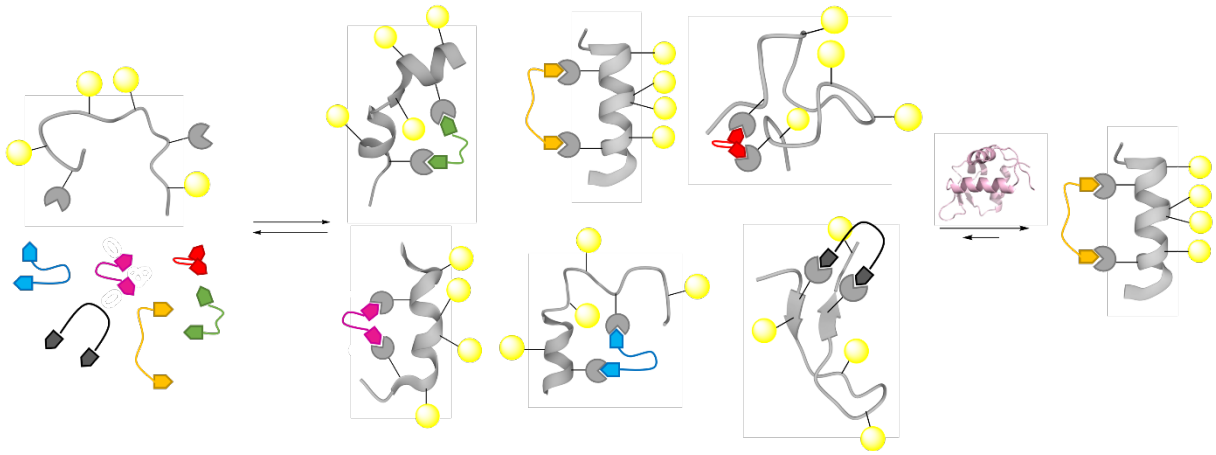

Figure. Step 1: Two-component peptide stapling by dynamic combinatorial chemistry. Step 2: Amplification of the best binder upon addition of oncoprotein hdm2.

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P A036

Catalytic (de)-hydrogenation as stimuli for a rotating molecular switch

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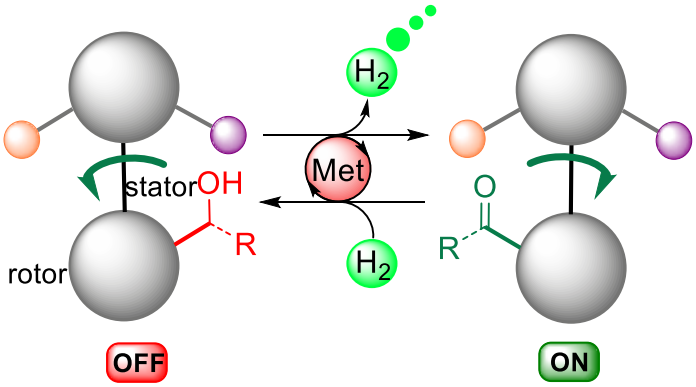
Molecular switches and machines require an energy input to operate, a stimuli which can be based on a chemical fuel such as ATP in nature's biomachinery. However, as a major drawback, most of these chemical stimuli produce undesired chemical waste whose accumulation in the system can rapidly inhibit the machinery. This problem is similar to the one encountered in organic synthesis where chemists have found numerous catalytic transformations considerably decreasing waste generation.
Recently, we launched a program to try to transpose catalytic transformations to the field of molecular switches, machines and smart materials.[1] By an analogy with the catalytic activation of organic molecules through reversible (de)-dehydrogenation,[2] we have transposed this principle to fuel a rotating molecular switch without any waste accumulation.[3] From an alcohol, metal-catalyzed dehydrogenation induces the release of H_2 from the system providing a ketone and a 180° rotation. Placing back the system under an hydrogen atmosphere switches back the system to the initial alcohol through another 180° rotation.



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P A037

Synthesis of new heptazines for photocatalysis, both for homogenous use and grafted on solid support

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Heptazines are a family of aromatic cyclic molecules composed of alternating carbons and nitrogens. They are little studied because of their difficulty in solubilizing. However, they have a very wide range of applications, from photocatalysis to TADF[1]. Our group has developed a synthetic route to create a starting synthon, 2,5,8-tris(3,5-diethyl-pyrazolyl)-heptazine (TDPH), which opens up the field of possibilities for the functionalization of these molecules and also for the modulation of their chemical properties.[22] Despite this, this molecule is expensive to synthesize and time-consuming to purify. The team therefore turned to its analogue, 2,5,8-tris(3,5-dimethyl-pyrazolyl)-heptazine (TDMPH - Figure 1), which is much cheaper to obtain, in order to study its reactivity compared to TDPH. The optimization of this synthesis will be presented, as well as our efforts to introduce substituents of various nature on the heptazine ring (alcohols, organomagnesiums). The objective is also to be able to modulate the degree of functionalization of the starting synthon and to compare the photophysical properties of the different compounds obtained.

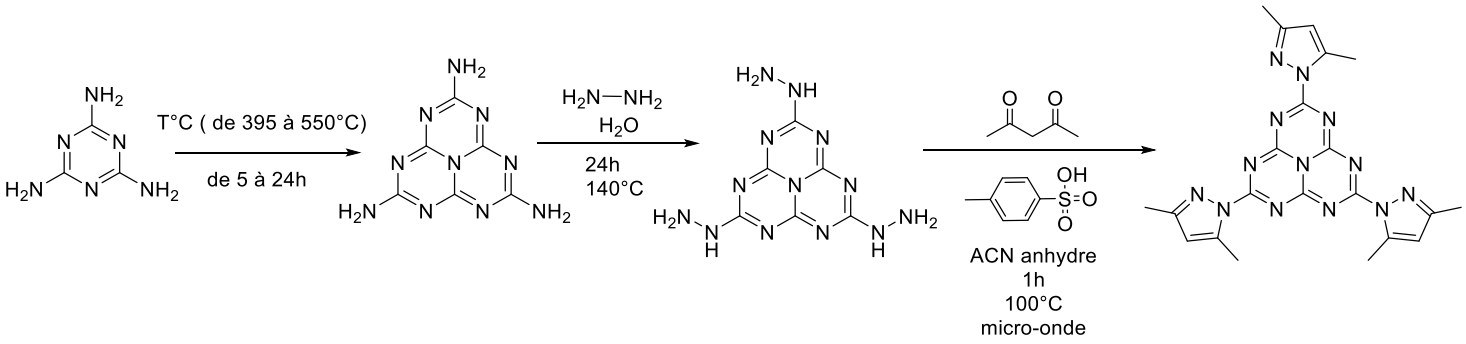

Figure 2- TDMPH synthesis

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P A038
Development of microfluidic devices to selectively detect bacteria by nanoluminescence

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The World Health Organization (WHO) recently reported that “Antimicrobial resistance (AMR) represents a growing threat to global public health and security". At least 50000 annual deaths, across Europe and the US alone, are due to antimicrobial-resistant infections. New resistance mechanisms continue to emerge and spread, undermining the world’s ability to treat common infectious diseases. The need for new antimicrobial agents is essential. Surveillance to monitor the emergence and spread of drug resistance is another crucial component of the global strategy to combat AMR. Thus physicians need to propose the best therapy to patients through (i) identification of the presence or not of bacterial infection and if yes (ii) identification of the bacteria strains involved and their eventual antibiotic resistance profile. Consequently, development of novel rapid, low cost and reliable assays for Antimicrobial Susceptibility Testing (AST) has thus become an urgent priority. Up to now, the gold standard diagnosis methodology for severe infections is done by blood culturing requiring 2-5 days with a low sensitivity (30 to 50% with regard to clinical outcome). Alternative methods have been developed to reduce the amount of time and sample necessary for a reliable measurement by detecting the presence of whole cells by quantifying the oxygen levels or the presence of specific nucleic acid sequences. The use of microfluidic devices has been developing rapidly because of the low sample volumes required, the possibility for multiplexing and the increased growth rate of bacteria due to the high O2 availability. Yet, the detection of the resulting small number of cells remains a challenge since current methods are either expensive (impedance spectroscopy) or lack robustness and reproducibility (SPR).

To address this problem, we propose to design and develop a milli or microfluidic system which could detect selectively a kind of bacteria (gram positive from gram negative at first) and their activity rapidly and efficiently by using luminescence. The design of the device contains quantum dots, known for their good luminescence properties, on which will be linked two probes : one to selectively detect the bacteria, the other to sense their activity by being a pH sensor. The interaction of the probes with the surface of the bacteria will induces changes of the photophysical properties of the nanoparticles. Then these quantum dots will be attached to the surface of the chip by swallowing. The device will then be very sensitive thanks to the detection method, adaptable and selective thanks to the probe used, and It should also allow a faster detection of the bacteria.

P A039

SO_2F_2-mediated *N*-polyfluoroalkylation of weakly nucleophilic nitrogen-containing compounds

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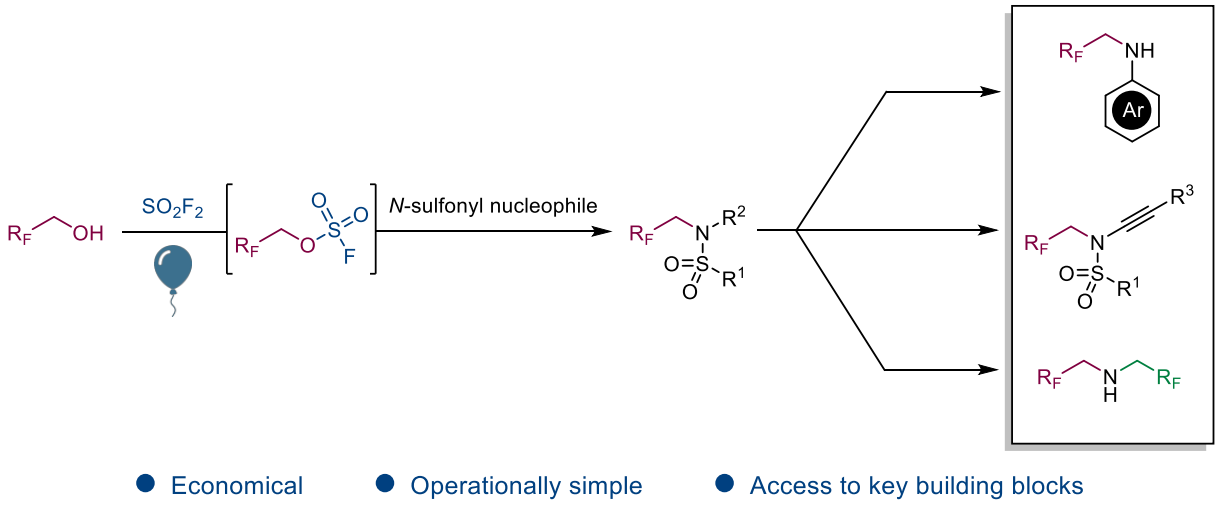
Fluorinated groups are ubiquitous in bioactive compounds as they can greatly improve their physico-chemical properties.[1] For example, one can tune the lipophilicity of a molecule by introducing appropriate fluorinated chains. The metabolic stability and the potency of active ingredients can also be significantly impacted by the introduction of fluorinated groups.

Our work is focused on *N*-polyfluoroalkylation methodologies to access key intermediates with agrochemical and pharmaceutical applications. Based on our expertise in sulfuryl fluoride (SO_2F_2) mediated activation of fluorinated alcohols,[2,3] we took advantage of this reactivity to achieve the *N*-polyfluoroalkylation of weakly nucleophilic nitrogen-containing compounds to access building blocks of high value in Life Science.[4,5]



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[5] Patent with internal number BCS224003 (Bayer CropScience AG / CNRS / Université de Strasbourg: filed 26/07/2022).

P A040

Toward the synthesis of electro- and photo-active rotaxanes

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An efficient synthesis of a family of polyaromatic bis-phosphonium has been recently developed in the laboratory (Fig. 1a). [1] These aromatic dications are electrodeficient systems that can be reduced to radical cation and neutral states (phosphorus bis-ylide) at relatively accessible potentials (Fig. 1b). In this sense, they can be considered as organophosphorus analogues of methylviologens (MV).[2] However, contrary to MV, they possess high quantum luminescence yields both in solution and in solid state and they could be used in electrofluorochromic devices.[3] Nevertheless, the switching sequences systematically led to partial degradation of fluorophores. [1]

On the other hand, it has recently been shown that the formation of rotaxane greatly improves the stability of reactive species and the photostability of certain luminophores through mechanical bonding.[4] Hence, the macrocycle surrounding the axles forms a steric shield protecting the axles from its environment.

The objective of the project is to stabilize bis-phosphoniums by integrating them into rotaxanes (Fig. 1c) in order to obtain fully reversible luminescent switches. The present communication will detail our synthetic efforts toward the preparation of these rotaxanes.

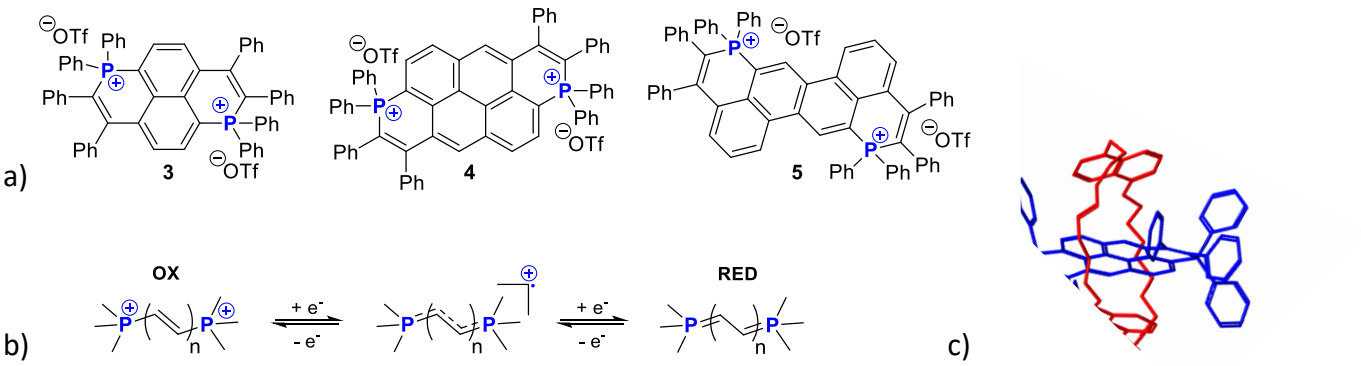

Figure: a) Example of synthesized polyaromatic bisphosphonium, b) General structure of the redox systems containing two phosphorus atoms, c) Representation of a targeted rotaxane.

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KEYWORDS: Bisphosphoniums, Tweezers, Rotaxanes, Molecular recognition

P A041

Hexaphyrin-Cyclodextrin hybrids : tuning aromatic Möbius twist with cavity size and coordination

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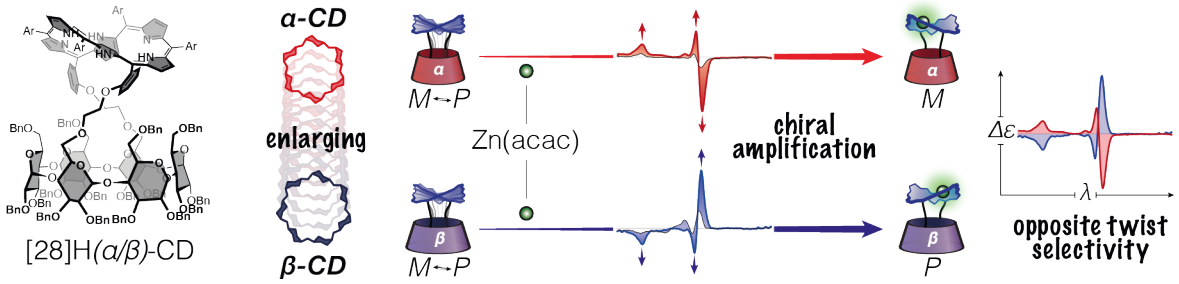
The Möbius [4n] twisted aromaticity, predicted by Heilbronner in the 60's,[1] has long been considered elusive because of its difficulty of access. However, this field has experienced a tremendous growth in the last 20 years since the first synthetic approach described by Herges[2] and the subsequent descriptions by Latos-Grażyński[3] and Osuka[4] of extended porphyrins naturally adopting this twisted aromaticity. Since then, this topology has been extended to other supports, but the control of the chirality inherent to the twist remains a real challenge. In this context, we have developed hybrid structures combining an hexaphyrin (able to adopt Möbius aromaticity) with a cyclodextrin (*i.e.* HCD hybrids).[5] The unique association of both platforms offer a high degree of control over their conformation, (anti)aromaticity and even their chirality. In this communication, we will disclose the different types of chirality and their interplay within the hybrid dimers.[6] Furthermore, we will also show that both the size of the cyclodextrin's cavity (α- vs. β-CD) and the coordination of the Möbius twisted hexaphyrin remotely influence the twisting preference.



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P A042

Development of heterogenous salen-metal catalysts based on porous silicon by means of controlled polymerization

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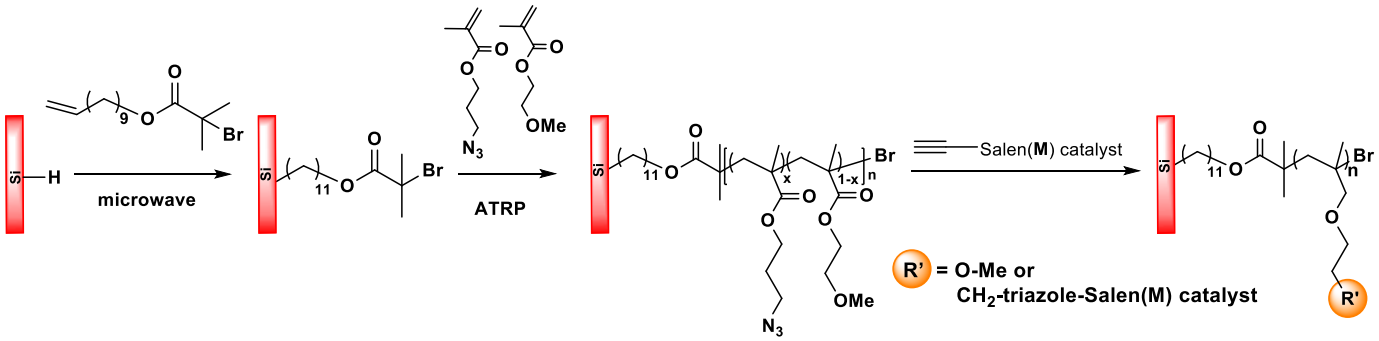
This project aims at the preparation of porous silicon functionalized by enantiopure metallic complexes of salen type, following robust, multi-step grafting processes. The immobilization of salen catalysts will be performed by macromolecular engineering to control the composition of the grafted chains[1], and the strategy relies on the copolymerization by atomic transfer radical polymerization (ATRP) of functionalized methacrylate-type monomers, which will then be modified by post-functionalization with salen complexes of different metallic salts (Mn and Cr) to be tested in tandem asymmetric catalysis. As for now, the salen-metal catalysts anchored in the free form of the copolymers of AZMA (azido-3-propylmethacrylate) and MEMA (2-methoxyethyl methacrylate) at different ratios have already been studied, and the results validated the efficacy of the catalysts, which provided a 99% conversion and 74% *ee* in the asymmetric ring opening of cyclohexene oxide[2]. On surface, the grafting of the initiator has been optimized by using microwave-assisted reaction in which the reaction time was greatly diminished. The initiated surface monolayer had a density of around 9.2×10^{13} molecules per cm^2 of silicon surface; and XPS measurements validated that the Br moiety is preserved and can be engaged for ATRP on surface. The homopolymerization of MEMA on surface has shown an increase of 60 times the C=O stretching band checked by ATR-FTIR, together with a thickness of around 9 nm provided by ellipsometry. Copolymerization trials on surface using various ratios of monomers are currently under study to proceed to the final step of the preparation of the heterogenous catalysts.



Scheme 2: Proposed multi-step grafting starting from a hydrogenated silicon surface.

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P A043

Synthesis of *N*-CF_3 hydrazines and access to new compounds

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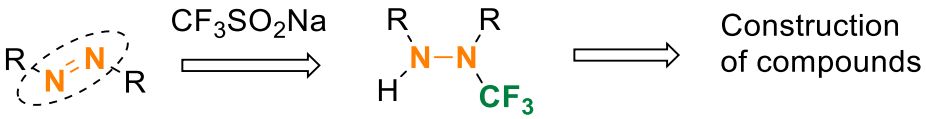
Physico-chemical properties of organic molecules are significantly modified by introducing fluorinated groups, whether their lipophilicity, biological metabolism, conformation, or basicity and acidity. Consequently, the presence and application of fluorine in drug design and agrochemicals, even in materials, continues to grow.[1],[2]

Hydrazines are important functional groups in the synthesis and formation of *N*-heterocycles and are commonly ubiquitous moieties in materials, dyes, and application of pharmaceuticals and agrochemicals.[3] However, the design of higher substituted hydrazines, especially dissymmetric and fluorinated ones, is always a challenge.[4]

In our interest in synthesizing original fluoro compounds, we investigated the development of new *N*-fluorinated-containing scaffolds. Thus, herein we report an efficient and economical approach to synthesizing *N*-CF_3 hydrazines through radical reaction.[5] Also, in this line, the construction of new compounds will be described.



Scheme 1.

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P A044

Sustainability and Green Chemistry at Evotec

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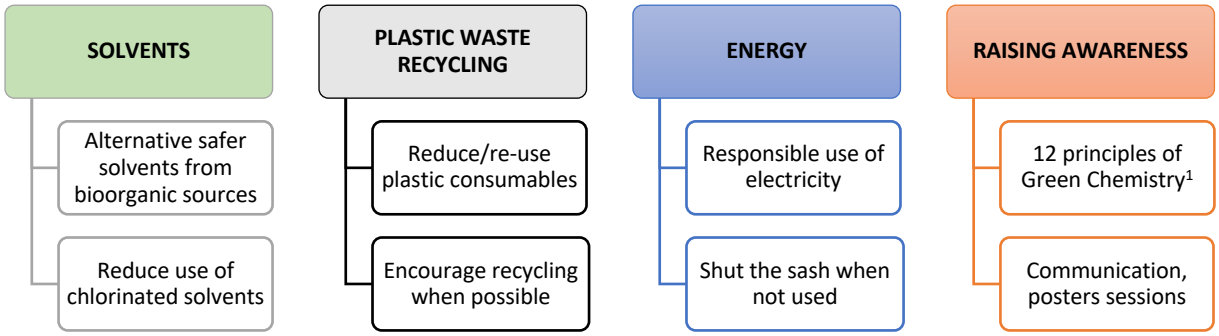
At Evotec –a world leading R&D partnering organization– we are committed to the development and usage of new technologies. With the objective to stay at the cutting edge of science and propose innovative solutions, several working groups have been created and are actively involved in various fields: photochemistry, electrochemistry, flow chemistry, biocatalysis... As part of this strategy, the working group "*green chemistry*" aims to design chemical products and processes that reduce or eliminate the use or generation of hazardous substances. We are always looking for safer, greener and cleaner methodologies to reduce the environmental impact of our activities and adopt the green chemistry principles[1]. Green chemistry applies across the life cycle of a chemical product, including its design, manufacture, use, and disposal. Moreover, we are also engaged in energy saving to decrease the global carbon footprint of the company. Sustainability and green chemistry are implemented while maintaining our level of excellence in drug discovery. To reach our objectives, we have identified four areas of improvements:



This poster is focused on two areas in continuous improvement at Evotec: solvent alternatives and energy saving. Some examples of reactions carried out in renewable solvents such as MeTHF[2] and DMI[3] are presented. Alternatives to DCM (potential ozone depletory and suspected carcinogenic solvent) usage for work-up and purification are also shown.[4]

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P A045

Synthesis and Functionalization of 3,6-Disubstituted 1,2-Dioxanes: Toward the Total Synthesis of Ethyl Plakortide Z.

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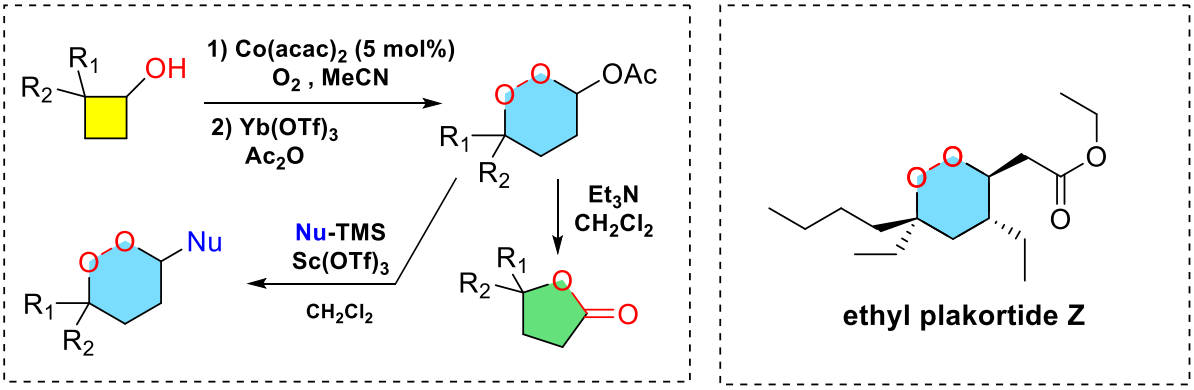
In the continuity of previous works achieved toward the synthesis of 1,2-dioxolanes,[1,2] investigations were conducted on 1,2-dioxanes using similar reaction sequences for the synthesis and functionalization. Thus, 1,2-dioxanes can be obtained by an oxidative ring expansion of cyclobutanols with $Co(acac)_2$ and triplet oxygen to give 1,2-dioxanols, with a regioselective insertion of molecular oxygen on the more substituted side of the ring. The 1,2-dioxanols, after being transformed into the corresponding acetate, can also be functionalized with the addition of neutral nucleophiles under catalytic Lewis acid conditions[3]. However, basic conditions usually lead to a ring contraction providing lactones[4]. We decided to use all the data collected in these studies to begin the total synthesis of the ethyl plakortide Z, a 1,2-dioxane that can be found in the sponge *Plakortis lita*.



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P A046

Ketenimines as versatile intermediates for accessing valuable difluoromethoxylated scaffolds

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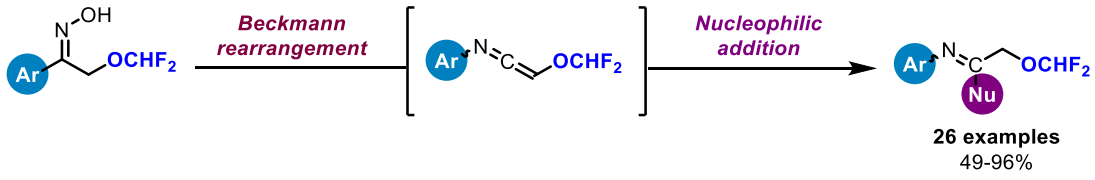
The use of fluorinated groups in medicinal and agrochemistry is constantly increasing. In fact, at least one fluorine atom is present in 18% of pharmaceuticals[1] and 53% of agrochemicals[2]. Fluorine has indeed demonstrated its ability to modify the physico-chemical and biological properties of molecules compared to their hydrogenated analogues, leading for example to an increase in metabolic stability. Nevertheless, most of these compounds are in fact bearing a single fluorine atom, or a trifluoromethyl group, thus explaining the need for more diversity. To this end, the development of new methodologies allowing the introduction of emerging fluorinated groups (CF_2H, SF_5, OCF_3, SF_3…) has become a major challenge.
Our group therefore focuses on the synthesis of a versatile building-block, namely a ketenimine[3], bearing a -difluoromethoxy group (-OCF_2H), for which the direct introduction methods, especially on alkyl chains, are still rare.[4]

First the synthesis of the oxime, as well as the *in situ* formation of the key intermediate, was optimized. Second, various nucleophiles were successfully added to the ketenimine, allowing us to build a library of molecules bearing the -OCF_2H motif.



⟹ **Access to F_2HCO-bearing building blocks**

⟹ **Versatile intermediate**
N-,S-, and *O-***Nucleophiles**

⟹ **Wide substrate tolerance**
Ar = *o-,m-,p-, EWG-,EDG-*Ar

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P A047

Synthesis, *in Vitro* Anti-inflammatory Evaluation of Novel Sulfamide-Containing Bisphosphonates Derivatives

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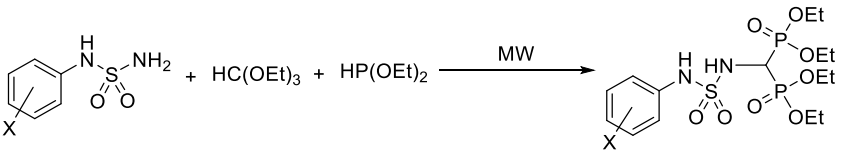
Nitrogen bisphosphonates, the most potent generation of bisphosphonates, constitute an important class of pharmacologically active molecules, which used as antiresorptive agents in the treatment of bone disorders.[1]

Furthermore, nitrogen bisphosphonate-based derivatives have considerable attention in the field of medicinal chemistry due to their role in many biological activities, including anti-inflammatory,[2] antifungal,[3] antibacterial and antiviral,[4] anticancer,[5] as well as herbicidal.[6]

Herein, we report an eco-friendly and one-step microwave-assisted green synthesis of new functionalized bisphosphonates derivatives by a three-component reaction of aromatic sulfamide with triethyl orthoformate and diethyl phosphite. The synthesized compounds were characterized by ^{1}H, ^{13}C, ^{31}P NMR and IR analysis. Some of these compounds were tested for *in vitro* anti-inflammatory activity by inhibition of protein denaturation method and showed moderate inhibition compared to diclofenac as standard drug.



X= H, 3-F, 4-F, 4-I, 4-Cl, 2-OMe

Scheme 1. Synthesis of sulfamide-containing bisphosphonates esters under MW.

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P A048

Benzene triimide hemicryptophanes for synergistic anion-π and cation-π interactions

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Noncovalent interactions involving aromatic rings play a key role in many processes of molecular recognition. Among them, π-π and cation-π interactions have been widely studied and are known to be important bonding forces in biological systems.[1] On the contrary, anion-π interactions, which can be broadly defined as the attraction of anions to electron deficient π-systems, have been recognized theoretically only since the beginning of this century.[2] The vital role of anions in many key chemical and biological processes, and the involvement of π-rings in molecular anion recognition and transport, indicate that anion-π contacts could be prominent players in medicinal and environmental applications.[3]
The recognition of zwitterions is a difficult task to achieve due to the two opposite charges that need specific opposite interactions. To address this challenge, heteroditopic molecular cages are promising receptors. By combining an electron rich and an electron deficient aromatic unit in a hemicryptophane,[4] we have been able to bind glycine through only anion and cation-π interactions. Moreover, these receptors are able to bind anions through synergistic anion-π interactions within the confined space of hemicryptophanes. The importance of linkers geometry and electronic properties are shown to have an important effect on the affinity for various guests.
The synthesis of hemicryptophanes, their special conformational isomerism and the study of their molecular recognition properties will be highlighted.

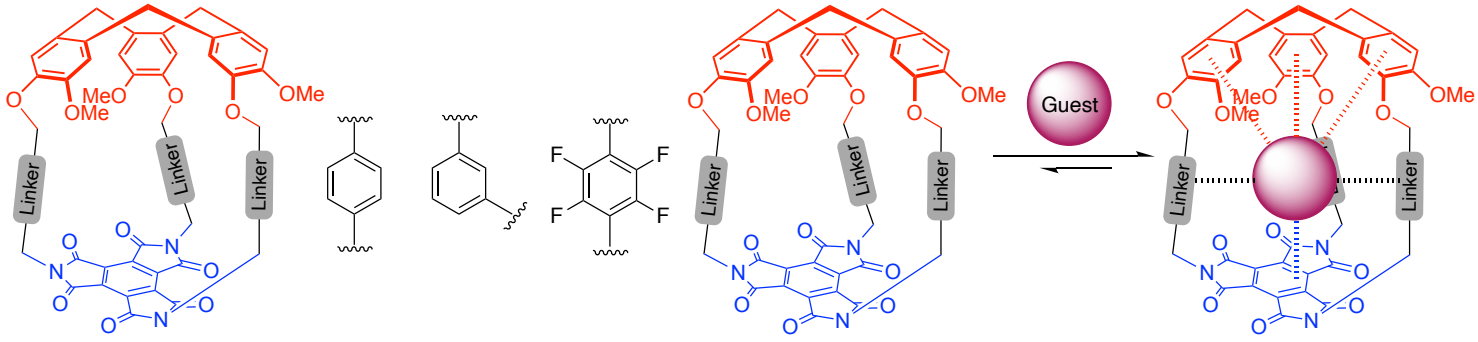

Figure 3. Left: General concept of the heteroditopic hemicryptophanes. Right: Host guest equilibrium and the possible interactions between the host and the guest.

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P A049

Tetra-*n*-butylammonium Decatungstate-Photocatalyzed C2-Acylation of Indoles

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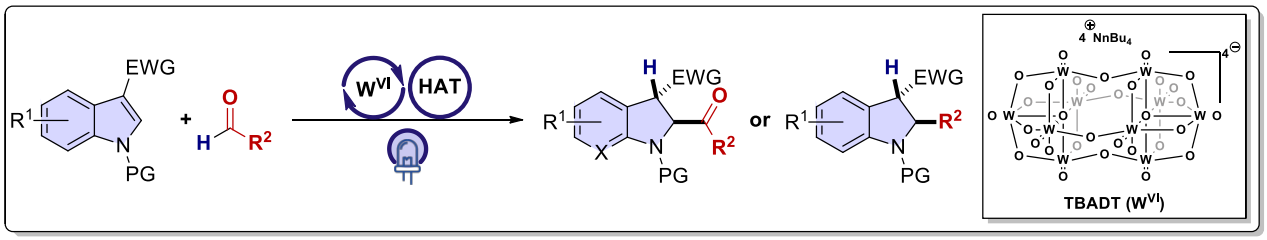
C-H bond selective activation represents a great challenge of synthetic chemistry. Hydrogen Atom Transfer (HAT), consisting in an electron and a proton concerted migration during a single step, is an appealing strategy to achieve this goal. Over the last decade, photocatalysis has become an inescapable and powerful approach to generate radicals thanks to UV- or visible light. However, classical ruthenium- and iridium-based photocatalysts are not capable to promote direct HAT without the use of a cocatalyst.[1] To address this issue, polyoxometalates have appeared as interesting alternatives, especially tetra-*n*-butylammonium decatungstate (TBADT) relying on an inexpensive, Earth's crust abundant and low toxic metal. It has been used to abstract hydrogens on a wide variety of substrates including alkanes, ketones, aldehydes, alkylpyridines, alcohols and ethers.[2]

Indoles and indolines are ubiquitous motive in natural and biologically relevant compounds. Hence, their functionalization are important transformations for purposes of increasing chemical diversity on such scaffolds. In particular, indolines syntheses via radical C2-functionalizations of indoles remain relatively elusive so far despite their great potential.[3] In this context, we proposed an unprecedented C2-acylation of electron-poor indoles where acyl radical intermediates are generated from aldehydes via TBADT-mediated HAT through purple-light irradiation.[4] This high-yielding methodology has a broad scope, is scalable and can be easily modified to obtain a diastereoselective version. In addition, a decarbonylative pathway has also been explored leading to alkylated products.



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P A050

Zincate-Mediated Remote Functionalisation of *p*-Iodobenzyl Derivatives Through Metallotropy

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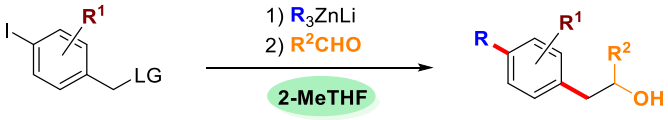
Metal-promoted remote functionalisation through internal induction is an efficient synthetic concept to swiftly access added-value molecular architectures with a high degree of structural diversity from simple and readily available substrates.[1] If perfectly implemented, such an approach leads to the selective functionalisation at a site away from a functional group initially interacting with the used reagent or catalyst. In this context, through-space metal migration[2] or intrinsic migration of the metal along a flexible carbon via unidirectional positional isomerisation sequence of a double C-C bond[3] are the most popular used internal communication processes between initiation and functionalisation sites. By contrast, metallotropic rearrangement[4] received very little attention from the synthetic community.

In this poster, we disclose the remote functionalisation of diversely decorated 4-iodobenzyl derivatives through metallotropy by using lithium tributylzincate as reagent and 2-MeTHF as solvent. The process leads to the selective formation of both a C(sp^3)-C(sp^2) and a C(sp^3)-C(sp^3) bond at sites localised at five atoms away from one another in a single operation and with a unique organometallic reagent. Compared with the literature precedent,[5] our reaction conditions allow reaching an unprecedented synthetic scope, both in terms of compatible substrates and electrophiles. The influence and the role of the eco-friendly solvent on key elementary steps of the overall transformation are discussed, namely (i) metalation step through I/Zn exchange, (ii) Bu 1,2-migration and (iii) generation of a benzyl zinc intermediate after dearomatisation / rearomatisation / metallotropy chain.



- 32 examples
- Compatibility with aromatic & enolisable aldehydes
- High R^1 tolerance
- 2-MeTHF as a green reactivity booster

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P A051

Earth-abundant metal catalysis: cross-coupling reactions and aryl migrations

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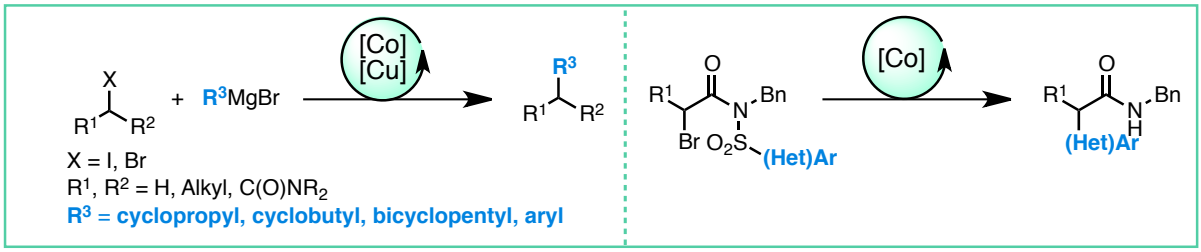
The development of eco-compatible and resource-economic synthetic pathways has become a necessity to access valuable compounds. In this context, earth-abundant metal complexes (Fe, Co, Cu, Ni) emerged as an attractive alternative to palladium catalysts, especially for C-C bond formation.[1] Beside their natural abundance, iron, cobalt or copper catalysts exhibit a complementary reactivity compared to other transition metal catalysts, broadening the substrate scope of cross-coupling reactions and offering new synthetic opportunities.[2] Herein, the power of cobalt- and copper-catalyzed cross-coupling reactions between alkyl halides and Grignard reagents is demonstrated. Simple, available and cost-effective catalytic systems promote efficient and chemoselective transformations allowing the synthesis of attractive building blocks including strained cycles[3]. The radical nature of the cobalt-catalyzed process is exploited in an organometallic-free arylation of α-halo amides proceeding through a desulfonylative 1,4-aryl migration.[4]



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P A052

Research of novel organocatalysts for reactions in water from plant extracts

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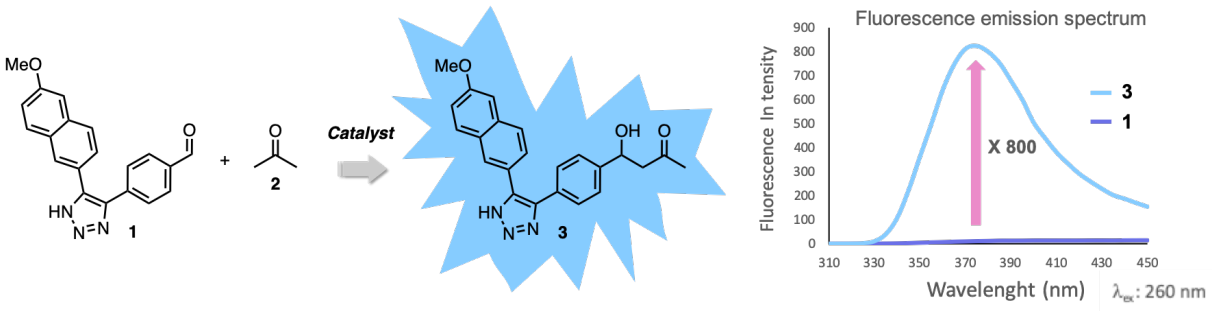
Natural products have a great structural diversity and are at the origin of numerous applications, mainly in the therapeutic field.[1] As an example, these substances and their derivatives represent more than half of the anti-cancer treatments. These molecules, often chiral, can also have an interest in organic chemistry as raw materials, ligands for organometallic catalysis or organocatalysts. The use of small molecules as catalysts has many advantages in the context of a more sustainable chemistry.[2] Although proline and cinchona alkaloids are at the origin of many advances in this field,[3] little effort has been made to develop new organocatalysts from natural origin and, in particular, no screening has been performed in this sense. Thus, identifying and developing new bio-based organocatalysts for reactions in water could offer new opportunities in organic chemistry. Our objective is to detect, isolate, identify and develop natural catalysts from the ICSN extract library, a unique collection of 16,000 tropical plant extracts.

We have therefore developed a fluorescence-based screening of plant extracts to detect new organocatalysts for aldolization reactions in water. The use of a fluorogenic probe **1**[4] as a reaction substrate allows the detection of the fluorescent aldolization product **3**, thus indicating the presence of an organocatalyst. After evaluation of more than 1000 plant extracts, a catalysis-guided fractionation of some hit extracts allowed the identification of three series of compounds capable of catalyzing an aldolization reaction in water. The methodology developed will be presented as well as the progress of the project.



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P A053

A Novel Methodology to Access a Wide Range of Chiral Amines

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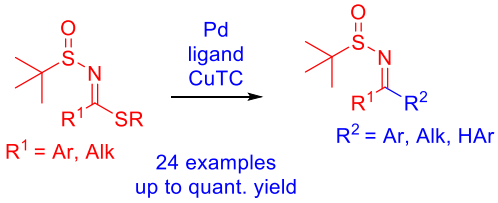
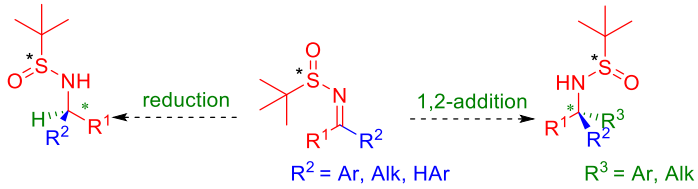
In the laboratory a new tool has been recently developed: sulfinyl thioimidate. [1] This family of molecule can easily be synthesized starting from commercially available esters, via the synthesis of thionoesters. We have demonstrated that these sulfinyl thioimidates are good partners in Liebeskind Srogl type cross coupling reactions to providing a wide range of sulfinyl imines with excellent yields (Scheme 1).[1]



Scheme 1: Unprecedented Liebeskind Srogl-type cross coupling reactions

Next, we could employ the sulfinyl ketimines in reduction[2] and organometallic additions[3,4] in order to investigate the substrate generality of our methodology, which could result to obtaining potentially very valuable chiral amines present in many natural products and bioactive compounds. A range of reduction reactions of sulfinyl imines as well as 1,2-additions of organometallic reagents onto sulfinyl imines substrates will be presented (Scheme 2).[4]



Scheme 2: Reduction and organometallic additions onto sulfinyl thioimidates

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[4] Achuenu, C.; Carret, S.; Poisson, J-F.; Berthiol, F. (unpublished results).

P A054

Synthesis of a first collection of glycosylated nucleosides for SAR study as potential inhibitors of the nucleobase J metabolism in kinetoplastid parasites

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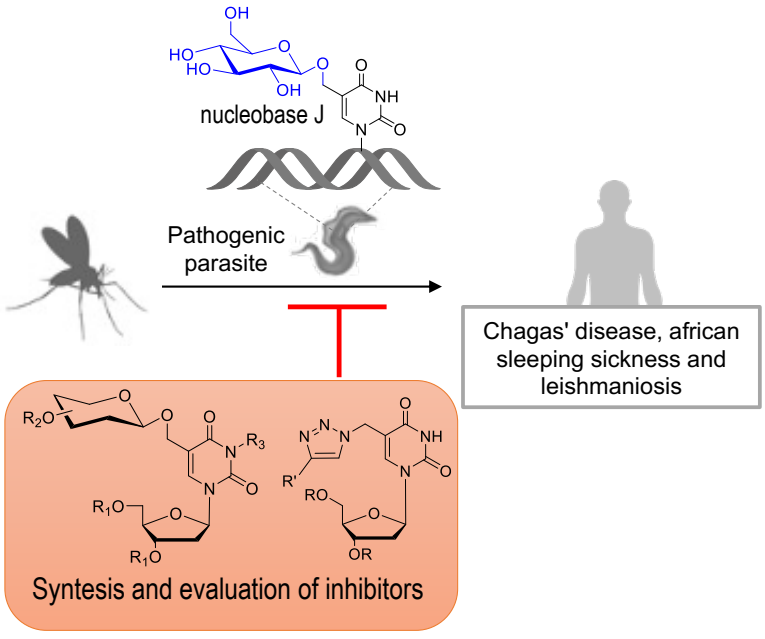
Leishmaniasis and trypasoniomasis are severe parasitic infections that have important impacts in veterinary and public health, affecting the poorest populations. The therapeutic arsenal against these tropical neglected diseases is limited and resistance emergence to the available medicines complicates the treatment. The kinetoplastid parasites are transmitted *via* the bite of insects and need to adapt their genes to the new host. In the last years, the importance of epigenetic regulation in these parasites has been highlighted. Thus, the study of new epigenetic mechanisms could provide new therapeutic perspectives in such disease where drugs are lacking.

β-D-Glucosyl-5-hydroxymethyluracil (glc-5hmU) or base J is a rare hyper-modified nucleobase discovered in kinetoplastid DNA[1] that seems to be crucial for the parasite survival. In this study, we will present an optimized synthetic chemical route to access to the nucleobase J and several related nucleosides analogues that could have the potential to interfere with either an enzyme directly involved in the biosynthesis of base J, or with J binding proteins. The results of the biological evaluation of a collection of selected synthesized molecules on several parasites will be presented.



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P A055

Synthesis and evaluation of heterocycle structures as potential inhibitors of *Mycobacterium tuberculosis*

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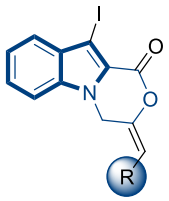
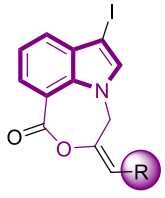
Due to their multiple biological properties, heterocycles have a central place in medicinal chemistry. Amongst all, the indole is one of the most important and attractive heterocycles, often reported as privileged scaffolds for the development of new therapeutic agents. The synthesis of polycyclic indole derivatives creates a broad structural diversity by varying the cyclic junction and the nature of the fused rings. Indoles and their fused derivatives have many interesting pharmacological properties, including anti-inflammatory, antituberculous, and antidiabetic.

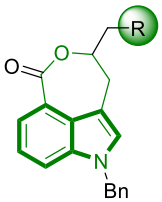
We have been particularly interested in indole-fused lactones since the combination of these two pharmacophores should offer scaffolds of interest in medicinal chemistry. Thus, we present the synthesis of 1,2-, 1,7- and 3,4-indole-fused lactones via a simple and efficient reaction sequence.[1,2] The functionalization of these "oxazino-indole", "oxazepino-indole" and "oxepino-indole" tricycles is carried out by palladocatalyzed C-C coupling, nucleophilic substitution or 1,3-dipolar cycloaddition. The evaluation of their activity against *Mycobacterium tuberculosis* shows that the “oxazino-indole” and "oxazepino-indole” structures are new inhibitors of *M. tuberculosis* growth *in vitro*.[2,3]



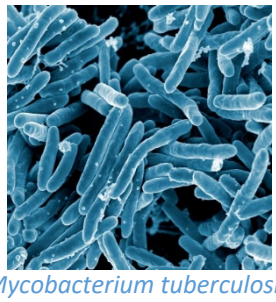
"oxazino-indole"
1,2 fused-indole



"oxazepino-indole"
1,7 fused-indole



"oxepino-indole"
3,4 fused-indole



Mycobacterium tuberculosis

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P A056
Synthesis of analogues of complex natural products for anticancer applications

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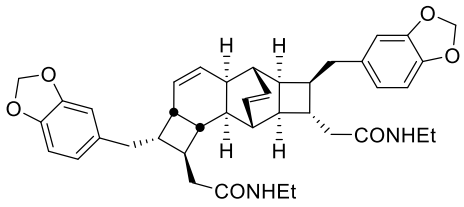
Kingianins[1] are natural products isolated from *Endiandra kingiana*, a Malaysian endemic tree. These molecules share a highly original and challenging pentacyclic skeleton. Their promising biological activity towards the anti-apoptotic proteins Bcl-xl and Mcl-1 could lead to the development of new anticancer therapies.[1]

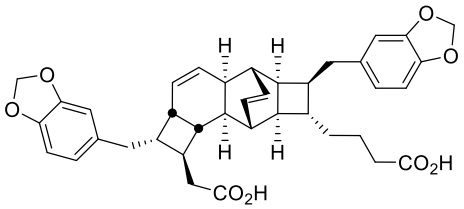
An optimised synthetic route is under development in our laboratory to synthesise a series of simplified analogues of kingianins, as well as some of the natural products themselves. Our approach addresses challenging selectivity problems, as well as functional group tolerance issues. The current sequence features an original decarboxylation step followed by an ester formation and a reductive ozonolysis reaction, with full diastereocontrol.

This strategy is very different from the few that have already been described in the literature and ensures much higher flexibility.[2,3,4] The molecules synthesised will be engaged in biological studies to test their binding affinity towards Bcl-xl and Mcl-1.



Kingianin A

(most abundant)



Kingianin G

(most active)

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P A057

Photo-mediated hydrofunctionalizations of unsaturated compounds

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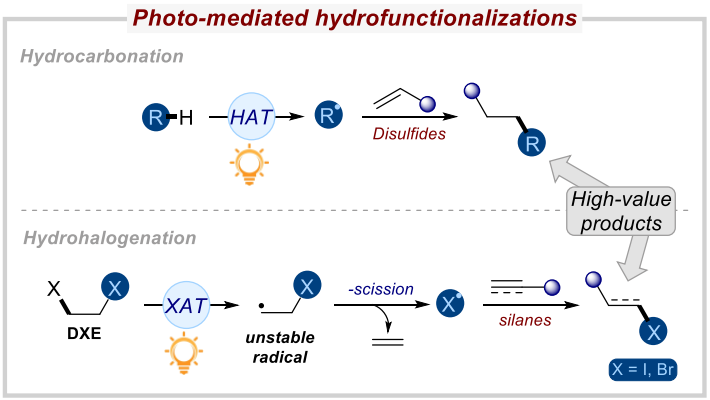
Unsaturated compounds are ubiquitous reagents in organic chemistry as they are inexpensive, stable, and readily available. As a consequence, they have been intensively used as starting materials in a plethora of organic transformations.[1] Among them, the hydrofunctionalization of unsaturated compounds has been recognized as a valuable method to construct complex molecules but, above all, to introduce a large variety of functional groups with full atom efficiency.[2] This transformation is still at the center of modern research as illustrated, for instance, by the recent developments in the photocatalyzed hydroaminations and hydroalkoxylations.[3] In this context, we got interested in developing photo-mediated methodologies allowing the hydrofunctionalization of unsaturated compounds. Two photoredox protocols developed in our laboratory concerning the hydrocarbonation[4] and the hydrohalogenation[5] of a wide range of unsaturated substrates will be discussed (***Scheme 1***).



Scheme 1. *Hydrofunctionalizations developed in our laboratory*

[1] a) H. Jiang, A. Studer, *Chem. Soc. Rev.* **2020**, *49*, 1790−1811; b) D. C. Silva Costa, *Arabian J. Chem.* **2020**, *13*, 799−834; c) M. M. Heravi, M. Dehghani, V. Zadsirjan, M. Ghanbarian, *Curr. Org. Chem.* **2019**, *16*, 205−243.

[2] a) M. T. Pirnot, Y.-M. Wang, S. L. Buchwald, *Angew. Chem., Int. Ed.* **2016**, *55*, 48−57. b) J. V. Obligacion, P. J. Chirik, *Nat. Rev. Chem.* **2018**, *2*, 15−34. c) S. Bezzenine-Lafollée, R. Gil, D. Prim, J. Hannedouche, *Molecules* **2017**, *22*, 1901−1929.

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P A058

Photo-Induced Halogen-Atom Transfer: Generation of Halide Radicals for selective Hydrohalogenation Reactions

Lilian Geniller[1], Marc Taillefer[1], Florian Jaroschik[1], Alexis Prieto*[1]
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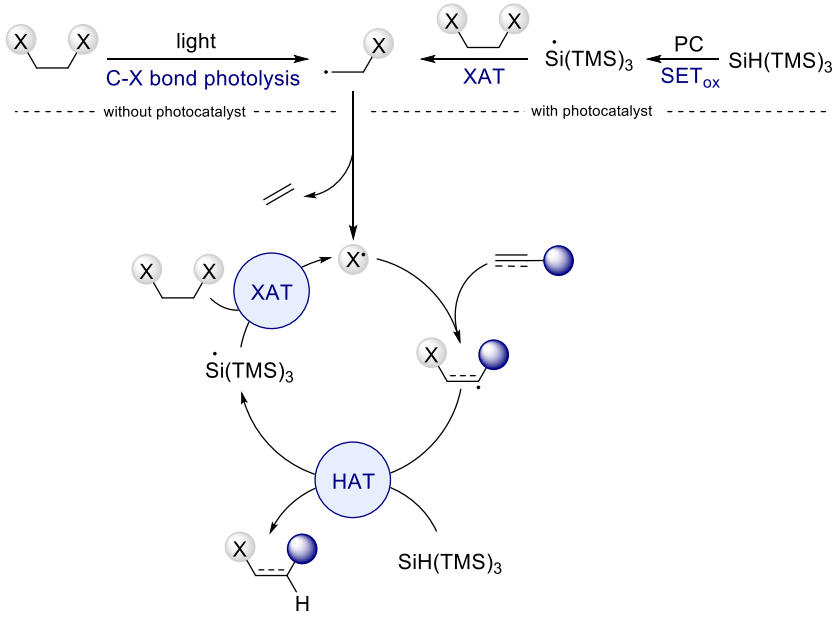
A selective hydrohalogenation of unsaturated hydrocarbons using 1,2-dihaloethanes (DXE) as the halide sources under mild conditions is reported.[1] Contrary to radical transformations involving halogen atom transfer (XAT),[2] which exploit stable carbon radicals, our unique approach uses 1,2-dihaloethanes for the generation of unstable carbon radicals by silane-mediated XAT. These transient radicals then undergo β-scission with release of ethylene and formation of more stable halide radicals which have been used for the hydro-bromination and -iodination of unsaturated hydrocarbons that includes Michael acceptors, unactivated alkenes and alkynes. Overall, a broad range of functionalities have been well tolerated in our photo-mediated hydrohalogenations, which contrast with previous methods in which the functional group tolerance was limited.[3] Mechanistic studies suggest that the reaction proceeds through a radical-chain manifold that propagates by the use of silane derivatives.



[1] Geniller, L.; Taillefer, M.; Jaroschik, F.; Prieto, A. Photo-Induced Halogen-Atom Transfer: Generation of Halide Radicals for selective Hydrohalogenation Reactions. *Chem. Eur. J.* **2022**, 28, e2022014.
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P A059

Helical bisphosphinite in asymmetric Tsuji-Trost allylation: a remarkable P/Pd ratio effect

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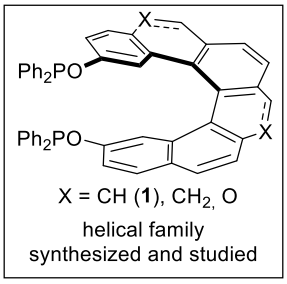
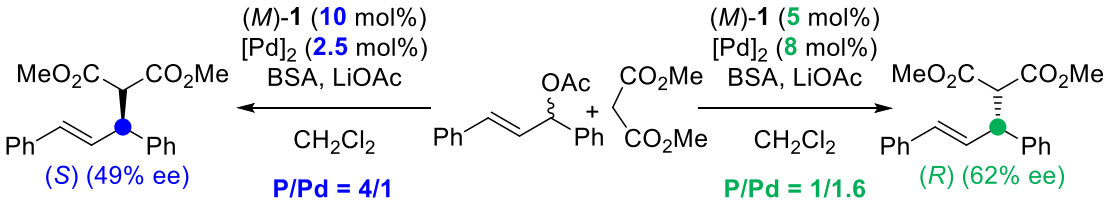
Helicenes are organic aromatic compounds formed of several *ortho*-fused rings which naturally adopt a helical configuration and possess high chiroptical properties. They have already found broad applications in optics, electronics and biology as well as in organic and supramolecular chemistry.[1] Nevertheless, utilization of these scaffolds as chiral ligands in organometallic catalysis still remains a challenge to tackle and only a few examples are disclosed in the literature.



This poster discloses a study on a chiral bis-phosphorylated-helical ligand family in the enantioselective palladium-catalyzed Tsuji-Trost allylation.

The use of 2,15-bisphosphinite[6]helicenes allowed to evidence a remarkable ligand effect, in which the (*R*) and (*S*) isomeric products can be selectively formed as a direct function of the amount of ligand introduced. Study of the organometallic species involved through ^{31}P NMR analysis of a model complex and X-Ray diffraction analysis together with DFT calculations shed light on this phenomenon.[2]



^{31}P NMR study (model complex)
X-ray diffraction
DFT

Acknowledgments: ANR-13-JS07-0013-HELCATS. Collaborative work with Corinne Aubert, Etienne Derat (DFT), Louis Fensterbank, Geoffrey Gontard (RX), Omar Khaled (HPLC), Cyril Ollivier, Marc Petit, Nicolas Vanthuyne (prep HPLC).

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P A060

Copper catalyzed atropoenantioselective C-N coupling

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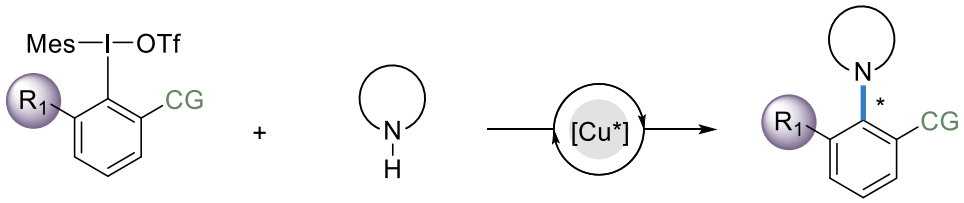
Chirality is an intriguing feature of many natural products and numerous bioactive molecules contain stereogenic centers. In particular, C-N axially chiral compounds have been attracting an increasing attention of the scientific community as a privileged class of biologically active compounds. Despite this expanding interest, only few catalytic enantioselective strategies allowing efficient synthesis of such compounds are reported.

Although direct C-N coupling is the most interesting strategy from a retrosynthetic point of view, direct atroposelective coupling remains rare. The inherent challenge of this approach arises from the antagonism between high steric hindrance required to warrant atropostability of the compound and high reaction temperature generally required to enhance a coupling between two sterically congested partners. [1]

To overcome these limitations our methodology is based on hypervalent iodine chemistry. Indeed, the use of diaryl iodonium salts enables Ullmann-type couplings under mild conditions. Thereby, we have recently reported the first example of atroposelective metal catalyzed *N*-arylation delivering C-N axially chiral compounds. [2]
We wish to extend this methodology to a large panel of *N*-coupling partners and activated aromatics to access an array of C–N axially chiral scaffolds. Moreover, mechanistic studies are carried out to better understand this reaction.



CG = coordinating group

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P A061

Frustrated Lewis pair-catalyzed hydrogenation of unactivated alkenes: the case of 9-phosphatriptycenes

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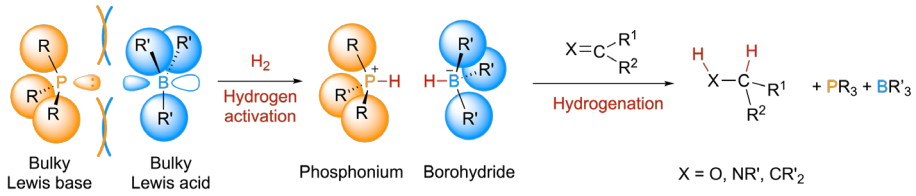
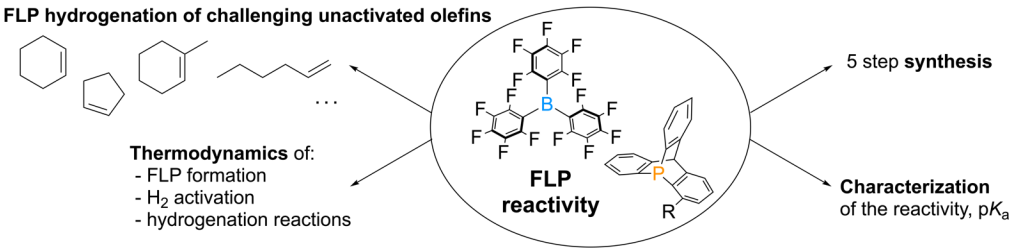
Frustrated Lewis Pairs (FLPs) consist in sterically hindered Lewis acids and bases that cannot form Lewis adducts because of steric repulsions. These bifunctional systems, usually consisting of a borane and a phosphine or amine, have been increasingly used as transition metal-free catalysts for the hydrogenation reaction of unsaturated substrates.[1]



Olefins are challenging substrates in FLP chemistry and the metal-free hydrogenation of unactivated alkenes was only seldom reported in the literature.[2] Due to their cage-shaped structure, 9-phosphatriptycene derivatives constitute promising Lewis bases to tackle this challenge. The enhanced pyramidalization of their phosphorus center results in a significant weakening of its Lewis basicity and the strategic addition of *ortho*-substituents increases their steric bulk compared to related triarylphosphines.[3] In this poster, our computational and experimental investigations on the reactivity of Lewis pairs based on 9-phosphatriptycene derivatives will be presented. The structural and electronic effects of the molecular scaffold on the phosphorus reactivity, the pK_a of these compounds as well as their thermodynamics in H_2 activation and hydrogenation reactions are investigated by density functional theory calculations.[4] Experimentally, their synthesis is based on the cyclization of functionalized triarylmethane precursors.[5] They are now exploited as catalysts for the hydrogenation of unactivated alkenes such as cyclohexene.[6]



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P A062

Development of Bifunctional Boron/Nitrogen System and New Non-Planar Borenium Ion

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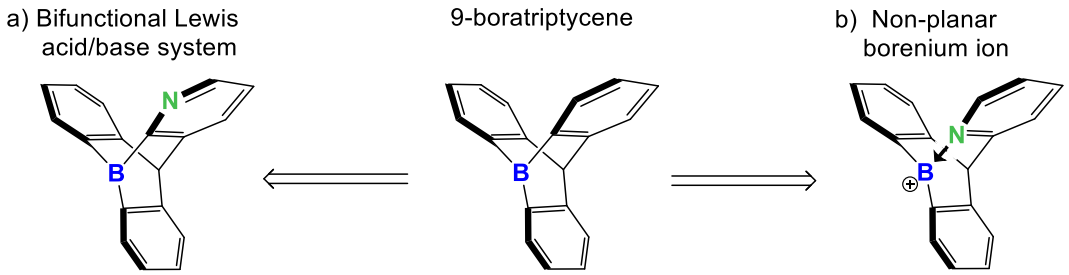
Due to their unique chemical, physical and photophysical properties, organoboron compounds and in particular triarylboranes are playing a central role in materials science, supramolecular chemistry and catalysis. [1]

Boron Lewis acids are usually planar trigonal species. However, constraining the boron atom in a pyramidal shape will significantly increase the Lewis acidity as demonstrated theoretically and experimentally in the RCO group at UNamur by the synthesis and reactivity studies of 9-boratriptycene derivatives. [2] It has recently been shown by quantum chemical calculations that incorporating an intramolecular Lewis base in 9-boratriptycene give access to a bifunctional boron/nitrogen system containing a pre-pyramidalyzed boron atom, the 9-bora-azatriptycene (Scheme 1a). It exhibits the potential to perform the C-H bond activation of methane. [3] On the other hand, the activation of methane was achieved recently by using borenium ion in 2021. [4]

In this research work, we focused on the synthesis of the 9-bora-azatriptycene (Scheme 1a) and of an unprecedent new type of non-planar borenium ion (Scheme 1b) to obtain a new kind of Lewis superacid. This work begins with the synthesis of triarylmethane precursors and finish with various attempts to obtain desired pyramidal compounds.



Scheme 4 : Overview of this work, 9-bora-azatriptycene (a) and non-planar borenium ion (b).

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P A063

Charge transport properties in nanohoops

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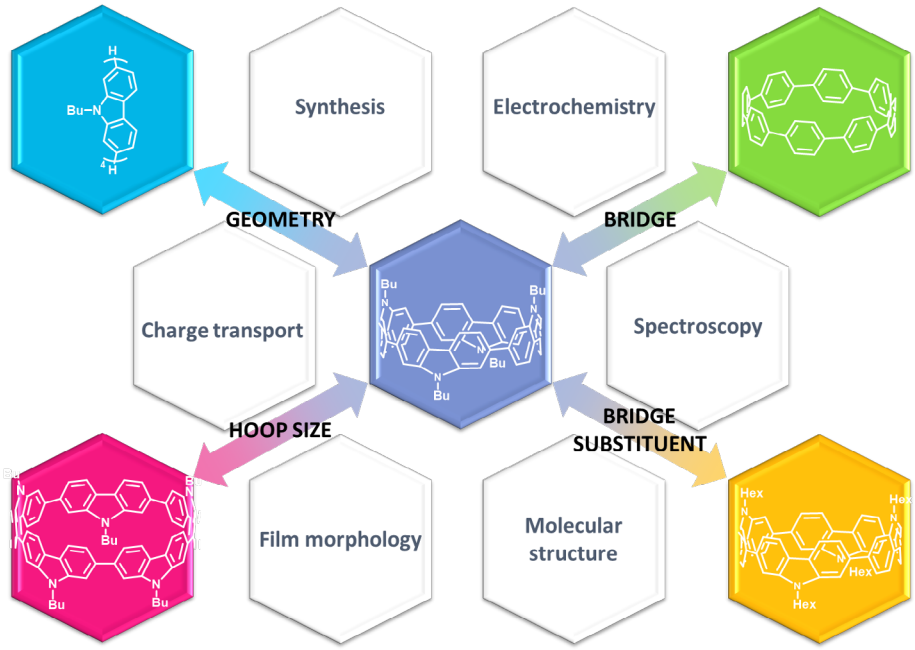
In the last ten years, the development of π-conjugated nanohoops has been considerable owing to their remarkable properties.[1-2] However, to date, their incorporation in organic electronic devices remains very scarce and their performance is low.[3-4] This could be linked to their weak charge transport properties.[5-6] In order to increase the efficiency of the nanohoops based organic semi-conductors, their charge transport properties should be first studied.[7-8] Thanks to a structure-properties relationship study centred on the cyclic tetracarbazole substituted by butyl chains, we evaluate the impact of:

- the cyclic geometry (by comparison with the linear tetracarbazole),
- the number of building units in the nanohoop (by comparison with the cyclic pentacarbazole),
- the presence of the bridgehead (by comparison with the [8]cyclo-*para*-phenylene),
- the length of the alkyl chains borne by the bridgehead (by comparison with the cyclocarbazole substituted by hexyl chains).



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P A064

Structural bases for the involvement of phosphatidylinositol-4,5-bisphosphate in the internalization of the cell-penetrating peptide Penetratin

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Cell-penetrating peptides cross cell membranes through various parallel internalization pathways. Herein, we analyze the role of the negatively charged lipid phosphatidylinositol-4,5-bisphosphate ($PI(4,5)P_2$) in the internalization of Penetratin. Contributions of both inner leaflet and outer leaflet pools of $PI(4,5)P_2$ were revealed by quantifying the internalization of Penetratin in cells treated with $PI(4,5)P_2$ binders. Studies on model systems showed that Penetratin has a strong affinity for $PI(4,5)P_2$, and interacts selectively with this lipid, even in the presence of other negatively charged lipids, as demonstrated by affinity photocrosslinking experiments. Differential scanning calorimetry experiments showed that Penetratin induces lateral segregation in $PI(4,5)P_2$-containing liposomes, which was confirmed by coarse-grained molecular dynamics simulations. NMR experiments indicated that Penetratin adopts a stabilized helical conformation in the presence of $PI(4,5)P_2$-containing membranes, with an orientation parallel to the bilayer plane, which was also confirmed by all-atom simulations. NMR and photocrosslinking experiments also suggest a rather shallow insertion of the peptide in the membrane. Put together, our findings suggest that $PI(4,5)P_2$ is a privileged interaction partner for Penetratin and that it plays an important role in Penetratin internalization.

P A065

Mixed aliphatic organozinc reagents as non-stabilized Csp3-nucleophiles in multicomponent reaction

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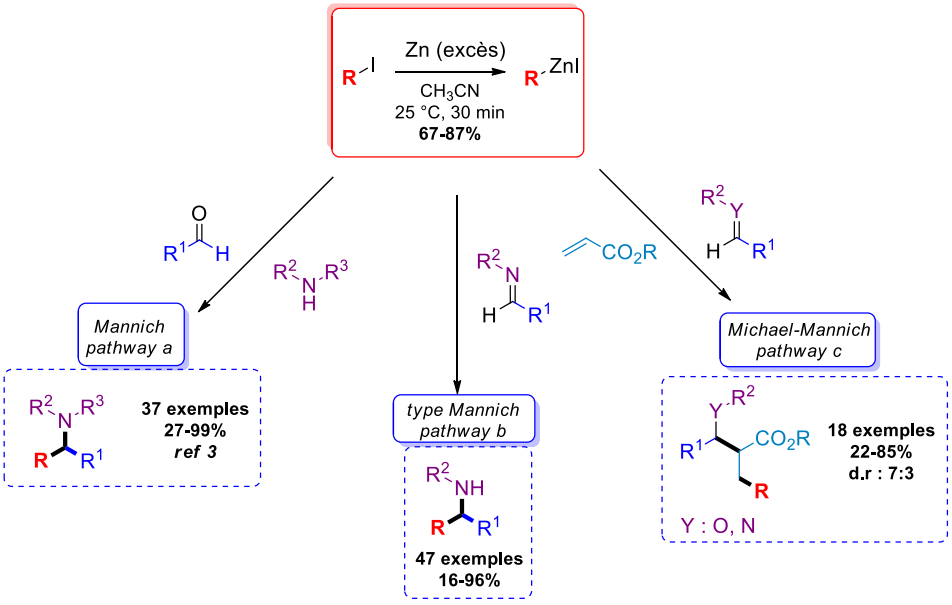
Multicomponent reactions (MCRs) constitute one of the most powerful tools to obtain complex scaffolds in one single step thus contributing to the development of more atom economic processes. Our group focuses its activities on the design of new MCRs involving aromatic organozinc reagents as nucleophiles, as they are easier to prepare and present a greater functional group compatibility compared to Grignard or organolithium reagents.[1] The present work aims at extending these reactivities to aliphatic organozinc reagents, as only resonance stabilized species had been reported in the case of mixed organozinc reagents.[2]
We began our studies with organometallic multicomponent Mannich reactions between an alkylzinc reagent, an aldehyde and a secondary amine. We discovered a strong influence of the solvent used in the zincation step on the MCR outcome. By performing both reactions in acetonitrile, the reaction successfully involved different organozinc reagents (primary, secondary and tertiary), aldehydes (aromatic or aliphatic) and secondary amines (cyclic and acyclic), allowing the obtention of tertiary amines under mild conditions and in good yields (pathway a)[3].
Moreover, the preparation of secondary amines was also possible under similar conditions using different imines (pathway b). Finally, by adding a Michael acceptor to the reaction mixture, catalyst-free Michael-aldol and Michael-Mannich reactions have been developed, affording β-hydroxy- and β-aminocarbonyls compounds (pathway c).



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P A066

Total Synthesis of Mavacuran Alkaloids

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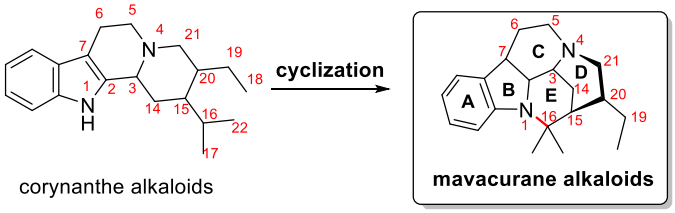
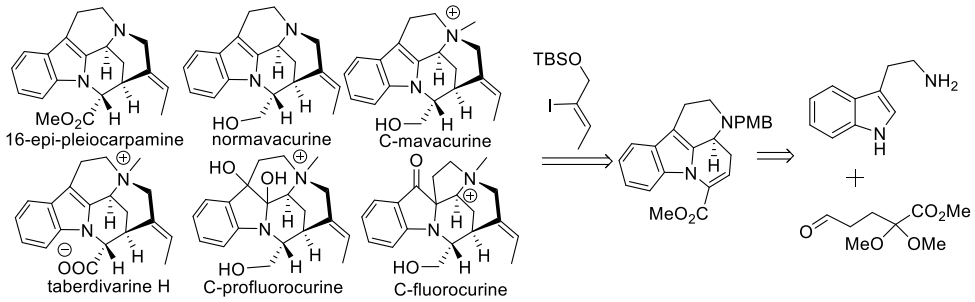
The mavacuran alkaloids are part of the Monoterpene Indole Alkaloids (MIAs) family and more precisely represent a restricted sub-family of the Corynanthes alkaloids with a characteristic bond between the N_1 and C_{16} of the corynanthe skeleton (**Scheme 1**).



Scheme 1 *Corynanthe and mavacurane skeleton*

Due to the strain nature of their skeleton, the last ring to be formed is key to the success of the synthesis of the mavacuran alkaloids. A few synthetic routes have been described in the last forty years involving as the last stage the formation of either the E ring and the N_1-C_{16} bond (Boekelheide[1], Takayama[2] and our group[3] in collaboration with the team of Evanno and Poupon) or the C-D ring junction and the C_3-N_4 bond (Sakai[4] and Harley-Mason[5]) or the C ring and the C6-C7 bond (Bosch).[6] In contrast to these strategies, we propose a shorter synthesis of the mavacuran alkaloids by the late stage formation of the D ring and the N_4-C_{21} bond. This new synthetic route involves an annulation process from an ABCE tetracyclic compound which was obtained *via* a Pictet-Spengler reaction and allowed us to achieve the total syntheses of 16-*epi*-pleiocarpamine, normavacurine, taberdivarine H, C-mavacurine, C-profluorocurine and C-fluorocurine (**Scheme. 2**).



Scheme 2 *Retrosynthesis of 16-epi-pleiocarpamine and other mavacuran*

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P A067
Hydrochlorination of alkenes

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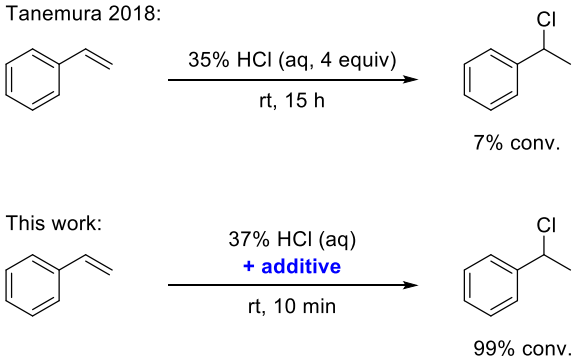
The hydrochlorination of alkenes has a long history and is utilized as an example in many organic textbooks to explain the Markovnikow rule.[1] However, in practice only certain alkenes (e.g. trisubstituted ones) readily undergo hydrochlorination when exposed to HCl gas.[2] Others, such as monosubstituted or 1,2-disubstituted alkenes react very sluggishly. In this presentation, we present our work concerning the use of hydrochloric acid which is able to hydrochlorinate activated and non-activated alkenes by addition of certain chemicals (Scheme 1).[3] The usefulness and practicality of this method is demonstrated by the hydrochlorination of styrene on a 500 mmol scale. Moreover, we have identified conditions allowing for the isolation of regioisomerically pure hydrochlorination products, a problem which has not been solved yet despite the long history of hydrochlorination reactions.

Scheme 1:



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P A068

Directing Group Assisted Rhodium Catalyzed *meta*-C–H Alkynylation of Arenes

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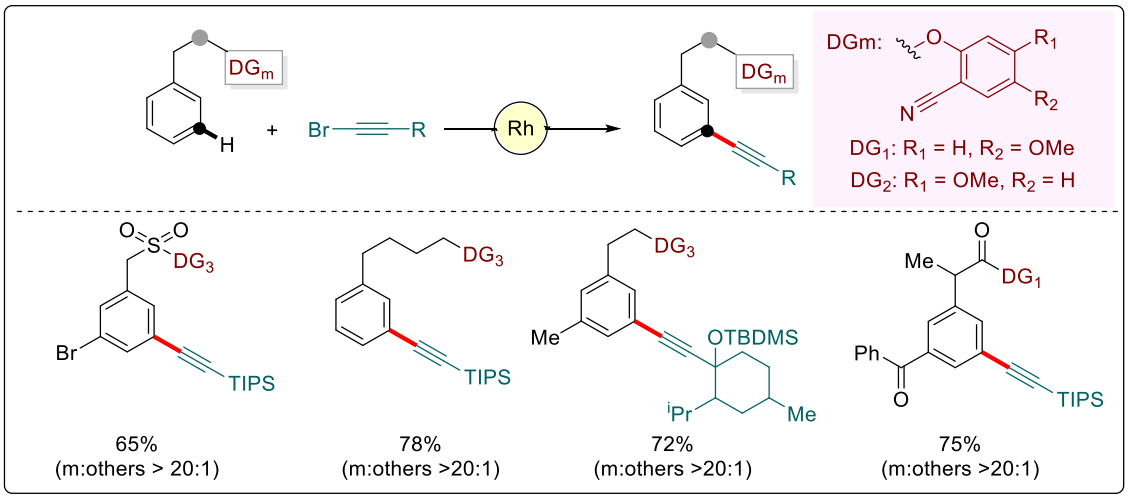
Transition metal catalyzed C–H activation has evolved as a powerful synthetic tool as it offered a simplified route to incorporate several functional groups by converting inert C–H bond into various carbon-carbon or carbon-heteroatom bonds.[1] Directed C–H activation in this regard provides a unique solution to ensure site-selective C–H activation in a predictable manner. The progress of directed C–H activation is majorly centered around the *ortho*-C–H activation, which is typically proceeded *via* five- to seven-membered metallacyclic intermediates. Nevertheless, distal *meta*-C–H functionalization aided by directing group assistance has recently attracted significant attention.[2] The formation of a large macrocyclic pre-transition state (usually greater than 11-memberered) is the prerequisite criteria to be successful in site-selective distal C–H activation.[3] We are intrigued in developing Rh-catalyzed methods for various *meta*-C–H functionalization. Hereby, we disclosed the first Rh(I) catalyzed *meta*-C–H alkynylation protocol through inverse Sonogashira coupling reaction.[4] The protocol is compatible with various substrate classes which include phenylacetic acids, hydrocinnamic acids, 2-phenyl benzoic acids, 2-phenyl phenols, benzyl sulfonates and ether-based scaffolds. The post-synthetic modification of *meta*-alkynylated arenes is also demonstrated through DG-removal as well as functional group interconversion.



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P A069

Late-stage functionalization of retinoids: in the pursuit of the *in vivo* active form of vitamin A

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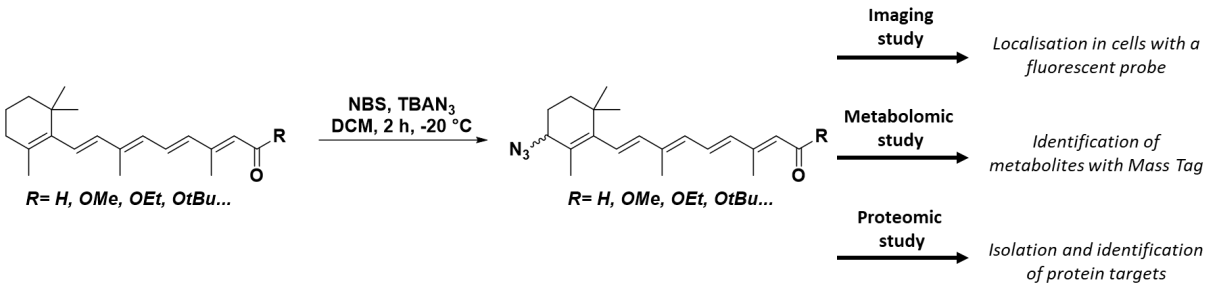
Vitamin A is a pleotropic micronutrient with different key roles in the organism such as vision,[1] cell differentiation[2] or even maintenance of the immune system.[3] Thus, strict homeostasis of the different forms of vitamin A, called retinoids, [4] has to be maintained by organisms to avoid disorders (hypervitaminosis, anemia, growth retardation…).[5,6] Nonetheless, lack of knowledge about the complete metabolism of retinoids hampers the apprehension of the biogenesis of these disorders. To get a deeper insight into the complex metabolic cascade of retinoids, a chemical biology approach was investigated, relying on the use of retinoid analogs functionalized with an azide group at the C4 position, a region not involved in ligand receptor binding. To avoid complex and lengthy synthesis of these photo and chemo-sensitive molecules, we have developed a late-stage modification strategy. A methodological study was performed on retinal to find the best conditions for regioselective azide incorporation before it was applied to other retinoids. In parallel, mass spectrometry and chemoproteomic probes were also synthesized and used in biological investigations.



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P A070

Iron-catalyzed Carbon-Carbon Double Bond Isomerization

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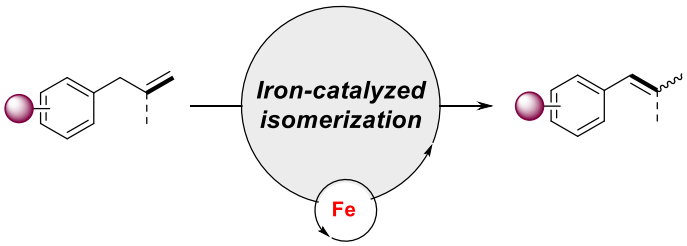
Metal-catalyzed carbon-carbon double bond isomerization giving rise to a new isomer has become a fundamental and powerful synthesis tool with extensive applications in the production of high value molecules as it offers a waste-free process with 100% atom efficiency.[1] This reaction has been widely investigated using noble metals-based catalysts such as rhodium, palladium, or iridium which are rare, expensive, and relatively toxic.[2] Thus, the development of alternative catalytic isomerization processes remains a major challenge in modern metal catalysis. Iron catalysis has emerged as a cost effective and an eco-friendly alternative for sustainable development.[3] Although many isomerization methodologies using abundant metals mainly cobalt-based catalysts have been reported, iron-catalyzed isomerization is still underdeveloped and often integrated into tandem isomerization-functionalization processes that drive the isomerization step.[4]

Thanks to our expertise in earth abundant metals-based catalysis,[5] herein we present our contributions to develop an iron-catalyzed carbon-carbon double bond isomerization methodology using a low-coordinate iron alkyl complex. This work is combined with mechanistic studies for an elucidation of the catalytic system involved in this process.



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P A071

SMAHOs: Greener Nucleophiles for Organic Synthesis

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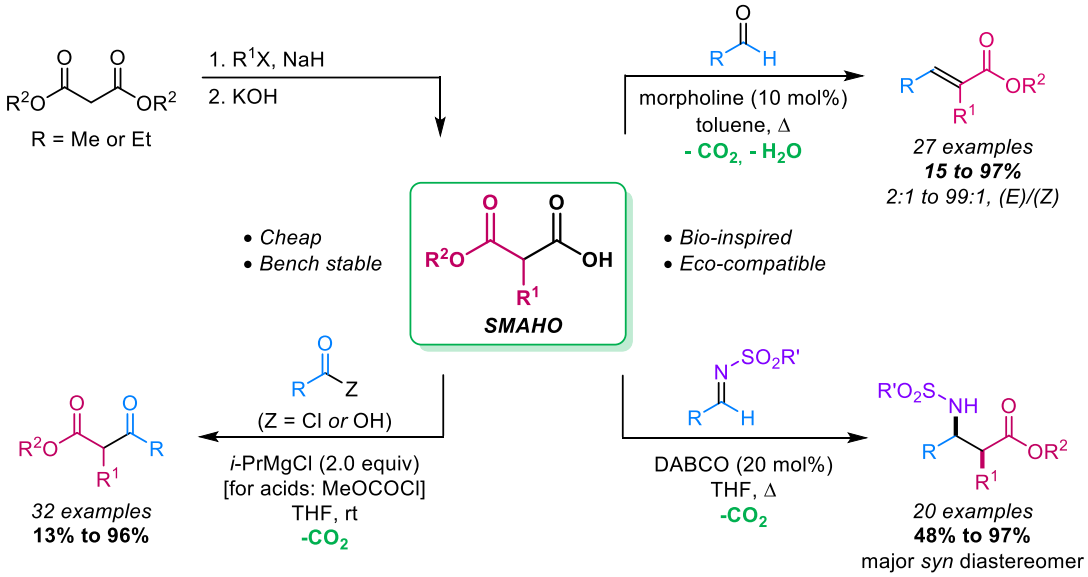
Malonic acid and its ester derivatives (malonates) are an important class of reagents in organic synthesis, as they provide a quick access to carbon centered nucleophilic species. Initially inspired by the biosynthesis of polyketides, malonic acid half oxyesters, which contain a carboxylic acid moiety together with an ester, constitute a very interesting subclass of compounds, particularly well adapted for the development of decarboxylative couplings. In sharp contrast with their unsubstituted or aminated derivatives, Substituted Malonic Acid Half Oxyesters (SMAHOs) are less described whereas they could represent relevant precursors for molecular complexity and the introduction of original organocatalyzed reactions. Our group has thus studied the use of SMAHOs as pro-nucleophiles in decarboxylative processes, where they act as enolate equivalents in the elaboration of greener methodologies.[1]

SMAHOs are bench-stable reagents that can be easily obtained from malonates by alkylation and mono-saponification.[2] Once in hands, we first demonstrated that they could be efficiently used in olefination reactions with aldehydes for the preparation of α,β-disubstituted acrylates, thus constituting an attractive alternative to existing methods in terms of scope and eco-compatibility.[3] Alternatively, they could serve as enolate equivalents in decarboxylative Mannich-type reactions with imines (preformed or *in situ*-generated), affording a straightforward access to β[2,3]-aminoesters, with moderate to good yields and diastereoselectivities.[4] More recently, we developed their use in decarboxylative Claisen reactions, with a variety of acyl donors.



