European Meeting on C-H Activation

C-H·AIR

January 23-24, 2024
Lisbon, Portugal
Pavilion of Knowledge

Book of Abstracts

Support & Sponsorship:

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This project has received funding from the European Union's Horizon 2020 research & innovation programme under Grant Agreement No 860762.


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C–H·AIR
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Sponsorship and Support

This meeting is made possible thanks to the support of:

- The EU Horizon 2020 research and innovation programme (Grant Agreement No 860762);
- Instituto Superior Técnico, University of Lisbon;
- The industrial sponsors Janssen Pharmaceutica and Boehringer-Ingelheim;
- Pavilhão do Conhecimento – Ciência Viva.

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Message from the Organizing Committee

Dear Colleagues,

We are honored to invite you to participate in the "European Meeting on C–H Activation" that is held from 23rd to 24th January 2024 in the Pavilion of Knowledge, Lisbon, Portugal.

The "European Meeting on C–H Activation" is organized by the IST/University of Lisbon as a part of the CHAIR project (www.chair-itn.eu).

CHAIR – "C–H Activation for Industrial Renewal" – is a Marie Sklodowska-Curie Action "Innovative Training Network" (ITN) gathering 15 leading research laboratories across Europe, and coordinated by the CNRS in Strasbourg, France. Our aim is to educate and train a new generation of chemists on C–H Activation, while developing new approaches to further improve the attractiveness of C–H activation for industrial purposes.

After 3 fruitful years of research, exchanges, training and workshops, the "European Meeting on C–H Activation" is organized as the final event that will conclude the project.

During this meeting, you will see:

- 4 plenary talks from renowned researchers;
- 14 CHAIR project communications;
- 12 oral communications by external speakers;
- 19 posters from external presenters.

We are very honored to welcome you in Lisbon and hope you will enjoy this event!

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European Meeting on C-H Activation
January 23-24, 2024 • Lisbon, Portugal

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C-H·AIR

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10.35-11.05	**Coffee Break | PS**
11.05-11.50	**PL-2, Eva Hevia**, Univ. Bern, Switzerland
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15.50-16.05	CH-7, Marco Di Matteo, Sorbonne Univ., France
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17.15-17.35	OC-5, Johanna Templ, TU Wien, Austria
17.35-17.55	OC-6, Aleksandrs Cizikovs, LIOS, Latvia
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*Group photo before Lunch: 12.30-12.40 (23-Jan-2024).

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12.30-12.50	OC-11, Martin Prechtl, Univ. Lisbon, Portugal
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14.20-14.35	CH-8, Gilvan Correia, Univ. Lisbon, Portugal
14.35-14.50	CH-9, Takuya Michiyuki, Univ. Göttingen, Germany
14.50-15.05	CH-10, Gana Sanil, ICHO PAN, Poland
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15.20-15.35	CH-12, Janis Zakis, Syngenta, Switzerland
15.35-15.50	CH-13, Pascal Hauk, CNRS Strasbourg, France
15.50-16.05	CH-14, Federico Belnome, ThalesNano, Hungary
16.05-16.35	**Coffee Break | PS**
16.35-17.40	**Panel | C-H Activation: Industrial Challenges & Perspectives** Alex Kirillov (moderation), Univ. Lisbon, Portugal Fabrice Gallou, Novartis Pharma, Switzerland Magnus Johansson, AstraZeneca, Sweden Maëva Mercier, Janssen, Belgium Tomas Smejkal, Syngenta, Switzerland
17.40-18.00	OC-12, Irène Arrata, CNRS Strasbourg, France
18.00-18.15	**Closing & Prizes (best poster & communication)**

PL – Plenary Lecture (45 min), **OC** – Oral Communication (20 min)
CH – CHAIR Project Communication (15 min)
PS – Poster Session (posters on display during both days)
Exhibition – Visit to Exhibition/Pavilion of Knowledge

Venue: Pavilion of Knowledge - Ciência Viva

European Meeting on C–H Activation (January 23-24, 2024) takes place in the Pavilion of Knowledge (Pavilhão do Conhecimento – Centro Ciência Viva), located at Largo José Mariano Gago n.1, 1990-073, Parque das Nações, Lisbon, Portugal.

Pavilion of Knowledge - Ciência Viva is the largest interactive science and technology museum in Portugal that aims to stimulate scientific knowledge, disseminate and promote scientific culture among all citizens. For these reasons, as well as because it is a reference place for science outreach and dissemination, the Pavilion of Knowledge was chosen as the Venue of the CHAIR project's final meeting.

Ciência Viva - National Agency for Scientific and Technological Culture is a Portuguese organization with a network of 21 science centers spread throughout the country, driving a social movement in favor of science and scientific culture, and involving thousands of researchers and citizens, students and teachers, young people and adults. From the outset, Ciência Viva has been an open programme, encouraging alliances between different sectors of Portuguese society, from universities to primary schools, from companies to research laboratories, from local authorities to private associations and professional organizations.

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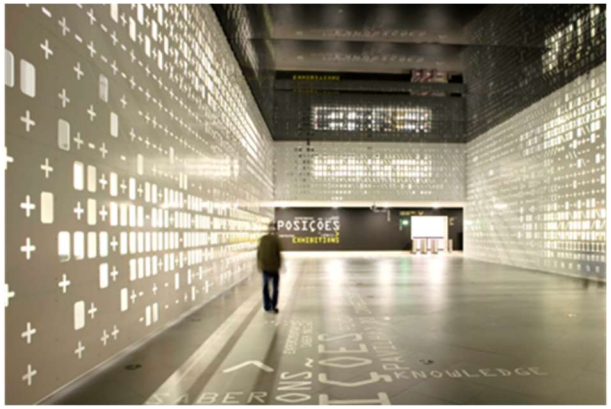

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Detailed Agenda

PL – Plenary Lecture (45 min), **OC** – Oral Communication (20 min)
CH – CHAIR Project Communication (15 min)
PS – Poster Session (posters on display during both days; max. size 80 cm (W) × 120 cm (L))
Exhibition – Visit to Exhibition/Pavilion of Knowledge

