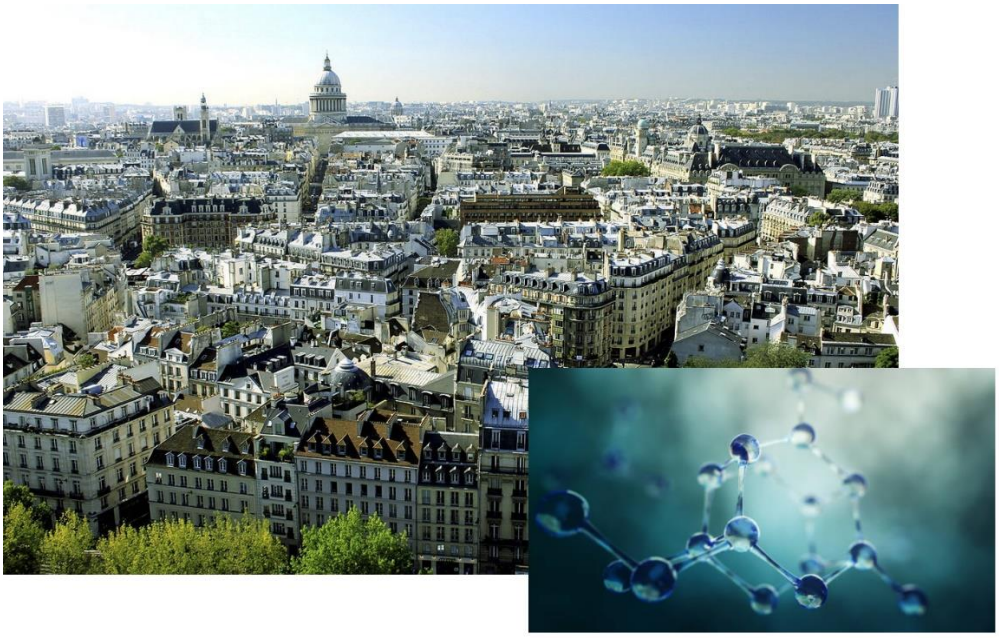
# 27ème Journée de Chimie Organique et Chimie Organique Biologique

# de la Montagne Sainte-Geneviève

**Mardi 11 Juin 2024, Institut Curie, 12 rue Lhomond, 75005 Paris**



# 27ème Journée de Chimie Organique et Chimie Organique Biologique de la Montagne Sainte-Geneviève

**Mardi 11 Juin 2024, Institut Curie, 12 rue Lhomond, 75005 Paris**

## PROGRAMME

**17** communications orales

**4** prix de communications

**2** conférences plénières :

Dr **Raphaël Rodriguez**

Pr **Troels Skrydstrup**

**Inscription** gratuite et obligatoire

https://montagne2024.sciencesconf.org/

## ORGANISATION

Le comité d'organisation est composé de membres d'instituts parisiens membres de PSL :

**Institut Curie**
Christine Gaillet
Yannick Bono
Frédéric Schmidt
Jean-Claude Florent

**Chimie ParisTech**
Virginie Vidal
Phannarath Phansavath
Guillaume Lefèvre

**ESPCI Paris**
Amandine Guérinot

**ENS**
Hélène Bertrand

**Collège de France**
Murielle Lombard

**27ème Journée de Chimie Organique et Chimie Organique Biologique**

**de la Montagne Sainte-Geneviève**

**11 Juin 2024, Institut Curie, Paris**

Présentation du colloque :

Pour la 27ème édition, cette journée sera dédiée aux jeunes chercheurs parisiens du campus de la Montagne Sainte Geneviève Paris-Centre concernés par la Chimie Organique et la Chimie Organique Biologique. Cette journée scientifique s'articulera autour de communications orales d'étudiants (doctorants et post-doctorants) et deux conférences plénières. Cette rencontre constitue pour les jeunes chercheurs l'occasion de présenter leurs travaux et également d'avoir des échanges fructueux. Cette manifestation a pour but de leur permettre d'exposer leurs recherches, de confronter leurs résultats et d'établir des contacts.

Elle a réuni, en 2023, 153 participants; 17 Communications orales et 27 posters ont été présentés. Des prix de poster et de communications orales ont été décernés à cette occasion. **En 2024, elle réunit 161 participants**.

Suite à l'épidémie de COVID, la journée a été annulée en 2020, l'édition 2021 a eu lieu en mode hybride avec les intervenants sur place à l'Institut Curie et les participants en visio. Elle a été ré-organisée en présentiel depuis 2022 en respectant les gestes barrière.

Le comité d'organisation de cette journée scientifique est composé de membres de PSL

- Institut Curie (Christine Gaillet, Yannick Bono, Frédéric Schmidt, Jean-Claude Florent)
- Chimie ParisTech (Virginie Vidal, Phannarath Phansavath, Guillaume Lefèvre)
- ESPCI Paris (Amandine Guérinot)
- ENS (Hélène Bertrand)
- Collège de France (Murielle Lombard)

Cette Journée est dédiée aux jeunes chercheurs et son succès ne s'est jamais démenti depuis sa première édition en 1997. Elle constitue la journée où tous les chimistes organiciens et bio-organiciens de la Montagne Ste Geneviève peuvent venir présenter leurs résultats et écouter leurs collègues. Pour une meilleure visibilité, cette journée accueille aussi des étudiants d'établissements proches comme l'Université de Paris (Facultés de Pharmacie et de Médecine), de l'Institut Pasteur, de Sorbonne Université, du Muséum National d'Histoire Naturelle. Elle comprend aussi deux conférences de chercheurs senior qui pourront faire profiter de leur expérience les chercheurs plus jeunes. La vision est de favoriser au maximum les échanges entre les différents participants et la journée est devenue au fil des années un événement incontournable de la vie scientifique pour les jeunes de PSL.

Les thématiques des interventions se répartissent approximativement pour moitié en chimie appliquée à la biologie (Chemical Biology et Medicinal Chemistry) et pour moitié en chimie organique. Un des buts affichés consiste à favoriser les interactions entre les intervenants des deux domaines pour faire émerger de nouvelles collaborations.

# Remerciements

Cette rencontre peut avoir lieu grâce au soutien de :

- l'Institut Curie

- Q-Life

- Chimie ParisTech

- la Société Chimique de France, section Ile-de-France

- l'UMR 8060 i-CLeHS (Chimie ParisTech – CNRS)

- Magritek

- Merck.

**27ème Journée de Chimie Organique**
**et Chimie Organique Biologique**
**de la Montagne Sainte-Geneviève**

***Organized by Institut Curie, Chimie ParisTech, ENS, ESPCI Paris, Collège de France***

**11 June 2024**

**INSTITUT CURIE, 12 rue Lhomond, Paris 5ème**
**Amphithéâtre Constant Burg**

## PROGRAMME

| | |
|---|---|
| 8 h 30 - 9 h 00 | Welcome of the participants |
| 9 h 00 - 9 h 20 | Opening of the event<br>Virginie BEL (***Institut Curie***)<br>Dr Christian LERMINIAUX (***Chimie ParisTech***) |
| 9 h 20-9 h 30 | Presentation of the programme<br>Dr Virginie VIDAL (***Chimie ParisTech***)<br>Dr Frédéric SCHMIDT |

## CONFERENCE

Moderator : Prof. Louis FENSTERBANK (***Collège de France***)

| | |
|---|---|
| 9 h 30 - 10 h 20 | Conference by **Dr Raphaël RODRIGUEZ**<br>***Institut Curie, France***<br>Chemical Control of Cell Plasticity |

## FIRST SET OF ORAL COMMUNICATIONS

Moderator : Dr Christophe MEYER (***ESPCI Paris***)