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P A072

Molecular information ratchet based on cyclodextrin [2]rotaxane

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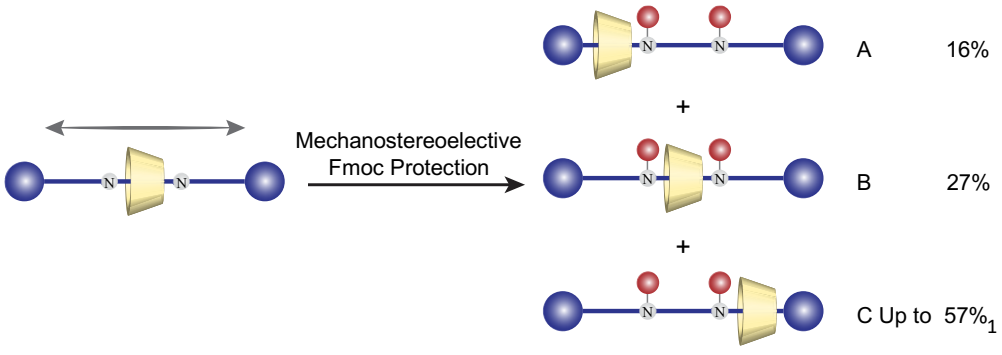
Molecular machines[1], defined as an assembly of a discrete number of molecular components designed to perform mechanical-like movements as a consequence of external stimuli[2], has drawn the attention of the scientific community. Although various examples of small molecular machines have been described[3], the regulation of the unidirectional movement remains a challenge.

Information ratchets[4] are a general class of mechanism in which an energy barrier is regulated on a potential energy surface in order to directionally drive the Brownian particle distribution away from equilibrium. Therefore, creating a molecular information ratchet is crucial to reaching the unidirectional movement of molecular machines. Cyclodextrins[5] could be good candidates for this system because of their asymmetric cone-like shape and chiral cavity.

Herein, we describe a permethylated cyclodextrin [2] rotaxane which can perform ratcheting motion. The rotaxane is composed of three equivalent stations separated by two secondary amines as reactive sites that can react with Fmoc derivatives. During the Fmoc-protection a kinetic bias resulting in a non-statistical distribution between the three possible mechano-isomers was observed. This bias can be rationalized by the asymmetry of the CD that favors the reaction when the amine is facing the secondary rim rather than the primary rim. Different factors controlling the ratcheting mechanism, such as solvent, reaction temperature, and reactivity of the Fmoc derivatives were investigated and will be presented.



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P A073

Access to unnatural glycosides by metal-catalyzed functionalisation of glycal substrates

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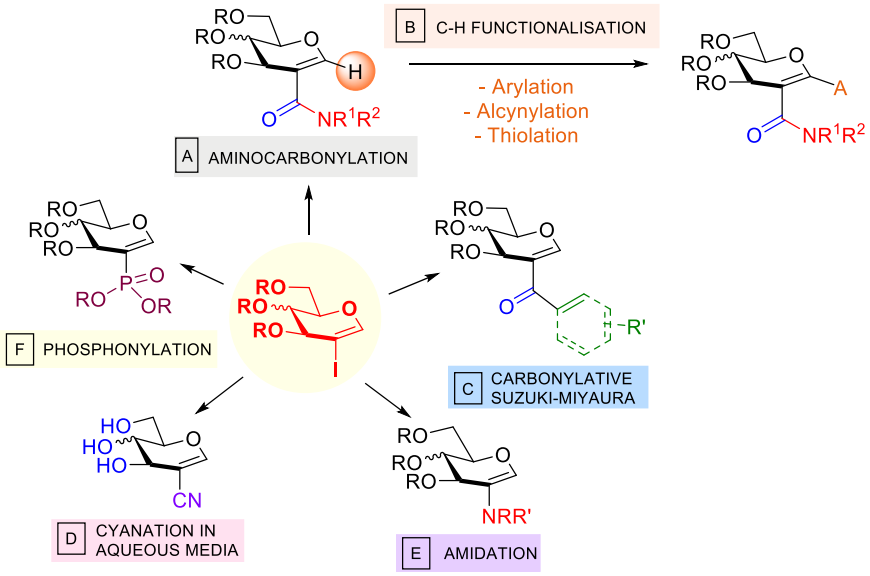
Development of new access to glycoconjugates has become of great interest in synthetic chemistry. In particular, glycoconjugates possessing an unnatural bond are largely studied due to their enzymatic and chemical stabilities towards C-O and C-N natural links.

Our expertise deals with the metal-catalyzed functionalisation of glycal substrates using two different reactivities:

- Cross-coupling reactions on 2-iodoglycal starting compounds for the formation of C-C, C-N or C-P bonds : (A),[1] (C),[2] (D)[3] (E)[4] and (F)[5].
- Directed C-H functionalisation reactions of the pseudo-anomeric position of C2-amidoglycals (B).[6]



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P A074

New Halogen Bond Donor Catalysts for a Microwave-Assisted CO_2 Conversion to Cyclic Carbonates

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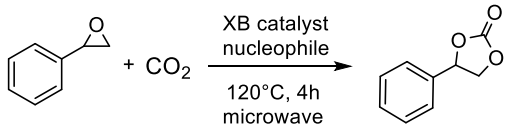
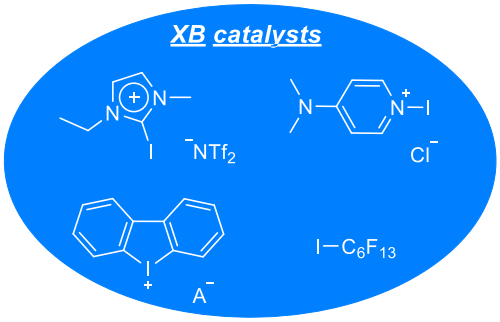
Since the beginning of the industrial age in the mid-18th century, the anthropogenic emission of carbon dioxide has shifted the natural carbon cycle and has become the most present greenhouse gas in the atmosphere. Therefore, reducing the net amount of carbon dioxide in the atmosphere by using it to produce added-value products is an attractive field. [1,2] Herein, we used carbon dioxide and epoxides to generate cyclic carbonates, used as electrolytes in Li-ion batteries, polar aprotic solvents, and as intermediates for chemical synthesis.[3] This reaction represents a green approach of CO_2 conversion with 100 % atom economy and without toxic organic solvents and reagents. In this context, new catalysts are tested regularly to increase the reactivity of the thermodynamically highly stable CO_2 by creating new chemical pathways for the reaction. From transition metal catalysts to organo-catalysts many examples are reported in literature. Recently, organo-catalysts containing halogen-bond donor sites have been employed successfully.[4] Halogen bonding (XB) has been defined as an attractive non-covalent interaction between the electrophilic site of a halogen atom (XB-donor) and a Lewis base (XB-acceptor).[5] In our present work, we propose an approach to catalyze the discussed reaction using microwave-assisted heating in the presence of Lewis acidic halogen bond catalysts.[6] Various halogen-bond catalysts have been tested, with a particular focus on an iodoimidazolium cation.[7] Our approach afforded cyclic carbonates in reproducible experiments with yields of up to 91 %.





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P A075

Divergent Total Synthesis of Grayanane diterpenoid family

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Grayanoids are [5.7.6.5] tetratracycle diterpenoids found exclusively in Ericaceae plants. This family of molecules is known to be very toxic.[1] However, grayanoids are used in traditional medicine and have known bioactivities, particularly as analgesics, sedatives, or even insecticides. There is therefore a real interest in carrying out the total synthesis of this family of compounds.

Nowadays in the literature, more than 130 compounds of the grayananes family have been identified. However only a few tedious or non-flexible syntheses of grayananes are described.[2,3]

Therefore, this research work will be to find a new divergent synthetic route that makes it possible to obtain the greatest number of compounds within the grayanane family. The first purpose of this research will be to identify and synthesize common intermediates. Key steps will be explored such as the Ireland Claisen rearrangement, a 1,4-silyl Prins allylic cyclisation and a pinacolic coupling.

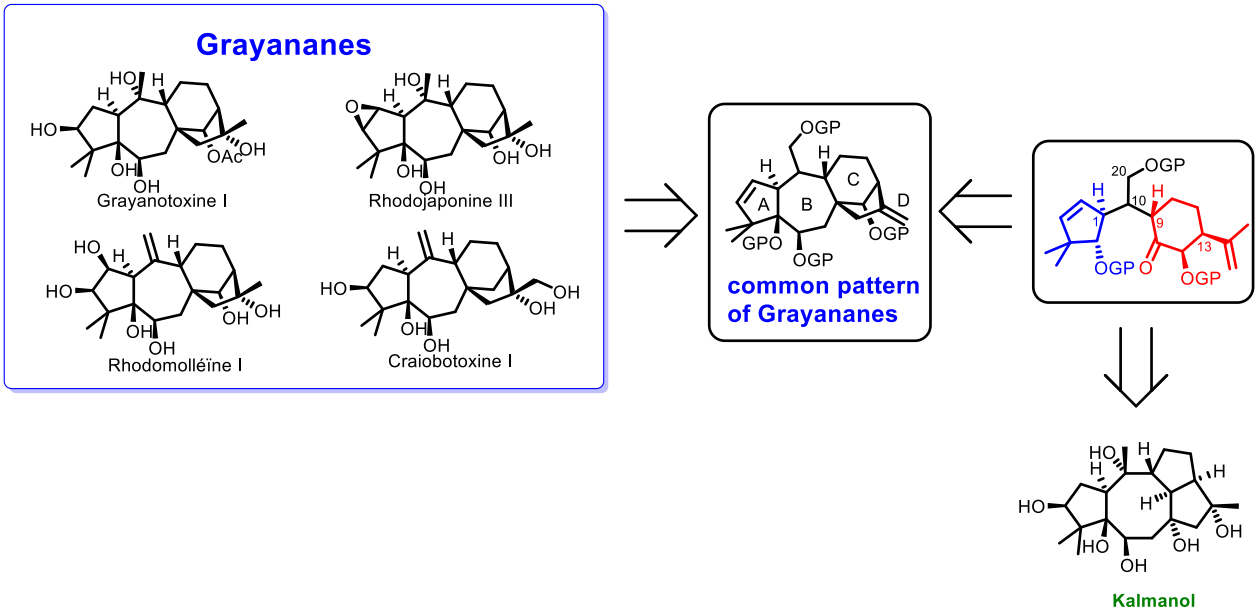

Figure : a general strategy toward the grayanane family

Due to the structural proximity with another terpenoid family, kalmanes, a collective strategy towards kalmanes and grayananes can be considered.

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P A076

Peptid nucleic acids for ultra-fast click and release reactions

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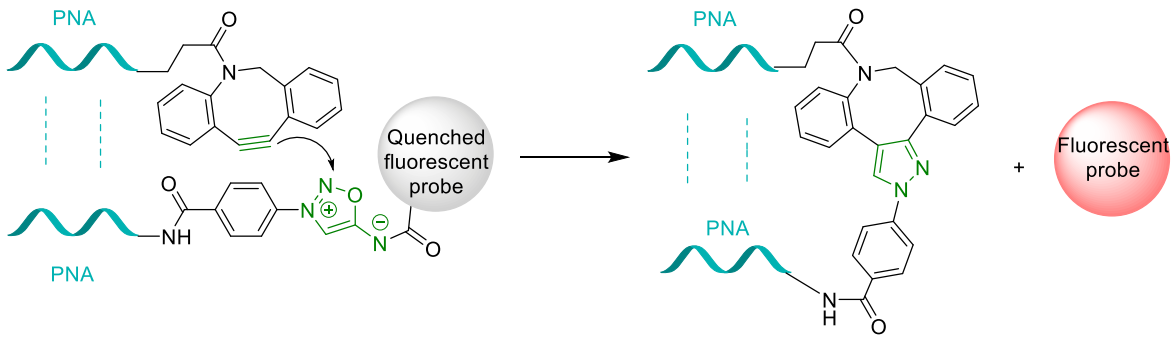
Biorthogonal click and release reactions are interesting new tools allowing the selective release of compounds of interest in biological media, including inside animals[1]. Our laboratory has recently discovered the reaction between iminosydnones and strained alkynes leading to two products resulting from ligation and fragmentation of iminosydnones under physiological conditions[2]. In this work, we designed complementary Peptid Nucleic Acids (PNAs) to increase the kinetic of this click and release reaction. Each reaction partner is attached to a PNA and the molecular recognition between the PNAs was found to induce huge enhancement of the reaction speed. Several couples of complementary PNAs were synthetized to determine optimal PNA size. Kinetics were determined by monitoring the release of a fluorescent probe. With molecular recognition, the reaction becomes a pseudo first order, making the kinetic nondependent of the concentration which opens up numerous application perspectives.



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P A077

Polycyclic heteroaromatic compounds from thioxanthone: Synthesis and properties

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Helical molecules are widely present in nature. Besides DNA which is probably the most known double helix structure, alpha-helices can also be found in many proteins. Our laboratory has previously prepared benzothieno[2,3-*b*]benzothiopyrano[4,3,2-*de*]quinoline (Figure 1, left, X = S), a fluorescent helicene-like polycyclic, heteroaromatic molecule that proved to be a promising inhibitor of disease-related PIM protein kinases.[1] This work focuses on a safer way to reach this compound and related aza analogues.

The synthesis of our key intermediate 1-aminothioxanthone was achieved in four steps and in 32% overall yield from commercially available thioxanthone. First, 1-iodothioxanthone was obtained by deprotolithiation and *in situ* transmetalation-iodolysis of the bare heterocycle. The amino group was next introduced by Gabriel's reaction involving copper-mediated *N*-arylation with phthalimide. While the tandem *N*-arylation/cyclisation appeared to be favoured by the absence of sulfur bridge, 2-iodo-*N*-methylindole gave higher yield than 2-iodobenzothiophene. Our efforts were next concentrated on the synthesis of benzofuro-, benzothieno- and 10-methylindolo- [2,3-*b*]benzothiopyrano[4,3,2-*de*]1,8-naphthyridines which are original hexacycles also endowed with interesting fluorescence properties. These compounds were further evaluated as originals inhibitors of Pim kinases related to cancer development, and the results were rationalized by molecular modelling experiments.

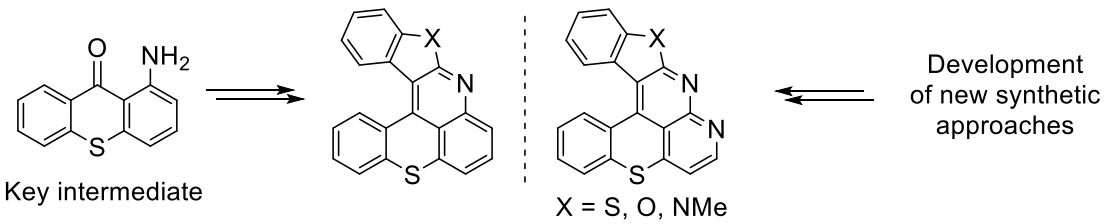

Figure 5: Structures of benzothieno-, benzofuro-, 10-methylindolo -[2,3-b]benzothiopyrano[4,3,2-de]quinolines (left) and -[2,3-b]benzothiopyrano[4,3,2-de]1,8-naphthyridines (right)

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P A078
Fluorinated Peptide Approach for the Inhibition of Rotamase

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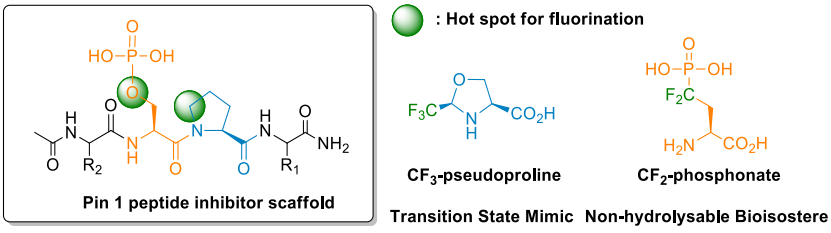
Pin1 is a small two-domain protein (18 kDa) member of the Parvulin subfamily of Peptidyl-Prolyl *cis-trans* Isomerases (PPIases). It differs from all others PPIases through its substrate specificity for phosphorylated Ser/Thr-Pro peptide bonds.[1] Pin1 plays essential roles in cell division and is involved in many diseases, including cancer and Alzheimer's disease. This enzyme is a promising drug target as it controls numerous cancer-driving pathways. Small molecules as well as peptide inhibitors of Pin1 have showed cancer suppression ability in multiple studies.[2] Compared to the small-molecule class, the peptide inhibitors display generally more selectivity towards the target but suffer of chemical and/or metabolic instability as well as poor cell-permeability.

The incorporation of fluorine into biomolecules has gained a considerable interest due to its ability to modulate properties of pharmaceutical compounds.[3,4] Our group has reported the effect of trifluoromethylated pseudo-prolines on the conformation of the peptidyl-prolyl bond.[5] We now aim at developing new fluorinated peptides containing those unnatural amino acids and taking advantage of the fluorine properties to develop Pin1 inhibitors. Therefore, we have considered the fluorination of peptide scaffolds to access potent Pin1 inhibitors with the goal to stabilize the transition state conformation or to improve their metabolic stability. Here, the synthesis and the conformational NMR studies of those inhibitors will be discussed.



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P A079

Docking molecular study of Mannitol structure

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Antibiotic therapy, urinary pain relievers and hydration are classic and effective methods that have long been used to treat urinary tract infections caused by Escherichia coli. However, the high multi-resistance of E-coli strains has called on researchers and scientists in the field of medical research to develop alternatives as effective as antibiotic therapy, but more natural, or even without side effects. The main objective of this study is precisely to contribute to the development of one of these natural molecules: Mannitol. In this context, a multitude of molecular modeling methods are used, in particular the "Molecular Docking" method which consists of predicts the structure of the complexes formed between the active ligands: D-Mannose and D-Mannitol and the FimH protein of Escherichia coli. This approach is carried out by determining the exploration surface, and by detecting probable binding cavities as well as the orientation of small molecules that bind to the different amino acids of the target protein, which makes it possible to calculate their affinity levels and activity.

This result supports the idea that the two complexes have good stability and a strong interaction with the FimH protein, however the comparative study shows that D-Mannitol has a better inhibitory activity against FimH compared with α-D-Mannose.
This finding may be the start of an innovative therapy and confirms the effectiveness of the D-Mannitol molecule, based on experimental tests in vivo and in vitro in the search for treatments of urinary tract infection caused by E- coli.

P A080
Metal free and scalable alternatives for reduction of sulfoxides

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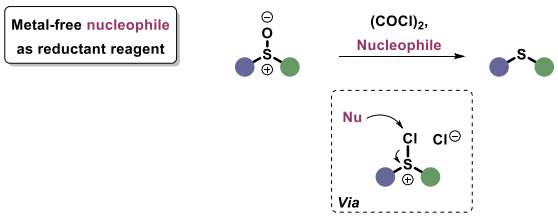
The chemistry of organosulfur is one of the most significant topics in organic synthesis nowadays.[1] For instance, sulfides are present in many biologically active molecules, and they are key intermediates for the synthesis of wide-ranging biological, pharmaceutical, and naturally occurring active molecules.[2] The deoxygenation of sulfoxides is among the most usual, efficient, and straightforward transformations to obtain the corresponding sulfides. During the last few decades, several methods for reducing sulfoxides into sulfides have been reported in the literature. Those methods are carried out using electrophilic reagents, Lewis acids and transition metal complexes; unfortunately, most of those strategies clearly need polluting reagents or expensive heavy metals.[3] Furthermore, in 2020, we report the use of highly nucleophilic 1,3,5 trimethoxybenzene (TMB) as the reducing agent in the deoxygenation sulfoxides as a general and forthright new method.[4] In addition, other teams have been working on greener and scalable strategies in recent years; one example of a successful methodology is the electrochemical reduction of sulfoxides published by Guo, Wen and co-workers.[5] Regrettably, chromatographic purification is mandatory in all the cases described before, making them unsuitable for multigram scale preparations. Considering those difficulties, we have been interested in developing new metal-free and scalable strategies as alternative methods for reducing sulfoxides, minimizing problematic or polluting waste and avoiding chromatographic purification. In that context, we present our advances on this topic.



Acknowledgments: This work was financially supported by Universidad de Los Andes, particularly the Faculty of Science (INV-2021-126-2269) and the Chemistry Department.

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P A081

Organocatalytic approach for a formal 1,6-conjugate addition

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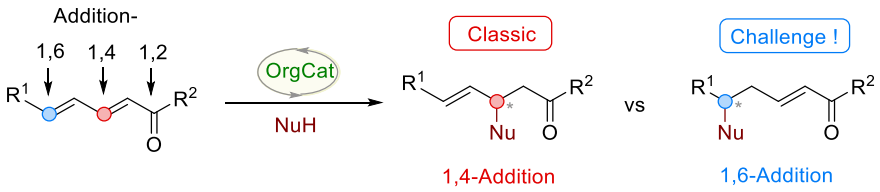
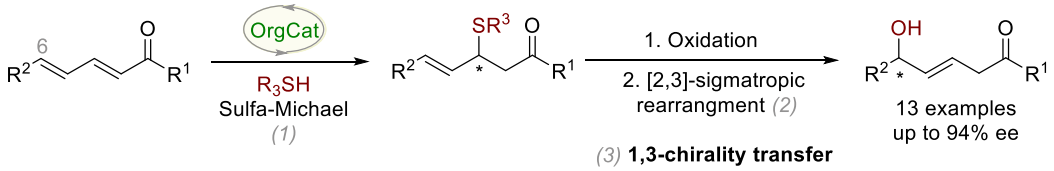
In asymmetric organocatalysis, 1,6-addition reactions on vinylogous Michael acceptors are challenging due to regioselectivity issues (1,2- *vs* 1,4- *vs* 1,6-additions).[1] Such processes face an additional difficulty related to the remote control of the absolute configuration of the created stereogenic center. Few solutions are reported in the literature to promote a selective 1,6-addition, either by modifying the nature of the substrates or by using specific organocatalysts.**Erreur ! Signet non défini.**



We are currently interested in developing an alternative and asymmetric sequence based on organocatalysis, leading eventually to the formal enantioselective 1,6-introduction of a nucleophile to vinylogous Michael acceptors. Accordingly, we planned (1) an organocatalytic and enantioselective sulfa-Michael addition process, revealing an allylic sulfide moiety, which allows, after mono-oxidation of the sulfur center, to promote (2) a [2,3]-rearrangement process to introduce a substituent at position 6 along with (3) a 1,3-chirality transfer.[2] The results of this investigation will be presented herein.



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P A082

Efficient and economical incorporation of oxygen isotopes into molecules using precursors of [*O]O_2

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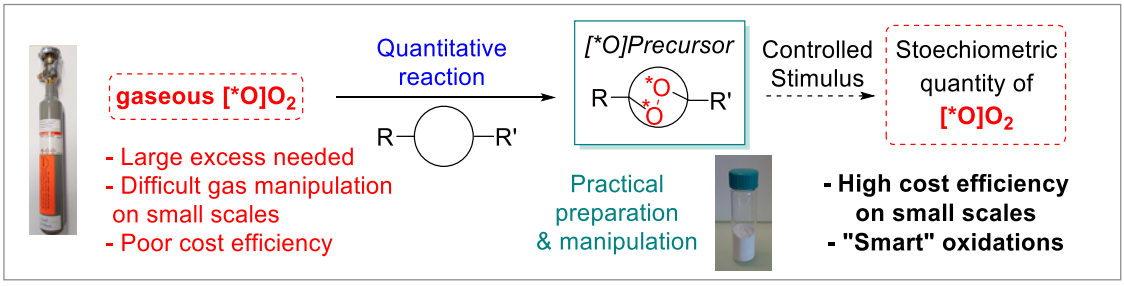
Among the various elements, oxygen plays a key role in many functional groups, and its isotopic labelling often proves determinant for mechanistic insights. Indeed, [^{18}O] can be easily differentiated by mass analysis from the predominant [^{16}O] (99.759%), and recent advances in NMR instrumentation allows efficient detection of the chemical shifts of [^{17}O] (-30 to +1000 ppm).[1] Due to the extremely low natural abundance of [^{18}O] and [^{17}O] (0.204% and 0.037%, respectively), the use of isotopically enriched compounds is essential, and synthetic methodologies for the incorporation of labelled oxygen (*O) have been extensively studied.[2] They generally rely on the use of one of the cheapest isotope precursors: [*O]H_2O (≈ 250 € for 1g of 97% [^{18}O]H_2O i.e. 5€/mmol, and ≈800 € for 250 mg of 86-90% [^{17}O]H_2O i.e. 55€/mmol*)*, but often require harsh conditions limiting their use to simple synthons, and/or involve reversible isotopic exchange yielding lessened isotopic enrichments. Advanced isotopic oxygen sources ([*O]CO_2, [*O]CH_3OH,…) are compatible with more specific reactions, but are extremely costly due to their low availability. Interestingly, some examples using gaseous *O-labelled dioxygen were also reported,[2] which theoretically presents a moderate molar cost of isotopic oxygen atoms (≈650 € for 1 L of 99% [^{18}O]O_2 i.e 8 €/mmol of ^{18}O, and ≈4500 € for 1 L of 90% [^{17}O]O_2 i.e. 60€/mmol of ^{17}O). However, the need to use large excesses and the difficulty to manipulate precisely these gaseous reactants greatly increase the costs of these procedures, which made them under-used. To solve these major drawbacks, we developed solid & stable precursors that are able to release stoichiometric amounts of [^{18}O]O_2 and [^{17}O]O_2 on demand. In combination with a two-chamber glassware,[3] this system enabled the synthesis of various *O-labelled molecules on small scales with good yields and excellent isotopic enrichments (>80% *O).



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P A083

High-pressure activation to circumvent product degradation in the reaction of unprotected glyconitrones with alkynes

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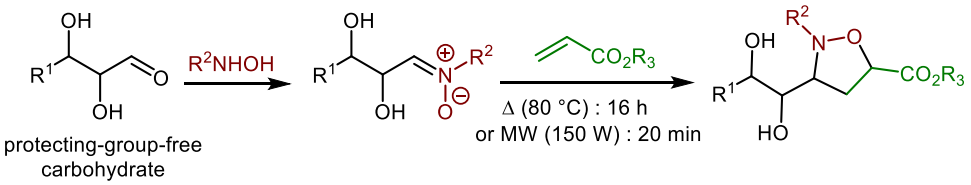
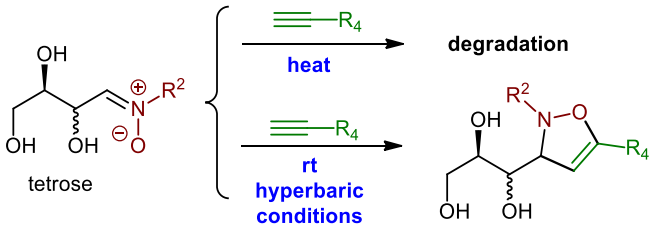
We have recently described the condensation between unprotected aldoses and hydroxylamines to form the corresponding nitrones, which undergo a 1,3 dipolar cycloaddition with alkenes to afford amphiphilic isoxazolidines.[1]



Under the same reaction conditions, the use of alkynes proved unsuccessful, due to the high sensitivity of the formed isoxazolines to heat and their degradation during the course of the reaction. Aside from standard activation methods, high-pressure has the particularity to be performed at room temperature and is energetically cost-free, which is well-suited for green chemistry approaches. High pressure is particularly advantageous for reactions which combine two or more molecules, such as Diels-Alder and 1,3 dipolar reactions.[2] This uncommon method of activation was applied here to achieve the reaction between our unprotected carbohydrate nitrones and various alkynes.



Erythrose and threose derived nitrones were used as models, which afforded the corresponding functionalized isoxazolines in good yields (70-90 %) in most cases.

Aside from their potential biological applications,[3] isoxazolines might also serve as intermediates for further transformations.[4] Valorization of our polyhydroxy-isoxazolines will be presented further.

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P A084

Titanium-mediated expedient synthesis of complex nitrogen heterocycles

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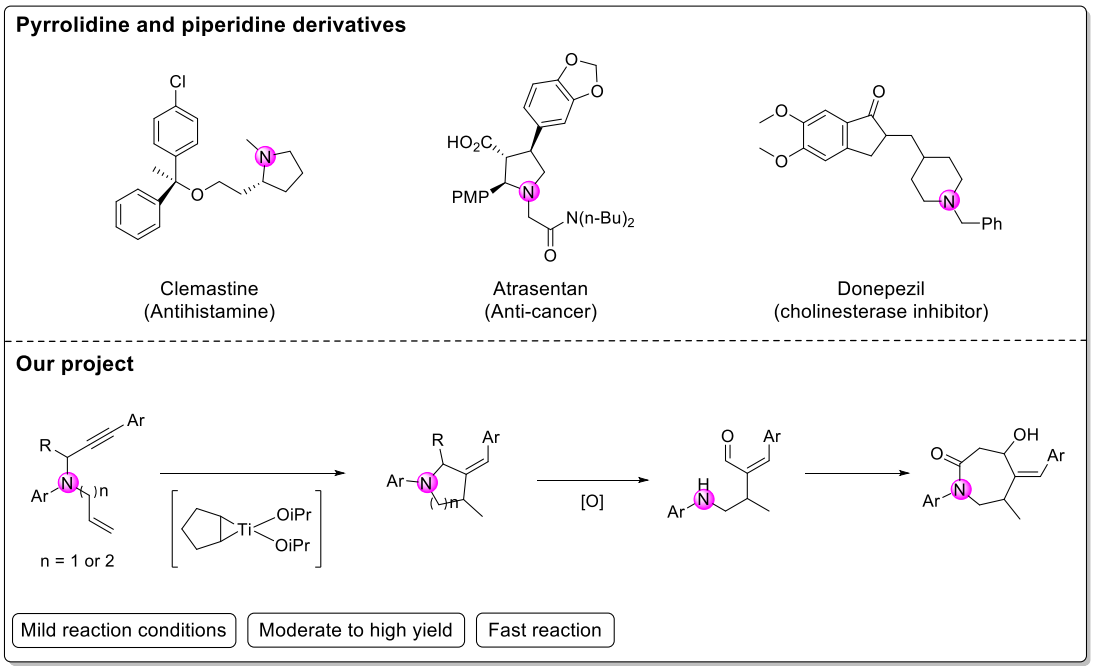
Nitrogen-containing heterocycles constitute a class of particularly important organic compounds. In particular, pyrrolidine and piperidine subunits are largely present in marketed drugs such as clemastine (antihistamine), atrasentan (anti-cancer) and donepezil (cholinesterase inhibitor). Therefore, developing and extending the synthetic tools for the preparation of heterocycles of this type, in a simple way, is an important research field.

Here, for this purpose, a Kulinkovich-type reaction was applied[1,2], combining titanium tetraisopropoxide and a Grignard reagent, to couple two C-C unsaturated bonds in an intramolecular fashion.[3] Electronically and sterically diverse starting materials underwent fast reaction to produce 5- or 6- membered rings under mild conditions.

In addition, a new post-functionalization process provides access to 7-membered rings in two synthetic steps: aerobic oxidation and acylation/intramolecular aldol reaction.



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P A085

Droplet-Surface ImmunoAssay (DSIA) for high throughput analysis of cytosolic protein at the single-cell level

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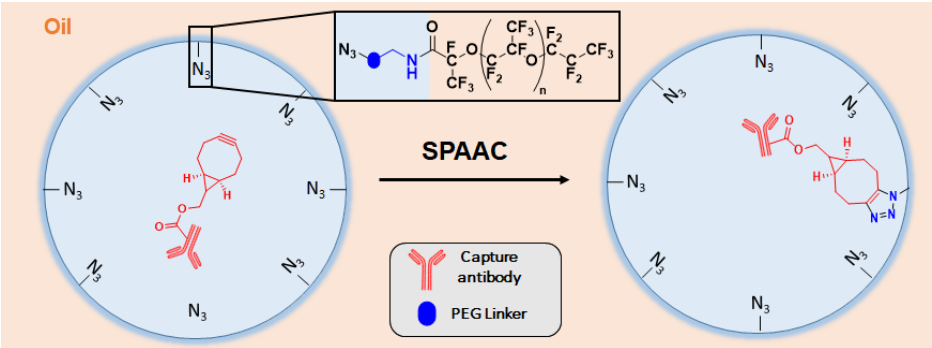
Enzyme Linked Immunosorbent Assay (ELISA) is central in biological science for the detection of proteins[1]. However, it often present limitations such as the need of a large amount of sample, or too low detection sensibility.[2] Using a droplet-based microfluidics format has allowed the development of miniaturized, less consuming and more sensitive protein detection methods by co-encapsulating the biological sample and functionalized particles to capture the protein to analyze.[3] This caused technological complexity due to difficult control of particle distribution in the droplet, complex readout due to erratic particle localization within the droplet.[3] We report herein an alternative in-droplet immunoassay format, which avoid the use of particles, the Droplet Surface Immunoassay (DSIA). It exploits the oil/aqueous phase interface as a protein capture and detection surface, using tailored perfluorinated surfactant bearing azide functionalized PEG-based polar heads. These azides spontaneously react *in situ* with strained alkyne functionalized antibodies via a Strained Promoted Azide/Alkyne Cycloaddition (SPAAC). The resulting functionalized inner surface is then able to capture a targeted protein leading a concomitant relocation of the labelled detection antibody at the surface. This relocation leads to a change of signal in the on-line analysis from a convex shape (not captured) to a characteristic concave shape (captured). The DSIA is fast, quantitative and sensible at 3.4 attomoles of analyte per droplet, and this new immunoassay method was demonstrated to allow detection of cytosolic proteins at the single cell level.



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P A086

γ-Perfluoroalkylation of α,β-unsaturated carbonyl compounds via photoredox catalysis

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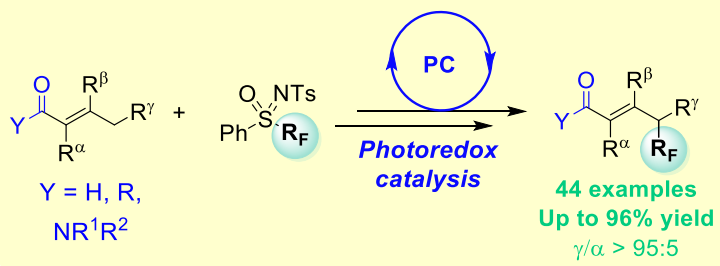
Considering the growing interest in the synthesis of trifluoromethylated molecules for pharmaceutical and agrochemical industries, research for new methodologies of C-H trifluoromethylation to introduce a $-CF_3$ group (or R_F group) on various substrates is crucial, especially for complex scaffolds. By their multiple reactivities, α,β-unsaturated carbonyl derivatives are choice targets for trifluoromethylation reactions.[1] However, if C(sp^2)-H trifluoromethylation studies are abundant for positions α and β of these molecules,[2] research for C(sp^3)-trifluoromethylation on γ-position are scarce.[3]

During this communication, we will present the γ-perfluoroalkylation of α,β-unsaturated carbonyl compounds (including enals, enones, and α,β-unsaturated amides) *via* visible-light catalysis which has been successfully performed with high regioselectivity (Scheme 1),[4] thanks to the recent development of photoredox catalysis and the of use of *N*-tosyl *S*-perfluoroalkylated sulfoximines.[5]



Scheme 1. γ-perfluoroalkylation via photoredox catalysis

An enantioselective version of the reaction was also set up, which consists in the first example of an enantioselective remote perfluoroalkylation reaction.

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P A087

Passerini-Smiles Reaction of α-Ketophosphonates: Platform for Phospha-Brook/Smiles Embedded Cascades[1]

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[2] *Laboratoire de Chimie Moléculaire (LCM -UMR 9168), CNRS, Ecole Polytechnique, Institut Polytechnique de Paris, 91128 Palaiseau Cedex, France*
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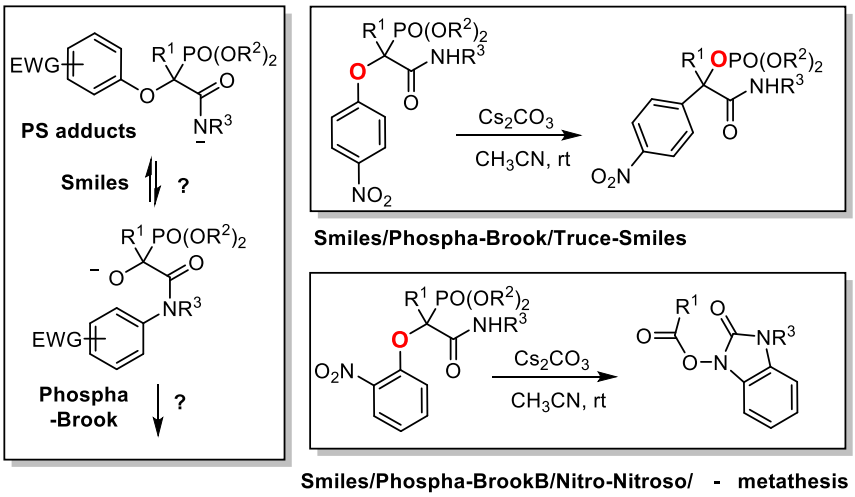
The Passerini-Smiles reactions[2] of α-ketophosphonates with nitrophenols has been used as a platform to observe complex cascades involving multiple Smiles transfers[3] coupled with Phospha-Brook rearrangement[4]. When using 4-nitrophenols a rare 1,3-Truce-Smiles rearrangement is observed leading to diarylacetamide derivatives. 2-Nitroderivatives lead to a completely different reactivity pattern that may be explained by a nitro to nitroso conversion followed by a s-p metathesis. All mechanistic assumptions are confirmed by DFT calculations performed on both families of adducts. The potential of this work has been further demonstrated by the use of N-aryl α-ketoamides as alternative starting materials for these cascades as well as the disclosure of new aza-Nazarov access to hydroxy-indolones.



Scheme. Passerini reaction of α-ketophosphonate followed by Phospha-Brook (PB) rearrangement.

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P A088

Palladium-catalyzed C-H alkoxycarbonylation of benzadehydes using a transient directing group strategy

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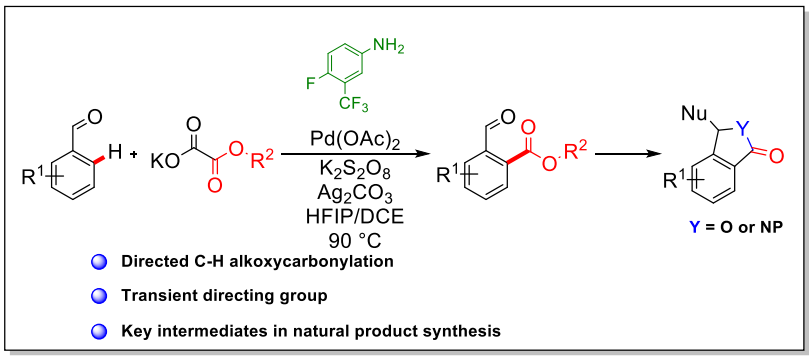
The widespread presence of C-H bonds has made C-H bond activation a hot topic in organic chemistry research in recent years.[1] So far, the selective activation of C-H has generally relied on the design of suitable directing groups and the selection of transition metals as catalysts to obtain target products.[2] Very recently, a strategy based on transient directing group has emerged which allows the use of more useful substrates in C-H activation reactions.[3] In this work, a palladium-catalyzed C-H alkoxycarbonylation of benzadehydes was described. In the process, a key aniline was selected to form a transient directing group, whereas non-toxic potassium oxalate compounds were used as ester group provider.[4] This reaction gave a fast access to very useful mono-alkylphthalates which can be converted into lactones and lactams used in natural product synthesis.[5]



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P A089

Synthesis of 1,3,5-triynes by alkyne metathesis

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The synthesis of 1,3,5-triynes suffers from a limited number of methodologies allowing their access. The Cadiot-Chodkiewicz coupling[1] and the Fritsch-Buttenberg-Wiechell rearrangement[2] are probably the two most popular methods to form the 1,3,5-triyne building block. Other methods were also reported but are more confidential.

In the 2010's, the Tamm group attempted to form 1,3,5-triynes by alkyne metathesis of 1,3-diynes.[3] Unexpectedly, only new 1,3-diynes were isolated. On the basis of this observation, we hypothesized that hindering one of the two triple bonds of the 1,3-diyne precursors may help to circumvent this problem. Actually, in 2020, we reported the first synthesis of 1,3,5-triynes by alkyne metathesis with Fürstner Mo-catalyst (Cat-1, figure 1).[4]

Since then, we initiated a collaboration with the group of Matthias Tamm in order to use more selective catalysts to overcome the necessity to use bulky groups to initiate the exclusive formation of 1,3,5-triyne motif. Today, a mesityl group is bulky enough to induce a total selectivity toward the 1,3,5-triyne over the 1,3-diyne.[5][5] This outcome will let us envisage the synthesis of new compounds bearing the 1,3,5-triyne motif in the future.

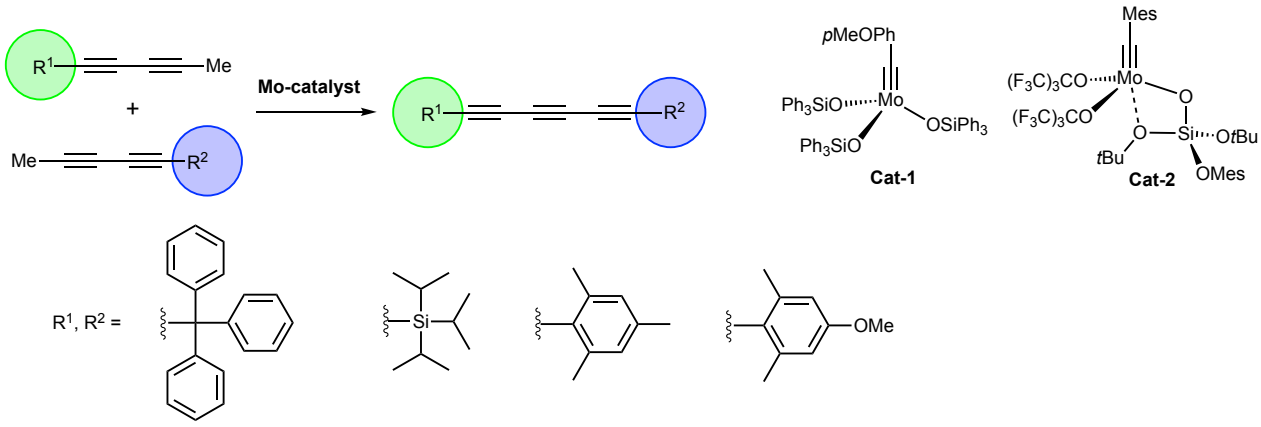

Figure 1. *Synthesis of 1,3,5-triynes by alkyne metathesis.*

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P A090

Mn-Mediated α-Radical Addition of Carbonyls to Olefins: Systematic Study, Scope, and Electrocatalysis

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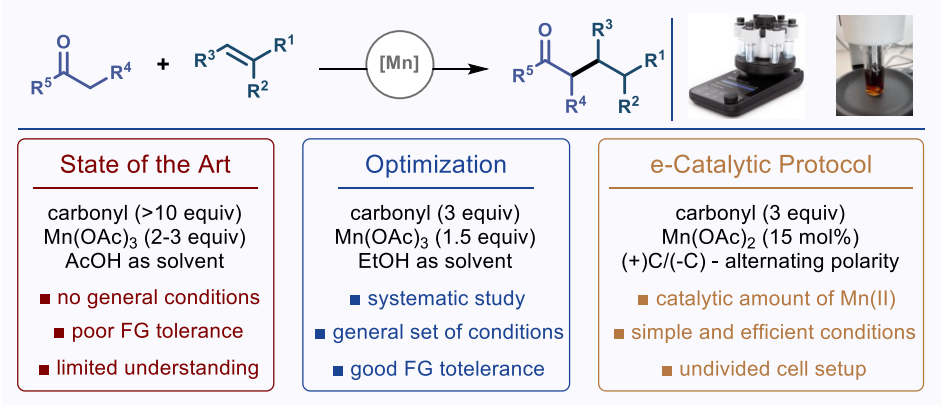
One of the central challenges of our century is the development of sustainable chemistry processes. Following this concept, the use of first row transition metals became essential in catalysis.[1] Manganese, part of these metals, is abundant, inexpensive, non-toxic, and participates in myriad of transformations due to the wide range of oxidation states it can adopt.[2] Since 1969 and the report of Vinogradov, Mn(III) has emerged as an ideal catalyst to promote oxidant free-radical reactions including the coupling between unactivated olefins and carbonyl compounds to forge a new C-C bond.[3] These processes have found applications in medicinal chemistry and total synthesis.[4] However, the intermolecular version of the reaction still suffers from major limitations such as: (1) the need for a stoichiometric amount of catalyst and a large excess of carbonyl starting material to be employed; (2) the absence of a general set of conditions; (3) A low functional group tolerance and (4) the lack of understanding with regards to reaction parameters.



Our group recently started a research program dedicated to the use of manganese in catalysis. We were motivated to investigate the parameters that govern this transformation and to assemble a general set of reaction conditions. We were able to identify a unified and very reliable set of conditions allowing the coupling of promising substrates that were so far inaccessible using previously reported conditions. The key parameters governing the outcome of the reaction as well as the development of a catalytic version of the transformation under electrochemical conditions will be presented on the poster.[5,6]

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P A091

Nickel-catalyzed direct cyanomethylation of ketones

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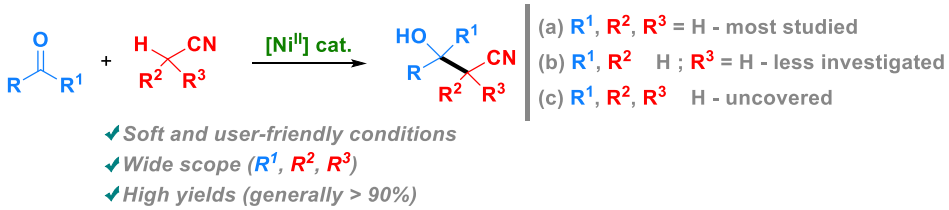
The β-hydroxynitrile moiety is commonly found in bioactive molecules. Among all the strategies reported to date to obtain this motif, cyanomethylation of carbonyl groups has attracted considerable synthetic efforts.[1] Nevertheless, direct deprotonation of non-activated acetonitrile, which exhibits a high pK_a value (31.3 in DMSO), usually requires a strong base raising the question about the functional group tolerance. To overcome this limitation, efficient catalytic Ru,[2] Pd,[3] Cu[4] complexes have enabled the addition of MeCN to various aldehydes and, to a lesser extent, ketones under less basic conditions (case a and, in few cases, case b). However, catalyzed addition of bulkier α-functionalized nitriles R^2R^3CHCN ($R^2 \neq H$, $R^3 = H$, case b or R^2 and $R^3 \neq H$, case c) to ketones appears to be more troublesome.[1-4]



In this poster presentation, we are pleased to report the synthesis of alternative Ni^{II}-pincer complexes[5] and their use as an efficient catalyst for the cyanomethylation reaction of a wide range of ketones under mild conditions, in generally high isolated yields (case a-c).[6]

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[6] Manuscript in preparation

P A092

Regioselective naphthalene C-H bond halogenation: new methodologies and total synthesis applications

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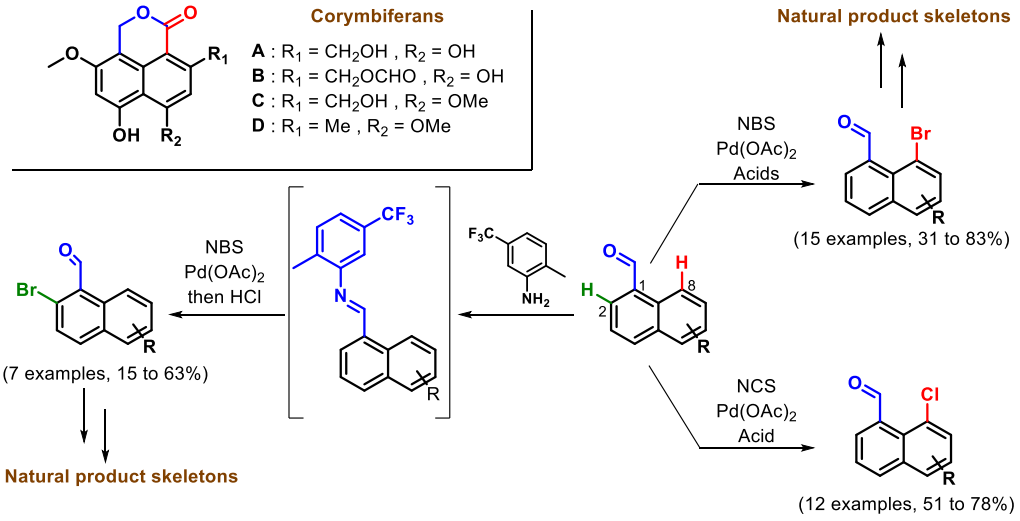
Throughout these previous decades, studies on the C-H bond allow to discover new methods to synthetise organic products. The main issue with C-H activation is the selectivity. Indeed, the C-H bond is predominant in the organic compounds.[1] C-H activations studies on naphthalene showed how to functionalize each position on the cycle.[2] Our group has showed that a carbonyl directing group (DG) in position 1 of the naphthalene, such as an amide, could selectively activate the C-H bond in position 8.[3] Concerning naphthaldehyde, specific imine DG could be formed and activate position 2.[4]

Inspired by these previous results, this work focused on a naphthaldehyde regioselective halogenation reaction. The bromination and chlorination were performed successfully in position 8. Catalysed by palladium (+II), fifteen brominated and twelve chlorinated *peri*-products were characterized. In parallel, several imines have been studied to find the best candidate to perform the bromination in position 2. By forming imines, from the 2-methyl-5-(trifluromethyl)aniline, seven *ortho*-products have been synthesized. Some DFT calculations permit to explain the regioselectivity. Direct applications could be performed in order to access to key skeletons. Thanks to these results, formation of natural compound like corymbiferans A-D and others potential biological molecules could be achieved.[5]



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P A093

Geometry constrained Hexaphyrin-Cyclodextrin Hybrids

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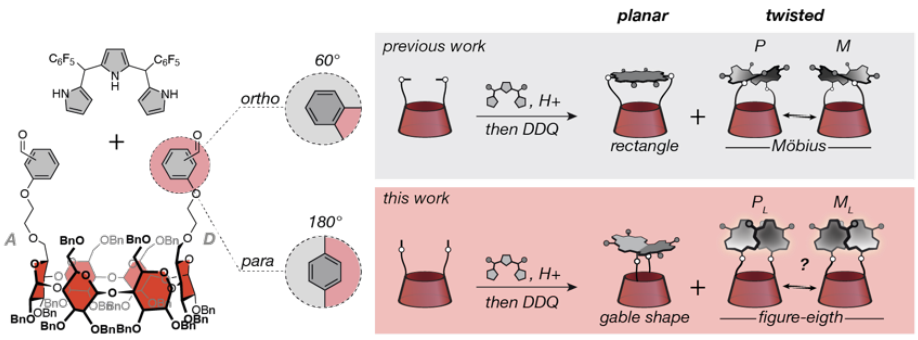
Cyclic molecules containing delocalized π electrons provide either a stabilizing aromaticity, or a destabilizing antiaromaticity. [1] This behavior is not only limited to the number of delocalized π electrons, but also to the topology of these molecules. Indeed, while planar ones having [4n] π electrons are unstable Hückel antiaromatic compounds, half-twisted (180°) derivatives become stable Möbius aromatic compounds. Interestingly, the incorporation of a second half-twist to the structure (360°) allows to recover the starting Hückel antiaromaticity with a non-planar topology. Being able to control both the number of electrons (oxidation state) and the number of twist (topology) of these molecules would certainly contribute to the development of new devices for information encoding.[2] We recently developed hybrid compounds made of a cyclodextrin coupled to an hexaphyrin being able to adopt both (anti)aromatic states and different topologies.[3] We also showed that the cyclodextrin can stabilize the antiaromaticity and influence the twisting chirality of a Möbius aromatic hybrid.[4] We decided to go further and introduce a more constrained linkers between both platforms using *para*-substituted linkers (linear connection) instead of the previously *ortho*-substituted ones (bent connection). In this communication we will describe the influence of this constraint leading to unprecedented Hexaphyrin-Cyclodextrin hybrids adopting gable-shape geometry and a topologically non-trivial figure-of-eight conformation with both aromatic and antiaromatic states.



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P A094

Transformation of α-diazo-β-hydroxyesters mediated by TMSOTf and rhodium catalysts

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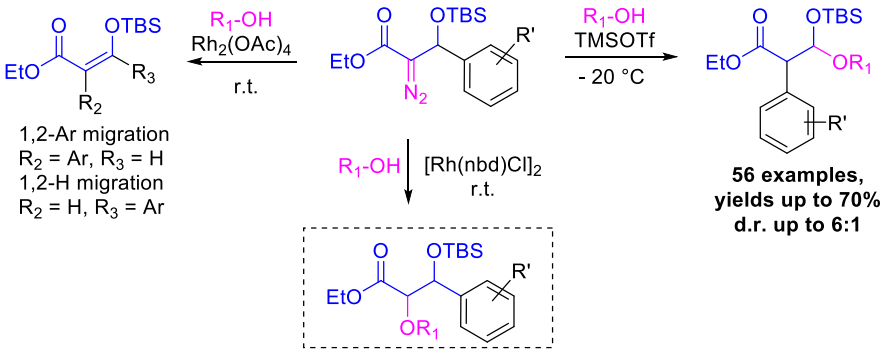
In the context of diverted total synthesis of structurally complex natural products derivatives, the development of new methods allowing the synthesis of natural products and a variety of analogues from a common advanced precursor is of high value. Our team is currently working on designing a diverted total synthesis of natural products implementing a diazo functionality, on which a wide range of transformations (C-H insertion, X-H insertion, migration, cyclopropanation,…)[1] could introduce structural diversity.

To achieve this goal, we are focusing on the reactivity of *O*-protected α-diazo-β-hydroxy-esters in the presence of acids or rhodium catalysts, especially to develop new stereoselective X-H insertions (X = O, NH, S, …). No X-H insertion has been reported so far on such diazocarbonyl compounds, certainly due to competitive 1,2-H and 1,2-R migration reactions. The challenge is therefore to develop reaction conditions which favor the insertion reactions over these 1,2-migrations.



We will present in this communication our journey through the reactivity of α-diazo-β-hydroxyesters focusing first on the synthesis of original mixed silyl acetals in the presence of TMSOTf and then on the development of O-H insertions mediated by rhodium (I) catalyst.

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P A095

Synthesis of fluorinated oligonucleotides

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Nucleic acid-based therapeutics such as miRNA, siRNA and more recently mRNA vaccine have emerged and represent, today, key targets in a wide range of diseases.[1] These different strategies are based on the design of oligonucleotides (ONs) having a complementary sequence to a specific messenger RNA (mRNA) to inhibit the transfer of genetic information from DNA to proteins. In order to be efficient as biopharmaceuticals, ONs must have several properties including: thermal stability of RNA duplex at 37 °C, resistance towards nucleases, efficient and specific delivery to certain tissues or cells, off-target effects absence and low toxicity. Since natural ONs are rapidly metabolized in biological media by nucleases, several chemical modifications were envisaged and led to the conception of ON analogues with good biological activities. However, in spite of the large number of ONs that are currently under clinical trials, the FDA approved only few of them and up to date, the ideal series containing all the required properties for optimal biological responses does not exist yet and deserves to be discovered regarding the growing economical market of ONs. Convinced by the high potential of ON-based therapeutics, our team is interested in the chemical modifications of the 2' position of nucleosides *via* the incorporation of difluorophosphonylated units in order to increase both the thermal stability of RNA duplex, resistance towards nucleases as well as cellular uptake.[2] In this context, several chemical strategies aiming to the preparation of **3** will be presented. These later involved a group transfer radical reaction between allylic carbohydrates or nucleosides **1** and iododifluoromethylphosphonates as a key step.

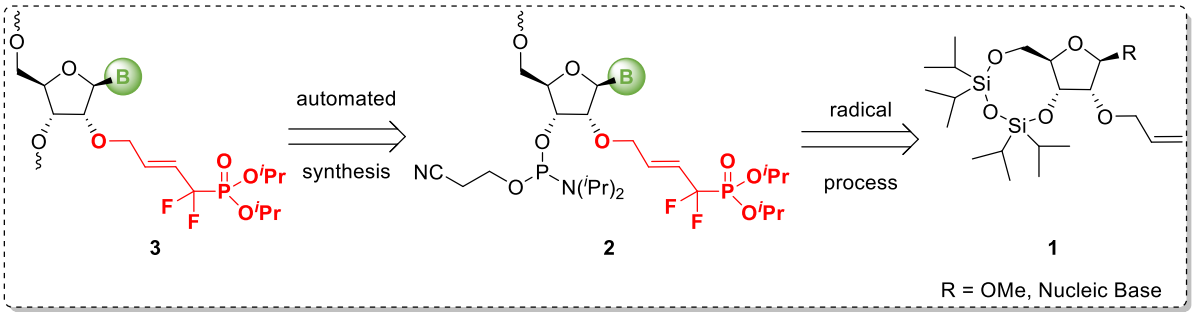

Figure 1 Synthesis of 2'-O-Allyldifluorophosphonylated nucleosides and oligonucleotides.

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P A096

Towards the enantioselective synthesis of complex molecules with eletrochemistry

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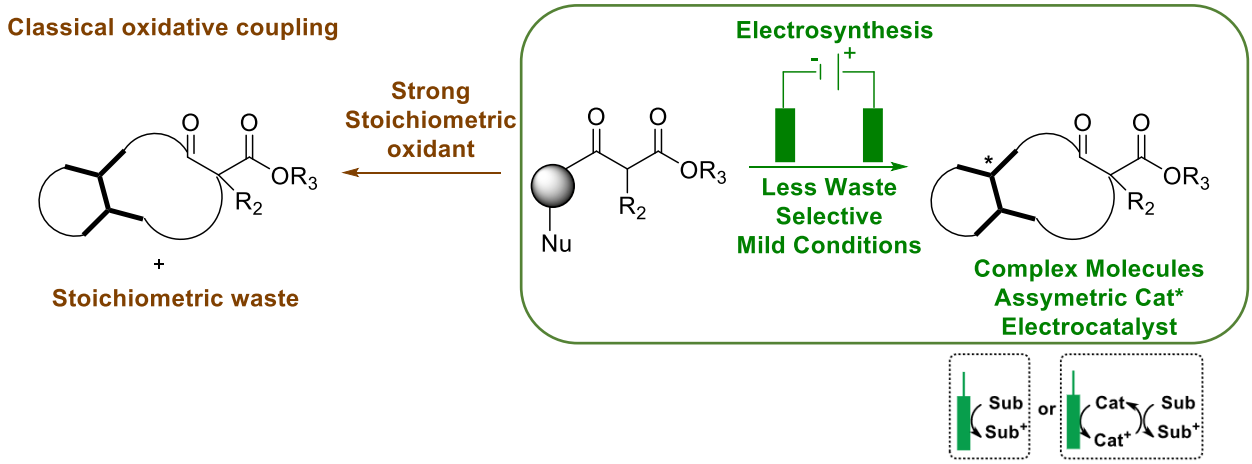
Electrosynthesis has regained an interest since a few decades[1]. Indeed this approach affords the opportunity to develop reaction conditions with minimal amounts of reagents (such as oxidants), in mild conditions.

It is in this context we are developing a methodology to enable the activation of β-ketoester derivatives to form reactive species (radical or cation) by direct or indirect electrosynthesis (use of an electrocatalyst[2]). The activated species should undergo cyclization or polycylization reactions[3] in presence of a chiral inducer, providing enantiopure complex diterpenoid structures.



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P A097

Metal-Free Reduction of Epoxides to Primary Alcohols Mediated by HFIP

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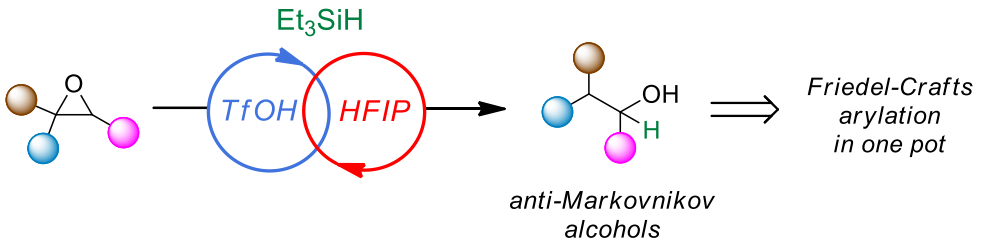
Primary aliphatic alcohols are ubiquitous functional groups in natural products, pharmaceuticals, agrochemicals, fragrances, and materials.[1] Among the numerous methods described toward their synthesis, anti-Markovnikov reduction of epoxides is very attractive. In this respect, various transition metal, Lewis and Brønsted acid, and electrochemistry have been applied to enable the regioselective ring opening of epoxides. However, despite remarkable progress made in this field, several major challenges still remain to be addressed such as the compatibility with strongly electronically deactivated substrates and the use of mild reaction conditions.

Recently, our group has demonstrated that the H–bond donating ability of hexafluoroisopropanol (HFIP) increased drastically the strength of catalytic Brønsted acids, rendering electronically deactivated substrates more reactive.[2]

Being inspired by our previous work on applicable Friedel–Crafts arylation of epoxides, including highly deactivated styrene oxides, using catalytic triflic acid (TfOH) in HFIP,[3] we wondered whether these abilities could be exploited in the reduction of epoxides. Gratifyingly, the acidic combination of TfOH/HFIP in the presence of triethylsilane (Et_3SiH) was found to be a highly efficient catalytic system at room temperature for the aforementioned deactivated styrene oxides but also for the more traditional epoxide motifs, such as aliphatic and electron-rich styrene oxides.[4] Other (hetero)cycles such as oxetanes, tetrahydrofurans, aziridines, and cyclopropanes can also be reductively opened. In addition, the generated primary alcohols can be conveniently functionalized *in situ* by a dehydrative Friedel–Crafts arylation without preactivation.



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P A098
Substrate-dependent selectivity in $Sc(OTf)_3$-catalyzed cyclisation

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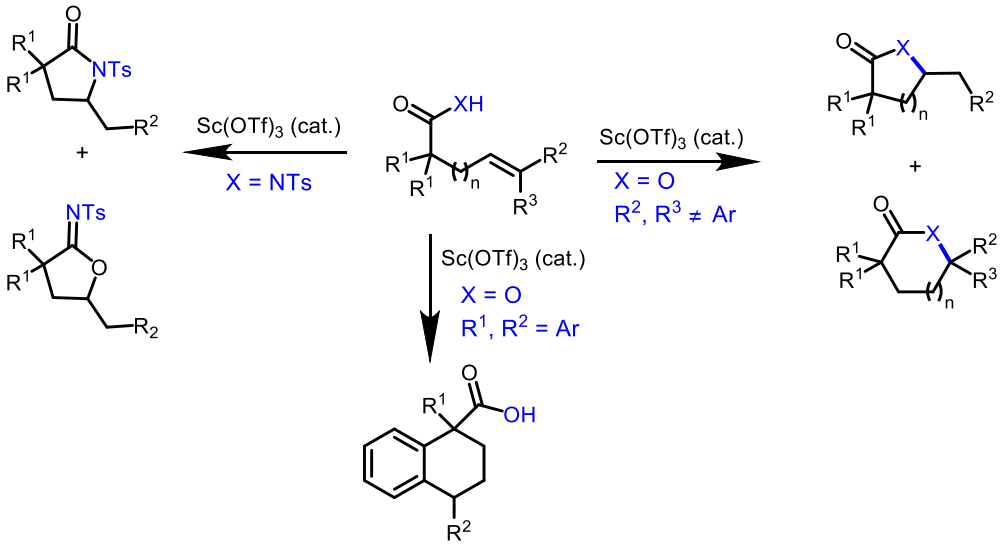
Five-membered ring lactone or lactam compounds are widely present in natural products or biologically important compounds.[1] Over the past decades, their constructions have attracted the attention of numerous chemists and triggered the development of novel, more efficient and selective catalytic systems. Among the numerous methods described towards their syntheses, metal-catalyzed intramolecular hydroelementations have proven to be an effective strategy thanks to its atom economy, waste and energy minimization.[2]
Herein, we report the efficient cyclization of alkenoic acids and *N*-protected alkenamides catalyzed by an easily accessible and practical Lewis acid, scandium triflate. Good conversions are noticed whatever the starting materials are but the selectivity outcome of the reaction is dependent on the substituent pattern of the alkenoic acids or alkenamides. For alkenoic acids, the corresponding lactone or Friedel–Crafts product are either formed while *O*- or *N*-cyclization occurs when *N*-tosyl alkenamides are engaged in the reaction.



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P A099

Construction of C-C Bonds from C - Heteroatom (N, S) Electrophiles by Cobalt Catalyzed Cross-Coupling

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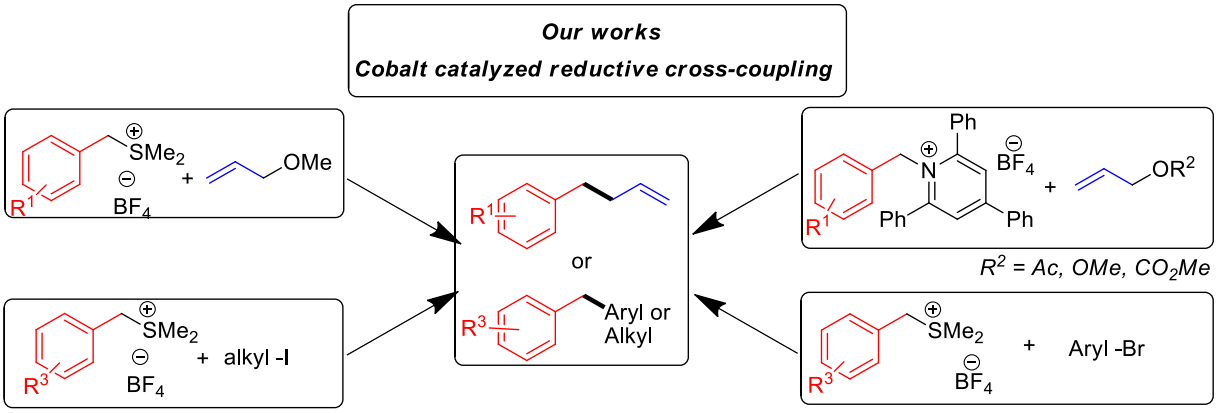
Transition-metal-catalyzed cross-coupling for construction C-C bond has been an important and attractive strategy in organic synthesis since the development of Suzuki, Heck and Negishi reaction. [1] In general, the cross-coupling occurs from organohalides and various organic metallic reagents. Despite significant progress on these transition-metal-catalyzed couplings, the use of both starting materials may sometime be limited by the high cost, toxicity and difficulty of preparation. Although, reductive cross-couplings avoid the need to prepare an organometallic species, the replacement of organohalides by other electrophiles is of great interest and attracts more and more interest in cross-coupling reactions. [2]

Compared to organohalides and organic metallic reagents, alcohols or amines are more available, environmentally benign and less toxic, as well as are prevalent in biomolecules, drugs, and natural products. [3] Due to the higher bond strength, their directly application in cross-coupling is still a great challenge. Sulfonium salts or pyridinium salts derived respectively from alcohols or amines, show higher leaving tendency due to the positive charge of the center ions. Thus, they have been reported successively as electrophilic partners by Watson, Yorimitsu *ect..*[4] A few reports have been published under Ni-catalyzed reductive manners. Inspired by these recent works, we have developed new Co-catalyzed reductive cross-couplings of sulfonium salts and pyridinium salts with other electrophiles.



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P A100
Electrochemical Benzylic C(sp^3)-H Functionalization for the C-C Bond Formation

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[2] *Laboratoire des Biomolécules (LBM), Département de Chimie, Ecole Normale Supérieure, PSL University, Sorbonne Université, CNRS, 75005 Paris, France*
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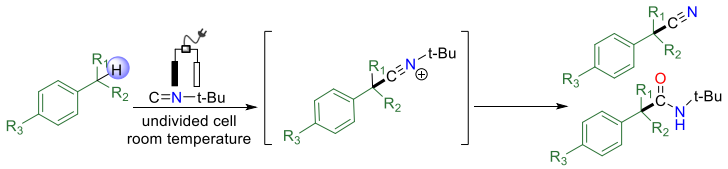
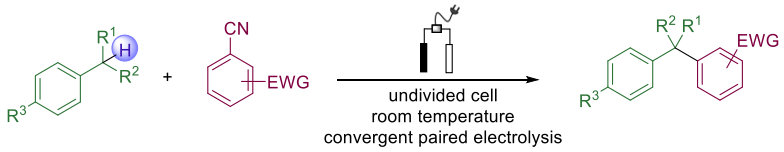
Electrochemistry has emerged as a proficient strategy in the functionalization of benzylic C(sp^3)-H bonds, a strategic step for synthesizing complex molecular structures and various bioactive molecules, such as for the formation of valuable C-N, C-O or C-halogen bonds at benzylic positions.[1] Nonetheless, the construction of a C-C bond by anodic oxidation remains challenging. It mainly relies on the use of activated substrates, the necessity to start from a prefunctionalized benzylic substrate, or the deployment of the cation pool method[2]. Hence, the development of new electrochemical methods that could permit direct benzylic functionalization for the C-C bond formation is highly desirable.

We developed the challenging direct carbamoylation or cyanation of benzylic C(sp^3)-H bonds with an isocyanide via an electrochemical process.[3] The anodic oxidation of the benzylic position and the subsequent addition of the isocyanide lead to the formation of a C-C bond and to a nitrilium cation that hydrolyzes to yield alpha-aryl acetamide derivatives, whereas the elimination of a t-butyl cation delivers alpha-aryl acetonitrile derivatives.



The direct arylation of benzylic C(sp^3)-H bonds with cyanoarenes via a convergent paired electrolysis[4] process was also developed by us, which is avoiding using a transition-metal catalyst[5] and any external oxidant. The combination of anodic oxidation of the benzylic position and the cathodic reduction of cyanoarenes lead to the formation of a benzylic C-C bond.



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P A101
Photocatalytic aminofluoroalkylation of alkene from sulfinates

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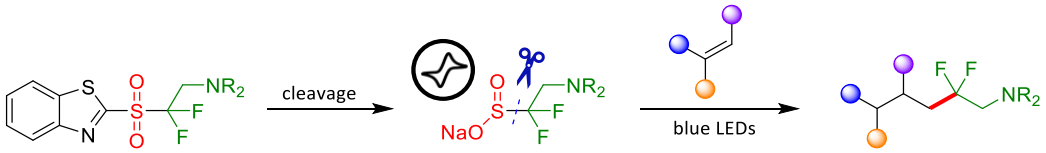
The introduction of fluorinated groups is recognized as a key to have a significant impact on their physicochemical and biological properties. Incorporation of fluorine can serve to influence the pKa of adjacent functional groups or increase the metabolic stability of the parent compound. Today, this approach has been a common strategy for the discovery of new drugs.

Radical chemistry is an efficient strategy for selective functionalization at a late stage synthesis and support fragile functional groups. This makes possible the direct addition of the CF_3 moiety to aromatic rings, natural products, nucleosides without a protective group, and this from sodium sulfinate CF_3SO_2Na or HCF_2SO_2Na as reagent and source of radicals. [1] However, this approach is generally limited by the availability of sulfinates. Indeed, the major inconvenient of this strategy is very few methods of preparation of fluoroalkylsulfinates are described in the literature.[2]

Over the past ten years, the laboratory has acquired know-how in the synthesis of fluorinated sulfones derived from benzothiazole. We have thus been able to develop different methods for preparing fluorosulfinates that have not been or little explored to date, and in particular β-amino-α,α-difluorosulfinates. In order to understand the behavior of these sodium salts, we conducted a study on their oxidation potentials to determine the best conditions for these new fluorinated radicals.



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P A102

Functionalized polyurethane foam as a versatile structured support for reusable photo- and hydrogenation catalysts

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Structured catalyst supports are widely used in continuous process applications due to their efficient mass transfer, low pressure drop, intimate mixing of the reagents, and easy separation of the catalyst from the products.[1] Among the variety of SCS, open cell foams are prime candidates, and our group recently proposed the use of flexible, mechanically resistant and inexpensive polyurethane foams (PUF) as an alternative to the commonly used expensive and fragile ceramic and metallic foams. These PUF can indeed be coated in buffered water (pH 8.5) with a thin layer of polydopamine (PDA) (Fig. 1A) inspired by the mussels' adhesion principle.[2] This allows then the grafting of both inorganic particles[3] and molecular compounds[44] that bear alkoxysilyl arms. In this context, we will present our work toward the development of reusable $[Ru(bpy)_3]^{2+}$- and Pd-based (photo)catalysts supported on PDA-coated PUF (PDA@PUF) and their applications in visible-light induced couplings and selective alkyne semi-hydrogenations, respectively. The heterogeneous Ru photocatalyst was obtained by post-functionalization of PDA@PUF with $Ru(bpy)_3^{2+}$ via a silanization process on the adhesive PDA layer of PUF (Fig. 1B). After thorough characterization by ^{29}Si CP-MAS NMR, ICP-AES and SEM-EDX, the resulting $Ru(bpy)_3$-APTES@PDA@PUF proved catalytically effective in visible-light mediated oxidative couplings and alkylations (Fig. 1C) and showed excellent reusability. In parallel, we also developed an easy-to-prepare Pd@PDA@PUF single-atom-type catalyst (Fig. 1D), that proved highly efficient and selective in alkyne-to-alkene hydrogenation under ambient H_2 pressure without prior reduction procedures (Fig. 1E). The Pd@PDA@PUF catalyst was extremely stable and showed no decay in either activity or selectivity for up to 15 cycles. The as-recovered catalyst even displayed improved catalytic performance due to the progressive *in situ* reduction of the Pd(II) catechol-coordinated species into Pd(0), as demonstrated by XPS studies.

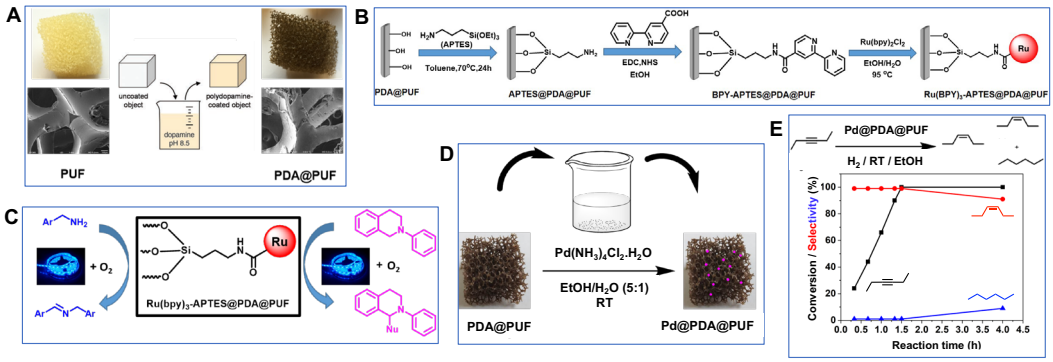

Figure 1. (A) PDA coating of PUF, (B) Immobilization of $[Ru(bpy)_3]^{2+}$ (C) Visible-light mediated oxidative couplings and alkylations (D) One-step strategy immobilization of a Pd(II) salt, (E) Alkyne-to-alkene hydrogenation

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P A103

Towards boron-assembled rotaxanes

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Several molecular assemblies containing one or more boron atoms have been reported in the litterature.[1,2] Boron offers a rich chemistry thanks to its ability to form bonds with many common atoms (C, O, N, S, …) while the lability of these bonds can be very varied. The synthesis of rotaxanes and catenanes with boron as a gathering atom has never been described so far and focused our attention. Some strategies are conceivable to obtain these structures such as the formation of pseudo-rotaxanes through the synthesis of a boronic ester. We describe herein the design of macrocycles and molecular threads that were thought and that are currently under investigation in the laboratory to reach this objective.

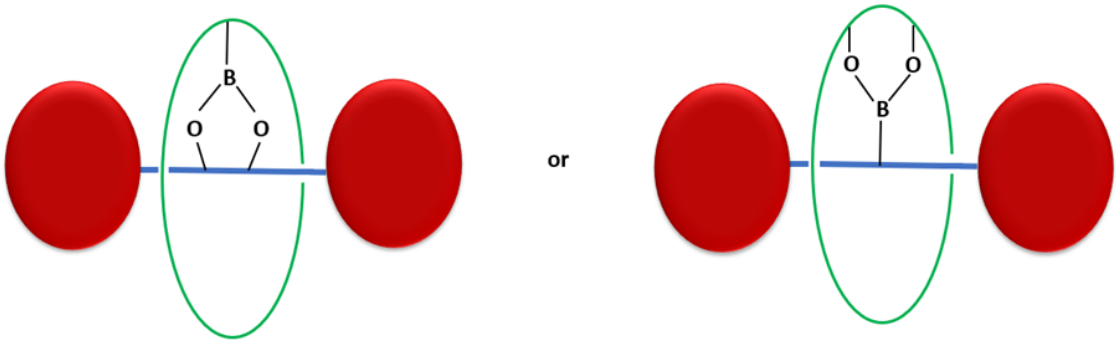

Figure 1 Schematic representation of two rotaxanes assembled with a boronic ester

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P A104

Catalysis as a Trigger for Redox-Economic Sequences and Application to Apratoxin A Synthesis

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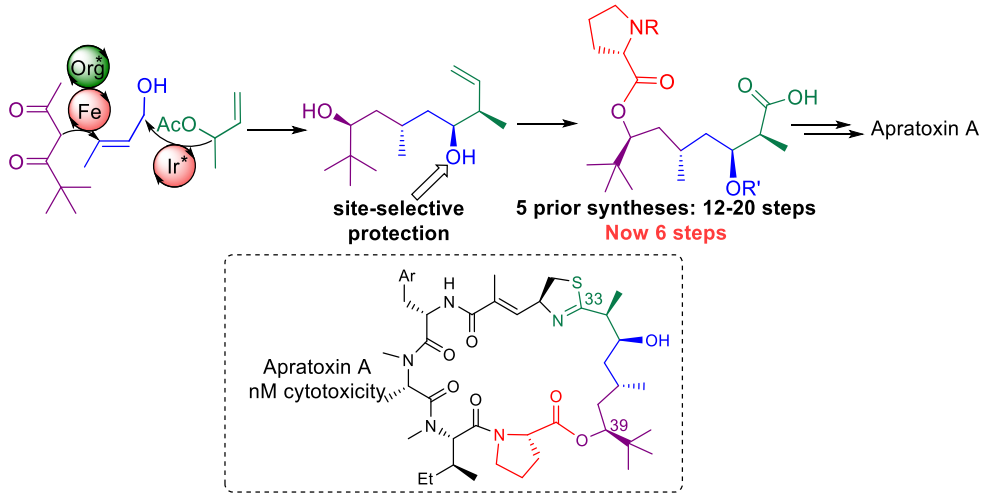
[2] *Aix Marseille Univ, CNRS, Centrale Marseille, iSm2, Marseille, France*
anestis.alexandridis@univ-grenoble-alpes.fr

Polyketides are key complex frameworks of many different biologically active natural products. However, most syntheses are still too often involving lengthy stepwise sequences and activation by stoichiometric reagents. The difficulty at synthesizing polyketides stems from the challenge associated with the control of multiple remote acyclic stereogenic centers requiring distinct chiral reactants or catalysts for each. Fulfilling the principles of redox-economy, different transformations have been developed where the activation consists in an initial alcohol dehydrogenation by a metal complex, such as redox-couplings developed by the group of Krische[1], or enantioselective multicatalytic borrowing hydrogen developed by our group.[2]

Apratoxin A is a potent anticancer natural product whose key polyketide fragment constitutes a challenge for organic synthesis, with 5 prior syntheses requiring 12 to 20 steps for its preparation. Herein, through the combination between different redox-economical catalytic stereoselective transformations, the key polyketide fragment could be prepared efficiently.[3] Combined with a site-selective protection of the obtained diol, this strategy enables the preparation of the known Apratoxin fragment in only 6 steps, representing the shortest formal synthesis of this polyketide.



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P A105
Taming the Lewis Superacidity of Non-Planar Boranes

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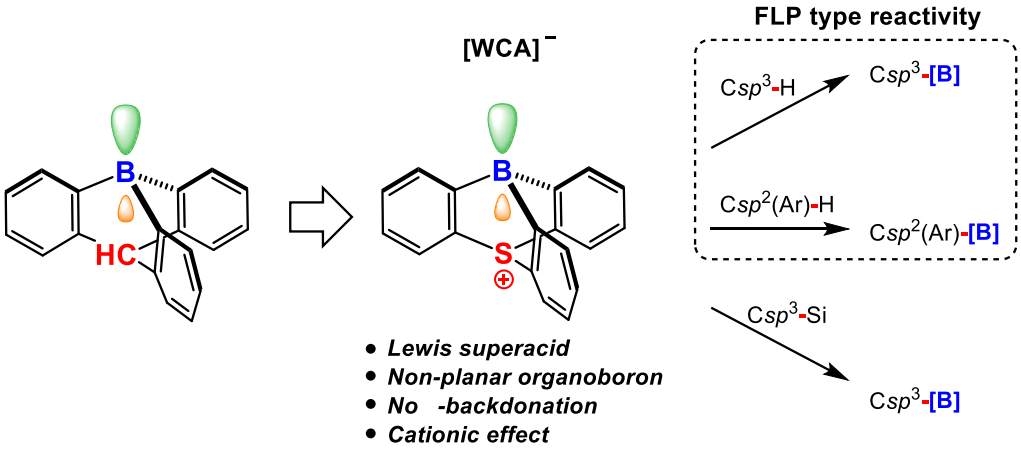
Although their popularization was spurred by the discovery of frustrated Lewis pairs (FLPs) in 2006,[1] trivalent boron species are recognized since decades as prototypical Lewis acids and have found, to date, numerous applications far outside this topic.[2] It is only recently that highly electron-deficient pyramidal boranes were predicted to enable the activation of small molecules and the formation of donor-acceptor complexes of noble gases.[3]

Three years ago, the first non-planar triarylborane derived from triptycene was reported as a Lewis adduct with weakly coordinating anion (WCA) and displayed a Lewis acidity exceeding by far all known triarylboranes.[4] Thereafter, the parent 9-boratriptycene was synthesized in turn and the factors governing the exceptional Lewis acidity of these species were rationalized.[5]

Very recently, the design and synthesis of a third member of the 9-boratriptycene family was achieved based on three guidelines: *(i)* the orthogonal arrangement between the triptycene aryl rings π-orbitals and the boron pz empty orbital to prevent π-backdonation at boron; *(ii)* the high pre-pyramidalization of the boron atom to minimize the structural reorganization energy and *(iii)* the strong withdrawing ability of the sulfonium linker to provide high Lewis acidity at boron and preventing fast protodeboronation.[6]



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P A106

Introduction of a chiral constrained fluorinated residue (α-TfmAla) into poly-Aib: a structural study towards the design of valuable foldamers

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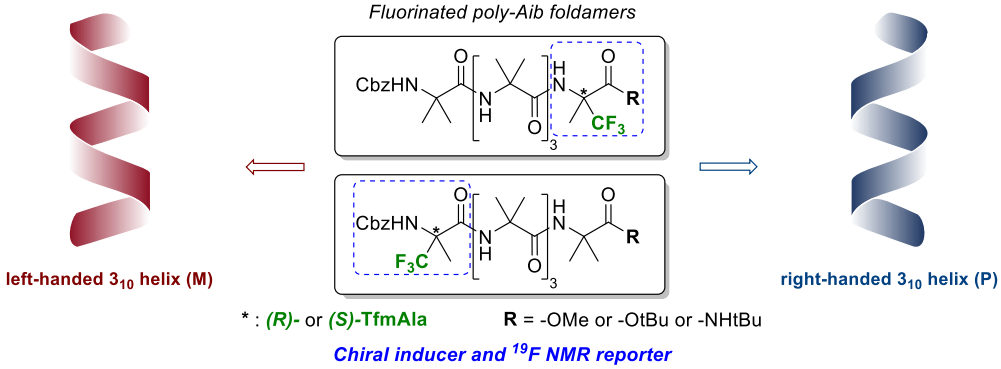
Peptidomimetic foldamers are a class of compounds capable of adopting well-defined secondary structures mimicking protein folding with the advantage of being very stable against proteases. Meanwhile, the use of fluorinated compounds in medicinal chemistry has become widely popular, with the incorporation of fluorine atoms being of major interest to modulate their physicochemical and therapeutic properties[1] but also as NMR probes. However, fluorinated foldamers remain scarcely explored compounds despite their obvious interest in both chemical biology and medicinal chemistry. Oligomers of α-aminoisobutyric acid (Aib) have been widely investigated for their ability to form stable 3_{10}-helices. The achiral nature of Aib does not allow a screw-sense preference of the helix and presents equal population of left- and right-handed conformers. However, the incorporation of a single chiral residue at *N*- or *C*- terminus may alter the equilibrium between the two forms, resulting in a screw-sense preference on the overall helical chain.[2,3]

In this work, we report the synthesis of new Aib foldamers based on the incorporation of *(R)*- or *(S)*- α-trifluoromethylalanine (α-TfmAla) at the *N*- or *C*-terminal position of Aib tetramers. NMR driven conformational studies, circular dichroism and X-ray crystallography confirmed the ability to adopt 3_{10} helical structure and showed that the introduction of chiral α-TfmAla allows to promote, quantify and in some case to assign the screw-sense preference of the helical chain. Results demonstrate that the stereo-electronic properties of the trifluoromethyl group and the *C*-terminal unit are of major interest to control the helical screw-sense. This thorough structural study opens the field to the development of finely tunable fluorinated helical foldamers towards application in chemical biology.