Tuesday, 23-Jan-2024

9.00-9.20	**Registration**
9.20-9.50	**Opening** | Alex Kirillov, Univ. Lisbon, Portugal (Organizing Committee Chair); Joanna Wencel-Delord, Univ. Würzburg, Germany (CHAIR Project Coordinator); Rosalia Vargas, Pavilion of Knowledge (Ciência Viva President)
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10.35-11.05	**Coffee Break | PS**
11.05-11.50	**PL-2, Eva Hevia**, Univ. Bern, Switzerland *Tailor-made Bimetallics for Chemical Cooperativity*
11.50-12.10	OC-1, Nicola Della Ca', Univ. Parma, Italy *Sequential Palladium-Catalyzed C-I Cleavage / ortho C-H Activation / ipso C-I Formation by the Catellani Strategy: Towards Highly Substituted Aryl Iodides*
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12.30-14.15	**Lunch | PS & Exhibition** *Group photo before Lunch: 12.30-12.40*
14.15-14.20	Sponsor presentation
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17.35-17.55	OC-6, Aleksandrs Cizikovs, LIOS, Latvia *Indole Synthesis by Cobalt-Catalyzed Intramolecular Amidation via the Oxidatively Induced Reductive Elimination Pathway*
17.55-18.15	OC-7, Duarte Clemente, Univ. Lisbon, Portugal *Continuous Flow Electrochemical Cyanation of Sparteine*

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Wednesday, 24-Jan-2024

9.30-10.15	**PL-3, Igor Larrosa**, Univ. Manchester, United Kingdom *Mechanistic Understanding-Led Transition Metal Catalyzed C-H Functionalization*
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11.25-12.10	**PL-4, Sabine Flitsch**, Univ. Manchester, United Kingdom *Engineering Biocatalysts for the C-H Activation of Fatty Acids*
12.10-12.30	OC-10, G. Guisado-Barrios, Univ. Zaragoza, Spain *Acceptorless Dehydrogenation of N-Heterocycles Catalyzed by a Single Iridium(III) Metal Complex Assisted by Visible Light*
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16.05-16.35	**Coffee Break | PS**
16.35-17.40	**Panel | C-H Activation: Industrial Challenges & Perspectives** Alex Kirillov (moderation), Univ. Lisbon, Portugal Fabrice Gallou, Novartis Pharma, Switzerland Magnus Johansson, AstraZeneca, Sweden Maëva Mercier, Janssen, Belgium Tomas Smejkal, Syngenta, Switzerland
17.40-18.00	OC-12, Irène Arrata, CNRS Strasbourg, France *C–H Activation for Industrial Renewal (CHAIR): the European ITN on C–H Activation*
18.00-18.15	**Closing & Prizes (best poster & communication)**

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Plenary Lectures (PL-1 - PL-4)

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Intermolecular HAT and Pyridine Functionalization

Armido Studer

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Water activation, which allows this earth-abundant resource to be transferred into value added compounds, is a key topic in the field of small molecule activation. We demonstrate a unique water activation strategy enabled by a photocatalytic phosphine-mediated radical process under mild conditions, generating a metal-free PR3-H2O radical cation intermediate, where both hydrogen atoms are used in the following chemical transformation through sequential heterolytic (H+) and homolytic (H•) cleavage of the two O-H bonds.[1] The method can be applied for the hydrogenation of alkene and arenes. Hydrogen atom transfer from iron hydrides to unactivated alkenes with subsequent oxygenation by using nitroarenes as radical trapping reagents will be discussed.[2] This Fe-catalyzed alkene hydration allows a formal water addition to alkenes with excellent selectivity in complex terpene natural products. Finally, pyridine C-H functionalization through a dearomatization/rearomatization sequence will be addressed in the lecture. The dearomatized oxazino pyridines can be easily prepared on a large scale, and functionalization becomes achievable through light-initiated radical alkylation.[3]

Acknowledgments: We are grateful to the Deutsche Forschungsgemeinschaft (DFG).

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Tailor-made Bimetallics for Chemical Cooperativity

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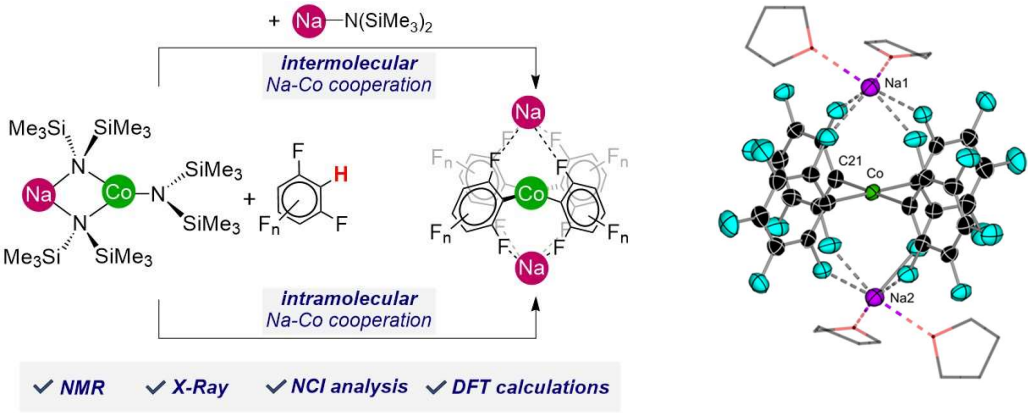
Recent advances in main group metal chemistry have established cooperative bimetallic reagents, prepared by combining two different s-block metals with distinct polarising powers as a versatile family of organometallic reagents capable of delivering new chemistry irreproducible by either of their single-metal components.[1] Extending bimetallic cooperativity to the sustainable divalent transition metals Fe and Co and Mn, this talk will describe new synthetic strategies to promote direct ferration, cobaltation and manganation reactions.[2] This includes applying sodium tris(amido)cobaltates for cobaltation of a range of aromatic molecules including pentafluorobenzene (see Figure)[2b] as well as introducing the first examples of Mn-mediated C-I activation/C-C coupling tandem processes.[3] These opening studies confirm the feasibility of using earth-abundant TM-based cooperative bimetallics to functionalise aromatic molecules, through transporting iron or manganese to positions inaccessible using other synthetic methodologies. Upgrading chemical cooperativity to catalytic processes, this talk will also show the synthesis and characterization of a new family of lithium nickel(ates) and their possible implication in Ni-catalysed cross coupling reactions of aryl ethers with aryl lithium reagents.[4]



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Mechanistic Understanding-Led Transition Metal Catalyzed C-H Functionalization