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|---|---|
| 10 h 20 – 10 h 35 | Total synthesis of Incednine : a natural product modulating the anti-apoptotic function of BcL-xL<br>Damien CORDEAU<br>***Université Paris Cité*** |
| 10 h 35 - 10 h 50 | Exploring SOD mimics-bearing oxaliplatin-based Pt(IV) anticancer prodrugs: from chemical synthesis to in vivo activity<br>Alvaro LOPEZ-SANCHEZ<br>***Ecole Normale Supérieure*** |
| 10 h 50 - 11 h 05 | Study of [4Fe-4S]-dependent enzyme involved in U34-tRNA thiolation<br>Sylvain GERVASON<br>***Collège de France*** |
| 11 h 05 - 11 h 20 | Clickable fluorescent probes for biological application<br>Léna ATLAN<br>***Institut Curie*** |
| 11 h 20 - 11 h 50 | **Coffee Break** |

## SECOND SET OF ORAL COMMUNICATIONS

Moderator : Prof. Virginie MANSUY (***Sorbonne Université***)

| | |
|---|---|
| 11 h 50 - 12 h 05 | Upgrading phosphinoferrocene structures through catalytic C–H bond functionalizations<br>Jian ZHANG<br>***Chimie ParisTech*** |
| 12 h 05 - 12 h 20 | Heterogeneous visible light photocatalyzed aerobic oxidation of amines in batch and flow enabled by a linear organic semiconductor<br>Basile WEYL<br>***ESPCI Paris*** |
| 12 h 20 - 12 h 35 | Iron-nitrene mediated intermolecular eco-friendly amination reactions<br>Gyeongeun LEE<br>***Université Paris Cité*** |

12 h 35 - 12 h 50 N,N,N-triacylamines as promising inhibitors of kallikrein-8, an emergent biomarker of Alzheimer's disease
Océane RONDOT
***Sorbonne Université***

12 h 50 - 14 h 30 **Cocktail break**

## THIRD SET OF ORAL COMMUNICATIONS

Moderator : Prof. Jean-François SOULE (***Chimie ParisTech***)

14 h 30 - 14 h 45 Reactivity study of trivalent phosphorus in a constrained geometry
Emile ESCOUDE
***Ecole Normale Supérieure***

14 h 45 - 15 h 00 Novel reaction of polyamines with AP sites in DNA as a tool to label and map DNA damage
Eka Putra GUSTI NGURAH PUTU
***Institut Curie***

15 h 00 - 15 h 15 A versatile, functional group-tolerant, and bench-stable iron precatalyst for building arene and triazine rings by [2+2+2] cycloadditions
William PARISOT
***Chimie ParisTech***

15 h 15 - 15 h 30 Dynamic stapled peptides for the inhibition of protein-protein interactions
Ashmi RODRIGUES
***Sorbonne Université***

15 h 30 - 15 h 45 Visible-light-driven carbon dioxide reduction catalyzed by iron Schiff-base complexes
Iulia COCOSILA
***Collège de France***

15 h 45 - 16 h 00 Photoinduced, iron-catalysed decarboxylative alkoxyamination
Milan INNOCENT
***ESPCI Paris***

16 h 00 - 16 h 15 Depolymerization of different structures of polyurethane by under pressure alcoholysis
Natacha JEANSON
***Chimie ParisTech***

| | |
|---|---|
| 16 h 15 - 16 h 30 | A locally-activated chemogenetic pH sensor for imaging protein exocytosis<br>Justine COIS<br>***Ecole Normale Supérieure*** |
| 16 h 30 - 16 h 45 | Synthesis and evaluation of narrow-spectrum antibiotics to combat the emergence of bacterial resistance<br>Katie BURKE<br>***Université Paris Cité*** |
| 16 h 45 - 17 h 10 | **Coffee Break** |

**CONFERENCE**

Moderator : Dr Virginie VIDAL (***Chimie ParisTech***)

| | |
|---|---|
| 17 h 10 - 18 h 00 | Conference by **Prof. Troels SKRYDSTRUP**<br>***Aarhus University, Danemark***<br>From Plastic Disassembly to Carbon Capture with Waste Plastic |
| 18 h 00 - 18 h 15 | **Presentation of the oral communication prizes**<br>Dr Amandine GUERINOT (ESPCI Paris) |
| 18 h 15 - 18 h 30 | **Closing of the day** |

**Raphaël Rodriguez**, PhD, FRSC, is a Research Director at the CNRS and a Senior Principal Investigator at Institut Curie where he holds the Skłodowska-Curie Chair of Chemical Biology. He acquired the knowledge of chemistry and biology under the mentorships of Sir J. E. Baldwin (Oxford, 2004), Sir S. Balasubramanian (Cambridge, 2005) and Sir S. P. Jackson (Cambridge, 2009). He established his lab in France (2012), where he investigates the molecular bases of cancer metastasis. There, Rodriguez discovered the central role of metals as regulators of cell identity.

**Chemical Control of Cell Plasticity**

He is a Fellow of the Royal Society of Chemistry (FRSC) and received a Knighthood of the National Order of Merit from Jean-Marie Lehn on behalf of Emmanuel Macron. He has received a few accolades for his scientific contributions including the CNRS Silver Medal, Liliane Bettencourt Prize for Life Sciences, Klaus Grohe Prize, Tetrahedron Young Investigator Award, Antoine Lacassagne Prize (Collège de France) and Charles Defforey Prize (Institut de France).

**Troels Skrydstrup** received a BSc degree in chemical engineering from Queen's University, Kingston, Canada and his MSc and PhD degrees from the Technical University of Denmark. After post-doctoral periods at l'Institut de Chimie des Substances Naturelles, Gif-sur-Yvette, and at the Carlsberg Laboratories in Copenhagen, he was employed as a Chargé de Recherche (CR1) in the CNRS both at l'Université d'Orléans and l'Université Paris XI. In 1997, he moved to Aarhus University first as an associate Professor at Aarhus University and then full professor in 2002. Currently, he is center leader of the Carbon Dioxide Activation Center, and the co-director of the Novo Nordisk Foundation $CO_2$ Research Center. Troels is an elected member of the Royal Danish Academy of Sciences, and received the Holm's Research Prize (2001), the Melvin Calvin Award (2018) from the International Isotope Society, the Bjerrum, Brønsted, Lang award (2022) and co-shared the JEC Innovation Award (2024). He was knighted by the Danish Queen in 2012.

**From Plastic Disassembly to Carbon Capture with Waste Plastic**

Troels is an organic chemist whose research concentrates on the development of innovative isotope labeling techniques, carbon dioxide conversion, and methods for polymer deconstruction and modification. He has developed various gaseous surrogates and reactor technologies for chemical synthesis applying transition metal catalysis, and more recently, new chemical methods for closed-loop recycling of plastics. His interests also include the synthesis of base chemicals from carbon dioxide.

The lecture will give an overview of his team's synthetic efforts on the use of transition metal catalysis for the disassembly of thermoset plastics to base chemicals, including products prepared from polyurethanes and epoxy composites. Thereafter, the latest work devoted to the selective chemical transformation of waste plastics to new materials with carbon capture properties will be presented.

# COMMUNICATIONS ORALES

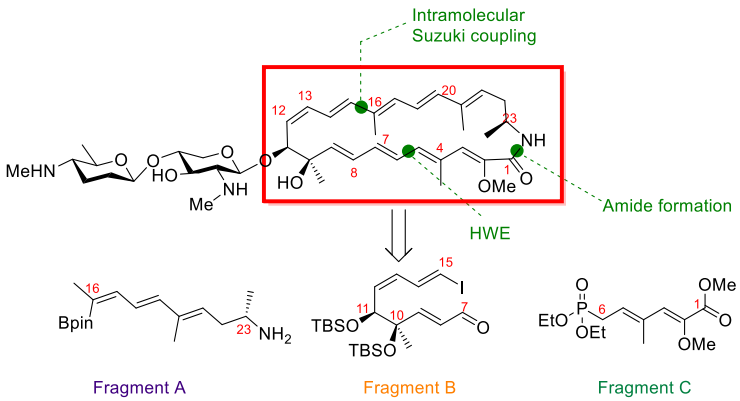
**-O1-**

# Total Synthesis of Incednine : a Natural Product Modulating the Anti-apoptotic Function of BcL-xL

Damien CORDEAU[a], Emmanuel ROULLAND[a,b]