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P A107

Synthesis of α-chloroarylacetic acid *via* electrochemical carboxylation of α,α-dichloroarylmethane derivatives

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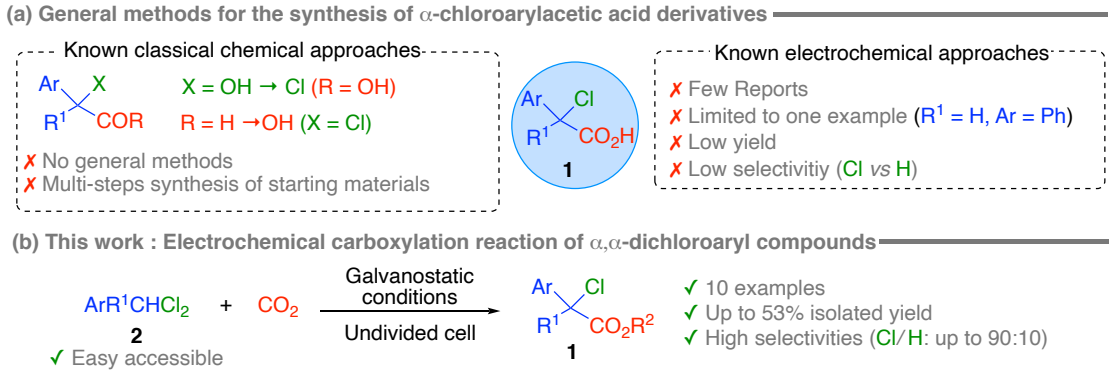
α-chlorophenylacetic acids **1** are versatile synthetic intermediates involve in the synthesis of several drugs[1] Therefore, several methods were reported to synthesize α-chlorophenylacetic acids including chemical (mainly oxidation of α-chloroaryl acetaldehydes[2] or chlorination of α-hydroxyarylacetic acid[3]) or electrochemical approaches but none of them proved to be general (Scheme a, left part). As far as electrochemical approaches are concerned, the electrocarboxylation reaction of α-chloroaryl derivatives have been extensively studied.[4] On the other hand, electrocarboxylation of α,α-dichloro species remains elusive (Scheme a, right part).[5] To the best of our knowledge, only one example has been described (R^1 = H, Ar = Ph) with low yield and selectivity (Cl *vs* H).



We would like to report herein our contribution to the electrocarboxylation reaction of α,α-dichloroarylmethane **2** derivatives in order to provide an efficient and selective synthesis of α-chloroarylacetic acid derivatives **1** (Scheme b).[6]

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[1] For examples, see: (a) Frank, R.; Bahrenberg, G.; Christoph, T.; Schiene, K.; DeVry, J.; Damann, N.; Frormann, S.; Lesch, B.; Lee, J.; Kim, Y.-S. and Kim, M.-S. (2010) PCT International Application WO2010/127856. (a) Murakami, K.; Ohashi, M.; Matsunaga, A.; Yamamoto, I.;Nohira, H. *Chirality* **1993**, *5*, 41–48.

[2] For an example, see: Paraskevas, S. M.;Paraskevas, M. S. *Catal. Commun.* **2004**, *5*, 687–690.

[3] For an example, see: Carnell, A. J.; Kirk, R.; Smith, M.; McKenna, S.; Lian, L. Y.;Gibson, R. *ChemMedChem* **2013**, *8*, 1643–1647.

[4] For examples, see: Murtaza, A.; Qamar, M. A.; Saleem, K.; Hardwick, T.; Zia Ul, H.; Shirinfar, B.;Ahmed, N. *Chem Rec* **2022**, *22*, e202100296 and references therein.

[5] (a) Silvestri, G.; Gambino, S.; Filardo, G.; Greco, G.;Gulotta, A. *Tetrahedron Lett.* **1984**, *25*, 4307–4308. (b) Silvestri, G.; Gambino, S.; Filardo, G.; Tiitta, M.; Sjöström, M.; Wold, S.; Berglind, R.;Karlsson, B. *Acta Chem. Scand.* **1991**, *45*, 987–992.

[6] Unpublished results

P A108
Transformation of Ferrocenesulfoxides Toward Polysubstituted Derivatives

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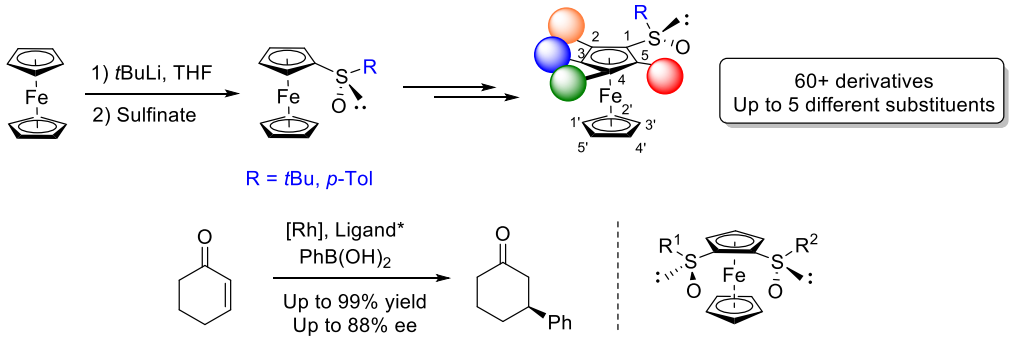
Given the manifold applications of sulfoxides in catalysis, syntheses of tailor-made ferrocenesulfoxide-based ligands continue to be of interest to many scientists.[1] Current functionalization of the ferrocenesulfoxides mainly relies on *ortho*-metalation by using lithium bases followed by electrophilic trapping; however, the examples generally concern 1,2-disubstituted forms and rarely more. Furthermore, as the oxygen of the chiral sulfinyl group ($R^1S(O)R^2$, $R^1 \neq R^2$) directs the deprotonation of the 2-position, the functionalization of the 5-position currently requires the configuration inversion at sulfur or its oxidation to sulfone.

Here, we combined deprotometalation–electrophilic trapping sequences, protecting groups, traceless directing groups and "halogen dance" reaction to reach polysubstituted derivatives, including the first hetero-2,3,4,5-tetrasubstituted (*S*)-*S*-*tert*-butylferrocenesulfoxide. We also established original ferrocene-1,2-disulfoxides as promising ligands in the rhodium-catalyzed 1,4-addition of boronic acid.[2,3] Based on these results, functionalizations of both cyclopentadienyl rings have the potential to unprecedented highly substituted enantiopure derivatives.

In summary, these novel methodologies afforded a series of previously unknown polysubstituted ferrocenesulfoxides which considerably expand the available chemical space and pave the way for applications in versatile fields.



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P A109
Asymmetric Ring-Closing Enyne Metathesis

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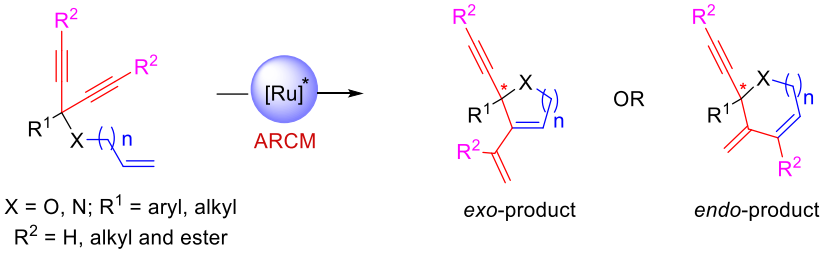
The metathesis reaction of alkenes discovered several years ago, was successfully applied to the synthesis of molecules for the creation of Csp^2 - Csp^2 bonds. In 2005, the Nobel Prize was awarded to Robert H. Grubbs, Richard R. Schrock, and Yves Chauvin since this powerful reaction has been widely used in the field of organic chemistry, for instance for the synthesis of natural compounds.[1] More specifically, asymmetric metathesis involving dienes as substrates has been well studied and reported in the literature.[2] However, ene-yne asymmetric metathesis is, to the best of our knowledge, scarcely referenced in the literature and, represents a great challenge for the preparation of enantioenriched dienes. Indeed, the first asymmetric metathesis of dienynes using [Mo] and [W]-catalysts was reported by the Schrock group in 2010.[3a] The same year, the study of diastereoselective metathesis of ene-diynes was reported by Gouverneur and co-workers.[1b] In this context, our group studied the desymmetrization of ene-diynes mediated by the use of chiral [Ru]-catalysts. Results recently obtained in our team concerning ring-closing metathesis reactions *via* desymmetrization of ene-diyne by using of new chiral ruthenium catalyst will be disclosed here (Scheme 1).



Scheme 3

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P A110

On Reuben G. Jones synthesis of 2-hydroxypyrazines

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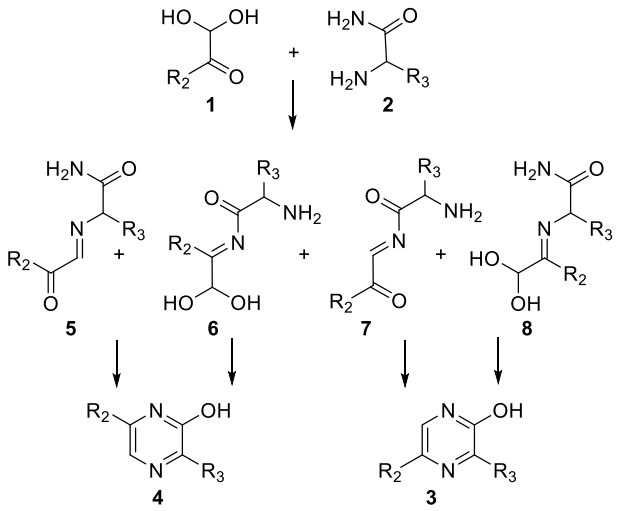
In 1949, Reuben G. Jones disclosed[1] an original synthesis of 2-hydroxypyrazines **3** and /or **4** involving a double condensation between 1,2-dicarbonyls and α-aminoamides upon treatment with sodium hydroxide at low temperature. This discovery turned out to be of importance as even today there are no simple alternatives to this preparation. Across the years, it was employed to prepare 2-hydroxypyrazines but some of its limits, notably regioselectivity issues when starting from α-ketoaldehydes **1**, certainly hampered a full-fledged generation of pyrazine-containing new chemical entities of potential interest in medicinal chemistry.



We will describe here some insights and improvements in the reaction parameters affecting the regioselectivity and yield when starting from phenylglyoxal and two α-aminoamides. We also suggest a mechanism explaining the counterintuitive occurrence of 3,5-substituted-2-hydroxypyrazine **3** as the major reaction product.[2]

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[2] Legrand, P.; Janin, Y. L., On Reuben G. Jones synthesis of 2-hydroxypyrazines. *Beilstein J. Org. Chem.* **2022**, *18*, 935-943.

P A111

On the quest of a sterically hindered Stenhouse salt and its derivatives

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Stenhouse's salts are dyes known since the 1850s[1], the synthesis of these salts consists of a mixture of aniline in the presence of furfuraldehyde in an acid medium. They are also known as intermediates in the formation of cyclopentenones[2]. The deprotonated form of Stenhouse salts **A** (Fig.1) lead to a non-Kekulé ketocyanines **B** which can only be assigned to a zwitterionic or a diradical resonance form.[3] By increasing the steric hindrance of the Stenhouse salt, we were able to observe and isolate intermediates in the chemistry of the Stenhouse salts, **B** and the cyclic form **C**, respectively[4]. The latter features a reactive and unusually long C-O bond (150ppm) and a rich electrochemistry, including the formation of an air-persistent radical cation **D**, all of which will be discussed in this contribution.

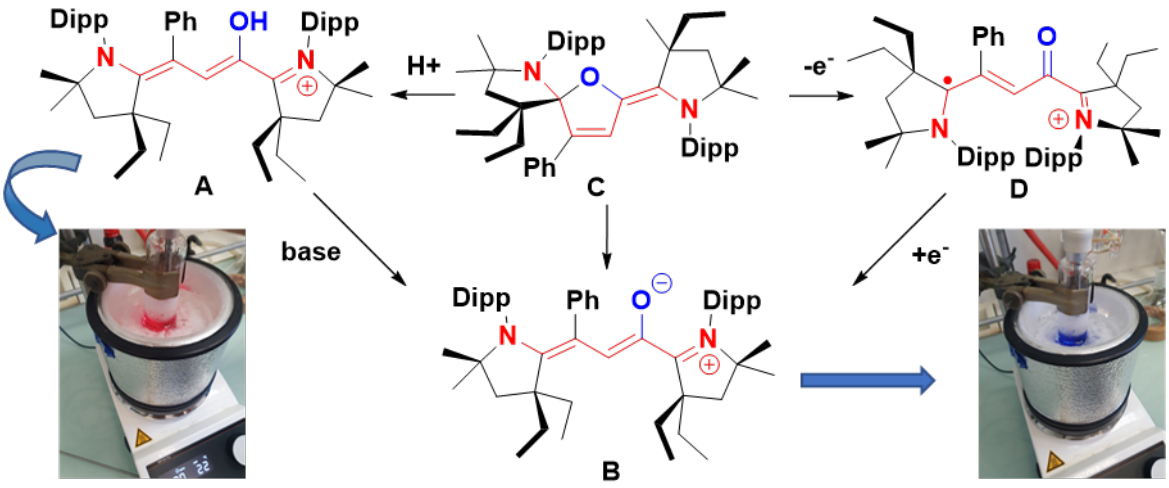

Fig. 6 *Reactivity of a sterically hindered Stenhouse salt and its derivatives.*

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P A112

Origins of the enantioselectivity in the phase transfer-catalyzed cyanation of enones

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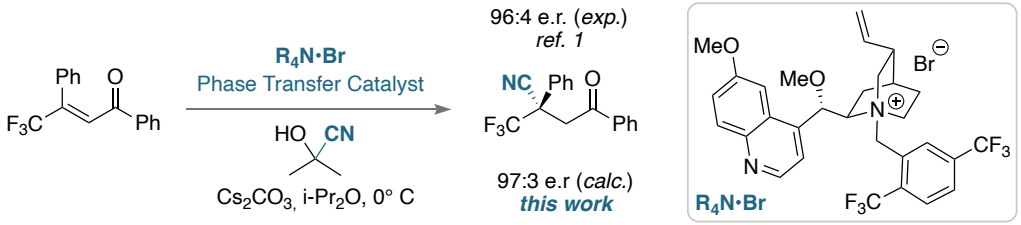
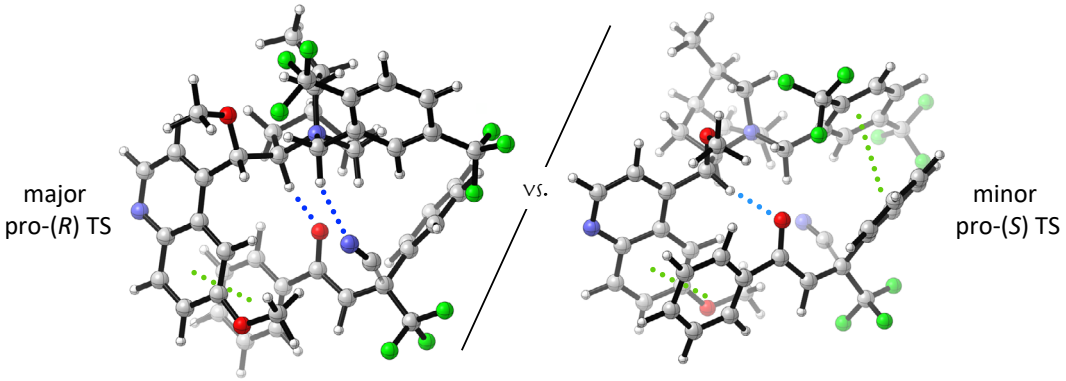
Even though enantioselective phase transfer-catalysis has become a powerful tool for asymmetric transformations, including for industrial applications, these reactions are still poorly understood, especially with nucleophiles other than enolates. In this context, we have studied the quinidinium-catalyzed cyanation of trifluoromethylated chalcones, reported by Shibata in 2012[1] and patented by the agrochemical company Syngenta in 2016[2], using Density Functional Theory calculations.



Our study reveals that π-stacking interactions are not the main drivers of the selectivity, as previously thought: a strong stabilization of the two reaction partners by the ammonium α-hydrogens is indeed critical to lower the activation barrier for the conjugate addition.[3]



One of the main challenges in the study of this kind of non-covalently bound complexes is the thorough exploration of the conformational space available to the system, which is highly computationally expensive. We will discuss our development of a multistage procedure which identifies the lowest energy transition structures while sparing on computational resources, along with the model of selectivity we proposed for this transformation, which mirrors the previously reported model for phase transfer-catalyzed enolate alkylations.[4,5]

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P A113

Gem-Binucleophilic Linchpins for Orthogonal Multicomponent Asymmetric Reactions

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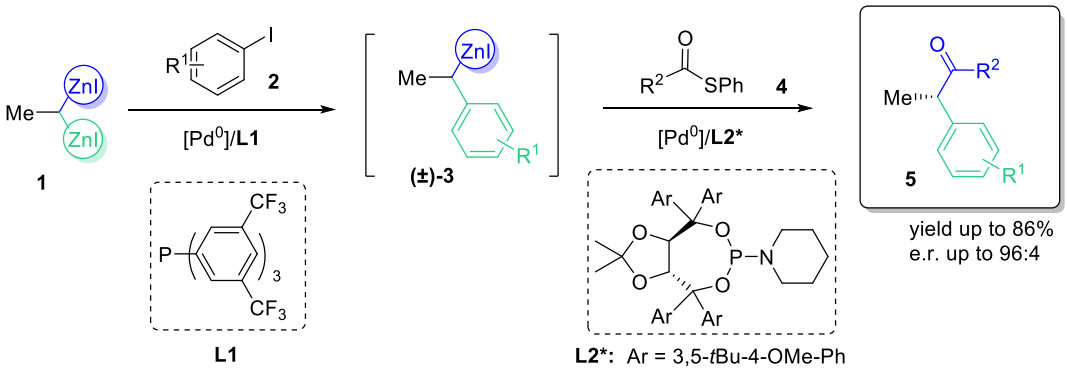
Multicomponent reactions (MCRs) represent an important endeavour in the development of more eco-compatible synthetic procedures.[1] Historically, the development of MCRs has been closely related to the use of specific synthetic linchpins (densely functionalized species) enabling the course of domino processes. In this context, the use of metal/metalloid-containing geminal binucleophilic linchpins has received very little attention for the development of asymmetric MCRs (AMCRs) which remain so far largely underexplored.

The case of {Zn,Zn} *gem*-bimetallic reagents is particularly interesting because this type of readily accessible linchpin has shown versatile reactivity with reasonable stability and environmental benignity. However, only one enantioselective transformation involving two sequential cross-coupling reactions of an achiral {Zn,Zn} *gem*-bimetallic reagent was reported,[2] but the *ee* was low.

We have thus engaged a general program to develop the use of {Zn,Zn} *gem*-bimetallic reagents in the context of enantioselective one-pot bi-directional functionalization and we report a first example. First, the Pd(0)-catalyzed mono-arylation of $CH_3CH(ZnI)_2$ by reaction with several (hetero)aryl iodides was achieved leaving intact the second C(sp^3)–Zn bond.[3] Then the acylation of the resulting secondary benzylic zinc reagents with thioesters through an enantioselective Fukuyama coupling was performed to furnish enantioenriched acyclic α,α-disubstituted ketones bearing potentially enolizable tertiary stereocenters.[4]



The scope and the limitations of the first general AMCR employing {Zn,Zn} *gem*-bimetallic linchpins through the Pd(0)-catalyzed arylation/enantioselective acylation sequence will be discussed.

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P A114
Platinahelicenes for CP-OLED applications

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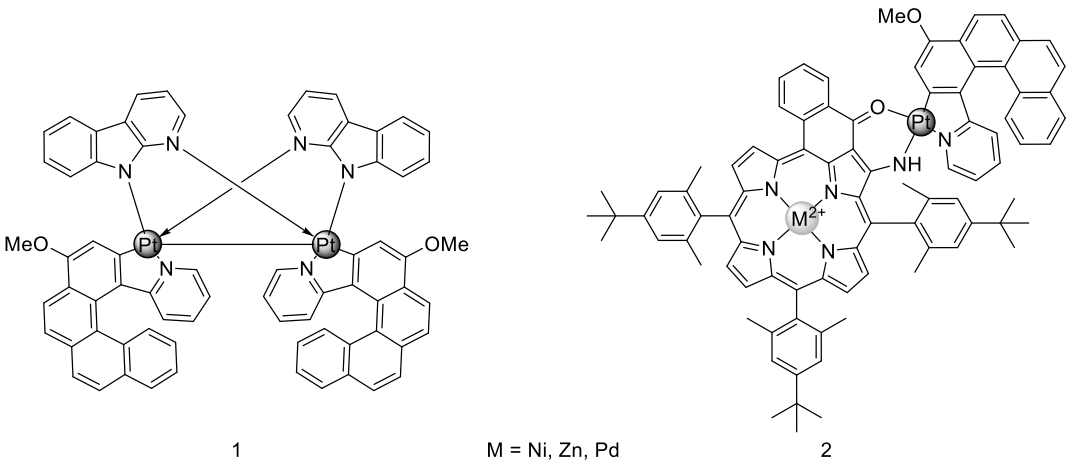
Platinum(II) complexes featuring conjugated aromatic ligands are widely studied for their property to display intense phosphorescence from triplet excited state.[1] Examples of multi-metallic platinum complexes are more seldom, yet a recent work from Zhang *et al.* has shed the light on the potential of bi-metallic architectures enabling ^{3}MMLCT to develop high efficiency OLEDs.[2] Our group having an expertise on helicenic chirality, we envisioned the use of enantiopure π-conjugated chiral ligand such as (M) or (P) helicene to endow these compounds with circularly polarized luminescence properties.[3] As such, these compounds are foreseen to be promising for usually hard to achieve long-wavelength CP-OLEDs. Two types of TMCs are synthesized. 1) Following a very recent procedure described by Zhang and co-workers a rigid double-decker platinum complex bearing helicenic ligands **1** has been synthesized and characterized. 2) Upon collaboration with Dr. R. Rupert (Strasbourg University), the synthesis of platinahelicenes linked with metalated porphyrin like in compound **2** is also under current investigation. Both complexes feature the helicenic C^N ligand which is foreseen to be emissive,[4] yet the photophysical studies are still ongoing.



*Chemical structures of compounds **1** & **2***

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P A115

Innovative MraY inhibitors with an aminoribosyl uridine structure and an oxadiazole linker

Hongwei Wan[1], R. Ben Othman[1], L. Le Corre[1], M. Poinsot[1], M. Oliver[1], A. Amoroso[2], B. Joris[2], T. Touzé[3], R. Auger[3], S. Calvet-Vitale[1], M. Bosco[1,*], C. Gravier-Pelletier[1,*]

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[2] *Unité de Physiologie et Génétique Bactériennes, Centre d'Ingénierie des Protéines, Département des Sciences de la Vie, Université de Liège, Sart Tilman, B4000 Liège, Belgium*

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The inexorable rise of antimicrobial resistance and the decline in the pipeline of antimicrobials call for the development of new drugs to tackle antibiotic resistance and prevent a return to the pre-antibiotic era.[1] There is an urgent need to discover and develop compounds with a different mechanism of action than the conventional drugs currently in use to help us address the problem of antimicrobial resistance. MraY has been suggested as a highly promising antibiotic drug target, this trans-membrane protein is involved in the early stages of peptidoglycan biosynthesis.[2] It catalyzes the first membrane step of peptidoglycan biosynthesis. Several families of natural MraY inhibitors are known, such as muraymycins.[3] (Figure 1). Their usually show a common aminoribosyl uridine scaffold, which is important for their biological activity. Building on previous studies,[4–6] we have synthesized and biologically evaluated a new panel of MraY inhibitors (Figure 2) by anchoring through an oxadiazole linker, various substituents on this amino ribosyluridine scaffold.[7]

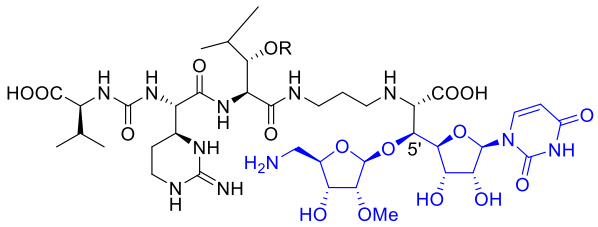

Figure 1: Structure of Muraymycins

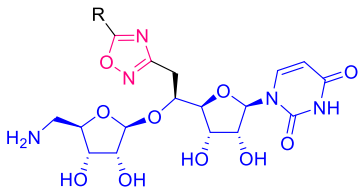

Figure 2: Structure of the targeted inhibitors

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P A116

Enantioselective Organocatalyzed Desymmetrization of Prochiral 1,3-Cyclohexanediones into strained Lactones

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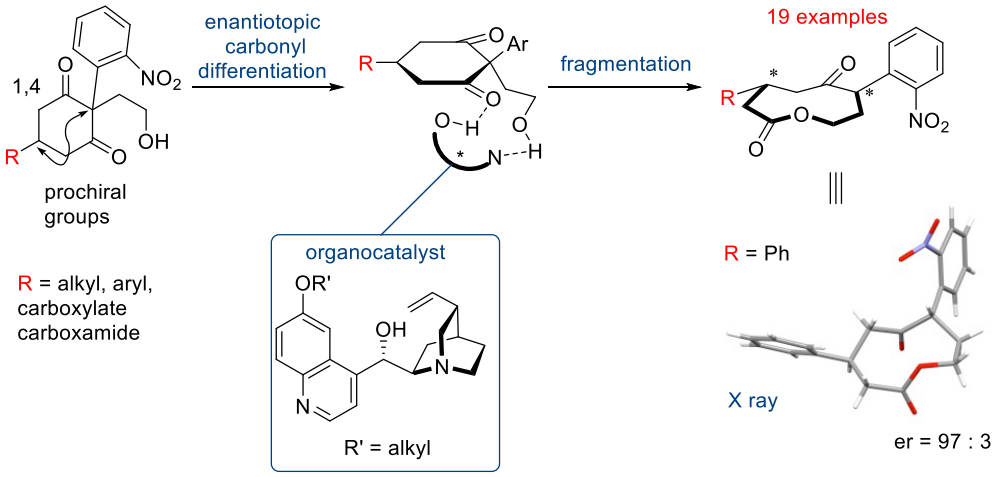
The isomerization[1] of prochiral and meso alcohols is reported under the mediation of a simple organocatalyst derived from quinidine. Strained nona- and decalactones are produced with up to three stereocenters in high er (up to 99:1) and dr (up to 99:1). Different scenario of substitution of the lactones involving alkyl, aryl, carboxylate and carboxamide groups were studied. To comprehend the mechanism of the isomerization and the noncovalent interactions at play, theoretical calculations were successfully carried out (M06-2X//6-31++G**).



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P A117

Ultrabright two-photon excitable red-emissive fluorogenic probes for fast bioorthogonal wash-free labeling in live cells

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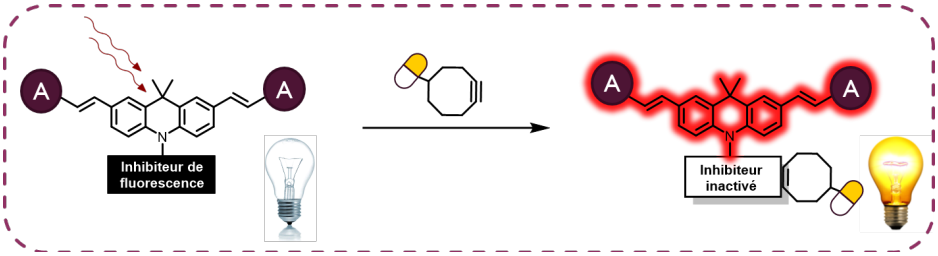
Despite the growing interest on the development of fluorophores for live-cell imaging, challenges to be tackled still remain[1,2]. An ideal fluorescent probe for bioimaging should be water-soluble, cell-permeant, photostable and should absorb and emit at wavelengths compatible with live-cell imaging, with a high fluorescence quantum yield. Two-photon excitation (2 PE) offers a great opportunity as it allows excitation wavelengths in the NIR window where the absorption and diffusion of light by biological samples are minimized. This primordial advantage provides the capability to image deep inside a tissue and avoids autofluorescence as endogeneous fluorophores are not excited by two-photon excitation or only following very specific protocols[3]. Moreover, 2 PE is confined to a small volume at the focal point of the optical system using a femtosecond pulsed laser. Thus, it provides high spatial resolution and limits excitation of the sample reducing photodamages and photobleaching. Recently, we have developed very bright biocompatible probes for labelling mitochondria in living cells[4]. We then derivatized them to develop fluorogenic probes that could constitute interesting chemical biology tools, in particular for localizing drugs in the cell environment[5]. These probes are poorly or non-fluorescent and restore their fluorescence after reaction. This turn-on property allows an unambiguous labeling in cells and an excellent signal to background ratio. We have thus obtained the brightest two-photon excitable fluorogenic probes described to date (absorption cross-section >3000 GM).



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P A118

Carbon-heteroatom bond formation by electrochemical approach, application to the synthesis of arylphosphinates and arylamines

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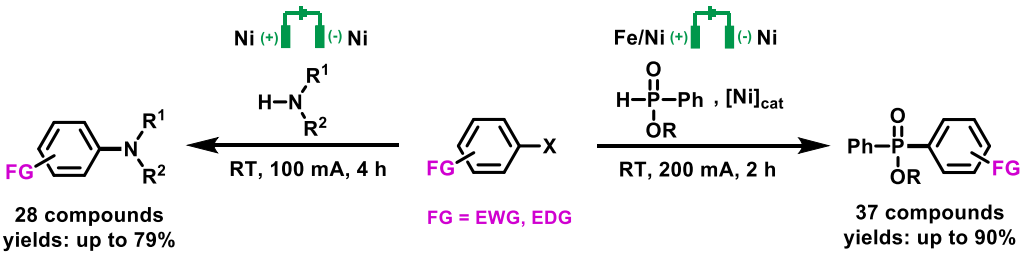
Modern organic chemistry is striving to meet the growing demand for new aromatic structures. Access to (hetero)aromatic rings with various functional groups is an important objective because their applications in life science or materials field are considerable. Methods devoted to carbon-heteroatom bonds formation (N, P, O, S, ...) most often require transition metals catalysis in the presence of a large quantity of reducing metals which can also display significant human and environmental toxicity.

Based on this observation as well as on the know-how of the laboratory, it is envisaged to use the electron as an advantageous reagent to *in situ* generate transition metal salts which role is to mediate the specific activation of carbon-halogen or carbon-hydrogen bonds allowing the functionalization of (hetero)aromatic compounds. Moreover, organic electrosynthesis is currently experiencing a renewed interest in the scientific community because it provides alternative solutions to conventional synthetic chemistry.

Previously, we reported the ability of electrochemical process, associated to added nickel catalysis, to achieve carbon-phosphorus couplings giving access to phosphonates compounds at room temperature under constant current electrolysis.[1] In the present work, this methodology has been firstly implemented to reach phosphinates as other phosphorus-containing organic compounds.[2] The second part will be mainly focused in the capacity of *in situ* electrogenerated nickel from the soluble anode to mediate carbon-nitrogen bond formation under mild conditions.[3] A panel of arylamines as well as arylphosphinates will be presented and mechanistic approach will be also discussed.



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P A119

Synthesis of novel clickable nucleosides for the post-synthetic functionalization of antisense oligonucleotides

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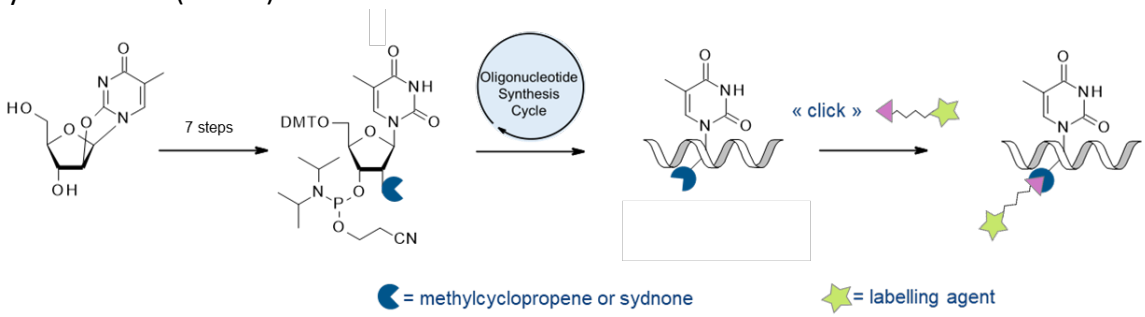
Many drugs target proteins. However, the knowledge gained in recent years about the genome has opened new opportunities therapy development by selectively targeting the expression of the genes responsible for the disease and by acting directly on nucleic acids, specially RNAs (mRNAs). Of the many ways to target the expression of RNA, antisense oligonucleotides (ASOs) have recently undergone considerable development[1]. These ASOs can be obtained by chemical synthesis and are used to specifically recognize a messenger RNA by complementary base pairing and inhibit the synthesis of the corresponding protein. By modifying their chemical structure, their stability in a cellular context and their affinity for their target have been significantly improved in recent years. Although there have been important advances in the field, their cellular trafficking and location and their ability to penetrate the cell still need to be studied.

Site-selective post-synthetic modification of oligonucleotides (i.e., after solid phase synthesis) provides a simple and effective method for incorporation of several probes in oligonucleotides. This procedure allows the synthesis of a range of diverse labelled oligonucleotides from a common precursor, compared to the classical linear synthesis, which requires tedious multi-steps synthesis of the corresponding phosphoramidite building blocks and its incorporation through solid phase synthesis.

We present here a seven-step synthesis[2] of two nucleosides, modified in the 2' position, by bioorthogonal moieties, a methylcyclopropene or a sydnone functions which would allow, after their incorporation into an oligonucleotide sequence, their post-synthetic functionalization by different agents likely to improve or monitor the biological activity via an inverse Electron-Demand Diels-Alder reaction (iEDDA) or a Strain Promoted Sydnone Alkyne Cycloaddition (SPSAC)[3].



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P A120

Development of original catalysts without transition metals designed for hydrogenation reactions

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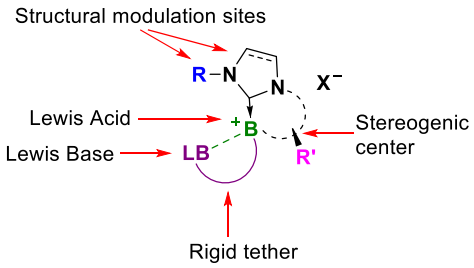
To answer the current societal issues, chemistry must imply a responsible approach by limiting its environmental impact, and by promoting green chemistry. This is one of the current challenges of chemists, and among the twelve principles of green chemistry; the field of catalysis holds a major place.
This project involves the development of modern tools for homogeneous catalysis based on original structures including a Lewis base and a Lewis acid. These platforms will be used in organic catalysis as Frustrated Lewis Pair (FLP) catalysts and their ability to activate small molecules.
Herein, we wish to disclose our efforts directed towards the synthesis of small molecules which will be used for the development, in a few steps, of a library of bifunctional and ambiphilic chiral main-group catalysts (see ***Scheme***). The design of these structures is based, on one hand, on a NHC skeleton previously developed in our group[1] and, on the other hand, on scaffold known in the literature to split the dihydrogen molecule.[2,3]



Scheme: *Design of new original ambiphilic catalysts based on scaffolds known to split the dihydrogen molecule by a FLP-type process.*

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P A121

DFT Elucidation of the Mechanism involved in Enantioselective Allylboration Reaction of Isatins Catalyzed by Chiral BINOLs

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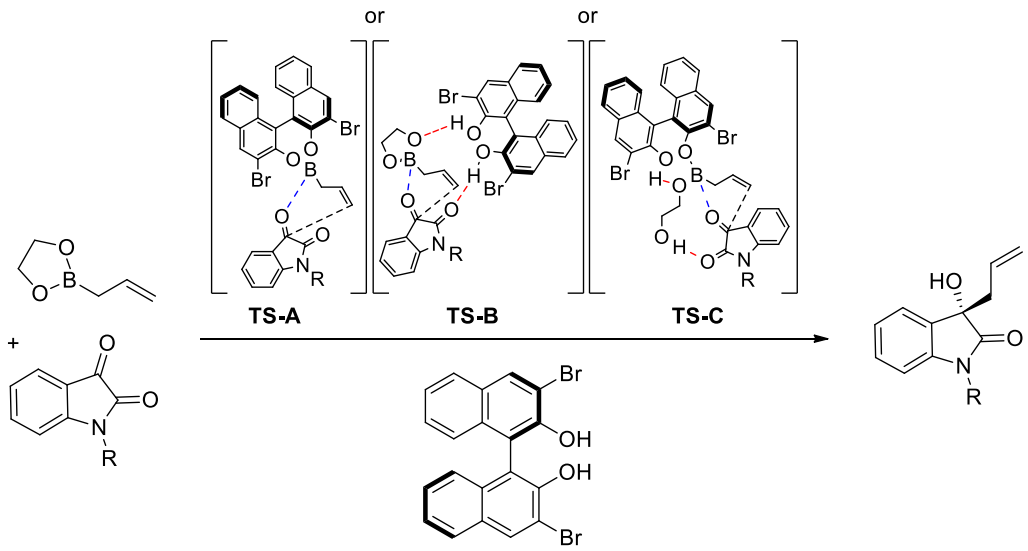
The BINOL derivatives-catalyzed allylboration of isatins was recently described[1] to proceed with a divergent facial selectivity from alkylarylketones such as indanone.[2] The mechanism involved in these reactions was investigated through a DFT study in order to identify the possible transition states and define the one occurring predominantly.[3] Three possible catalytic activation were considered : *via* a cyclic boronate (TS-A), *via* the formation of hydrogen bonds with the catalyst (TS-B) or *via* the mono-transesterification of the boronate and the creation of an hydrogen bond with the oxygen atom of the amide group (TS-C).



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P A122

Synthesis and studies of dipyrido[1,2-b:1',2'-e][1,2,4,5]tetrazine and derivatives : towards the organic electronics applications

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π-Conjugated molecules have attracted much attention as materials for the development of organic electronics. Numerous structures have already been published[1] but the search for new architectures is still very active.

Polycyclic aromatic 1,4-dihydro-s-tetrazines, have a strong potential for such applications as electron donors because they are easily oxidized. In addition, they absorb light between 300 nm and 700 nm depending on their structure. However, these compounds have never been used in organic electronic.

The synthetic route to obtain such molecules is described in Figure 1[2,3]. The use of a so-called "electrophilic nitrogen" reagent is necessary in order to create a nitrogen-nitrogen single bond. A cyclization step follows to form the tetrazine ring.

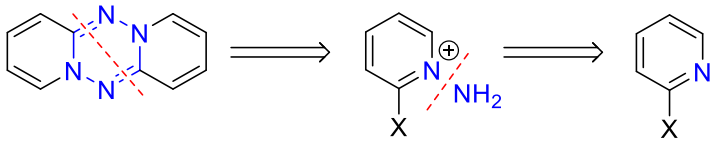

Figure 1 : Retro-synthesis of dipyrido[1,2-b:1',2'-e][1,2,4,5]tetrazine.

Using this method several tetrazines have been prepared and in particular di-halogenated tetrazines (Figure *2*).

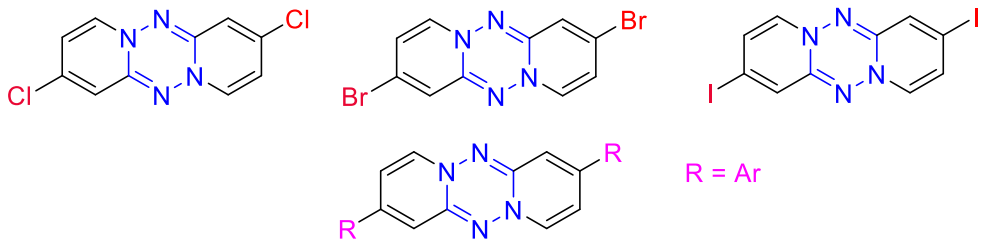

Figure 2 : Di-halogenated and other aromatics derivatives of dipyrido[1,2-b:1',2'-e][1,2,4,5]tetrazine.

The photophysical properties of the series have been studied in solution and rationalized with DFT calculations. These compounds represent a first step toward functional molecular materials since the halogen atoms will then be used to perform organometallic couplings.

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P A123

Cytidine deaminase deficiency in tumor cells is associated with sensitivity to a naphthol derivative

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[2] *Institut Curie, CNRS UMR 9187, INSERM, U1196, Univ. Paris-Saclay, PSL Research Univ., F-91405, Orsay, France*

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Identifying new molecular targets for novel anticancer treatments is a major challenge in clinical cancer research. Our biologist collaborator (team 1) previously reported that cytidine deaminase (CDA) expression is downregulated in about 60% of cancer cells and tissues. In this study, we aimed to develop a new anticancer treatment specifically inhibiting the growth of CDA-deficient tumor cells. High-throughput screening of the Curie-CNRS chemical library led to the identification of a naphthol derivative, X55 targeting CDA-deficient tumor cells preferentially, without affecting the growth of non-tumoral cells, expressing or not CDA (Fig 1 & 2)[1]. Metabolomic profiling revealed that CDAdeficient HeLa cells differed markedly from control HeLa cells. X55 treatment had a moderate effect on control cells, but greatly disturbed the metabolome of CDA-deficient HeLa cells, worsening the deregulation of many metabolites. We also identified the drastic downregulation of MAPT (microtubule-associated protein Tau) expression as a reliable predictive marker of X55 sensitivity of tumor cells. However, due to a fast metabolization of X55 into its glucuronide derivative, its half-life is not compatible with an in vivo proof of concept. We prepared about 200 compounds[2] in order to prevent this issue and identified a phosphate ester derivative which possesses a comparable biological activity while keeping an acceptable PK profile for in vivo evaluation in both xenograft and PDX mice model.

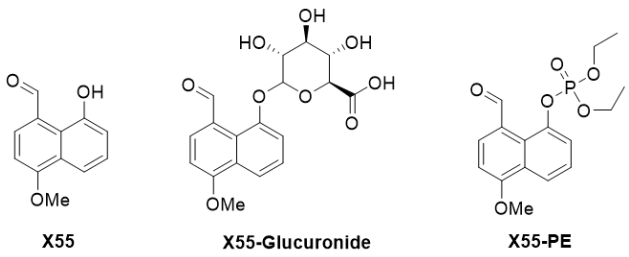

Figure 1 : Chemical structures

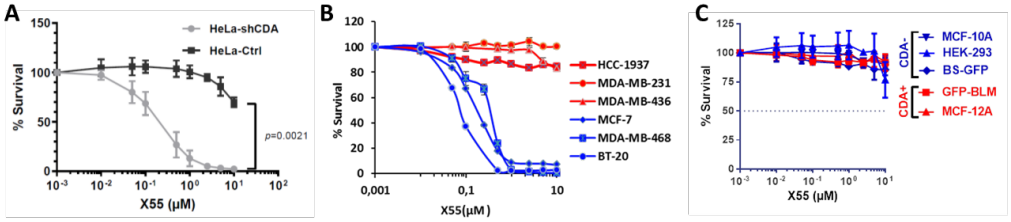

Figure 2 : Cytotoxicity of X55 in A) Isogenic HeLa cell lines (black, control HeLa cells; gray, CDA-depleted HeLa cells) B) tumoral C) non-tumoral cells CDA deficient cells (in blue) or in cells expressing CDA (in red)

[1] H. Mameri, G. Buhagiar-Labarchède, G. Fontaine, C. Corcelle, C. Barette, R. Onclercq-Delic, C. Beauvineau, F. Mahuteau-Betzer and M. Amor-Guéret. Cytidine deaminase deficiency in tumor cells is associated with sensitivity to a naphthol derivative and a decrease in oncometabolite levels. *Cellular and Molecular Life Sciences,* **2022**, 79:465 - doi.org/10.1007/s00018-022-04487-9

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P A124

Microwave-Assisted 1,3-Dioxa-[3,3]-Sigmatropic Rearrangement of Substituted Allylic Carbamates: Application to the Synthesis of Novel 1,3-Oxazine-2,4-Dione Derivatives

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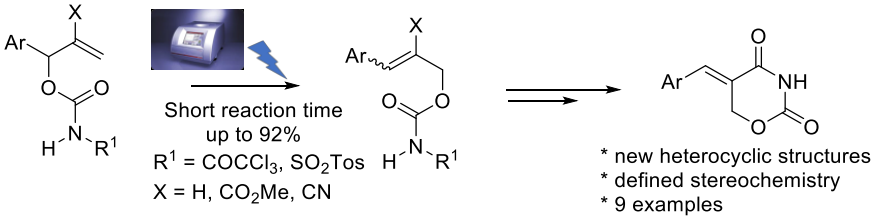
Recently, we brought to light an unexpected metal-free 1,3-dioxa-[3,3]-sigmatropic rearrangement of allylic carbamates from α-aryl allylic alcohols.[1] In order to expand this metal-free process to a larger number of aryl substituted allylic alcohols due to synthetic interest of allyl carbamates, we investigated the usefulness of the microwave technology as a non-conventional heating to improve the sequential reaction.[2] Under these new conditions, the reaction acceleration was clearly highlighted compared to conventional heating conditions. Depending on the electronic nature of substituents on the aromatic group, this type of rearrangement can be as much as 40 times faster with similar or improved yields. Due to this experimental improvement, the diversity of aryl allylic carbamates able to undergo this rearrangement in a reasonable reaction time (30 min.) and with acceptable to high yields was greatly extended. Finally, an original synthetic way involving this microwave-assisted process to access new six-membered heterocyclic structures such as (E)-5-arylidene-1,3-oxazinane-2,4-diones was developed from Morita-Baylis-Hillman (MBH) adducts showing the interest of this molecular rearrangement approach.



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P A125

Design/synthesis of water-soluble and photoactivatable Cu complexes based on modified cyclodextrins for *in cellulo* applications

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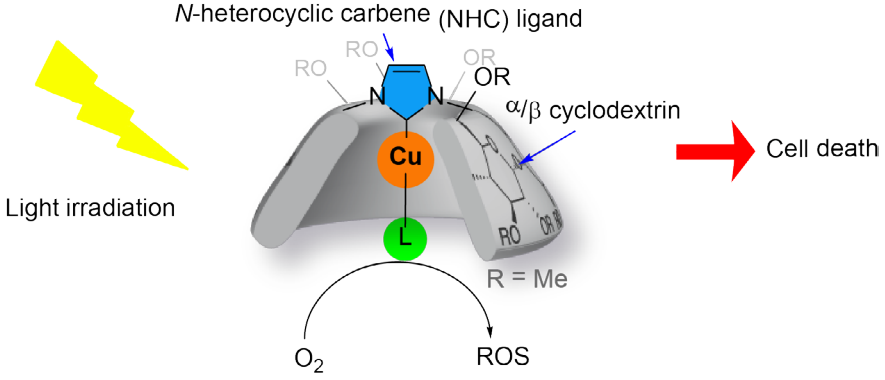
Our team previously has extensively studied the selective modification of the cyclodextrin (CD) structure by different chemical transformations. One of this modification, involving the covalent capping of the CD by a NHC ligand, allowed encapsulation of several metal complexes deep inside the cavity of the cyclodextrin. Although encapsulated, the metal complexes inside the cyclodextrin are still catalytically active and can perform reactions in various solvents (organic or aqueous). Significant cavity effects have been observed in copper and gold-catalyzed reactions (control of regio- and stereoselectivity and stabilization of reactives species).[1] Furthermore, the encapsulation was shown to induce a dramatic decrease of complex cytotoxicity.

The aim of the CataCLiSMS project is to synthetize copper(I) complexes encapsulated inside a cyclodextrin able to perform photocatalysis *in cellulo* to induce cells death. This could be done through generation of reactive oxygen species (ROS) in the cells. For that, we are developing a series of water-soluble permethylated cyclodextrin capped with NHC ligands bearing a photoactivatable copper-ligand unit inside the cavity. We present here preliminary results on the synthesis of such complexes and their photophysical properties. (We will next study their photocatalytic activity in water, their toxicity toward cells and their mode of action *in cellulo*.)



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P A126

Highly enantioselective formation of quaternary stereocenters by BINOLs catalyzed allylboration and related reactions on isatins, and mechanistic studies

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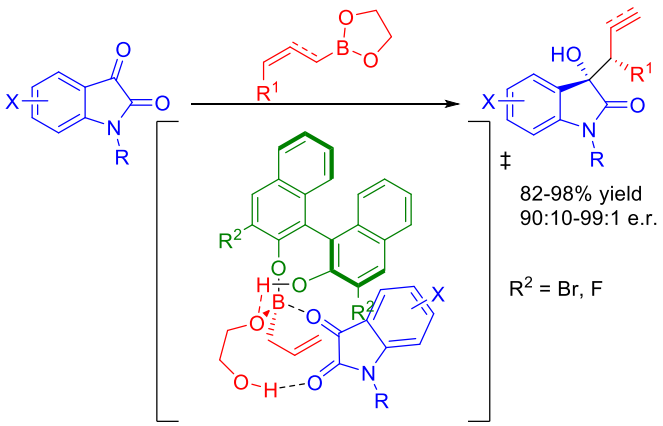
The allylboration and related reactions constitute a powerful C-C bond forming transformations which largely satisfy the criteria of stereoselectivity and step economy for the construction of highly functionalized motifs. The application of this approach in synthesis offers a straightforward entry to complex natural products and pharmaceutical ingredients. Moreover, this methodology allows the construction of quaternary stereocenters which represent a great challenge especially in an enantioselective fashion. While the asymmetric allyl / crotyl and allenylboration of carbonyls have been described,[1] those organocatalytic transformations on isatins are scarcely reported.[2] We have disclosed the enantioselective BINOLs catalyzed allylboration of isatins leading to 3-allyl-3-hydroxyoxyndoles in up to 98% yield and 98:2 e.r.. This methodology was applied to the synthesis of the (*R*)-chimonamidine natural product.[3] Kinetic studies and DFT calculations shed light on the origins of the enantioselectivity and on the key role of the additives in the allylboration reaction, suggesting a transesterification of the allylboron reagent with BINOL *via* proton transfer process and an internal hydrogen bonding between this chiral boronate ester intermediate and the amide group of isatin. We have also demonstrated that the catalytic system is effective for the crotylboration and the allenylboration of isatins in up to 99:1 e.r..[4]



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P A127
Synthesis Of Multivalent Chondroitin Sulfate (CS) Oligosaccharides

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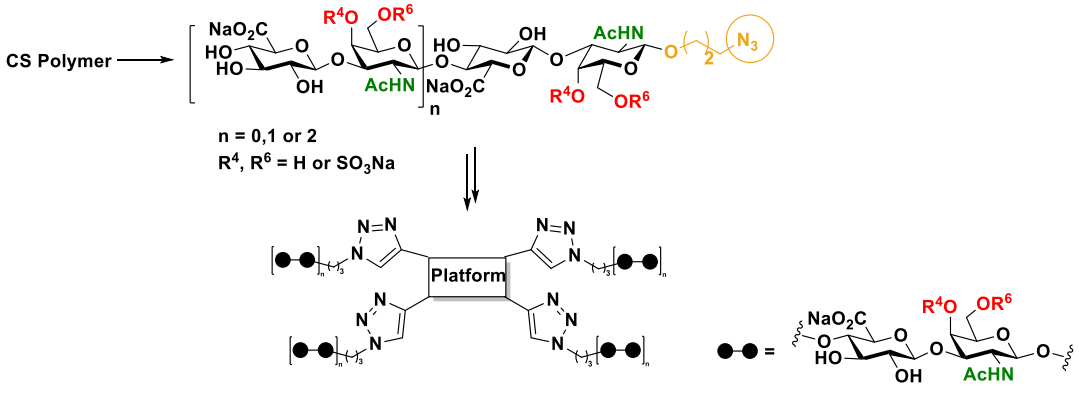
Chondroitin sulfates (CS) are polysaccharides which belong to a family of linear polyanionic polymers named glycosaminoglycans (GAGs). They consist of a repeating dimeric unit composed of a D-glucuronic acid (D-GlcA) linked to a 2-acetamido-2-deoxy-D-galactose (D-GalNAc) and contain sulfate groups at various positions. The most common ones are located on position 4 (CS-A) and/or on position 6 (CS-E/CS-C) of the D-GalNAc moiety.[1] CS play an important role in different physiological and pathological processes[2] through their interaction with numerous proteins such as lectins, cathepsins or midkines. As an example, CS are involved in the process of osteoporosis by forming a complex with the exosites of cathepsin K (Cat K). This complex is involved in the excessive degradation of collagen.
In order to better understand and to inhibit CS-Cat K interactions, we are particularly interested in the design and synthesis of variously sulfated multivalent oligosaccharides of CS.[3] Indeed, multivalency is widely observed in nature because it improves activity and affinity towards the ligands. Very few synthetic multivalent GAGs mimetics have been reported and the field of CS remains largely unexplored.[4]
We first envisage to synthesize new CS oligosaccharides bearing an azido group on the aglycone, then ligation will be conducted on various platforms to obtain new multivalent CS oligosaccharides. Thanks to various partnerships, the multivalent CS will be assessed on Cat K and on other proteins. We will present here our recent results towards the synthesis of new CS di- and tetrasaccharides.



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P A128

The synthesis and application of *N*-coordinated boronate ester containing polymers

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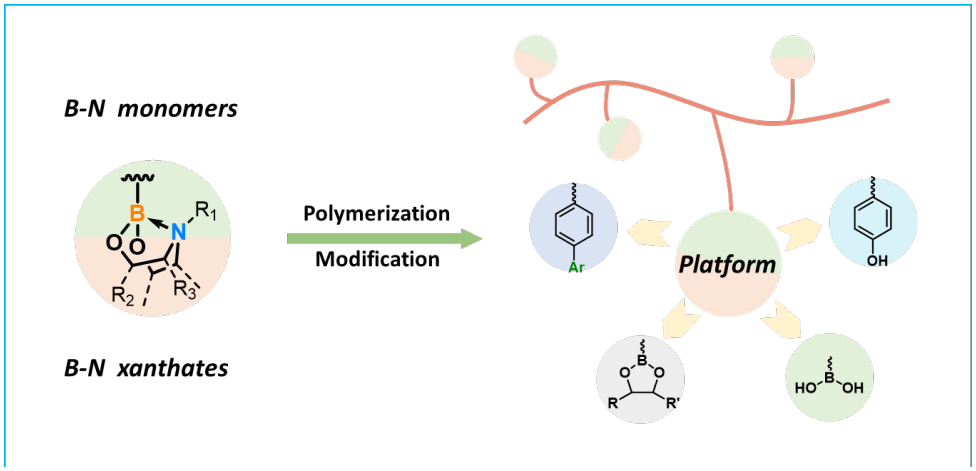
Recent years, boronate esters have been utilized to turn the polymer into valuable materials, such as medical materials and healable resins. Tetrahedral *N*-coordinated boronate esters, which are tetrahedral configuration compound formed *via* the complexation with trivalent ligands, are demonstrated to endow polymers with modifiable site and better heat resistance. Our work focused on the synthesis of polymers bearing *N*-coordinated boronate esters through direct polymerization and post modification. Boronate MIDA esters containing monomers were polymerized by RAFT/ATRP polymerization with superior results. [1,2] Obtained polymers can be used as versatile platform for modification, including Suzuki coupling, oxidation and boronate ester transformation. In further research, platform polymers with multiple reactive sites were obtained *via* RAFT copolymerization of monomers bearing different *N*-coordinated boronate esters (MDA, DABO, IDA, etc.). Hydrolysis and coupling reactions revealed the specificities of these boronate esters in reaction. Based on these specificities, selective step-by step modification was successfully realized on the platform polymers. *N*-coordinated boronate esters containing polymers could also be obtained through the post modification by RAFT/MADIX technology. Here, we utilize the xanthate bearing *N*-coordinated boronate esters to modify the industrial polybutadiene with expected results. We will further optimize the reaction condition and explore the application of modified polymers.



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P A129
Selective C–H Functionalization of Furfural and its Derivatives

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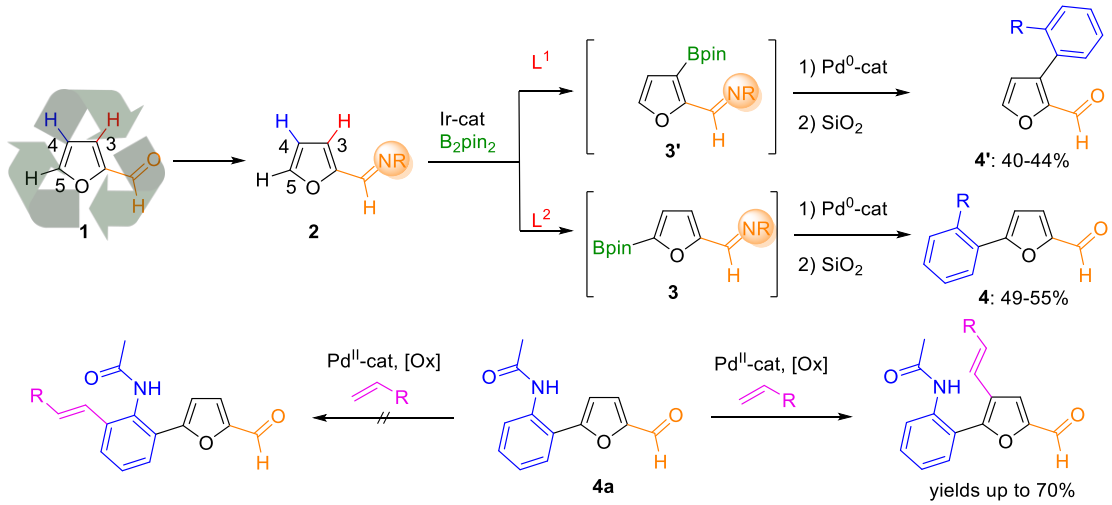
Furfural and 5-hydroxymethylfurfural (HMF) are versatile bio-based platform molecules derived from renewable lignocellulose. These simple aromatic heterocycles are of great importance to prepare bio-fuels, monomers for material science, as well as to reach more value-added chemicals in the frame of crop, fragrance, and medicinal chemistry. In this context, the selective functionalization of the aromatic ring of these molecules is a topic of interest to obtain new sets of emerging molecules endowed with higher chemical and/or thermal stability.[1] In particular, the C3–H borylation on such substrates has been reported only on C5-substituted furfural derivatives, that skips the natural selectivity for the C–H bond α to the oxygen atom.[2] We have now developed a method to achieve selective C–H borylations at C3 or C5 on furfural **1**. This can be obtained via ligand-controlled Iridium-catalyzed borylation of appropriate imine derivatives. The resulting borylated derivatives (**3** and **3'**) can be in turn submitted *in situ* to Suzuki-Miyaura cross-coupling reactions, affording *ortho* substituted heterobiaryl compounds. The spontaneous removal of the imine group occurs during the chromatographic purification step, affording to the desired products (**4** and **4'**) in 40-55 % overall yields (3 steps). Finally, installation of the 2-acetamidophenyl moiety at C5 opens the way to C4–H functionalizations. Indeed, the Fujiwara-Moritani olefination of **4a** takes place cleanly at C–4, without competition of the C–H *ortho* to the acetamide moiety. [3]



The development of this method is key to solving the well-known problem of furan instability and paves the way for the synthesis of new and robust biomass-derived building blocks of interest for new industrial applications.

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P A130

Allyl double substitution of vicinal alkenyl diols

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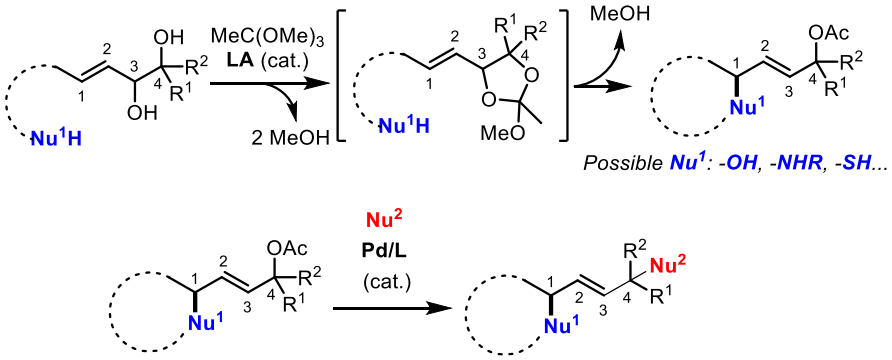
The allylic substitution reaction is one of the fundamental transformations in organic synthesis which can be applied for the formation of new C-C and C-heteroatom bonds.[1] The best example is the Tsuji-Trost reaction, widely used for the formation of C-C, C-O, C-N and C-S bonds in a regio- and stereoselective way. On the other hand, examples of double allylic substitution are relatively rare, although this type of reaction would allow access to high level of molecular complexity.[2]

In this project, we study the reactivity of alkenyl diols in double allylic substitution reactions through the combination of two catalytic systems. The use of an orthoester in the presence of Lewis or Brønsted acid catalyst will allow a first intramolecular allylic substitution. The product resulting from first step will be an allylic acetate which can be further functionalized by Tsuji-Trost reaction (Scheme 1).



Scheme 1: double substitution of vicinal alkenyl diols

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P A131

The role of short-range N-H···N interactions in peptides

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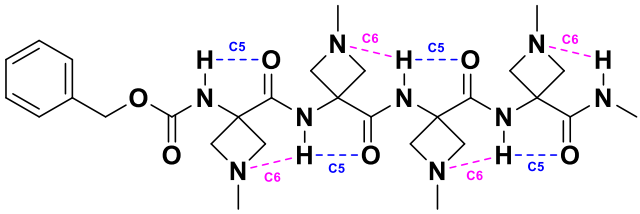
Foldamers are artificial molecular structures. They are constructed as sequence-specific oligomers of a defined length and are inclined to fold into well-defined secondary and tertiary conformations, such as helices, sheets, or ribbons.[1] Taking inspiration from Nature, chemists have conceived and studied a large number of peptide-based foldamers, and have sought useful applications thereof.[2,3]

Our research project is designed to study three new aspects of foldamer science. The overall objective is to improve our understanding of the behaviour of these compounds and identify new applications thereof. In the first aspect, we examined the folding pattern of γ/α-hybrid peptides, tested its ability to fold into a 12/10-helix. In the second aspect, we used a well-defined 12-helical foldamer scaffold to display functional groups with two potential applications: a) use as organocatalysts, or b) ligands for formation of "metallo" complex. For this moment, our study focuses on the third aspect of stabilizing a weak intra-residue C5 H-bond.

Herein, we present a specific folding pattern which is rare in peptide secondary structure. The C5 H-bond conformation is a weak interaction, and successive C5 interactions form the basis of the so-called 2.05-helix,[4] which is adopted by very few synthetic peptides that rely essentially on steric constraints to do so.[5] Our strategy was successfully to stabilize the C5 interaction by combining it with a C6γ H-bond implicating the nitrogen of an azetidine-derived building block.

In this communication, we will interpret how the peptide synthesis up to tetramer was carried out, why the azetidine derivative was selected as coupling monomer, and what kinds of experimental and theoretical techniques were used to perform the conformational analysis.



Scheme. N-H···N H-bonds stabilize the C5 interactions

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P A132

Cobalt-Catalyzed Formation of Alkylzinc Halides and their Application in Negishi Cross-Coupling

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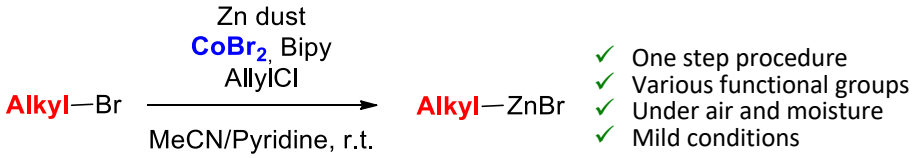
Since the discovery of Grignard reagent in 1900, this organometallic compound has become one of the most useful reagent used in organic and organometallic chemistry.[1] The simple preparation and versatility of this reagent made it a frequent choice for synthesis in laboratories and industries. Therefore, numerous industrial chemical processes employ Grignard reagent such as in pharmaceuticals, agrochemicals and polymers.[2] However, this reagent possesses some limitations towards its functional group's tolerance and chemists often prefer to use its zinc analogous which tolerate a wider range of functional groups and possess a lower toxicity of the resulting zinc salts.[3] Various methods have been reported to prepare organozinc reagents such as halogen/metal exchange,[4] deprotonation,[5] direct insertion[6] or transmetallation.[7] However, these methods are not straightforward and mostly require the multiple activation of metallic zinc under strict and tedious conditions, or the use of organolithium or Grignard reagent with zinc salts which do not allow the synthesis of highly functionalized organometallic species. In 2003, our group has developed a simple and direct method to prepare arylzinc reagents using cobalt catalysis.[8] This reaction involves simple cobalt bromide as catalyst and zinc dust in acetonitrile. In this communication, we present a novel straightforward and simple preparation of alkylzinc compounds from alkyl bromides under mild conditions giving access to highly functionalized organozinc reagents. This method tolerates a wide range of functionalities such as ketones and aldehydes. These alkylzinc reagents were employed in Negishi type Pd-catalyzed cross-coupling in order to demonstrate the applicability of this methodology. The overall procedure tolerates well air and moisture conditions, making it a straightforward and robust synthetic methodology.[9]



Scheme 1: Cobalt-Catalyzed formation of alkylzinc reagent

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P A133
Multivalency undressed

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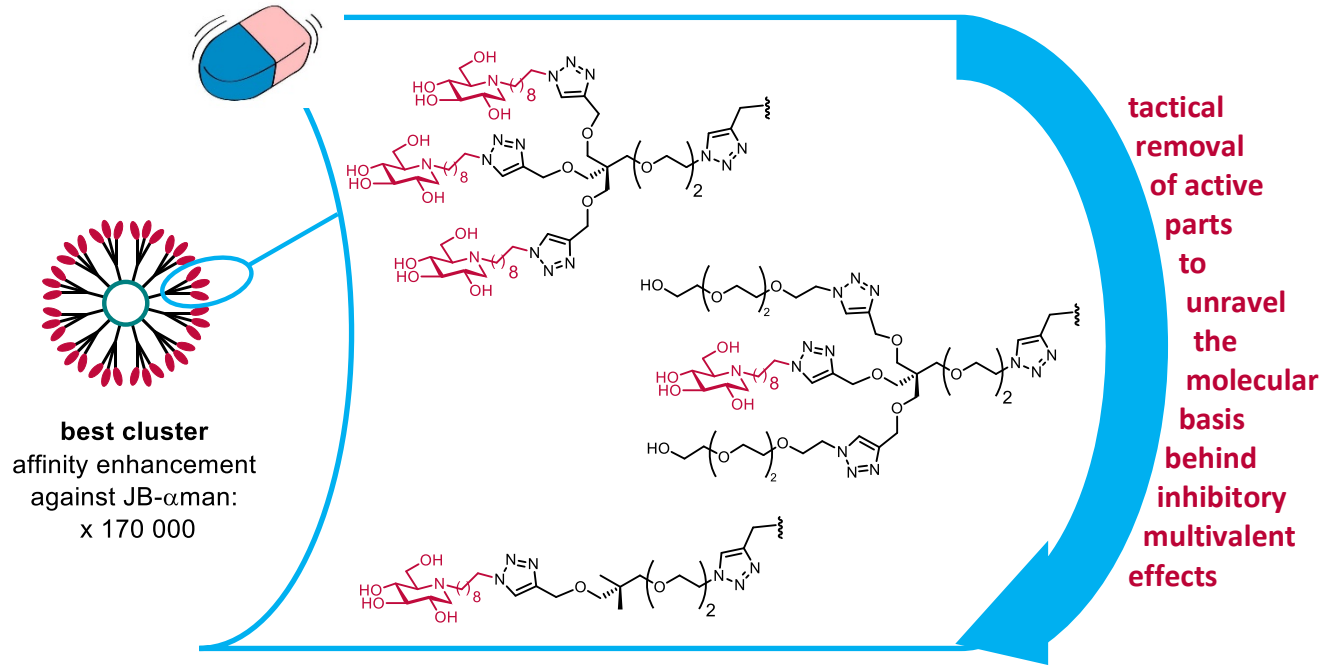
Multivalency represents an appealing option to modulate selectivity in enzyme inhibition and transform a moderate glycosidase inhibitor such as deoxynojirimycin (DNJ) into a high-affinity multivalent inhibitor.[1] The design of powerful multivalent clusters is however complex even when the enzyme structure is known[2] because global affinity enhancement relies on several interconnected local mechanistic events such as bind-and-recapture processes, chelate effect, secondary interactions and aggregation whose relative impact is unknown. The 36-valent non-polymeric inhibitor showing the best affinity enhancement on a glycosidase to date[3] was used as a starting point for this study. It has been gradually dispossessed from its inhibitory epitopes, arms and whole dendrons to design a set of new clusters in order to unravel the impact of distinct mechanisms. Their interaction with Jack bean α-mannosidase was evaluated by enzymatic assays and the stoichiometry of enzyme:inhibitor complexes was assessed by analytical ultracentrifugation.



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P A134

Hypervalent iodosulfoximines synthesis : an acces to new perfluoroalkylating reagents

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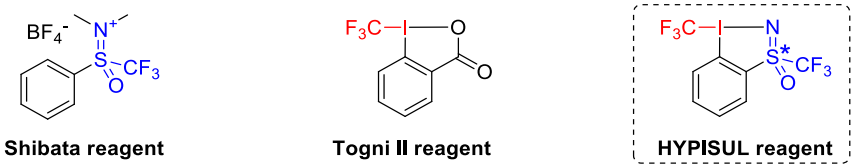
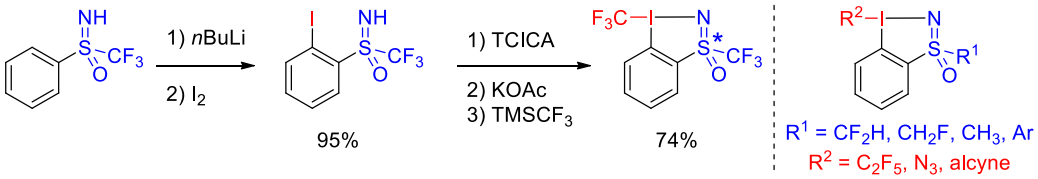
Major advances in the study of perfluoroalkylation reactions have been made possible by the development of trifluoromethylation reagents, such as the Shibata[1] or Togni[2] reagents. We have recently combined hypervalent iodine and sulfoximine moieties to obtain a new class of reagents, the chiral hypervalent iodosulfoximines, of which the HYPISUL reagent is a part.



The synthesis of the HYPISUL reagent is a multi-step process that includes two key points: the *ortho*-iodination of a trifluoromethylated sulfoximine and the formation of a hypervalent iodine. The detailed synthesis and complete characterisation of this new reagent will be presented, as well as a comparative study with the Togni reagents to which it is structurally related.[3] The variations of the group linked to the hypervalent iodine atom will be discussed in terms of synthesis. The stability and reactivity of new compounds will be briefly discussed.[4]



Finally, the first results of trifluoromethylation by ionic or radical route (photoredox catalysis) utilizing this new class of reagent will be detailed.[3,5]

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P A135

Cyclic(alkyl)(amino)carbene Ruthenium Complexes for *Z*-Stereoselective (Asymmetric) Olefin Metathesis

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[2] *UCSD-CNRS Joint Research Chemistry Laboratory (IRL 3555), Department of Chemistry and Biochemistry, University of California, San Diego, La Jolla, California 92093-0358, United States*
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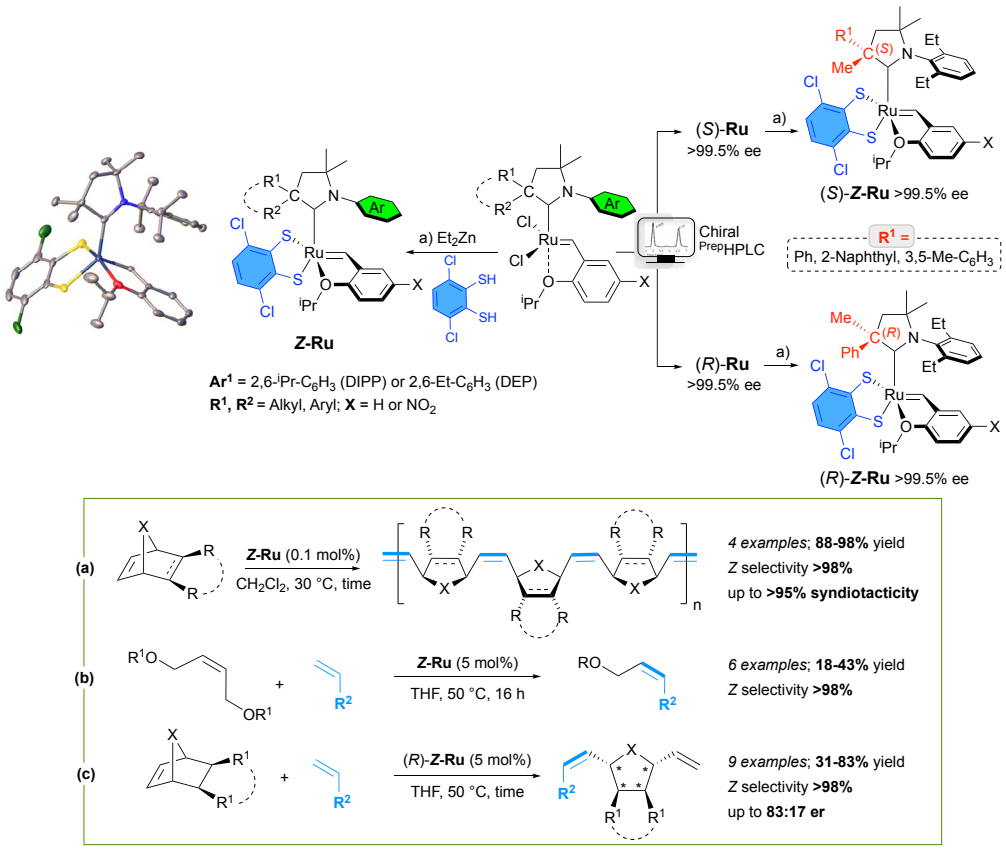
The first *Z*-stereoselective catechodithiolate ruthenium complexes ***Z*-Ru** containing cyclic(alkyl)(amino)carbene ligands are reported. Isolated in nearly quantitative yields or in-situ generated, these catalysts demonstrated remarkable *Z* selectivity (*Z*/*E* ratio up to >98/2) in ring-opening metathesis polymerization (ROMP), ring-opening-cross metathesis (ROCM) and cross-metathesis (CM). Thanks to the efficient chiral HPLC resolution of racemic CAAC-complex precursors, optically pure dithiolated complexes (*S*)- or (*R*)-***Z*-Ru** were also synthesized allowing to produce enantioenriched *Z*-ROCM products in >99/1 *Z*/*E* with good levels of enantioselectivity.



MORVAN, J.; VERMERSCH, F.; LORKOWSKI, J.; TALCIK, J.; VIVES, T.; ROISNEL, T.; CREVISY, C.; VANTHUYNE, N.; BERTRAND, G.; JAZZAR, R.; MAUDUIT, M. Cyclic(Alkyl)(Amino)Carbene Ruthenium Complexes for Z-Stereoselective (Asymmetric) Olefin Metathesis . ChemRxiv 2022 10.26434/chemrxiv-2022-t2dhm

P A136

Visualization of mitochondrial reductases with fluorogenic probes

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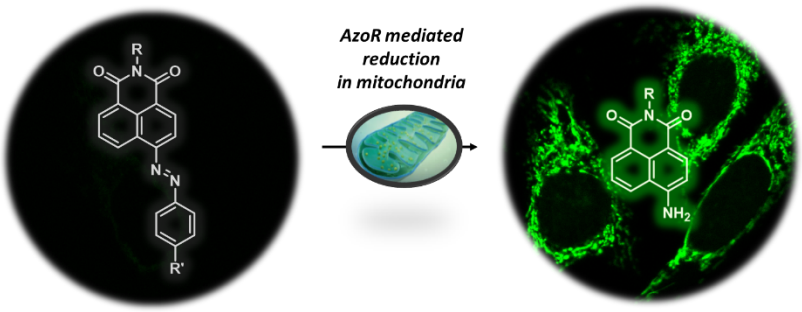
Mitochondria is the center of energy metabolism in the cell. Dysfunction of this organelle have been related to many diseases, such as cancer, diabetes, cardiovascular or neurodegenerative diseases, and more[1]. It is thus a promising therapeutic target which has been extensively studied in the last decades. A recent approach aims to design prodrugs exclusively activatable inside mitochondria and structurally designed to carry them into it by using mitochondriotropic targeting moieties such as triphenylphosphonium or pyridinium. Recently, promising results using the mitochondrial nitroreductase (NTR) as prodrug activating enzyme have been obtained[2]. Unlike cytosolic NTRs which are exclusively active in a hypoxic environment, mitochondrial NTRs are active in a normoxic context thus making them serious candidates as intramitochondrial activators of prodrugs. This example shows the interest of the use of reductases, so it appears relevant to look at other enzymatic activities in order to extend the panel of endogenous biocatalysts which can be used for in situ activation of mito-targeted pro-drugs.

Here we describe our works on the design of fluorogenic probes to detect such mitochondrial reductase activities and focus on Azoreductase (AzoR). Azo based probes were obtained from 4-amino-1,8-Naphthalimides *via* their diazonium salt and S_EAr type addition of enriched aromatic partner. Their azo bond can be reduced by an AzoR activity. These sensors have been studied *in vitro* and were found to be not only highly sensitive but also selective to AzoR. Confocal microscopy experiments conducted on different living cell lines showed the presence of a mitochondrial AzoR, expressed at different levels depending on the cell line. This interdisciplinary work involving organic chemistry, photophysics and cell biology has provided convincing results making AzoR a plausible and promising alternative to NTR for specific drug delivery into mitochondria.



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P A137

Combining Gold(I) catalysis and biocatalysis

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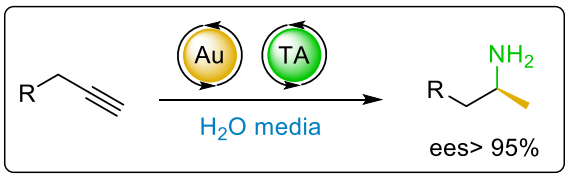
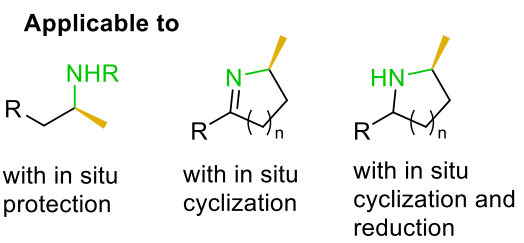
Over the last decades, biocatalysis has emerged as a relevant tool in the chemical industry providing an efficient, sustainable way to catalyze many reactions with high enantioselectivities.[1] Gold catalysis has similarly established itself as a key player in organic synthesis due to its use in a variety of reactions.[2] The combination of transition metal catalysis and biocatalysis allows to access chiral molecules in an efficient, fast and sustainable manner.[3] However, examples merging enzymes and Au(I) catalysis are scarce in the literature.[4]

In our approach, the combination of a gold catalyzed hydration of an alkyne is combined with a stereoselective reductive amination of the resulting ketone using an ω-transaminase[5] is studied. This highly efficient approach provides chiral amines with high enantioselectivities, from unfunctionalized, inexpensive hydrocarbons, in a one pot sequential relay manner in aqueous media. The chiral amines obtained are highly valuable chiral building blocks that may be used for synthesis of biologically active compounds. The method can be applied to simple alkynes or more complex molecules that lead to further cyclization. In situ protections, reductions can be performed to access a large variety of chiral compounds.





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P A138
(3+2) cycloaddition of ketenes

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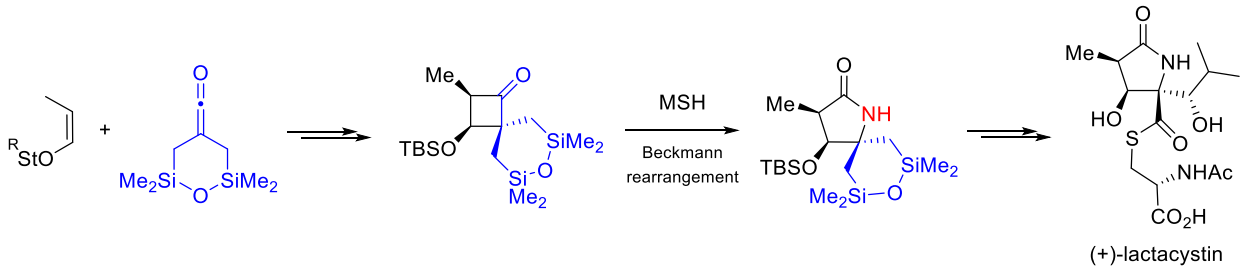
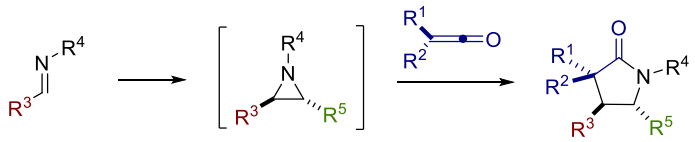
For several years, our research group team has been working in the area of ketene chemistry for several years,[1] exploring their reactivity and selectivity in [2+2] cycloadditions with various enol ethers and ketenes' substituants.[2] This expertise was apply to the total synthesis of (+)-lactacystin,[3] a proteasome inhibitor.



During this study, our research group found that aziridines can react with ketenes through a formal (3+2) cycloaddition, affording the γ-lactam scaffold in excellent yields.[4] With unsymmetrical ketenes, a single *cis* diastereoisomer is observed. The reaction with an enantiopure aziridine afforded the lactam with no erosion of the enantiomeric excess and retention of the configuration.



Due to their high reactivity, ketenes are generally unstable, leading to dimerization products, with a limited variety on the substituents. To extend the scope of the (3+2) cycloaddition and allow a wide diversification of substituents on the lactams, a study has been initiated on the generation of ketenes in continuous flow chemistry.[5]

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[5] ANR program KetFlo : ANR- 18-CE07-0035-01.

P A139
Hydroelementation of SF_5-Alkynes and Applications

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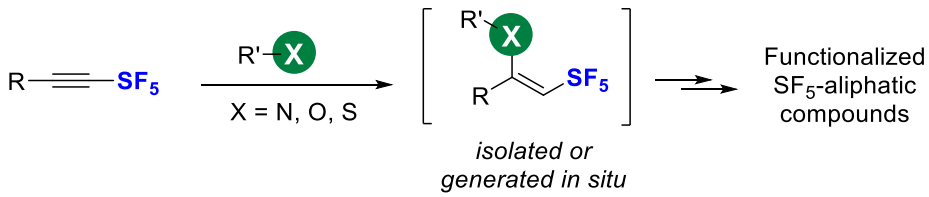
Nowadays, development of novel synthetic routes towards SF_5-containing compounds is on the rise, but the access of structural diversity such as SF_5-heterocycles remains highly challenging.[1] Pentafluorosulfanylated alkynes are easily accessible and versatile SF_5 building blocks, which have been mainly used in cycloaddition, heterocyclic synthesis and few hydrofunctionalisation reactions.[2] To our knowledge, only two reports about the hydroelementation of SF_5 alkynes are known in the literature and rely on gold-catalyzed methods for the hydratation and hydrofluorination of SF_5 alkynes.[3] In this presentation is disclosed a very efficient method to perform a fully regio- and stereoselective hydroelementation reaction of SF_5 alkynes in mild reaction conditions which does not require the use of any transition metal. This fully atom-economical process gives an easy access to various heterosubstituted vinylic-SF_5 scaffolds (X = N, O, S), as very attractive platforms for downstream functionalization and/or transformation.



[1] V. Debrauwer, I. Leito, M. Lõkov, S. Tshepelevitsh, M. Parmentier, N. Blanchard, V. Bizet *ACS Org. Inorg. Au* **2021**, *1*, 43.
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P A140

Asymmetric autocatalysis applied to Strecker reaction

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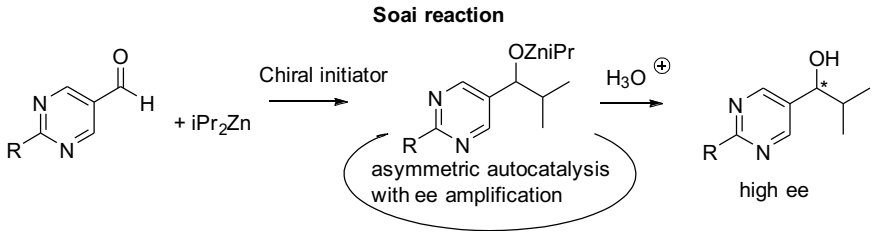
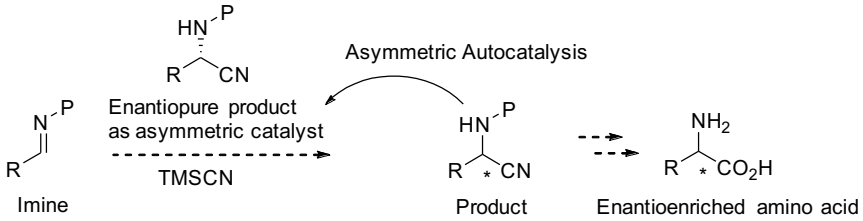
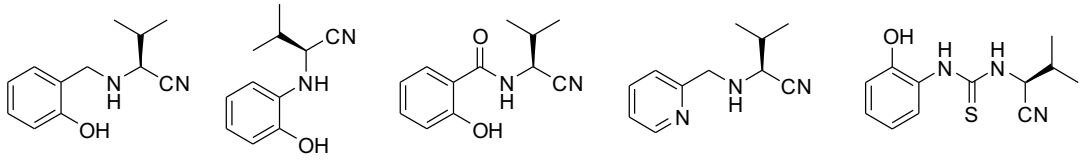
Our group is for a long time interested by original concepts of asymmetric synthesis, and we want now to tackle asymmetric autocatalysis. This field is very challenging, the most efficient examples coming from Prof. Soai's group.[1] In asymmetric autocatalysis, the final enantioenriched product is also the catalyst. It can be used as chiral ligand of a metal (Soai's work) or as an organocatalyst (very few examples). [2]



Asymmetric autocatalysis could also be an explanation of the origin of biomolecules homochirality. Strecker reaction being one of the prebiotic reactions involved in the synthesis of amino acids, working on asymmetric autocatalysis of Strecker reaction could really improve the understanding of the origin of homochirality. The principle of autocatalysis applied to Strecker reaction is described below:



We designed some compounds (single chiral molecules synthesized from L-valine). We expect that these molecules can serve as an initial source of chirality to promote the autocatalytic process of the Strecker reaction.