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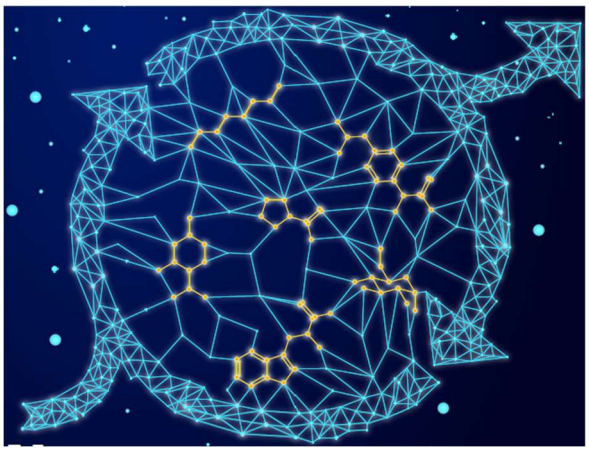
The development of greener and more efficient synthetic methodologies is essential for organic chemistry to reach its full potential in its application to many applied and fundamental scientific problems. Over the last two decades C-H activation has emerged as a powerful tool to streamline syntheses,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

Mechanistic understanding is a cornerstone for progress in organic chemistry. In this talk I will present some of our group's approaches in applying the knowledge derived from mechanistic studies into the design of more efficient processes and of novel catalysts and catalytic systems, such as the use of bimetallic Pd/Ag,[1] Pd/Cr[2] and Au/Ag[3] synergistic systems, and Ru-catalysts for late stage functionalization.[4,5] Additionally, recent developments in the application of machine learning to mechanism elucidation will be discussed.[6]



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Engineering Biocatalysts for the C-H Activation of Fatty Acids

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Selective, one-step C-H activation of fatty acids from biomass is an attractive concept in sustainable chemistry. Biocatalysis has shown promise for generating high-value hydroxy acids but to date enzyme discovery has relied on laborious screening and produced limited hits, which predominantly oxidise the sub-terminal positions of fatty acids. We have shown that ancestral sequence reconstruction (ASR) is an effective tool to explore the sequence-activity landscape of a family of multi-domain, self-sufficient P450 monooxygenases. We resurrected eleven catalytically active CYP116B ancestors, each with a unique regioselectivity fingerprint that varied from sub-terminal in the older ancestors to mid-chain in the lineage leading to the extant, P450-TT. In lineages leading to extant enzymes in thermophiles, thermostability increased from ancestral to extant forms, as expected if thermophily had arisen de novo. Our studies show that ASR can be applied to multi-domain enzymes to develop active, self-sufficient monooxygenases as regioselective biocatalysts for fatty acid hydroxylation.

Acknowledgments: This work was supported by the European Research Council (788231-ProgrES-ERC-2017-ADG).

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Oral Communications (OC-1 - OC-12)

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Sequential Palladium-Catalyzed C-I Cleavage / ortho C-H Activation / ipso C-I Formation by the Catellani Strategy: Towards Highly Substituted Aryl Iodides

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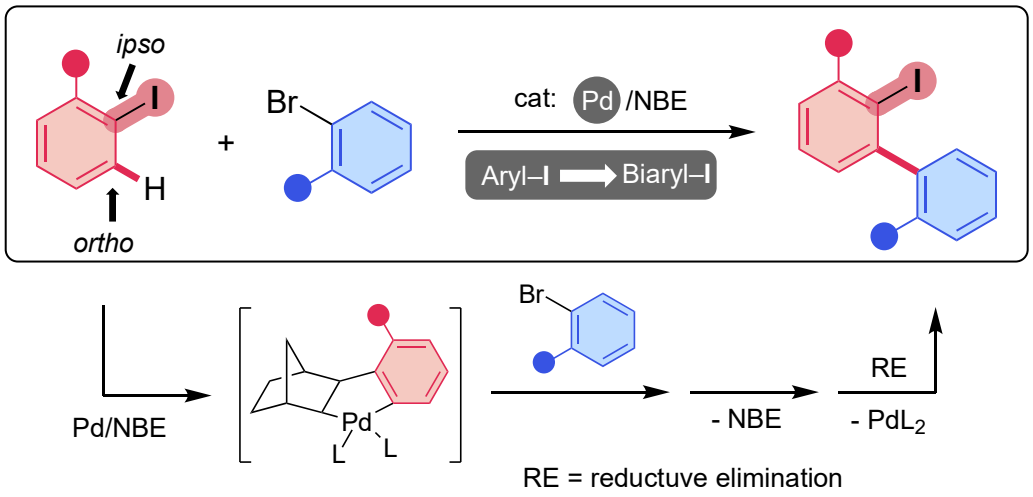
The *Catellani reactions* have been discovered in 1997 by Marta Catellani and co-workers after years of seminal works.[1] Later, several research groups have contributed to increase their impact for the synthesis of highly substituted arenes, heterocycles and natural products.[2-4] After more than two decades, this singular reaction sequence, that features the cooperative catalysis of palladium and norbornene, continues to attract the interest of researchers. In this contribution, the traditional Catellani reaction sequence, starting from an *ortho* substituted aryl iodide, passing through the formation of an aryl norbornyl palladacycle and an arylation step, ends with the formation of a C-I bond in the same position (*ipso*) of the initial C-I one.[5] This is the first example of a C-I termination step in the Catellani reaction and one of the rare C-I to C-I reaction sequence. The synthesized *ortho*-iodo biaryls can be a versatile platform for further derivatizations. A transmetallation pathway is likely at work in the reductive elimination step to the new formed C-I bond.



Scheme 1. Access to *ortho*-iodo biaryls exploiting the *Catellani reactions* strategy

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CH Activation as a Tool for Fluorescence Amplification in Pd-Complexes of Oxazolones

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4-Arylidene-5(4*H*)-oxazolones (Figure 1a, X = O) are heterocycles widely used in organic synthesis as precursors for α-amino acids (phenylalanine). Additionally, they possess notable photophysical properties, which have been much less studied, and which prove to be extraordinarily dependent on the environment.[1] Thus, in a very rigid environment (for example, in solid state), they exhibit intense fluorescence, whereas in solution, the existence of a greater number of degrees of freedom and internal motions like hula-twist lead to the opening of non-radiative deactivation channels, and the fluorescence is completely lost. A striking example of this behavior is observed in the GFP (Green Fluorescent Protein), whose chromophore is an imidazolone (Figure 1a, X = NR^2), structurally closely related to the oxazolone. When this chromophore is inside the protein, it displays intense green fluorescence with a quantum yield of Φ=1, while outside the protein, the yield drops to zero.[2] Among the various solutions proposed to limit the number of degrees of freedom and restore fluorescence, the introduction of an intramolecular lock between the heterocycle and the *ortho* position of the arylidene ring is particularly interesting, although it has been scarcely developed as only examples with BF_2 are known (Figure 1b).[3,4]

In this work, the results obtained using Pd as an intramolecular lock (Figure 1c) for oxazolones and imidazolones are presented, so that the incorporation of Pd into the oxazolone and imidazolone skeleton occurs through CH bond activation. The photophysical characterization of the obtained orthopalladated complexes is also presented, showing that it is possible to achieve quantum yields up to 28% in solution at room temperature, along with an in-depth DFT study that helps understand these results. Lastly, we employed the automated machine learning workflows of the ROBERT program to discover new luminescent Pd complexes with a modest dataset of 23 points.[5] This digitalized approach enabled us to discover three new luminescent emitters with good QYs from a pool of over 15 potential candidates while conducting a minimal number of experiments.