[a] *UMR 8038 CITCOM, Université Paris Cité, damien.cordeau@etu.u-paris.fr*
[a,b] *UMR 8038 CITCOM, Université Paris Cité, CNRS, 4 Avenue de l'Observatoire, 75006, Paris, emmanuel.roulland@parisdescartes.fr*

Nature offers an inexhaustible source of bioactive molecules of high medicinal potential often displaying daunting complex structures that constitute very attractive challenge for synthetic chemists. Among them, incednine (**1**)[1] which was isolated from the strain ML694-90F3 of *Streptomyces* displays the ability of circumventing cell resistance to apoptosis by interacting with anti-apoptotic oncoproteins Bcl-2 and Bcl-xL, a unique property making this compound particularly interesting. The aim of this project funded by the ANR is to perform the first total synthesis of incednine (**1**). For this purpose, we designed a strategy relying on catalysis, atom-economic steps as well as enantio- and diastereoselective reactions to tend towards more sustainability. Incednine (**1**) is a rather complex molecule with a highly strained macrolactam core (incednam) decorated with two rare amino-sugars. Incednam presents three stereogenic centers, a tetra-ene and a penta-ene units. The retrosynthetic plan (Scheme 1) relies on the synthesis of fragments **A**, **B** and **C** prior to their assemblage via Horner-Wadsworth-Emmons reaction, and amide bond formation. Due to the very tense nature of the macrocycle, the two previously reported strategies were found to be poorly efficient (27% yield for macrolactamization[2]and 17 % for Ring Closing Metathesis[3]). As an alternative method of cyclization we propose an intramolecular Suzuki that relys on DFT calculations predicting that this approach is favorable as it feature an iterative ring contraction process. While our team will be focusing on the synthesis of the incednam, our partners at ICSN (Institut Chimique des Substances Naturelles) is synthesizing the sugar moiety with the two fragments to be later assembled via glycosylation.




**Scheme 1** Retrosynthetic plan for the synthesis of the aglycone of incednine

1) Y. Futamura, R. Sawa, Y. Umezawa, M. Igarashi, H. Nakamura, K. Hasegawa, M. Yamasaki, E. Tashiro, Y. Takahashi, Y. Akamatsu, M. Imoto, *J. Am. Chem. Soc.* **2008**, *130*, 1822.
2) T. Ohtani, S. Tsukamoto, H. Kanda, K. Misawa, Y. Urakawa, T. Fujimaki, M. Imoto, Y. Takahashi, D. Takahashi, K. Toshima, *Org. Lett.* **2010**, *12*, 5068.
3) A. Takada, K. Uda, T. Ohtani, S. Tsukamoto, D. Takahashi, K. Toshima, *J. Antibiot.* **2013**, *66*, 155.

# Exploring SOD mimics-bearing oxaliplatin-based Pt(IV) anticancer prodrugs: from chemical synthesis to in vivo activity

Alvaro LOPEZ-SANCHEZ[a], Henri CHEDOTAL[a], Priya RANJAN SAHOO[a], Martha ZOUMPOULAKI[a], Giorgia PASTORIN[b], Giulia ADRIANI[c], Romain CORIAT[d], Clotilde POLICAR[a], Carole NICCO[d], Hélène C. BERTRAND[a].

[a] *Laboratoire des Biomolécules, LBM, Département de chimie, Ecole normale supérieure, PSL university, Sorbonne Université, CNRS, 24 rue Lhomond 75005 Paris, France alvaro.lopez-sanchez@ens.psl.eu*
[b] *Faculty of Pharmacy, National University of Singapore, 18 Science Drive 4 SINGAPORE, Singapore*
[c] *Singapore Inmunology Network (SIgN), A*STAR, 8A Biomedical Groove SINGAPORE, Singapore*
[d] *Development, reproduction and cancer department, Institut Cochin, 22 rue Méchain PARIS, France*

Pt(II)-based anticancer drugs are used in around 50% of all chemotherapeutic treatments and display potent cytotoxic activities linked to their DNA crosslinking ability.[1] However, their lack of selectivity and other mechanisms of action at interplay such as oxidative stress are key responsible for their side-effects or resistance development. An illustration of this is oxaliplatin-induced peripheral neuropathy (OIPN), the main dose-limiting side-effect of oxaliplatin (>80% in its acute form, >40% in its chronic form), the front-line chemotherapy for colorectal cancer (Fig.1).[2] Although the pathogenesis is intricate, Pt accumulation in dorsal root ganglia followed by neuronal mitochondrial damage, oxidative stress and neuroinflammation are thought to be key regulators of this condition.[3] Anti-inflammatory or antioxidant agents are therefore found among the possible treatments to alleviate OIPN.[4] In this regard, our approach is to exploit redox modulation combined with the intrinsic cytotoxicity of oxaliplatin for an improved anticancer activity and neuroprotection. Particularly, small molecular weight Mn(II) complexes mimicking the active site of superoxide dismutase have been largely studied in our group in the context of cellular and *in vivo* models of inflammation for their antioxidant and anti-inflammatory properties.[5] Interestingly, Mn1 (Fig. 1) also showed, when combined with oxaliplatin, encouraging neuroprotective *in vivo* results on balb/C mice.[6] From these results, we develop new combination treatments of oxaliplatin and SOD mimics as redox regulators, as well as Pt(IV) prodrugs based on an oxaliplatin scaffold,[7,8] and study them in both a chemical and biological context: from the round-bottom flask to mice, going through spectroscopic characterization, anti-superoxide activity, or cell biology-based experiments. We present here the development of a new superoxide dismutase mimic, more efficient than Mn1, and its *in vitro* and *in vivo* evaluation to assess its neuroprotective effect when combined with oxaliplatin either equimolarly or in a Pt(IV) prodrug strategy.

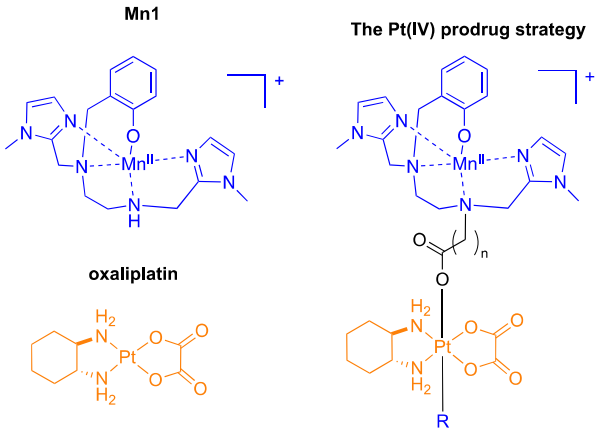



*Figure 1. Chemical structures of Mn1, oxaliplatin and Pt(IV) prodrugs.*

1) N. J. Wheate *et al*., *Dalton Trans*. **2010**, *39*, 8113-8127.
2) M. W. Saif, J. Reardon, *Ther. Clin. Risk Manage.*, **2005**, *1*, 249-258.
3) A. Areti *et al*., *Redox Biol*., **2014**, *2*, 289-295.
4) Y. Yang *et al*., *J. Exp. Clin. Cancer Res*., **2021**, *40*, 331.
5) E. Mathieu *et al*., *Inorg. Chem*., **2017**, *56*, 2545-2555.
6) M.-A. Guillaumot *et al*., *Oncotarget*, **2019**, *10*, 6418-6431.
7) A. Lopez-Sanchez, H. C. Bertrand, *Inorg. Chem. Front*, **2024**, doi : 10.1039/d3qi02602g
8) C. Prieux-Klotz *et al*., *Int. J. Mol. Sci*., **2022**, *23*, 12938.