Some of them have been obtained and are under investigation.

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P A141

New synthetic strategy of *C,C*-glycosyl amino acids by iron catalyzed hydrogen atom transfer

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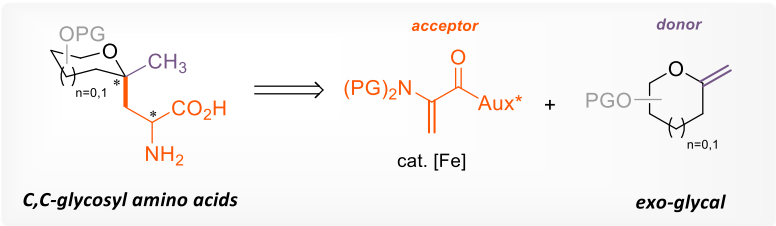
Glycoproteins made up of a chain of amino acids linked to at least one sugar, represent a class of biomolecules involved in a wide variety of physiological processes (immune response, tissue differentiation) and diseases (cancers, autoimmune diseases). The design of *C*-glycosidic analogues of these entities theoretically should allow to obtain glycopeptide mimetics of therapeutic interest, resistant to enzymatic hydrolysis *in-vivo*. However, the synthesis of *C*-glycosyl amino acids remains poorly described and represents a real synthetic challenge.

Here, a versatile method for synthesizing *C,C*-glycosyl amino acid building blocks has been developed based on the MHAT (metal catalyzed hydrogen atom transfer) methodology previously developed in the laboratory[1]. In this methodology, a tertiary pseudo-anomeric radical is formed starting from an *exo*-glycal and can subsequently react with an engineered dehydroalanine used as a Michael-type acceptor.

Under these conditions, the challenge is to control the stereochemistry of the two asymmetric centers formed both at the level of the pseudo-anomeric position and at the level of the amino acid unit.

C,C-glycosyl amino acids synthesis methodology



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P A142

A new approach to the total synthesis of myricanol

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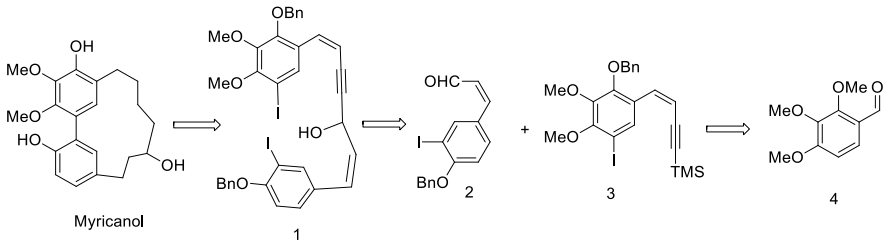
Given the important pharmacological potential of myricanol, a natural *meta,meta*-cyclophanicheptanoid, as anti-cancer and promising anti-Alzheimer compound[1], the aim of this research is to develop a new synthetic strategy that could lead to the total synthesis of myricanol in a few steps, with good yields and high diastero- and enantio-meric excesses. The previously described racemic syntheses of myricanol[2] are disadvantaged by the critical step of macrocyclization. The difficulty of this cyclization comes from a difference of the freedom degrees between the strained cyclic structure and the linear one. The macrocyclization is therefore characterized by a decrease in entropy which makes this process unfavorable; if the starting substrate has already a rigid side chain, cyclization should be less unfavorable. Due to these considerations, our retrosynthetic strategy (**scheme 1**) involves an ene-yne system (**1**) as the *seco*-precursor having a rigid and highly directed (*cis* configuration) structure which would promote the intramolecular cross-coupling reaction (such as a Suzuki-Miyaura domino).The seco-precursor **1** could be obtained by a fluoride mediated addiction of compound **3** on compound **2** and The ene-yne system **3** arises from the commercially available trimethoxybenzoaldehyde (**4**), by a regio-selective demethylation, iodination, benzylation and finally stereoselective Julia-Kociensky olefination.



Scheme 1. Retrosynthetic Approach

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P A143

Formal Glycosylation of Quinones with *exo*-Glycals Enabled by Iron-mediated Oxidative Radical-polar Crossover

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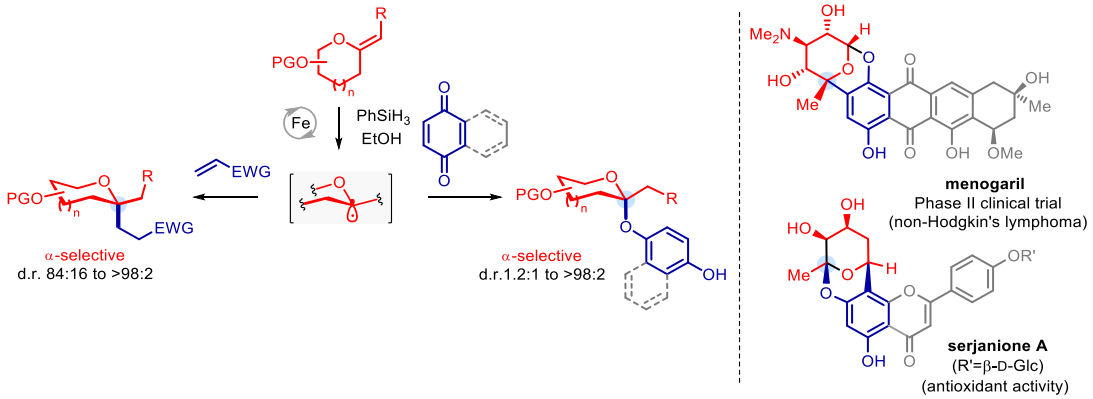
O- and *C*-aryl glycosides represent important classes of compounds of therapeutic interest.[1] Among them, serjanione A[2a] and menogaril,[2b] a clinically active antitumor drug derived from the natural product nogalamycin, are synthetically attractive. In these unique structures, the sugar residue is joined to the aromatic moiety *via* both glycosidic and C-C bonds to form a benzoxocin ring system. In conjunction with our continuing studies on carbohydrate mimetics, we have recently reported a convenient strategy for the synthesis of *C*,*C*-glycosides - also referred to as *C*-ketosides - from *exo*-glycals by way of a Metal-mediated Hydrogen Atom Transfer (MHAT).[3] The capture of the transient tertiary pseudoanomeric radicals by a range of Michael acceptors enables the stereocontrolled *C*-quaternization of the anomeric center. With the objective of developing a convergent, step-economical access to the benzoxocin core found in *C*,*O*-fused glycosyl hetarenes such as serjanione A or nogalamycin, we envisioned the direct coupling of MHAT-generated glycosyl radicals with 1,4-quinones. The control in regio- chemo- and diastereo-selectivity in the generation of quaternary (pseudo)anomeric centers involving an *exo*-glycal and a quinone was expected to be highly challenging. In this work, we report that quinones can be successfully coupled with a variety of *exo*-glycals to produce phenolic *O*-ketosides, demonstrating their applicability in demanding cross-coupling transformations initiated by iron-catalyzed HAT[4]. Preliminary mechanistic studies suggest the formation of a glycosyl oxocarbenium ion intermediate *via* a charge transfer complex involving the tertiary pseudoanomeric radical and the quinone.



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P A144

Synthesis of 4-Arylpyridine Atropisomers by the Combination of Enantioselective Organocatalysis and Aerobic Central-to-Axial Conversion of Chirality

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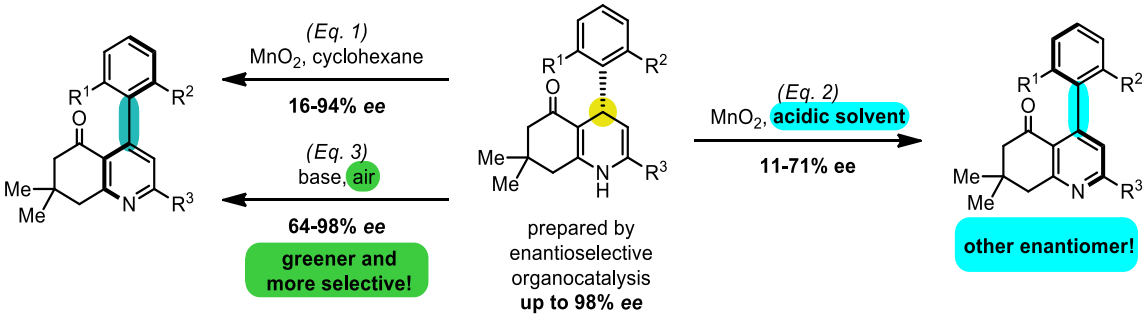
Atropisomers are very important scaffolds with numerous applications in various fields, such as medicinal chemistry and catalyst design. Despite numerous recent achievements, their enantioselective preparation represents a dauting synthetic challenge.[1] Indeed, in addition to the necessity of favoring the formation of one enantiomer, the kinetic stability towards enantiomerization has to be considered.

Some time ago, we have developed a strategy inspired by Hantzsch pyridine synthesis to prepare enantioenriched 4-arylpyridine atropisomers.[2] It combines enantioselective organocatalysis to prepare centrally chiral 4-aryl-1,4-dihydropyridine and oxidative aromatization with MnO_2, with central-to-axial conversion of chirality (*Eq. 1*).[3]

We now disclose that only a solvent change from cyclohexane to an acid can inverse the stereoselectivity of the central-to-axial conversion of chirality, delivering the opposite enantiomer of the atropisomers with moderate enantiomeric excesses (*Eq. 2*).[4] Moreover, we recently designed a greener and more efficient protocol obviating the requirement of super-stoichiometric metal oxidants: using oxygen from air as the oxidant in basic conditions provided a dramatic improvement of enantioselectivity (*Eq. 3*).[5]



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[5] *manuscript in preparation.*

P A145

Late-stage diversification of alkylketone-based polymers Through C(sp^3)-H bond activation (CH-PAK)

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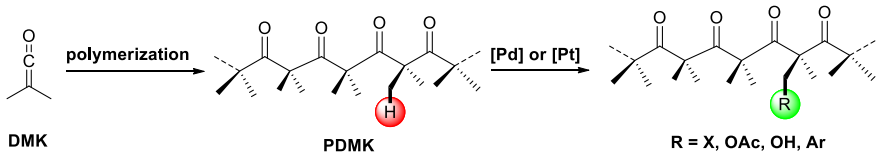
Advances in medical and food packaging play a primary role in keeping the companies' product supply among the safest in the world. Simply, packaging enables products to travel safely for a long distance from their point of origin till at the time of consumption. Thus, the core purpose of packaging is the preservation and safety of products against moisture, temperature, oxygen, light, and biological microorganisms. Municipal solid waste (MSW) consists of items commonly thrown away, including packages. The U.S. Environmental Protection Agency (EPA) found that 31% of the MSW generated in a year was from packaging-related materials.[11] Therefore, packaging technology must balance products protection and the safety of the environment by having strict regulations on MSW disposal that can be achieved by packages recycling. In the last decades, new biodegradable and recyclable coating materials, based on hybrid organic-inorganic polymers, were studied and developed to be used in food, and medical packaging.[2] Molecular chemistry could be able to be used as a major pathway for the development of novel polymer materials to meet our needs in food and medical packaging applications. In this sense, aliphatic polyketones constitute a rapidly growing family of polymers as it attracts interest in both the context of packaging, due to their outstanding impermeability against oxygen,[3] as well as innovative organic synthesis. An elegant and original way to obtain polyketones lies in the polymerization of ketenes,[4] the use of dimethylketene (DMK) even allowing the excellent barrier properties to be retained in a wet environment for polydimethylketone (PDMK).[5] Despite its exceptional physico-chemical properties, PDMK shows tricky processability as the melting point and degradation point are too close. Our work aims to extend this processability window, by modifying the chemical structure of PDMK. In this context, we are looking forward to developing a new methodology for direct functionalization of C(sp^3)-H bonds on PMDK throughout using **T**ransition **M**etal-catalysis (**TM**-catalysis), such as Pt(II) or Pd(II).[6,7,8] Afterward, upon success, the structural, chemical, thermal, and permeametric properties of modified PDMK polymers would be systematically studied.



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P A146
Synthesis of SAM-adenosine conjugates to study RNA methyltransferases

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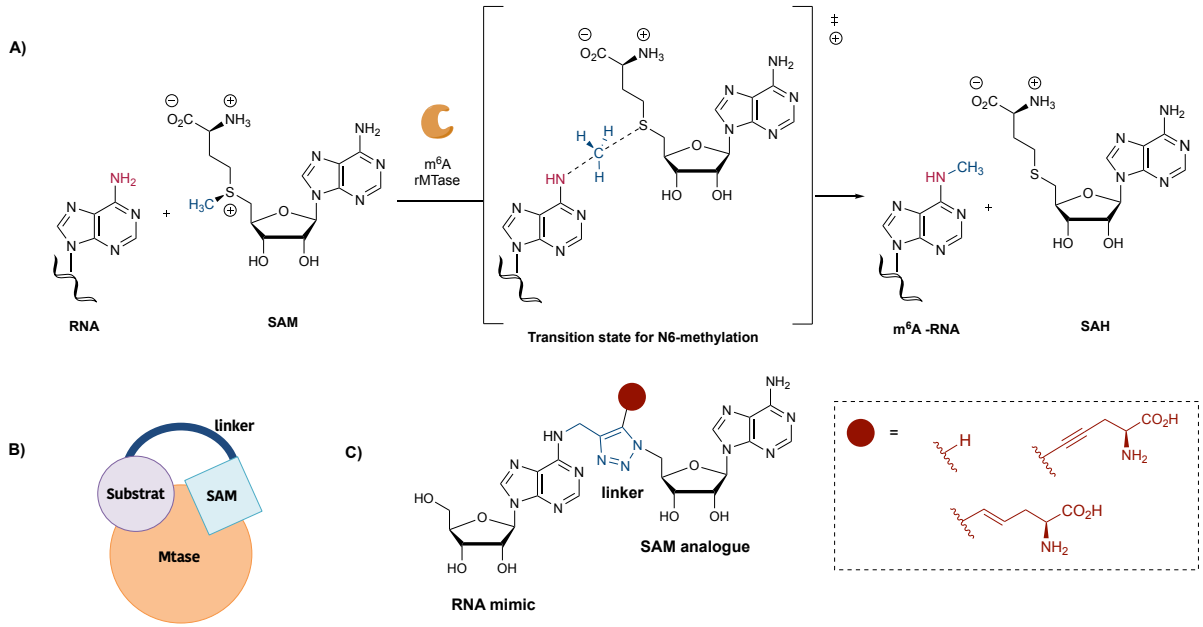
RNAs undergo numerous post-transcriptional modifications regulating their fate and function at the cellular level. Among these modifications, methylation at the N6 position of adenosine (m^6A) in mRNA is crucial for RNA metabolism, stability, and other important biological events. These modifications are installed by m^6A RNA methyltransferases (m^6A rMTases) that catalyze the transfer of the methyl group of the *S*-adenosyl-*L*-methionine (SAM) cofactor to the N6 position of adenosine, following a SN_2 mechanism (Scheme 1A). In humans, the deregulation of m^6A rMTase activity is associated with many diseases including cancer, neurological and metabolic diseases.[1] However, rMTases remain little studied, due to a lack of structural data. In particular, the RNA recognition process and the molecular mechanism involved in methyl transfer are to be elucidated. Here, we report the synthesis of SAM-adenosine conjugates which were designed as potential bisubstrate analogues of m^6A rMTases (Scheme 1B) that could be used for structural studies. These conjugates, which contain a triazole linker branched at N-6 position of adenosine, were obtained by organometallic post-functionalization reactions such as Copper(I)-Catalyzed Alkyne-Azide Cycloaddition (CuAAC) and palladium catalyzed cross-coupling reactions (Scheme 1C).[2]



Scheme 1. A) Methylation of adenosine at N6 position catalyzed by m^6A rMTases. B) Representation of the bisubstrate strategy. C) SAM-adenosine conjugates synthetized by post-functionalization.

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P A147

Molecular probes for the study of PIMs biosynthesis

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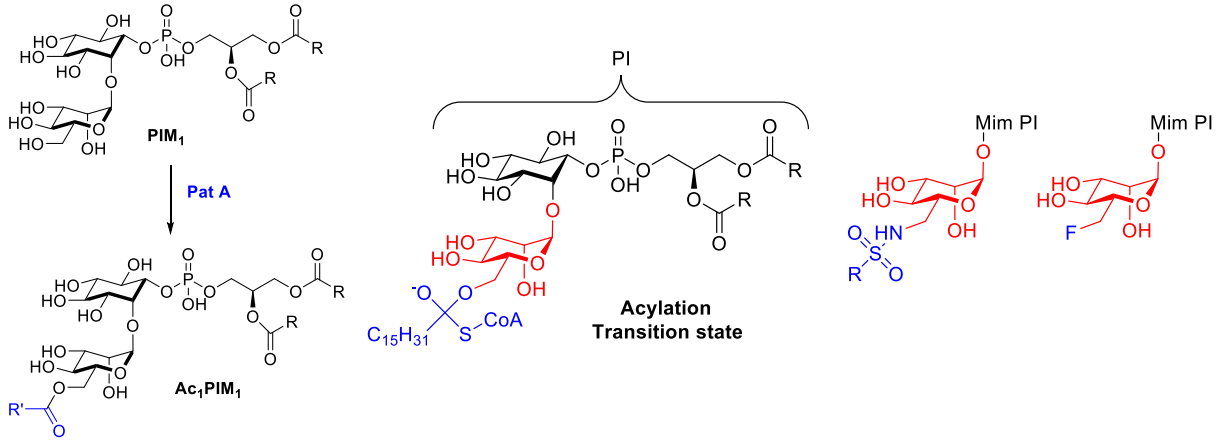
Mycobacterium tuberculosis is the second most deadly infectious agent in the world after COVID-19. Drug treatment is a laborious process, requiring daily dosage of two to four drugs over six months, and compliance is poor. Most recently, there has been an alarming rise of multi-drug resistant (MDR) and extensively drug resistant (XDR) TB worldwide, making discovery of new drugs crucial. Current anti-TB drugs are targeting diverse biological processes.[1] There are currently no molecules designed to target PIMs biosynthesis as anti-TB drugs.

PIMs (Phosphatidyl-*myo*-Inositol Mannosides) are the precursors of two major lipoglycans implicated in host-mycobacteria interactions. Their biosynthesis starts with the transfer by mannosyltransferase PimA of a mannopyranosyl residue to the 2-position of the *myo*-inositol ring of PI (Phosphatidyl-*myo*-Inositol) leading to PIM_1. The next step of PIMs biosynthesis is the acylation of PIM_1 by the essential membrane-associated acyltransferase PatA.[2] Although no co-crystallization of PatA in complex with the acceptor substrates has been realized yet, docking calculations and complex with 6-*O*-palmitoyl-α-D-mannopyranose gave useful information for inhibitors design.[3]

We are currently focused on the synthesis of a panel of molecules with mannopyranosyl scaffold with the aim to develop new inhibitors of PatA. Structures present different aglycones to mimic the PI part and different groups at the 6-position of mannose like fluor or sulfonamide mimicking the acylation tetrahedral transition state. The following step will be to study the molecule/enzyme interactions and to test the potential inhibitors on *Mycobacterium smegmatis* and *Mycobacterium tuberculosis.*



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P A148

The Piancatelli rearrangement for the synthesis of highly functionalized cyclopentenones

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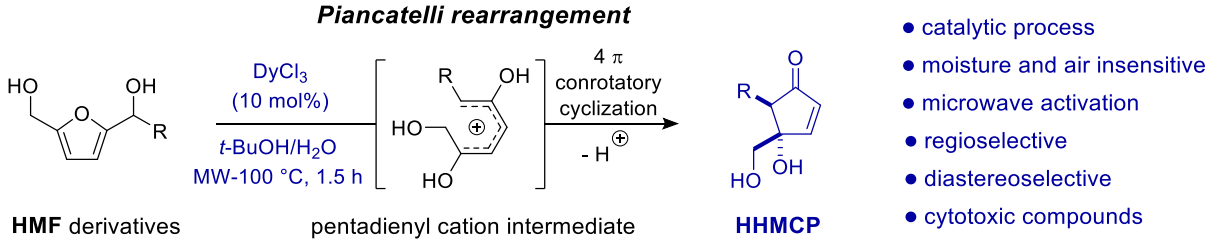
In the field of biomass transformation, the production of 5-hydroxymethylfurfural (HMF), as a versatile sustainable substitute of petrochemical building blocks, is one of the most successful and promising routes.[1] Despite the number of studies on the Piancatelli rearrangement and the effectiveness of this process, direct transformations of HMF close derivatives and, more generally C-5 substituted 2-furylcarbinols, have scarcely been explored.[2]

We have recently shown that substituted and non-symmetrical furan-2,5-dicarbinols, readily obtained in one step from HMF, affords 5-substituted-4-hydroxy-4-hydroxymethyl cyclopentenones (HHMCP), in a regio- and diastereoselective manner, through Piancatelli rearrangement catalyzed by $DyCl_3$ and under microwave activation.[3]



This methodology can be extended to *aza*-Piancatelli type reactions by using nitrogen nucleophiles to furnish the corresponding aminocyclopentenone derivatives. These synthetized bis-hydroxylated cyclopentenone derivatives exhibited significant cytotoxicity against eight human tumor cell lines.[1]

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P A149

Enantioselective Allylboration and Related Reactions of Isatins Catalyzed by Chiral BINOLs

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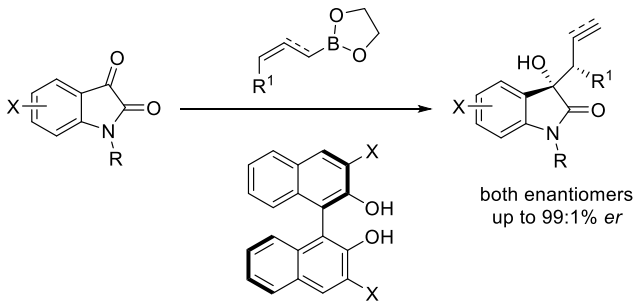
The catalytic formation of carbon quaternary stereogenic centers from privileged structure such as isatins continues to be a very challenging task for the organic chemistry community since the 3-substituted-3-hydroxyoxindole scaffold is widely found in natural products.[1] More specifically, 3-allyl-3-hydroxyoxindoles have a great potential for the synthesis of bioactive compounds,[2] so there is a need to avoid metals in their preparation. Among the existing allylation reactions of carbonyl compounds, the asymmetric allylboration constitutes probably one of the most reliable and predictable stereoselective methods for the formation of homoallylic alcohols *via* a Zimmerman-Traxler transition state.[3] Herein, we report the BINOL derivatives-catalyzed allylboration of isatins, in particular with *N*-unprotected substrates.[4] We also show that this catalytic process is effective for the crotylboration reaction with excellent enantiomeric ratios as well as for the asymmetric synthesis of tertiary homopropargylic alcohols through the addition of an ethylene glycol allenylboronate to isatins.



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P A150

From total synthesis to photosynthesis, a detective journey to the site of action of a phytotoxic natural product

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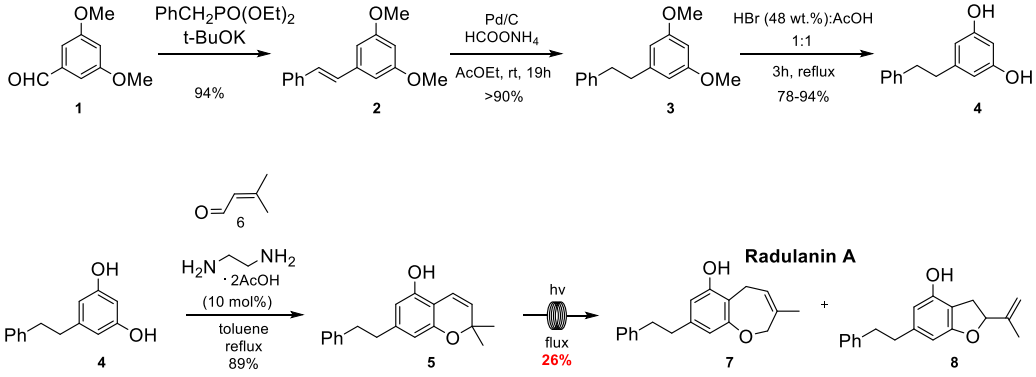
The current cost of production of new herbicides[1] and the increased regulation related to ecotoxicity[2] have impaired investments in herbicide development. Nonetheless the emergence of herbicide-resistant weeds and European regulation around the use of several herbicides have renewed interest in alternatives affecting new or known biological targets. In 2019, an application of the retro-Claisen rearrangement to the total synthesis of radulanin A was described. Further experiments carried out on seedlings of model plant *Arabidopsis thaliana* highlighted the phytotoxicity of this molecule and its potential as a new and innovative herbicide, yet with an unknown mechanism.[3]

The work presented in this poster highlights a new synthetic route giving the shortest and highest-yielding total synthesis of radulanin A, featuring a largely unexplored photochemical ring expansion.[4] During this work, complemented by 13 structural analogs, detailed biological studies led to precious insights on the mode of action of radulanin A. This poster thus presents the investigation that led to the discovery of the radulanin A site of action.



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P A151

Opening of the chemical space of functionalization C—H of carboxylated-azoles heterocycles

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Keywords: C(sp³)—H direct functionalization; imidazoisoindole; palladium catalysis; arylation

Abstract: Imidazoisoindole scaffolds are very important backbone that are commonly found in pharmaceuticals and bioactive compounds including anticancer[1] (indoleamine 2,3-dioxygenase-IDO inhibitor, Figure 1a), potent neurotransmitter Neuropeptide S antagonist[2] (NPSR, Figure 1b), antimalarial[3] and antiparasitic[4]. Of the two isomeric imidazoisoindoles, the 5*H*-imidazo[2,1-a]isoindole scaffold is the most popular. Palladium-catalyzed intramolecular direct C—H arylation is a powerful method to prepare imidazoisoindole scaffolds from the corresponding imidazole moieties bearing arylhalides[5]. We have recently reported the synthesis of several fused-imidazole-based tricycle scaffolds by using palladium-catalyzed direct intramolecular C—H arylation of 4- or 5-carboxyimidazoles in good to excellent yields[6].

Here is reported a new post-functionalization methodology on the sparsely studied imidazoisoindole scaffolds (Scheme 1), selectively on the C(sp³)—H position, using mild basic conditions. This gives access to a new family of 5-(hetero)arylated imidazoisoindoles, which some of them may have some interesting biological activity.

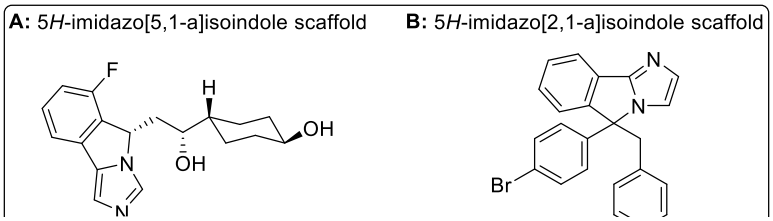
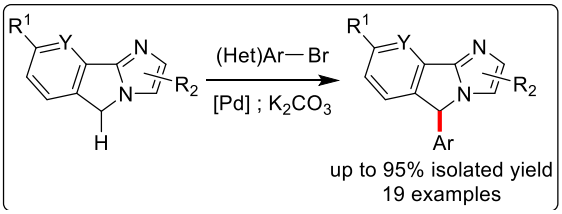


Figure 1: Examples of imidazoisoindole structures. A: Navoximod, IDO1 inhibitor; B: Potent NPSR antagonist



Scheme 1: Post-functionalization of imidazoisoindoles and derivatives

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P A152

Gold catalyzed synthesis of heterospirocycles for molecular diversity

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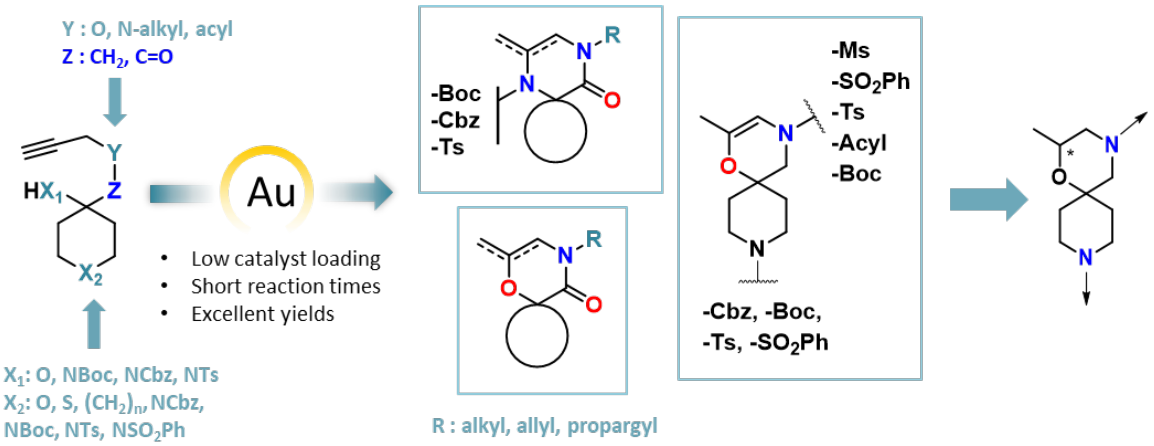
Spirocycles are characterized by the presence of a fully substituted sp3 carbon which defines a well-organized 3D orthogonal structure. Due to their molecular rigidity, and an increased number of Csp3 carbons, interest in the synthesis of new and original spirocyclic compounds is increasing, in both academia and the pharmaceutical industry.[1,2] In this work, we focused our attention on the synthesis of diverse heterospirocycles, compounds that possess a heteroatom directly attached to the quaternary spirocyclic carbon. To achieve this goal, we developed a simple and robust gold-catalyzed annulation reaction, giving N- and O-spirocycles in good to excellent yields. A screening of different transition metal catalysts and fine tuning of the reaction parameters led to the best cyclization conditions : low catalyst loading under microwave irradiation with a short reaction time. The optimized conditions were then applied to a variety of substrates, to study the reaction scope and explore molecular diversity.[3,4] Double bond reduction and selective protecting group manipulation gives synthetically useful spiropiperidine and spiromorpholine derivatives available for further functionalization.



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P A153

Domino Photochemical Synthesis of Thietane Derivatives

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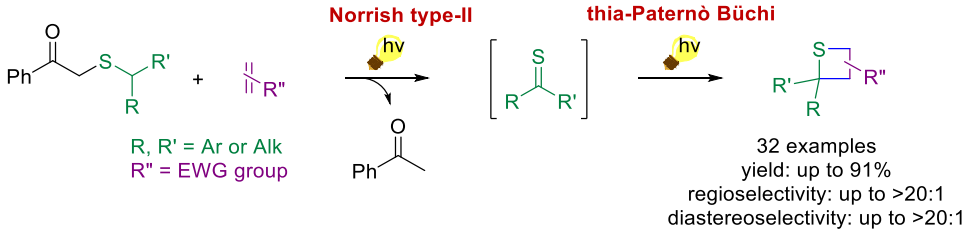
Photochemical reactions constitute powerful tools for the creation of chemical diversity from simple and readily available starting materials.[1] They provide access to complex molecular structures that are difficult to obtain using other methodologies.[2] These transformations induced by light absorption are attractive in the context of sustainable development and they can address this challenge more efficiently when they are incorporated in multiple bond-forming transformation processes, such as domino reactions.[3-4]

This presentation describes a straightforward access to a large collection of thietane derivatives through an innovative two-step domino photochemical reaction involving a Norrish-Type-II fragmentation and a thia-Paternò–Büchi reaction. Starting from stable diaryl or aryl alkyl phenacyl sulfides, unprecedented thiocarbonyl intermediates were generated *in-situ* and underwent reaction with diverse electron-deficient alkene partners to form a thietane core. The regioselectivity and the diastereoselectivity of the thia-Paternò–Büchi reaction were successfully rationalized and controlled by adjusting the electronic an steric properties of the thiocarbonyl intermediates.[5]



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P A154

Synthesis of SAM cofactor analogues to study viral RNA

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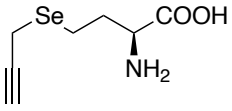
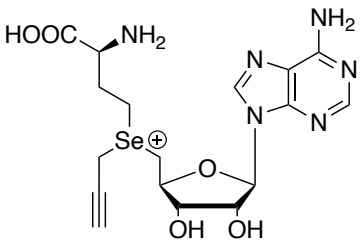
In host cells, retroviruses such as HIV-1 replicate through a double strand DNA intermediate which is imported into the cell nucleus and integrated into a chromosome. The proviral DNA genome is transcribed giving rise to genomic RNA (gRNA). The gRNA is used as mRNA for regulatory protein synthesis after splicing whereas the unspliced gRNA reaches the cytoplasm to be used as an mRNA for the synthesis of Gag and Gag-Pol polyproteins and acts as a genome packaged into assembling viral particle.[1]Discrimination between packageable and translatable gRNA molecules by the Gag proteins is still not clear.

The role of m^{6}A in HIV-1 physiology has been the object of several studies,[2] the conclusions and the mechanisms involved remaining controversial, which may be due to the dynamic of the RNA methylation. The m^{6}A are detected through an imprecise method that pinpoints a 50nt region rather than a precise methylation site. In order to study the influence of the specific methylation identified on gRNA structure, translation, dimerization and trafficking into the cell, we develop tools to follow m^{6}A methylation along the virus cycle.

Here, we present the synthesis of SAM cofactor analogues to modify RNA *in vitro* and in cell to study the roles of m^{6}A methylation in HIV-1 gRNA. In 2018, the team of Rentmeister developed a chemical biology approach for the precise mapping of methyltransferase (MTase) target sites based on the introduction of a bioorthogonal propargyl group in cells and *in vitro*.[3] This strategy uses cellular MTase and propargyl-L-selenohomocysteine (for in cell assay) and wild type MTase METTL3-METTL4 complex with synthetic AdoMet analogues carrying the propargyl group (for *in vitro* assay). So far we have completed the synthesis of SAM analogues containing a selenium instead of a sulfur bearing a propargyl group for *in vitro* labeling and propargyl-L-selenohomocysteine for cell labeling, which will be used to explore the roles of m^{6}A methylation in HIV-1 gRNA.



Propargyl-L-selenohomocysteine



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P A155

Light-Frozen Dynamic Covalent Synthesis of Electron-Deficient Conjugated Materials

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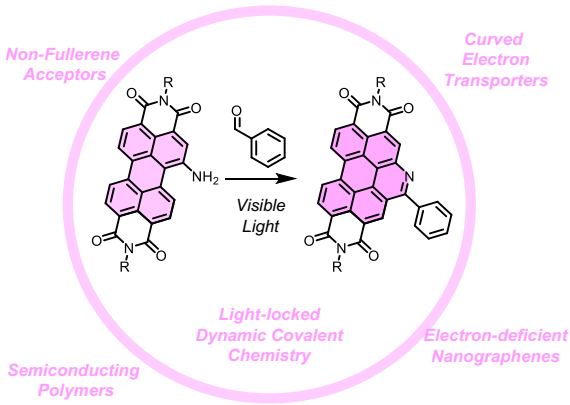
Organic electronics devices are now all around us and the chemistry of organic semiconductors of various optical and electronic properties is blooming. If the development of p-type (holes transporting, electron-rich) organic semiconductors has seen the synthesis and characterization of a wide variety 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 cyclisations. 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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P A156

Diazapentalène, a promissing unexplored azaheterocyclic scaffold: synthesis and reactivity

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Organic energetic materials based on fused nitrogen containing heterocycles are a unique class of large conjugate structures which contain two or more rings that share two atoms and one bond. They have been identified as promising contenders to traditional energetic materials[1]. In this context, several [5,5]-bicyclic heterocycle-fused compounds, such as DNPP[2] or TATOT[3], were described for energetic applications. Studies conducted in our laboratories have highlighted that triazapentalenes compounds exhibit an original structure, which confers them interesting properties and an attractive carbon/nitrogen ratio for energetics applications[4].

To further explore azapentalene structures and their properties, our group is now working on diazapentales derivatives. These mesoionic compounds are characterized by a fused biheterocyclic system connected by two nitrogen atoms (Fig 1). Since their discovery by Trofimenko[5,6] in 1965, very few papers have been dealing with the synthesis of this 3a-6a-diazapentalene scaffold. Because of the tricky synthetic pathways and the very small scope of compatible substituents on this aromatic ring, no more studies on its reactivity/chemistry were reported. To overcome this situation, we succeeded in developing an efficient approach for the synthesis of stable and diversely functionalized diazapentalenes and were able to consider some aspects of their reactivity.

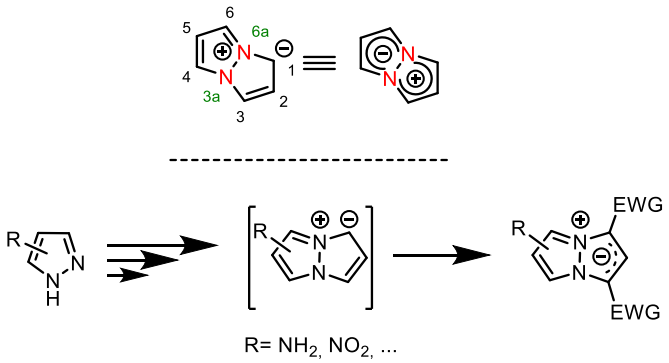

Figure 3: Structure and Synthesis of diazapentalenes

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P A157

Allylsulfones via Palladium-Catalyzed Allylic C–H Activation

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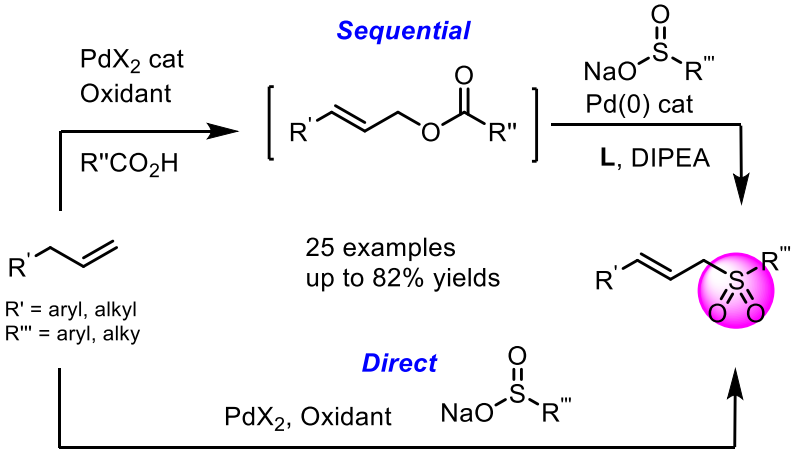
Sulfones are important motifs in biologically active molecules, and serve as versatile bulding blocks in a number of carbon-carbon bond-forming reactions, such as the Julia-olefination or the Ramberg-Bäcklund reaction.[1] In particular, the preparation of allylsulfones usually requires multi-step syntheses and starting materials not commercially available. In the frame of recent studies by us and others on the Pd-catalyzed direct allylic C–H activation of alkenes involving C–O, C–C, and C–N bond formation,[2] and on the synthesis and the reactivity of allylsulfones under Pd-catalysis,[3] we have now developed two protocols for the direct conversion of terminal alkenes into allylsulfones. While the former method involves a Pd(II)-catalyzed allylic C-H acylation[4] followed by *in situ* Pd(0)-catalyzed sulfonylation of the resulting allyl ester, the latter one involves a Pd(II)-catalyzed direct allylic C–H sulfonylation.[5] A variety of allylic sulfones could be isolated in moderate to good yields with a wide functional group tolerance for both protocols.



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P A158
Decarboxylation of alkyl formates into methane

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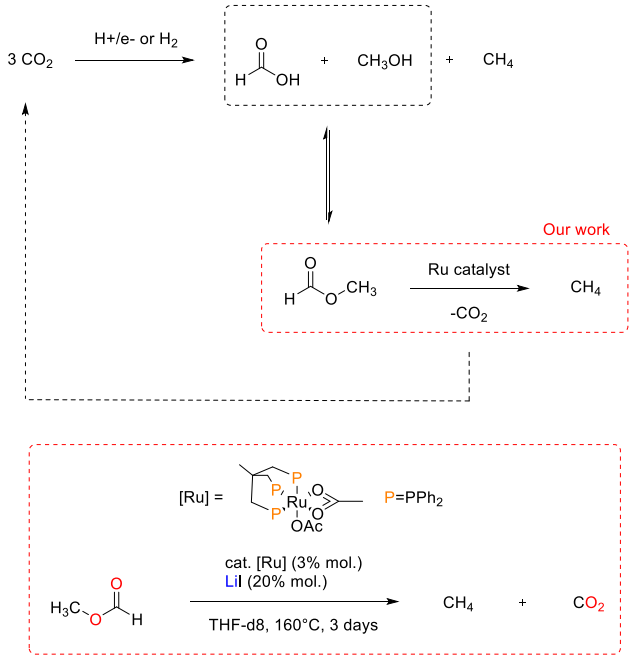
Methane is a widely used molecule with an annual consumption of 3.67 billion m^3 in 2017, [1] and its production is almost entirely relying on fossil sources. Some renewable solutions have been proposed, such as the biogas facilities which produce methane by anaerobic digestion, [2] or the direct hydrogenation of CO_2 into methane. [3-5] The conversion of CO_2 into methane can lead to several reduction products with different oxidation states such as formic acid, methanol, as well as methyl formate which comes from the esterification reaction between the alcohol and acid intermediates. In order to help driving the reaction towards methane we considered the challenging decarboxylation of methyl formate: only one example to our knowledge has been reported by Jenner in 1995 but his reaction faced selectivity issues. [6]
We report here the homogeneous decarboxylation of methyl formate and more generally alkyl formates by activation of the C-O bond thanks to the combination of a ruthenium triphos catalyst and an additive, lithium iodide, in THF. This allows the indirect reduction of methanol into methane with methyl formate as starting material, using formic acid as a reducing agent. Methyl formate is a low-boiling, non-toxic liquid that can be easily obtained by esterification between formic acid and methanol. NMR quantification confirmed the selective formation of methane (in the case of methyl formate) with a yield of more than 95 %.



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P A159

Progress in the total synthesis of a photocaged latrunculin B

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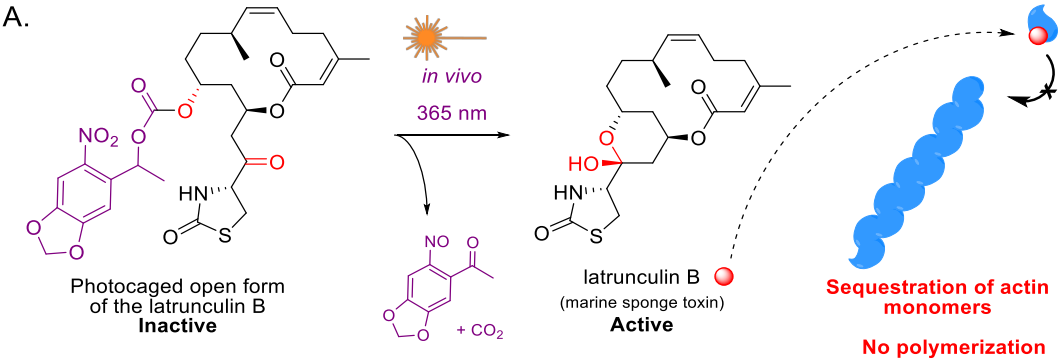
The marine sponge toxin latrunculin B was discovered in 1980 and has shown the ability to disrupt cellular microfilaments by binding and sequestrating free actin monomers.[1,2,3] This actin polymerization inhibiting effect has brought interest to the molecule and made it popular among cellular biologists working on the cytoskeleton.

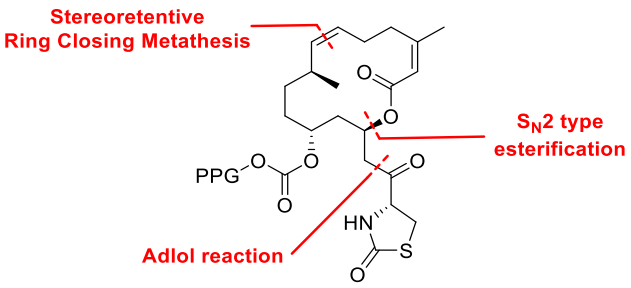
To go further in the control of actin polymerization, the total synthesis of a photocaged latrunculin B could provide a molecular tool for the local and on demand inhibition of the actin network in cells. Using light, we could trigger the photodeptrotection of an inactive photocaged latrunculin B to release locally the active natural product (Scheme A).

The total synthesis of this compound was planned in a convergent way by three main disconnections, isolating three intermediate fragments. The thiazolidine heterocycle will be grafted by a diastereoselective aldol reaction and the macrocycle formed by esterification followed by a recently developed stereoretentive ring closing metathesis (Scheme B).[4]

A.



B.



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P A160

Rhodium-Catalyzed Asymmetric Synthesis of Cyclopropane α-Amino Acids

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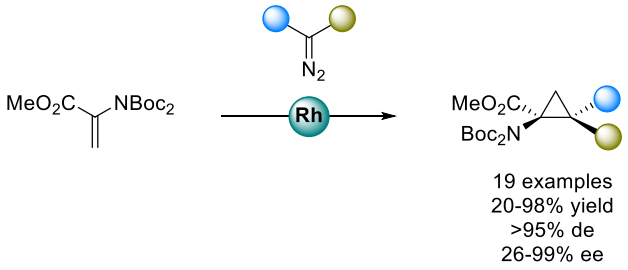
Cyclopropane, as the smallest and most constraint cycloalkane, represents an interesting motif, naturally present in organic molecules.[1] The introduction of a three-membered ring can enhance a drug's potency.[2] Among this class of compounds, cyclopropane α-amino acids have raised a particular interest, as they represent a unique form of constraint amino-acids found in nature.[3] Yet, their synthesis remains challenging especially under asymmetric conditions, as only a few methods have been reported up to date and describing only tri-substituted cyclopropane α-amino acids.[4]

We report here a general and mild method to access enantiomerically pure tetra-substituted cyclopropane α-amino acids, from amino-acid alkenes, in the presence of diazo compounds and a chiral rhodium catalyst.



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P A161

Gold(I)-Catalyzed Alkynylation of *N,O*-Acetals: An Easy Access to Alkynylated Saturated *N*-heterocycles

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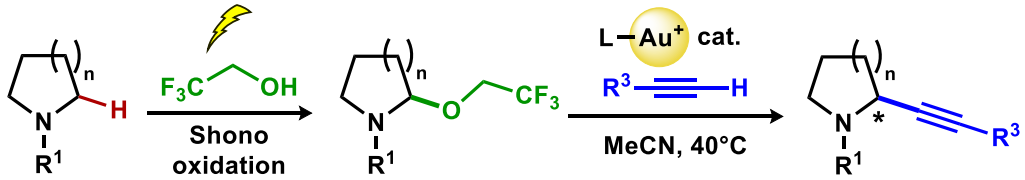
Over the past decades, gold-catalyzed reactions emerged as powerful tools for organic synthesis. Indeed, gold catalysts proved to be excellent candidates for the selective activation of various π-systems and subsequent functionalization.[1] In this context, it appeared that gold(I) catalysts can easily react with terminal alkynes or silylated alkynes to form the corresponding gold acetylides. Despite their moderate nucleophilicity, this kind of organometallic intermediate can react with activated electrophiles such as iminium.[2] Nevertheless, these reactions usually require the use of stabilized iminium and/or silylated alkynes.[3] Although copper can be used as an alternative catalyst, the addition of stoichiometric base and Lewis acid remain necessary.[4] We present here the gold(I)-catalyzed reaction of terminal alkynes and *N,O*-acetals, the latter being prepared by electrochemical Shono oxidation of readily available tosyl-protected cyclic amines.[5] This gold(I)-catalyzed transformation takes place under simple conditions without addition of any additives and can be performed on a variety of reaction partners. Overall, this new methodology allowed the access to a range of alkynylated saturated *N*-heterocycles over a step- and atom-economical process. In addition, preliminary results using chiral gold(I) catalysts led to promising enantiomeric ratio up to 85:15.[6]



✓ **Simple conditions, no additives, under air**

✓ **Atom- and step-economy**

✓ **Preliminary results for an asymmetric version**

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P B001

Access and modulation of pyrrolo[2,3-*d*][1,2,3]triazoles using a Regioselective Multicomponent Cyclisation and cross coupling reactions

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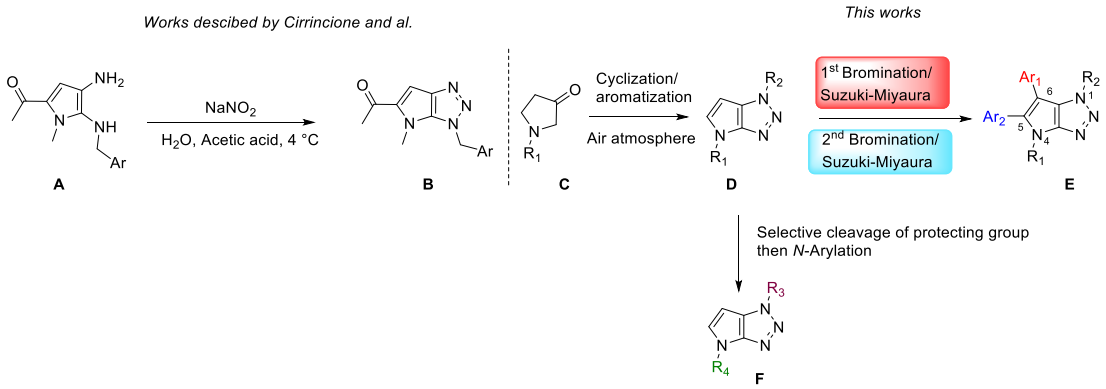
Pyrrole and triazole derivatives are powerful moieties to elaborate drugs which are used in various areas of medicine.[1] For these reasons, their introduction in medicinal chemistry programs has grown, in particular in the context of molecular diversity and innovative chemical space research.[2] These two small heterocycles have been fused in bicyclic systems[3], nevertheless, the literature reports only one example of these two cycles combined together in a [5:5] fused ring to access benzylated pyrrolo[2,3-*d*][1,2,3]triazoles of type **B**.[4] To date, no method is available to introduce the chosen substituents in *N-1*, *N*-4, *C*-5, and *C*-6 positions. This lack of references and methods induces a gap in the exploration of the chemical space and prompted us to search for novel and efficient strategies from a unique versatile platform towards highly diversified structures in a minimum number of steps.

In order to introduce a wide range of functional groups, a solution consists in building a library of pyrrolo[2,3-*d*][1,2,3]triazole platforms **D** from commercially available 3-pyrrolidinone **C** patterns using a regioselective MCR cyclisation sequence and then elaborating its selective functionalization using arylation procedures.



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P B002

Intramolecular reaction of alkenes with trifluoromethylated *N*-acyliminium ions derived from L-tartaric acid : towards original alkaloid-inspired polycyclic scaffolds

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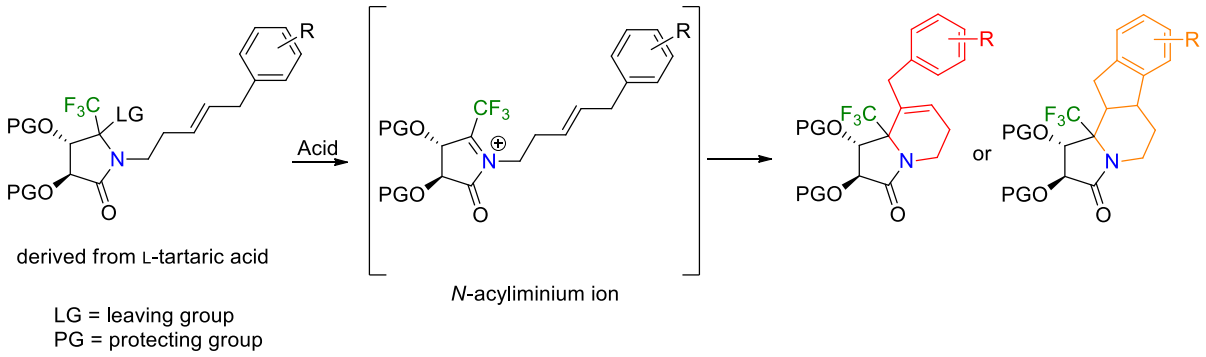
N-acyliminium ions are recognized as highly reactive electrophilic intermediates for C-C and C-heteroatom bond formation.[1] However, in the literature, very few examples involving trifluoromethylated *N*-acyliminium ions have been described.[2–7] Indeed, the presence of the strongly electron-withdrawing CF_3 group not only stabilizes the *N*,*O*-acetal precursors, which makes the formation of *N*-acyliminium ions difficult, but also greatly destabilizes and hinders these ions rendering their reactions with nucleophiles arduous. These intermediates have been mainly involved in intramolecular reactions with aromatic nucleophiles (Pictet-Spengler type reaction).[2,4,7] As well as intramolecular reactions with F-,[3] O-,[5] and N-[6] nucleophiles have also been described.

In this context, we are studying the intramolecular reaction of alkenes with trifluoromethylated *N*,*O*-acetals derived from L-tartaric acid under acidic conditions. Our recent results will be presented.



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P B003

Theoretical and Experimental Investigations of the Hock rearrangement with $InCl_3$ as catalyst

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The Hock rearrangement (path (1), Figure 1) is a reaction with significant applications in industry. For instance, since the development of the cumene process by Hock and Lang[1], this reaction plays a crucial role for the production of millions of tons of phenol and acetone each year[2]. Nevertheless, this rearrangement remains scarcely used in organic synthesis. Fully harnessing its potential to develop efficient synthetic routes remains a real challenge for organic chemists. Herein, we report for the first time a computational study at the DFT level on the Hock reaction in combination with experimental studies to fully assess its mechanism and thus provide a clear view of the key parameters to understand the observed reactivity. Innovative proposals were implemented to this reaction: (i) transforming the classical Hock rearrangement into a catalytic reaction using a Lewis acid, and (ii) trapping the oxocarbenium intermediate formed *in situ* with an external nucleophile. This work builds the foundations of the "interrupted Hock reaction" (path (2), Figure 1). In addition, this study challenges the classical Hock reaction by enabling the migration of aliphatic carbons rather than sp^2 carbons.

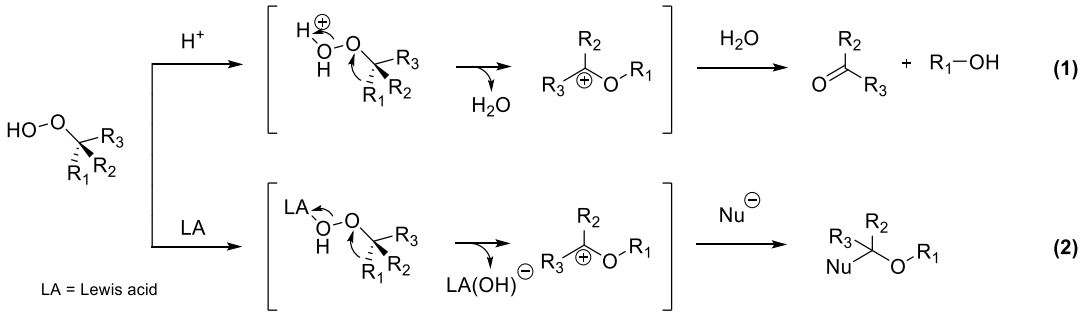

Figure 1: Classical Hock rearrangement (1) "interrupted Hock reaction" (2)

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P B004

Bambusurils: New platforms for biological applications

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Bambusurils (BU[4,6], Figure 1) are cyclic oligomers composed of *n* glycoluril units[1] (n = 4 or 6). BU[6] can bind anions with high affinity inside their cavity due to twelve C-H··X^- bounds. BU[6] are the best complexing agents known so far for iodides.[1,2] BUs can have different R substituents, making them soluble either in organic or in aqueous media and modifying anions recognition.[3,4]

In our laboratory, two families of functionalizable bambusurils have been developed: allyl$_{12}$BU[n] and propargyl$_{12}$BU[n]. Thanks to their alkenes or alkynes substituents, they can be fully post-functionalized by various chemical groups, using thiol-ene click reaction for allyl$_{12}$BU[n] and click chemistry for propargyl$_{12}$BU[n]. Affinity constants of BU[6] with anions were measured using Isothermal Titration Calorimetry (ITC), providing high affinities for both families.[3]

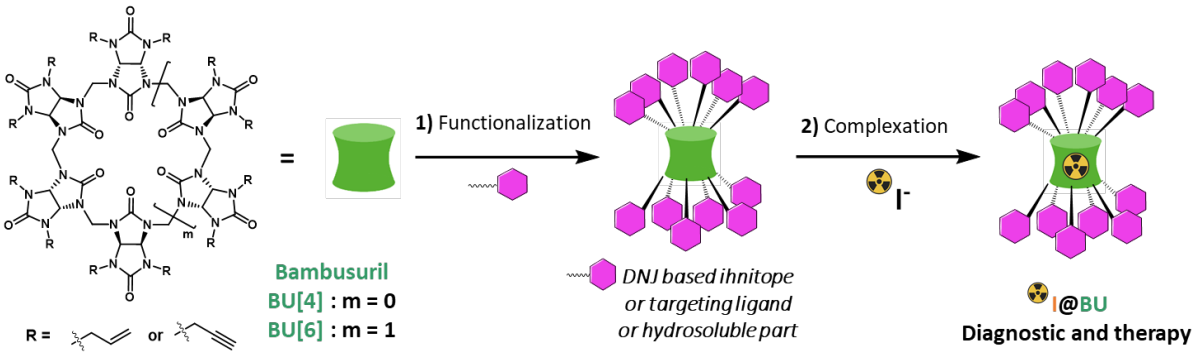

Figure 1: Functionalization of Allyl$_{12}$BU[6] and Propargyl$_{12}$BU[6] and radioiodide complexation

BU[4] and BU[6] were used for the first time as multivalent scaffolds to link glycosidases inhibitors derived from 1-deoxynojirimycine (DNJ).[5] *N*-alkylDNJ derivatives were clicked on propargylated BUs using CuAAC reaction to generate multivalent clusters bearing up to 24 iminosugars. The NeoglycoBU[n] were evaluated against Jack Bean α-mannosidase, showing strong affinities especially for BUs bearing trivalent dendrons (K_i = 24 nM for BU[4] with 24 DNJ units).

Thanks to its different isotopes, iodine has a great use in nuclear medicine such as tumours diagnostic with TEMP (^{123}I) and PET (^{124}I) but also in radiotherapy with ^{125}I (Auger electrons emissions) and ^{131}I (β^- emissions). By complexing these various radioiodides, bambusurils could be used either in diagnostic or in therapy after appropriate functionalization (Figure 1).

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P B005

Total synthesis of cyclotripeptide natural products with a quinazolinopiperazine structure

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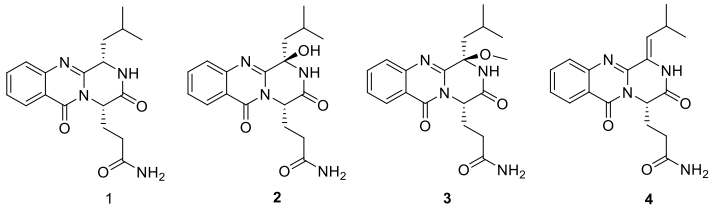
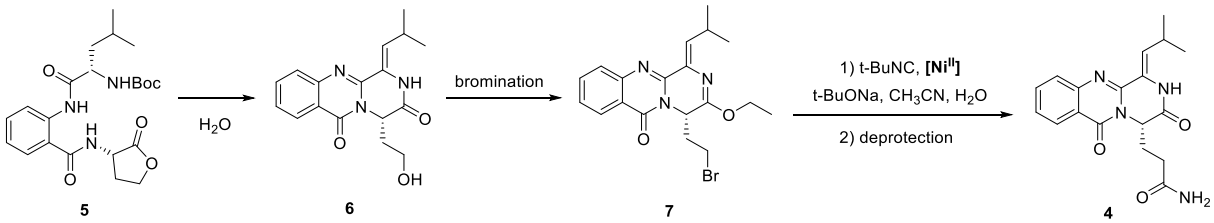
The quinazoline heterocycle is taking important proportion in recent anticancer drug discovery, especially as a 2,3-fused quinazolinone pharmacophore,[11] which is also found innumerous natural products. For example, anacine and its derivatives (*e.g.* aurantiomide C, **4**) have a quinazolinopiperazine core, and have been isolated from *Penicillium* species.[2] They displayed good biological activities as antibacterial, anti-insect or cytotoxic. It has been reported that the methods of synthesis of fused quinazolinopiperazine can be challenging,[3,4] offering the opportunity of further developments. During this work focused on the total synthesis of anacine (**1**) and aurantiomides A-C (**2-4**), our strategy used a key cyclocondensation step performed on an α-peptidylamino-γ-butyrolactone (**5**), which was accompanied by a fortuitous oxidation step to release the quinazolinopiperazine core of the natural products, bearing a hydroxyethyl substituent (**6**). After bromination of this terminal alcohol (**7**), we successfully performed a nickel-catalyzed aminocarbonylation in presence of an isocyanide.[5] Although this last step needed an amide protection, it is particularly original as it uses a rare transformation here applied to the synthesis of a highly functionalized natural product **4**, aurantiomide C.



Natural products anacine and aurantiomides from *Penicillium* species



The cyclocondensation and aminocarbonylation steps of total synthesis of aurantiomide C

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P B006

Iron(III) chloride-mediated protection of trehalose: a key step for the synthesis of chemical tools for the study of the cell wall of mycobacteria

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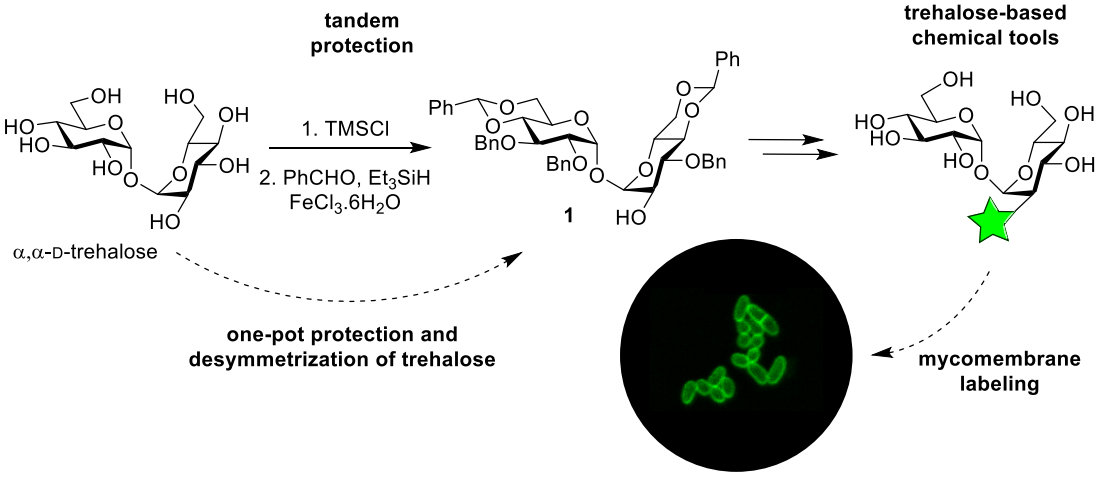
The synthesis of complex glycoconjugates usually requires multi-step synthesis including protection-deprotections steps. In this context we have developed a tandem protocol mediated by $FeCl_3.6H_2O$ for the regioselective protections of saccharides.[1] During our studies we found $FeCl_3.6H_2O$ to be very efficient for the protection of trehalose, a symmetrical disaccharide found in the cell wall (mycomembrane) of mycobacteria such as *M. tuberculosis*, the etiological agent of tuberculosis. This iron(III) chloride-mediated protocol has been successfully applied for the synthesis of complex sulfolipids found in the mycomembrane of *M. tuberculosis*, which are antigens able to control the mycobacterial infection.[2] Recently, we have modified our tandem protocol in order to obtain the desymmetrized trehalose derivative **1**, and we have used this key compound for the synthesis of chemical tools for the study of the mycomembrane.[3] Regioselective protection of trehalose leading to **1** and the synthesis of these chemical tools will be presented as well as their use for the labeling of the mycomembrane of corynebacteria.



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P B007

Rearrangement-based total syntheses of oxacyclic natural products

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Agathe Fayet, Alexandra Bosnidou, Bastien Nay*
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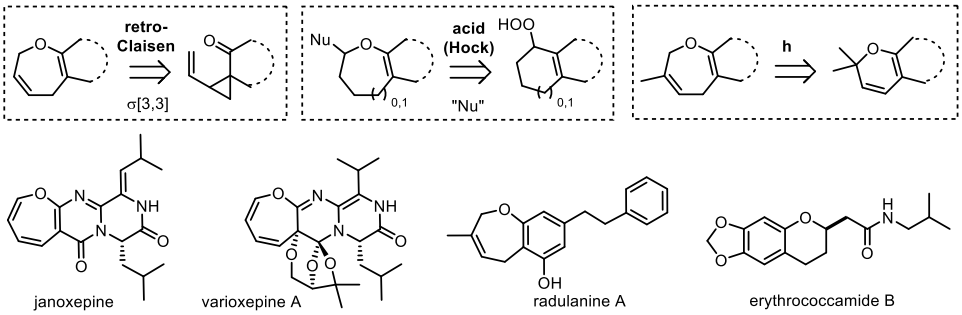
Oxacycles are commonly found in natural products. Some compounds of interest to us, due to their complexity and biological properties, are based on the seven-membered oxepane or oxepin motif, like the fungal cyclotripeptides janoxepin and varioxepin A, or the plant 2,5-dihydrobenzoxepin radulanin A. Numerous strategies have been described in the literature for their synthesis through C-C (*e.g.* metathesis) or C-O (*e.g.* Mitsunobu reaction) bond formation. However, these strategies use long synthetic sequences to reach the precursors. In this poster, we want to disclose our latest results on the synthesis of oxacycles. Several rearrangement-based methodologies will be described. First, the retro-Claisen [3,3] rearrangement of *cis*-2-vinylcyclopropane carboxaldehydes allowed us to synthesize two different natural products using a fragment-based strategy: janoxepin[1] and radulanin A.[2] Second, an interrupted Hock cleavage of 1-hydroperoxycycloalkanes led to new oxacycles and allowed us to synthesize substituted benzoxepanes and chromanes like the natural product erythrococcamide B. In addition, a photochemical rearrangement should complete this panel of methodologies.[3]



Our total synthesis of janoxepin, including a strong methodological development for each key step, uses a fragment-based strategy leading to an important increase of complexity through the retro-Claisen rearrangement. The completion of the synthesis was particularly challenging, when it came to oxidize the dihydrooxepin intermediate into the oxepin ring. Our total synthesis of radulanine A employed a similar rearrangement but here, the challenge lied on the aromatization step. Overall, these works show that the retro-Claisen rearrangement can be useful in total synthesis.[4]

Acknowledgements: French Ministry of Research, CNRS, *Institut Polytechnique de Paris*, Labex CHARM3AT, French Research Agency (RHOCKI project n° ANR-19-CE07-0012) for financial supports.

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P B008

Synthesis of Benzo[*c*][2,7]naphthyridinones and Benzo[*c*][2,6]naphthyridinones via Ruthenium-mediated [2 + 2 + 2] Cycloaddition between 1,7-Diynes and Cyanamides

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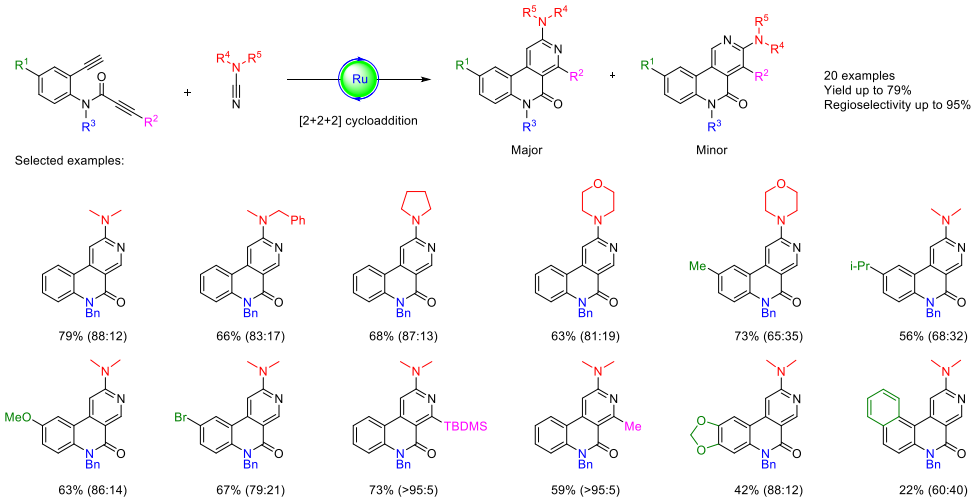
Benzo[*c*][2,7]naphthyridinones are privileged tricyclic motifs in various natural alkaloids and diverse organic chemicals.[1] These scaffolds exhibit great interest as biologically active molecules. Because of the increasing importance of benzo[*c*][2,7]naphthyridinone derivatives, several synthetic strategies have been developed over the last decades (e.g: cascade Suzuki-cyclization, palladium-catalyzed cross-coupling).

[2 + 2 +2] cyclization between alkynes and nitriles is a powerful method for the preparation of heterocyclic structures [2-4] and could represent an alternative synthetic route to access naphthyridinone derivatives.



A convenient method for the synthesis of benzo[*c*]naphthyridinone derivatives was described. The [2+2+2] cycloaddition of various mono- or di-substituted 1,7-diynes and electron-rich cyanamides in the presence of 2 mol % of ruthenium catalyst provided benzo[c]naphthyridinones with yields up to 79% and regioselectivities up to 95%. The versatility and the robustness of the reaction have been demonstrated by achieving gram scale synthesis and post-functionalizations.[5]

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P B009

Merging C–H Bond Activation and Rearrangements in Rh(III)-Catalysis: N-Heterocycle Synthesis from Nitroarenes

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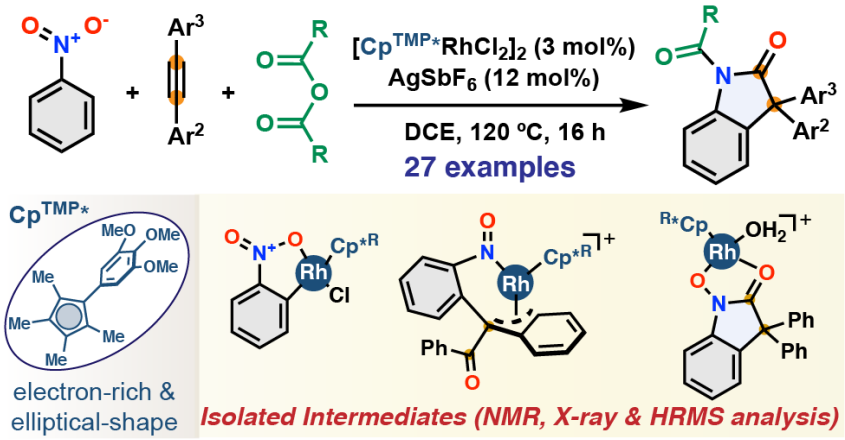
Nitrogen-containing heterocycles are of great importance to life science.[1] Therefore, their formations, manipulations, and diversifications represent a significant socioeconomic stake for chemical companies, and the discovery of novel synthetic approaches fulfilling modern reaction ideals of green chemistry is still an important challenge. Nitroarenes constitute interesting starting materials for the construction of *N*-containing molecules due to their low cost and ready access by nitration of bulk arenes.[2] To date, the modification of nitro compounds through C–H bond functionalizations are limited to single C–C bond formation and required post-functionalization of the nitro group to deliver heterocycles.[3]

In this project, a novel Rh(III)-catalyzed cascade reaction involving C–H bond functionalization – O-atom transfer and rearrangement from of nitroarenes, 1,2-diaryl alkynes and anhydrides will be presented. The reaction unexpectedly affords 3,3-disubstituted oxindoles containing an α-carbonyl quaternary center in a one-pot under redox-neutral conditions with a good functional group tolerance. A series of Rh(III) complexes were investigated leading to the development of a new functionalized cyclopentadienyl (Cp^{TMP})Rh(III) [Cp^{TMP} = 1-(3,4,5-trimethoxyphenyl)-2,3,4,5-tetratmethylcyclopentadienyl] catalyst which combines an electron-rich character and elliptical-shape. The mechanistic pathway was clarified with the isolation of three fully analyzed rhodacycles intermediates. Details of these mechanistic studies will be reported.



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P B010

Methanophosphocines: from unusual topologies to promising organocatalysts

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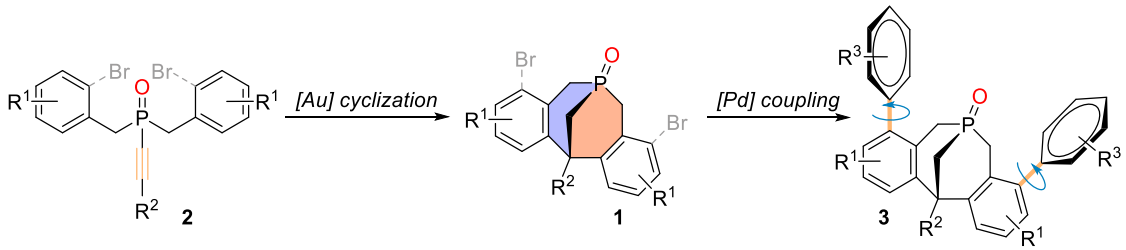
Conformationally restrained bridgehead phosphine oxide derivatives, such as 1-phosphabicyclo[3,3,1]-nonanes **1** (also called methanophosphocines) were originally described by Issleib in the late seventies. They were obtained through the radical cyclization of unsaturated and highly pyrophoric primary alkenylphosphines.[1] We reinvestigated such approach using gold-catalyzed double cyclization of bis(arylmethyl)ethynylphosphine oxides **2** to afford a collection of diversely substituted methanophosphocines.[2]

In the meantime, the last decade has seen the emergence of strained cyclic phosphine oxides as a novel class of organocatalysts. P(III)/P(V) redox cycling showed numerous applications from classic phosphine promoted reactions like Wittig olefination or Staudinger ligation to cascade or cross-coupling reactions. The best catalysts showed a clear tendency to narrow the heterocyclic core thus facilitating the rate limiting reduction step.[3] Nonetheless, significant efforts are still needed to increase their efficiency. In this context, conformationally restrained *P*-bridgehead methanophosphocines are yet to be explored and preliminary results clearly indicate that they could be a very promising core for P(III)/P(V) redox cycling.

To explore the potential of this new organocatalyst, a wide range of bis(biaryl) methanophosphocines **3** have been synthesized in moderate to high yields through a double Suzuki-Miyaura coupling between easily accessible dibromo derivative **1** and various arylboronic acids. Surprisingly, ortho-substituted unsymmetrical derivatives presented an original combination of axial and central chirality. Such unusual symmetry for 2,2' disubstituted systems and the corresponding chirality will be discussed based on both experimental and computational results.



[8 examples]
[4 steps from $NH_4.H_2PO_2$]

[6 examples][Strained phosphine oxides]
[P^{III}/P^{V} organocatalysis applications]

[14 examples][Atropochiral ligands]
[Computation and NMR study]

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P B011

Self-Sensitized Photooxidation of Hydroxynaphthalenes to Naphthoquinones and the use of Naphthoquinones as Visible-Light Photosensitizers

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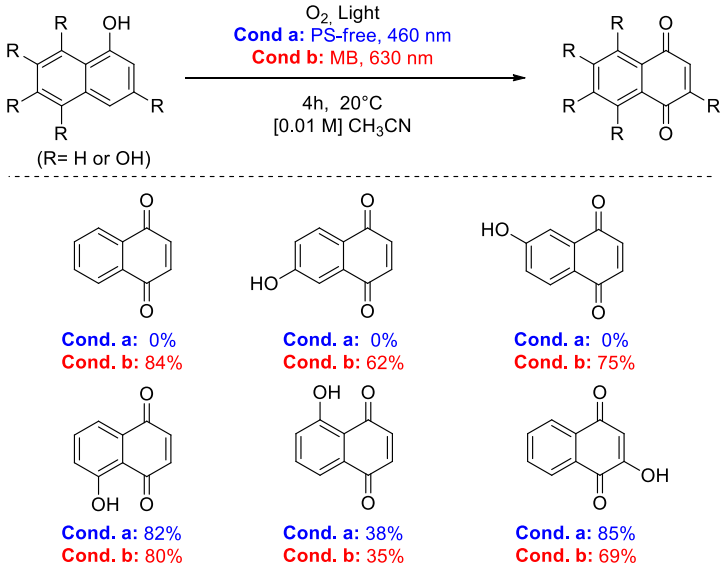
Photochemically generated $^1O2$ remains to date the most important industrial application of visible light photochemistry with well-known examples such as the production of the fragrance compound rose oxide from citronellol and the synthesis of the antimalarial drug artemisinin from dihydroartemisinic acid (***Scheme 1.A***).[1]
Visible-light photooxidations of naphthols to produce naphthoquinones, such as the natural product juglone, has been known for decades and has been widely utilized to benchmark the performances of a variety of photocatalytic systems. We discovered that naphthoquinone derivatives, such as juglone, and their naphthol precursors, such as 1,5-dihydroxynaphthalene, display photosensitization properties and are able to efficiently produce singlet oxygen upon photoexcitation with blue-light.[2] Spectroscopic characterizations indicate that juglone is a particularly attractive visible-light photosensitizer. This results in an intriguing and inherently greener self-sensitization process. The extrapolation from batch experiments to continuous flow reactors also demonstrates how this could translate into a more environmentally benign alternative to commonly used organic and organometallic photocatalysts.



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P B012

Molecular probes to isolate DLODPs, orphan enzymes involved in the dolichol cycle

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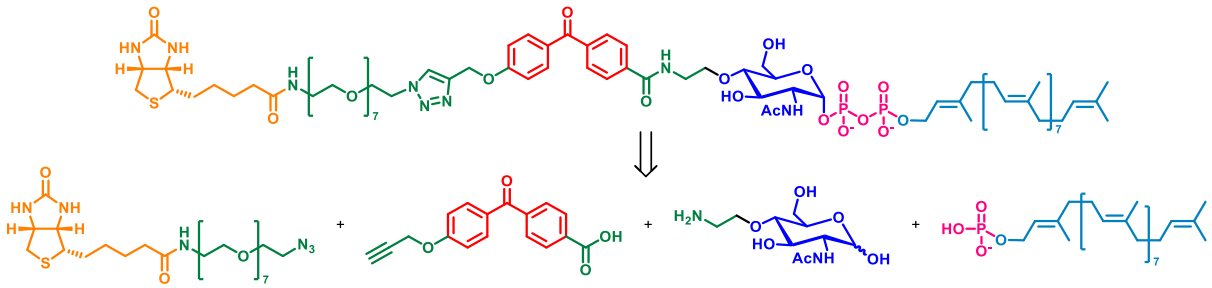
In man, *N*-glycosylation of glycoproteins involves the synthesis of a complex oligosaccharide, linked by a diphosphate to a lipid carrier (dolichol), followed by its transfer onto the amine of a nascent protein. Mutations in genes required for the synthesis of this dolichol-linked oligosaccharide (DLO) or the transfer of its oligosaccharide onto proteins provoke accumulations of phosphorylated truncated DLO intermediates and hypoglycosylated proteins. They are hallmarks for rare diseases called Type I Congenital Disorders of Glycosylation (CDG I) that can affect different organs.[11]

DLO diphosphatases (DLODPs) cleave the diphosphate of truncated DLO resulting in the formation of truncated oligosaccharides phosphates which are characteristic of CDG. We hypothesize that DLODPs destroy toxic truncated DLO intermediates, which are generated under pathological conditions like CDG-I, that would otherwise cause cell pathology.[2]

In order to identify DLODP genes and test this hypothesis, our goal is to synthesize a biotinylated probe with which to prepare affinity matrices for DLODP purification.[3] This affinity probe (Figure), able to generate a covalent bond with the diphosphatase is based on a substrate analog[4] for protein recognition, a photo-activable anchor, that will establish a covalent linkage with the protein after irradiation and a biotin moiety allowing immobilisation of the probe on streptavidin-based matrices. Recent results towards the synthesis and activity of these probes will be discussed.



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P B013

Heterogeneous photocatalysis in flow: continuous synthesis α-acylaminoamides

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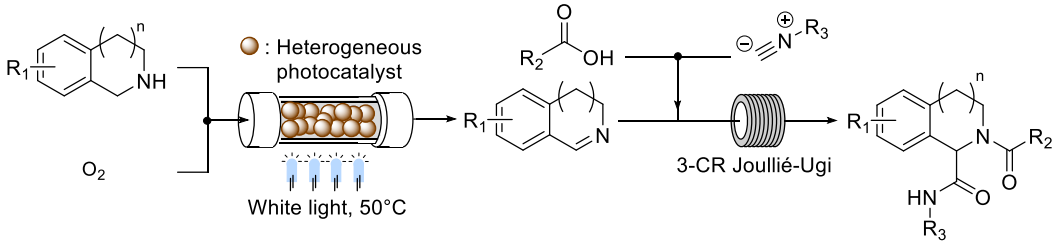
Over the last two decades, photoredox catalysis has become a powerful and versatile tool that provides synthetic chemists with a greener and safer way to achieve radical processes. This chemistry has initially been developed using highly efficient Ru and Ir based homogeneous photocatalysts[1,2]. What with the sky-high costs and poor recyclability of these rare-earth metal complexes, there is a growing need to find more sustainable alternatives and further expand the synthetic applicability of light-driven organic reactions.

In this context, the development of easily recyclable and efficient heterogeneous photocatalysts appears as an ideal solution. However, heterogeneous photocatalysis remains a daunting task because of light penetration issues within solid materials which decrease drastically the resulting photocatalytic activity. To overcome this limitation, one solution is to exploit semi-conductors as light-sensitive solid supports. Indeed, appropriately designed semi-conductors with band-gaps corresponding to the visible range can, upon light irradiation, form active sites (electron-holes pairs) enabling electron shuttle throughout the whole material[3].

By exploiting this concept, this presentation will emphasize our efforts for the development of semi-conductor-derived heterogeneous photocatalysis with a special focus on continuous-flow reactions using single-pass packed bed reactors. Specifically, we will describe our investigations on the direct oxidation of amines into imines under aerobic conditions in flow[4] using a conjugated porous polymer doped with immobilized Rose Bengal. Applications towards multistep flow synthesis of α-acylaminoamides *via* a three-component Joullié-Ugi protocol will also be depicted.



Scheme. Continuous-flow formation of α-acylamino-amides.

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P B014

Efficient Synthesis of Nucleoside Mimics as Potent DltA Inhibitors

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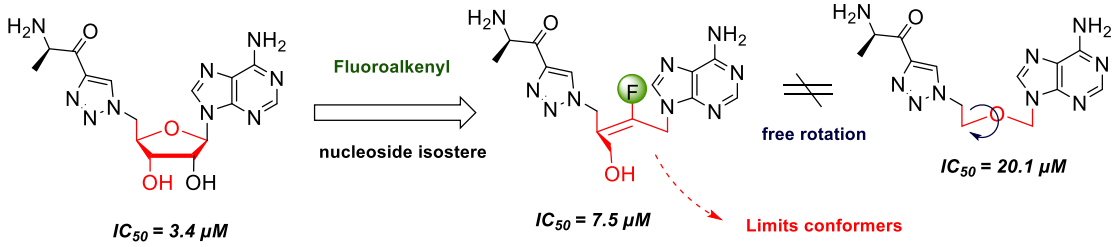
The emergence of the phenomenon of antibiotic resistance favoured by the action of bactericidal antibiotics exerting microbial stress, would prevent antibiotics of the glycopeptide or beta-lactam type from penetrating and fixing on the cell membrane.[1] It has been shown that antibiotic resistance in bacteria to GRAM + was due to a process of D-Alanylation of teichoic acids (LTA) leading to a structural modification of the outer wall and the electronic density of the bacterial membrane with anionic character.[2]

Following these results,[3] different series of DltA inhibitors have been developed through polyfunctional syntheses allowing access to highly functionalized fluorinated acyclonucleoside analogues. The approached strategy is based on a structural modification of the nucleoside by the introduction of a fluorine atom on the trans butenyl moiety allowing the development of highly functionalized tetra-substituted fluoroalkenes.[4] Access to the ribosyl mimetic has been possible through various synthetic methodologies including the aza-Michael reaction, followed by highly regioselective opening of fluorinated alkylidene-oxetane to obtain 1,2,3-triazolylcarbonucleosides. Adenosine fluoroalkenyl derivative was evaluated towards DltA enzyme as nucleoside mimic. This study demonstrated the structural analogy of the fluorobutenyl moiety with the ribosyl ring in order to increase the activity of acyclic derivatives.