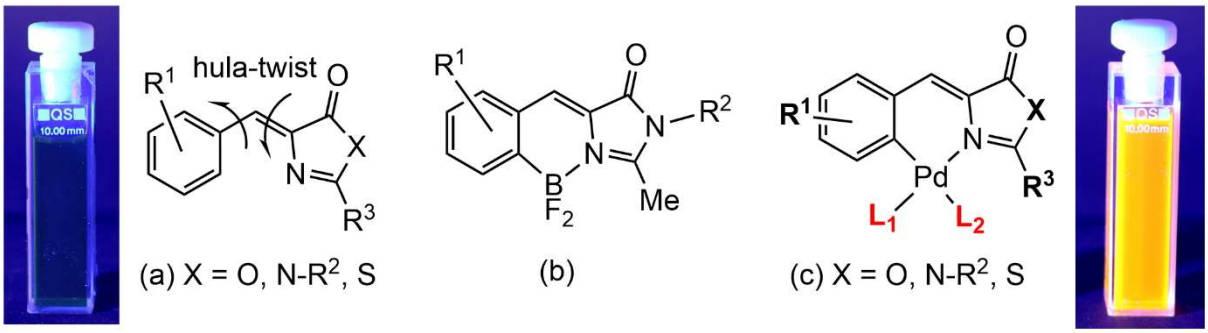

Figure 1. (a) non-fluorescent azlactones; (b) B as intramolecular lock; (b) Pd as intramolecular lock for fluorescence amplification.

Acknowledgments: We thank the Spanish Government (Grants PID2019-106394GB-I00, IJC2020-044217-I and PID2022-140159NA-I00 funded by MCIN/AEI/10.13039/ 501100011033) and Gobierno de Aragón-FSE (Spain, groups Química Inorgánica y de los Compuestos Organometálicos E17_23R and Química de Oro y Plata E07_23R) for funding. D.D. thanks Gobierno de Aragón-FSE for a PhD fellowship.

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Visible Light Promoted Photoredox C(sp3)-H Bond Functionalizations of Tetrahydroisoquinolines in Flow

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Lately, the application of microfluidic devices has been a very promising strategy in organic chemistry, and one of the research fields in which microfluidics have shown great potential is visible light photochemistry. There are several advantages when conducting transformations in flow compared to the batch reactions, in particular: a more predictable reaction scale-up, decreased safety hazards, improved reproducibility and yields and thus lowered waste generation, shorter residence times leading to decreased energy consumption, higher reaction selectivity and product purity and lower catalyst loading leading to overall more sustainable and greener processes. In addition, for photochemical transformations, the high surface-area-to-volume ratios typical of flow reactors allow for improved light efficiency. Even though significant progress has been achieved, greener alternatives to many common industrial processes still remain elusive, especially in the fine chemicals industry. To render processes greener and cheaper, catalysis is a key tool to reduce energy consumption and to develop more atom-economical transformations. We have applied microfluidic chemistry and merger of photoredox and organocatalysis in the synthesis of the functionalized Tetrahydroisoquinolines, valuable fine chemicals with important biological and pharmaceutical effects. Use of microreactors allowed shorter reaction times, superb yields and decreased waste generation compared to standard batch conditions. All the tested microreactors were custom made and optimized to perform synthesis of desired materials in the most efficient manner.

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Double Cobalt-Catalyzed Atroposelective C–H Activation: One-step Synthesis of Atropisomeric Indoles bearing Vicinal C–C and C–N Diaxes

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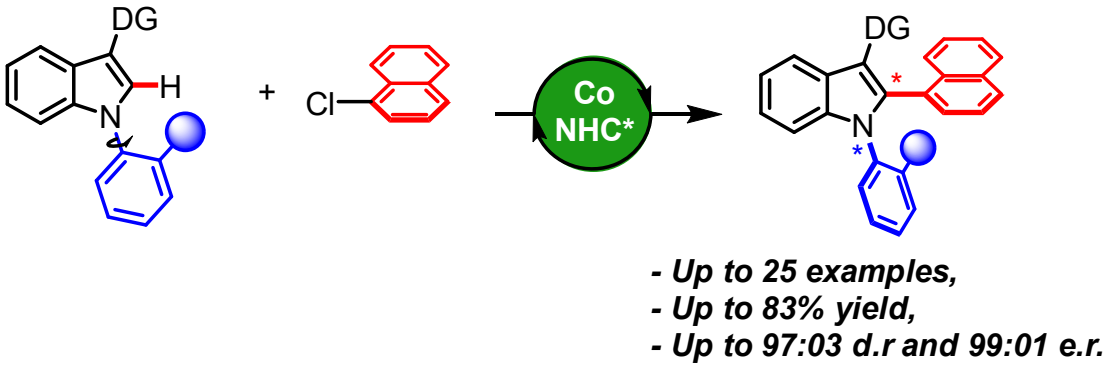
Atropisomers result from a restricted rotation around a single bond. These scaffolds are getting further attention over the last decade thanks to their wide applications especially in the pharmaceutical and agrochemical industries. Recently, atropisomers bearing multiple stereogenic axes have emerged as a new class of intriguing molecules.[1] Synthesis of such multichiral skeletons present a great scientific challenge and it is therefore essential to find adequate step-economical synthetic routes.[2] We report herein a unique cobalt-catalysed asymmetric C–H activation reaction to afford indoles bearing vicinal C2-atropisomeric Ar–Ar' axis and C–N axial chirality with high yields and high stereoselectivities under mild conditions.[3]



Scheme 1. One-step synthesis of Atropisomeric indoles bearing C-C and C-N diaxes *via* Cobalt-Catalysed C-H activation

Acknowledgments: We thank the CNRS (Centre National de la Recherche Scientifique) and the Ministère de l'éducation Nationale et de la Recherche (France) for financial support. We also acknowledge the ANR (Agence Nationale de la Recherche) and DFG collaborative project ANR PRCI (grant ANR-17-CE07-0049-01). We acknowledge the European Commission for the ERC Starting Grant AlCHIMIE (grant 949804).