**-O3-**

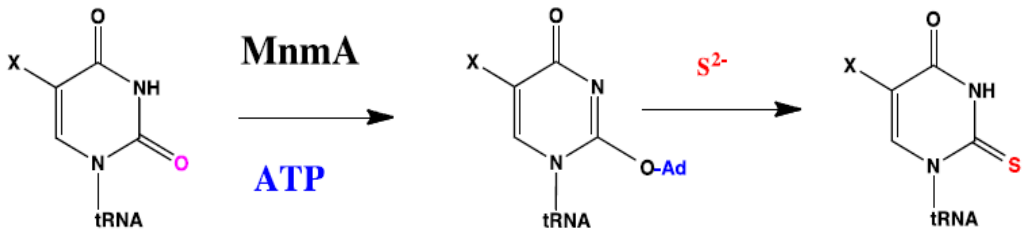
# Study of [4Fe-4S]-dependent enzyme involved in U34-tRNA thiolation

Sylvain GERVASON[1], Sambuddha SEN[1], Ludovic PECQUEUR[1], Christophe VELOURS[2], Marc FONTECAVE[1], Béatrice GOLINELLI-PIMPANEAU[1]

[1] *Laboratoire de Chimie des Processus Biologiques, Collège de France, CNRS, Sorbonne Universités, 11 Place Marcelin Berthelot, 75231 Paris cedex 05, France*
[2] *Fundamental Microbiology and Pathogenicity Laboratory, UMR 5234 CNRS-University of Bordeaux, SFR TransBioMed. Bordeaux, France*

The ubiquitous nucleoside modification 5-aminomethyl-2-thiouridine (xnm5s2U) at uridine 34 in the anticodon loop of transfer RNAs is crucial for genetic translation in all domains of life. The thiolation of uridine 34 is catalyzed by nonhomologous MnmA- and NcsA-type enzymes in bacteria and archaea/eukaryotes, respectively. The bacterial MnmA sequences shows the existence of two subfamilies: D-type like MnmA from *Escherichia coli* (EcMnmA), containing a conserved DXXC + C motif and C-type like MnmA from *Thermus thermophilus* (TtMnmA), containing the CXXC + C motif. In 2020, TtMnmA was shown to be able to bind a [4Fe-4S] cluster, coordinated by the three cysteines of the conserved motif, which proved to be essential for activity (1). In contrast, the [Fe-S]-dependency of D-type MnmA enzymes is a matter of controversy. Aerobically purified EcMnmA did not reveal the presence of a cluster, and a persulfide-based mechanism was first proposed to account for the experimental data. Yet we showed later that a [4Fe-4S] could be anaerobically reconstituted in EcMnmA, that it was essential for activity and most likely bound by the two cysteines and aspartate of the conserved motif (2). In contrast, a recent report claims that cluster binding to EcMnmA inhibits the thiolation activity (3). To address this contradiction, we report here spectroscopic analysis, *in vitro* catalytic assays, mutagenesis studies and crystallographic data of MnmA from two Gram positive bacteria.

1) Shigi N, Horitani M, Miyauchi K, Suzuki T, Kuroki M. *RNA*. **2020**, 26, 240-250.
2) J. Zhou, M. Lénon, N. Touati, JL Ravanat, C. Velours, M. Fontecave, F. Barras, B. Golinelli-Pimpaneau. *Nucleic Acids Res*. **2021**, 49, 3997-4007.
3) Ogunkola, M., Wolff L., Fetneg, E.A., Duffus, B.R., Leimkühler, S. *Inorganics* **2024**, 12, 67.



-O4-

# Clickable fluorescent probes for biological application

Léna ATLAN [a], Marie AUVRAY, Aurélie RODRIGUEZ, Delphine NAUD-MARTIN, Kévin RENAULT, Gaëlle FONTAINE, Florence MAHUTEAU-BETZER

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Chemical biology continuously seeks innovative tools to study and manipulate biological systems with high precision. One such innovation is the development of fluorogenic probes based on bioorthogonal chemistry[1]. We are focusing on a new fluorogenic probe using the unique reactivity of tetrazine and sydnone (Fig. 1).

The synthesis of this fluorogenic probe capitalizes on the rapid and specific IEDDA[2] and SPSAC[3] reaction, which is based on the quenching capabilities of tetrazine and sydnone. This property allows for real-time visualization of dynamic biological processes with minimal background interference. The probe is designed to be non-fluorescent in its initial state, becoming fluorescent only upon reaction with a tetrazine or sydnone-tagged biomolecule.
The fluorogenic probe Acri-Py offers the best compromise between emission wavelength (665 nm in water) and biphotonic brightness (330 GM, 870 nm)[4].

The different applications of this fluorogenic probe are vast, including the tracking of protein-protein interactions, monitoring metabolic pathways, and visualizing cellular events with high specificity[5].

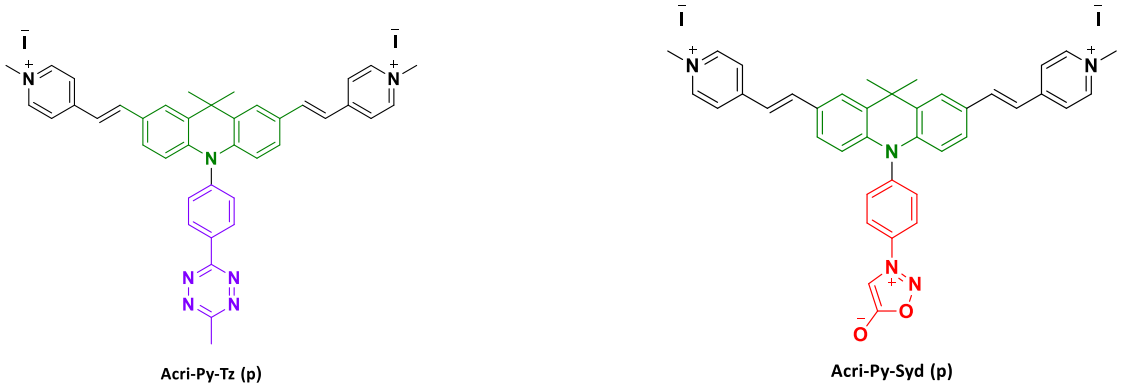



Figure 1: Fluorogenic probe Acri-Py-Tz (p) and Acri-Py-Syd (p)

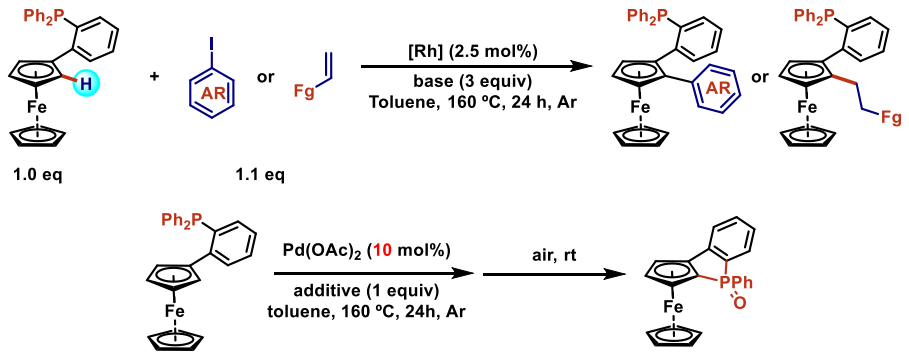
1. Bernard, S. *et al.* Bioorthogonal Click and Release Reaction of Iminosydnones with Cycloalkynes. *Angew Chem Int Ed* (2017).
2. Oliveira, B. L., Guo, Z. & Bernardes, G. J. L. Inverse electron demand Diels–Alder reactions in chemical biology. *Chem Soc Rev* (2017).
3. Porte, K., Riomet, M., Figliola, C., Audisio, D. & Taran, F. Click and Bio-Orthogonal Reactions with Mesoionic Compounds. *Chem Rev* (2021).
4. Auvray, M. *et al.* On the Road Toward More Efficient Biocompatible Two-Photon Excitable Fluorophores. *Chem. – Eur. J.* **28**, e202104378 (2022).
5. Decuyp, E. Sydnone-coumarins as clickable turn-on fluorescent sensors for molecular imaging. (2018).