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P B015

Molecular tweezers for multifunctional switchable organogels

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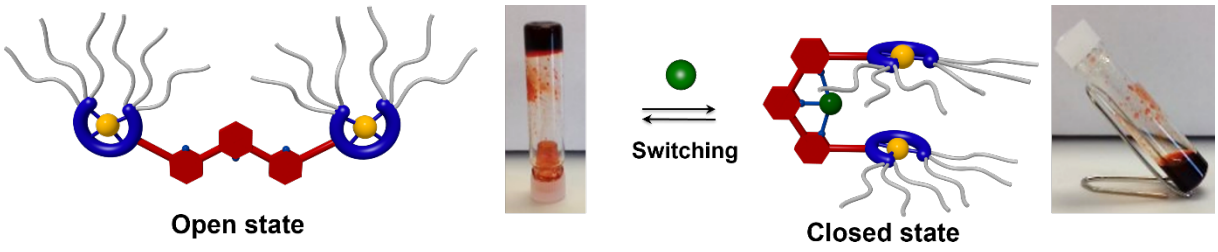
Organogels are a particular class of gels that result from the self-assembly of low molecular weight gelators (LMWG) into fibrous networks trapping solvent molecules. This new type of soft materials has attracted great interest due to their potential applications as smart materials.[1] The recent development of molecular machines and among them molecular switches has allowed the design of controlled dynamic multi-state molecular systems.[2] We are currently interested in exploiting the mechanical motion of molecular switches to develop multifunctional switchable organogels.

In the past years, we have developed stimuli-responsive molecular tweezers composed of a terpyridine switching unit and of M-salen functional units with properties depending on the complexed metal ion. The coordination-induced closing-opening motion of the system has been used to modulate various physico-chemical properties (luminescence, catalysis, magnetism, …) with remarkable versatility.[3-6] Herein we report a new class of tweezers functionalized by C_{12} akyl chains as gelling groups. The large structural reorganization driven by the motion results in reversible sol-gel transition by promoting inter- or intramolecular interactions between the tweezers depending on their conformation. The synthesis of these platinum-based molecular tweezers and the studies of their reversible gelation properties will be presented.



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P B016

Synthesis of *C*-Aryl ketosides by Fries-type rearrangement of *O*-Aryl ketosides

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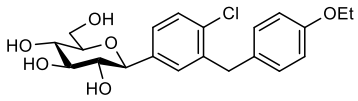
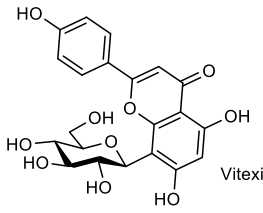
C-aryl glycosides constitute an important family of biologically active compounds with a large panel of therapeutic potential including antidiabetic, antibiotic, antiviral and antitumoral activities.[1] Several synthetic methodologies have been reported for the synthesis of this class of compounds.[1,2] However the formation of *C*-aryl ketosides, characterised by the presence of a quaternary pseudoanomeric centre is challenging and few examples of synthesis of these compounds have been reported in the literature. We have recently studied the formal glycosylation of quinones with *exo*-glycals *via* a metal-mediated hydrogen atom transfer yielding *O*-aryl ketosides[3]. Conversion of these products into *C*-aryl ketosides by Fries-type rearrangement catalysed by Lewis acid will be presented.[4] To our knowledge, this reaction has no precedent for the synthesis of bis-*C*,*C*-glycosyl compounds.

Examples of biologically active *C*-aryl glycosides

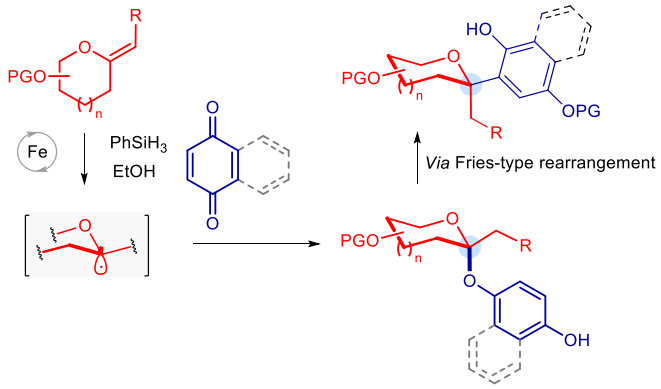


Dapagliflozin (antidiabetic)



Vitexin (thyroid peroxidase inhibitor)

Proposed methodology for the synthesis of challenging *C*-aryl ketosides



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P B017

Tuning the reactivity of transition metal ions with divalent lanthanide complexes: applications to catalysis

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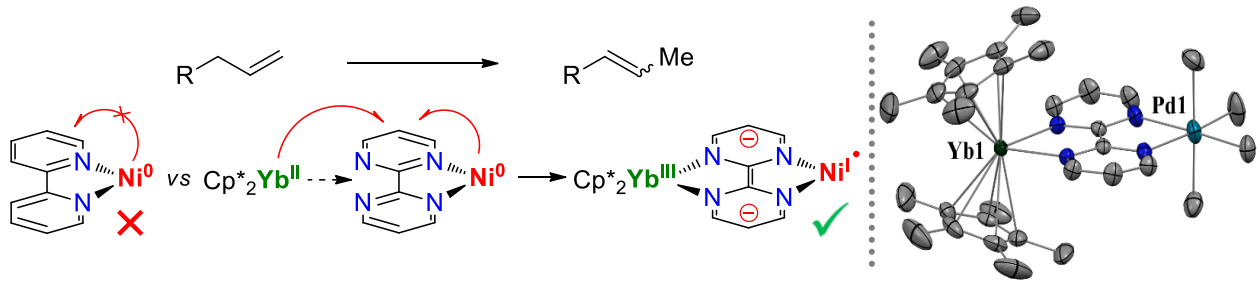
With the expansion of the organic synthesis needs in terms of synthetic protocol efficiency or new reactivity, the understanding of organometallic chemistry is always pushed further and the precise study of reactive transition metal complexes at various oxidation states is of high importance to keep renewing the textbooks.[1]

With this idea, our research group has been studying heterobimetallic complexes combining a divalent lanthanide (Ln) and a transition metal linked by a redox active ligand (RAL). The aim is to observe the impact of the divalent 4f-ion on the d-block metal center's reactivity.[2]

In these systems the RAL's ability to accept an electron from the reductive divalent lanthanide center[3] has already led to clear evidence that the resulting electronic density impacts the transition metal's behavior:[4] the Ln-RAL fragment influences the stabilization of key step intermediates at different oxidation states, thus expanding our reach in terms of reactivity tuning.

This presentation will be focused on our most recent advancements concerning the understanding and the use of this cooperative architecture with, on one hand, its application to low-valent nickel catalyzed alkene isomerization through an electron shuttle type of mechanism and,[5] on the other hand, the synthesis and isolation of the first tetraalkyl Pd(IV) system which led to envision catalytic alkyl-alkyl cross-coupling reactions.



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P B018

Merging photoredox catalysis and ball-milling for a brighter future

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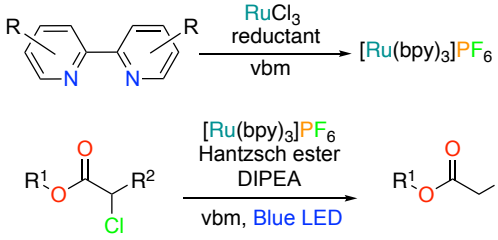
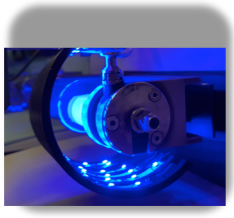
One of the challenges of the 21st century is to develop sustainable chemistry. In this context, we recently merged two approaches that both have benefits in terms of respect of the environment, namely photoredox catalysis and ball-milling. Indeed, in 2019, IUPAC recognized mechanochemistry as one the ten technologies that could change our future.[1] Thus, in continuation of our work on the facilitated access to coordination complexes,[2] we developed the expedient mechanosynthesis of photoredox ruthenium catalysts featuring different substituted bipyridines. Complexes $[Ru(N\text{-}N)_3](PF_6)_2$ could be obtained in high yields and short reaction times. These complexes were then evaluated in the photoredox reductive dehalogenation reaction,[3] which is an alternative to tin-promoted methods, under ball-milling conditions. Mechanophotoredox reaction could be performed under solvent-less conditions, using tiny amount of solvent as liquid assistant, in short times compared to literature conditions.

Mechanosynthesis of photoredox catalysts and reductive dehalogenation





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P B019

Glucosinolates anchoring on surfaces, first approaches

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Glucosinolates are sulfur-containing secondary metabolites whose structures are based on a β-D-glucopyranose unit linked through an *O*-sulfated (*Z*)-thiohydroximate function to a variable aglycon. Found in the cruciferous vegetables, such as broccoli, mustard, arugula, wasabi, they play an important role in the defence mechanism of these plants against potential predators. Hydrolysis of the anomeric C-S bond by myrosinase, a specific β-thioglucohydrolase, leads to the formation of isothiocyanate species (ITC). The result is a shift from stable, non-toxic, and water-soluble precursors to a toxic, highly reactive, difficult to prepare and store, and in most cases, water-insoluble function.[1] This unique enzyme-substrate system in nature can be explored as a novel tool for various applications.[2] Herein, we want to describe our recent approaches on the synthesis, and reactivity of various surfaces design to anchor artificial glucosinolates as smart surface against bacteria. We also showed that those glucosinolates are substrates of myrosinase and can be hydrolysed into their corresponding ITCs and thus be useful reagent in conjugation.

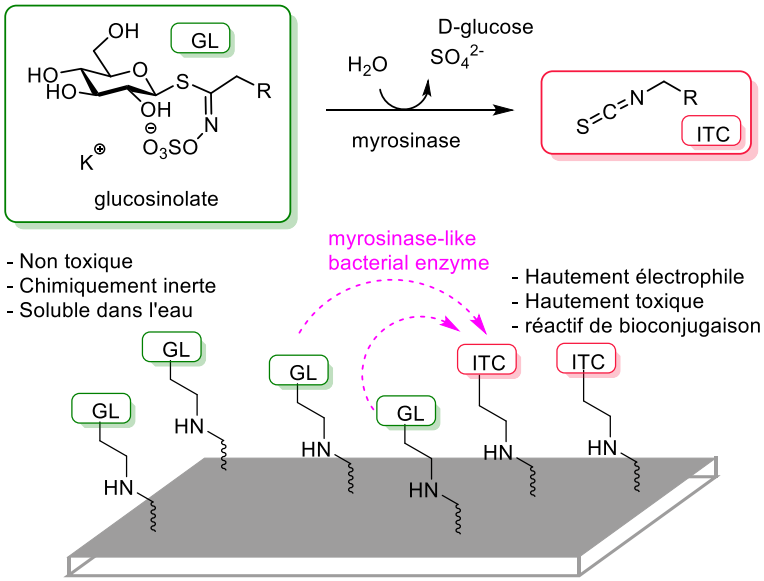

Figure 1. Myrosinase-Glucosinolate system to generate isothiocyanates

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P B020

Copper-Catalyzed 1,4-Carboalkynylation of 1,3-Dienes Using Diaryliodonium Salts as Radical Precursors

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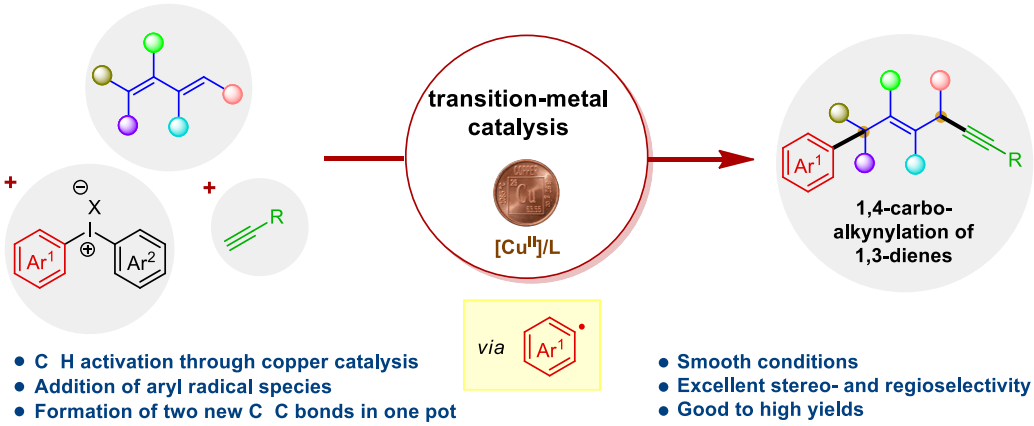
1,3-butadiene, an abundant raw material in the chemical industry, is produced on a multiton scale every year and obtained from petroleum cracking.[1,2]The direct conversion of this inexpensive feedstock chemical into diverse and valuable compounds represents an attractive strategy from an environmental and economical perspective.[3] Over the past decade, the transition-metal-catalyzed difunctionalization of 1,3-dienes, mostly through transformations involving π-allyl metal intermediates, has been extensively studied.[4] Although noticeable progress has been achieved in this domain, the selective dicarbo-functionalization of unactivated 1,3-dienes in a single step is an ongoing challenge, especially for radical processes.[5] In this context, a new methodology has been developed to generate two C–C bonds in a one-pot process, from C–H bond activation and using transition metal complexes. Unprecedently, 1,3-butadiene was functionalized with monosubstituted alkynes and various radical precursors such as diaryliodonium salts, to deliver the corresponding 1,4-enyne products.



This newly developed multi-component methodology couples three different substrates under smooth reaction conditions (no photo-mediated reaction, room temperature), shows high functional group tolerance, and provides facile formation of two C–C bonds in a one pot process. The 1,4-enyne products were obtained in good to high yields, and excellent stereo- and regioselectivity.

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P B021

Synthesis of boranes and diphosphines from chloroboranes and chlorophosphines by hydrogenolysis

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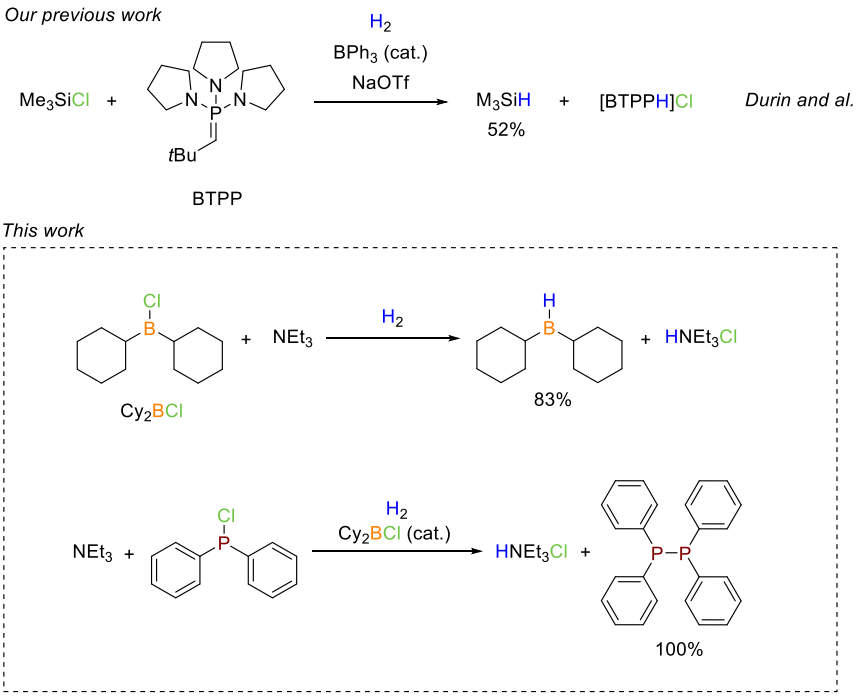
New challenges in chemistry requires to improve the preparation of common reagents; reductive agents, especially hydride compounds present a strong interest in the Carbon Circular Economy (CCE) perspectives. We developed several reactions to achieve the synthesis of hydride of main group elements by hydrogenolysis of chlorinated derivatives. Our group showed the formation of silanes (Si–H) from chlorosilanes (Si–Cl) and H_2 with a boron catalyst.[1] Further investigations on the reactivity led us to develop the first example hydroboranes synthesis by H_2 activation followed by the cleavage of the B-Cl bond to lead products in quantitative yields. We suspect that activation of H_2 operating through a Frustrated Lewis Pair (FLP) mechanism between the boron and a base, leading to a cleaner reaction with the protonated base as sole by-product contrary to reported methods that involves an exchange with BH_3.[2] The boranes thus synthesized are very useful reductants and hydride sources. This methodology was applied to the synthesis of phosphines from chlorophosphines by boron-catalyzed H_2 activation followed by H/Cl metathesis step. These new examples of main group elements hydrogenolysis open a path to various E-H type compounds without the use of strong reductants usually described.



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P B022

Preparation and reactivity of α-silylated diazoalkynes

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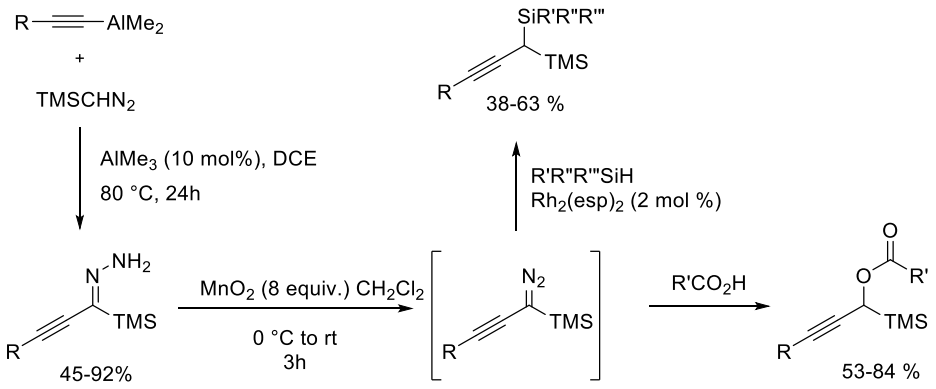
One of the research axes of our group is devoted to study the reactivity of dimethylalkynylaluminum compounds,[1] prepared in non-coordinating solvents in batch or flow conditions, [2] allowing to take advantage of their enhanced Lewis acidity and reactivity.[3,4] We have reported that these reagents can react in an unusual manner with trimethylsilyl diazomethane (TMS-diazomethane), affording α-silylated alkynyl hydrazones.[5] Treatment with MnO_2 of this completely new class of compounds provides the corresponding α-silylated diazoalkynes, a new class of compounds that presents an interesting reactivity.

These compounds can act as precursors for the preparation of metal carbenoids that cleanly insert into Si-H bonds, leading to unusual bis-silylated alkynes.[6] We will report more classical metal-free reaction of O-H Insertion with carboxylic acids, either in organic medium to afford interesting class of α-acyloxy-α-alkynyltrimethylsilanes[7] or in buffer to selectively functionalize peptides or proteins.



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P B023

Fluorogenic borinic acid-based probes for efficient hydrogen peroxide detection

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Reactive Oxygen Species (ROS) are involved in many physiological processes. Hydrogen peroxide (H_2O_2), which is the most stable ROS, plays a major role as signaling molecule in several biological mechanisms.[1] However, its overproduction or accumulation (oxidative stress conditions) can be responsible for cellular lesions associated with aging, cancers or neurodegenerative diseases such as Alzheimer's or Parkinson's.[2] Thus, its detection could help for a better understanding of its role in these processes.
Many fluorescent molecular probes based on various triggers have been developed to allow the detection of H_2O_2.[3] The laboratory has shown that H_2O_2-mediated oxidation of arylborinic acids is dramatically faster than the commonly used boronic acid triggers (Figure 1, A).[4] We recently designed a new H_2O_2-selective fluorogenic probe, possessing a borinic acid as trigger and a 4-methylcoumarin as pro-fluorescent moiety.[5] However, this probe must be optimized for the detection of endogenously produced hydrogen peroxide for biological application.
Therefore, we present herein the synthesis of new optimized probes in terms of photophysical properties and the preliminary results for *in vitro* H_2O_2 detection (Figure 1, B).

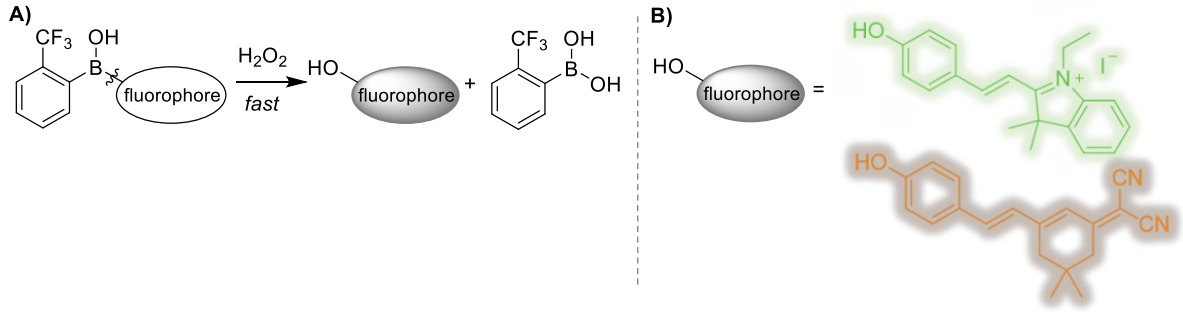

Figure 1: A) H_2O_2-mediated oxidation of borinic acid; B) Fluorophores used in this work.

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P B024

CyClick: A Click Approach for Copper-Catalyzed Construction of Drug-like Macrocyles

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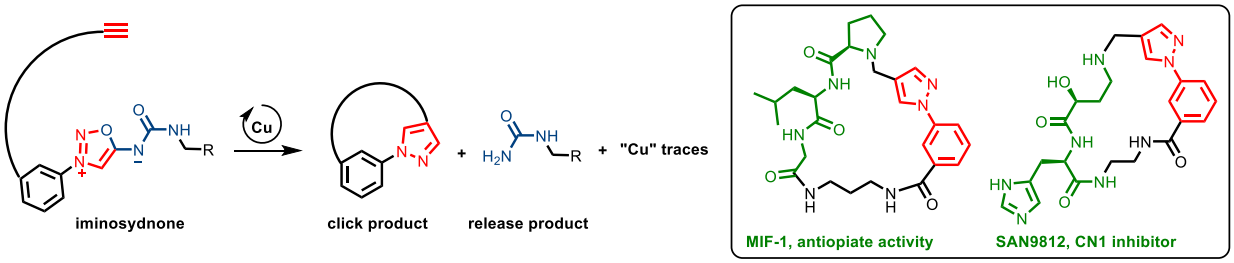
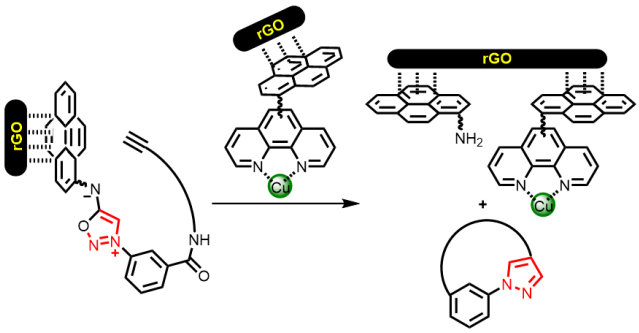
Cyclic drugs, in particular cyclic peptides and pseudo-peptides have recently received considerable attention in the pharmaceutical industry. Their structural preorganization compared to their linear counterparts provide them with high biostability, cell permeability and enhanced potency.[1] However, despite their importance, the synthesis of cyclic compounds remains challenging, with the difficile preparation of linear precursor and tedious purifications. Our laboratory have been working on the discovery of new biorthogonal tools and developed a click and release reaction of iminosydnones with cycloalkynes for protein modification, drug release and target-fishing applications.[2] Based on the recent developments of a new "click and release" reaction using a copper catalyst and aza-iminosydnones,[3] we decided to investigate the intramolecular macrocyclization of peptides using iminodydnones (Scheme 1).



***Scheme 1**: Cu-catalyzed click & release reaction leading to targeted macrocyclised compounds*

Preliminary results show limitations such as challenging purifications of the click and release products and the presence of copper traces associated with the cyclic product. One approach to overcome these problems is to develop a click type, Cu-catalyzed intramolecular cyclisation as a key step and the use of non-covalent immobilization (π-stacking) of pyrene-tagged catalysts and reactant on carbon supports like rGO (reduced Graphene Oxide) for easy removal and recovery (Scheme 2).[4]



***Scheme 2**: Supported intramolecular Cu-catalyzed click&release*

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P B025

White LED initiation of Sonogashira cross-coupling with a photo-caged triphenylphosphine

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[1] *Photophysique et Photochimie Supramoléculaires et Macromoléculaires (PPSM), Université Paris-Saclay, ENS Paris-Saclay, CNRS, 4 avenue des Sciences, 91190, Gif-sur-Yvette (France)*

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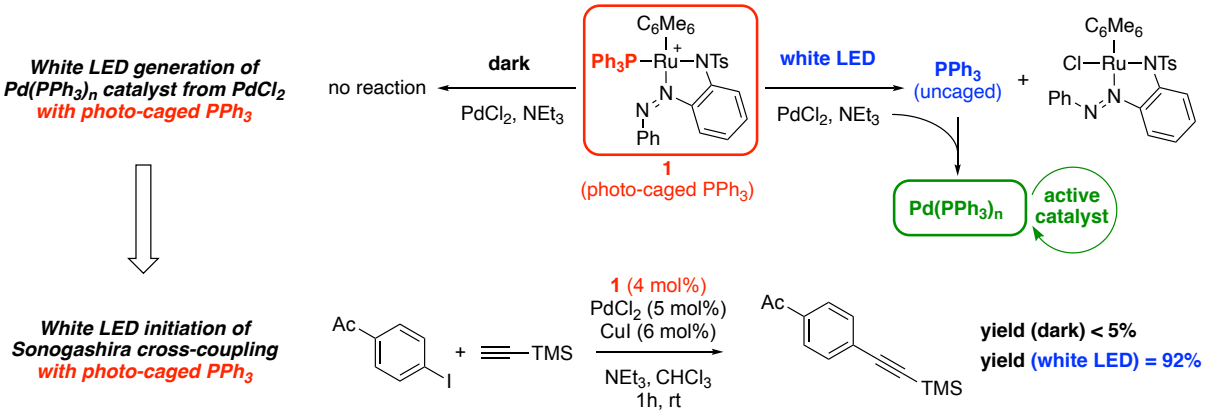
The photo-release of a chemical entity, often referred as "photo-uncaging", is a conceptually and practically simple process for the unidirectional and irreversible generation of active species. It has been employed since the late 1970s for the control of biological processes, and more recently for the construction of polymeric materials and the induction of catalytic transformations.[1]

Taking advantage of our previously reported complex **1**[2] (one of the very few examples of photo-caged phosphine) we recently succeeded in promoting the photo-controlled activation of $Pd^{II}Cl_2$ into catalytically competent $Pd^0(PPh_3)_n$ and subsequent initiation of Sonogashira cross-couplings. The system described herein makes use of simple white LED strip lights without a need for sophisticated photochemistry apparatus and allows high temporal response and fine tuning of cross-coupling kinetics according to irradiation time.[3]

The results of our mechanistic investigations regarding active catalyst generation, as well as a detailed description of substrate scope for cross-coupling will be presented.



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[3] Rocard, L.; Hannedouche, J.; Bogliotti, N. Visible-Light-Initiated Palladium-Catalyzed Cross-coupling by PPh_3 Uncaging from an Azobenzene Ruthenium–Arene Complex. *Chem. Eur. J.* **2022**, *28*, e202200519. https://doi.org/10.1002/chem.202200519.

P B026

Synthesis of both anomers of constrained *C*-glycosidic analogues of Tn antigen.

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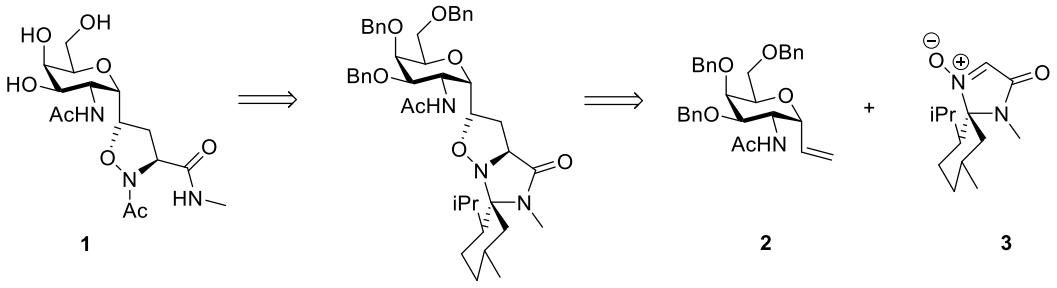
Tumor associated carbohydrate antigens (TACAs) are highly present on cancer cells, but almost no detectable on normal cells. Therefore, these components are of great interest as therapeutics targets, particularly in anticancer vaccines. By incorporating such structures into this kind of vaccine, the immune system should produce a more efficient response against cancer cells. However, the chemical instability of the *O*-glycosidic link in biological system towards glycosidases presents a major downside of their use in this purpose.[1] The replacement of the glycosidic bond is well known to afford more stable analogues such as *C*-glycosidic ones. Furthermore, constrained analogues of Tn antigen in vaccine could improve the anticancer immune response.[2]

Very recently we focus our attention on the synthesis of original constrained *C*-glycosidic analogues of the Tn antigen. For that, a synthetic strategy based on a [3+2] cycloaddition between a *C*-vinylGalNAc **2** and a chiral cyclic nitrone **3** has been developed (scheme 1). This key step provided access to constrained *C*-glycosidic analogues stereoselectively and regioselectively controlled[3]. The synthesis of the main compound **1**, including the [3+2] cycloaddition will be presented.



Scheme 1 - Retrosynthetic scheme

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[2] Nativi, C.; Papi, F.; Roelens, S. *Chem. Commun.* **2019**, *55* (54), 7729–7736.
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P B027

C-N Bond Formation Via Odet Strategy

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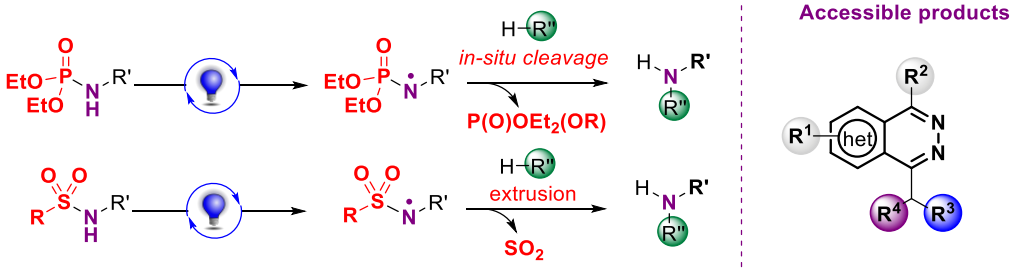
Since the early beginning of organic chemistry, the synthesis of nitrogen-containing heterocycles constantly attracted the interest of the chemistry community. Indeed, their ubiquitous presence in natural products lead to the development of several strategies to build them. [1] Until now, despite many synthetic efforts, many useful structures are still unattainable. For instance, phthalazine structures are one of the less explored scaffolds and therefore development of new synthetic methods is still desirable.

In this aim, we focused our research projects on the development of new photoredox strategies to build the carbon-nitrogen bond.[2] The search of new precursors able to generate efficiently a nitrogen centered radical intermediate is thus highly needed. This kind of intermediate is indeed attractive because it can be then added on unsaturated derivatives for instance and thus lead to the CN bond formation.

In our laboratory we tried to develop phosphono- and sulfono-hydrazone precursors in order to build interesting heterocyclic scaffolds. Starting from simple ortho-alkynylbenzaldehyde patterns, already well-mastered in our group towards silver catalysis,[3] we thought to develop a new photoredox cyclization reactions leading in one step to phthalazine derivatives.[4] Thanks to this new reaction, many useful phthalazine derivatives are now accessible.

Mechanistic studies, scope and limitations of these methods will be presented.



Scheme 2 : strategies for C-N bond formations

[1] a) A. Brancale, R. Silvestri, Med. Res. Rev. 2007, 27, 209.b) G. Zeni, R. Larock, Chem. Rev. 2004, 104, 2285.
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P B028

Enantioenriched allylsilanes: preparation through Cu-free S_N2' catalyzed addition of Grignard reagents

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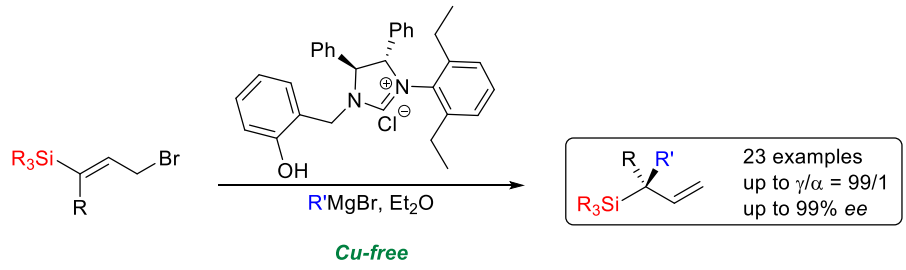
Allylsilanes are very useful and versatile structures extensively used in organic synthesis with a large number of applications on it.[1] Their bench-stability and easy-handling along with their low toxicity and functional group tolerability, allow them to occupy a unique place in the armory of the organic chemist. Furthermore, as they can undergo a great variety of silicon transformations such as cross-coupling reactions or ring-close and cross-metathesis processes, and because they are suitable substrates to perform stereocontrolled C-C bond formations, for instance the enantioselective addition of allyl patterns to electrophiles such as carbonyl groups or imines (representing a complementary method to the enolate based aldol reaction),[1a,2] its enantioselective synthesis has attracted wide attention, especially in the last 35 years, where deep investigations have been carried out and several reliable reaction protocols developed. Since Hayashi and Kumada reported the first preparation of enantioenriched allylsilanes in 1982,[3] many other synthetic strategies had been unveiled based in Pd-catalysis, Claisen rearrangement, Asymmetric Allylic Alkylation (AAA) or Asymmetric Allylic Silylation (AAS) methods among others.
However, the increasing demand for these molecules and the lack of a general established method to access optically active allylsilanes with good regio- and enantioselectivity, bearing tertiary and quaternary stereogenic centers, that allows facile modification of silyl moieties and other substituents, encourages us to develop a new synthetic strategy. Based on previous results published by Alexakis *et al.* we developed our method on the basis of a Cu-free asymmetric alkylation of Si-substituted allylic electrophiles with Grignard reagents in the presence of a chiral *N*-Heterocyclic Carbene (NHC). The scope and limitations of this new enantioenriched allylsilane preparation by a copper-free AAA will be presented and discussed.



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P B029

Synthesis of TMM analogs for the study of protein mycoloylation in *Corynebacteriales*

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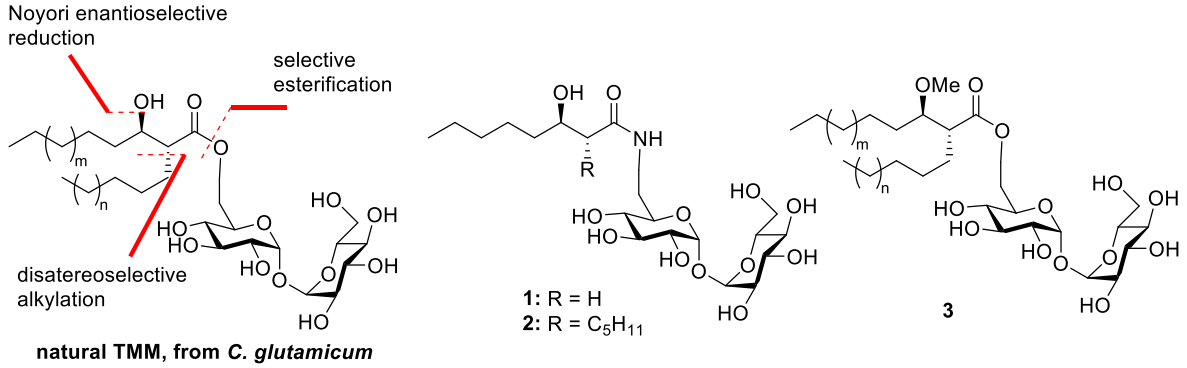
paulin.rollando@universite-paris-saclay.fr

Corynebacteriales are a family of Gram-positive bacteria including *Mycobacterium tuberculosis*, the etiologic agent of human tuberculosis. *Corynebacteriales* are highly resistant towards chemotherapeutic molecules and this exceptional resistance might be due to their particular outer membrane, called mycomembrane. This rigid membrane is composed of specific fatty acids (mycolic acids) esterified to an arabinogalactan complex and to trehalose, a symmetrical disaccharide. Mycolic acids are long α-ramified and β-hydroxylated fatty acids produced in the cytoplasm and then transferred to trehalose, leading to trehalose monomycolate (TMM). TMM acts as a donor of mycolate in the biogenesis of the mycomembrane. Indeed, TMM is processed by enzymes, called mycoloyltransferases (Myt), and its mycolate moiety is transferred to another TMM (giving rise to trehalose dimycolate (TDM)) or to arabinogalactan. Recently one mycoloyltransferase (MytC) was identified to be responsible of mycoloylation of small membrane proteins (porins) in *Corynebacterium glutamicum*.[1] This is a unique post-translational modification in bacteria.
Our laboratory is interested in the chemical synthesis of molecular tools for the study of the biogenesis of the mycomembrane,[2] and one of our projects is to synthetize a large collection of TMM analogs in order to get insight in the mycoloylation mechanism of porins in *C. glutamicum*. The enantio- and diastereocontrolled synthesis of the three TMM analogs **1**, **2** and **3** will be presented.



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P B030

Noncanonical Strigolactone Analogues Highlight Selectivity for Stimulating Germination in Two *Phelipanche ramosa* Populations

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[2] *6 rue Louis Lumière (Hemp-It ADN, 49250, Beaufort en Vallée, France)*

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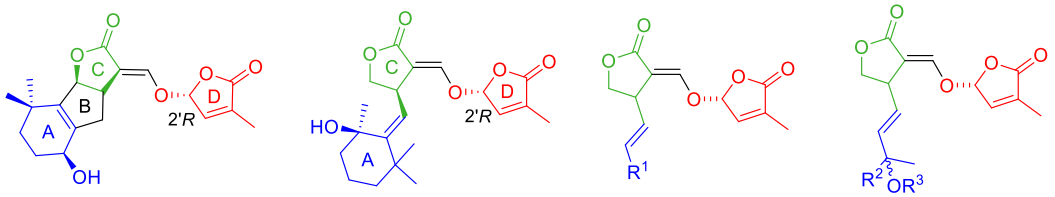
Strigolactones (SLs) are the ninth class of plant hormones[1]. They control the shoot and root plant architecture. They are also exuded in the rhizosphere where they have a signaling role for the development of arbuscular mycorrhizal (AM) fungi[2] and as stimulants of seed germination of the parasitic weeds *Orobanche*, *Phelipanche*, and *Striga*[3], the most threatening weeds of major crops worldwide. *Phelipanche ramosa* is present mainly on rape, hemp, and tobacco in France. *P. ramosa* 2a preferentially attacks hemp, while *P. ramosa* 1 attacks rapeseed.

There are two types of SLs[4]: canonical SLs (as strigol) have au tricyclic lactone ABC as structural core, noncanonical SLs as for them, present an unclosed BC-ring. The main structure is connected via an enol ether bridge to an invariant α,β-unsaturated furanone moiety (D-ring). All natural SLs have the same *R*-configuration at the C-2' position.

The recently isolated cannalactone from hemp root exudates has been characterized as a noncanonical SL that selectively stimulates the germination of *P. ramosa* 2a seeds in comparison with *P. ramosa* 1.

In this communication, the synthesis of two cannalactone analogues types and their biological evaluations will be presented. (±)-SdL analogues are able to selectively stimulate *P. ramosa* 2a, revealing that these minimal structural elements are key for this selective bioactivity.



Strigol | **Cannalactone** | **Type I analogues** | **Type II analogues**

(±)-SdL

R^1= H, CO_2Me

(±)-SdL

R^2= Me, Cyclopropyl

R^3= H, Me_3Si

[1] Gomez-Roldan, V.; Fermas, S.; Brewer, P. B.; Puech-Pages, V.; Dun, E. A.; Pillot, J.-P.; Letisse, F.; Matusova, R.; Danoun, S.; Portais, J.-C.; Bouwmeester, H.; Bécard, G.; Beveridge, C. A.; Rameau, C.; Rochange, S. F. *Nature* **2008**, 455, 189−194.

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P B031

Transition-Metal-Free Silylation of Unactivated C(sp^2)–H Bonds with *tert*-Butyl-Substituted Silyldiazenes

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Aromatic organosilanes bearing C(sp^2)–Si bonds have found increasing applications across the chemical science and have traditionally been synthesized from the corresponding arylhalides (bromide or iodide). The direct intermolecular silylation of C(sp^2)–H bonds represents an atom-economical alternative as it bypasses the substrate pre-functionalization step, yet poses significant reactivity and selectivity challenges. In this respect, the most common strategy still relies on stoichiometric C–H metalation/silylation sequences mediated by organolithium (RLi) or Grignard reagents (RMgX), which nonetheless generate large amount of metallic wastes and display limited scope of application.

Catalytic protocols, mostly using hydrosilanes (R_3SiH) as silicon sources, have also been described,[1] but they display unfavorable thermodynamics and are typically based on expensive catalytic systems, often derived from noble metals, or lack generality.[2] In this communication, we will introduce the use of an alternative silicon source, namely the *tert*-butyl-substituted silyldiazenes (*t*Bu–N=N–SiR_3), that are readily accessible from commercially available precursors and structure of which enables the C(sp^2)–H bond silylation of unactivated heteroaryl and aryl compounds under ambient, transition-metal-free catalytic conditions.[3] Conceptual implications as well as mechanistic considerations will be discussed along with the synthetic potential of this new methodology.

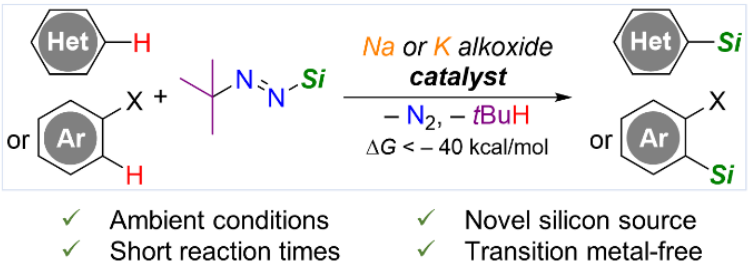

Figure 1: Silylation of unactivated C(sp^2)–H Bonds with tert-butyl-substituted silyldiazenes catalyzed by potassium or sodium alkoxides.

[1] For recent reviews, see: (a) Cheng, C.; Hartwig, J. F. Catalytic Silylation of Unactivated C-H Bonds. *Chem. Rev.* **2015**, *115*, 8946–8975. (b) Richter, S. C.; Oestreich, M. Emerging Strategies for C–H Silylation. *Trends Chem.* **2020**, *2*, 13–27.

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P B032

Photosensitive Bimetallic Complexes Base on Cyclodextrin

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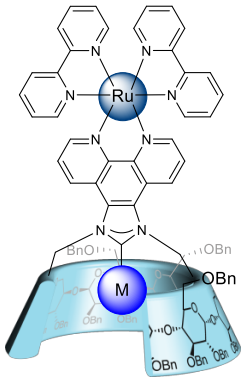
Bimetallic ruthenium complexes have been developed as photosensitive catalysts along with other transition metals[1,2]. These types of compounds could be applied in many realms, exhibiting great prospects[3-5]. Previously our group reported series of NHC-modified metallic cyclodextrins (CD) and their steric selective catalytic effects which derive from the size of CD[6--9]. We envisage that electron communication, which could be manipulated by many means such as irradiation, between two metals in conjugated bimetallic complexes could influence the catalytic process of the transition metal center situated inside the cavity. In this project, we aim to combine the photosensitivity of ruthenium complex and the steric selectivity of the CD, synthesizing a bimetallic complex to catalyze reactions through a light control. Thus, we hope to control the catalytic process and obtain specific reactions due to the CD steric selectivity.



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P B033

A new synthetic route towards racemic Phytofurans

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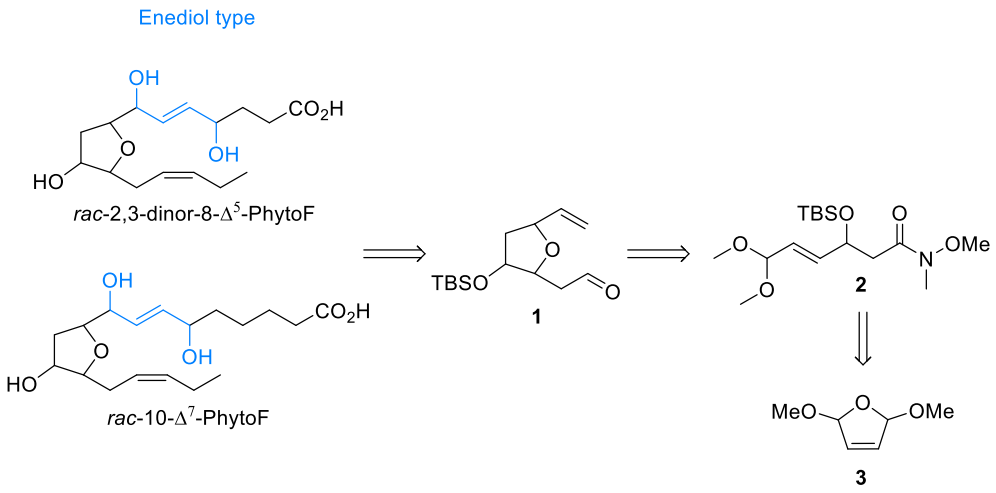
Isofuranoids are natural products discovered in 2002 by Fessel *et al.,* formed from the peroxidation of polyunsaturated fatty acids (PUFAs).[1] Two types of isofurans (IsoFs) were isolated: the alkenyls and the enediols. Their biological roles are still unrecognized even though they are known as biomarkers of oxidative stress in vertebrates and plants. Isofuranoids are preferentially formed when the tension of oxygen is high, such as in Parkinson disease or reperfusion. Thus, they could be specific biomarkers of such diseases.
Four asymmetric strategies to access isofuranoids have been developed by Taber, Zanoni and our group, but they remain long and/or complex especially for the preparation of the 2,3,5-substituted tetrahydrofuranic core.[2] To this end, our new strategy permits to obtain the cyclic core, in 7 steps from commercial 2,5-dimethoxy-2,5-dihydrofuran **3** using a Weinreb amide. An important work was performed in order to identify the proportion and relative configurations of each diastereoisomer of intermediate **1** thanks to NMR experiments, despite the fact that they were not separable. Then, two side chains were inserted using Wittig and HWE reactions and the two racemic 10-Δ^7-PhytoF and 2,3-dinor-8-Δ^5-PhytoF belonging to the enediol family were obtained, in 19 steps and 1.9 and 2.8% yield respectively.



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P B034

Light-driven reductive cleavage of sulfonamides promoted by thiourea organophotocatalysts

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Sulfonamides can be considered as useful amine protecting groups due to their advantageous properties including ease of introduction, general inertia to acids, bases, electrophiles, or mild reducing agents, and stability under oxidizing conditions.[1] In addition, some of these derivatives can easily crystalize, a characteristic that may simplify products purification.[1] As of today, the main drawback limiting the potential widespread use of sulfonamides in organic synthesis is the difficult cleavage of these functions, which can require quite harsh reaction conditions. Indeed, classical deprotection of N-sulfonyl protected compounds usually involves treatments with strong acids, bases or reducing agents.[2] Hard to implement electrochemical methods have also been described over the years,[3] together with different procedures relaying on SmI_2-promoted electron transfer cleavage.[4]
Recently, the advent of photocatalysis has opened up new possibilities for performing light-driven desulfonylation reactions under milder conditions. However, most of the processes described up to now require stoichiometric amounts of various reagents, and only few metal-based catalytic approaches have proven to be successful.[5]
In this communication, we describe a light-driven photocleavage of sulfonamides promoted by thioureas organophotocatalysts in the presence of tetrabutylammonium borohydride as a reducing agent (Figure 1).[6] This straightforward process occurs under mild reaction conditions (30 °C, irradiation at 350 nm), and tolerates a variety of substrates. On the basis of experimental evidences and theoretical studies, the reaction is supposed to proceed via energy transfer from the triplet excited-state thioureas to the sulfonamides.

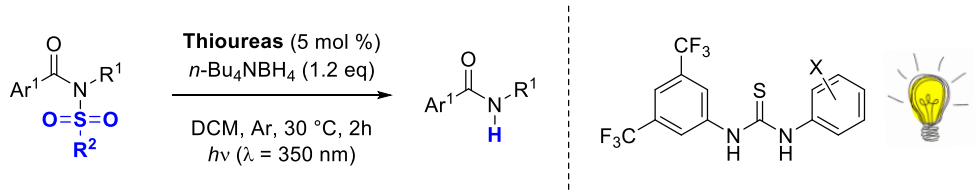

Figure 1

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P B035

Multivalent pharmacological chaperones based on dendrimers against Gaucher disease

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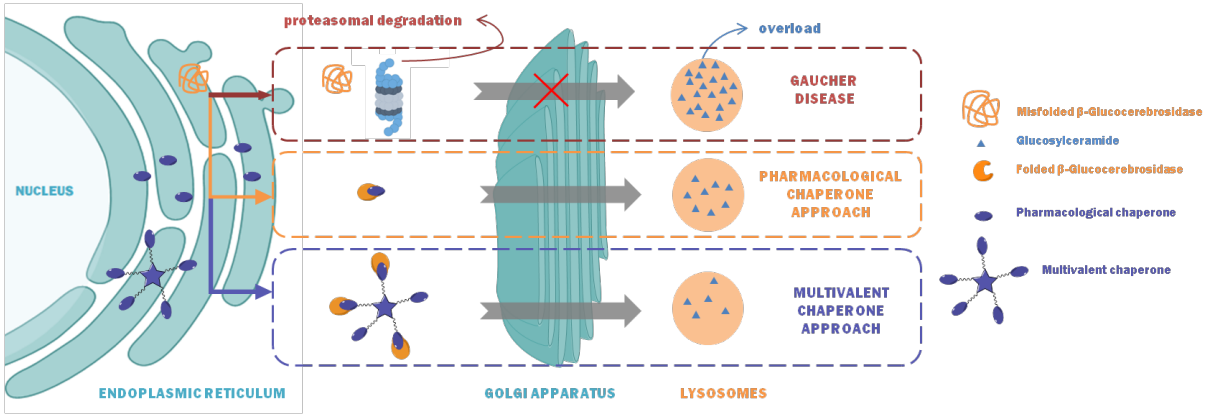
Gaucher disease (GD), the most common among lysosomal disorders, is caused by the enzyme β-Glucocerebrosidase (GCase) misfolding, leading to a lack of GCase hydrolytic activity and resulting to accumulation of glucosylceramide in lysosomes. The most common, type 1 GD, is characterized by bone involvement and hepatosplenomegaly whereas neurological disorders are present in types 2 and 3. Two strategies are currently used for symptomatic treatment: enzyme replacement therapy and substrate reduction therapy.[1] Pharmacological chaperone therapy is an innovative strategy consisting in the use of small molecules which bind specifically to the enzyme. It allows the proper folding and stabilization of GCase helping its trafficking to lysosomes where it exerts its hydrolytic activity.[2] To date, there is no pharmacological chaperone marketed for GD.



We will present a new series of multivalent scaffolds with several pharmacological chaperones. The expected multivalent effect is the significant increase in ligand affinity for its receptor by incorporating several copies of an identical motif on the surface of a multivalent template.[3] To allow efficient grafting of the pharmacophores on the surface of multivalent platforms, click chemistry (SPAAC) has been used. Clickable iminosugars analogues were synthetized and original dendrimers carrying 6 or 12 activated alkynes units have been prepared to allow Cu-free grafting of the pharmacophores (collaboration with Dr. C.-O. Turrin, LCC, Toulouse). Then, those compounds were evaluated for their cytotoxicity, their inhibitory activity on GCase, their multivalent effect and finally their chaperone effect.

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P B036

Ferrocenesulfonyl fluorides: an original family of ferrocene derivatives

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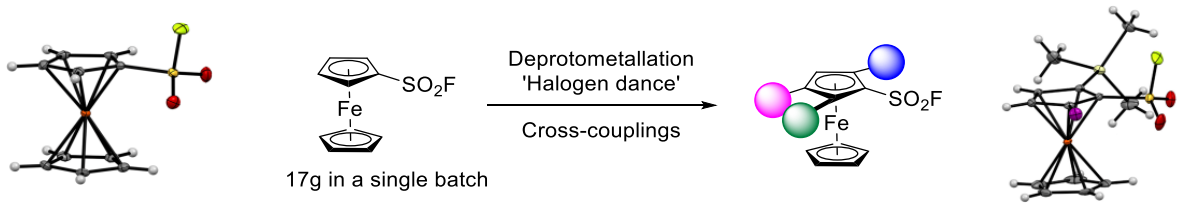
Over the last decades, ferrocene chemistry has reached an exquisite level of refinement, leading to application of ferrocene derivatives in all areas of chemistry.[1] This results from the ability to tune the electronic and steric properties of this organometallic through the introduction of selected substituents. However, the same substituents (ester, amide, ketones, etc.) are often encountered is this field, and vast areas of chemical space thus remain virtually unexplored.

Ferrocenesulfonyl fluorides represent a good example of such original and disregard compounds. While the first derivatives were reported back in 1959,[2] it was not until 60 years later that this family of compounds regained attention.[3] Here, we report the first easy and scalable synthesis of ferrocenesulfonyl fluoride allowing its further functionalization in various reactions. Deprotolithiation-electrophilic trapping sequences and the 'halogen dance' reaction can be efficiently used to introduce various substituents, leading to a wide diversity of substituted derivatives. The orthogonal reactivity of ferrocenesulfonyl fluorides was further demonstrated in many reactions as well as the possibility to carry out a Sulfonyl Fluoride Exchange towards various sulfonamides, sulfonates and sulfones.



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P B037

Diastereoselectivity control in MAC methodology for the preparation of α-hydroxy-β-amino acid derivatives

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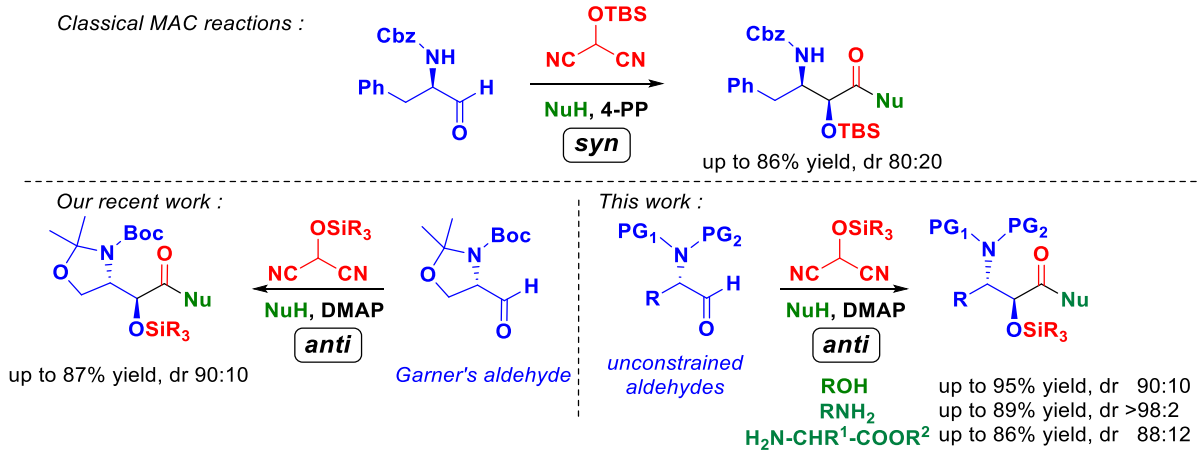
Many natural and synthetic molecules of biological interest contain an α-hydroxy-β-amino acid (AHBA) structural feature and considerable attention has been directed towards the development of stereoselective synthetic methodologies for these compounds. Our group is interested in the one-pot "MAC" (Masked Acyl Cyanide) methodology which commonly employs silylated 2-hydroxymalononitriles as *umpolung* reagents. The three-component MAC reaction can be used to combine an α-amino aldehyde, a MAC reagent and a nucleophile to build an AHBA moiety. MAC reactions have been employed in the synthesis of (–)-bestatin,[1] an aminopeptidase inhibitor, and in the total synthesis of cyclic pentapeptide cyclotheonamide C,[2] a potent thrombin inhibitor.

Classical MAC reactions have invariably shown a *syn* diastereoselectivity (dr 80:20). A recent discovery in our group was the reversal of diastereoselectivity of the MAC reaction: when Garner's aldehyde was used as the electrophile, MAC oxyhomologation reactions proceeded in good yields and with an unprecedented *anti* selectivity (dr up to 90:10).[3]



In order to exploit *anti* selective MAC reactions, strategically *N*,*N*-diprotected derivatives of unconstrained α-amino aldehydes have been studied as electrophiles. Various alcohols, amines and α-amino esters have been employed as nucleophiles, leading to the corresponding orthogonally protected esters (11 examples, yield up to 95%, dr 90:10), amides (10 examples, yield up to 89%, dr >98:2) and dipeptides (11 examples, yield up to 86%, dr 88:12). We will also disclose the rapid synthesis of (–)-allophenylnorstatin[4] and (2*S*,3*S*,*S*)-*epi*-bestatin, as single enantiomers in high yields. This methodology provides also a highly diastereoselective one-pot oxyhomologation and peptide coupling protocol for the preparation of peptide derivatives of α-hydroxy-β-amino acids with an *anti* configuration.

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P B038
Synthesis and properties of highly contorted triphenylene–based multiple helicenes

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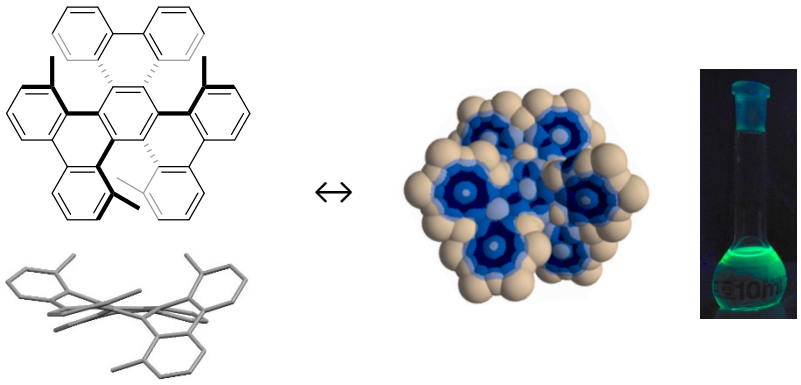
Polycyclic aromatic hydrocarbons (PAH) embedding a single π system are diverse by their size and shape. They have for long been considered as planar and rigid molecules, with only a few exceptions, for instance the helicenes, regarded as laboratory curiosities at the time of their discovery. This paradigm has gradually shifted, and nowadays it is well recognized that PAH are flexible and stretchable molecules. Thus, thousands of 3D curved PAH have been described in the last decade. Curvature in PAH can induce chirality[1] and largely affects their electronic properties. However, structure–property relationships have sparingly been examined for these molecules[2,3], in part because the synthesis of series of comparable contorted PAH is a difficult task.

To tackle this problem, we have designed an original approach to access a series of tetrabenzotriphenylene–based multiple helicenes using aryne chemistry. Geometric factors and electronic properties in these molecules were determined and correlated (see illustration). This work establishes structure–properties relationships in this series of chiral PAH, which is expected to allow the rational design of other multiple helicenes with predicted properties.



geometry ↔ *conformational behavior*
aromaticity
gap HOMO–LUMO
fluorescence
chiroptical properties

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P B039
New supramolecular anti-adhesive agents against SARS-CoV-2

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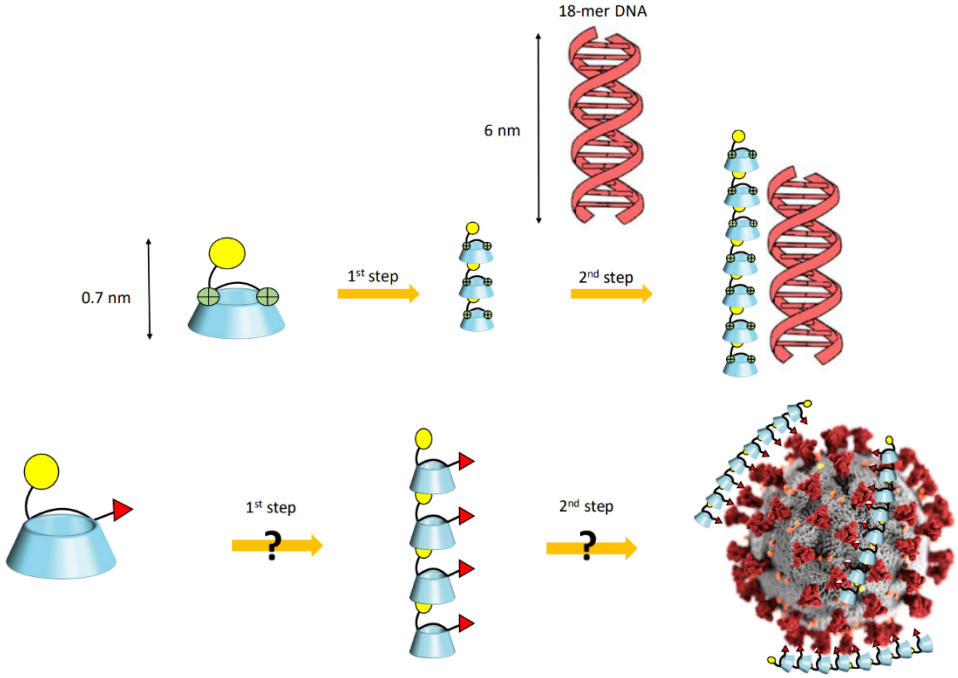
Our team previously showed that it was possible to form fibers from cyclodextrins functionalized by an adamantane and ammoniums together with small oligomers of DNA. Thanks to the interaction of the hydrophobic cavity of the cyclodextrin and the adamantane, it is possible to form small supramolecular polymers by self-assembly. Then, through electrostatic interactions between the monomers and DNA the assembly of cyclodextrins becomes a lot bigger thanks to the two cooperative interactions: inclusion and electrostatics.[1] We now wonder if it is possible to obtain self-assemblies of cyclodextrins functionalized with other functional groups than ammoniums, for example with biologically relevant carbohydrates. For that, we synthesized cyclodextrins functionalized with an adamantane, allowing the self-assembly, and also with a sialic acid derivative. We are studying their self-assembling ability. We will next study their capacity to interact with many sialic acid receptors that can be found at the surface of some viruses such as SARS-CoV-2 or Influenza, and potentially observe cooperative assembly. Indeed, it has been proven that multivalent agents of sialic acid derivatives can bind to the surface of this type of virus. We then wonder if it is possible to obtain a similar interaction with cyclodextrin assemblies.[2]



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P B040
Engineering of bacterial sialic acids

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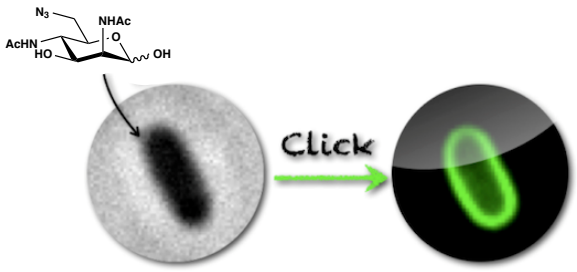
Most eukaryote cells are covered by a dense glycan layer, called glycocalyx. This glycan chain is often terminated by neuraminic acid (one saccharidic compounds from the sialic acids (SA) family), which is essential for many biological processes such as cell recognition and adhesion.

The outer membrane of Gram-negative bacteria is also covered by a dense layer of glycan, called lipopolysaccharides (LPS). Pathogenic bacteria have developed strategies taking advantage of sialic acid, both as a nutrient that can be withdrawn from the surface of host cells, and as a component to coat their own surface. This later strategy allows to escape defenses from our innate immune response.

The incorporation of an unnatural SA bearing a chemical reporter into LPS of living Gram-negative bacteria by glycan metabolic engineering using click-chemistry offers a rapid strategy to detect and potentially identify bacteria. And the modulation of their LPS-biosynthetic processes might restore immune response-sensitivity and lead to new therapeutic strategies against pathogenic and antibiotic-resistant bacteria.

In this communication, we will show synthetic pathways towards new unnatural SA analogues, bearing an *azido* anchor, based on a general synthetic strategy previously explored in our laboratory.



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P B041

Synthesis and characterization of tren-bridged cyclodextrin regioisomers for enantioselective applications

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Our group developed NHC-bridged cyclodextrins (CDs) that complex transition metals inside their cavity. [1] The resulting complexes are active in catalysis and display interesting chemo-, regio-, and stereo-selectivities.[2,3,4] It was proved that the 2-point bridging of CD induces an helicoidal distortion of its cavity, and that this distortion accounts for the observed stereoselectivity.[3] However, no control of the stereoselectivity was possible through 2-point bridging as it can only lead to a distortion into a M-helix (Figure A). To obtain the corresponding P-helix and reverse the selectivity, it would be necessary to build an enantiomeric CD, i.e. from L-glucose.

The aim of this project is to study the distortion of the cavity when the CD is bridged asymmetrically. This can be achieved through a three-point bridging using tripodal moieties such as tren groups, necessary to access 2 regioisomers with mirror-image anchoring patterns (Figure B). Preliminary results showed that Cu(II) complexes of such compounds display opposite circular dichroism, indicating a chiral environment around the copper center. (Figure C) Future goals include to further characterize metal-complexes of tren-bridged CDs and use them for molecular recognition of chiral guests or in asymmetric catalysis. Additionally, the synthesis of permethylated analogues have been carried out to access crystallizable and water-soluble compounds for structural determination as well as chiral recognition and asymmetric catalysis in water.

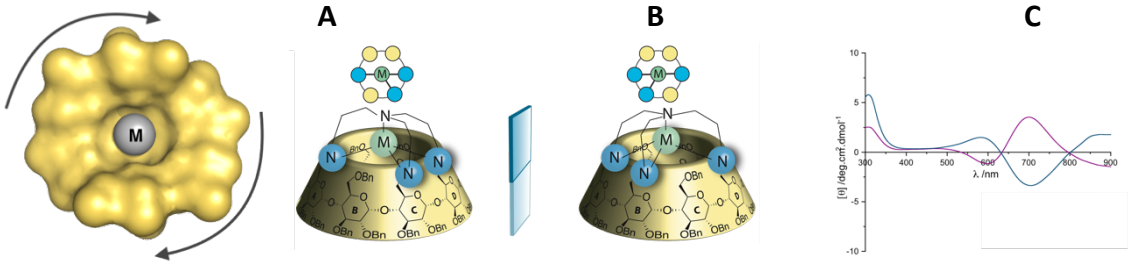

Figure **A**: M-helicoidal distortion of NHC-capped α-CD. **B**: Schematic representation of asymmetrically bridged CD tren-metal complexes. **C**: Opposite circular dichroisms obtained with the corresponding copper complexes.

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P B042

Aggregation-Induced Emission and Circularly Polarized Luminescence Duality in Tetracationic Binaphthyl-Based Cyclophanes

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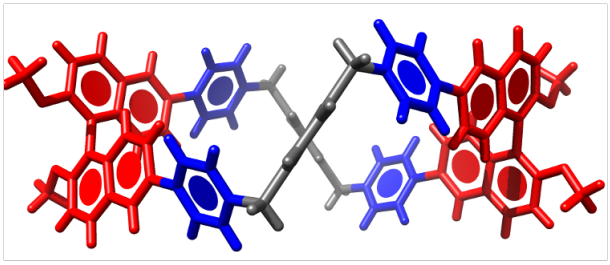
Combination of CPL and AIE has become a focus of major interest[1] since, in the aggregated state, the CPL response can be enhanced and red shifted while the handedness of the signal can be inverted. Although a plethora of chiral cyclophanes have been described, few examples have combined both CPL and AIE. Herein, we report the synthesis of two enantiopure binaphthyl-based tetracationic cyclophanes by the insertion of axially chiral enantiomeric binaphthyl moieties into the constitutions of pyridinium-based macrocycles.[2] These cyclophanes exhibit a significant AIE compared to the neutral binaphthyl precursors and display CPL responses both in solution and in the aggregated state. This duality of AIE and CPL in these tetracationic cyclophanes is destined to be of major importance in future development of photonic devices and bio-applications.



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P B043

Selective remote γ-functionalization of enals using photoredox catalysis

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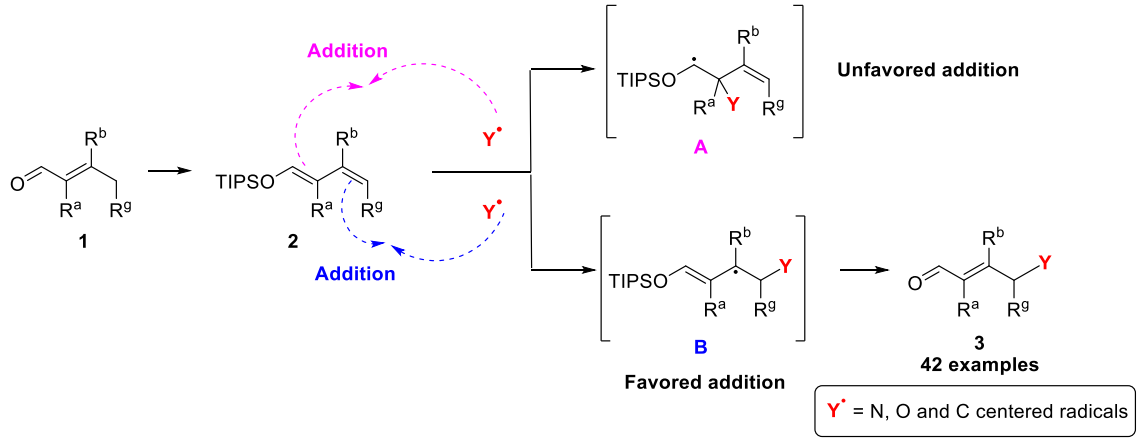
Remote functionalization is a powerful concept in organic synthesis. It permits a reaction to proceed at a distal and less reactive position of an organic molecule.[1] In the case of γ-enolizable α,β-unsaturated aldehydes (enals), it becomes possible to functionalize these enals at the distal γ position, *via* the formation of silyl dienol ethers.[2] We have previously developed a visible-light mediated method to functionalize the α-position of a variety of carbonyl compounds with alkoxy groups *via* the formation of silyl enol ethers.[3] Encouraged by these previous results on the α-alkoxylation on carbonyl compounds, we further explored this visible light-mediated approach to selectively functionalize the distal γ position of enals.

However, the major issue encountered in this remote functionalization is the α/γ regioselectivity. To overcome this issue we envisioned a radical based strategy in which a Y· radical will add onto the silyl dienol ether partner (Scheme 1). We hypothesized that this radical addition will occur at the γ position preferentially over the α position. Indeed, the γ addition pathway will generate a more stable allylic radical intermediate **B** compared to the unconjugated radical intermediate **A** formed with the α addition pathway. With this methodology, we were able to successfully functionalize a wide scope of enals at the γ position with complete regioselectivity, introducing a wide range of alkoxy, amino and alkyl functionalities.[4]



Scheme 3 Radical γ-functionalization of α,β-unsaturated aldehydes

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[4] Submitted article

P B044

Synthesis of Fluorinated Carbo- and Heterocycles through Asymmetric Transfer Hydrogenation/Dynamic Kinetic Resolution

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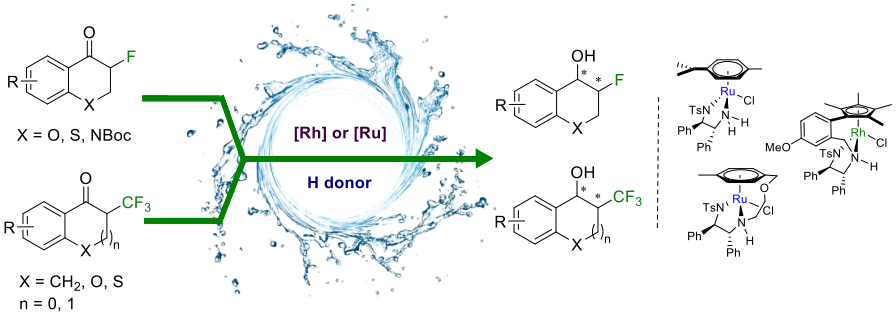
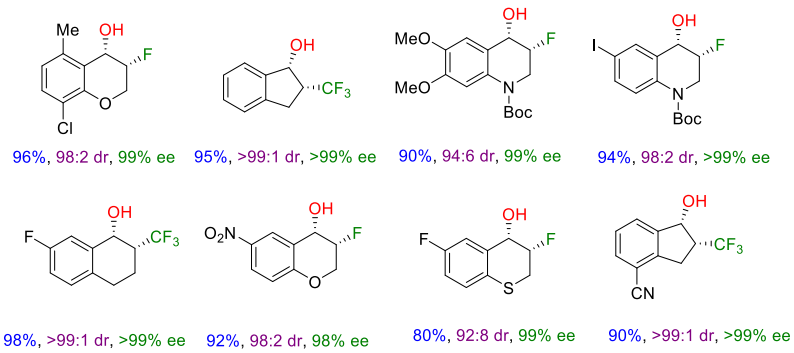
Fluorine is an important element for medicinal chemistry.[1] Based on this premise, we reported a practical method for the asymmetric transfer hydrogenation/dynamic kinetic resolution of 3-fluoro chromanones, *N*-Boc 3-fluoro-dihydrotetrahydroquinolin-4-ones, 3-trifluoromethyl chromanones, 2-trifluoromethyl tetralones and 2-trifluoromethyl indanones into the corresponding *cis*-fluoro and *cis*-trifluoromethyl alcohols in 56-98% yields, up to >99:1 dr and up to >99% ee by using the rhodium complex (*R,R*)-Rh-*teth*-TsDPEN [2] or the ruthenium complexes (*R,R*)-RuCl(*p*-cymene)TsDPEN or (*R,R*)-TsDENEB, and a formic acid/triethylamine (1:1) mixture as the hydrogen donor under mild conditions.[3,4,5]



Selected examples:



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P B045

Synthesis of functionalized alkylidenecyclobutanes

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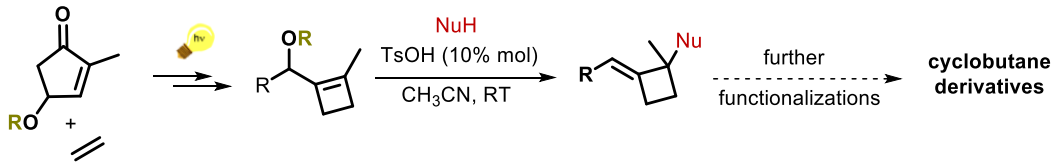
Cyclobutane derivatives have become increasingly important as molecular building blocks because of their inherent ring strain and the selective modification of their structures can be strategically used in organic synthesis.[1] Cyclobutane rings also appear in the molecular structures of a wide panel of natural and synthetic molecules that display interesting biological activities.[2]
Within this large family, alkylidenecyclobutane subunits are encountered in natural products, such as providencin,[3] and they exhibit enhanced reactivity providing access to complex molecular structures, including enlarged ring and highly functionalized cyclobutane derivatives.[4]

We recently developed an efficient synthesis of functionalized cyclobutenes through a photochemical domino reaction starting from cyclopent-2-enones and ethylene.[5] In this communication, we describe our recent developments of this methodology including the transformation of functionalized cyclobutenes into alkylidenecyclobutanes. This synthetic procedure provides an access to a wide variety of post-functionalized cyclobutane derivatives.



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P B046

Rh(III)-Catalyzed Asymmetric Transfer Hydrogenation/DKR of 3-Benzylidene Chromanones

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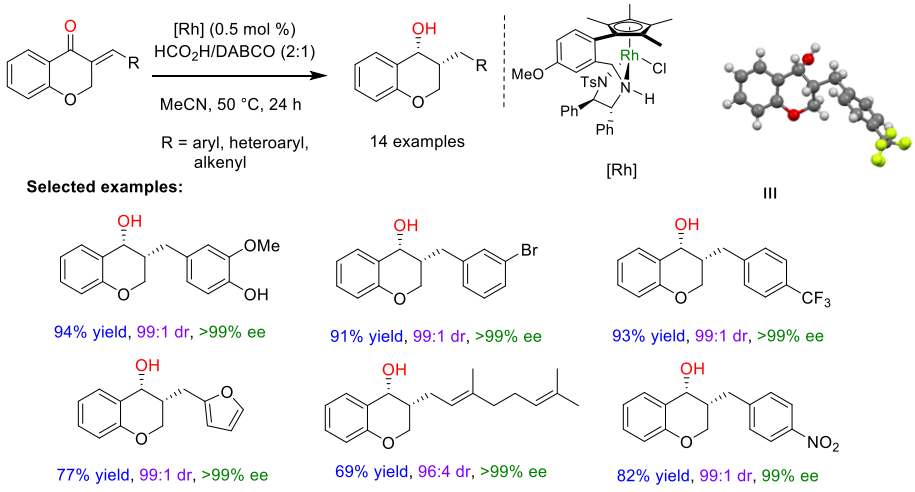
Homoisoflavonoids are a widespread family of molecules, naturally occurring in plants, which possess a promising set of biological activities. Among those, benzyl chromanols are a promising family that could be accessed through a key step of asymmetric transfer hydrogenation combined with a dynamic kinetic resolution process (ATH/DKR). [1] Continuing our interest in asymmetric transfer hydrogenation (ATH),[2] we developed a straightforward access to enantiomerically enriched *cis*-3-benzyl-chromanols from (*E*)-3-benzylidene-chromanones through a Rh-catalyzed[3] asymmetric transfer hydrogenation. This transformation allowed the reduction of both the C=C and C=O bonds and the formation of two stereocenters in high yields with excellent levels of diastereo- and enantioselectivities (up to >99:1 dr, up to >99% ee) in a single step through a dynamic kinetic resolution process using a low catalyst loading and HCO_2H/DABCO as the hydrogen donor. This efficient and straightforward catalytic route provides access to synthetically useful chromanol derivatives and valuable chroman pharmacophores as well and tolerates a broad range of functionalities.[4]



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P B047

Mechanochemical development of sydnone derivatives: How to make sydnones rock!

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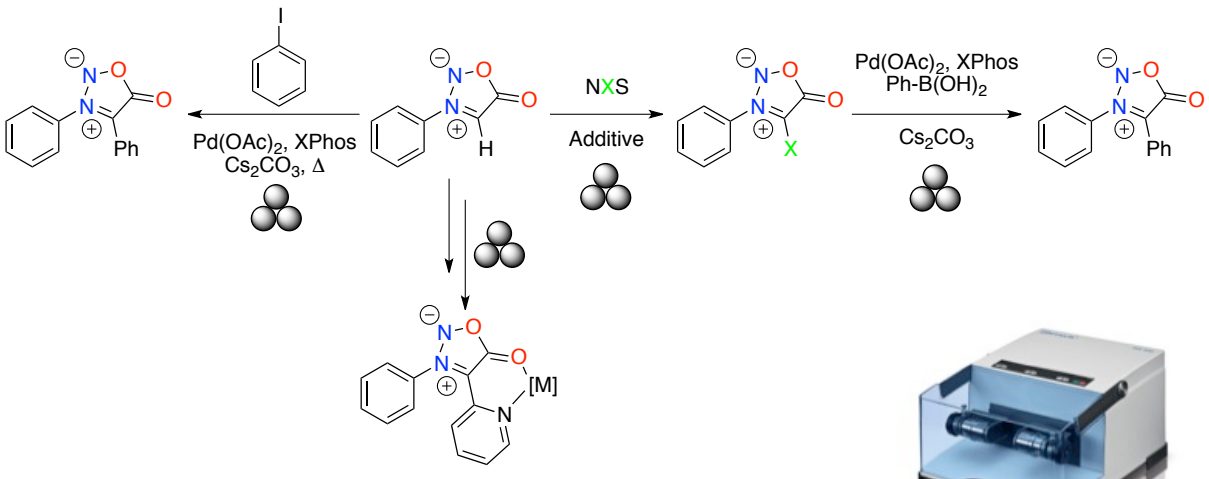
Sydnones are the most studied class of mesoionic compounds over the past decades mainly because of their biological activity[1] and their propensity to undergo 1,3-dipolar cycloaddition reactions yielding pyrazole scaffolds.[2] Sydnone compounds are usually synthesized from *N*-substituted amino acids by nitrosation and subsequent cyclization.[3] Our team has recently developed two straightforward mechanochemical methods to obtain *N*-substituted amino acids from anilines and a subsequent one-pot two-step sequence to obtain sydnones, which could be used as ligand in coordination complexes.[4] Mechanochemistry is indeed a promising technique[5] leading to better yield, better selectivities and enhanced kinetics compared to classical solution chemistry. Moreover, in 2019, the IUPAC has cited mechanochemistry as one of the 10 chemical innovations that will change our world.[6]

Herein will be presented the latest developments in green methodologies concerning sydnones. High yielding halogenation reactions were performed and the corresponding halo-sydnones could be subsequently used in a mechanochemical Suzuki-Miyaura cross-coupling reaction. In parallel, direct mechanochemical C-H activation of sydnones allowed to obtain arylated sydnones.



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P B048

Simple push-pull multimers based on biosourced isommanide, isosorbide and glycerol: electronic properties and photovoltaic applications

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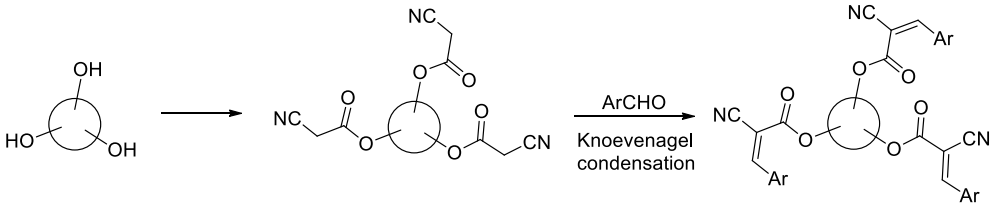
Use of solar energy will be a great challenge of this century as this energy represents less than 1% of consumed energy in the world versus 78% of fossil one. It is now well established that the petro-sourced resources for energy is also responsible for the climate change of our planet. With the announced depletion of resources, the transition to the use of living renewable resources must be initiated. Very recently, we started a research program aiming at producing devices for organic electronics using bio-sourced compounds[1]. In that context, we intend to graft biomass-derived electron donor or acceptor conjugated systems onto biomass derived platforms (chiral or not) such as glycerol, carbohydrates and their derivatives using the tools of sustainable chemistry.

A preliminary study was focused on the grafting of push-pull compounds on biosourced polyols in order to evaluate the effect of the chirality[2] or polarity of such platforms on the efficiency of the grafted push-pull structures as donors in photovoltaic cells.



Scheme 1. Synthetic strategy of biomass-derived multimers.

Synthesis of compounds, the opto-electronic properties and the performance of the different compounds used as donors in photovoltaic cells will be presented.

[1] For the use of bio-sourced compounds in OPV cell, see for example : Rajkumar, B.; Khanam, L.; Koukaras, E. N.; Sharma, G. D.; Singh, S. P.; Lochab, B., *ACS Sust. Chem. & Eng.* **2020,** *8*, 5891.

[2] For a beneficial effect on the organization of the layer, see for example: a) Aytun, T.; Barreda, L.; Ruiz-Carretero, A.; Lehrman, J. A.; Stupp, S. I., *Chem. Mat.* **2015,** *27*, 1201. b) Sakai-Otsuka, Y.; Nishiyama, Y.; Putaux, J.-L.; Brinkmann, M.; Satoh, T.; Chen, W.-C.; Borsali, R., *Macromolecules* **2020,** *53*, 9054

P B049

Cascade reaction for the formation of spirocyclic scaffolds

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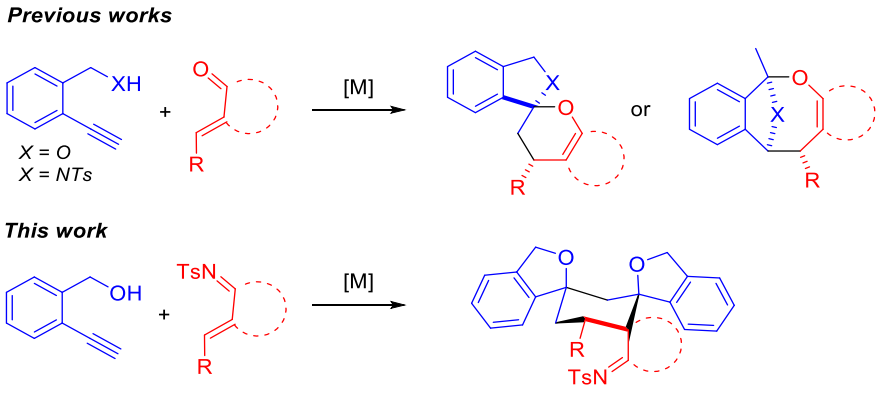
Constructing molecular complexity and diversity from simple and readily available substrates is still pursued by the synthetic community. The development of domino polycyclizations is one of the most appealing strategies to access intricate molecular architectures in a single operation.[1]

Among others, catalytic cycloisomerization-initiated domino reactions of alkynols or alkynylamines allow the formation of diverse polycyclic scaffolds. In recent years, different methodologies using this approach including α,β-unsaturated ketones as reaction partners have been described in the literature.[2]

We will disclose our own investigations employing this strategy in the presence of α,β-unsaturated imines leading to unusual molecules bearing three spirocyclic units.