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Mashing up Tsuji-Trost Allylation – A Mechanochemical Approach

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The palladium-catalyzed Tsuji-Trost allylation is a versatile and fundamental reaction with widespread application in organic synthesis. By eliminating a leaving group in the allylic position, various allylic compounds can form a π-allyl metal complex with a Pd(0) species, which in turn can be attacked by a range of nucleophiles, resulting in the formation of allylated products. An alternative approach to achieve nucleophilic allylation is through the use of allyl bromide. However, this conventional allylating agent presents significant health concerns, such as high toxicity and mutagenicity. Additionally, its high flammability poses hazards during reaction setup.

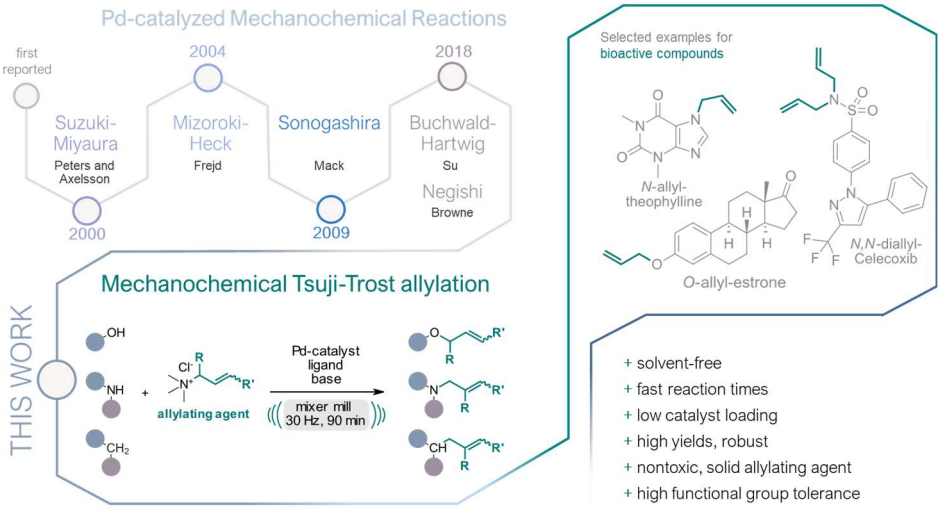

Figure 1. Previously published Pd-catalyzed mechanochemical reactions *(left, top)* and the recently reported mechanochemical Tsuji-Trost reaction *(left, bottom)* suitable for a late-stage modification of bioactive compounds *(right, top)* and the method's outstanding features *(right, bottom)*.

Given the aforementioned toxicological and safety issues, we were encouraged to expanded our previous research on the use of quaternary ammonium salts as safe and non-toxic alkylating agents[1,2] to allylation reactions. We have identified allyl trimethyl ammonium chloride as an ideal allylating agent for various *O*-, *N*-, and *C*-nucleophiles in a Pd-catalyzed, mechanochemical Tsuji-Trost reaction. This reaction can be performed solvent-free in a ball mill and exhibits short reaction times (90 minutes), very low catalyst loadings (0.5 mol%), and mild basic conditions. During the oxidative addition step of the catalytic cycle, solely trimethylamine is released as a gaseous by-product, eliminating the need for an additional separation step. This environmentally friendly approach employs easy-to-handle and non-toxic reagents, providing access to numerous allylated substrates. The high yields, excellent functional group tolerance, and broad applicability of this novel method are expected to facilitate late-stage functionalization of complex natural products and pharmaceutically active compounds, paving the way for a more sustainable approach in allylation.

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Indole Synthesis by Cobalt-Catalyzed Intramolecular Amidation *via* the Oxidatively Induced Reductive Elimination Pathway

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C-H bond functionalization methodology using high-valent cobalt catalysis recently emerged as a highly efficient and selective tool for the construction of a wide range of valuable compounds. In the last couple of decades this approach has been widely exploited in fields of medicinal chemistry, material sciences, organic synthesis and total synthesis, mainly due to its step- and atom- economical nature.[1] Evidence collected over the years from mechanistic experiments and isolated intermediate species gave insight into the general operative C-H functionalization mechanism, which suggested Co(III)/Co(I) or Co(II)/Co(III)/Co(I) catalytic cycle for the major part of the developed transformations.[2,3] Although the catalytic cycle involving Co(IV) species has been considered in several cases, so far only two literature reports contain detailed undisputable evidence of the involvement of Co(IV) species in C-H functionalization under high-valent cobalt catalysis.[4] Herein we report and efficient synthesis of indole-2-carboxylic esters **2** *via* intramolecular amidation of phenylalanine derivatives **1** (Figure 1) and experimental and computational studies of the reaction mechanism, which involves oxidatively induced reductive elimination (ORE) from Co(IV) species.

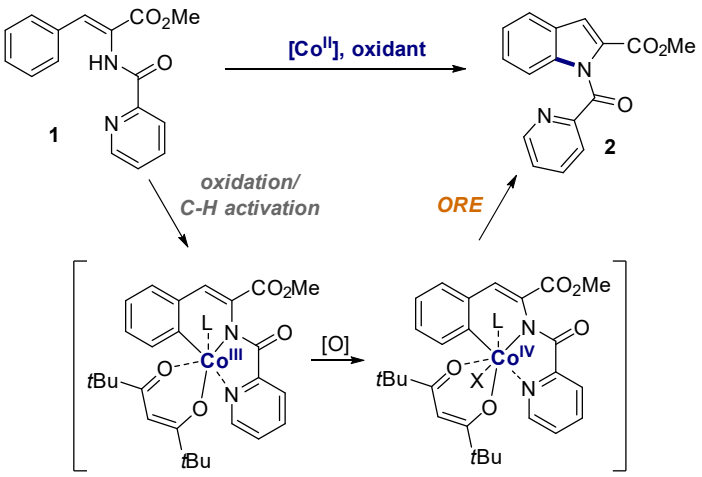

Figure 1. Indole **2** synthesis *via* cobalt-catalyzed intramolecular amidation.