# Upgrading Phosphinoferrocene Structures through Catalytic C–H Bond Functionalizations

Jian ZHANG,[a, b] Lunan ZHOU,[a] William ERB,[a] and Jean-François SOULE [b]

[a] *OMC, ISCR-UMR 6226, Univ. Rennes, 35700, Rennes, France*
[b] *Institute of Chemistry for Life and Health Sciences, Chimie ParisTech, PSL University, CNRS, 75005, Paris, France*
*jian.zhang@chimieparistech.psl.eu; jean-francois.soule@chimieparistech.psl.eu*

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] To overcome this limitation, a promising approach lies in the utilization of P(III)-chelation-assisted C−H bond functionalization. [5] This technique, predominantly applied for the diversification of biarylphosphines, has seen limited use with phosphinoferrocene. In this presentation, we delve into our latest advancements in synthesizing planar chiral phosphinoferrocene through C–H bond functionalization. [6] Central to our methodology is the use of ferrocene holding a 2-phosphinophenyl unit. This configuration efficiently directs the arylation of the C–H bond at the ortho-position, with the P(III) atom serving as an effective directing group. Furthermore, we will showcase the transformation of these planar chiral phosphinoferrocenes into phospholes via palladium catalysis, revealing their exceptional chiroptical properties. [7] This synthetic breakthrough signifies a major progression in the field of chiral phosphorus-containing molecules, emphasizing the influential potential of C–H bond functionalization within the realm of material sciences.




1) (a) Ni, H. Z.; Chan, W. L.; Lu, Y. X. *Chem. Rev.* **2018**, *118*, 9344-9411. (b) Guo, H. C.; Fan, Y. C.; Sun, Z. H.; Wu, Y.; Kwon, O. *Chem. Rev.* **2018**, *118*, 10049-10293.

2) (a) Ruiz-Castillo, P.; Buchwald, S. L. *Chem. Rev.* **2016**, *116*, 12564-12649. (b) Colacot, T. J. *Chem. Rev.* **2003**, *103*, 3101-3118.

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-O6-

# Heterogeneous Visible Light Photocatalyzed Aerobic Oxidation of Amines in Batch and Flow Enabled by a Linear Organic Semiconductor

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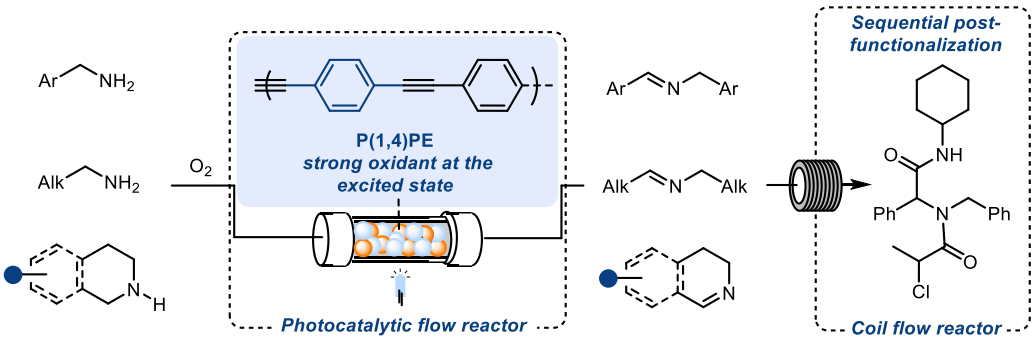
Over the last two decades, photoredox catalysis has become a powerful and versatile synthetic tool that provides chemists with a milder way to do radical chemistry. What with the sky-high costs and poor recyclability of the commonly used Ru and Ir-based homogeneous photocatalysts,[1,2] there is a growing need to find more sustainable replacements.

Developing easily recyclable organic heterogeneous photocatalysts could be a promising solution. However, heterogeneous catalysts being mostly opaque, their activity as photoactive species can be drastically limited. Today, the most elegant solution to this problem is to use solid-state semiconductors as heterogeneous photocatalysts. Under light irradiation, appropriately designed semiconductors can reach an electronically excited state that triggers redox events throughout the whole solid-state species.[3] Despite these promising properties, such heterogeneous photocatalysts are often shunned by organic chemists because of the absence of commercial availability and, crucially, the lack of rational behind their reactivity.

Trying to address these issues, this presentation will focus on the synthesis, characterization and use of a simple linear conjugated polymer, poly-(phenyleneethynelene) (P(1,4)PE), which display strong oxidative properties at the excited state. This reactivity will be showcased in the aerobic oxidation of amines into imines in batch and flow reactors.[4] Finally, in-line post-functionalizations that access bioactive compounds via a telescoped 3-CR Jouillé-Ugi process[5] will be presented.

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-O7-

# Iron-nitrene mediated intermolecular eco-friendly amination reactions

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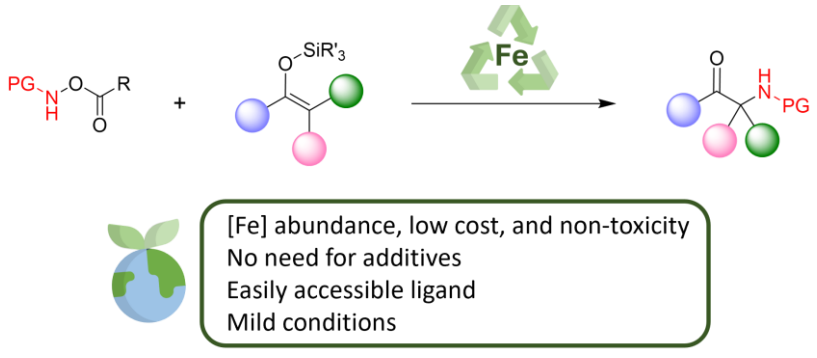
Due to the prevalence of α-amino acid and ketone moieties in natural compounds and medications the α-amination of simple ketones and esters is a crucial process in organic synthesis. Recent and straightforward approaches in this field include the development of catalytic, enantioselective α-aminations and α-oxygenations of carbonyl compounds, which are particularly useful in constructing complex natural products and bioactive molecules.[1]
Among the various amination methods, research on metallo-nitrene mediated nitrogen transfer reactions has become very popular with their ability to transfer nitrogen atoms to organic compounds. Especially iron-nitrene catalysis offers several advantages, including its abundance, low cost, and relative non-toxicity.[2] These properties make it a sustainable and attractive option for various reactions. Additionally, iron availability and environmental friendliness make it a practical alternative to other transition metals in catalysis.[3] Che highlighted the efficiency of iron complexes in intramolecular C-H amination.[4] White further underscores the diastereoselectivity of this method.[5] More recently, Strom expanded the scope to α-amination of ketones in the presence of stoichiometric oxidant showing its potential in drug discovery and natural product synthesis.[6]
Despite those developments, there are still challenges in terms of sustainable chemistry. Many studies have used potentially explosive azides as nitrogen sources or stoichiometric strong oxidants. In addition, the use of complex ligands raises questions regarding their availability. Toxic solvents and harsh reaction conditions can also be considered far from environmentally friendly chemistry.
In this communication, we will report our results towards a sustainable α-amination of silyl enol ether via iron catalysis. Optimisation of the reaction conditions, scope, and limitations of the process as well as mechanistic insights will be presented.

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**-O8-**

# N,N,N-triacylamines as promising inhibitors of kallikrein-8, an emergent biomarker of Alzheimer's disease.

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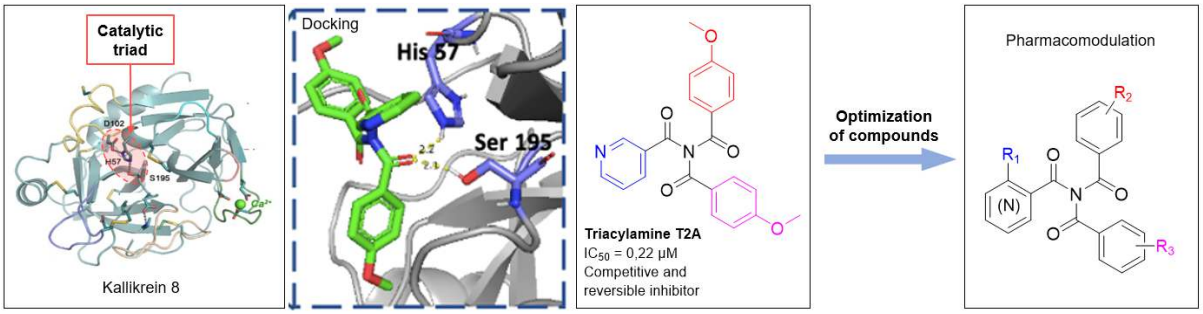
Alzheimer disease (AD) is the most common progressive neurodegenerative disease with devastating effects on cognition and memory. About 2 million people suffer from Alzheimer's disease type dementia and 55 million patients worldwide. Currently, there is no treatment nor pre-mortem diagnosis with specificity and selectivity.[1] One of the challenges of research on this disease is to diagnose it before the appearance of irreversible symptoms. Recently, studies underlined that kallikrein 8 (KLK-8),[2] a serine protease, would be involved in the development of different pathophysiologies associated with this disease.[3,4] Moreover, it has also been demonstrated that antibody mediated inhibition of KLK-8 restores a normal cognition activity in the mouse model of AD.[5,6] Despite a growing interest in this target, no potential therapeutic inhibitor has been identified to date.