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P B050

An Environmentally Sustainable Synthesis of Enantioenriched CF_3-Chromanol, Indanol and Tetralol Derivatives by Rh-Catalyzed Asymmetric Transfer Hydrogenation

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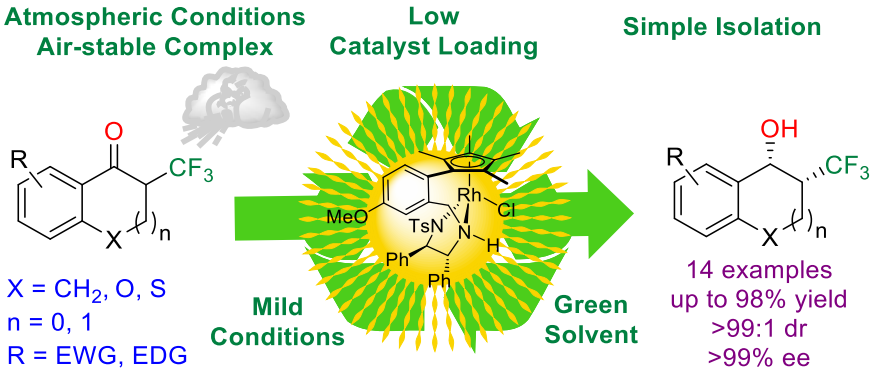
The effect of fluorine in the design and the synthesis of new bioactive compounds has been widely studied during the last two decades but still needs to be explored and understood into deeper levels. [1] Consequently, the potential of fluorine in organic and medicinal chemistry has prompted us to pursue our investigation[2] and develop an environmentally-sound way to access enantioenriched trifluoromethyl-containing building blocks. We report here a Rh(III)[3]-catalyzed asymmetric reduction of α-trifluoromethyl ketones through transfer hydrogenation under mild conditions to access a series of enantioenriched *cis*-trifluoromethyl alcohols via a dynamic kinetic resolution process. The reaction was efficiently performed in the green solvent 2-MeTHF with HCO_2H/Et_3N (1 :1) as the hydrogen donor. Good yields alongside high diastereo- and enantioselectivities were obtained for the synthesis of CF_3-chromanol, CF_3-indanol and CF_3-tetralol derivatives. [4]



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P B051

Medicinal mechanochemistry for the efficient discovery of novel 5-HT$_6$ receptor ligands

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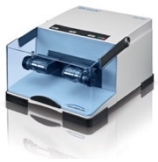
The 5-HT$_6$ receptor, a receptor coupled to the Gs protein, has emerged as a promising target to alleviate cognitive symptoms of neurodevelopmental diseases [1]. In the past years, we developed the synthesis of heterocyclic compounds that showed a high affinity for the receptor in binding assay and interesting antagonist properties towards different signaling pathways of 5-HT$_6$ receptor.[2] In this context, new ligands were designed and synthesized using an innovative technology, namely mechanochemistry. To date, 25 new molecules were obtained in short reaction time and without the use of toxic, costly and dangerous reagents and solvents. Their pharmacological properties were tested to determine the effects of each compound toward the different signaling pathways of 5-HT$_6$ receptor. Finally, highly potent compounds were identified, showing the benefits of medicinal mechanochemistry.[3]

In solution:
- Toxic reagents
- Long reaction time : overnight for each step
- Use large amount of toxic solvent DMF, CH_2Cl_2
- Silica gel chromatography

Vs

Mechanochemistry:
- Less or no toxic reagents
- Shorter reaction time : 60 to 140 min
- Few drop of solvent
- No silica gel chromatography



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P B052

An efficient, chiral, L-shape N-heterobicyclic carbene ligand for asymmetric gold(I) catalysis

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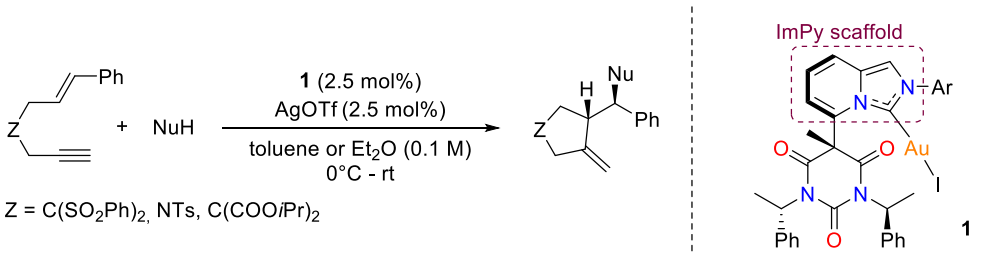
Despite the outstanding advances realized in homogeneous gold(I) catalysis over the last two decades, the asymmetric version has not experienced the same growth.[1] The main challenge resides in the specific, linear coordination geometry of gold(I) complexes, which limits an efficient chirality transfer from the ligand to the substrate. In recent years, the rigid, bicyclic imidazo[1,5-*a*]pyridin-3-ylidene platform (ImPy) has proven to be a privileged scaffold in this context, since it leads to L-shape NHC ligands, in which the C5-substituent is positioned in front of the gold center and forms a kind of "lateral wall".[2]

In 2019 our groups reported a first series of such "achiral" L-shape ImPy ligands functionalized with a flanking barbituric heterocycle and those tunable ligands appeared highly efficient in gold(I)-catalyzed C-N, C-O, and C-C bonds formations.[3]

We present herein a second series of chiral ImPy-Au(I) complexes **1** derived from the first one and featuring a chiral lateral barbituric heterocycle obtained by use of enantiopure (*S*)-1-phenylethylamine. The synthesis and characterization of the chiral NHC precursors and complexes **1** are described as well as the implementation of the latter catalysts in the domino cycloisomerization/nucleophilic addition of 1,6-enynes with various nucleophiles. This reaction proceeds in excellent yields and good enantioinduction affording functionalized heterocycles.[4]



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[4] Unpublished results.

P B053

A general procedure for carbon isotope labeling of urea derivatives with carbon dioxide

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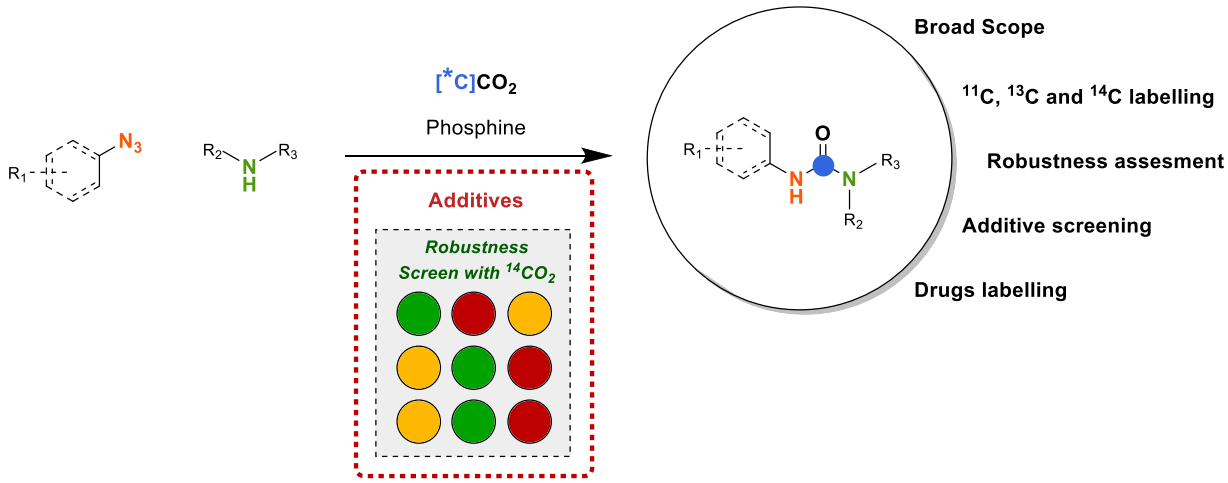
Carbon isotope labeling is a precious technology, which allows tracking organic compound either in the living organisms or environment. While long-lived β^- isotope carbon-14 (^{14}C, $t_{½}$ = 5730 years) is of paramount importance for the collection of biological data through ADMET studies, short-lived β^+ isotope carbon-11 (^{11}C, $t_{½}$ = 20 min) is routinely employed for PET imaging studies in humans and primates.

Nowadays, traditional multi-step synthesis with ^{14}C generates high amounts of radioactive waste and are extremely demanding in terms of resources and sustainability. On the other hand, ^{11}C is produced in limited amounts and requires fast and efficient reactions for its valorization in a radio-synthetic process [1].

In order to overcome such limitations, our group developed a Staudinger/ aza-Wittig cascade reaction using stoichiometric amounts ^{13}C, ^{14}C and ^{11}C-labeled-CO_2, that allows a rapid and straightforward access to different radio-labeled carbonyl derivatives, minimizing the generation of radioactive waste [2a, 2b].



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P B054

Photoinduced isotope equilibration between format salts and CO_2 : application to carbon labeling

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Carbon radioisotope labeling has a remarkable impact on public health. Long lived β^- isotope carbon-14 (^{14}C, $t_{1/2}$ = 57300 years) is of paramount importance for the collection of biological data such as absorption, distribution, metabolism, excretion (ADME) studies.[1]
Unfortunately, traditional ^{14}C-radiosynthesis is marred by multiple pitfalls, including lack of available starting materials ($[^{14}C]CO_2$ being the universal building block), high costs of reagents and generation of considerable amounts of radioactive waste, which are poorly sustainable and difficult to dispose of.

We have explored a photocatalytic approach for the synthesis of labeled carboxylic acids, based on the hydrocarboxylation of alkenes (*i.e.* the Giese reaction).[2,4] Based on a dynamic isotopic equilibration between format salts and [^{13}C and ^{14}C]CO_2, C-labeled radical anion $CO_2^{\bullet-}$ could be accessed for the first time,[3] under extremely mild conditions and low photocatalyst loading (0.5 mol%). This methodology was employed for labeling drug derivatives and the late-stage carbon isotope labeling of complex substructures and pharmaceutically relevant compounds.

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P B055

Synthesis and reactivity of 5-Hydrazino-3-Nitro-1,2,4-triazole (HNT) : an amphoteric energetic platform

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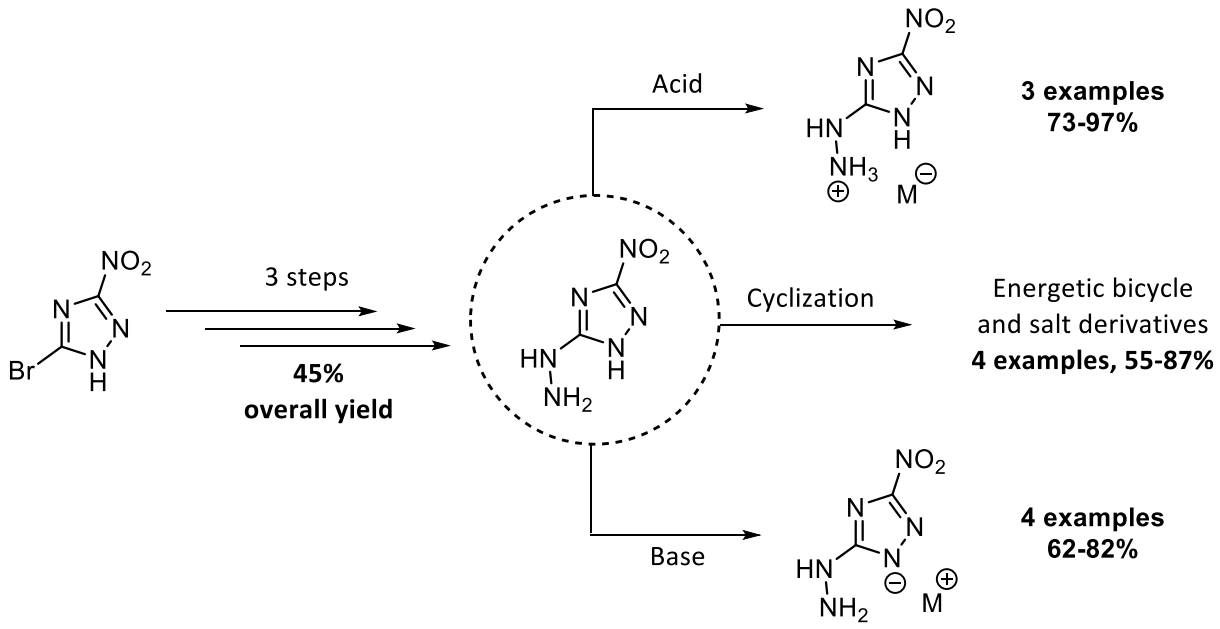
Triazoles are a major class of heterocyclic compounds, widely used in pharmaceutical and energetic applications due to their high nitrogen content coupled with the presence of explosophoric groups like nitro, hydrazino or azido.
Although some hydrazino-1,2,4-triazoles have been described lately,[1] HNT is still surprisingly missing, making it doubtful as a free base, as only hydrochloride and sulfate salts were reported.[2]
Herein, the first synthesis of HNT is described from 5-bromo-3-nitro-1,2,4-triazole (BNT) in three steps, as well as other energetic compounds derived from it, including salts, thus demonstrating that HNT is not only a feasible, stable molecule, but also a valuable platform towards powerful and thermally stable energetic compounds.



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P B056

Design, structural analysis and biological evaluation of fluorinated polyproline-type foldamers

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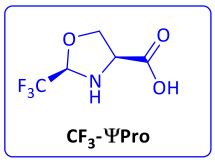
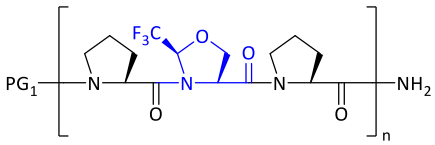
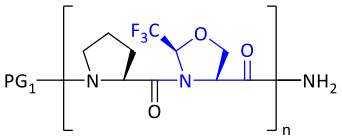
Foldamers are oligomers with a strong tendency to adopt a well-defined conformation.[1] Peptidomimetic foldamers appear to be a useful tool in medicinal chemistry for the exploration of protein-protein or protein-membrane interactions thanks to their ability to mimic the secondary structure of the target protein while being stable against proteases.[2] Meanwhile, the use of fluorinated compounds in medicinal chemistry has become widely popular. Indeed, the incorporation of fluorine atoms is of major interest to modulate the physicochemical and therapeutic properties of drug candidates,[3] and can also serve as ^{19}F NMR probes.[4] Although the combination of fluorine and foldamers appears to be an innovative strategy in medicinal chemistry, fluorinated foldamers remain under-explored to date.

Our group reported the synthesis of the fluorinated pseudoproline **CF_3-ΨPro**, its incorporation into peptides and its effect on the *cis*/*trans* amide bond conformation. We demonstrated that in Fmoc-Pro-**CF_3-ΨPro**-OMe dipeptides, the **CF_3-ΨPro** is a useful tool to tune the amide bond conformation.[5] Knowing that oligomers of proline can adopt a polyproline secondary structure (PPI: all-*cis*, PPII: all-*trans* amide bonds), we aim to design and synthesize fluorinated oligomers based on (Pro-**CF_3-ΨPro**)$_n$ and (Pro-**CF_3-ΨPro**-Pro)$_n$ scaffolds. Our objective is to evaluate their ability to mimic a polyproline secondary structure and to increase their biological profile (binding affinities to protein or membrane, proteolytic stability…). Here, the first studies and results about (i) the synthesis, (ii) the conformational studies using NMR and circular dichroism spectroscopy, (iii) the cytotoxicity and stability assays of our oligomers (n = 1, 2 or 3) will be presented.







PG_1 = H, Ac n = 1, 2, 3

Conformational anaylsis, Proteolytic stability, Cytotoxicity

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P B057

Au(I)-Catalyzed regioselective deuteration of indoles

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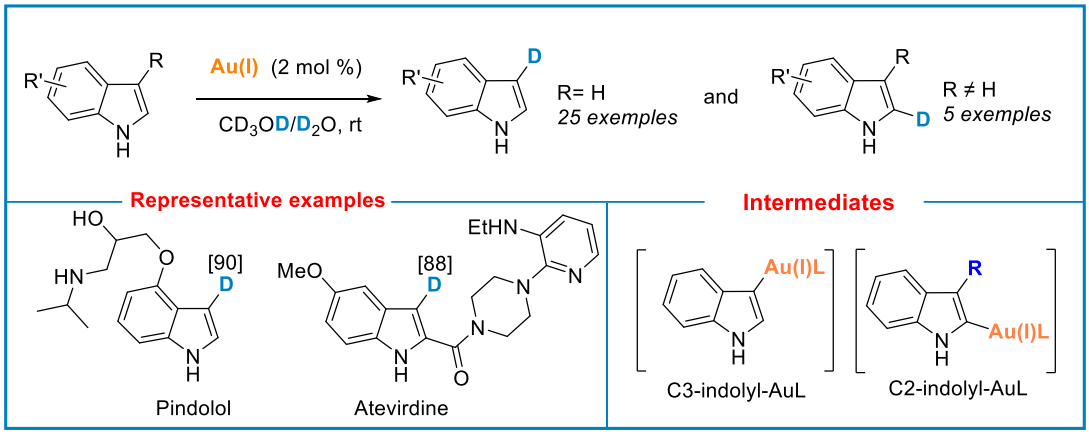
Isotopic labeling of bio-actives compounds is extensively studied in order to modify their properties, such as pharmacokinetics or biological properties, and/or use them as probes.[1] Deuteration of indoles has been studied but proceeds most of the time under harsh, or poorly selective conditions.[2]

In the context of our studies on the Au(I)-catalyzed Pictet-Spengler reactions,[3a,b] we hypothesized indolyl-Au(I) species as key intermediates. Despite plethoric examples of reactions involving gold(I) catalysis and indoles,[3c] indolyl-Au(I) species are not well known in the literature and most of the time have been only hypothesized as potential intermediates in non-neutral redox reactions.[4]

On the basis of this hypothesis, we developed a highly efficient Au(I)-catalyzed regioselective deuteration of indoles, that proceeds via aurated indolyl intermediates. High deuterium incorporation rates were reached at C3 –or C2, depending on the substitution pattern of the indole– using 0.5 mol% catalyst using CD_3OD and/or D_2O as low expensive deuterium source. This methodology was used for the regioselective, mild gold-catalyzed deuteration of ca 30 indoles derivatives, including biologically active Pindolol and Atevirdine, as representative examples of highly functionalized compounds.



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P B058

Visible-Light Photoredox Synthesis of 6- and 7-Membered Ring Scaffolds *via N*-Centered Radicals

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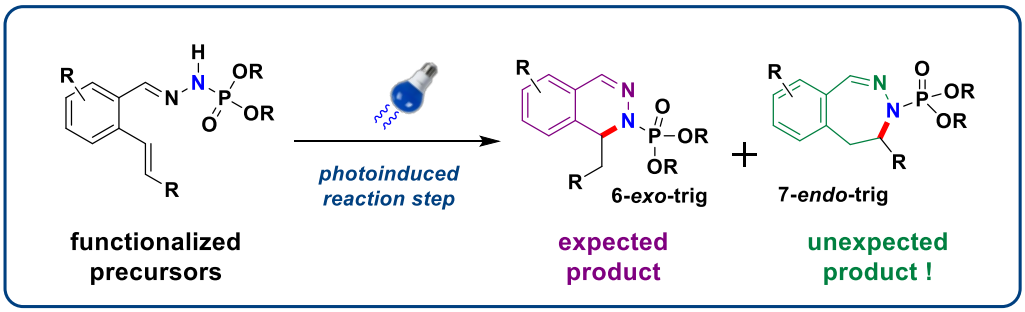
For the chemists' community, the ubiquitous presence of nitrogen-containing heterocycles in natural compounds have been the source of many inspirations for design and synthesis of new biological molecules. But the synthesis of these heterocycles remains an important challenge in organic chemistry, we report on this work a fast and easy to setup method to obtain 6- and 7-membered ring scaffolds.[1] The key point of this work is the use of visible-light photocatalysis that could allow us to go through drawbacks and difficulties of conventional organic chemistry. To our knowledge, this work represents the first example of photo-induced 7-endo-trig cyclization involving nitrogen-centered radicals.

To develop new bioactive compounds and synthetized unprecedented structures, our team is interested on visible-light photocatalysis. Using visible-light as an exclusive energy source has proved his ability to generate nitrogen centered radical. Previously interested on *N*-tosylhydrazones as radical precursors,[2] our team is now working on phosphonohydrazone precursors that have a different behavior.[3-4] This kind of compound shows good results on cyclisation with a nitrogen centered radical on alkene and now on alkyne.

In our lab, we synthetized and functionalized some phosphonohydrazones substrates. Then, the possibility of generating a nitrogen centered radical *via* photoinduced reaction was evaluated and optimized. At this step, the expected 6-exo cyclisation product was obtained but also the 7-endo one with a good ratio. In addition, further experiments shown that it was possible to manage selectivity with modifications of the conditions. This work using visible-light photocatalysis demonstrates that this method has a great potential on synthesis of new bioactive compounds.



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P B059

Access to Phthalazine Derivatives Using an Original Photoredox Cascade Reaction

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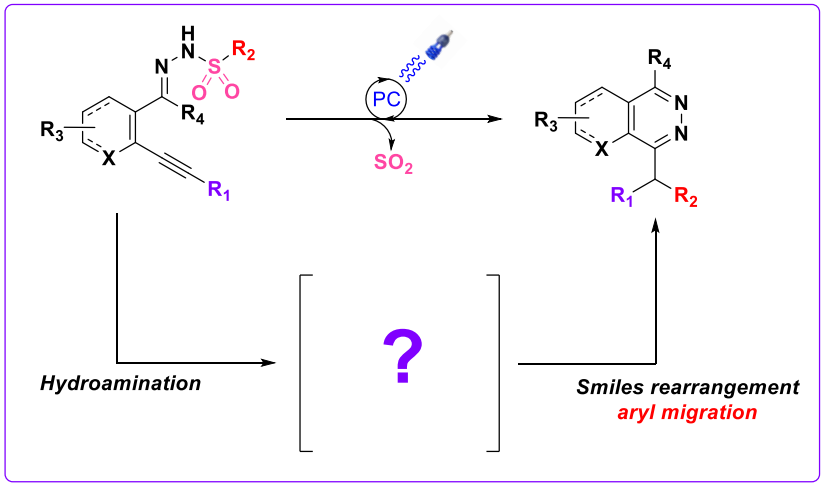
Nitrogen-containing heterocycles are particularly interesting compounds due to their ubiquitous presence in natural products. Indeed, since the beginning of organic chemistry, scientists took up the challenge to find efficient strategies for their formation[1]. Among the constant improvements in this field, the synthesis of phthalazine derivatives remains highly requested. Thus, the development of new strategies to efficiently build these compounds is still desirable.

In this aim, we focused our research projects on the development of new photoredox synthetic methods to build the carbon-nitrogen bond[2], *via* the generation of a nitrogen centered radical. This kind of intermediate is attractive because it can be added on unsaturated derivatives for instance and thus lead to the carbon-nitrogen bond formation.

In our laboratory, we developed *ortho*-alkynylsulfonohydrazone precursors in order to access to a broad scope of phthalazine derivatives[3]. This synthesis *via* a new cascade reaction, is initiated by visible light photocatalysis, involving a radical hydroamination reaction followed by a radical Smiles rearrangement. Thanks to this reaction, many useful phthalazine derivatives are now accessible.



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P B060
The Synthesis of Biindole via Molybdenum-Catalayzed Cylization

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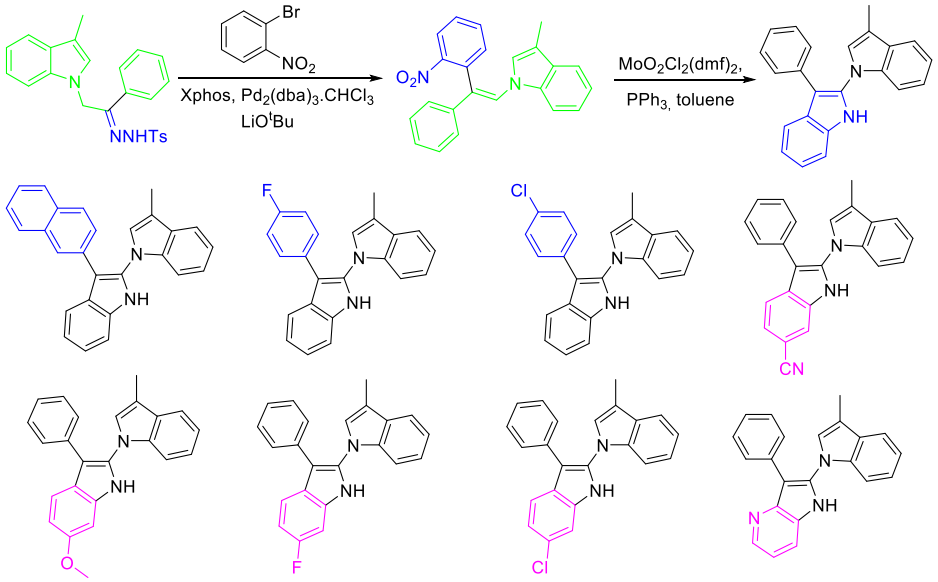
Indoles are ubiquitous components of both biologically active natural products and important pharmaceuticals[1]. Therefore, great efforts have been made to synthesize the structural diversity of indoles[2]. In this article, a new strategy for the construction biindoles is described. The reaction starts from the coupling between N-tosylhydrazones (NTH) and 1-bromo-2-nitrobenzene leading to the formation of 1-(2-(2-nitrophenyl)-2-phenylvinyl)-1H-indole derivatives[3]. Under optimized Cadogan reductive conditions[4], a new scaffold of type 3'-phenyl-1'H-1,2'-biindole was obtained. The method provides rapid access to new libraries which intends to generate small molecules with a large structure diversity in an efficient manner.



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P B061

TieFighter-NHCs for Supramolecular Transition Metals Catalysis

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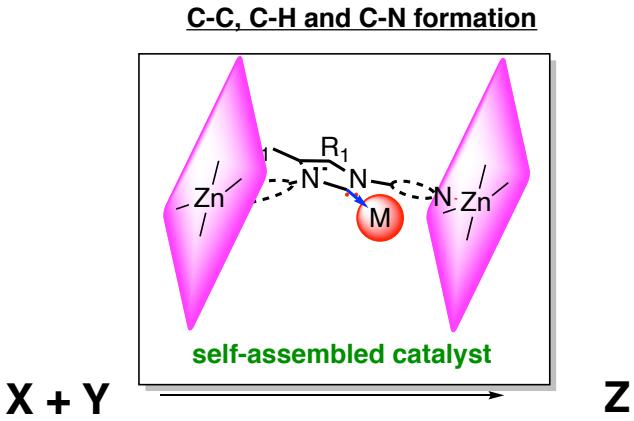
The development of chemical processes that allow a rapid increase of the molecular complexity in a limited number of steps is a major goal in modern organic chemistry. It has a strong impact in diverse areas such as the elaboration of new drugs, production of materials with specific properties... Among the various strategies, transition metal catalysis has played an increasingly key role in the economic development of many countries during the 20th century. The properties on a transition metal catalyst are mostly related to the ligands herself, which are coordinated with the metal. However, the approach is always the same and the problem lies in the stretched and painful synthesis of ligands and complexes. The ligand's electronic and steric properties will modify the metal center's primary coordination sphere, so much research directly focuses on altering the ligand structure. However, the approach is always the same; the problem lies in ligands' stretched and painful synthesis.[1] Based on these considerations, we design unprecedented self-assembled bulky NHC-transition metal complexes. We intends to design a new class of dyads (**TIE-NHCs**) based on NHCs whose steric hindrance and metal-interaction would be modulated by the supramolecular assembly with easily accessible Zn-salen. Therefore, we wish to contribute to the replacement of catalyst optimization methodologies currently applied by a ready-to-use available *in-situ* strategy, in which inclusion of the steric bulk by supramolecular coordination would yield improved performance and selectivity.



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P B062

Oxidation of perfluoroalkylselenides

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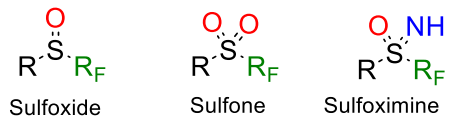
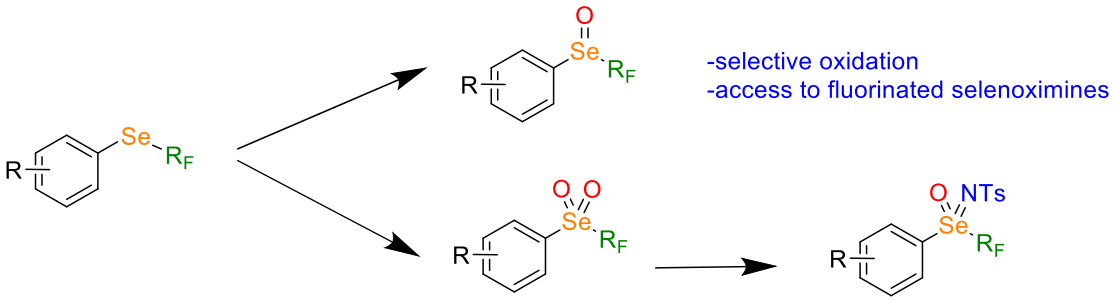
For several years, the emergence and the development of fluorinated groups have taken a prominent place in the scientific community.[1] More recently, there has been a growing interest in the synthesis of groups combining fluorine and selenium, in particular because of the high Hansch-Leo lipophilicity parameter (Π_{SeCF_3} = 1.61) which contributes to improve the bioavailability of molecules.[2] Surprisingly, if the S-perfluoroalkylsulfoxides, sulfones, and even sulfoximines are widely known, the oxidation of $SeCF_3$ (or more generally SeR_F) motif has been barely studied. Indeed, although selenoxides and selenones are widely represented in the literature, perfluorinated versions of these molecules have been scarcely described[3] and fluorinated selenoximines have not yet been reported.[4]





The continuity of our work in the laboratory on the trifluoromethylselenolation[5] reaction has led us to develop new approaches in order to selectively obtain perfluoroalkylated selenoxides and selenones. Finally, the first formation of perfluorinated selenoximines will be presented as well as the study of their lipophilicity.

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P B063

Tryptophan 2,3-dioxygenase (TDO): the new promising target of 18F PET tracers as markers of neuroinflammation

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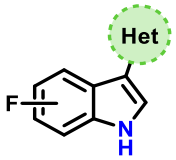
In the past decades, most research has been focused on the development of molecular probes targeting the central nervous system (CNS) and more particularly the neuroinflammation. Neuroinflammation is the main and early physiological process implicated in neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD) and amyotrophic lateral sclerosis (ALS). According to the 2016 World Health Organisation (WHO) report, the number of affected people could triple by 2050 as a result of population ageing.[1] Consequently, this proves the urge about the development of new tools permitting to visualise the progression of neuroinflammation in neurodegenerative disorders.

Currently, several targets have been listed to be involved in the neuroinflammation phenomenon and have been the centre of attention of clinicians. Lately, tryptophan 2,3-dioxygenase (TDO) has been discovered as a new interesting target taking place in the kynurenine pathway. This enzyme catalyses the first and limiting step tryptophan's conversion into kynurenine which leads to the secretion of neurotoxic species.

To date only two ^{18}F PET tracers could be potential candidates on TDO toward PET imaging application but remain untested on humans.[2,3] However, no ^{18}F radioligands have been placed on the market yet. Consequently, the search of new ^{18}F radiotracers remains essential.
Thanks to the literature results our team explored structure-activity relationships through the synthesis of references and analogues and their biological evaluation. Thus among the 25 tested molecules, 2 of them have shown promising inhibition effects. Our team is currently providing novel fluorinated indoles and analogues with optimised synthetic routes. Syntheses, biological activities and preparation of precursors for radiolabelling will be presented in this communication.



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P B064

Towards a general approach to 2-azaspiro ring systems *via* photoinduced decarboxylative radical cyclization

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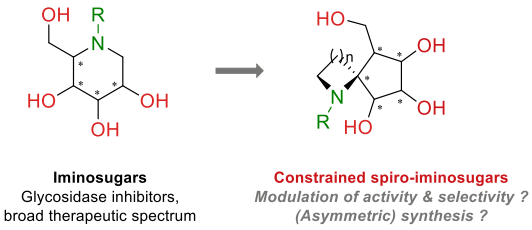
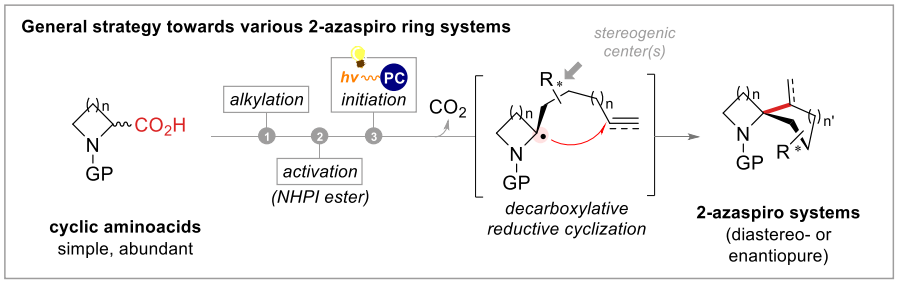
Iminosugars stand as a prevalent class of glycomimetics in view of their broad spectrum of therapeutic activities.[1] However, aiming to develop credible drug candidates, continuous efforts are required to improve their activities and selectivities for the inhibition of diverse carbohydrate-processing enzymes. Inspired by modern trends in medicinal chemistry calling for the incorporation of emergent, high ''F*sp*^{3}'' motifs,[2] it is anticipated that novel iminosugar mimics based on constrained scaffolds will offer new opportunities through fine modulation of their 3D-shape, chemophysical and pharmacokinetic properties.

Although elegant strategies were recently developed to access diverse spirocyclic motifs, approaches for the construction of functionalized 2-azaspiro ring systems in diastereo- or enantiopure fashion are very scarce.[3] Herein, we will present our efforts to develop a convenient methodology to these valuable scaffolds through a short sequence involving the alkylation of simple cyclic aminoacids followed by a mild decarboxylative, metal-free photoredox reductive cyclization. Two sets of conditions were found to enable the facile obtention of a range of 2-azaspirocycles in moderate to high yields, and mechanistic insights were provided by experimental and spectroscopical investigations.[4]





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P B065

New trifluoromethylthiolated aromatic amino acids as highly hydrophobic building blocks for the rational design of peptides

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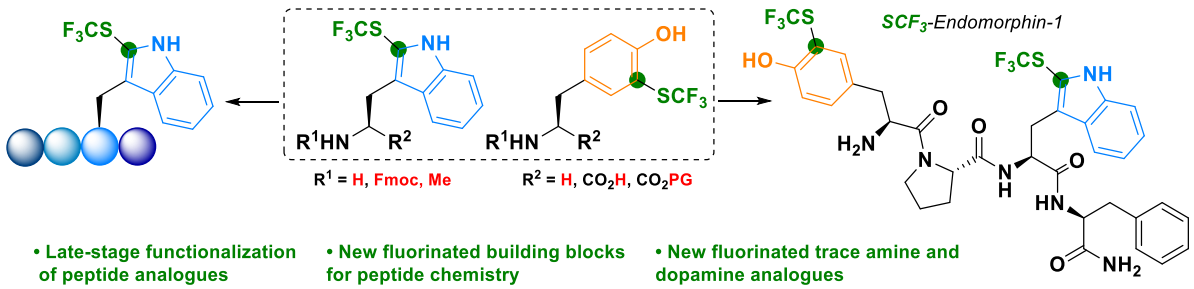
Fluorinated amino acids (F-AAs) are known to have a major impact on peptide assembly, hydrophobicity, resistance to proteolytic degradation and to induce conformational constraint.[1] Currently, more than 30% of small molecule drugs are composed of tailor-made AAs.[2] Given the increasing importance of peptide pharmaceuticals and the firmly established role of fluorine in drug design, it is important to advance the synthetic and effective late-stage modification strategies towards diverse fluorine-containing AAs to expand the toolbox for rational peptide design.

The trifluoromethylsulfanyl group (SCF_3) is a promising motif in medicinal chemistry because it has one of the highest lipophilicity parameters of the common functional groups (Hansch constant; Π = 1.44) and strong electron-withdrawing properties.[3] Reports on the incorporation of SCF_3 into AAs or peptides have been scarce to date and mainly limited to trifluoromethionine (TFM) and trifluoromethylcysteine (TfmCys) derivatives. Recently, our group has reported that the incorporation of TFM or TfmCys into peptides leads to an outstanding increase in local hydrophobicity, making SCF_3 a group of interest in peptide design.[4]

We will present here our recent work focused on the methodology studies for direct electrophilic trifluoromethylthiolation of aromatic AAs and their biologically-relevant amine analogues. The method was applied to late-stage functionalization of aromatic AA-containing short peptides. SCF_3-AAs have also been used as highly hydrophobic building blocks in solid-phase peptide synthesis of peptides of interest, e.g. endomorphin-type analgesic tetrapeptides.



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P B066

Functionalization in position 6,6' of BINOL for the Synthesis of Supported Chiral Phosphoric Acids

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Asymmetric organocatalysis has proved to be an efficient way to obtain chiral multifunctional compounds rapidly and with good enantiomeric selectivity. Since the first work of Terada and Akiyama in 2004, Chiral Phosphoric Acid (CPA) have been shown to catalyze a large variety of asymmetric transformations. [1] However these organocatalysts can be obtained with a large number of steps or a rather expensive price, they are also difficult to recover easily.[2[

Immobilization on a support would be a solution to CPA re-use and recovery. We propose the use of magnetic iron nanoparticles (MNP) easy to obtain with low toxicity, a simple magnet is needed for their recovery.[3]

In order to link CPA on a support, introduction of a function is necessary. Herein, we will describe the synthesis of functionalized BINOL on 6,6' position with an allyl chain and an amine (Figure 1, Scheme 1).

We already proved the feasibility to link CPA to MNP with a double bond.[4]

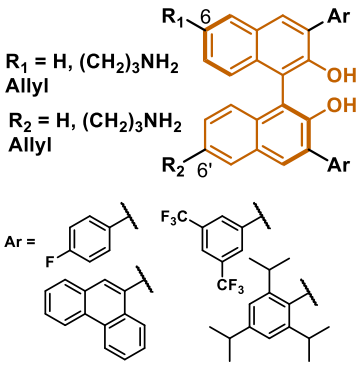
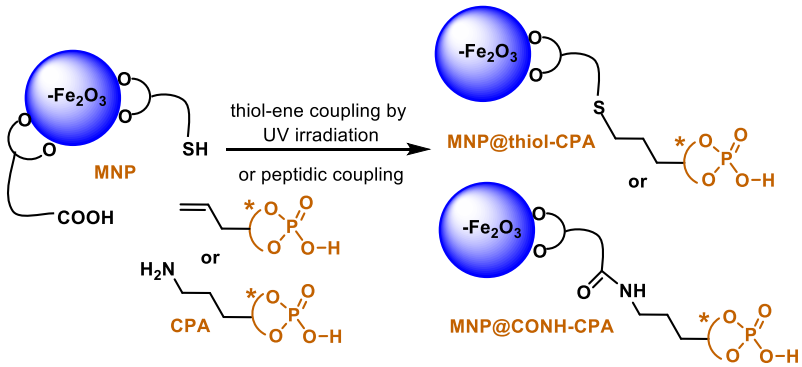


Figure 1



Scheme 1

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P B067

Catalytic Asymmetric Synthesis of Alkylidenecyclopropanes from Allenoates with Donor-acceptor and Diacceptor Diazo Reagents

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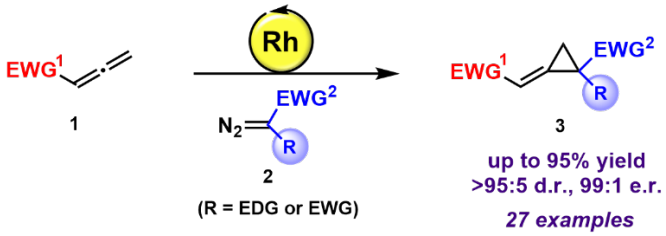
Enantioenriched alkylidenecyclopropanes (ACPs) are attractive structural motifs due to the high potential as synthetic key intermediates in a vast array of transformations.[1] Many syntheses of biologically important compounds were developed using ACPs as a strategic intermediate. The chiral transition metal catalyzed cyclopropanations of allene derivatives with diazo reagents are powerful pathways to access chiral ACPs with high levels of regio-, diastereo- and enantioselectivity. However, only a handful of catalytic asymmetric cyclopropanation reactions using electron-enriched allenes has been reported yet.[2] In addition, asymmetric cyclopropanation of less nucleophilic allenes such as allenoates to access chiral ACPs having electron-deficient olefin had never been reported.

Herein, we reported the first diastereo- and enantioselective cyclopropanation of allenoates **1** with donor-acceptor and diacceptor diazo reagents **2** to give optically active ACPs **3** bearing multiple electron-deficient substituents. The desired enantioenriched ACPs **3** were obtained in high yields with high diastereo- and enantioselectivities in the presence of Rh_2((*S*)-TCPTAD)$_4$ or Rh_2((*R*)-BTPCP)$_4$ catalysts (up to 95% yield, >95:5 d.r. and 99:1 e.r.). This methodology gave a direct access to ACPs bearing multiple electron-deficient substituents and allows to further expand the availability of ACPs chemistry.



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P B068

Cell permeabilty of cyclopseudopeptide: photoactivation and penetration mechanism

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A variety of uncharged cyclopeptides are found in nature, with their targets localized in the cell (cyclosporin A, griselimycin, FR235222 ...). However, their mechanism of cell penetration remains poorly understood. We have recently studied the case of a highly cell permeable cyclotetrapeptide inspired by FR235222 and identified that the presence of a "flexible" β turn allows it to easily adopt all the conformations necessary for its cell permeability (Figure 1A).[1,2]

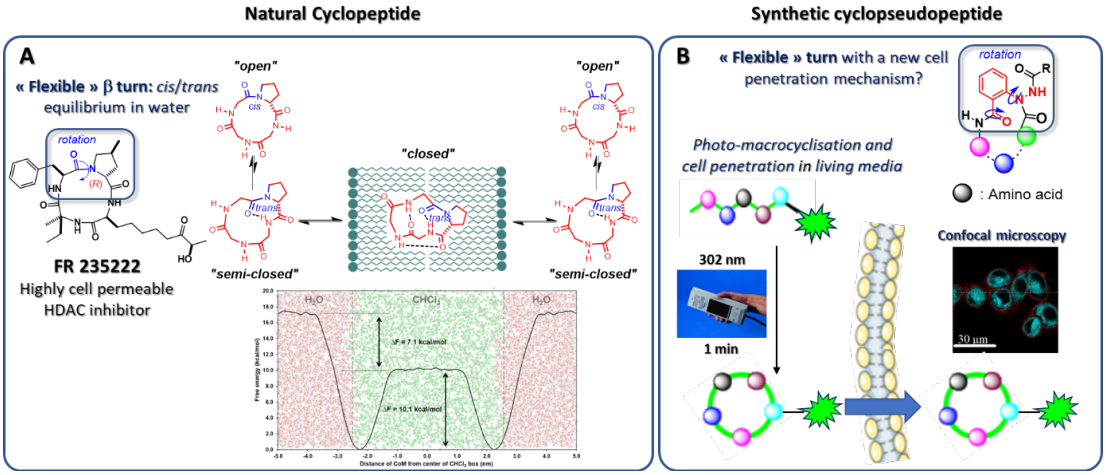

Figure 1

We would like to present our latest work on a new family of cyclopseudopeptides possessing a new "flexible" turn motif, the anthranilamide hydrazine function (Figure 1B in red). Moreover, its tetrazole precursor has the particularity of being photoactivatable to trap the carboxylic groups allowing to perform the macrocyclisation step.[3] We identified new cyclopseudopeptide frames that are highly permeable to cells. This strategy allows to make a linear peptide sequence highly permeable to cells by photo-macrocyclisation. Umbrella sampling,[4] biased molecular dynamics, reproduces the experimental results and provides insights to the cell permeability properties of our best compounds.

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P B069

Synthesis of hydrogen peroxide-sensitive caged nucleosides: access to antisense oligonucleotides

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Nucleic acids play a fundamental role in biological processes and are notably involved in the regulation and expression of genetic information. The modulation of their biological activities is of major interest in the development of therapeutic tools. Hence, the synthesis of antisense oligonucleotides (ASOs) represents an interesting therapeutic approach for the negative regulation of specific genes. By hybridization with their complementary mRNA, ASOs inhibit protein translation of specific proteins. [1] However, it is very challenging to control the activity of ASOs in a designated manner, which represents a major drawback for therapeutic applications.

In this context, we propose to develop *"caged"* antisense oligonucleotides, i.e., oligonucleotides whose biological function is temporarily blocked until restored by specific stimuli, thus allowing a high spatial and temporal control.[2] We are particularly interested in species that will react with hydrogen peroxide,[3] a reactive form of oxygen, involved in many pathologies such as cancers and neurodegenerative diseases.

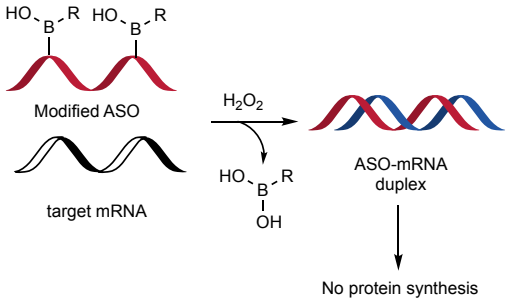

Figure 1. Schematic of H_2O_2-triggered ASO activation

We present herein our preliminary results on the synthesis of caged nucleosides possessing a borinic acid moiety as hydrogen peroxide-responsive trigger. Their reactivity toward H_2O_2 thus restoring the native nucleobase was also evaluated. Once incorporated into oligonucleotides, such caged nucleosides could find diverse applications as prodrug-type nucleic acid therapeutic for selective disease treatment.

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P B070

TMSCl/NaI a Useful Combination for the Deprotection of Dithioacetals

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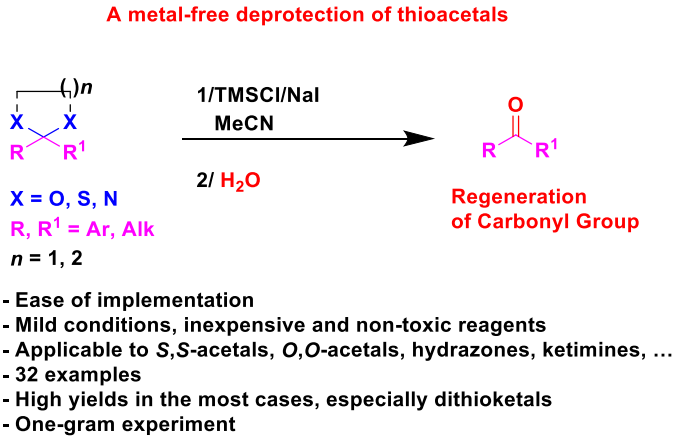
This presentation will be mainly focused on a combination of TMSCl and NaI in acetonitrile for deprotection of dithioacetals.[1-2]



As you could see, the picture shows the general chemical structures involved and main advantages. In conclusion, this is a mild process using a combination of TMSCl and NaI in acetonitrile is used to regenerate carbonyl compounds from a variety of dithiane and dithiolane derivatives. This easy-to-handle and inexpensive protocol is also efficient to deprotect oxygenated and mixed acetals as 1,3-dioxanes, 1,3-dioxolanes and 1,3-oxathianes quantitatively. As a possible extension of this method, it was also shown that nitrogenated substrates such as hydrazones, *N*-tosylhydrazones, and ketimines reacted well under these conditions to give the expected ketones in high yields. The methodology proposed herein is a good alternative to the existing methods since it does not use metals, oxidants, reducing agents, acidic or basic media, and keto-products were obtained in high to excellent yields.

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P B071

Metal-catalyzed hydrogen atom transfer-induced radical cascades for the formation of molecular complexity

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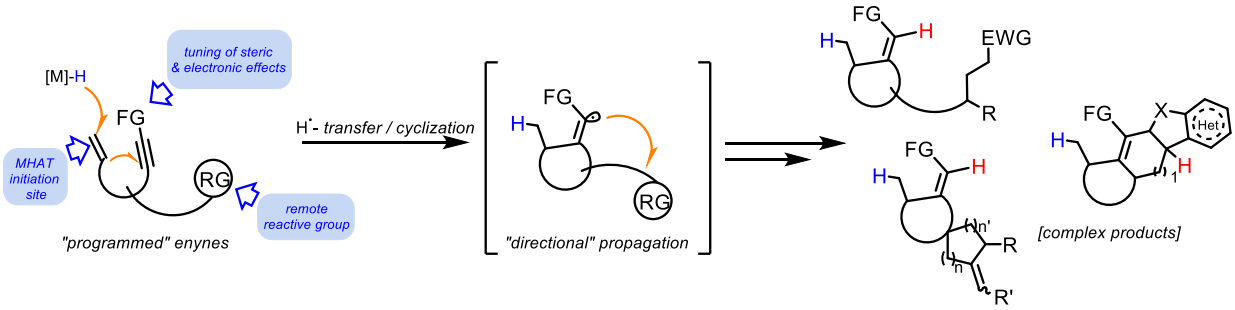
Radical reactions enabling C-C bond formation are in great importance due to radicals' high reactivity and early transition state, along with mild reaction conditions and functional group tolerance[1]. Therefore, sequencing such elemental radical steps into cascades[2] leads to attractive, atom economical ways to form complex structures. The synthetic value of radical cascades could be further increased if catalytic approaches, based on non-toxic earth-abundant metals, could be used.

Metal Hydrogen Atom Transfer (MHAT)[3] is a modern promising tool that was investigated in terms of various hydrofunctionalizations in numerous settings as well as multiple C-C bonding sequences[4]. However, more challenging enyne cascade sequences using this tool are underexplored.

Thereby, we intend to re-engineer MHAT reactivity in order to achieve a broader range of transformations via novel enyne cascade sequences. Our synthetic strategy is based on MHAT that will be used as a main prominent tool enabling access to a variety of complex and diverse (hetero)polycyclic scaffolds through radical cyclization cascades (Scheme 1).



Scheme 2

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P B072

Cobalt or Nickel Complexes Electrocatalyzed Asymmetric Carboxylation of Benzylic Halides with CO_2

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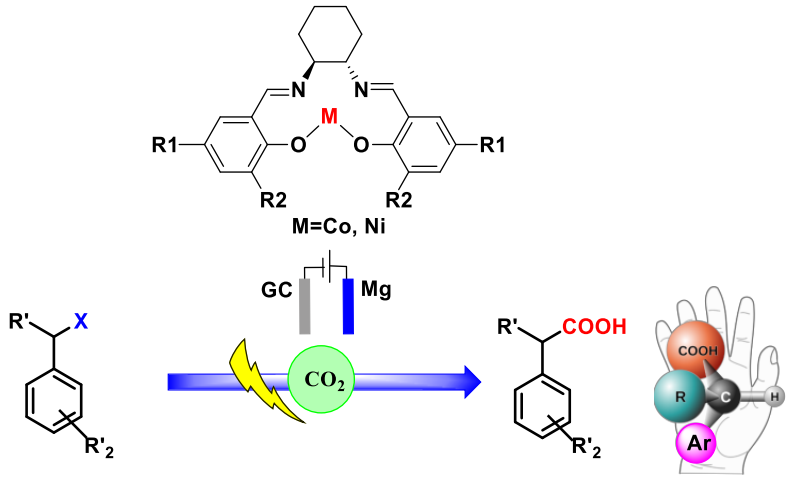
CO_2 is currently an obvious and practical C1 building block to construct C-C bonds since it is abundant, cheap, environmentally friendly, and inherently renewable. Over the past decades, many examples have been reported for the carboxylation of aryl and alkyl halides with CO_2 promoted by transition-metal complexes catalysis, photocatalysis, and electrochemistry.[1] Among these approaches, electrochemistry seems promising leading to more selective transformations. However, until now only a few studies deal with the asymmetric electrocarboxylation of organohalides with CO_2.[2] Meanwhile, these reactions are in great demand to overcome drawbacks such as limited substrate scopes and low yields.



Recently, our team developed efficient methods to achieve the electrocarboxylation of aromatic and aliphatic halides with CO_2 in the presence of $SmCl_3$.[3] Herein, we aim to study a new mild and effective route for the enantioselective electrochemical carboxylation of benzylic halides with CO_2 by using chiral transition metal complexes, such as cobalt and nickel chiral salen derivatives.

We will therefore present our results of several electrochemical studies to control the different parameters involved and our preliminary electrosynthesis results using these chiral salen complexes.

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P B073

Semi-hydrogenation of alkynes to E or Z-alkenes enabled by nickel and photoredox dual catalysis

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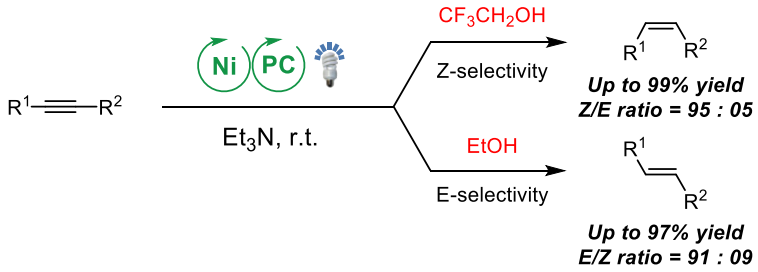
The development of reliable and predictable methods that can convert chemo- and stereoselectively alkynes to alkenes is of fundamental importance to industries and academia, owing to the prevalence of the alkene functionality in fine chemicals, pharmaceuticals and natural products.[1] The recent advent of nickel and photoredox dual catalysis has stimulated new conceptual strategies toward the conversion of alkynes to functionalized alkenes under mild conditions.[2] However, applications to semi-reduction reactions remain elusive in this area, with seminal examples being essentially based on heterogeneous catalyst systems and providing Z-alkenes, preferentially, with moderate levels of selectivity.[3] Herein, we report our preliminary results towards a nickel/photoredox-catalyzed new methodology enabling additive controlled semi-reduction of alkynes to E- or Z-alkenes using triethylamine and alcohol additives as effective sources of hydrogen atoms.



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P B074

Synthesis and Biological Study of Ganglioside GM3 Derivatives as Anticancer Vaccine Candidates

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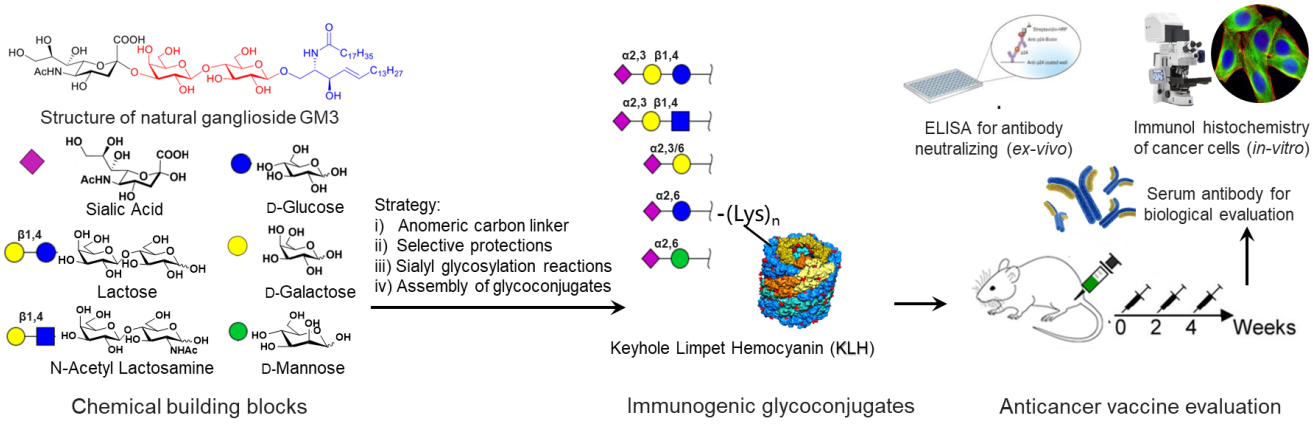
Glycosphingolipids (GSLs) are cell-surface antigens, and it was therefore suggested that changes in their composition would result in changes in the antigenicity (affinity to the corresponding antibody) and immunogenicity (ability to induce immune response) of the tumor cells expressing them [1]. As one of them, GM3 (Sia-α2,3-Gal-β1,4-Glc-β-Ceramide) is over expressed on some cancer cells, which makes it as a typical tumor-associated carbohydrate antigen (TACA) and as an important target for cancer vaccine development [2].

Although natural carbohydrates can be applied as vaccine components directly, in many cases chemical modification of carbohydrates is necessary for enhanced efficacy [3]. As one of our research projects on cancer therapy, we have synthesized previously a series of ganglioside GM3 analogues and evaluated their anticancer activities [4,5]. In this project, with building blocks of sialic acid (Sia), glucose (Glc), galactose (Gal), mannose (Man), lactose (Lac) and *N*-acetyl lactosamine (LacNAc), we plan to develop a new type of anti-cancer vaccine by using GM3 analogues as antigens, the compounds to be synthesized and their bioactivity evaluation scheme are shown as follows.



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P B075

The Role of Homocysteine in the Peptide Synthesis in the Origin of Life

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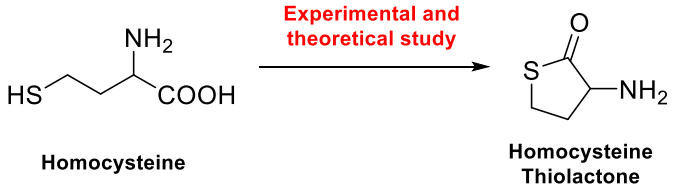
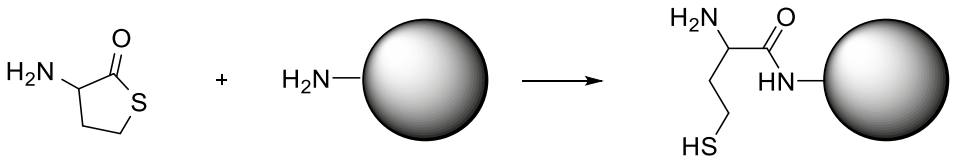
Homocysteine is not a proteinogenic amino acid. However, Its biochemistry is closely related to those of the two proteionogenic sulfur amino acids, cysteine and methionine[1]. This thiol containing amino acid is capable of forming an activated species intramolecularly, its thiolactone, which could have made it an interesting molecular building block at the origin of life on Earth.

First, we studied the cyclization of homocysteine in water and showed, theoretically and experimentally, that in an acidic medium the proportion of thiolactone is significant.



Then we studied the ability of the thiolactone to react with amino acids to form dipeptides. At pH 7 and 8, all tested reactions were efficient.



We also evaluated the reactivity of the *N*-formyl and the *N*-acetyl homocysteine thiolactone and their efficiency regarding peptides formation[2].

These intersting results showed us that although homocysteine does not participate in building proteins, It is still an important amino acid in the current metabolism.

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P B076
Synthesis of Novel N(SCF_3)(CF_3)-Amines

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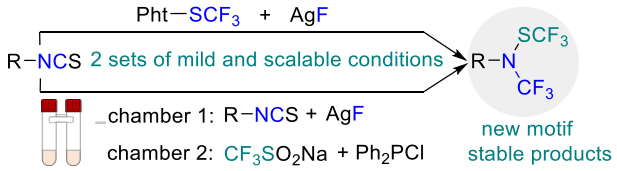
Organic fluorine chemistry is an important area of modern organic chemistry. The unique properties induced by the fluorine atom or fluorinated motifs including high lipophilicity, increased solubility and metabolic stability have witnessed the efforts for extensive development during the last years.[1] Nowadays, fluorinated molecules are widely used in agrochemicals[2] as well as in pharmaceuticals[3]. More recently, fluorinated amines have also attracted much attention. Indeed, N-CF_3 has demonstrated excellent in vitro aqueous stability which might improve metabolic stability and membrane permeability compared to their N-methyl counterparts. In this context, several groups developed straightforward procedures to access trifluoromethylated amines as well as bis(trifluoromethyl)amines. Therefore, there is a clear need for developing new motifs that could be easily and robustly accessible while modulating the properties around the nitrogen atom such as the lipophilicity In this context, we report herein an unprecedented, mild and efficient protocol for accessing novel *N*-((trifluoromethyl)thio)-*N*-(trifluoromethyl)amines starting from isothiocyanates and an electrophilic trifluoromethylthiolation reagent (**Scheme 1**).



Scheme 1

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P B077

A sydnone-based route to indazolo[2,3-a]quinoxaline derivatives

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Sydnones are mesoionic compounds well-known for their reactivity in 1,3-dipolar cycloadditions with strained alkynes (Strained Promoted Sydnone Alkyne Cycloaddition)[1] and with terminal alkynes in presence of copper catalyses (Copper Catalysed Sydnone-Alkyne Cycloaddition).[2]

Indazolo[2,3-a]quinoxaline derivatives represent an important class of antitumor drugs due to their ability to intercalate between the base pairs of double-stranded DNA, but only few procedures for their preparation are described in the literature.[3]

Herein, we described a new synthetic route to access to indazolo[2,3-a]quinoxaline derivatives from polyaromatic sydnones, which were prepared by a Staudinger/aza-Wittig reaction and a subsequent copper-promoted intramolecular cyclisation on the C-4 position of sydnones, in one single operation.

These polyaromatic sydnones can further undergo 1,3-dipolar cycloadditions in presence of arynes, generated from the corresponding Kobayashi precursors in presence of TBAF, to give the desired indazolo[2,3-a]quinoxaline products (Fig. 1).

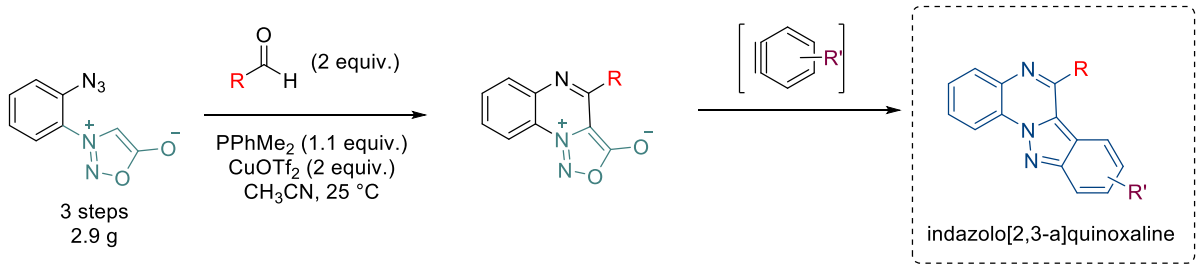

Figure 1 : Sydnone route to indazolo[2,3-a]quinoxalines

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P B078

Rhodium-mediated asymmetric transfer hydrogenation of 3-substituted chromones: a route to enantioenriched *cis*-3-(hydroxymethyl)chroman-4-ol derivatives through dynamic kinetic resolution

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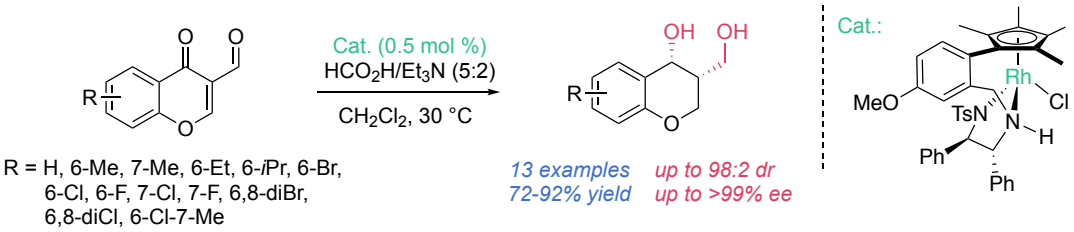
As part of our ongoing program aimed at developing efficient methods for the asymmetric reduction of functionalized ketones,[1] we developed a convenient method to access enantioenriched *cis*-3-(hydroxymethyl)-chroman-4-ol derivatives which were prepared by rhodium-catalyzed asymmetric transfer hydrogenation (ATH) of 3-formylchromones through a dynamic kinetic resolution process (DKR).[2] The reaction proceeded under mild conditions using a low catalyst loading of the in-house developed Rh(III)-complex[3] and HCO_2H/Et_3N (5:2) as the hydrogen source, delivering the reduced compounds in good yields, high diastereomeric ratio (up to 98:2 dr), and excellent enantioselectivities (up to >99% ee).[4] The 3-hydroxymethyl chromanols produced in this study can serve as useful scaffolds for further functionalization to access diversely substituted chromanol derivatives.



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P B079

Trifluoromethylselenolation of phenol derivatives under nickel catalysis

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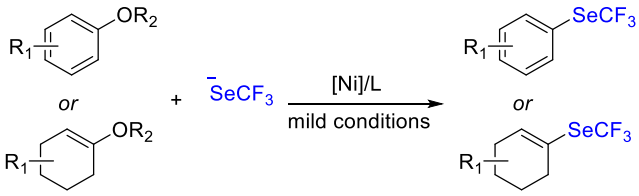
Organofluorine chemistry is a very active research topic in modern organic chemistry, driven by the interesting properties of fluorinated molecules in a plethora of cutting-edge applications. The incorporation of trifluoromethylchalcogene derivatives is by far the most investigated research area in organofluorine chemistry these last years. Herein, transition metals are playing pivotal role on the installation of chalcogen trifluoromethyl groups. Although, several procedures have been reported for the C-SCF_3 bond formations. Their selenylated analogues remains scarce. To date, only two examples of trifluoromethylselenolation of aryl halides catalyzed by nickel have been reported. [1,2] In this context, we turned our attention to the trifluoromethylselenolation of phenols derivatives. Herein, we report the first example of the trifluoromethylselenolation of phenols derivatives using nickel catalysis. The reaction proceeds under mild conditions and features a good functional group tolerance. The novel methodology was also applied to biologically active and pharmaceutical relevant targets, showcasing its robustness and wide applicability.[3]



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P B080

3-Sulfonyl Indoles *via* Gold- or Silver-Catalyzed Cyclization – 1,3-Sulfonyl Migration Sequences under Visible Light Irradiation

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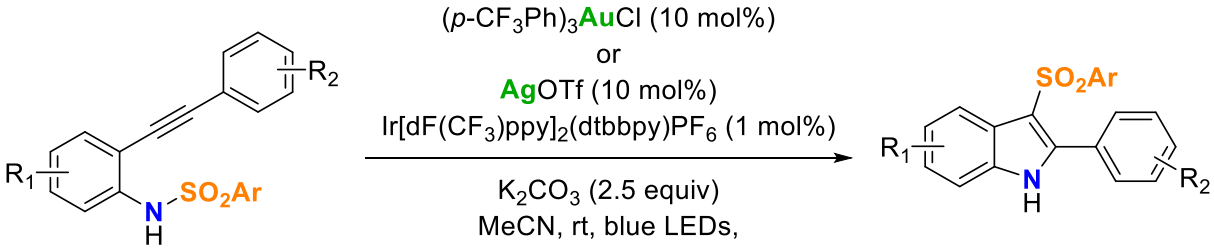
Indole structures are one of the most abundant skeletons in a wide variety of natural products and they are also useful targets in drug discovery.[1] Among them, 3-sulfonyl indoles show interesting biological activities, such as L-737,126, which is a non-nucleoside inhibitor of HIV-1 reverse transcriptase.[2] A pathway for the synthesis of 3-sulfonyl indoles has been devised. Upon blue LED irradiation, in the presence of a gold(I) or a silver(I) salt, 2-alkynyl *N*-sulfonyl precursors readily undergo a 5-*endo-dig* cyclization concomitant with a 1,3-sulfonyl migration. While the gold-catalyzed reaction takes place in photocatalyst-free conditions, an iridium photocatalyst ($Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$) is necessary with silver catalysis. Mechanistic studies featuring the generation of a sulfonyl radical support this dichotomy.



R_1= H, Me, Cl
R_2= Me, OMe, F, Cl, CF_3

48-65% yields

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P B081

Optically Pure Atropisomeric-NHC Ruthenium Complexes for (*Z*)-Asymmetric Ring-Opening Cross Metathesis

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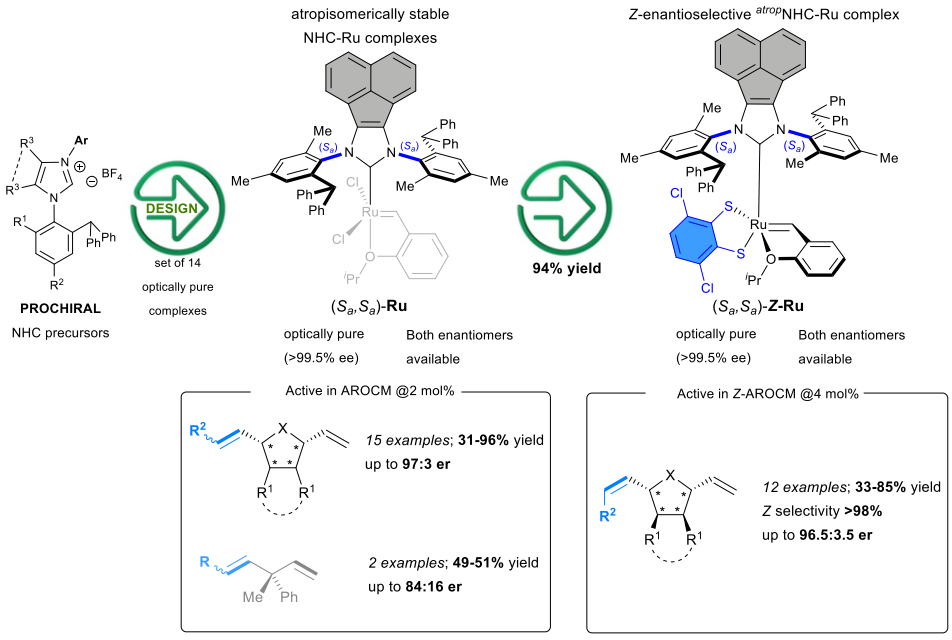
During the last decades, olefin metathesis has emerged as one of the most powerful methods to create new carbon-carbon bonds.[1] In addition to the inherent *Z*/*E* selectivity, metathesis can provide access to enantiomerically enriched products when symmetrical starting materials are used. Despite several developments, combining *Z*-selectivity with enantioselectivity remains a challenging task. In this work, optically pure ruthenium complexes containing atropisomerically stable N-Heterocyclic Carbene (NHC) ligands are described.[2] Isolated in excellent optical purities (up >99.5% ee) by a successful chiral HPLC resolution on a chiral stationary phase, these catalysts demonstrate excellent enantioselectivities in asymmetric ring-opening-cross metathesis (AROCM) (up to 97:3 er). Additionally, optically pure Z-stereoretentive catechodithiolated complexes were also synthesized in nearly quantitative yield (or in-situ generated), furnishing enantioenriched *Z*-AROCM products in excellent 99:1 *Z*:*E* ratio with high enantioselectivity (up to 96.5:3.5 er).



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P B082

Crossing indazole and benzothiadiazole or benzoselenodiazole: toward new fluorophores and photosensitizers

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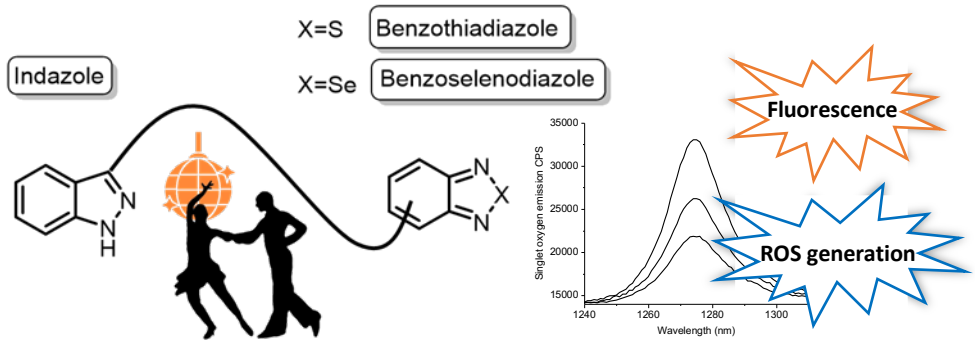
Indazole moiety is one of the most important heterocyclic systems in drug development. Besides being involved in many commercially available drugs, indazole derivatives exhibit a wide range of pharmacological activities as well as improved biostability compared to indoles. On the other hand, benzothiadiazole (BTD) and benzoselenodiazole (BSD), are efficient electron-withdrawing cores which were popularized by OLED technology and dye sensitized solar cells due to their photostability.[1] However, both moieties remain relatively unexplored for developing fluorescent small molecule probes and photosensitizers. In this context, indazole as electron-donor was crossed with BTD/BSD to design a new D-π-A conjugated system. In this purpose, an efficient late-stage coupling synthesis[2] was developed. Moreover, the optical properties of these compounds were studied, showing promising brightness and/or ROS generation under light irradiation.



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P B083

Total Synthesis of Terpene Natural Products

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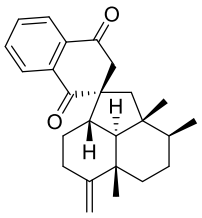
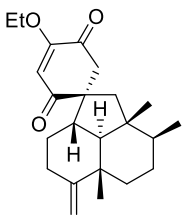
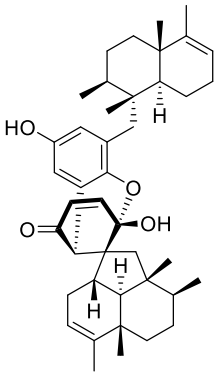
Our objective during this project is to carry out the total synthesis of natural products possessing a spirocyclized sesquiterpene quinone motif. Thus, spiroetherones A and B[1], septosones B and C[2] and dysiarenone[3], which have been isolated from marine sponges, are attractive synthetic targets. One of the challenges of this project will be to build the spirocyclic motif of these compounds and even more interestingly, to obtain the tricyclic central part of dysiarenone in a bioinspired manner.



Spiroetherone A



Septosone B



Dysiarenone

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P B084
Electrochemical Silylation Reactions

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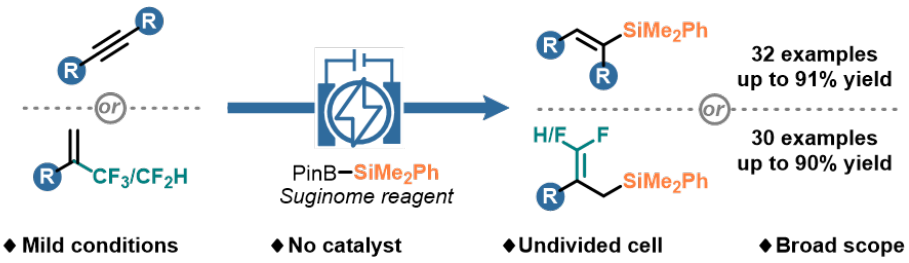
Silicon-containing molecules are key compounds in organic synthesis and found widespread application in material and life sciences[1] as well as in drug discovery programs.[2] In addition, organosilicon species are strategic building blocks with application in various important transformations (*e.g.* Hiyama-Denmark cross-coupling, Brook rearrangement, Hosomi-Sakurai allylation…). Reaction to form organosilicon species mainly rely on the use of expensive transition metal complexes (*e.g.* Speier and Karstedt catalysts), although outstanding progress in the development of earth abundant metal catalyzed reactions were recently outlined.[3] Very recently, under the auspices of photocatalysis, an impetus to design new silylation reactions, through the generation of silyl radical, was witnessed and significant contributions were reported.[4] Electrosynthesis has known a resurgence of interest and allowed the design of challenging transformations in a sustainable manner.[5] Considering these statements, we have developed a method for the electro-generation of silyl radicals from the Suginome reagent ($PhMe_2Si$—BPin). This strategy was used to develop the electrochemical hydrosilylation of alkynes and the electrochemical defluorosilylation of α-(di/trifluoromethyl)styrenes to access fluorinated allylsilanes.[6]



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P B085

Development of new Calcium-Catalyzed Cascade Reactions

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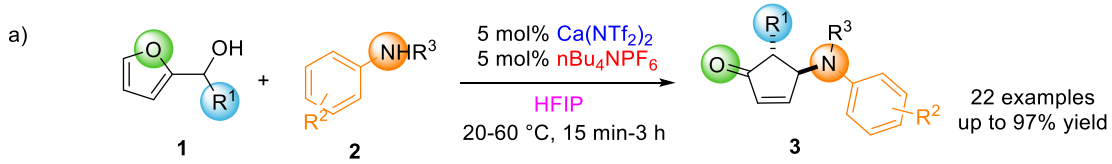
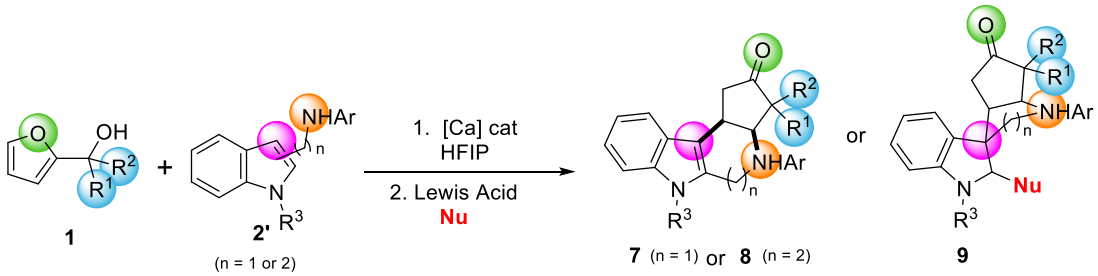
Since the Niggemann's group demonstration of the activation of $Ca(NTf_2)_2$ by an ammonium salt of a weakly coordinating anion such as nBu$_4$NF$_6$ to give a highly oxophilic Lewis, calcium-based Lewis acids has attracted much attention in organic synthesis.[1] In our previous works, we reported the use of such catalysts in combination with hexafluoroisopropanol (HFIP) as solvent, especially for the promotion of the aza-Piancatelli reaction (scheme 1).[2] Exploitation of this catalytic system in one-pot reaction sequences featuring the aza-Piancatelli reaction as a key step allowed the access to previously inaccessible compounds such as cyclopenta[*b*]pyrroles **4**,[3] cyclopenta[*b*]piperazinones **5**[4] and tetrahydrobenzo[*b*]azepines **6**.[5]



Scheme 1. Calcium-catalyzed aza-Piancatelli reaction in HFIP developed in the lab.

Our preliminary results onto the development of new catalytic cascade reactions using anilines **2'** bearing an indole moiety to access to biologically relevant polycyclic skeletons such as tetrahydro-β-carbolines **7**, cycloheptaindoles **8** or spiroindolines **9** (Scheme 2) will be presented.



Scheme 2. Preparation of tetrahydro-β-carbolines **8**, cycloheptaindoles **9** or spiroindolines **10** using a calcium-catalyzed aza-Piancatelli reaction as a key step in cascade reaction.

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P B086

Electrochemical Difluoromethylation of Alkenes

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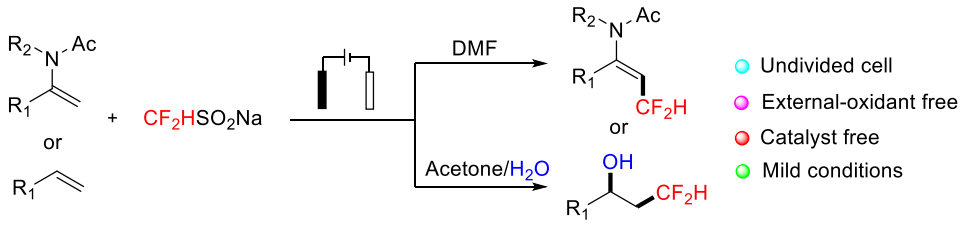
Organofluorine compounds play a crucial and prominent role as privileged scaffolds in the development of agrochemicals and pharmaceuticals, because of their unique biological, physical, and chemical properties, and their ability to enhance the metabolic stability and lipophilicity.[1] Therefore in the past few decades impressive advances have been made in fluorination and trifluoromethylation of molecules.[2] In contrast, simple and widely applicable introduction of a difluoromethyl (CF_2H) group to various carbon skeletons is still underdeveloped, although the CF_2H motif exhibits impressive bioisosteric properties.[3]

To date, radical difluoromethylation reaction has been one of the most employed approaches to forge CF_2H-containing chemical products.[4] In that purpose, various CF_2H-based reagents have been developed for the difluoromethylation of alkenes and (hetero)arenes. Although significant milestones were reached, rare examples of direct difluoromethylation of alkenes have been disclosed.[5]

As a green and enabling synthetic tool, organic electrochemistry has been gaining increasing attraction during the past decade.[6] Herein and as part of our ongoing program dedicated to the development of original electrochemical transformations,[7] we disclosed the electrochemical 1,2-hydroxydifluoromethylation and C–H difluoromethylation of alkenes using CF_2HSO_2Na as readily available CF_2H source. Importantly, no transition metal catalysts, nor external chemical oxidants are needed for these transformations.



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P B087

α-Trialkylsilyl-α-diazoacetones: polyfunctional building blocks to create molecular diversity

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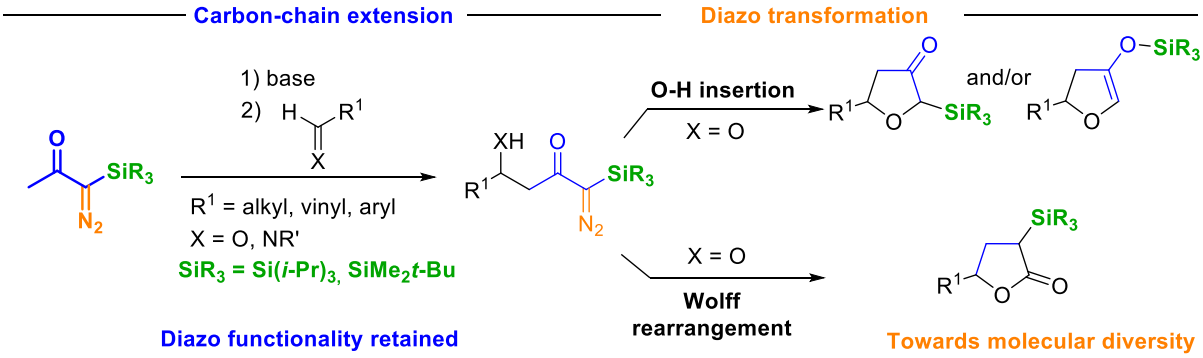
Diazocarbonyl scaffolds are well-known as a powerful source of molecular diversity through the numerous chemical transformations that can be performed on the C=N_2 moiety such as cyclopropanation, X-H insertion or Wolff rearrangement.[1] In this field, our project aims at studying the synthetic potential of *α*-trialkylsilyl-*α*-diazoacetones.[2] On this polyfunctional three-carbon building block, the trialkylsilyl group acts as a temporary protection of the most reactive diazo carbon in order to allow carbon-chain extension while constituting a source of diversity afterwards. We will focus here on the synthesis and aldol-addition of α-trialkylsilyl-α-diazoacetones in order to access original *C*-trialkylsilyl diazoaldols and related scaffolds.[3] In addition, preliminary results concerning the transformation of the retained diazo moiety by intramolecular O-H insertion or Wolff rearrangement will be presented, targeting synthetically useful silylated 5-membered heterocyclic scaffolds.



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P B088

Upgrading Phosphinoferrocene Structures through Catalytic C–H Bond Arylation

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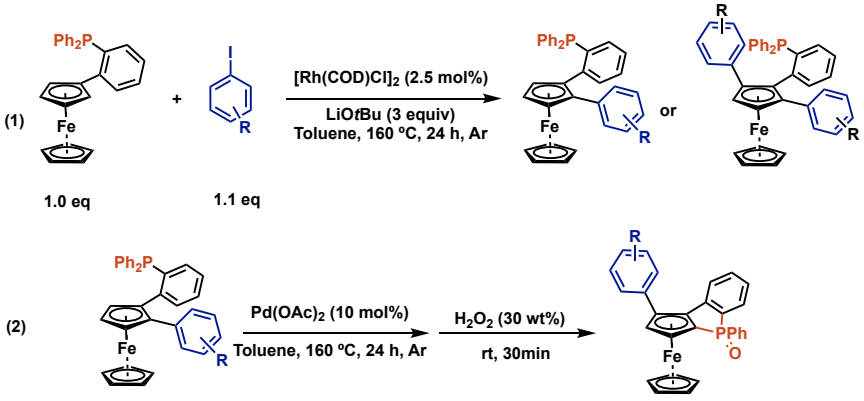
Phosphorus-containing molecules represent a powerful and prominent platform for forming active motifs pervasive in bioactive drug molecules and materials.[1] Moreover, phosphines widely serve as ligands in catalytic transformations, allowing to discover of novel reactivities and/or alternative regio- or chemoselectivity.[2] Combined with ferrocene scaffolds, such hybrid structures have also proven to be privileged ligands in asymmetric catalysis.[3] However, phosphino-ferrocene is found little application in materials sciences due to challenging access to molecular diversity.[4]

Following the pioneering work of Hartwig and co-workers on Pd-catalyzed direct polyarylation of 1-(di-*tert*-butylphosphino)ferrocene,[5] and our recent work on P(III)-chelation-assisted C–H bond functionalization of biarylphosphines,[6] we turned our attention to C–H bond functionalization of 2-[2-(diphenylphosphino)phenyl]ferrocene. We discovered that C–H bond arylation occured regioselectively on the same Cp ring at the *ortho*-position of 2-phosphinophenyl unit. The system employs a rhodium(I) center, and the P(III) atom acts as the directing group. Moreover, catalytic conditions to transform these modified phosphinoferrocenes to phosphole derivatives for material applications will be also presented.