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Continuous Flow Electrochemical Cyanation of Sparteine

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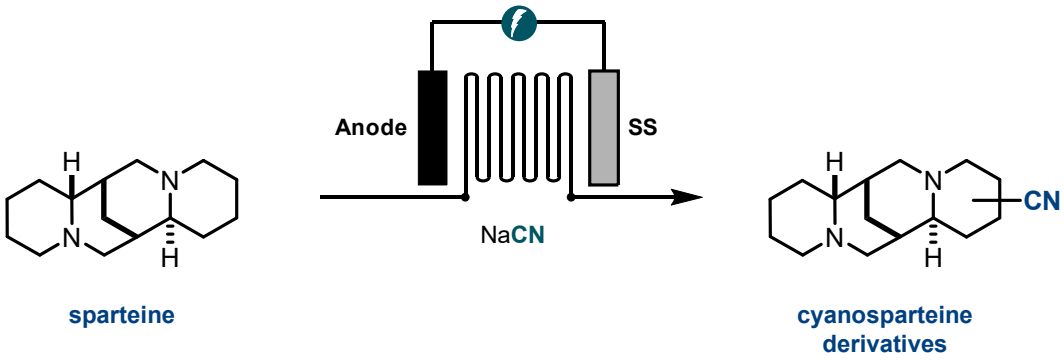
Synthetic organic electrochemistry has resurged in the last decades as a sustainable methodology that offers chemists the possibility of performing highly chemoselective C-H activation reactions under mild conditions, with consequent high functional group tolerance.[1] The transposition of electrochemical processes to continuous flow enables an increased control over the reaction parameters, which translates into enhanced reactivity, selectivity and reproducibility of electrochemical methodologies.[2,3] Sparteine is a bisquinolizidine alkaloid with vast applications in asymmetric synthesis both as a stoichiometric chiral auxiliary and as a ligand for metals such as lithium, copper, and palladium.[4] Herein, we report a novel method for the electrochemical cyanation of sparteine under continuous flow conditions towards the functionalization of this alkaloid, yielding several cyano derivatives with potential interest as intermediates for the development of unprecedented sparteine-based organocatalysts (Scheme 1).



Scheme 1. Electrochemical cyanation of sparteine in continuous flow.

Acknowledgments: We thank FCT for financial support (UIDB/04138/2020, UIDP/04138/2020, UIDB/00100/2020, UIDP/00100/2020, LA/P/0056/2020 and PTDC/QUI-QOR/1786/2021). JASC thanks FCT for Scientific Employment Stimulus 2020/02383/CEECIND. The project leading to this application has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 951996.

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Climbing the Oxidase Phase of Sesquiterpenoids by Dioxygen as the Sole Oxidant

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The emergence of preparing diverse natural product scaffolds is firmly associated with the need of our society for more potent and selective biomodulators. In response, nowadays, divergent synthesis utilizing common synthetic scaffolds that can be readily transformed into an array of diverse natural compounds is progressively gaining ground in drug discovery.[1] Our work highlights the drawbacks and the potential solutions towards the development of a unified synthetic plan for accessing biologically potent sesquiterpene lactones (Figure 1).[2-5] Towards this goal, herein we report our effort to mimic part of the oxidase phase used in sesquiterpenoid biosynthesis to achieve the protecting group free total synthesis of various natural sesquiterpenoid lactones by using dioxygen as the sole oxidant. Various oxidation steps, including chemoselective epoxidations, allylic oxidations, and CH-oxidations in various positions of complex sesquiterpenoid carbocyclic cores by organocatalytic activation of dioxygen are described.

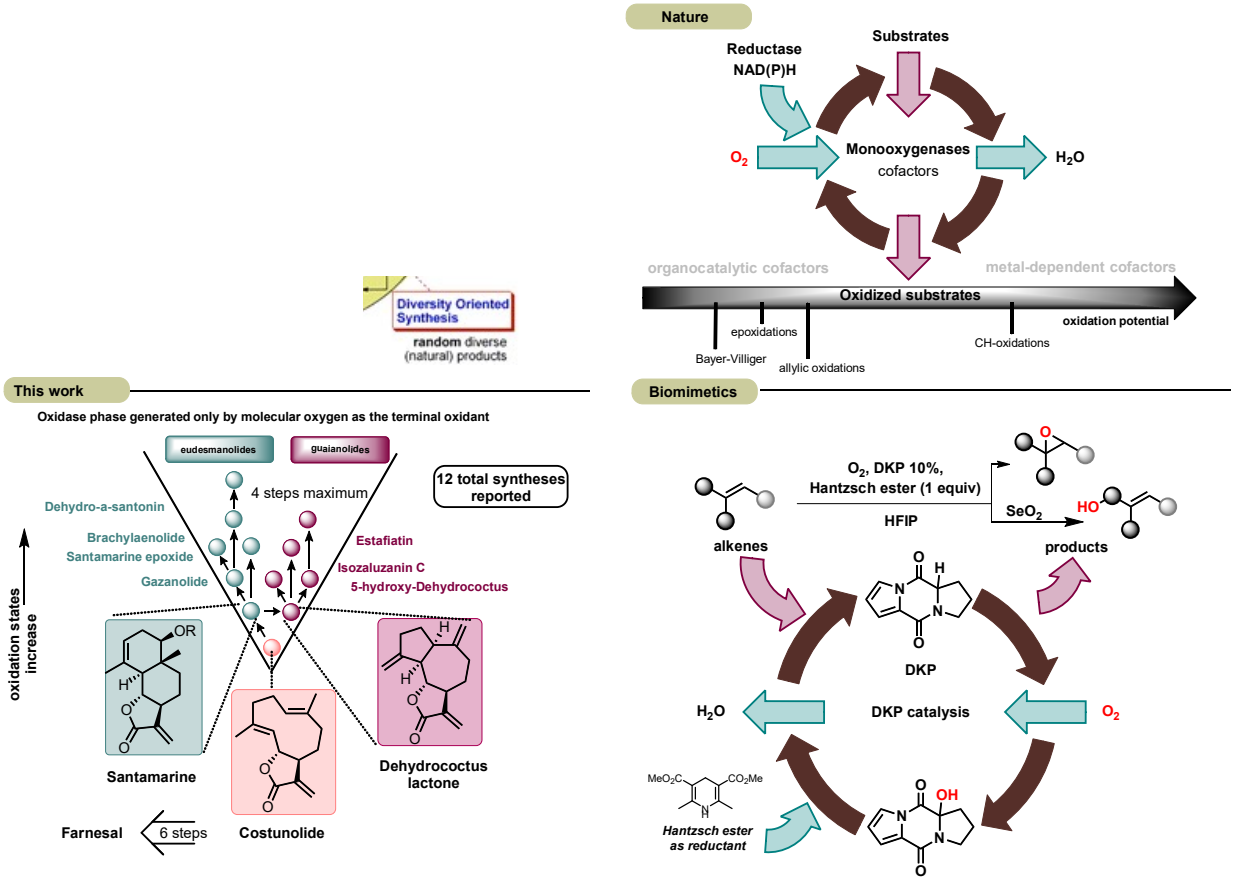

Figure 1. Divergent plan for accessing various sesquiterpenoid lactones.