The aim of this work is to design and synthetize the first organic KLK-8 inhibitors with high selectivity. We have recently discovered and characterized a series of molecules based on N,N,N triacylamines (T2A) as reversible and competitive inhibitors on KLK8 with $IC_{50}$ in the range of submicromolar.

We present here a structure-activity relationship approach using pharmacomodulation on triacylamines to design structural analogues with improved activity and studied their selectivity towards other proteases.

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# Reactivity study of trivalent phosphorus in a constrained geometry

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Trivalent phosphorus compounds geometrically constrained by a pincer ligand are a particular class of non-trigonal phosphorus compounds with 3 substituents organized around the phosphorus in a $C_S$ or[4,5,6] in the most extreme cases, a $C_{2V}$ environment.[7]

Due to their constrained structure, the LUMO is especially low in energy thus making the P(III) compound electrophilic, which is rather unusual for trivalent phosphorus compounds. They are actually ambiphilic and even capable of formal oxidative addition on activated carbon-halogen bonds.[8]

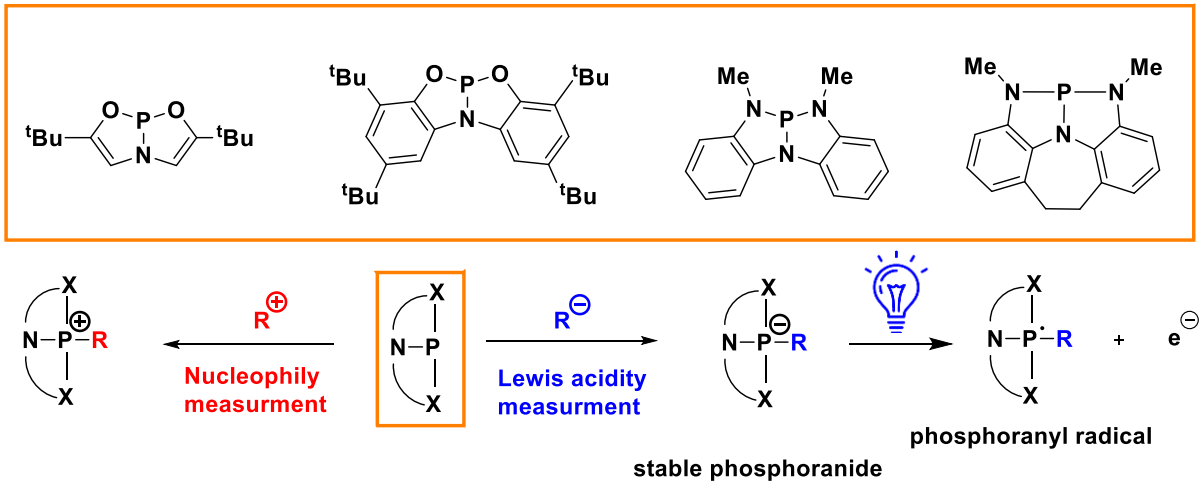


**Figure 2:** The four constrained phosphorus studied in this work and their reactivity

With the desire to explore such new reactivity, our team, in collaboration with the team of Dr Sami Lakhdar (LHFA, Toulouse) wanted to investigate and quantify the ambiphilic properties of these species. In the way, we managed to isolate stable Lewis acid-base adducts with carbanions in the form of potassium phosphoranide salts. The photoredox chemistry of these stable phosphoranide salts was then investigated leading to the development of a new method to generate phosphoranyl radicals.

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**-O10-**

# Novel reaction of polyamines with AP sites in DNA as a tool to label and map DNA damage

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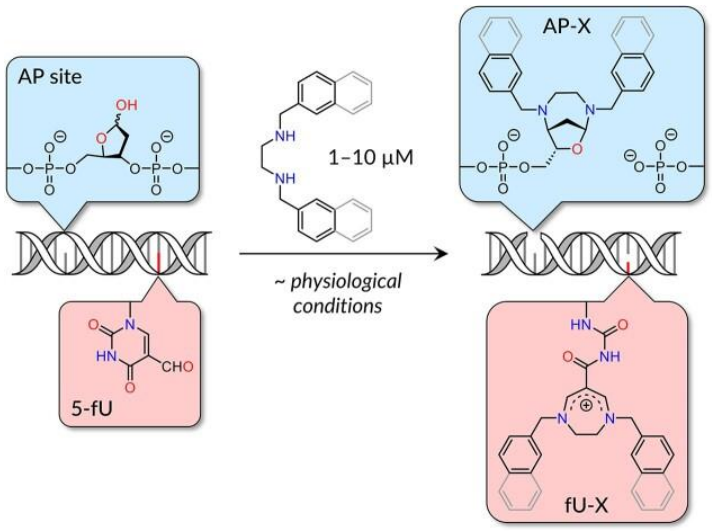
Apurinic/apyrimidinic (AP) sites, 5-formyluracil (fU) and 5-formylcytosine (fC) are abundant DNA modifications that share aldehyde-type reactivity [1-2]. Previously, we demonstrated that several polyazamacrocylic compounds can bind non-covalently to AP sites, interfere with their enzymatic repair, promote the cleavage of AP sites by β- and/or β,δ-elimination mechanisms, and eventually form covalent adducts with cleaved AP sites through an unknown mechanism [3]. In this work, we show that secondary 1,2-diamines endowed with aromatic units form covalent DNA adducts upon reaction with AP sites (with concomitant cleavage of the AP strand), fU and, to a lesser extent, fC residues. Using small-molecules mimics, we show that the reaction of secondary 1,2-diamines with AP sites leads to the formation of unprecedented 3′-tetrahydrofuro[2,3,4-*ef*]-1,4-diazepane scaffold (termed "ribodiazepane", or AP-X), whereas the reaction with fU produces cationic 2,3-dihydro-1,4-diazepinium ("fU-X") adducts via uracil ring opening. The reactivity of polyamines towards AP sites versus fU and fC can be tuned by modulating their chemical structure and pH of the medium, enabling > 20-fold chemoselectivity for AP sites with respect to fU and fC. This reaction is efficient in near-physiological conditions at low-micromolar concentration of polyamines and tolerant to the presence of a large excess of unmodified DNA. Remarkably, 3′-ribodiazepane adducts are chemically stable and resistant towards APE1 and TDP1, two DNA repair enzymes known to cleanse a variety of 3′ end-blocking DNA lesions [4].