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P B089

Construction of enantioenriched fused bicyclic piperidines through a multicatalytic sequence merging gold and amine catalysis

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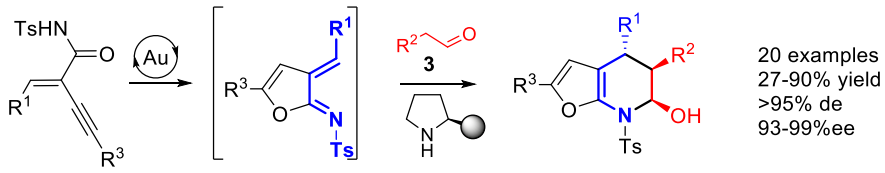
Asymmetric catalysis remains a challenge to synthetic chemists as the demand for enantiomerically enriched drug-like molecules continues to increase.[1] The development of multicatalytic processes using the complementary of distinct catalysts for consecutive transformations in a single flask has allowed the construction of enantioenriched complex structures from readily available starting materials.[2]

In this context, a series of enantioenriched fused bicyclic piperidines were accessed by a cycloisomerization/cycloaddition strategy. Starting from ynamide derivatives and aldehydes, good yields and high levels of stereoselectivity were obtained through sequential relay catalysis. The concurrent use of a gold complex with a diphenylprolinol silyl ether was applied to a combination of diversely functionalized substrates.[3]



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P B090

Regioselective C(sp^3)–H Bond Arylation of Allylamines by Dual Photoredox and Nickel Catalysis

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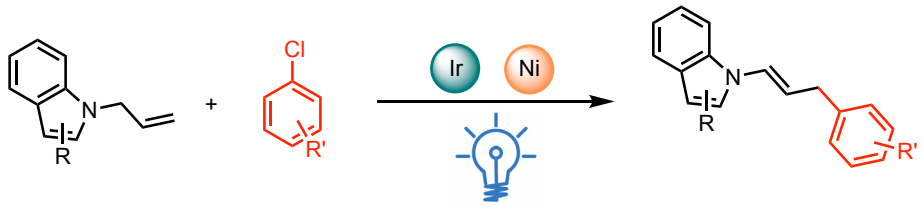
Allylation reaction is a textbook organic reaction widely employed in synthesis because the resulting products are valuable and versatile building blocks. Moreover, their omnipresence in bioactive species makes them valuable in the medicinal science and pharmaceutical industries. Among the various methods to access allylarenes, the noble metal-catalyzed allylic substitution of pre-activated allylation agents (*e.g.*, allylic carboxylates, carbonates, and halides) with aryl nucleophiles have been extensively studied.[1] Recent efforts have focused on converting C(sp^3)–H bonds directly to C(sp^3)–C bonds to minimize pre-functionalization and streamline the synthesis of complex molecules.[2-4] This strategy has been widely applied for the allylation of C(sp^2)–H bonds using pre-activated allylation agents and transition metal catalysis.

In view of the above studies and the emergence of the merge of nickel(0) with photoredox catalysis,[5] we decided to investigate a reverse strategy, namely the direct arylation of C(sp^3)–H allylic bond. With the optimal conditions in hand, we investigated the allylic C–H alkylation of N–allyl heterocycles with various aryl chlorides. The reaction is regioselective and gives only linear products. The reaction may involve the formation of a radical cation of N–allyl heterocycle followed by H-atom transfer to deliver a C-center radical, which can react with Ni^{II}-Ar complexes.



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P B091

On the reactivity of *N*-substituted imidates towards 1,4-bisnucleophiles: An experimental and theoretical study

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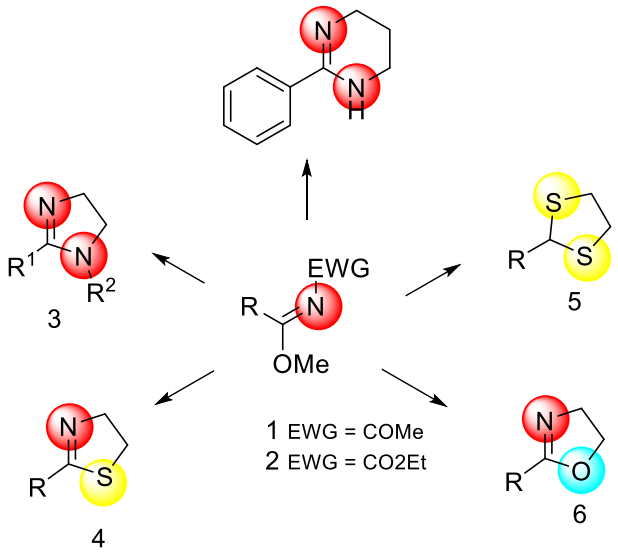
This work focuses on the use of N-acylates and *N*-ethoxycarbonylated imidates in heterocyclic synthesis. The action of bisnucleophiles-1,2 and -1,3 made it possible to obtain various families of heterocycles with 5 and 6 chains.[1,2] As a follow-up to this line of research, the reaction of *N*-acyl and *N*-ethoxycarbonyl imidates with 1,4-bisnucleophiles is described here. This reaction selectively led to 5-membered heterocycles in good yields instead of expected 7-membered ring systems. Besides, 2-imidazoline, benzimidazoline, 2-oxazoline, and 2-thiazoline derivatives were obtained under mild reaction conditions. These experimental results were further supported by theoretical DFT calculations. Additionally, our approach has been further extended to 1,5 bis amines towards tetrahydropyrimidine scaffolds.



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P B092

Membranotropic peptides modified by constrained amino acids: between conformation and membranotropic properties

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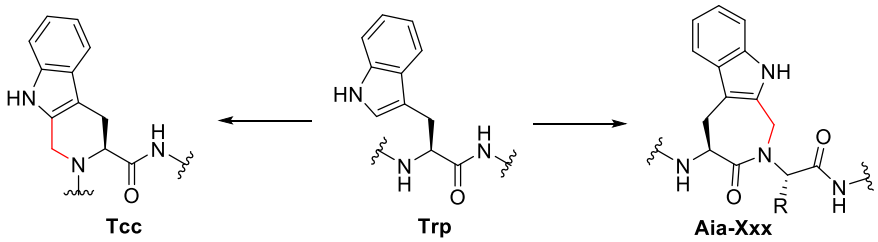
Fusion peptides (FPs) are short and hydrophobic sequences that are found in viral proteins. FPs are able to insert into cellular membrane to subsequently allow the viral membrane to merge during the infection process.[1] Our group developed a vectorization method using FPs of hepatitis C virus (HCV) as anchors into biological membranes.[2] However, preliminary results showed a moderate membranotropic activity probably due to their lack of structuration - a crucial feature for membranotropic interactions.

Therefore, it was suggested to introduce constrained amino acids to induce or facilitate peptide structuration. Interestingly, membranotropic peptides often bear aromatic residues and particularly tryptophan (Trp) residues.[3] Thus, the constrained Trp surrogates (**Tcc** and **Aia-Xxx**) were chosen as local constraints to be incorporated in membranotropic peptides. These cyclic surrogates present constrained dihedral angles and limited side chain orientation which may influence the peptide's structure or its membrane activity.[4]



By means of this project, we intend to study the influence of local constraints on the membrane activity or the peptide's structure in four references peptides: one CPP (**RW9**) and three viral peptides (**HCV7**, **Flav** and **C8**). The membranotropic activity of these peptides was tested by monitoring the indole fluorescence in presence of liposomes.[5] While the incorporation of a single **Tcc** did not seem to promote membrane insertion, modifications with several **Tcc** as well as one **Aia** restored or even enhanced membranotropic activities.

The first results of structural studies (CD and MD simulations) highlighted the gain of structuration of modified sequences compared to the native ones. Furthermore, MD simulation results in presence of membranes seem to be in accordance with the experimental ones.

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P B093

Ruthenium Catalyzed Enantioselective Cyclopropanation of Allyl Derivatives with Ethyl Diazoacetate

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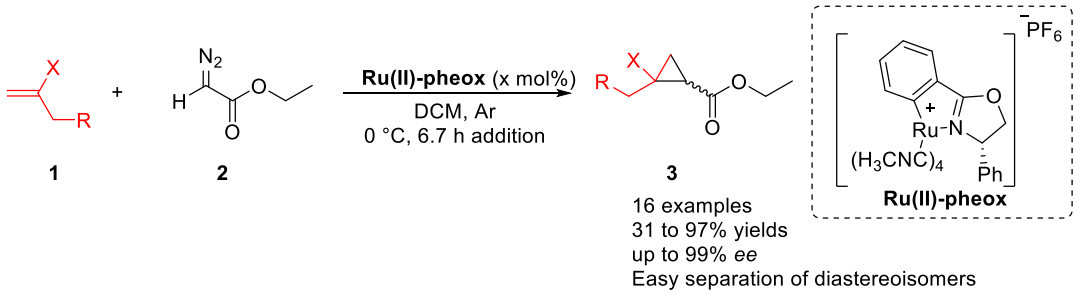
As an important organic motif with smallest carbocycle and largest ring strain, cyclopropane possesses unique properties comparing to other cycloalkanes.[1] It widely exists in nature products as well as it is widely used in medicinal research programs to improve the pharmaceutical profile of drugs candidates.[2] Along with the development of organic and pharmaceutical chemistry, versatile molecules containing cyclopropane fragments, especially optical active ones, are demanded increasingly year by year.[3]
In this work, we described a methodology using the Ru(II)-pheox complex to carry out very efficiently the cyclopropanation between a large range of allylic derivatives (bearing important functional groups such as sulfones, silanes or halogen atoms) and mono-acceptor ethyl diazoacetate. The expected cyclopropanes were obtained in moderate to excellent yields (31-97%) and excellent ee (up to 99%) for each diastereoisomer.



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P B094

Efficient Pd-catalyzed S-glycosylation of cysteine containing peptides at room temperature

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Glycosylation of polypeptides plays essential roles in a wide range of biological processes, such as immune response, viral infection, and cancer metastasis[1]. Compare to *O*-glycans, S-glycosylation on the cysteine residues is less common, but still has unique advantages. S-glycans are considerably more resistant toward chemical hydrolysis and enzymatic degradation, and thus have longer lifetimes in biological systems[2]. Due to these advantages, the development of novel methodologies for the efficient and selective synthesis to prepare S-linked glycopeptides and glycoproteins under mild reaction conditions has attracted tremendous attention.[2]

In continuation of our work in glycochemistry[3], here we report a palladium catalyzed strategy for S-glycopeptide synthesis (Figure 1). This method which involves the use of stable 1-iodoglgcals as the glycosylating agents with various unprotected peptides proceeds under mild reactions conditions and in a highly selective fashion.[4]

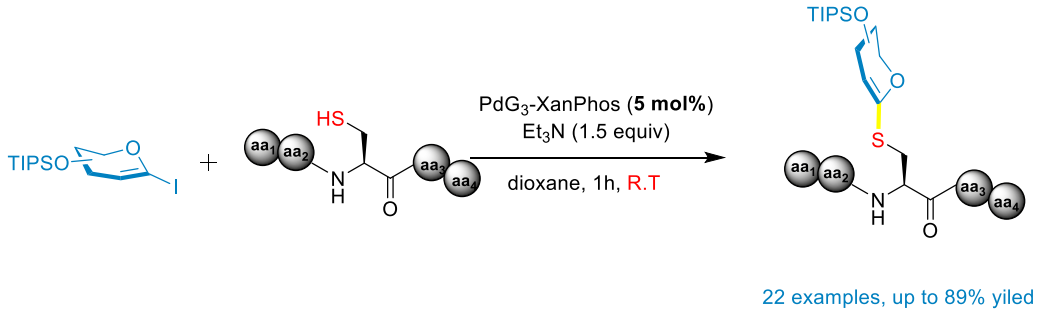

Figure 1.

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P B095

Synergistic hydrogen bonding and anion-π interaction for anion recognition

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Anion recognition is one of supramolecular chemistry pillars. It is based on the association between an anion and a host via specific noncovalent interactions in order to form host-guest complexes. This phenomenon underlies some organocatalysis processes[1] and many biological functions such as transmembrane anions transport [2]. In this regard, a new family of bifunctional anion receptors has been designed by associating a urea, as hydrogen bonding donor and a tetrazine as a fluorescent anion-π interaction donor.[3] Both moieties are separated by a flexible linker. In this work, the impact of the H-bond strength and the linker flexibility on the complexation have been evaluated by DFT calculations and experimental studies (NMR titration and photophysics).

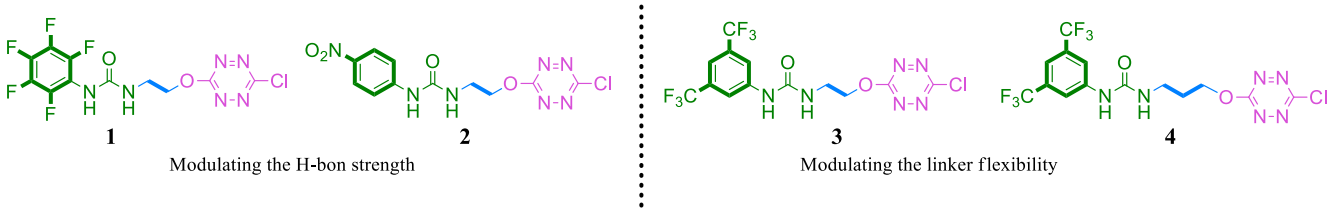

Figure 1: New family of anion receptors combining a hydrogen bonding donor and an anion-π interaction donor

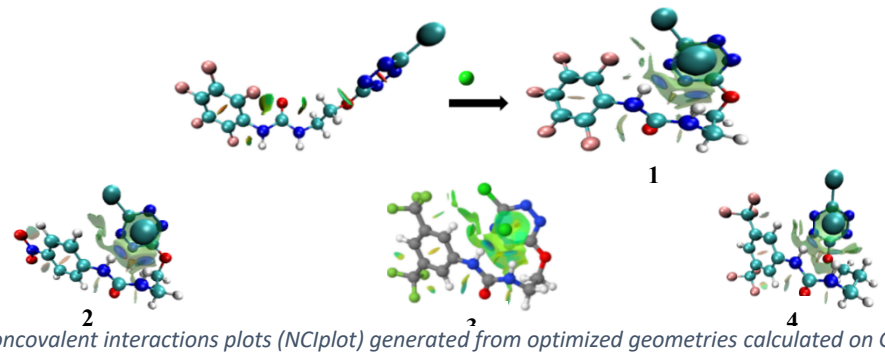

Figure 2: Noncovalent interactions plots (NCIplot) generated from optimized geometries calculated on Gaussian software

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P B096

Double addition of propargylzinc reagents onto acylcyanohydrins and cyanocarbonates

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Amines bearing a tertiary carbon (tertiary carbinamines) are present in various natural products and synthetic bioactive compounds such as alkaloids for instance.[1] Usual accesses to these compounds are the Ritter reaction,[2] the use of nitro compounds[3] or the addition to imine derivatives,[4] but these methods require several steps to afford the tertiary carbinamines. In this context, the double addition of organometallics onto nitriles represents an attractive and convergent alternative.[5] Indeed, this reaction is generally limited to a single nucleophilic addition which affords ketones after acidic hydrolysis. Our team recently reported the double addition of organometallic reagents onto acylcyanohydrins to access tertiary carbinamines.[6] The topic of this communication deals with the development of efficient and mild conditions to extend the methodology to the double addition of propargylzinc reagents onto acylcyanohydrins and cyanocarbonates. This synthetic tool will allow the straightforward preparation of functionalized α,α-disubstituted hydroxyamides and *N*-Boc-protected amino alcohols. The valorization of the so-obtained compounds will be highlighted by cobalt-catalyzed [2+2+2] cycloaddition reactions to provide functionalized pyridine derivatives.

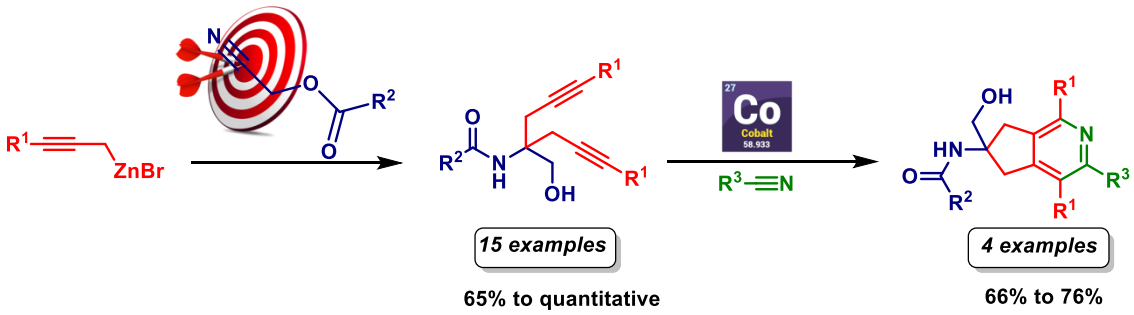

Figure 1: Double addition of propargylzinc reagents onto acylcyanohydrins

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P B097

DFT study of the Rhodium(II)-Catalyzed C(sp^3)–H Amination of Propylbenzene

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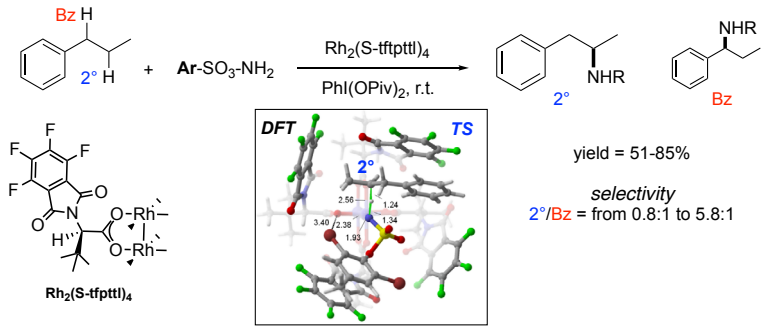
The design of site-selective C–H functionalization reactions is a great challenge with important applications in organic synthesis. Dirhodium(II) complexes are among the best catalysts to perform selective insertion of nitrenes into C(sp^3)-H bonds.[1] In this respect, recent experimental results showed a remarkable selectivity for the amination of propylbenzene with the dirhodium complex Rh_2(S-tfpttl)$_4$ as a catalyst. To understand this selectivity, we perform a DFT calculation to reveal the structural and electronic factors guiding the catalytic system. Our strategy involves evaluating the mechanism by Density Functional Theory (DFT) to disclose the electronic or steric factors controlling the selective functionalization of the secondary (2°) vs activated benzylic (Bz) C–H bond.



In this study, we computed the general mechanism for the formation of the C-H bond which involves either *i)* a concerted C–H insertion or *ii)* a stepwise process of hydrogen atom abstraction, followed by radical recombination. We analysed the aromatic substitution of phenolsulfamates used as the nitrene source and the full atoms of the Rh_2(S-tfpttl)$_4$ catalyst. A thorough examination of all the possible substrate approaches and spin states was also conducted to highlight the preferential pathway.

The mechanism found computationally indicates that the singlet concerted mechanism was favoured, with a hydride-transfer preferentially occurring at the non-activated 2° position as observed experimentally. These results[2] provide insight from a mechanistic viewpoint and suggest that the role of the catalysts pocket in Rh-Rh is important to control the regioselectivity of the C(sp^3)-H amination. In this context, we also applied the Activation Strain Model method to understand the factors controlling the selectivity. Our results evidenced the role of our catalysts' pocket preorganization in stabilising key intermediates, thus influencing the activations barriers for the C–H amination.

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P B098

New access to spiroketal enol ethers derivatives under relay catalysis

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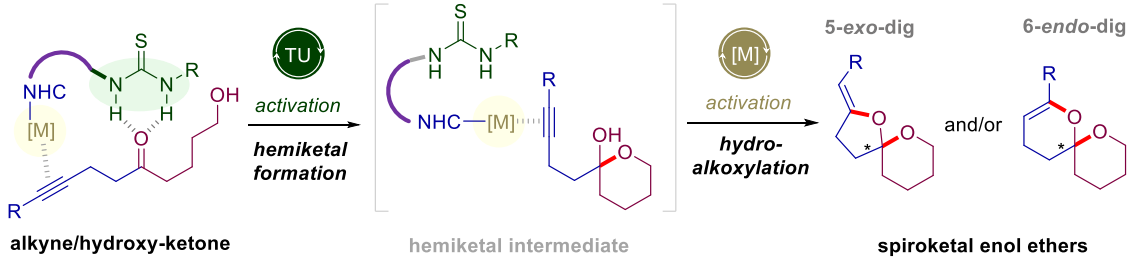
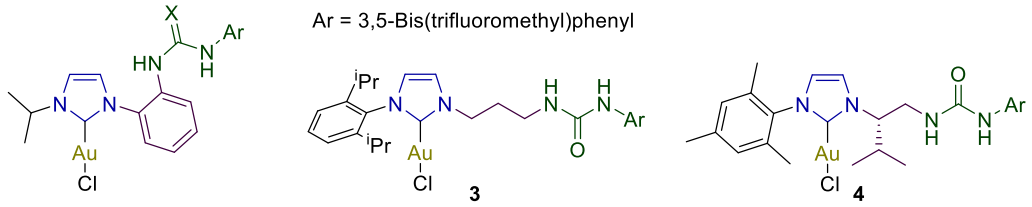
The main goal of this project is to develop a new and efficient access to chiral spiroketal enol ether derivatives from simple achiral substrates. For this transformation, it was intended to make use of the potential of relay catalysis, combining activation of the carbonyl functionality with thiourea[1] and activation of the alkyne functionality with transition metal from group 11 with π-acid properties.[2] For this purpose, new bifunctional catalysts were synthesized, using NHC catalysts already prepared in the group as a template.[3]



4 new catalysts were then prepared: 3 achiral catalysts with aryl and alkyl linkers either with urea or thiourea moieties and 1 chiral catalyst containing an urea moiety.

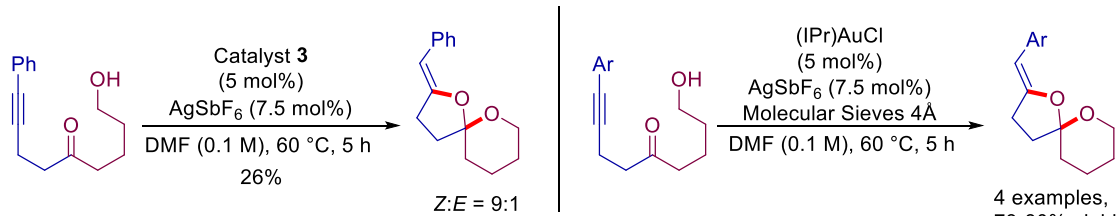


1, X = S, 6 steps, 19% overall yield
2, X = O, 6 steps, 22% overall yield

6 steps, 11% overall yield

8 steps, 18% overall yield from L-Valinol

The desired spiroketal enol ether was obtained in 26% yield using catalyst **3**. After optimization of the reaction conditions, it was found that the urea moiety was not needed and that commercial catalyst (IPr)AuCl was more efficient.



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P B099
Synthesis of photoswitchable glycomacrocycles as chiral dopants for liquid crystals

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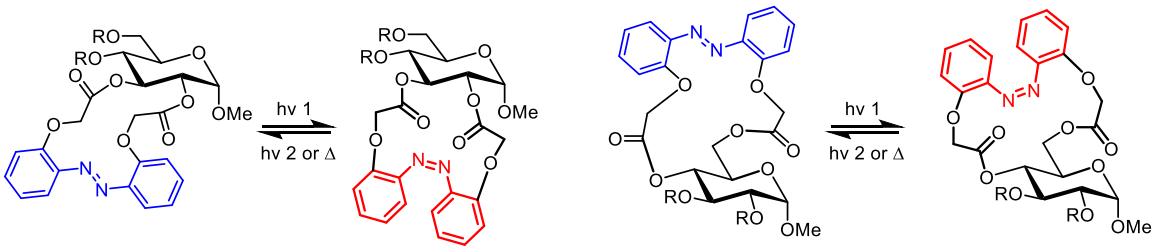
Glycomacrocyclic compounds are of growing interest because of their natural existence, their interesting biological, physicochemical properties, and potential applications in various fields.[1] Photoswitchable molecules can be reversibly isomerized by light into isomers featuring different structural and electronic properties, such as azobenzene.[2] Photoresponsive liquid crystalline (LC) system has attracted considerable interest to a very promising area of soft photonics and mechanics.[3] Under light irradiation, it is possible to modulate or switch the orientation of LC molecules to achieve desired optical and mechanical properties of this system remotely and selectively. Photo-tunable self-organized helical superstructures of cholesteric liquid crystals (CLCs) have shown promising results. Its helical orientation and pitch length can be dynamically light-controlled enabling the practical photonic applications. The most convenient and economical approach to obtain CLCs is to add a chiral dopant into a commercially available achiral nematic liquid crystal host at the appropriate concentration to induce selective reflection in the wavelength of interest.[4] We have demonstrated the promising properties of azobenzene-derived glycomacrocycles as chiral dopants in providing dynamic control of helical superstructures in response to light stimulus.[5]

In this project, we decide to develop photoswitchable glycomacrocycles containing azobenzene and natural carbohydrate which are linked at 2, 3 or 4, 6 positions of carbohydrates to take advantage of their innate chirality for chirality transfer. By introducing different R groups on 2, 3, or 4, 6 positions of the carbohydrate (structures as below), we will explore the influence in LC system. Then, we will study their photophysical and photochemical properties in order to identify some good candidates as potential chiral dopants for liquid crystals.



R = H, C_6H_{13}, Ac, $C_5H_{11}CO$

Figure: Structure and isomeration of target photoswitchable glycomacrocycles

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P B100

Synthesis of water-soluble glycosyl azobenzenes and their photoswitching properties in water

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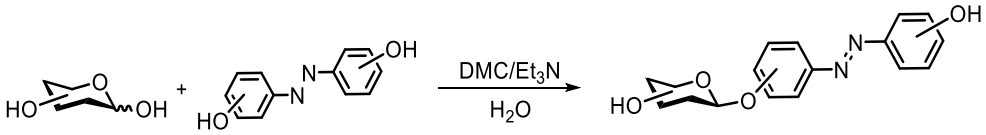
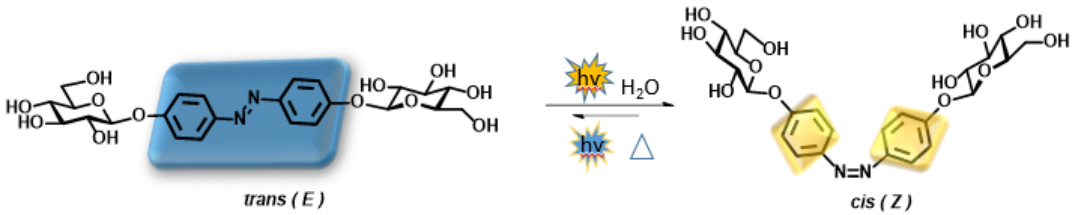
Molecular photoswitches with photoswitching ability in aqueous medium are highly demanding for biological applications and photopharmacology.[1,2] However, the commonly developed photoswitches like azobenzenes, diarylethenes are barely soluble in water. Linking carbohydrates to a photoswitching unit is an interesting approach to obtain water-soluble photochromic compounds. Since several years, azobenzene-functionalized photoswitchable glycoconjugates have been developed for light-controlled carbohydrate-protein interactions,[3] cell adhesion,[4] enzyme inhibitors[5] and glycolipid mimics[6], and so on. However, glycosylation with unprotected sugars in aqueous media remains a challenging task.[7] Recently, DMC (2-chloro-1,3-dimethylimidazolinium chloride) mediated glycosylation of unprotected sugars with phenols in aqueous medium has shown promising results.[8] As a continuing interest in the development of photoswitchable carbohydrates,[9] we are developing the DMC-mediated glycosylation of hydroxyazobenzene with unprotected sugars (Scheme **1**). After optimization of reaction conditions, we are able to prepare a series of water-soluble glycosyl azobenzenes. Furthermore, the synthesized glycosyl azobenzenes displayed remarkable photoswitching behavior in water (Scheme **2**). These new results will be presented.



Scheme **1**: DMC-mediated glycosylation of hydroxy-azobenzene derivative.



Scheme **2**: Isomerization of glycosyl azobenzene upon light and heat.

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P B101

Iron-Catalyzed C(sp^3)-H Lactonization Using Hydroxylamine Derivatives

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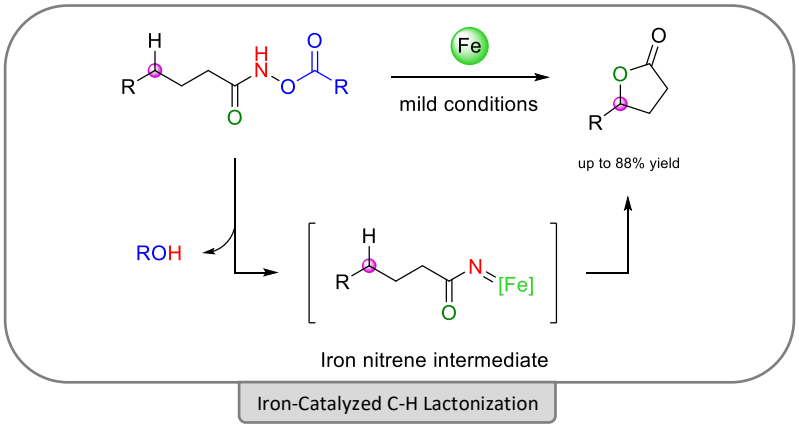
Lactones are highly valuable intermediates in the synthesis of many natural products, as well as prominent scaffolds in bioactive compounds.[1] Direct functionalization of C-H bonds represents the most straightforward route to these compounds in the context of sustainable chemistry. There has thus been an ongoing effort into the development of efficient and robust methodologies for C-O bond formation.[2] However, most of these developed processes are poorly atom economical, require external oxidants, and are based on the use of rare and expensive transition metals such as palladium.[3]

Nitrenes are well-known for their ability to perform aziridination, alkene difunctionalization and C-H amination.[4] Our group aims to achieve sustainable nitrene transfer processes using iron as the catalyst and hydroxylamines as the nitrogen source.[5] Iron is cheap, abundant, and non-toxic while hydroxylamines are bench-stable, easily accessible, and can form a metallonitrene intermediate in the presence of a transition-metal without the addition of external oxidants.[6] During our investigation on C-H amination, we serendipitously discovered that nitrene chemistry can also allow C-H oxygenation.

In this communication, we will present in detail our recently developed iron-catalyzed lactonization using hydroxylamine derivatives. This sustainable process allows for an efficient access to new C(sp^3)-O bonds, yielding various lactone derivatives in good-to-excellent yields using very mild conditions.



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P B102

Photocatalyzed Minisci Reaction as a Key Step to Access New *N*-Heterocycles

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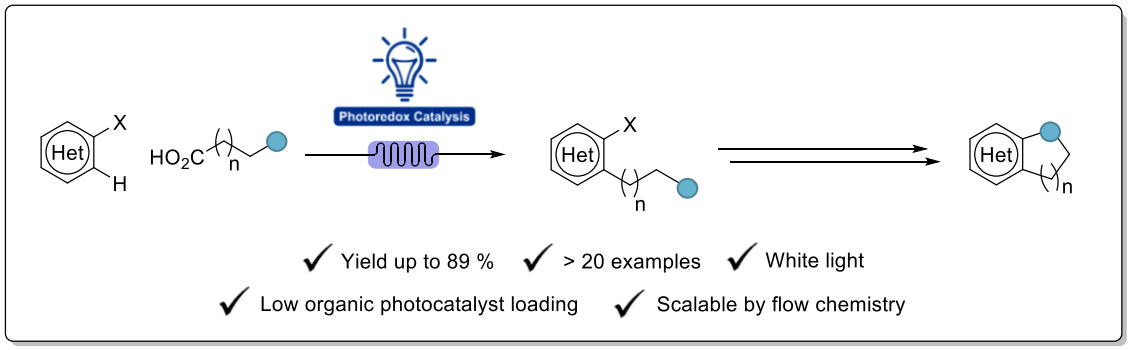
In pharmaceutical research, access to original heterocyclic scaffolds remains a major challenge. Indeed, they constitute molecular structures with unique chemical and biophysical properties. They are also innovative molecular frameworks on which various chemical functionalities can be grafted and are therefore pivotal structures for drugs discovery.[1]

The Minisci reaction, a nucleophilic radical substitution, is a strategic reaction manifold to functionalize electron deficient heterocycles, widely used in medicinal chemistry program.[2] The seminal reactions conditions require harsh conditions to generate radicals, leading to moderate yields and limited scopes.[3] Photoredox chemistry is an interesting alternative to easily generate radicals under mild conditions.[4] Herein, we developed a photocatalytic Minisci reaction applicable on a large panel of heterocycles, more than 20 examples with yields up to 89 %. Cyclisations were then developed to access original *N*-heterocycles as new building blocks for drug discovery programs.



Moreover, the photocatalyzed Minisci reaction was developed in continuous flow to allow an easy scale up of the reaction and overcome the limitations of photochemical transformations in batch.[5]

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P B103
Counter-ion effect of $Ru(bpy)_3(X)_2$ complexes in intermolecular [2+2] photocycloaddition

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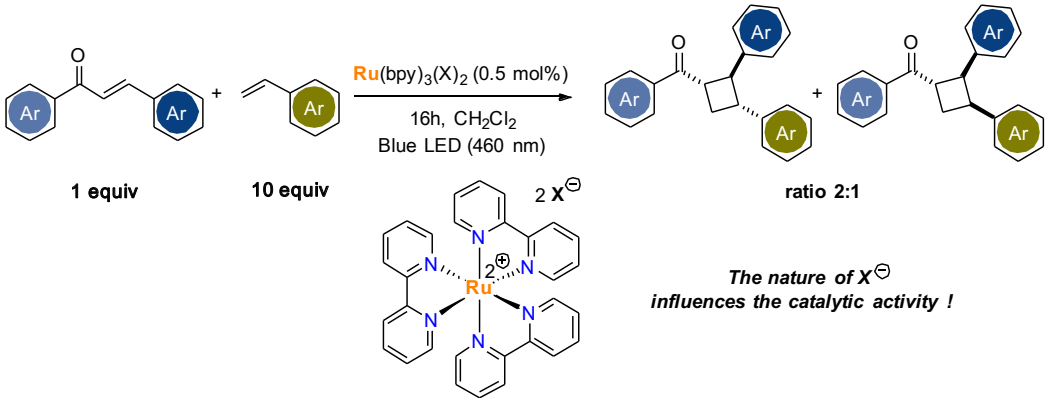
Ruthenium tris(bipyridine) complexes have been widely used and studied over the past decades. These Ru(II)-based complexes are indeed well-known for their unique reactivity and their valuable photophysical and electrochemical properties.[1] In particular, they have been used as catalysts in a large range of photo-induced electron and energy transfer processes.[2] Previous studies have notably shown the effect of the counter-ion in such metal complexes for photoredox reactions.[3] Nevertheless, this effect has never been exploited in photocatalyzed reactions by energy transfer such as in intermolecular [2+2] cycloaddition.[4]

In this contribution, we report that the modification of the counter-ion X has a dramatic impact on the catalytic activity of $Ru(bpy)_3(X)_2$ complexes. Experimental results were then rationalized by measuring different physicochemical parameters showing that the catalytic activity can be directly related with the excited-state lifetime, the stability and the excited-state energy of the $Ru(bpy)_3(X)_2$ complexes. Under the optimal catalytic conditions, the impact of the structure of the olefin partners has been also investigated.

Thus, based on catalytic results, photophysical studies and a scope of substrates, we have demonstrated that a judicious choice of the counter-ion can modulate the reactivity of $Ru(bpy)_3(X)_2$ complexes in intermolecular [2+2] cycloadditions.[5]



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[5] Publication submitted.

P B104

Design and synthesis of new molecular “off-on” fluorescent photoswitches for studying protein allostery

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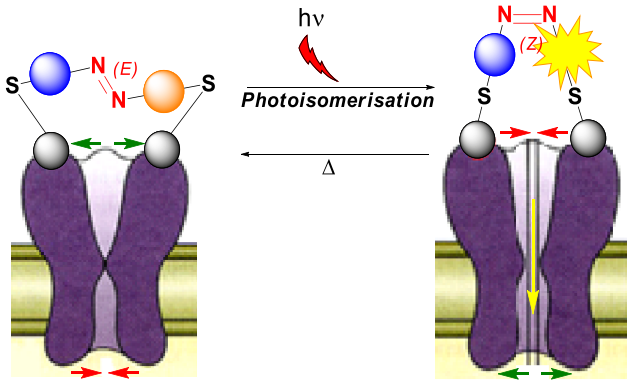
Nicotinic receptors belong to the Superfamily of pentameric ligand-activated ion channel receptors. Amongst the different receptors in this family, we are particularly interested in, is the $\alpha5(\alpha_4\beta_2)_2$ receptor, which is a promising therapeutic target for the design of anti-smoking molecules and against the metastatic proliferation of lung cancer.
In this context, understanding the protein allostery is essential because it makes it possible to connect the conformations that the receptors adopt to the functions and thus saves time in the design of new ligands.
However, there is no crystallographic structure of nicotinic acetylcholine receptors of sufficient resolution. An alternative is the use of the bacterial homologous receptor GLIC which could be crystallized under three conformations, open, closed and locally closed.
To do this, we propose to design a photosensitive clamp that will be fixed on the extracellular domain of the receptor and use a light irradiation that compels the opening of the ion channel, as assumed in previous works.
The photosensitive nucleus will be of the azobenzene type for which a fluorophore will be incorporated in order to result in an “on/off” photoswitchable and fluorescent probe. Hence, we will have complementary biophysical methods.



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P B105
Flexible total synthesis of natural chromenes

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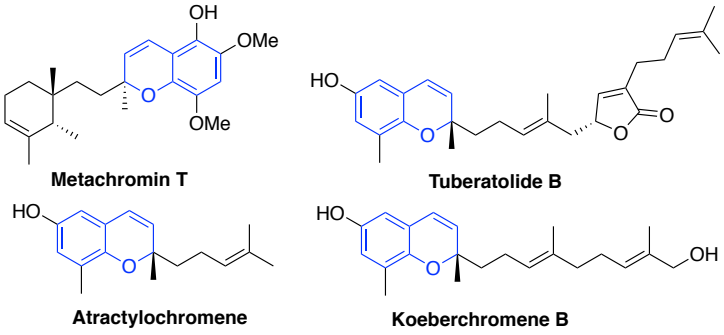
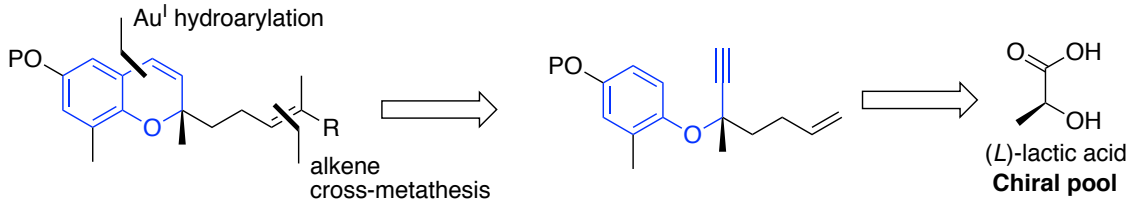
Herein we present our strategy towards the total synthesis of a class meroterpenes natural products featuring a 2H-chromene fragment. This strategy is flexible, convergent in order to allow the synthesis of both natural chiral chromenes, and non-natural analogs. One of the first targets is the metachromins family and its representative member, metachromin T that is known to display cytotoxicity against L1210 murine leukemia and KB human epidermoid carcinoma cells.[1] Another target which we will fully disclose its first total synthesis is tuberatolide B, initially isolated as a natural product showing a compelling biological activity as an FXR antagonist, but more recently new activities as inhibitor of ROS-mediated of STAT3 signaling and LPS-stimulated inflammatory response were described.[2]
The strategy developed for the synthesis of tuberatolide B allowed us to also attain the total syntheses of atractylchromene and Koeberchromene B.[3]



The retrosynthesis of the targeted natural chromenes has two key reactions, the first one is the Au^{+1} hydroarylation that allowed us the construction of the enantio-enriched chromenes then, on the convergence side, the alkene cross metathesis was key in order to install different side chains towards the final structures.



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P B106

Gold-Catalyzed Domino Cycloisomerization/Nucleophilic Addition /C→O Rearrangement of Acenaphtylene Carbaldehyde

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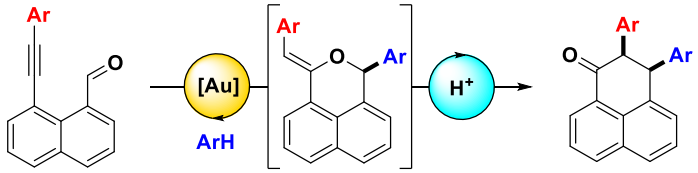
Gold catalysis has been widely demonstrated to be useful for to achieve the synthesis of complex structure according to atom-economical and green processes.[1] Gold complexes are highly interesting tools due to their ability to activate unsaturated bonds, leading to nucleophilic additions. In the case of aldehyde-yne substrates, it is possible to access a wide range of highly functionalized O-heterocycles.[2] Recently, HFIP emerged as a new tool notably for its Lewis-acid proprieties due to its hydrogen donor bond. Many studies report its use in the presence of metals such as Pd, Fe or Au.[3] In the course of our ongoing program towards gold catalysis,[4] our group recently described the gold-catalyzed cyclization / acetalization using alcohol as nucleophile.[5] In this context and this new interest in HFIP, we developed a domino reaction of cycloisomerization/nucleophilic addition/C→O rearrangement. A large range of acenaphtylene carbaldehyde has been engaged in such process with various aromatic nucleophile leading to cyclic ketones.[6]



Optimization of the reaction conditions as well as the scope, limitations and post-functionalization will be presented.

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P B107

Synthesis towards diversity of potential SGLT−2 inhibitors for the treatment of type 2 diabete

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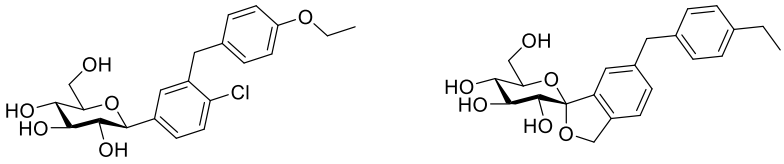
450 million people around the world are suffering from type 2 diabete, and its prevalence is increasing each year. In this context, gliflozines like Dapagliflozin **1** have been marketed in 2013 as a new class of anti-diabetic agents acting as inhibitors of the sodium-glucose co-transporter SGLT−2.[1] Among them, spiro-bicyclic compounds like Tofogliflozin **2** (Figure 1) showed great promises, but they have been underestimated because of synthetic approaches that only give rises to [6,5]-spiroacetals having an α configuration.[2]

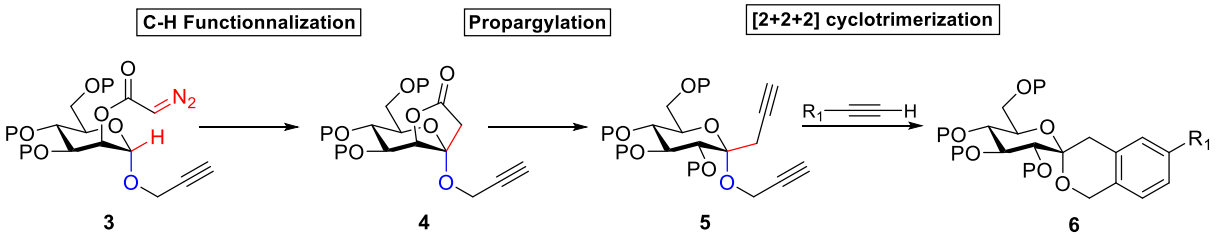


Dapaglifozine **1** FORXIGA®
IC_{50} (SGLT-2) = 1nM

Tofoglifozine **2** DEBERZA®
IC_{50} (SGLT-2) = 3nM

Figure 2 : Structure of marketed gliflozines.

In this context, we wish to report herein a new approach towards potential inhibitors of SGLT-2, where a carbene-mediated functionalization of the anomeric C-H bond of carbohydrate would first give rise, on demand, to quaternary sugars of α- or β-configuration[3]. Starting from mannose, the α-propargyl 2-diazoacetyl mannoside **3** was first prepared and engaged in a Rh(II)-catalyzed 1,5-C-H insertion to yield γ-lactone **4**. After conversion into the key *C,O*-bis propargyl glycoside **5**, a [2+2+2] cyclotrimerization gave rise to [6,6]-spiroacetals **6** fused to an aromatic ring (Scheme 1).



Scheme 1: Divergent synthetic approach towards unprecedented [6,6] spirobicyclic potential inhibitors of SGLT-2.

This new approach allowing introduction of key pharmacophores in a late stage of the synthetic sequence provide a fast entry towards a large molecular diversity of unprecedented potential inhibitors of SGLT-2.

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P B108

Radical synthesis and functionalization of acylsilane and acylboronate derivatives by the xanthate transfer process

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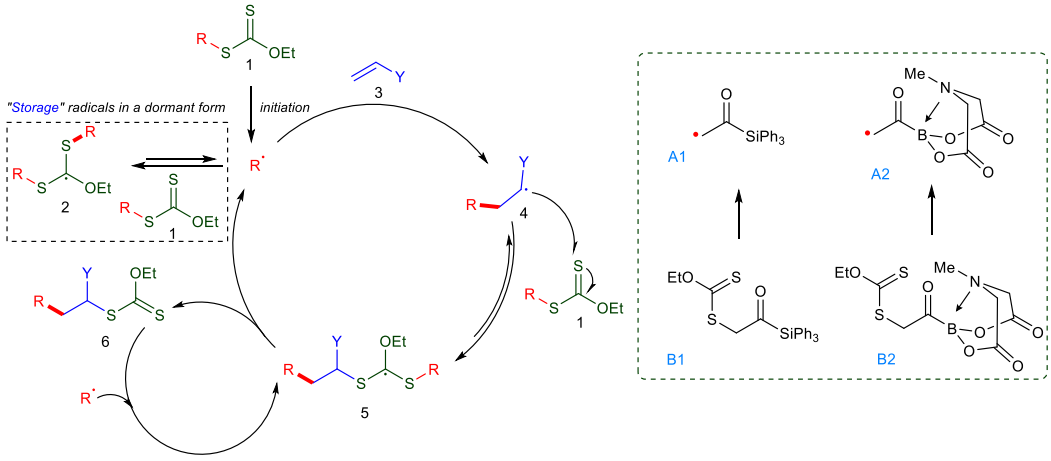
The degenerative reversible transfer of xanthate is emerging as one of the most effective tools for the generation of C-C bonds in recent years[1]. It has a unique ability to store reactive radicals through a series of reversible processes and thus remarkably extend the effective lifetime of the formed radicals. It allows intermolecular radical additions, especially to non-activated olefins, to construct C(sp^3)-C(sp^3) bonds[2]. Acylsilanes (RCOSiR´$_3$) and acylboronates are intriguing classes of compounds that are of wide interest[3-4]. Their remarkable properties and reactivities have only recently been recognized. The xanthate addition-transfer process has been exploited as a convenient method for the synthesis of functionalized acylsilanes and acylboronates. As reported herein, the first synthesis of two novel and reactive xanthates B1 and B2, bearing an acylsilane moiety and an acylMIDA boronate moiety, respectively, was developed. A series of adducts were prepared in a high yield using the xanthate addition-transfer process and could be further transformed to pyrrole and furan derivatives[5-7]. Notably, the mildness of the reaction conditions and broad tolerance for diverse functional groups provide a new synthesis method for various compounds of this class that are not readily accessible by other routes.



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P B109

Design, Synthetis and Biological Evaluation of Fluorinated Cathepsin D Inhibitors

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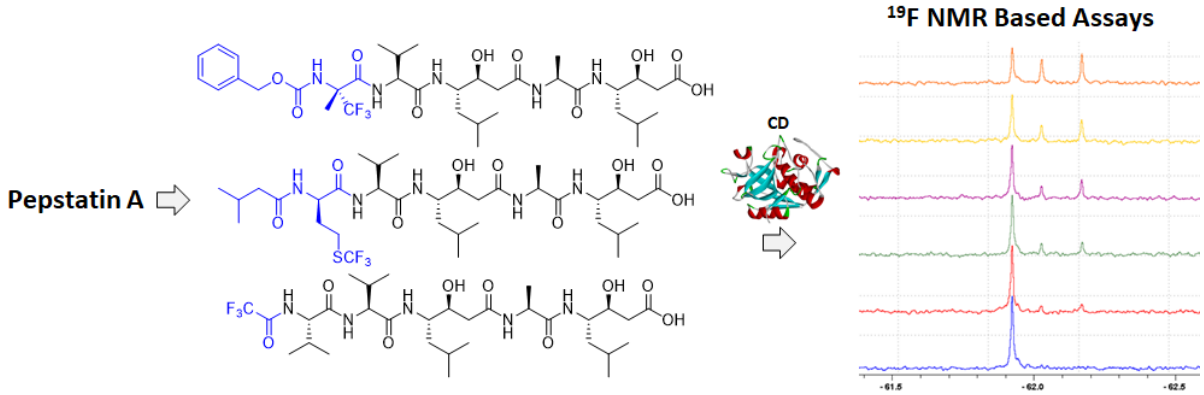
Cathepsin D (CD) is considered as a potential target for the treatment of breast cancer. In this context the development of efficient inhibitors and inhibitor screening methods is a major need for the scientific community.[1] Pepstatin A, a natural pseudopeptide isolated from cultures of various Actinomyces is considered as the gold standard among the natural inhibitors of CD. Nevertheless, due to Its poor bioavailability and Its poor metabolic stability, no application has been found for the treatment of the diseases mentioned above with this molecule. The synthesis and the evaluation of peptide-like ligands of CD containing fluorine atoms constitutes an innovative strategy that could lead to the development of new molecules as ^{19}F NMR probes and/or new potential inhibitors towards CD.[2] The introduction of fluorinated amino acids in the peptidic scaffold could: i) transform the ligand into an efficient ^{19}F NMR probe opening the way to NMR's based functional assays;[3] ii) help the cellular membrane uptake; iii) improve the bioavailability.[4]

The introduction of the fluorinated scaffold has been performed using two strategies: i) Introducing a fluorinated protecting group on the *N*-terminus moiety of the peptide; ii) incorporating non-natural fluorinated amino acids into peptidic scaffolds.[5]

These Fluorinated analogues of Pepstatin A have been tested *via* fluorimetric techniques and fluorinated based NMR assay (FABS). These two synthetic strategies and preliminary biological results.



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P B110

From *Catalpa* Fruits to Promising Prostanoïds Precursors

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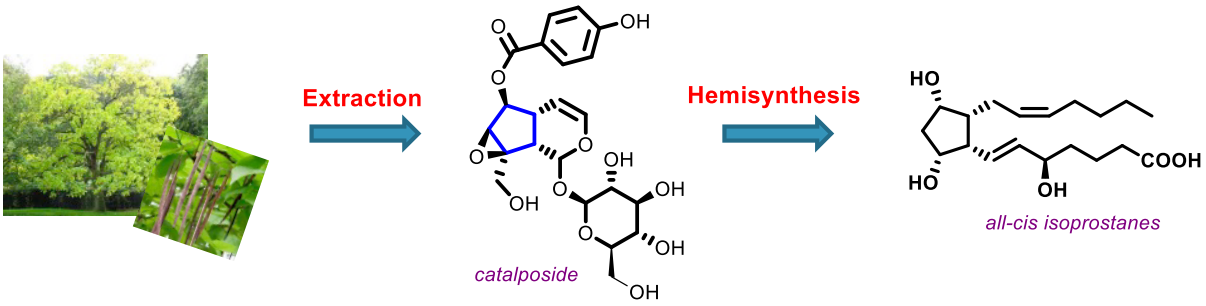
Nature is a great source of chemical diversity. Currently, it is the origin of the discovery and design of many active molecules.[1] The extraction or the synthesis of complex natural structures can be very challenging. However, nature may also provide abundant small compounds which can be used as polyfunctional chiral skeletons for the hemisynthesis of more complex molecules.

Isoprostanes, metabolites of polyunsaturated fatty acids following non-enzymatic pathway, are an important class of natural products containing polysubtituted cyclopentane ring. Indeed, some of these metabolites are biomarkers of oxidative stress in biological systems and have interesting biological properties, such as anti-inflammatory, neuroprotective and antiarrhythmic activities.[2] In order to study these compounds, various synthetic strategies have been developed.[3] However, some stereoisomers of this family are still synthetically very difficult to obtain in particular the all-*cis* isoprotanes due to the steric hindrance.

To ease access to these molecules, we propose a hemisynthetic route from iridoïds, small bicyclic monoterpenes, as a suitable polyfunctional chiral skeletons (Scheme 1). Catalposide is a relevant iridoïd for this project by its *cis* cycle junction of stereochemistry *cis*. Moreover, catalposide is one of major iridoïds present in *Catalpa bignonioïdes W.* fruit,[4] known as bean tree. This latter is a very common ornamental plant that can be found in our green spaces and along roadsides making it a particularly accessible source.



Scheme 1 : Isoprostanes hemisynthesis from Catalpa fruits

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P B111

New Photo-Induced Alkoxyarylation of 3-Methylene-Isoindolinones Using Aryl Diazonium Salts

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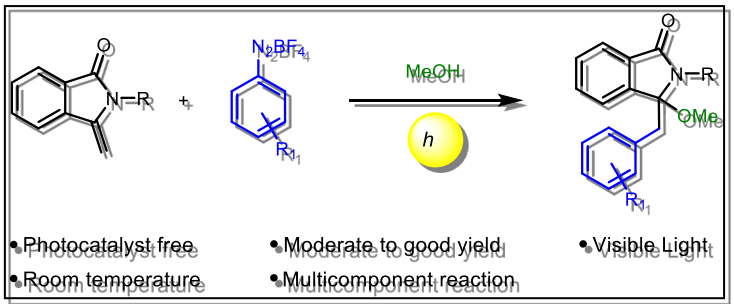

Since the discovery of aryl diazonium salts by Griess in 1858, the reactivity of these compounds has been extensively studied. Indeed, these highly reactive species allows readily access to a wide array of chemical transformation such as substitution, cross-coupling reactions or grafting functionalization. From a mechanistic point of view, most of these reactions involve the thermo- or photo-catalyzed formation of an aryl radical from the diazonium salt.[1] Nowadays, the development of sustainable processes has become a great challenge. In this context, photochemical reactions appear to have a significant potential by reducing the energy demand of the transformations and in absence of chemical activators. Thanks to the work of Deronzier,[2] describing the synthesis of Pschorr by photocatalysis, aryl diazonium salts have revealed their full potential in visible-light photoredox reactions.[3] In parallel, benzo-fused γ-lactams such as isoindolinones are widely represented among natural and biologically active molecules. As example, Chilenin from *berberis empetrifolia* is used against cancer.[4] Given the importance of isoindolinones, a more environmentally friendly synthesis strategy would be highly desirable.

In this work, we described a Meerwein-type alkoxyarylation of 3-methylene isoindolinones via aryl diazonium salts. This three-component reaction performed at room temperature has been enhanced under visible light and without photocatalyst to allow the obtention of a wide array of 3-substituted isoindolinones with good to moderate yields (57 to 92%). Mechanistic studies suggest two complementary initiation steps, thermo- and photo-induced, which allow the formation of the aryl radical from the diazonium salt.

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P B112
Measuring Lewis acidity with fluorescent dithienophospholes

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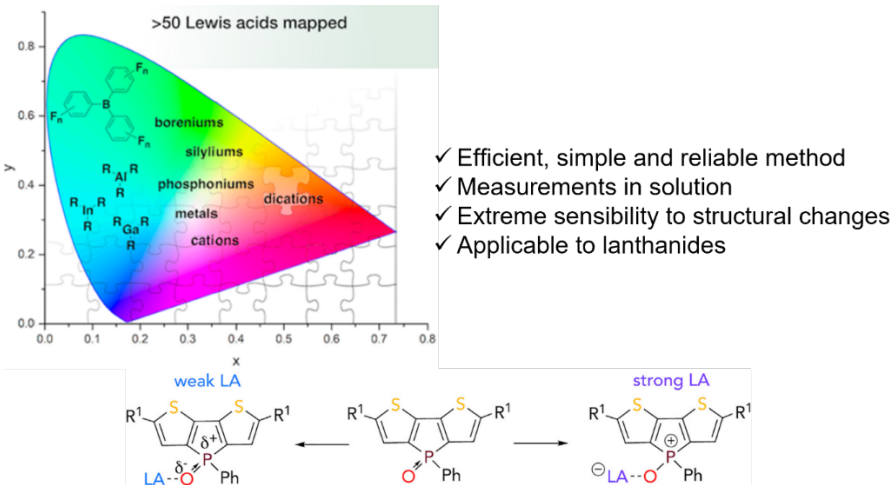
Lewis acids, ie electron-pair acceptors, play a prominent role in chemistry. In particular, their use as catalysts make them key reagents in organic synthesis. Unlike traditional Brønsted acids, whose acidity can be easily measured by the p*K*a scale, there is still no broadly accepted method for quantifying Lewis acidity to date. Available experimental methods such as the Gutmann-Beckett or the Childs method still suffer from limitations including inconsistent results. We recently reported a new and efficient method for evaluating the relative acidity of Lewis acids.[1] This method uses a set of Lewis basic dithienophosphole oxide as fluorescent probes, which can be easily synthesized and functionalized in a few steps from commercially available reagents. Upon coordination to a Lewis acid through the P=O bond, the emission of the probe is red-shifted. The chromaticity of the resulting Fluorescent Lewis Adduct (FLA), assessed by its Commission Internationale de l'Éclairage (CIE) coordinates, correlates very precisely with the strength of the Lewis acid. We were then able to attribute a specific Lewis Acid Unit (LAU) to more than 50 Lewis acids belonging to very different classes of compounds,[2] including rare-earth metal triflates.[3] In this case, successful measurements were still able to be performed despite the fact that lanthanides generally display similar physicochemical properties. We hope that the FLA method will be of use in organic chemistry, as the reactivity of a Lewis acid catalyst strongly depends on its strength, which can now be easily, precisely and reliably assessed. This should greatly simplify the choice of an optimal Lewis acid catalyst for a given chemical transformation.



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P B113

β-Selective *C*-Sialosides Synthesis by Reductive Samariation

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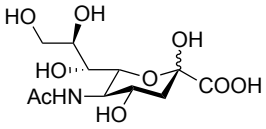
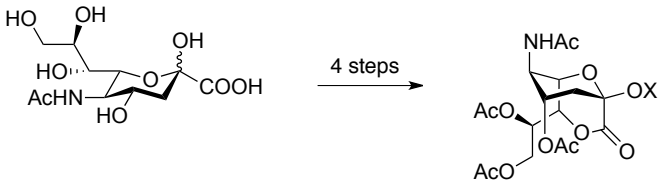
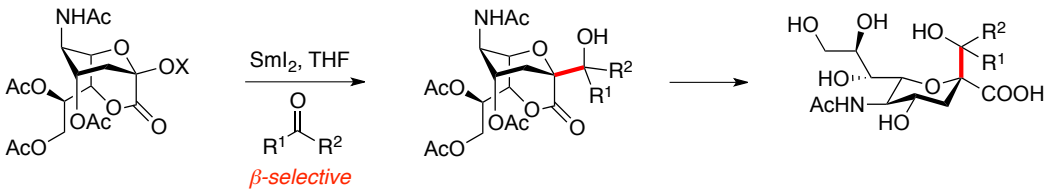
N-Acetylneuraminic acid (Neu5Ac),[1] (scheme), which belongs to a complex sugar family, is involved in many biological phenomena including pathological interaction of human cells with *Influenza* viruses.[2] Due to their stability to chemical and enzymatic hydrolysis, *C*-glycosides analogues of Neu5Ac-containing conjugates are interesting targets, and in the last years we have developed a rapid and stereoselective preparation of α-*C*-sialosides using samarium diiodide (SmI_2).[3] We will present our results concerning the selective preparation of the isomeric β-*C*-sialosides, using reductive samariation and coupling reaction with electrophiles, on the chair inverted 1,7-sialyllactone derivatives, easily obtained from the commercial Neu5Ac (scheme 2).





Scheme 2.

Due to the bicyclic structure of the 1,7-lactone, the coupling reaction is totally selective in favor of an equatorial orientation of the new C-C bond, thus leading to β-C-sialoside derivatives (scheme 3).



X = Ac, Bz, Ts, Ms, CS_2Ph, COC_6H_4F, COC_6F_5...

Scheme 3.

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P B114

N-azaiodoimidazolium salts: a new class of strong mono Halogen Bond donors

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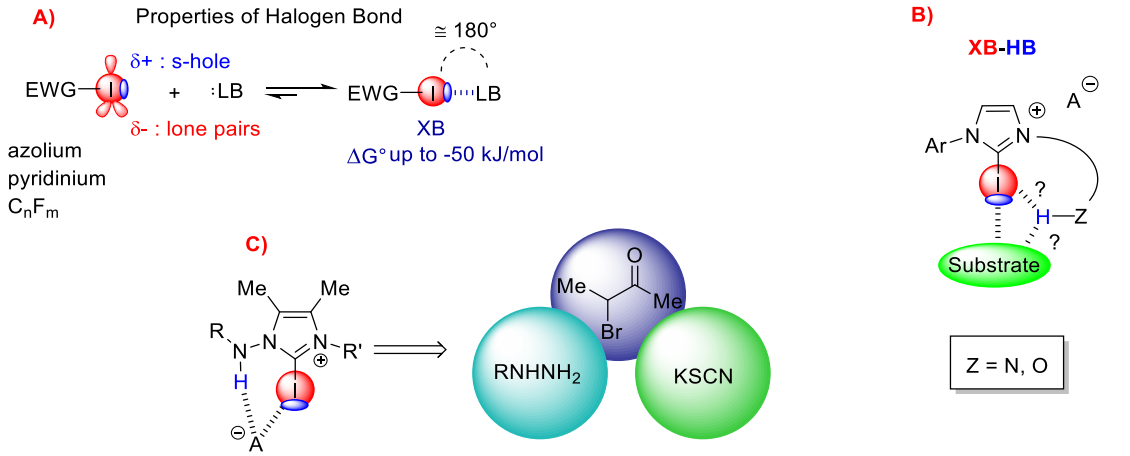
Non-covalent interactions play an important role in all subfields of chemistry, including catalysis, where interactions of different natures can work together to improve reactivities and selectivities. Several families of molecules that incorporate both hydrogen bond (HB) and halogen bond (XB) donors (Scheme A)[1] have already been studied. Based on our previous work on the research of cooperation between halogen bonding (XB) and hydrogen bonding (HB), applied in different catalysed reactions (Scheme B),[2] we are developing a novel class of strong mono XB donors with as general structure an iodoimidazolium salt (Scheme C).

We share the synthesis of a library of *N*-azaiodoimidazolium salts starting from a hydrazine pattern,[3] to try to lower the degrees of freedom between the XB and HB donors and facilitate their cooperation.[4] We have also realized that different substituents could also be placed on the extracyclic nitrogen atom to modulate the XB donor character. Along with a study of their physico-chemical properties using different techniques (X-ray diffraction and ITC[5]), the behaviour of the *N*-azaiodoimidazolium salts in different catalytic transformations was also evaluated: hetero-Diels-Alder reaction with *N*-arylimines, transformations of bromodiarylmethanes (Friedel-Crafts alkylation) and others.



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P B115

Novel methodologies for the synthesis of polycyclic derivatives using gold catalysis

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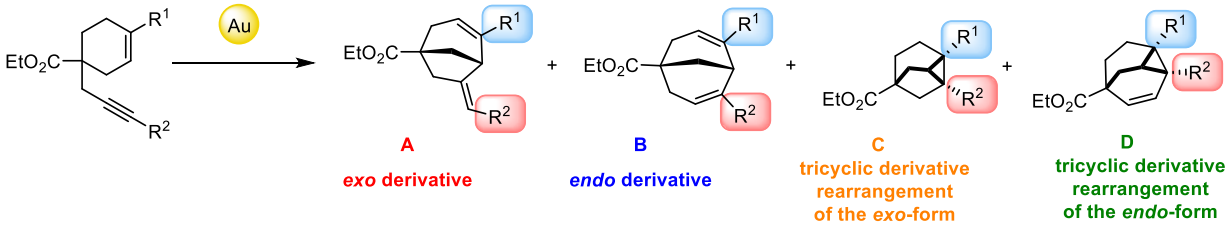
The great majority of medicinal chemistry-relevant structures tend to have a planar geometry.[1] Recently, in an effort to increase the molecular diversity in fragments libraries, a particular attention has been devoted to the three-dimensionality of chemical structures.[2] However, synthesizing these new and original building blocks using a fast and efficient methodology remains a key challenge for an organic chemist. Gold catalysis is a powerful tool for the synthesis of complex core structures according to atom-economical and green processes. Indeed, gold complexes possess a carbophilic Lewis acid character which provides it a particular reactivity able to activate π-systems towards nucleophilic additions.[3] This reactivity offers new possibilities of chemical synthesis which allows to reach various carbocyclic or heterocyclic scaffolds, starting from simple substrates, enhancing significantly the molecular complexity. In this context, as part of our ongoing research program on metal activation of alkynes,[4] we developed an efficient and mild synthetic route for the preparation of functionalized bicyclo[3.2.1]oct-2-ene and bicyclo[3.3.1]nonadiene via gold-mediated cycloisomerization of 1,6-enynes.[5] Depending on the substitution of the starting enyne and the reaction conditions, the process occurred under a 5-*exo* or a 6-*endo* pathway. These



different mechanistic routes allowed the formation of four different polycyclic derivatives. These building blocks represent privileged scaffolds in a search for increased molecular diversity of drug-candidate libraries.

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P B116

Photoinduced Alkynylation of Activated Primary Amines Through the Formation of an EDA Complex.

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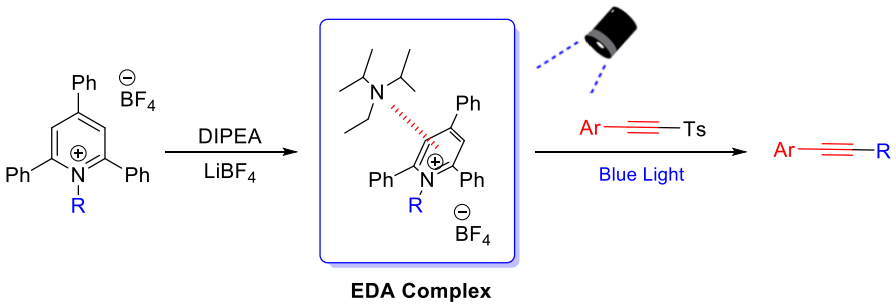
In a society where the environment protection is a central concern, processes using the solar energy has a key role. Resulting from the discoveries made over the last fifty years, photochemistry is now considered as a promising alternative to usual chemical process, commonly used in industry. [1,2,3] In this context, there is a growing interest for the development of original methodologies that can reduce 1/ the impact on the environmental footprint and 2/ the energy demand. There is no doubt that the use of reactions mediated or initiated by photons (light) as one of the simplest reagents in chemical transformations is becoming a crucial tool in drugs development in a close future.

This study discloses a de-aminative reaction for the formation of alkynes and allenes derivatives using a photoinduced process via an EDA complex.[4,5] Proofs of the formation of such complex have been given. The absence of metals or of an external photosensitizer in this methodology and the use of continuous flow chemistry, that should permit the development of this synthesis in one row, enhance its interest for industrial application.



EDA Complex

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P B117

New Bifunctional Organocatalysts: Design, Synthesis and Characterization. Applications in asymmetric organocatalysis

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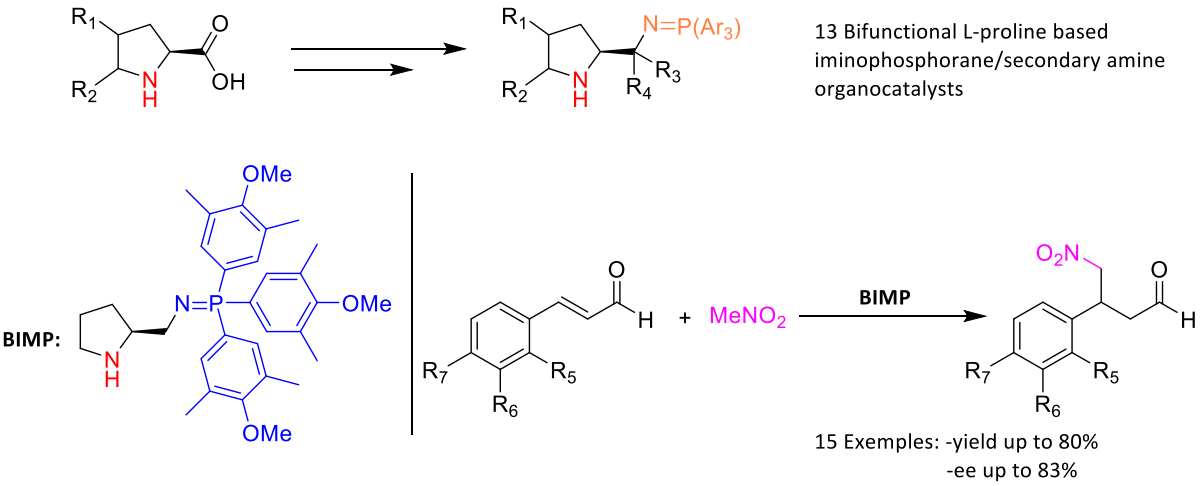
Bifunctional iminophosphorane organocatalysts (BIMP) have attracted much attention from researchers in recent years. Their very high basicity gives access to pro-nucleophiles with high pKa such as nitromethane or thiols, which improves the variety of pro-nucleophiles and reactions studied. The design and synthesis of novel chiral BIMP has been a challenging task and received great attention. However, BIMP still remains an underdeveloped field, only hydrogen bond donors associated with the iminophosphorane function have been reported so far.[1]

Herein, we described a flexible and efficient synthesis of a series of chiral iminophosphorane/secondary amine catalysts. These BIMPs were then evaluated in asymmetric organocatalysis. Thus, addition of nitromethane to cinnamaldehyde via the formation of an iminium intermediate has been investigated in order to prove the potential of our new BIMPs.[2]



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P B118

Silicon-based nanocages as supports for molecular catalysts

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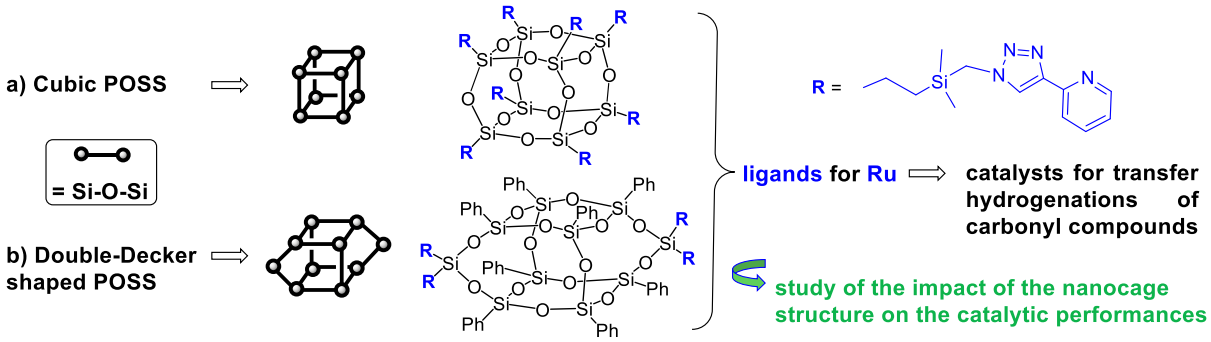
The development of eco-compatible catalytic systems enabling the preparation of organic compounds is of great concern. One possible approach consists in grafting molecular catalysts onto supports allowing their recovery and further recycling.
This work concerns the use of supports based on Polyhedral Oligomeric Silsesquioxanes (POSS), perfectly defined nanosized cages composed of an inorganic Si-O-Si core decorated with organic substituents.[1] POSS having a cubic shape (Fig, a) have been the most studied and several functionalizable versions reported. The latter are exploited as building blocks for the construction of molecular materials finding applications in many fields including catalysis.[2] To reach desirable macroscopic properties, the design of novel functionalizable cages is needed. Along these lines and in collaboration with Masafumi Unno (Gunma Univ. Japan), expert in the preparation of silicon nanocages, we have recently designed POSS with original cores (different from the cube) and bearing organic functional groups.[3] The latter allow the covalent attachment of molecular catalysts. In this presentation, we describe the synthetic routes to cubic and unprecedented "double-decker" nanocages bearing eight or four 2-pyridyl-1,2,3-triazole ligands respectively (Fig, a & b respectively).[4,5] The catalytic activities of the corresponding ruthenium complexes are compared in transfer hydrogenations of carbonyl derivatives. The cage structure is shown to greatly influence the catalytic activity of the nanocatalyst and the tetrafunctional double-decker silsesquioxanes constitute promising tools in supported catalysis. The recyclability of the systems is studied as well.



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P B119

Green Suzuki-Miyaura cross-couplings in aqueous media involving O-electrophiles and air-stable nickel precatalysts

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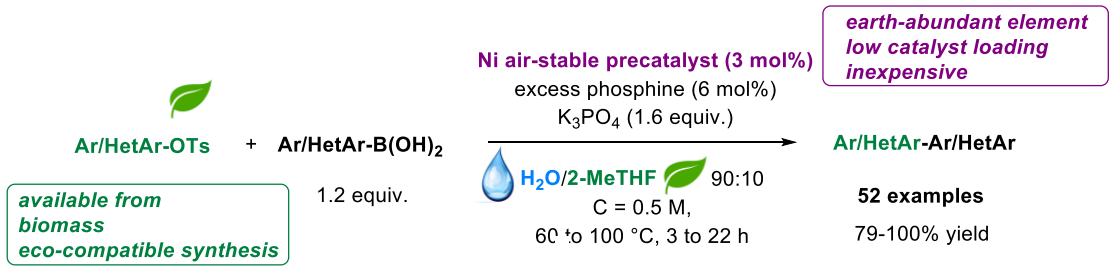
In the context of the sustainability-focused development plan outlined by the United Nations in 2015, the need for green and sustainable chemistry and engineering has been clearly identified as a major challenge. However, the lack of "green" manufacturing processes is an unsolved problem in major areas especially in organometallic catalysis. Hence, despite their exponential development, cross-coupling (C-C) reactions remain highly polluting by associating toxic organic halides to over-exploited low-abundant palladium (0.015 mg/kg earth crust) and organic solvents, which represent over 80% of the chemical waste of the chemical industry.[1] Although significant advances have been made in the field thanks to micellar systems, these works only focus on organic halides and none of them concern eco-compatible O-based electrophiles.[2]

For this reason, we have developed an eco-compatible Suzuki-Miyaura cross-coupling[3] which allows access to biaryl as well as heteroaryl compounds. The process combines a non-noble metal complex and sustainable O-based electrophiles in a green media composed of 90% water. In details, the association we have targeted gathers the use of:

- Aryl/heteroaryl tosylates, which represent a sustainable alternative to corresponding halides since they are readily available from biomass (phenols) and chemically stable and they can be synthesized in an eco-compatible manner.[4]
- An air-stable catalyst issued from "non-noble" abundant and inexpensive nickel (84 mg/kg earth crust). A low catalyst loading was utilized (3 mol%) and evaluation of residual nickel by atomic absorption spectroscopy (AAS) revealed amounts lower than 10 ppm.
- Aqueous reaction media composed of 90% water and 10% of a biosourced organic solvent (methyl tetrahydrofurane) for solubility issues, allowing a significant reduction of chemical wastes (Scheme 1).



Scheme 1

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P B120

Metal encapsulated inside NHC-capped cyclodextrins: cavity-controlled selective reactions

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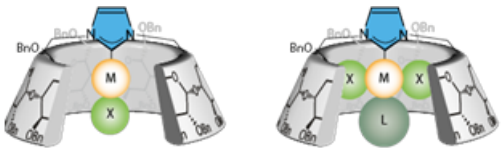
Encapsulated metal complexes with well-defined spaces show distinctive properties thanks to the primary and secondary coordination spheres. The association with α, β or γ-cyclodextrin (CD) moiety and N-heterocyclic carbene (NHC) ligand, called ICyD, led to the formation of encapsulated complexes in helicoidal distorted cavities[1]. Our group reported that this series of ligands allowed to form linear coordination with coinage metals (Cu^{I}, Au^{I}, Ag^{I}), which could induce stereo-[2,3], regio-[4] and chemoselective[5] reactions. We also showed the formation of square planar coordination complexes (Au^{III}, Pd^{II}) inside α, β or γ-CD cavities[6].

To get further insight into ICyD-metal complexes, we extend our study to the synthesis and characterization of Ni complexes. Group 8 metal nickel exhibits multiple oxidation states and coordination types. Nickel catalysts could undergo either two electron transfer pathway or radical pathway[7]. Therefore, we synthesized two types of ICyD-Ni^{II} complexes and studied the relationship between their coordination modes and CD cavity.



(ICyD)MX
linear complex
M = Cu^{I}, Au^{I}, Ag^{I}

(ICyD)MX_2L
square planar complex
M = Au^{III}, Pd^{II}, Ni^{II}

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P B121

Efficient synthetic strategy to access analogues of an original natural bioactive flavone

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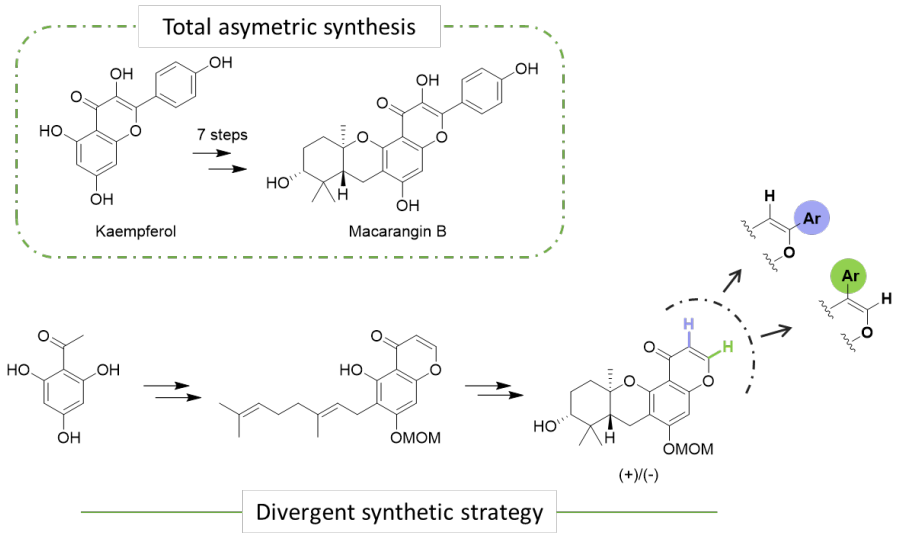
Recently, an original bioactive molecule, macarangin B, has been isolated in our group from *Macaranga tanarius* plant extract. This molecule binds with a strong affinity (Ki = 80 nM) to OSBP (OxySterol Binding Protein),[1] a protein implicated in the intracellular transport of cholesterol. This protein is implicated in the replication of many types of viruses[2] and is a promising target to develop new antiviral agents. However, the only OSBP inhibitors described so far are highly cytotoxic which precluded their application as antivirals. In contrast, macarangin B is at least one hundred times less cytotoxic while keeping strong antiviral properties. A biomimetic total synthesis has been achieved in seven steps recently.[3] Following another synthetic route, our goal is now to prepare a library of analogues in a divergent fashion in order perform structure-activity relationships. For that purpose, a chromone-fused hexahydroxanthene has been elaborated at gram scale. Finally, to access macarangin B analogues, challenging regioselective functionalizations have been carried out. The optimization of this synthetic pathway together with the analogues prepared will be presented.



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P B122

Borylated Super Acids: A Super Acidic Story

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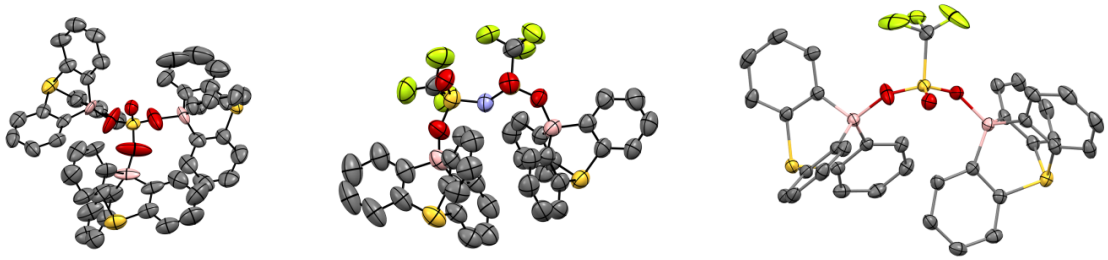
Back in the 1960's, stronger electrophiles emerged with the replacement of sulfate or halide by triflate ion $[CF_3SO_3]^-$ owing to its weaker coordinating properties. It was commonly thought that triflate ion, along with other anions such as $[BF_4]^-$, $[ClO_4]^-$, $[AlX_4]^-$ and $[MX_6]^-$ did not interact with their paired cation and were therefore considered as "noncoordinating anions".[1] These anions were actually coordinated to the electrophilic center, and even fluorinated tetrarylborates or halogenated carboranes, extensively developed by Reed to stabilize highly electrophilic species demonstrated coordinating abilities.[2]

Some anions such has halides have shown the ability of coordinating two electrophiles forming halonium species and some of them such as fluoronium or chloronium cations have been observed and isolated as bridged species resulting from the coordination of two boranes, silylium, borenium and carbeniums ions. However, the twofold coordination of even weaker coordinating anions to main-group electrophiles is hitterto almost unknown.

In this report we will show how the unforeseen Lewis acid properties of our recently reported 9-sulfonium-10-boratriptycene[3] open the access of the unique borylated sulfuric, triflic and triflimidic acid; the heavier analogs of the corresponding super Brønsted acids.[4] Beyond their unique spectroscopic, molecular structures and reactivity's, we believe that this work will considerably broadens our fundamental knowledge in the area of Lewis acids, main-group chemistry and will push forward our common point of view of classical chemical bonding and main-group element reactivity.



- ***Full family of borylated Bronsted super acids***
- ***X-ray structures determined***
- ***Quantum Chemical Investigations***
- ***Reactivity Studies***

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P B123

Regio- and stereoselective synthesis of trifluoromethoxylated tetrasubstituted ethylenic compounds

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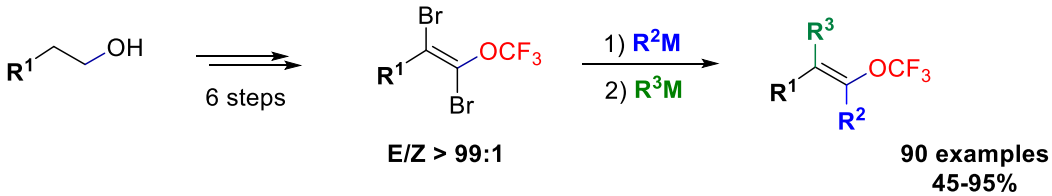
Due to its unique properties (strong electron-withdrawing effect,[1] high lipophilicity,[2] moderate steric bulk[3] …), the trifluoromethoxy group has received a growing interest in the last few decades, especially in the fields of pharmaceuticals, agrochemicals and materials. Although strong efforts were devoted to developing new approaches,[4] there is still no general and practical methodology to introduce a OCF_3 moiety on a large scale and on a wide range of substrates. Indeed, the large majority of the trifluoromethoxylated compounds described in the literature belong to the aromatic series.

Herein, we describe the efficient and highly diastereoselective synthesis of dibromo-trifluoromethoxy styrenes.[5] These small molecules are valuable building blocks that can be involved in cross-coupling reactions, leading to tetrasubstituted olefins bearing a OCF_3 group. Their Suzuki-Miyaura and Sonogashira coupling reactions proved to be completely regioselective. One-pot sequential reactions with two different coupling partners allowed the synthesis of a large variety of trifluoromethoxylated tetrasubstituted olefins. Activities of these molecules on calcium entries involved in breast cancer cells migration are now under investigation.



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P B124

Ag_2CO_3/TFA-catalyzed intramolecular annulation approach to imidazo[1,2-*c*][1,3]oxazin-5-one and pyrano[3,4-d] imidazole-4(3H)-one derivatives

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Over the past two decades, the intramolecular cycloisomerization of 2-alkynylbenzoates, by activation of the carbon-carbon triple bond, has become a powerful tool and an efficient process for the synthesis of isochromenone derivatives. These heterocyclic rings are an important class of natural lactones with a wide range of biological and pharmacological activities.[1]

The general strategy for the synthesis of the 1,3-oxazinone motif described in the literature, is either an intramolecular cyclization via the activation of the carbon-carbon triple bond by transition metal catalysts such as Au, Zn, Ag, and Fe, either by using electrophilic species such as I_2, Br_2, Cl_2, or by using a Bronsted acid such as TFA or *p*-TSA.[2-3] In our work, we develop a strategy for the synthesis of novel imidazo[1,2-*c*][1,3]oxazin-5-ones[4] and novel pyrano[3,4-*d*] imidazole-4(3*H*)-ones, by Ag_2CO_3/TFA-catalyzed intramolecular annulation, according the following retrosynthetic schemes.

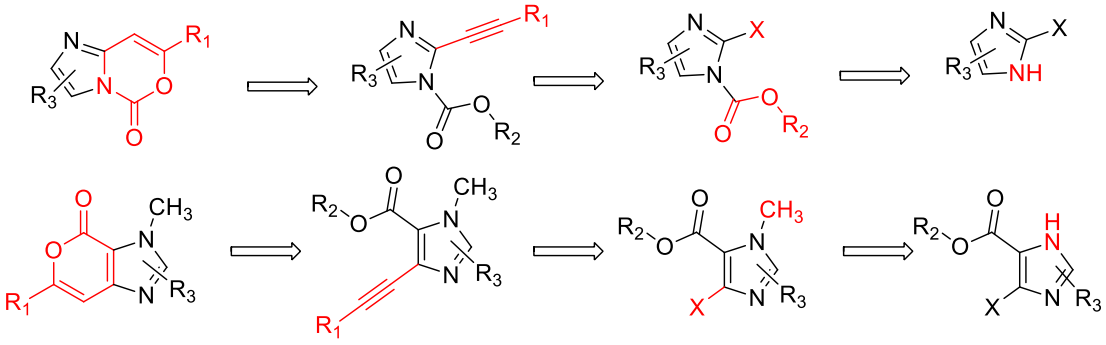

Figure 3: Retrosynthesis scheme for imidazo[1,2-*c*](3,5)oxazinones and and pyrano [3,4-*d*] imidazole-4(3*H*)-ones

Keywords : Imidazo-oxazinones, pyrano-imidazoles, Lactonization, Intramolecular cyclization

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P B125

Neuropilins antagonists to block SARS-CoV-2

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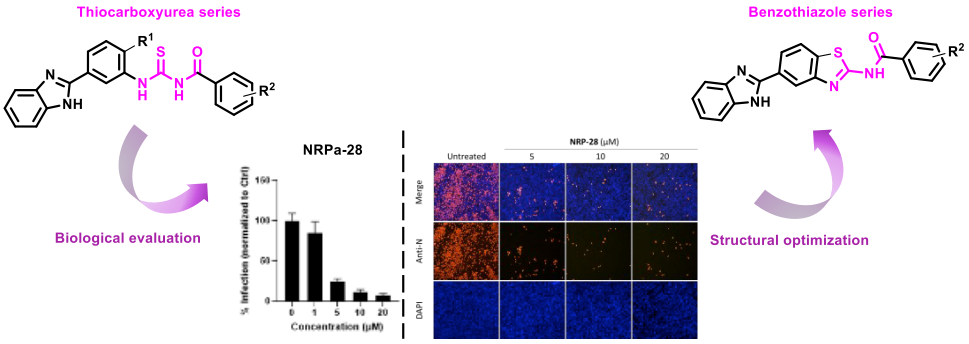
SARS-CoV-2, that caused the COVID-19 pandemic and approximatively 6M deaths, remains a global medical problem. Angiotensin-converting enzyme 2 (ACE2) was identified as the SARS-CoV-2 Spike protein primary recognition receptor. However, recent studies showed that enhanced spreading of the virus may be related to the interaction of SARS-CoV-2 with additional receptors, such as Neuropilin-1 (NRP-1).[1] Thus, blocking this interaction could significantly reduce SARS-CoV-2 infectivity.