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C-H Bond Activation with Use of 1-Halopolyynes

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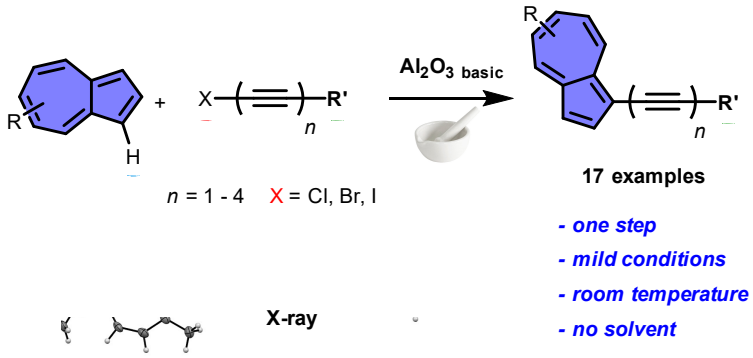
Long chain organic, organometallic and metal-containing polyynes are being constantly at the horizon of modern synthetic and materials chemistry. Such compounds are not only investigated as models for still elusive sp-carbon allotrope - carbyne,[1] but have been proved to possess many unusual properties which extend from uncommon structural features to spectacular physicochemical behavior. In this regard, specific termini which are σ-attached to the carbon chain play a crucial role in moderation of those properties. Especially interesting are red-ox active end-groups which use the unsaturated $(C{\equiv}C)_n$ bridge to communicate one with the other. The introduction of a polyyne chain into an organic compound can be achieved in many synthetic ways. One of the less explored approach is the C-H bond activation which can be performed both in solution and in the solid state. 1-Halopolyynes are excellent substrates for such transformations since the terminal carbon in those species is (sometimes highly) electrophilic. Using common knowledge on the *C*-nucleophilicity of organic compounds (from for instance Mayr's scale) functionalization with C-H bond activation can be designed leading to useful derivatives. Our results on C-H functionalization with use of 1-halopolyynes obtained for azulenes[2] and pentafulvenes will be presented.



Scheme 1. Functionalization of azulenes with 1-haloalkynes.

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Acceptorless Dehydrogenation of N-Heterocycles Catalyzed By A Single Iridium(III) Metal Complex Assisted By Visible Light

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The acceptorless dehydrogenation of tetrahydroquinolines (THQs) has recently received considerable attention, not only because it avoids the use of stoichiometric oxidants in these organic reactions, but also owed to their prospective use in alternative energy technologies as Liquid Organic Hydrogen Carriers (LOHCs) for hydrogen storage in the liquid form.[1]

Still, the development of effective catalysts for hydrogen-storage has proven difficult since they must fulfill a series of technical specifications in practical terms. One of the most limiting factors is hydrogen's discharge temperature from carrier (90-300°C). In contrast, visible light irradiation can provide energy inputs thermally inaccessible. Effective photocatalytic systems for the acceptorless dehydrogenation of N-heterocycles have been recently reported.[2] However, despite their success, they rely on a ruthenium-based photosensitizer $[Ru(bpy)_3]^{2+}$ and a cobalt complex $[Co(dmgH)_2PyCl]$ (dmgH = dimethylglyoximate). Additionally, a third iridium catalysts $[\{Ir(Cp^*)(Cl)\}_2(thbpym)]$ bearing (thbpym = 4,4' ,6,6'-tetrahydroxy-2,2' -bipyrimidine) is required to efficiently catalyze the reverse process (i.e. hydrogenation of N-heterocycles). Herein, the availability of a single effective catalyst for both transformations is highly desirable.

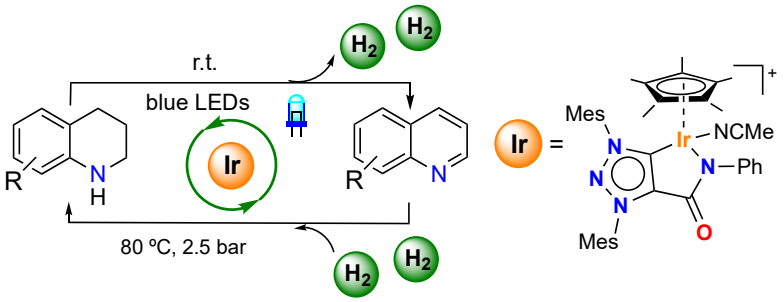

Figure 1. (De)hydrogenation of N-heterocycles catalyzed by a Ir(III) metal complex.

Thus, the synthesis and catalytic performance of a standalone iridium complex towards the visible light assisted acceptorless dehydrogenation of N-heterocycles and the thermal reverse reaction will be presented in this contribution (Figure 1).

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C-H bonds of Small Molecules and Their Role for Hydrogen Storage and Organic Synthesis

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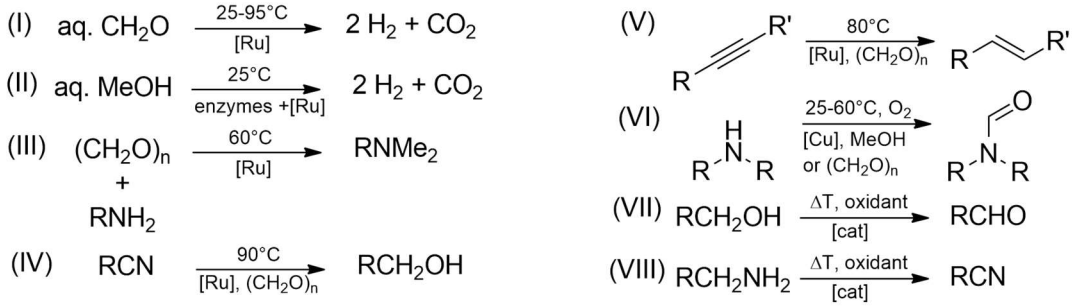
Small hydrogen-rich molecules are widely investigated for the generation of hydrogen for its use in organic synthesis and energy storage application. In addition to the high content of these molecules, other properties of interest cover practical aspects to improve the efficiency and the safe handling. In this regards liquid molecules or soluble molecules are beneficial in comparison to molecules in the gaseous state. In addition, albeit hetero atoms increase the molecular weight in comparison to hydrocarbons, one can observe that the activation energy required to activate C-H bonds in a dehydrogenative reaction pathway is lower. These observations can be found in synthetic experimentation but also in natural processes. In Nature, biological, enzymatic processes frequently activate small molecules with alcohol, aldehyde or amine moieties to enable energy conversion, hydrogen transfer or detoxification at low temperature. In continuation of our research on bioinspired and biomimetic hydrogen production and synthetic application using C1 molecules; we reported on: hydrogen evolution with formaldehyde dehydrogenase mimics (I), methanol formation with dismutase mimics, chemoenzymatic methanol reforming (II), chemoenzymatic transfer-hydrogenation using methanol, *N*-methylation (III), deamination of nitriles (IV), transfer-hydrogenation (V), *N*-formylation (VI), among others (Scheme).[1-5] More recently, we report on the ability to mimic nitrous oxide reductase (N_2OR) and alcohol oxidase.[6-8] This study explores the oxidation of benzylamines to yield benzonitriles (VII) and the conversion of benzyl alcohols into benzaldehydes (VIII) while nitrous oxide simultaneously decompose in presence of hydrogen donating molecules like amines and alcohols (Scheme).[7] In our ongoing studies, beyond the activation of C-H bonds, we explore the decomposition of the greenhouse gas N_2O, wherein the catalyst acts as a nitrous oxide reductase (N_2OR).