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# A versatile, functional group-tolerant, and bench-stable iron precatalyst for building arene and triazine rings by [2+2+2] cycloadditions

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Guillaume LEFÈVRE[1] and Virginie VIDAL[1]
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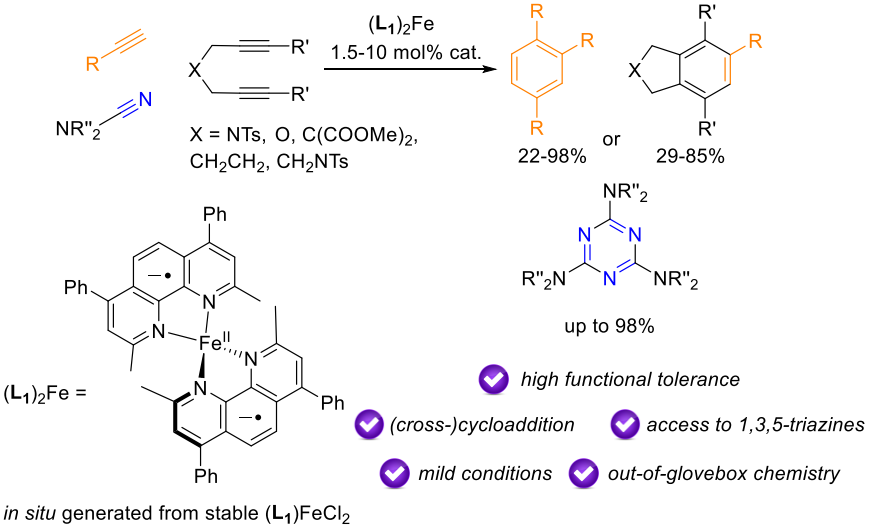
The construction of (hetero)aromatic rings by [2+2+2] cycloadditions is an extremely appealing tool since it allows the introduction of a high structural diversity in a single, atom-economical step. The noble metal catalyzed version has been extensively studied,[1] however substituting these expensive and polluting methodologies is a key challenge for the future processes. Despite tremendous efforts to develop [2+2+2] cycloadditions using cheap and eco-friendly transition metals the iron-catalyzed version remains to be explored.[2] We report an efficient iron-catalyzed cycloaddition procedure leading to the construction of (hetero)aromatic rings by alkyne [2+2+2] cycloisomerization. This method relies on the use of an air-stable (*N*,*N*)Fe(II) precursor easily prepared from a commercially available ligand derived from 1,10-phenanthroline, reduced *in situ* into a catalytically active non-innocent $(N,N^{\bullet-})_2$Fe(II) species.[3] This system displays a large scope applications, operates under mild conditions and at low catalytic charges (25 cycloadducts formed, up to 1.5 mol% catalyst).




Moreover, this method also enables access to 29 cycloadducts by [2+2+2] between 1,6- or 1,7-diynes and alkynes in near-equimolar conditions. 1,3,5-Triazines can also be prepared with this procedure starting from the corresponding cyanamides. Scale-up reactions and post functionalization of several cycloadducts also show that this [2+2+2] cycloaddition can be used in multistep sequences.[4]

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**-O12-**

# Dynamic stapled peptides for the inhibition of protein-protein interactions

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In the search for new target-directed strategies, the use of Dynamic Combinatorial Chemistry (DCC) has been expanding over the last few years. Thanks to DCC, large libraries of thermodynamically stable constructs can be generated by employing reversible reactions.[1] More interestingly, it is possible to explore the self-adaptative potential of such libraries simply by the addition of biological targets into complex mixtures, which could lead to the discovery of new therapeutics. In this project, we wish to implement DCC in the context of finding peptidic inhibitors for Protein-Protein Interactions (PPIs). This strategy would allow the simultaneous and rapid screening of multiple constructs without facing difficulties related to rational design and synthesis. Therefore, we are currently working on a proof of concept that relies on the generation of dynamic libraries of stapled peptides for the identification of PPI inhibitors. The project focuses on the p53-HDM2/HDMX PPI, known to play a crucial role in cell-cycle regulation and apoptosis.

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# Visible-Light-Driven Carbon Dioxide Reduction Catalyzed by Iron Schiff-Base Complexes

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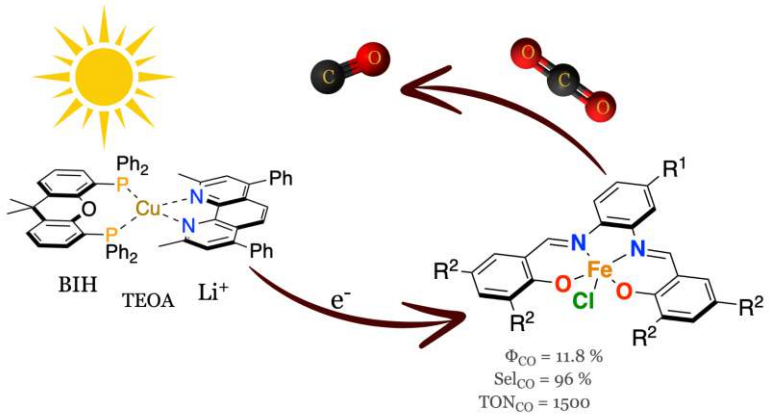


Light-dependent reduction of carbon dioxide ($CO_2$) can be sustainably developed using non-expensive and abundant molecular catalysts and inorganic photosensitizers, based on non-noble metals. The photoreduction of $CO_2$ catalyzed by a series of eleven metal-salophen complexes, based on variously functionalized salophen ligands, has been investigated using a Cu-based photosensitizer, [$Cu^I$(bathocupoine)(xantphos)], for light-harvesting. This provides one of the currently few fully earth-abundant systems for efficient $CO_2$ reduction driven by visible light. Using 1,3-dimethyl-2-phenyl-2,3-dihydro-1H-benzo[d]imidazole (BIH) as the sacrificial reductant in acetonitrile/triethanolamine solution, a maximum turnover number for CO production of 900-1600, a maximum initial turnover frequency of 1300-1700 $h^{-1}$ with 93-96 % CO:$H_2$ selectivity, and a high quantum yield of 12-15% (at 420 nm) were achieved with Fe-based complexes. Thorough photophysical studies coupled to DFT calculations allowed reaction intermediates tracking and provided insights into the reaction mechanism. These results are promising for further investigation. Especially, due to the similarity of this catalyst with the active site of heme protein, studies of the activity for $CO_2$ reduction within the heme oxygenase will be considered.

-O14-

# Photoinduced, Iron-catalysed Decarboxylative Alkoxyamination

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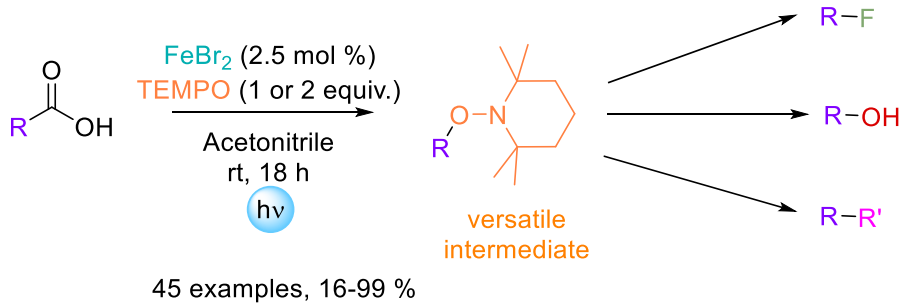
Lately, chemists have focused on developing greener synthetic methods, using less toxic chemical elements, more sustainable energy sources and abundant, ideally biobased raw material. In this context, carboxylic acids embody a class of molecules worthy of interest as they are the second most represented in Nature. They can be engaged in various chemical reactions, one of them being decarboxylative transformations. Although noteworthy because of their intrinsic chemoselectivity, such processes rely mainly on the use of transition metal catalysis (Pd, Ni, Ag) under generally harsh conditions.[1] The quest towards sustainability leads chemists to develop a growing interest in photocatalysis, as (visible) light is a relatively clean source of energy. This approach gave birth to photocatalysed decarboxylative processes.[2] Most of these reactions harness the attractive photophysical properties of iridium or ruthenium catalysts, but the rareness of these metals causes deleterious environmental impact and high costs that are not in adequation with the objective of developing sustainable processes. In order to bypass those drawbacks, an effort is being made to design photoinduced decarboxylative transformations using more naturally abundant metals.[3]

Herein, we focus on the synthesis of alkoxyamines using a photoinduced decarboxylative reaction catalysed by an iron complex in the presence of TEMPO (Scheme 1). Among those tested, $FeBr_2$ was identified as the most efficient catalyst, allowing the formation of a wide range of alkoxyamines under blue or purple light irradiation at room temperature. The reaction mechanism supposedly involves the photoactivation of an iron carboxylate leading to a ligand-to-metal charge transfer triggering the homolytic cleavage of the O-Fe bond.[3] The resulting alkoxyamines can be viewed as versatile intermediates and their high synthetic potential has been highlighted.