NRPs are transmembrane proteins abundantly expressed in the respiratory and olfactory epithelium as well as in tumors. We have recently disclosed the first non-peptidic NRP-antagonists (NRPas) that exerted antiproliferative effects on NRP overexpressing cells.[2]

In this project we took advantage of our expertise in NRPas, in order to propose their development as therapeutic agents to prevent the SARS-CoV-2 entry mediated by Neuropilins. Accordingly, SARS-CoV-2 infectivity assays have been conducted in presence of NRPas showing a dose dependent decrease of the number of SARS-CoV-2 infected cells as well as a significantly reduced SARS-CoV-2 RNA production.

These results encouraged us to perform NRPas structural optimization and new leads identification. Consequently, different chemical modifications were carried on R^1 position leading us to the discovery of a new benzothiazole series.



Scheme 1: NRPas blocking SARS-CoV-2 activity

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P B126

Regioselective Synthesis of New 2,6-disubstitueded Ethyl Pyrazolo[1,5-*a*]pyrimidine-3-carboxylate via Palladium-Catalyzed Cross-Coupling Reactions

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An efficient and original synthesis of various 2,6-disubstituted pyrazolo[1,5-*a*]pyrimidines is reported. A library of compounds diversely substituted in C-2 and C-6 positions was easily prepared via sequential site-selective cross-coupling reactions of 2,6-dibromopyrazolo[1,5-*a*]pyrimidine.[1] The Suzuki-Miyaura and Sonogashira regio-controlled reactions[2] performed with excellent selectivity in favour of the C6-position after careful optimization of the cross-coupling conditions. The monobrominated compounds, obtained on a large scale, were subjected to a second arylation, alkynylation or amination, leading to a new series of ethyl 2,6-disubstituted pyrazolo[1,5-*a*]pyrimidine-3-carboxylate. These unprecedented results constitute the first regioselective approach for diversification of the chemically and biologically interesting pyrazolo[1,5-a]pyrimidine heterocycles at C2 and C6 positions.

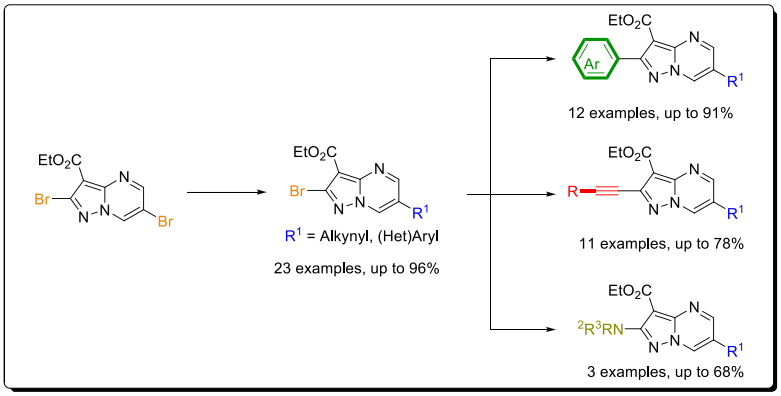

Schéma 1 : Metal-catalyzed selective couplings of 2,6-dibromopyrazolo[1,5-*a*]pyrimidine

Keywords : 2,6-dibromopyrazolo[1,5-*a*]pyrimidine, cross-coupling reactions, regioselective, 2,6-disubstituted pyrazolo[1,5-*a*]pyrimidines.

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P B127

Multicomponent Tandem Process toward Five- and Six-membered *N*-substituted Aza-heterocycles

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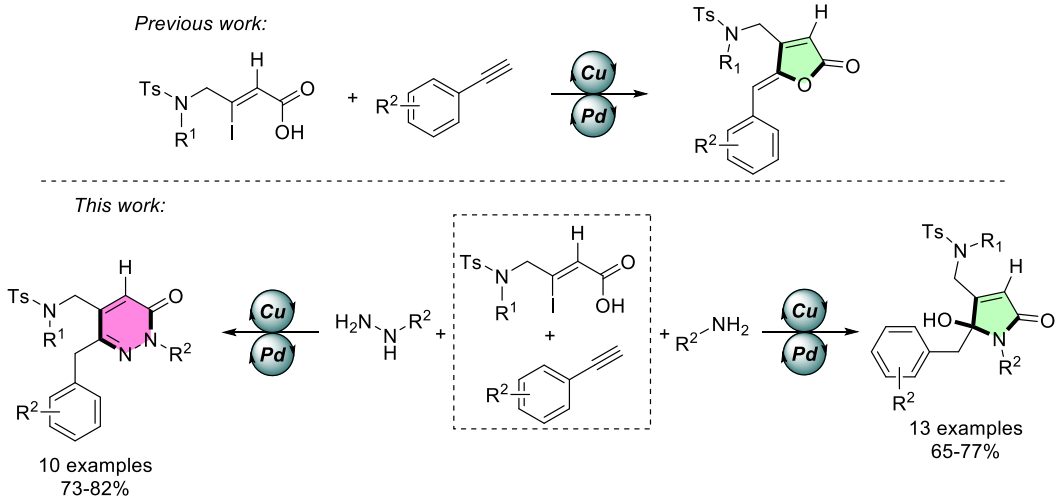
Five- and six-membered heterocycles, containing one or two nitrogen atoms in the structure, are a structural motif of particular interest in synthetic and medicinal chemistry: they possess a diverse set of biological activity and pharmaceutical activities.[1] Following previous work, we have developed a useful method for the synthesis of β-iodo-α,β-unsaturated carboxylic acid bearing an amino group in four steps from readily available primary amine. We have then demonstrated that the resulting (*Z*)-4-(*N*-alkyl)-3-iodobut-2-enoic acids afforded a novel series of *N*-substituted pyranones and *N*-substituted γ-alkylidenebutenolides, prepared using a tandem coupling/cyclization reaction.[2] In the continuation of this research, a highly efficient multicomponent tandem process for the multicomponent synthesis of *N*-substituted γ-hydroxylactams and *N*-substituted pyridazinones has been developed. This transformation proceeds *via* 1) the formation of an γ-alkylidenebutenolides intermediate obtained by intramolecular cyclization of corresponding ynenoic acid catalyzed by a palladium catalyst, 2) a nucleophilic addition of hydrazines or primary amine. A wide range of substrates have been transformed to the respective *N*-substituted aza-heterocyclic products, depending on the nature of the nucleophile (primary amines or hydrazines), in satisfactory yields.



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P B128

Preparation, structure investigation of functionalized boroxines and application as crosslinking nodes for self-healable polymers

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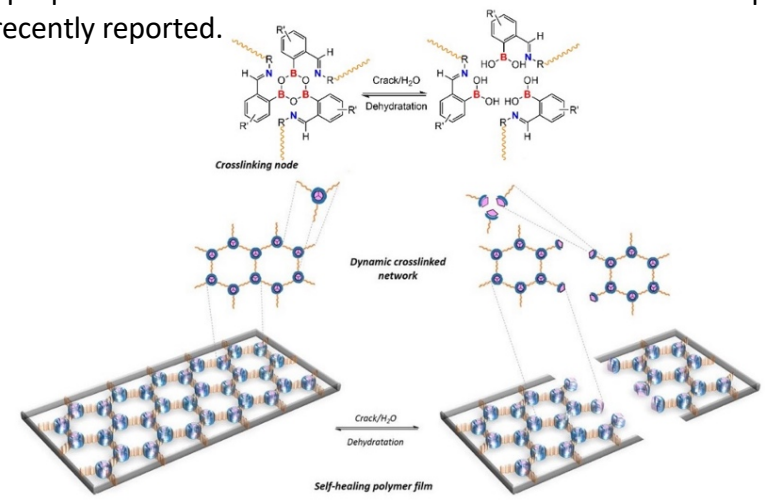
The development of polymers has been a major turn in the modern industry, based on their low-cost manufacturing, low density, the great resistance compared to metals and so on. But this kind of materials have their drawbacks, such as the limited strength, also the disposal becomes an issue as some polymer cannot be recycled or with a lower quality and reduced life span caused by microcracks. Self-healable polymers can tackle this last problem by designing materials whose mechanical properties are preserved after healing. The development of self-healing polymers allows to increase the materials reliability, longevity and preserving their thermo-mechanical properties by avoiding degradation and ensuring their self-reparation.[1] In this project we initially developed new formyl-boroxines and iminoboroxines and investigated their structures which feature three intramolecular Lewis acid-base interactions. The boronic acid/boroxine equilibrium is exploited for forming a star shaped poly(propylene glycol) bis(2-aminopropyl ether) (PPG) polymer. This boroxine will act as the crosslinking node of this polymer increasing its rigidity and making it behaving a dual stimuli-responsive networks to water and heat, allowing self-healing properties.[2] Once the polymer is physically damaged, the hydrolysis of the boroxine will lead to the formation of three boronic acids at the terminal position of the polymers chains, allowing to form afterward a three-dimensional mesh which upon heating will restore the boroxine nodes. Compared to previous works, we synthetized new boroxines with different substituents which can modify healing and mechanical properties of boroxine/ppg polymers. The effect of substituents on the imine is also studied to obtain stronger Lewis interactions between imine and the boroxine leading to mild temperature stimulus.[3] The self-healing polymer properties will then be determined in the LPCM and compared with the reference polymers recently reported.



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P B129
Synthetic studies of Sporochartines

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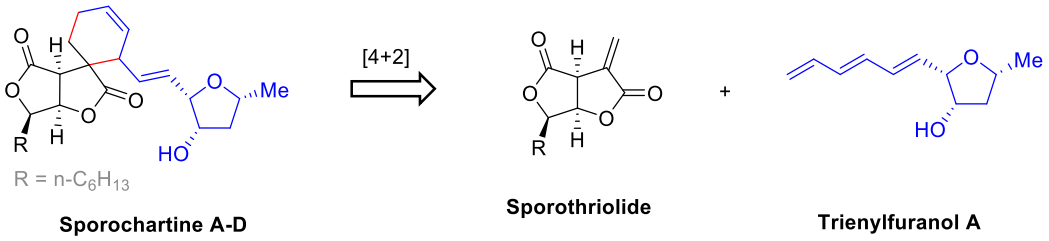
Recently, Dr. Jamal OUAZANI's team isolated five new compounds, named Sporochartines, obtained from an extract of the fungus *Hypoxylon monticulosum*.[1] These new compounds display good cytotoxic activities against cancer strains HCT-116, PC-3, and MCF-7.[1] Thus, a project for the synthesis of Sporochartines have been proposed in order to develop this new family of natural products, to perform (i) a more complete evaluation of their biological properties and (ii) to study their biosynthetic pathways. The proposed biosynthesis is based on the discovery of two metabolites in the fungus: Sporothriolide[2], which has already been studied since its discovery in 1994, and the Trienylfuranol A[3], recently isolated in 2017. Indeed, the formation of the Sporochartines seems to be based on a Diels-Alder cycloaddition reaction between these two metabolites.



The cultivation of *Hypoxylon monticulosum* offers significant quantity of Sporothriolide, while Trienylfuranol A is only detected in very low amount.[1] Only one racemic synthesis of the all-*cis* Trienylfuranol has been realized in the laboratory.[4] So, to study the biosynthetic pathway of Sporochartines, a synthesis of the Trienylfuranol A in its enantiopur form has to be developed. The synthetic pathway should allow the control of the relative all-*cis* stereochemistry of the three stereogenic centers on the furan cycle. Here, we propose an organocatalysis approach using nucleophilic phosphines. Furthermore, the previously synthetized Trienylfuranol A and the availability of the Sporothriolide will allow us to study the Diels-Alder cycloaddition reaction. Thus, chemoenzymatic reactions will be engaged to establish unambiguously the Sporochartines biosynthetic pathway. Indeed, natural enzymes are known to catalyse such cycloaddition reactions [4+2].
During this work, a complete profile of the biological activities of cycloaddition products, but also of synthetic intermediates, will be evaluated.

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P B130

Palladium-Catalyzed Regioselective C–H Oxidative Arylation of 7-Azaindazole *N*-Oxide at C6 Position

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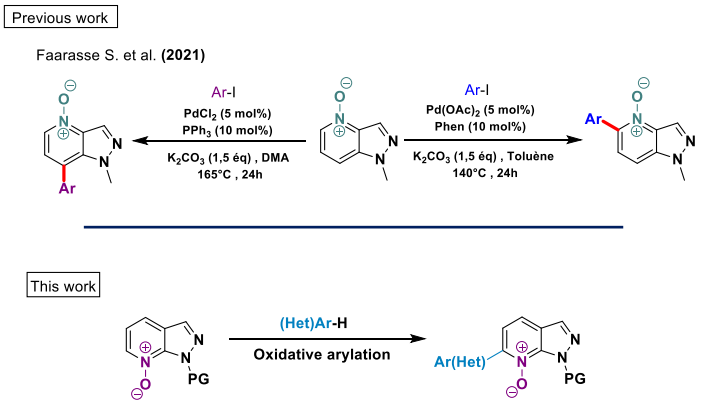
C-H Activation reactions represent nowadays an attractive approach for the development of new heterocyclic systems with various applications, particularly in biological and pharmaceutical fields. In recent years, C-H activation reaction, considered as a simplified and economical methods, has been well studied. However, due to the abundance of C-H bonds in heterocyclic systems, the reaction suffers from the problem of regioselectivity. Especially in the case of 6,5-fused bicyclic compounds because of the high reactivity of the five-membered ring compared to the six-membered ring. Thus, very little reports have been published on regioselective C-H functionalization of the six-membered ring. The efforts made to circumvent this problem of regioselectivity dealt with either the introduction of directing groups [1,2,3,4] or the use of *N*-oxide groups. This last strategy has been used to perform direct arylation reactions on pyridine[5], azaindole[6] and azaindazole[7] as well as oxidative alkenylation reactions [8,9]. Nevertheless, until now no regioselective controlled oxidative arylation reactions have been described on azine *N*-oxides. In this communication, we wish to present a new synthetic methodology allowing the regioselective functionalization of the six-membered ring of 7-azaindazole *N*-oxide derivatives using oxidative arylation reaction.



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P B131

Silicon phthalocyanines as efficient red-light photosensitizers for greener photo-oxidations

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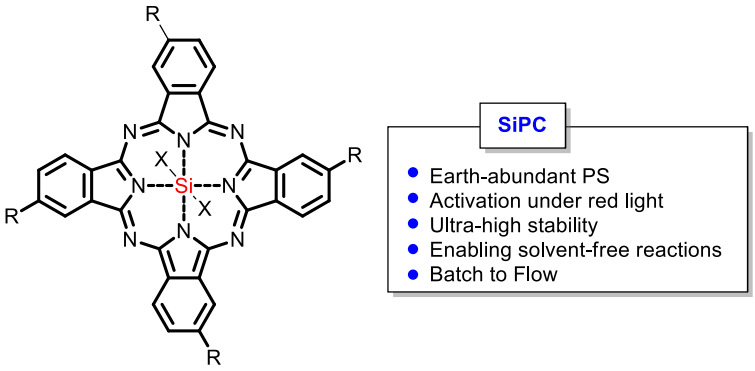
Visible light photocatalysis has revolutionized photochemistry since it allows to avoid the use of high energetic UV light.[1] Today, interests are given to extend visible-light activated photoreactions to activation under lower energetic red to near-infrared light. These wavelengths offer numerous advantages such as better penetrations depth in photochemical reactors, improved selectivity and safety.[2] However, photochemistry upon these wavelengths is relatively challenging since photosensitizers capable of absorbing red/ NIR light are usually subject to rapid aggregation due to π-π stacking interaction and important photobleaching. In this presentation, the novel use of phthalocyanines in photocatalysis will be described. These photosensitizers are good candidates for red to NIR photochemistry since the Q band is located around 670 nm. We studied the reactivity of heavy metal-based platinum (PtPC) and palladium (PdPC), as well as more environmentally friendly silicon phthalocyanines (SiPC), among others, in photooxidation reactions in batch and continuous flow photoreactors. We found that SiPC had a very high reactivity and stability, comparable with platinum and palladium ones. Finally, we demonstrated how these results could unlock the development of what we believe to be a truly more sustainable photocatalytic photooxidation process applied to the transformation of β-citronellol into rose oxide which is a multi-ton scale photochemical process in industry. The combination of a very reactive and stable heavy metal-free red-light photocatalyst with the high performances of flow photochemistry allowed for the development of a high performance solvent-free continuous flow process.



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P B132

Alkoxyamine as a probe to quantify the efficiency of the photochemical or thermal homolysis of C-O bond in nanostructured silica

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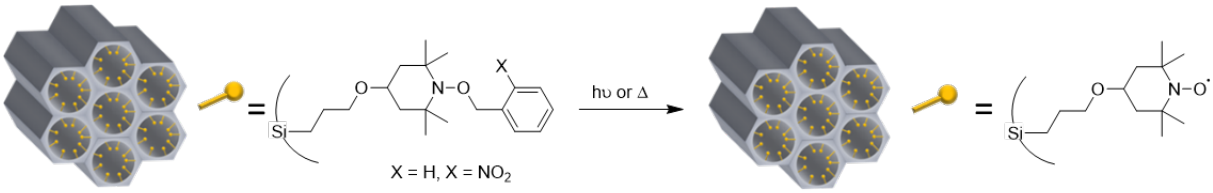
Development of new materials with unusual functional groups, such as radicals, is of topical interest to enable new advances in spin sciences. Properties related to the presence of unpaired electrons, such as conductivity or magnetism, have been studied in order to develop smart devices.
Recently, our group focused his attention on the effect of nanostructuration on the behavior of transient radical. Therefore, it has been shown that confinment of organic radicals in porous material allows a great increase of radical lifetime.[1-6] Mesoporous silica, obtained *via* sol gel process is a powerful and intricate tool to stabilize elusive organic intermediates.
In extension of this work we focused our attention on confined alkoxyamines within porous matrices. We report the design of a nanostructured silica functionalized with an alkoxyamine which can led to a stable nitroxide radical upon either light irradiation or thermal heating. The formation of the nitroxide radical can be quantify and enables to evaluate the efficiency of the C-O bond homolysis in a mesoporous material (scheme 1).[7]



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P B133

Chiral Binol phosphate derivatives as multi-task chiral anions for asymmetric tandem catalysis

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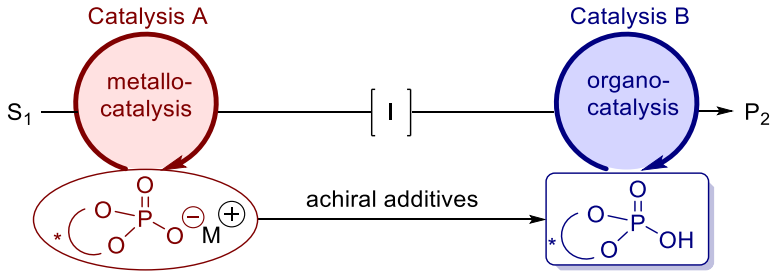
Assisted tandem catalysis refers to processes, in which two successive and mechanistically distinct catalytic reactions are performed by one initial (pre)catalyst and for which the change in mechanism is triggered by the chemical reagent addition or a change in the reaction conditions.[1] Asymmetric applications of assisted tandem catalysis have been scarcely described and so far, rely on a multitask metal strategy in which the initial (chiral) metallocatalyst is converted into the second chiral catalyst of an identical metal source.[2]

Our group has recently reported the first proof of concept of the use of a multitask chiral ligand in an asymmetric assisted tandem catalysis sequence, by combining successively a metallo and an organo process.[3] Herein we want to expand this chiral relay ligand concept to ion pair catalysis[4] in which the enantiopure anion of a metallocatalyst will then be either transferred or converted to a chiral organocatalyst. The rich applications of binol-derived phosphoric acids[5] in organic catalysis via protonation activations and in metal catalysis via ionic complexation, elect them as ideal chiral-inducing agents for the realization of asymmetric tandem-assisted catalysis sequences, based on the concept of chiral relay ligand applied to ion pair catalysis.



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P B134

Gold(I)-Catalysis: Development of New Asymmetric Methodologies and Total Synthesis of Natural Products

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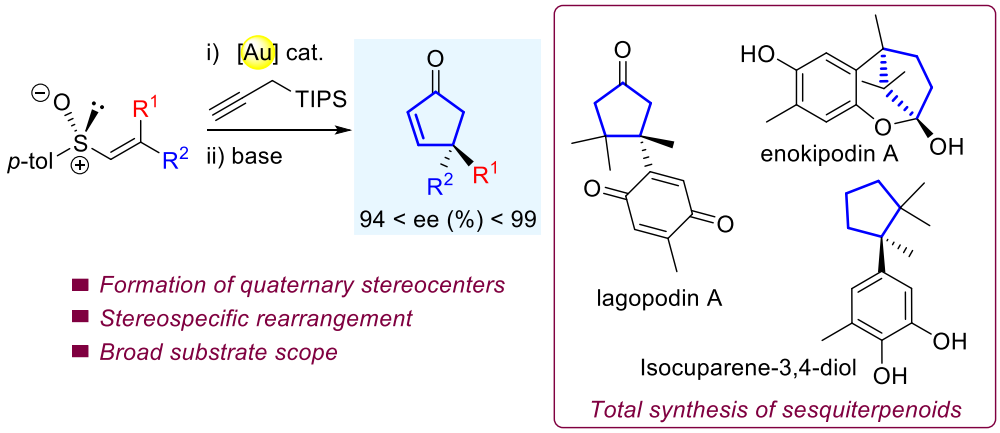
Homogeneous gold catalysis has emerged as a powerful method in organic synthesis due to the unique ability of cationic gold complexes to activate unsaturated bonds. In recent decades, gold(I)-catalyzed reactions have been widely applied to access complex molecular frameworks. Furthermore, the recent development of efficient chiral gold catalysts has increased the potential of isolation of enantioenriched molecules. In recent years, we have developed new chiral phosphahelicene-Au(I) catalysts[1] and established new asymmetric transformations involving the cycloisomerization of 1,5-enynes[2] and the synthesis of chiral polycyclic *N*-heterocycles via gold(I)-catalyzed 1,6-enyne cyclizations.[3]

Recently, we have also developed the synthesis of cyclopentenones with C4-quaternary stereocenters through a stereospecific gold-catalyzed [3,3]-sigmatropic rearrangement. The application of this simple asymmetric methodology allowed the total synthesis of five natural sesquiterpenoids, including hitoyopodin A, lagopodin A, isocuparene-3,4-diol and enokipodin A and B.[4,5]



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P B135

New Weakly Coordinating Anions of type $[In(OTeF_5)_4(THF)_2]^-$ and $[In(OTeF_5)_6]^{3-}$

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Recently, the reactivity of vinyl cations has been exploited to design new reactions. Our subsequent research has shown the interest in using WCAs such as $[Al(OR^F)_4]^-$ ($R^F = C(CF_3)_3$) to promote bimolecular vinylation of aromatics via vinyl cation intermediate. (Fig. 1)[1] However, the generation of vinyl cations that are sufficiently electrophilic through heterolytic Csp^2-X (X = Cl, Br, F, OSO_2R …) cleavage remains a very challenging task. We assume that using other WCAs which exhibit even weaker coordinating properties than those used previously, we can improve the reactivity of vinyl cations and overcome the current limitations. Recently, Riedel's team reported the synthesis and characterization of species of type $[Y][M(OTeF_5)_4]$,[2] (M = Al and Ga; Y = Li, K, Na, Ag, H, Ph_3C, Ph_4P, C_9H_{13}, Me_2C ...).

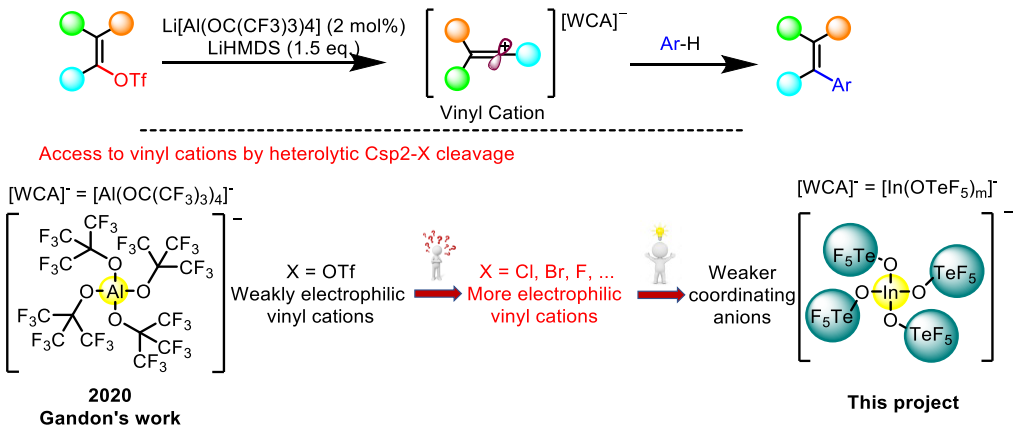
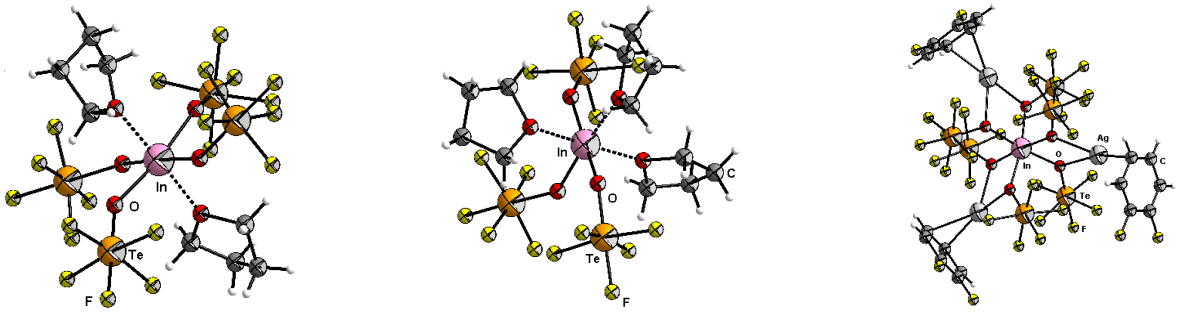


Figure 4 : Bimolecular vinylation reaction via vinyl cation



To extend the repertoire of WCAs, we were interested in indium and more particularly on the synthesis of unprecedented $[Y][In(OteF_5)_4(THF)_2]$ (Y = Ag, Ph_3C, $(Ph_3PAu)_2Cl$, Ph_4P) as well as $Ag_3[In(OteF_5)_6]$. Here we will present the synthesis and the spectroscopic characterization as well as the X-ray structures of salts of WCAs $[In(OTeF_5)_4(THF)_2]^-$ and $[In(OTeF_5)_6]^{3-}$.

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P B136

Lewis Acid-Catalyzed Tandems Dehydrative Cyclization/Transfer Hydrogenation or Friedel-Crafts Reaction of 1,2-Diphenylalkene-1-ol

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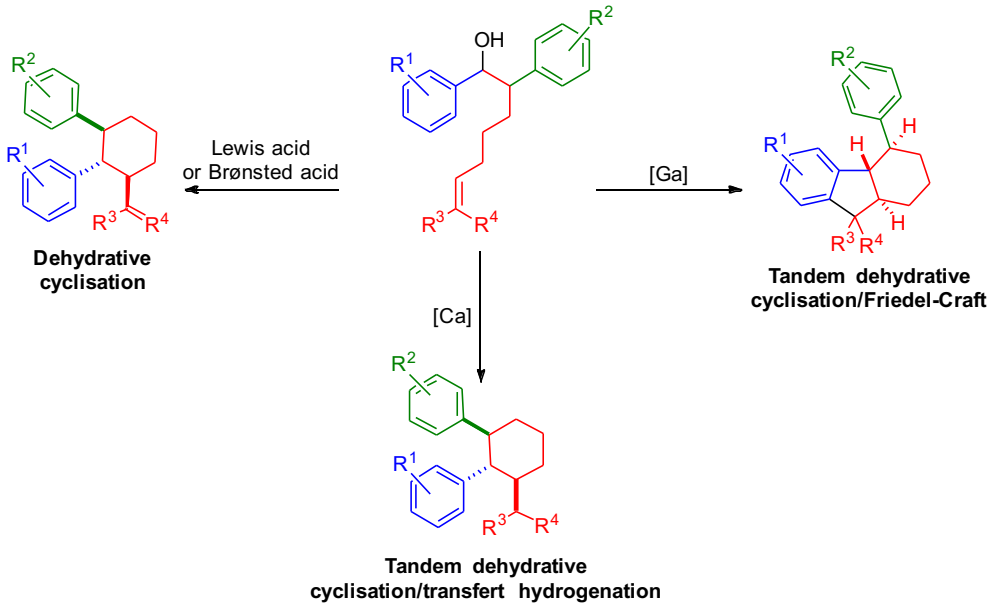
The synthesis of medium sized carbocycle rings from linear subtract is challenging in organic chemistry. Among all the numerous effective methods for the synthesis of polysubstituted carbocycles,[1,2] the dehydrative cyclization reaction of a C-OH bond with an alkene bond is an attractive protocol for the formation of C-C, as it uses readily available and inexpensive alcohols, without requiring unnecessary pre-functionalization, and generates mainly water as the only by-product. Following our previous work on the development of a gallium-catalyzed carbonyl-olefin metathesis/transfer hydrogenation tandem,[3] our attention in this work was focused on the development of a new dehydrative cyclization/Friedel-Crafts or transfer hydrogenation sequences starting from 1,2-diphenylalkene-1-ol derivatives. The first results show that according to the experimental conditions, in particular the Lewis acids used, the reaction outcome is affected. This new chemoselectivity and the scope of these tandem reaction are still under investigations.



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P B138

Advancing the Chemistry of the C–(C=O)–N Synthon: New Transition-Metal-Catalyzed Asymmetric Cycloadditions

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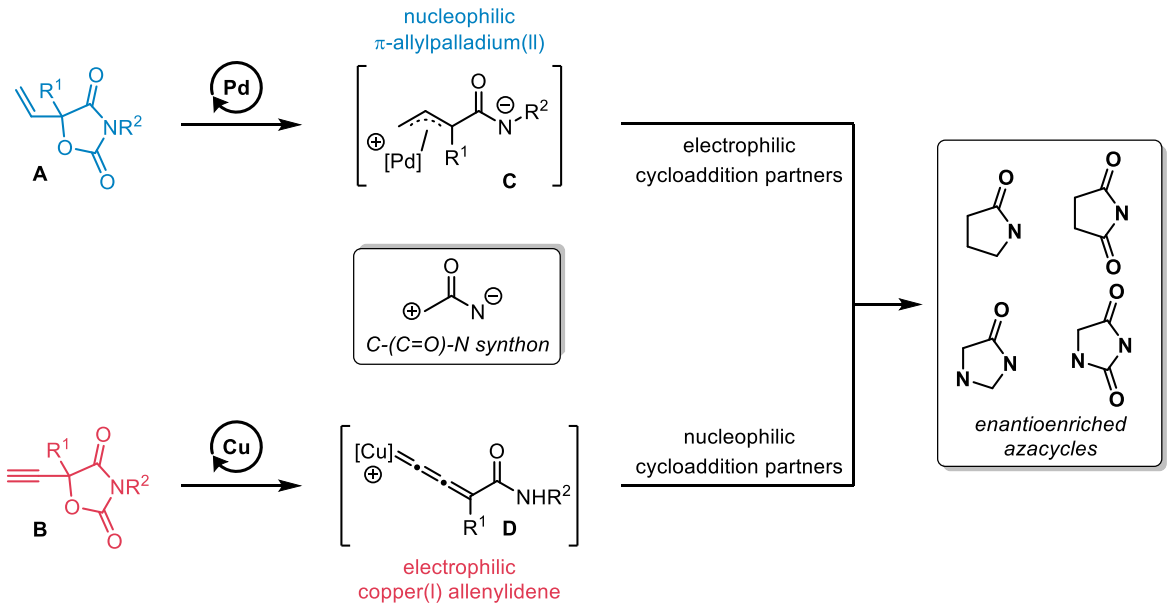
Due to their ability to engage in both hydrogen-bond donation and acceptance, nitrogen-containing heterocycles display better interactions with biological targets and therefore are widely found in biologically active molecules. Among these latter, lactams and associated heterocycles bearing a C–C(=O)–N synthon are of high importance and numerous methods have been developed to introduce this important moiety by cycloaddition reactions. α-Haloamides[1] and others[2] are well-described synthetic equivalents for this synthon, but very few examples describe the formation of cycloadducts in an enantioselective fashion.[3]
Our research group has focused on the development of two complementary enantioselective methods to expand the chemistry of the C–C(=O)–N synthon using transition metal catalyzed cycloadditions.
We demonstrated that vinyloxazilinediones **A** and alkynyloxazilinedione **B** are efficient precursors of π-allylpalladium(II) zwitterion[4] **C** and copper-allenylidene[5] complex **D**, respectively. When the first one displays nucleophilic properties, the other can react with nucleophilic dipolarophiles. Through this complementary approach, enantioenriched γ-lactams, 4-imidazolinones, hydantoins and succinimides have been obtained.



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P B139

Titanium-catalysed transformations of alkynes into complex molecular architectures

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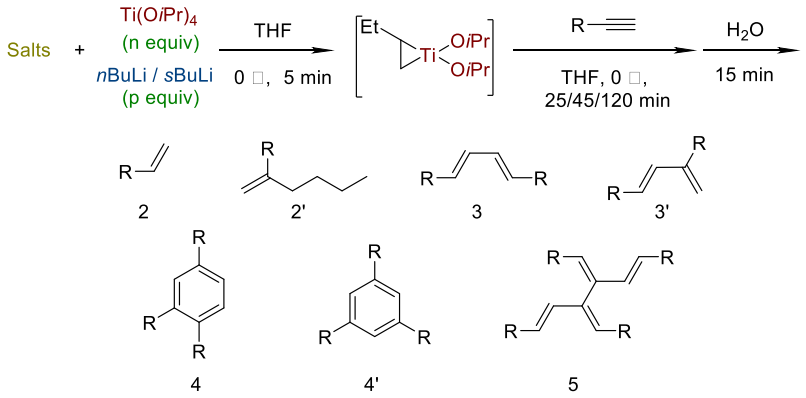
Since their first discovery by O. G. Kulinkovich's group[1], a series of powerful synthetic tools have been developed using a combination of Ti(O*i*Pr)$_4$ and an excess of Grignard reagent.[2] After a careful study of the reaction between Ti(O*i*Pr)$_4$ and *n*Buli was carried out by Rassadin *et al.*[3] and new results in the cyclotrimerisation of alkynes,[4] we recently tested the reactions of various aliphatic terminal alkynes, under different experimental conditions. These experiments lead to the formation of several products characterised by NMR and other analytic methods (Scheme 1).



Scheme 1

Results of a second study involves 1,3-diyne substrates are also presented. The reactions of these substrates, under similar conditions, reliably and selectively lead to the production of enynes having a Z-configuration (Scheme 2).

Scheme 2

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P B140
Trifluoromethylselenolation via Pd-Catalyzed C-H Activation

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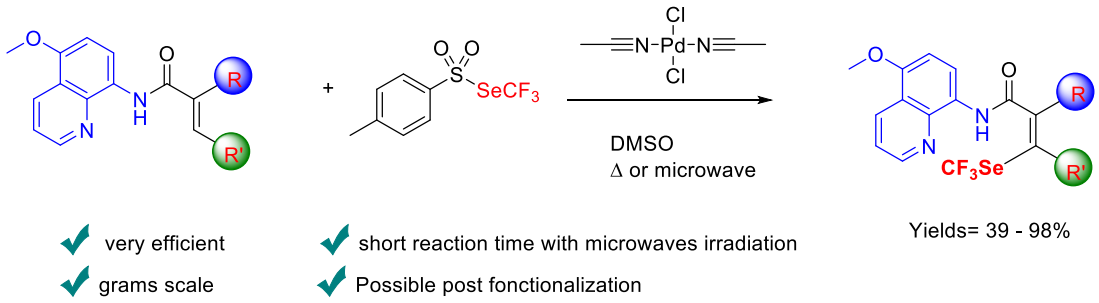
For several decades, fluorine chemistry has taken a prominent place in scientific community. Indeed, this atom is present in many fields such as pharmaceutical science, materials, agriculture.[1] Associated with chalcogens, fluorine modifies the electronical and chemical properties of molecules and specifically increases the lipophilicity of molecule ($\Pi_{OCF_3} = 1.04, \Pi_{SCF_3} = 1.44, \Pi_{SeCF_3} = 1.62$).[2] The chemistry of CF_3Se group remains still underdeveloped despite the fact that some trifluoromethylselenolated molecules have recently shown promising results as potential anticancer agents.[3] Vinylic compounds bearing a CF_3Se constitute original and useful fluorinated building-blocks. Nevertheless, synthetic methods to obtain such substrates remains limited. Direct trifluoromethylselenolation of non-prefunctionalized olefins is still required to easily obtain CF_3Se-vinylic compounds. Although these last years, direct functionalization through transition metal-catalyzed C-H activation has known a rapid infatuation to become a standard reaction well-documented.[4] Nevertheless, despite the efficiency of such reactions, their applications have remained unexploited, until recently, in CF_3Se chemistry.[5] Herein, a palladium catalyzed trifluoromethylselenolation of vinylic C-H bonds is described, no such vinylic functionalization has been yet reported.[6]



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P B141

Exploring the Two-Electron Oxidation of Silver(I) Complexes

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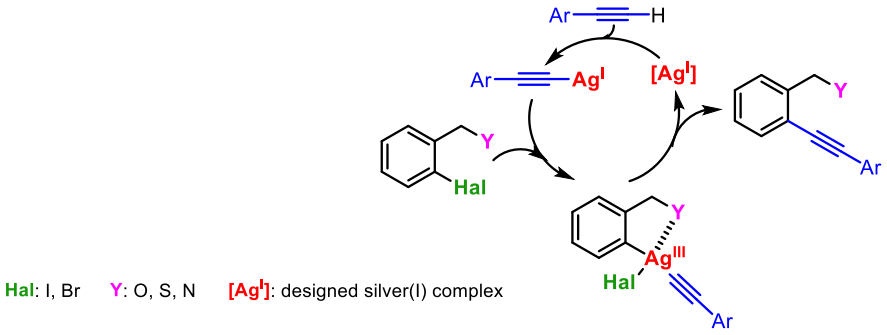
Homogenous catalysis is an important tool for sustainable chemistry, taking part in the 12 principles of *Green Chemistry.*[1] C-C and C-Heteroatom cross-coupling reactions represent a powerful tool in organic synthesis for the construction of scaffolds in numerous areas such as pharmaceutical derivatives or molecular materials. These reactions are promoted by transition metals undergoing two-electron redox processes, most of the time palladium and copper.[2] Silver has generally been excluded from this kind of reactivity. This coinage metal is commonly employed for its moderate Lewis acidity, its halogenophilicity and as a one-electron oxidant, however its redox properties are still not well understood. Indeed, it is generally accepted that silver is only involved in one-electron redox chemistry.[3] This fact was denied very recently with the discovery of Ribas' group in 2014. The authors reported the experimental evidence of a two-electron redox Ag(I)/Ag(III) catalytic process where the triazamacrocycle-Ag(III) intermediate has been fully characterized.[4] Their work was further extended in 2018 with the use of acyclic ligands.[5] Apart from these two publications, reports about the Ag(I)/Ag(III) redox properties are very scarce and often lack of mechanistic evidences.[6] Motivated by the discovery of Ribas' group and others,[6] we are currently working on the development of a new Ag(I)/Ag(III) Sonogashira-type catalytic cycle to study in more depth this underexploited reactivity of silver.



Scheme 1: Envisioned Ag(I)/Ag(III) catalytic cycle to explore.

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P B142

Synthesis and study of new ligands with a cavity and their applications for redox-active and fluorescent systems

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Molecular recognition involves weak interactions between at least two molecules. In supramolecular chemistry, the study and usage of these weak interactions involves the development of molecular receptors. Calixarenes, which are at the heart of this project, are part of this class of receptors. Calixarenes have a conical shape and have two differentiated rims (small rim and large rim), which opens the way to functionalization chemistry on one and/or the other rim. The functionalization of the small rim has been the subject of much work within the two groups[1], resulting in molecular receptors associating a metal cation with a cavity, with the aim of studying biomimetic systems of metalloenzymes. Following the results obtained for the small rim, the functionalization of the large rim was also considered, giving this project.

Via a method developed by both groups[2,3], the functionalization of the large rim is possible through the insertion of an anilin group on the large rim. The intermediate is obtained in 3 steps from a commercially available calixarene. Then to the intermediate is grafted the coordinating group (e.g. imidazole unit) in order to obtain the desired ligands (Figure 1).

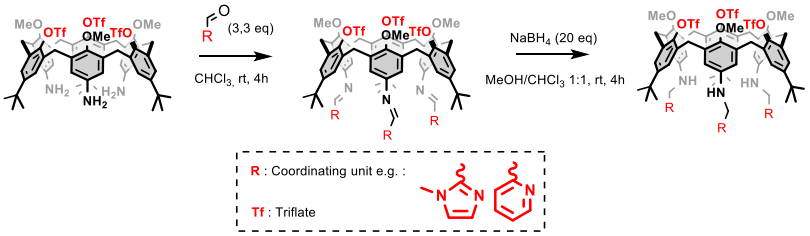

Figure 5 : General method for the synthesis of the new ligands.

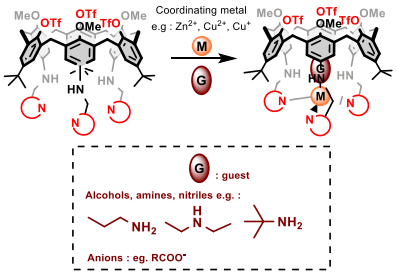

Figure 6 : General method for the synthesis and host guest study of the complexes.

The next step was the synthesis of the corresponding complexes. Zinc and copper are transition metals responsible for the activity of many metalloenzymes in the human body. For this reason, biomimetic systems containing zinc or copper are interesting targets to study. The Zn and Cu (I)/(II) complexes were therefore synthesized first. Complexes synthesized were then employed in host guest studies, these revealed that they could recognize a wide range of different guests (e.g. acetonitrile, amines, carboxylates). These host guest studies were done through different methods, such as NMR, EPR, UV-visible and IR spectroscopy.

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P B143
Synthetic approaches for Cathepsin S inhibitors and fluorinated analogues

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Atherosclerosis is responsible for a large part of cardiovascular events and causes more than 19 million deaths each year.[1] The detection of « unstable » plaques, which will evolve and are likely to break down is therefore a major current issue in the prevention of such cardiovascular accidents.
Positron emission tomography (PET) represents an extremely promising imaging technique for their detection since it allows an in vivo non-invasive visualization of atheromatous plaques which will be qualitatively defined through selective targeting.[2]
Cathepsin S belongs to the cysteine protease family and recent studies have shown that these proteases are overexpressed in the above-mentioned cardiovascular pathologies. More precisely, its expression has been specifically identified in human atherosclerotic lesions and not in healthy arterial segments.[3] Identification of atheromatous lesions by PET might thus be investigated in vivo by labelling of Cathepsin S with radiofluorinated inhibitors.
Our project aims to synthesize such fluorinated analogues of Cathepsin S inhibitors, especially LHVS **Fig.1.** This Leucine derivative compound exhibits the required properties for building a relevant library of analogues: a very good inhibition constant (Ki) of 5nM for Cathepsin S as well as an excellent selectivity. We will present our recent synthetic efforts in the generation of a library of such fluorinated analogues, including ones featuring new scaffold variations.

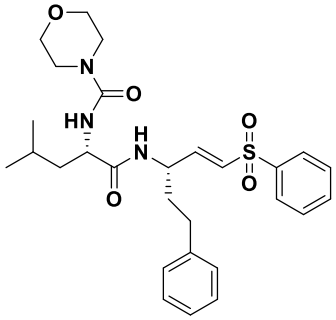

Fig. 1 LHVS a lead toward fluorinated Cathepsin S inhibitors

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P B144

Access to fluorescent azobenzene photoswitches by a double Buchwald reaction

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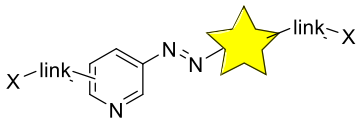
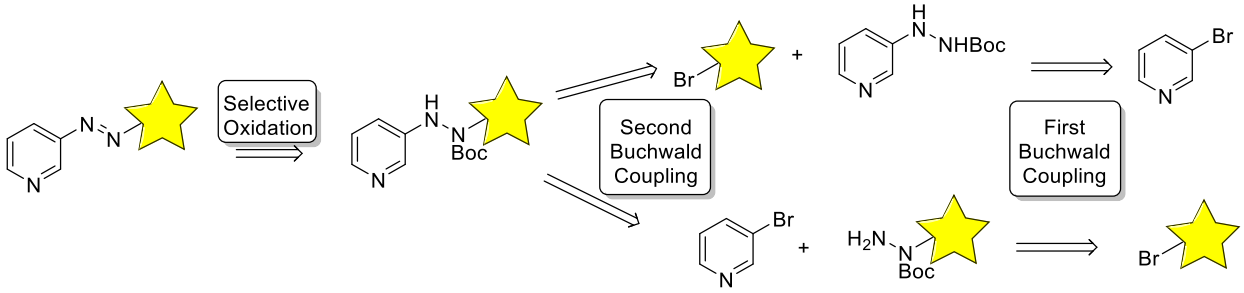
Pentameric ligand-gated ion channels (pLGICs) are key players of neurotransmission and neuromodulation in the brain and thus are considered as major drug targets for diverse neuropathologies. However, their molecular mechanisms of function remain poorly understood and studying these proteins is essential to understand how pLGICs convert the neurotransmitter binding into the opening of their ion channel. Over the last years, identification of GLIC, a bacterial homolog from *Gloeobacter violaceus,* has allowed the X-ray resolution of three conformational structures,[1,2] and the proposal of a mechanism for the ion channel opening with the initial blooming of the extracellular domain followed by the twist of the transmembranar part.[3]

To comfort this mechanism, we decide to design fluorescent azobenzene photoswitch which will be attached to GLIC by means of two reactive functions. This allowed us to control GLIC conformation changes by fine light tuning and to follow it by measurement of the fluorescence changes.



Methodology used for the synthesis of the core structure, based on a challenging double Buchwald reaction with hydrazine derivatives, will be presented.



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P B145

Synthesis of a new family of 4-phosphonomethyl- 4,5-dihydropyridazin- 3(2H)-one

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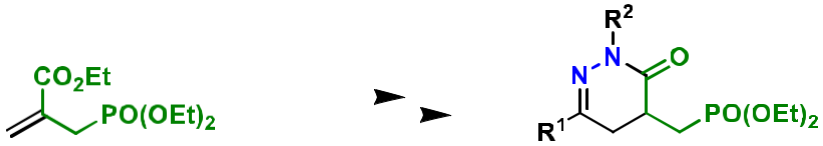
The synthesis of a new class of 2,4,6-trisubstituted pyridazin-3(2H)-one derivatives is described. The construction of the pyridazinone scaffold is based on two steps involving 1) conversion of the allylphosphonate into γ-ketoester through Michael addition-Nef sequence, 2) action of hydrazine derivatives on the corressponding γ-ketoester leading to the formation of a new serie of phosphonated pyridazinones with exellent yields.



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P B146

Aza-Wacker Mediated Access to 3-Amino-3-Deoxyglycals

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3-amino-3-deoxyglycosides are a class of rare glycosides of high relevance found both on bacterial natural products and on a large number of bioactive compounds.[1] As noteworthy examples, they can be found in the structures of anticancer agents (ravidomycin **1**) or macrolide antibiotics (azithromycin **2**). More recently, Nilsson et *al.* also showed that 3-*N*-Aryl-3-deoxy-β-D-galactosides such as **3** are selective inhibitors of galectin-9C (figure 1).[2]

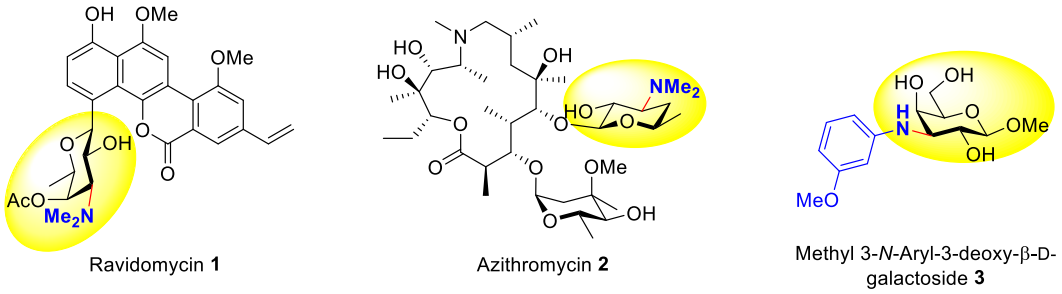
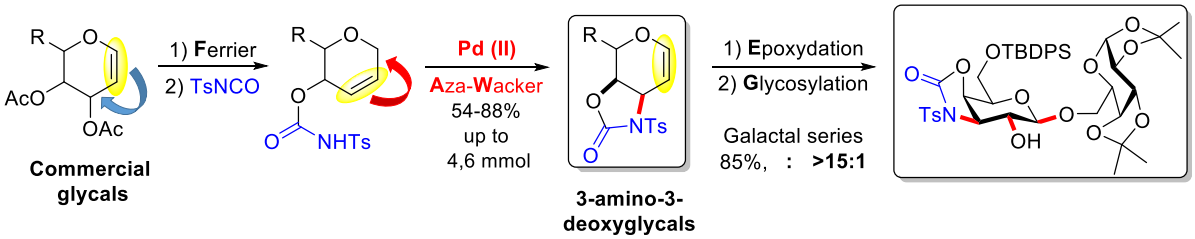


Figure 7 : Selected examples of relevant 3-amino-3-deoxyglycosides

Owing to their biological importance and since they are either priceless or commercially unavailable, the development of an expedient stereoselective approach to synthesize 3-amino-3-deoxyglycoside donors has attracted formidable interest.[3] Here, we describe an expedient synthesis of 3-amino-3-deoxyglycals *via* an original Ferrier rearrangement / aza-Wacker sequence starting from commercial glycals as bio-sourced derivatives.



*Scheme 1: **FAWEG** (Ferrier/**A**za-**W**acker/**E**poxidation/**G**lycosylation) sequence*

Starting from these orthogonally protected 3-amino-3-deoxyglycals, an original epoxidation / glycosylation sequence was performed, defining **FAWEG** (**F**errier / **A**za-Wacker / **E**poxidation / **G**lycosylation) as a new and efficient strategy to access 3-amino-3-deoxyglycosides (scheme 1).[4]

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P B147

Synthesis of fluorinated amino acids for the design of injectable hydrogels

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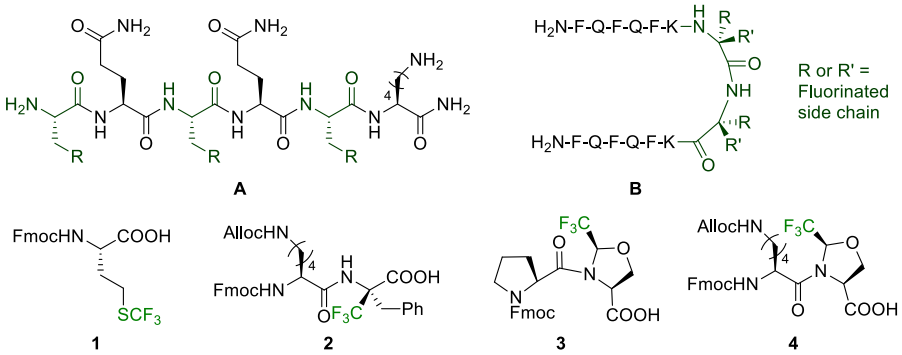
Amphipathic peptides, composed of alternating hydrophobic and hydrophilic amino acids, have been shown to form self-assembled hydrogels. These hydrogels proved adequate drug delivery platforms that can deliver pharmaceutical cargoes in a stable and prolonged manner when injected subcutaneously[1]. Such systems can increase patient compliance by subcutaneous administration of therapeutics by limiting the amount of injections required for the efficient treatment of chronic diseases. Currently, however, the drug release window of these peptide hydrogels is limited to a maximum of four days and this window ideally needs to be extended for optimal use in the clinical setting. As the role of fluorine within the field of medicinal chemistry continues to develop, fluorinated amino acids have shown their utility in promoting and stabilizing well-defined secondary structures, as well as increasing local hydrophobicity and enhancing the biological profile of drug candidates[2]. Thus, the rational introduction of fluorine atoms into peptide hydrogels might provide access to a new class of injectable controlled-delivery systems that incorporates the favorable properties of fluorine atoms. Two strategies are investigated for the synthesis of fluorinated peptide hydrogels based on the hexapeptide consensus sequence developed at ORGC. The first relies on the incorporation of fluorinated amino acids along the hydrophobic face of the amphipathic peptide type **A**. The second incorporates the design of fluorinated b-hairpin peptide hydrogelator type **B**. The synthesis of FmocTFM **1** but also building blocks containing aTfmPhe (**2**) and TfmYPro (**3** and **4**)[3] will be presented. Additionally, first results in the synthesis of fluorinated peptide hydrogelators and their structural characterization will be presented and discussed.



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P B148

Synthesis of Functionalized Cyclopentenes via $InCl_3$-Catalyzed Ring-Closing Carbonyl-Olefin Metathesis

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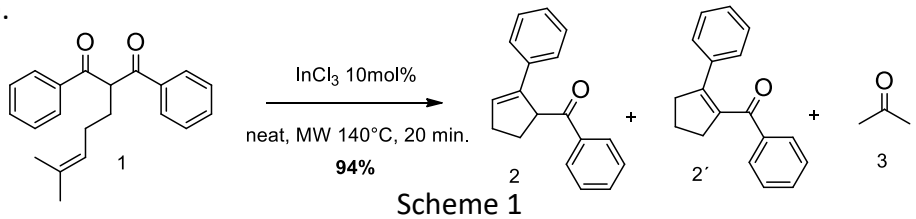
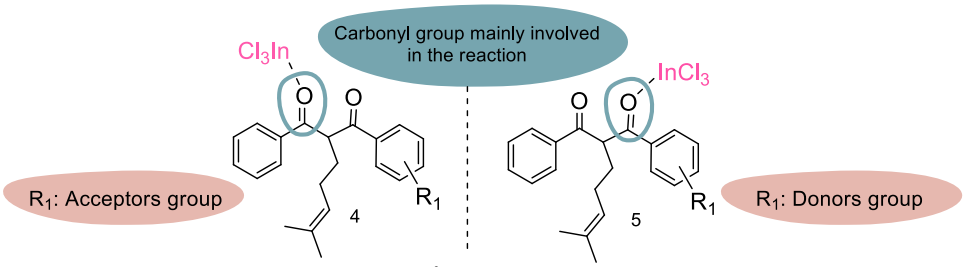
Carbonyl-olefin metathesis has become one of the most important organic reactions emerged in recent years. Alike its predecessor, olefin metathesis, it is a very useful tool for the generation of C-C sp^3 bonds, which are essential for the construction of complex molecules in organic synthesis.[1] In this work, we present the optimization of ring-closing carbonyl-olefin metathesis reaction through an environmentally friendly approach. Our development strategy was based on three key aspects. On the one hand, the use of $InCl_3$ as catalyst, which stands out for its easy availability, non-toxicity, low cost, moisture stability, compatibility with air and water.[2] On the other hand, reactions were optimized under solvent-free conditions, avoiding the use of organic solvents to reduce the impact on the environment. Finally, we employed microwave heating as a tool to considerably shorten reaction times. For reaction conditions optimization we used 1,3-diaryl-1,3-diketone **1** to obtain cyclpentenes **2** in 94% yield (**Scheme 1**).



Scheme 1

We applied the optimized conditions shown above to a series of alkylated 1,3-diaryl-1,3-diketones bearing different electron-donor and electron-acceptor substituents on one of the aromatic rings (**Scheme 2**). Our main objective was to evaluate the preferential cyclization mode, which *a priori* should depend on the nature of the substituent.



Scheme 2

Our results allowed us to conclude that participating carbonyl on metathesis reaction is the one with the highest electronic density (**Scheme 2**). These findings are supported by NMR spectroscopy experiments: ^1H, ^{13}C, HSQC, HMBC, COSY, TOCSY.

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P B149
Organic Charge Transfer Complexes for Catalysis

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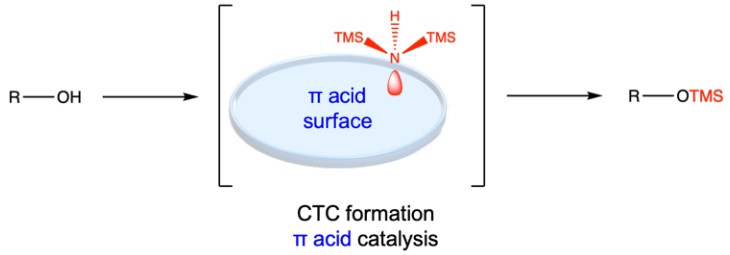
Charge transfer complexes (CTCs) have been extensively studied in materials science owing to their inherent properties in the fields of charge transport, light emission, nonlinear optics and external stimuli responsiveness.[1] Their π-acid component are UV absorbers and their color changes upon contact with π or Lewis bases provide evidence for CTC formation.[2]

While the propensity of CTCs to absorb light has been advantageously and massively used to excite molecules and trigger reactivity,[3] in sharp contrast, the use of the π-acidity to stabilize anions or activate electron-rich molecules in the context of catalysis has hardly been studied. Indeed, it has only been demonstrated in the seminal reports of Matile[4] using π-acid molecules based on naphthalene diimide and fullerene. However, his focus lays mainly in reproducing biologically relevant processes like anion transport through membranes and polyketide/terpenoid biosynthesis (i.e. π-acid catalysis of malonate/enolate chemistry).
In order to probe more generally the catalytic ability of CTCs, we settled on the study of the activation of electron-rich nitrogen. It is well known that the interaction of Lewis or Bronsted acids with the nitrogen atom of HMDS facilitates N–Si bond cleavage. Notably, on reaction with alcohols, this promotes the transfer of the trimethylsilyl group to the oxygen atom.[5] We have demonstrated that such alcohol protection reactions can be similarly achieved in the presence of catalytic amounts of electron-deficient aromatic molecules and developed useful methodology for the catalytic silylation of a large array of alcohols with HMDS as silicon source under neutral conditions and at room temperature. The catalysts are easy to handle, recyclable and allow the reaction to be carried out in near to quantitative yield in an open-air reaction vessel. Regarding the activation mechanism, we have substantiated with UV studies the formation of CTC's between the nitrogen atom and the π-acid arenes. Thus, a very mild and efficient alcohol silylation method has been achieved using a new supramolecular activation mode.



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P B150

Access to indazole fluorophores from azobenzenes via tandem double C-H activation and Michael addition: developments and applications

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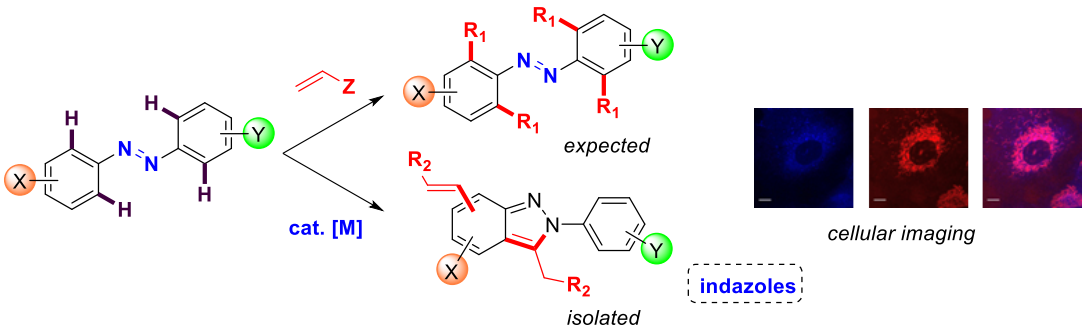
Azobenzenes have attracted considerable attention due to their unique photochromic properties and quite recently, our group started a diversity-oriented program for their synthesis.[1] If the preparation of simple azo units is efficiently reported, the synthesis of densely-substituted azo compounds remains a perpetual challenge for the organic chemist.[2] In our quest to generate original photo-switches, we speculated that the use of azobenzenes in the presence of alkenes could generate the targeted highly functionalized azos. However, after preliminary experiments, it rapidly turned out that this strategy provides various poly-substituted indazoles exhibiting interesting fluorescence after excitation at 365 nm under a UV lamp. This finding stimulated us to design a new eco-friendly process for the synthesis of 2H-indazoles via tandem oxidative dehydrogenative cross coupling – Michael addition at room temperature and to explore their photophysical properties. Several compounds exhibit high fluorescence quantum yield in water and allow a vesicles labeling in live cells upon one-photon and two-photon excitation (Scheme 1).



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P B151
Chemical tools for the identification of Lysosomal OligoSaccharide Transporter (LOST)

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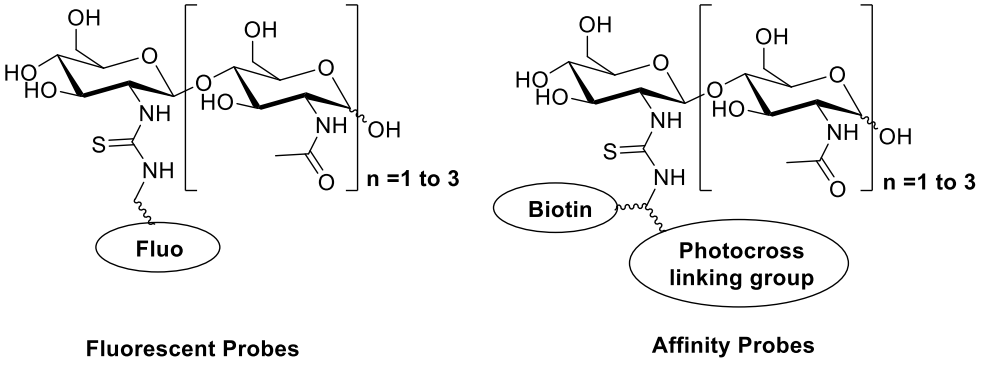
Glycoconjugates and oligosaccharides derived from pathogens and the extracellular matrix are detected by elements of the innate immune system.[1],[2] More recently free oligosaccharides generated during protein N-glycosylation (fOS) have also been shown to be proinflammatory (fOSp) after demannosylation and contribute to certain rare inherited inflammatory diseases.[3]

A non-vesicular fOS subcellular trafficking pathway in which fOS are transported out of the ER into the cytosol relies on unidentified ER oligosaccharide transport machinery (ERT) and, after trimming by cytoplasmic glycosidases (Engase1p and Man2C1p), a lysosomal fOS transport machinery (LOST) in order to be demannosylated into lysosomes.

In order to better define the role of this non-vesicular fOS trafficking pathway in normal and disease states, LOST must be manipulated. Therefore, our objective is to develop chemical tools to facilitate the study, characterization and identification of LOST proteins.[4] In this communication, the design and the synthesis of these oligosaccharidic fluorescent, biotinylated and photoactivatable probes will be described.



Fluorescent Probes **Affinity Probes**

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P B152
Sustainable Synthesis of Metallic Nanoparticles

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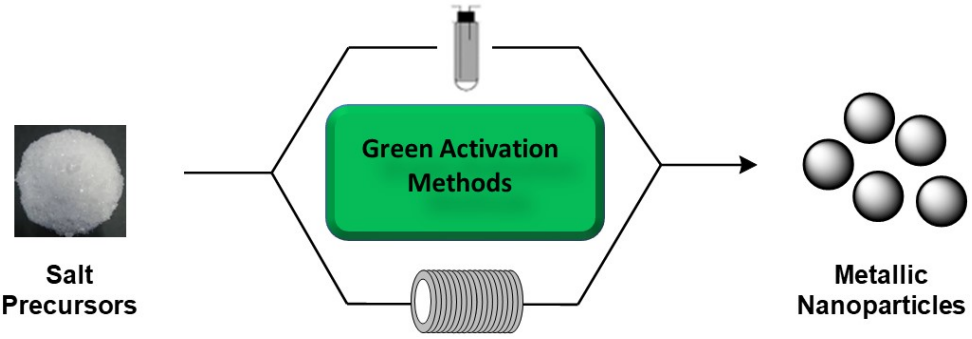
Nanoparticles synthesis is increasingly developed but is often considered wasteful, expensive and requires toxic reagents. This is particularly problematic when it comes to scale-up. In this context, the use of more environmentally friendly approaches is a major challenge.[1] Our latest results will be presented on the development of greener syntheses of metallic nanoparticles complying with the green nanochemistry principles[2] defined from the twelve principles of Anastas and Warner. Our conditions are further optimized in continuous flow to increase productivity and enable larger scale production.



Different activation methods to synthesize metallic nanoparticles in batch and continuous flow

The methodology employed demonstrates the production of metallic bismuth (0) nanoparticles, which displays many important features such as a low cost, high biocompatibility and high X-rays absorption. These properties can be useful in a variety of applications such as in photochemistry, catalysis and in medicine including the development of new theranostic agents. In spite of these interests, few green syntheses of bismuth (0) nanoparticles have been described to date. Our study drastically reduces the amount of coating agents and uses only environmentally and health benign reagents to minimize chemical hazards. It compares the efficiency of two activation methods: microwave[3] or sonochemical[4] activations, both in terms of reproducibility and productivity. Our approach uses a newly designed continuous-flow device and an ultrafiltration device to obtain pure, stable and monodisperse nanoparticles.

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P B153

Proof of concept: Use of tritiated spy ligands for fragment-based drug design

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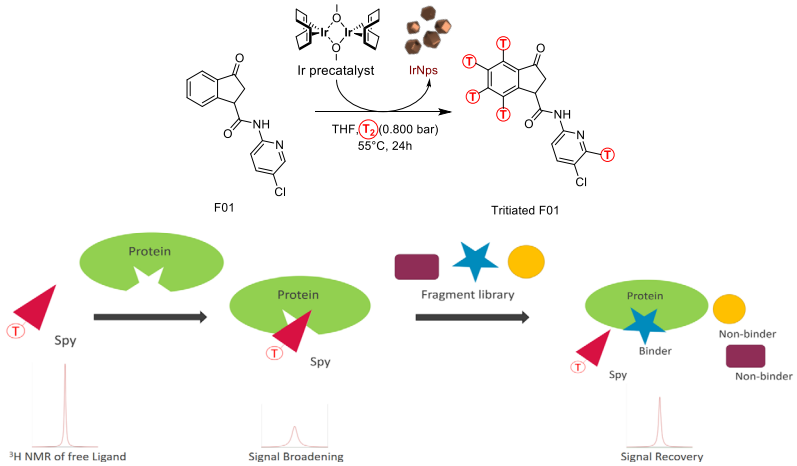
Fragment-Based Drug Design (FBDD) is a powerful tool for the identification of lead compounds in drug discovery processes. NMR is widely used when performing FBDD as it plays a crucial role in ligand-protein binding detection. Over the last years, many NMR techniques have been developed including Saturation Transfer Difference (STD),[1] transverse relaxation rate filtering methods,[2] and ^{19}F NMR[3].



Recent advances in hydrogen isotope exchange reactions allow multiple site tritium labelling of complex molecules in a single synthetic step.[4] By taking advantage of these innovative reactions, an easy access to compound F01 which is an inhibitor of 3Clp,[5], the main protease of SARS-CoV-2, was obtained. Using this tritiated analog, we have demonstrated for the first time, that ^{3}H-labeled molecules can be used as spy ligands in NMR experiments to study ligand-protein interactions. ^{3}H NMR takes advantage of tritium's highest gyromagnetic ratio among all nuclei (which makes it very NMR sensitive) and also from the absence of background signal. As the incorporation of tritium atoms does not cause any structural change and therefore does not affect ligand-protein interactions, this proof of concept opens the way to the use of tritiated spies for FBDD.

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P B154

Design and synthesis of molecular gears for mechanical studies at the single-molecule scale

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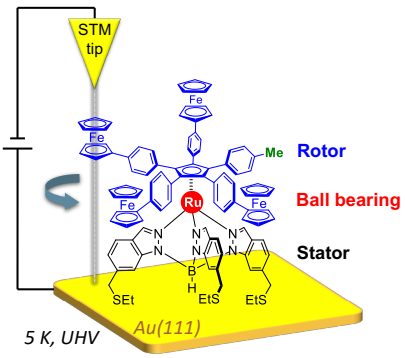
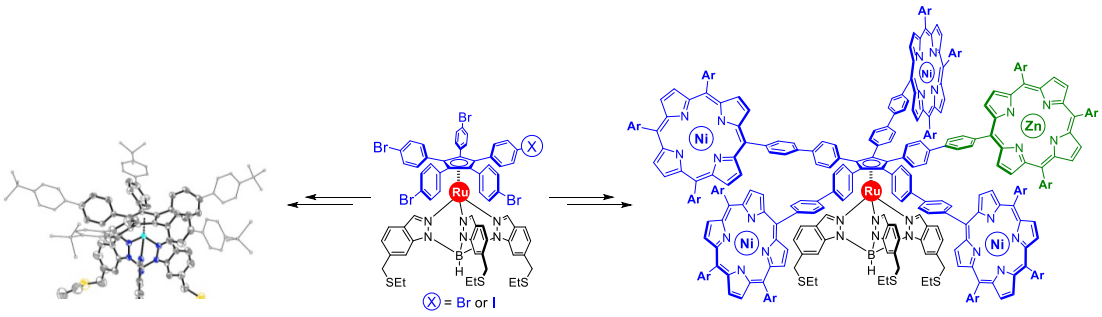
In a context of ultimate miniaturization, obtaining nanometer-sized devices and mastering their controlled motion triggered by an external stimulus is highly desirable. Following a bottom-up approach, our group has designed and synthesized electron-fueled molecular motors, to be studied on surface at the single-molecule scale by Scanning Tunneling Microscopy (STM). One of these ruthenium-based organometallic motors, featuring a dissymmetric rotating subunit, has been shown to undergo unidirectional rotary motion upon excitation, with a direction of rotation governed by the location of the STM tip.[1]



Unidirectional and reversible rotation

Our next aim is to investigate the mechanical transfer of rotary motion between neighbouring molecules, so as to propagate the unidirectional motion of the motor through a train of molecular gears anchored on a surface. A series of star-shaped ruthenium complexes bearing penta(aryl)cyclopentadienyl ligands geometrically analogous to cogwheels has thus been designed, with diameters up to 5 nm.[2]



Symmetric cogwheels with pseudo-1D teeth

Desymmetrized cogwheels with 2D paddles

The synthetic efforts towards these new ruthenium-based rotary molecular machines will be presented, with a special emphasis on our modular strategy relying on the post-functionalization of penta(*p*-halogenophenyl)cyclopentadienyl ruthenium(II) key building blocks.[3]

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P B155

Design of chemical probes derived from schweinfurthins to hijack osbp implicated in cholesterol homeostasis

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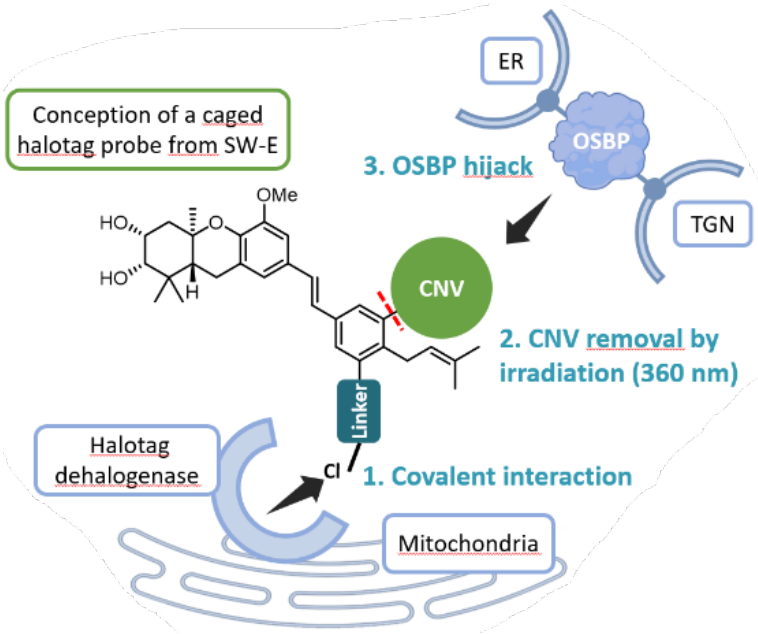
Schweinfurthins (SWs) are natural fluorescent molecules isolated from plants of the genus *Macaranga spp* (Euphorbiaceae) that are highly cytotoxic against specific cancer cell lines[1]. Their original mechanism of action implies a new target in the field of cancer: OxySterol Binding Protein (OSBP)[2]. This protein[3], responsible for cholesterol transfer, is located at membrane contact sites between endoplasmic reticulum (ER) and trans-golgi network (TGN)[4]. However, the complete mechanism of action of SWs remains unclear[5]. To better understand it, we designed various chemical probes and evaluated them *in cellulo*. One of the strategies explored in the team relies on hijacking OSBP from its normal localization to observe the consequences on lipids transfers, cell structure and cell viability. To achieve this goal, we synthesized novel SW probes carrying a HaloTag substrate (*i.e.* capable of interacting specifically with a halotag protein fused to a mitochondrial membrane protein) and a photoremovable protecting group[6] (PPG) temporarily preventing their interaction with OSBP.



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P B156
Photocatalysis and Silver Chemistry for Heterocycles' Synthesis

William Boiledieu, Clara Faure, Yurong Yuan, Maxime de Abreu, Thanina Berrouhane, Mathieu Berthelot, Etienne Brachet, Philippe Belmont

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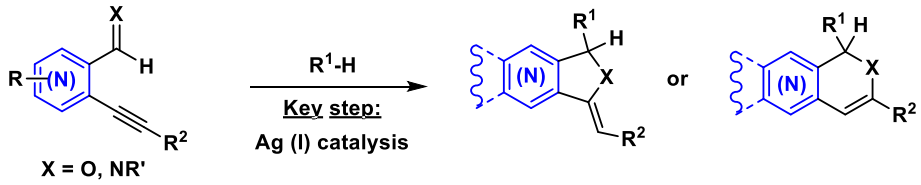
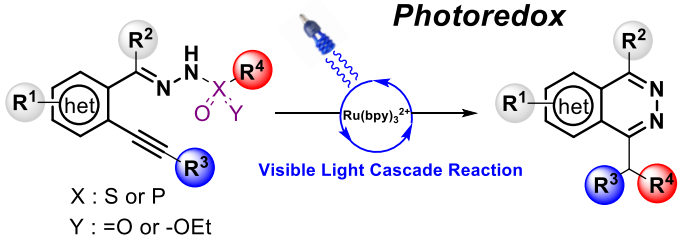
From *ortho*-alkynylbenzaldehyde patterns, cyclofunctionalization reactions led to oxygen- or nitrogen-containing heterocycles such as 1H-isochromenes, furo- or pyranoquinolines.[1] We then proposed methodology of hydroarylation/cycloisomerization reactions of *ortho*-alkynylbenzaldehydes using aromatic compounds as nucleophiles and extend this process to more complex and polysubstituted substrates 1H,1-arylpyrano[4,3-b]quinolines.[2]

Cyclofunctionalization



Also, starting from the same substrates as before, *ortho*-alkynylbenzaldehyde patterns,[1, 2] we developed a photoredox cascade leading in one step to substituted phthalazine structures.[3a] This strategy implies a radical hydroamination reaction on the alkynyl residue, followed by a Smiles rearrangement, with the migration of the R^4 substituent. We are more recently developing this strategy on phosphonohydrazones substates and also on pendant alkenes.[3]

Photoredox



Easy Access to Phthalazine Heterocycles
- Mild reaction conditions
- One step formation of a **C-N** and a **C-C** bond
- Various R^1, R^2, R^3, R^4 = aryl-, heteroaryl-, alkyl-, halogen-

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P B157

Towards a catalytic process via P(III)/P(V) redox cycling for the synthesis of 2-azetines

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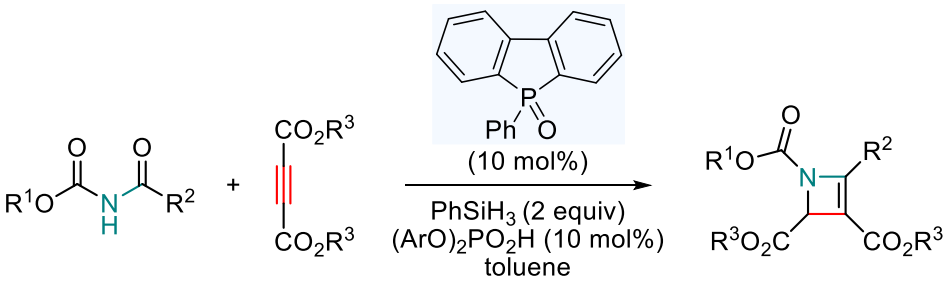
Phosphines play a crucial role as stoichiometric reagents in a variety of reactions, daily used in organic synthesis (e.g. Wittig, Staudinger and Mitsunobu transformations). Despite their usefulness, these venerable reactions suffer from several drawbacks; in particular the concomitant formation of a stoichiometric quantity of phosphine oxide and the limitation to the formation of achiral or racemic compounds.[1] In an effort to address these concerns, the first Wittig reaction, catalytic in phosphine, has been investigated by O' Brien *et al.* in 2009.[2] More recently, the first aza-Michael addition/Wittig olefination reaction, catalytic in phosphine, has been developed in our laboratory for the synthesis of 9*H*-pyrrolo[1,2-*a*]indoles, and other *N*-heterocycles.[3] Subsequently, an efficient catalytic and asymmetric method has also been developed for the synthesis of chiral cyclobutenes.[4]

In the present study, we will show a straightforward tandem transformation for the synthesis of substituted 2-azetines. This backbone is an interesting key building block to access active pharmaceutical ingredient (APIs) and an advanced precursor for synthetic applications.[5] However, the current syntheses are perfectible and it is interesting in this context to propose new synthetic pathways.



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P B158
Synthesis of Glycolipids for the Development of New Vaccine Adjuvants with Modulation of the Immune Response

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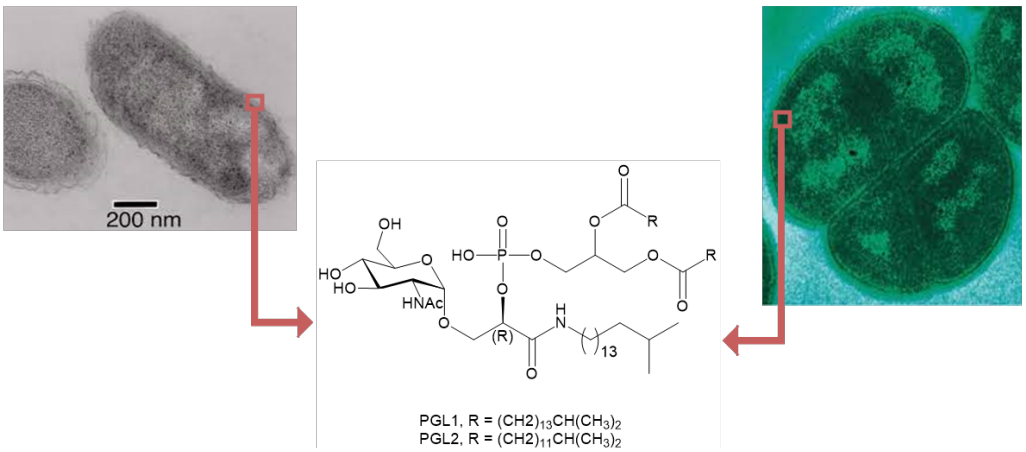
The development of vaccines has become crucial in the fight against influenza pandemics as well as other diseases such as tuberculosis and HIV. A major factor in their effectiveness is the adjuvant. This component can induce an innate immune response, which can then trigger the development of specific acquired immunity. The use of bioactive adjuvants, agonists of TLR4, is beneficial, as observed with lipid A.[1] The aim of this project is to develop new adjuvants from the structure of natural products isolated from bacterial membranes.[2] A new synthesis methodology developed in the laboratory will be used for a more efficient total synthesis of these molecules. Molecular modeling will allow the synthesis of analogues obtained by chemical modification of the natural product.[3] We will present our recent progress in the synthesis of those natural products and their analogues.

Thermus thermophilus *Deinococcus radiodurans*



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P B159

Total Synthesis of Enacyloxin IIa, an Antibiotic of Natural Origin Displaying an Original Mechanism of Action

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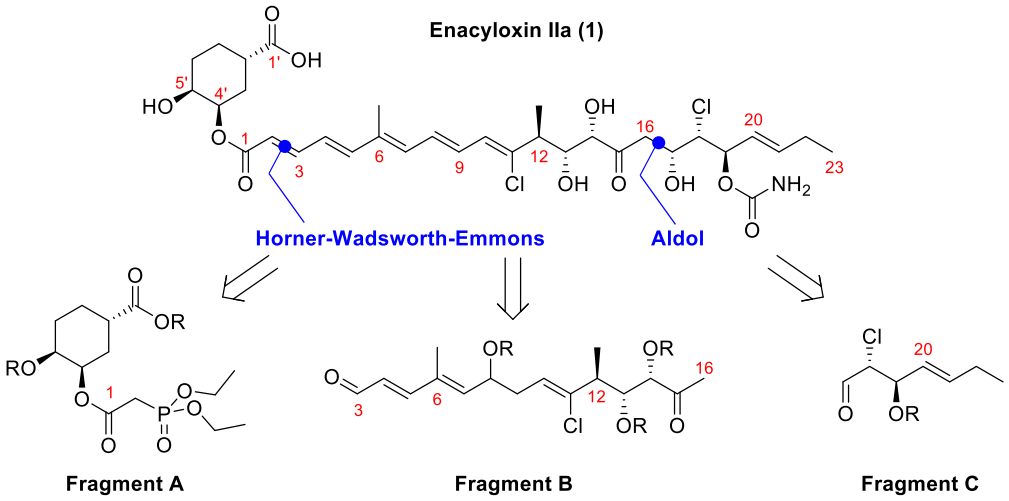
The antibioresistance crisis threatens modern medicine but finding new antibiotics interacting with new biological targets is one of the most efficient answers to circumvent these resistances. Isolated in 1982 by Watanabe et al. from soil bacteria *Gluconobacter* sp. W-315, enacyloxin IIa (**1**) meets these requirements as it displays activity against both Gram-positive and negative bacteria as well as a slight activity against fungi through an original mode of action.[1] Our project aims to perform the first total synthesis of enacyloxin IIa (**1**) and for this purpose we devised an optimized strategy relying on catalysis, atom-economic steps as well as enantio- and diastereoselective reactions to tend towards more sustainability. As a long term objective, this synthesis will provide access to analogues allowing the exploitation of this new biological target. Enacyloxin IIa (**1**) is a rather complex polyketide consisting of a 23 carbons linear chain bearing 6 stereogenic centers, whose one is chlorinated, alongside a conjugated chlorinated penta-ene attached to a cyclohexane with 3 stereogenic centers. The structural complexity of this target induces a high degree of synthetic difficulty involving the synthesis of the fragile polyene unit or the control of the halogenated carbon stereochemistry. Our retrosynthetic plan (Scheme **1**) features the synthesis of fragments **A**, **B** and **C** prior to their assemblage through Horner-Wadsworth-Emmons and aldol reactions. Due to its high functional density, a special interest was taken in the preparation of fragment **B**. The synthetic strategy developed hitherto relies on a key Pd-catalyzed alkyne chloroallylation[2] followed by a Pd/Cu-catalyzed alkyne hydrocarbation of allenes.[3]



***Scheme 2** : Retrosynthetic plan for enacyloxin IIa (**1**)*

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P B160
Synthesis of Novel Potentially Bioactive Nucleoside and Nucleotide Analogs Based on D-Glucuronamide Moieties

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The synthesis of nucleosides, nucleotides and their analogs or mimetics have occupied a major place in organic and in medicinal chemistry, due to their ability to display a variety of bioactivities. Their therapeutic interest is well demonstrated by the various compounds of these types which are effective anticancer and antiviral drugs, acting by interference with nucleic acid synthesis.[1,2] The antimicrobial potential of synthetic and natural nucleos(t)ides has also been well documented.[3] Their clinical use has however some limitations such as low bioavailability and the acquisition of chemotherapeutic resistance.[1]
The design and synthesis of novel bioactive nucleos(t)ide-like structures that may overcome these drawbacks, potentiate alternative mechanisms of action and open new therapeutic opportunities is of significant interest.

In this context, in this communication the synthesis of a variety of nucleoside, nucleotide and sugar diphosphate analogs/mimetics constructed on D-glucuronamide templates will be presented. A 1,2,3-triazole moiety was installed in some molecules as a surrogate of a nucleobase or as a potential neutral and rather stable surrogate of a phosphate group when combined with other moieties such as phosphonate or amide to establish new potential neutral diphosphate group mimetics. The synthetic methodologies used D-glucofuranuronolactone and azido pyranoses as precursors and employed key steps such as amidation, N-glycosylation, azide-alkyne 1,3-dipolar cycloaddition, or Arbuzov reaction. Further biological evaluation revealed some molecules displaying potent antiproliferative effects in cancer cells with GI_{50} values comparable or lower to those of standard drug, thus turning them promising lead molecules for further investigations.

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