**Scheme 1.** Decarboxylative alkoxyamination reaction

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**-O15-**

# Depolymerization of different structures of polyurethane by under pressure alcoholysis

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Nowadays, the plastic waste management is crucial and the current most common ways to treat it are landfilling, incineration with energy recovery and mechanical recycling (which consists of sorting plastics followed by their regeneration). A very few types of plastics can be recycled by physical recycling limiting the recycling rate: 35 % in Europe in 2020. That is why the chemical recycling has gained more and more interest over the past few years, mostly for particularly thermoset polymers, such as polyurethane. Included in the chemical recycling, the solvolysis appears interesting: it consists in the attack of the polymeric chains by a solvent, mostly water (hydrolysis) or alcohol (alcoholysis). Regarding polyurethanes, hydrolysis produces $CO_2$ and also a toxic diamine; while the alcoholysis with a glycol (namely glycolysis) produces a mixture of several molecules that are difficult to separate. This is why this study focuses on the use of single alcohol, as a solvent: the major benefit of the alcoholysis is the formation of two molecules (the recovered polyol and the *O*-dimetylcarbamate of the used diisocyanate moiety). The reactivity of several polyurethane structures (aromatics and aliphatics) have been studied varying several parameters, in order to determine the best conditions for an efficient and quantitative depolymerization. An easy separation of the reaction products has been successfully completed, obtaining products with a high purity which can be used as raw materials in order to form new polyurethane through transurethanisation.

**-O16-**

# A Locally-Activated Chemogenetic pH Sensor for Imaging Protein Exocytosis

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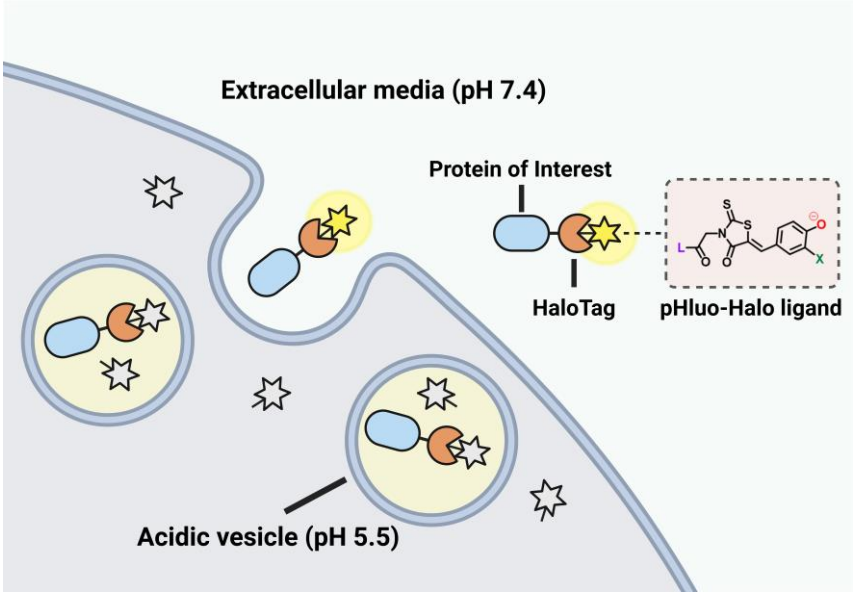
Fluorescent protein-based pH biosensors enable the tracking of pH changes during protein trafficking and in particular exocytosis. The recent development of chemogenetic reporters combining synthetic fluorophores with self-labeling protein tags offer a versatile alternative to fluorescent proteins that combines the diversity of chemical probes and indicators with the selectivity of the genetic-encoding. However this hybrid protein labeling strategy does not avoid common drawbacks of organic fluorophores such as the risk of off-target signal due to unbound molecules. Here, we describe a novel fluorogenic and chemogenetic pH sensor based on a cell-permeable molecular pH indicator called **pHluo-Halo-1** whose fluorescence can be locally activated in cells by reaction with HaloTag ensuring excellent signal selectivity in wash-free imaging experiments. **pHluo-Halo-1** displays good pH sensitivity and a $pK_a$ of 5.9 well-suited to monitor biological pH variations. It was applied to follow the exocytosis of CD63-HaloTag fusion proteins using TIRF microscopy. This chemogenetic sensor, based on a tunable and chemically-accessible protein chromophore analog is expected to be a versatile alternative to fluorescent proteins for elucidating the dynamics and regulatory mechanisms of proteins in living cells.



# Synthesis and evaluation of narrow-spectrum antibiotics to combat the emergence of bacterial resistance.

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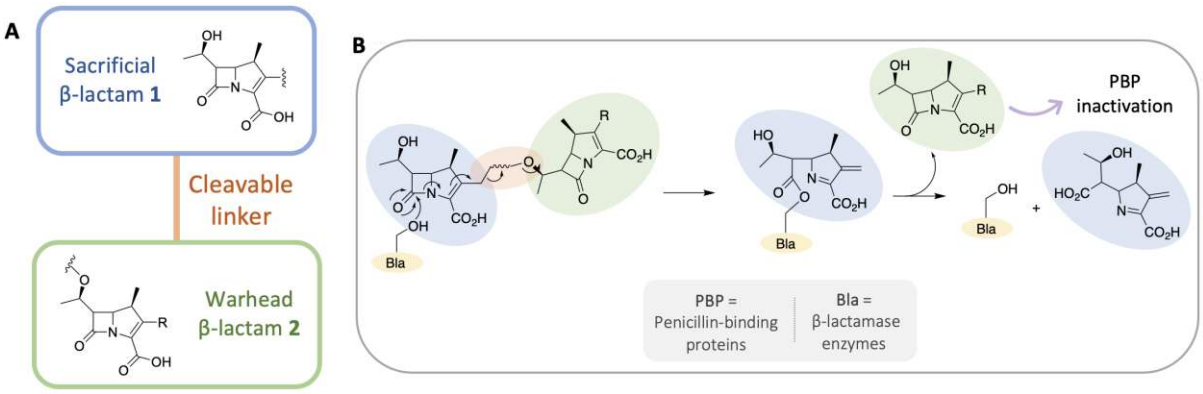
The World Health Organisation (WHO) endorsed a global action plan in 2015 surrounding antimicrobial resistance, in which it was announced that by 2050 no effective antibiotics will be available due to bacterial resistance.[10] This could lead to a catastrophic situation, in which WHO responded and has called for the development of new antibiotics to combat the bacterial resistance. Our project aims to develop a new family of antibiotics with a narrow spectrum which will exclusively target resistant bacteria in gram-negative bacterial cells, whilst reducing the collateral damage on human commensal flora. The strategy consists of the synthesis of innovative prodrugs as shown in Scheme 1A, which contain two β-lactam structures linked together *via* a cleavable linker. β-lactam **1**, the sacrificial moiety of the prodrug, is voluntarily targeted and degraded by the serine active β-lactamases as shown by the mechanism in Scheme 1B. The degradation is caused by the nucleophilic attack of the hydroxy moiety of the serine active β-lactamases (Bla).[11] This gives rise to the release of the second warhead β-lactam **2** which is then envisaged to target and inhibit Penicillin-binding proteins (PBPs), which are part of the bacterial cell wall. By inhibiting PBPs we aim to inhibit the synthesis of the bacterial cell wall and kill the bacterial cell. The research on the synthesis of both carbapenem skeletons and the optimisation of the different cleavable linkers will be presented. The chosen synthetic pathway includes several C-C bond formations by metal catalysed cross-coupling reactions and the functionalisation of the warhead. Biological evaluation of the synthesized prodrugs will also be presented.




**Scheme 1.** (A) Structure of prodrugs. (B) Envisaged mechanism of action of the synthesized prodrugs.

[10] World Health Organisation, https://www.who.int/news-room/fact-sheets/detail/antibiotic-resistance#:~:text=A%20global%20action%20plan%20on,with%20safe%20and%20effective%20medicines. (Accessed 22/06/2023).

[11] X. Zeng, J. Lin, *Front. Microbiol.* **2013**, *4*, 128-136.

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