Scheme 1. Selected biomimetic activation of small molecules.[1-5,7]

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C–H Activation for Industrial Renewal (CHAIR): the European ITN on C–H Activation

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C–H activation is one of the most rapidly expanding fields of synthetic chemistry. Yet, its implementation in the non-academic sector is still scarce, as numerous obstacles still need to be overcome to render C–H Activation truly appealing for a large-scale production of drugs, new materials, or key building blocks. In addition, current academia-industry interactions are still limited and young researchers able to implement these new competences are rare.

CHAIR "C–H Activation for Industrial Renewal" is a Marie Skłodowska-Curie Innovative Training Network (ITN) project, gathering 15 leading academic and industrial laboratories to target those challenges, coordinated by the National Centre for Scientific Research (CNRS) in Strasbourg, France. Our objectives are: to educate a new generation of young chemists in C–H Activation, to design new cost-efficient and environmentally sustainable C–H Activation methodologies, and to bridge the gap between industry and academia to enable to widespread use of C–H Activation in R&D.

Figure 1. CHAIR: a European and interdisciplinary consortium gathering academic and industrial leaders in chemistry R&D.

Initiated in 2020, our consortium has recruited and trained 15 Early-Stage Researchers (ESRs), working collaboratively within our interdisciplinary and international consortium. The "European Meeting on C–H Activation" is the closing event of the CHAIR programme.

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CHAIR Project Communications (CH-1 - CH-14)

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Kinetic Resolution of *β*-Substituted Cyclopropane Carboxamide Using Pd-Catalysed Enantioselective C-H Arylation

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Asymmetric C-H activation is an extremely challenging but also an important topic[1]. Indeed, implementation of a chirality transfer from an enantiopure metal-catalyst to the newly generated functionalized product holds great promise for the rapid synthesis of a diversity of high-value-added molecules. However, C-H activation is still mainly limited to the direct functionalization of aromatic compounds, while direct metallation of C(sp^3)-H bonds and following functionalization are more challenging. Therefore, assembly of enantiopure aliphatic compounds employing asymmetric C-H activation is still rather rare. Following this general goal and capitalizing on our previous work on diastereo- and enantioselective direct functionalization of cyclopropanes using Pd-based catalyst[2], we have focused on establishing a new protocol for asymmetric C-H activation of small cycloalkanes, motifs frequently used in pharmaceutical and agrochemical industries[3]. In the current project, we have extended our ambitions by focusing on much more challenging 2-substituted cyclopropanes. The difficulty of such an asymmetric reaction relates however to the intimate nature of the enantiodeterminant C-H metallation event. Indeed, in the case of simple cyclopropanes bearing a directing group, *cis*-selective metallation occurs and the enantioselectivity is determined while distinguishing two enantiotopic protons (Figure 1). In contrast, asymmetric functionalization of disubstituted cyclopropane substrates implies kinetic resolution-type transformation, i.e. the chiral catalyst is expected to react selectively with one enantiomer of the substrate, thus allowing its conversion into the desired product, while the other enantiomer of the substrate should remain unreactive in the reaction mixture. In consequence, in the ideal situation, at the end of the reaction, the desired functionalized product is isolated as a single isomer in up to 50% yield, together with 50% of the unreacted, enantiomerically enriched substrate. Although several kinetic resolution-type processes have already been designed in the C-H activation field, to the best of our knowledge kinetic resolution of cyclopropanes remains unprecedented.

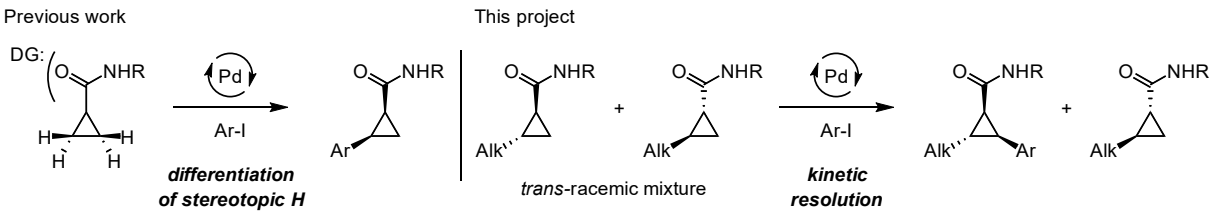

Figure 1. Kinetic resolution of *β*-substituted cyclopropane carboxamide

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References: [1]C. G. Newton, S.-G. Wang, C. C. Oliveira, N. Cramer, *Chem. Rev.* **2017**, *117*, 8908−8976. [2]S. Jerhaoui, J.-P. Djukic, J. Wencel-Delord, F. Colobert, *ACS Catal*. **2019**, *9*, 2532−2542. [3]T. T. Talele, *J. Med. Chem.* **2016**, 59, 8712−8756.

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Regioselective Halogenation of Cyclic Biaryl Hypervalent Br(III) and Cl(III) Compounds

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Halogenated biaryl compounds are common motifs found in agrochemicals, pharmaceuticals and functional organic materials, among other scientific fields. The synthesis of complex polyhalogenated biaryls, however, often poses significant challenges, particularly when applying traditional cross-coupling methodologies. Not only do these approaches require harsh conditions, expensive transition metals and complex precursors, but they also incur significant chemo- and regioselectivity issues when multiple reactive halogens are present, resulting in unwanted side products, over-functionalizations and polymerizations. In light of these limitations, a more direct and convenient approach to functionalize biaryl scaffolds is preferable. Yet, existing direct halogenation methods, such as electrophilic aromatic substitutions or C-H activations, are frequently highly substrate-specific, relying on intrinsic regioselectivity effects or pre-installed directing groups. A new, more attractive solution for the regioselective halogenation of biaryl compounds can be achieved by harnessing aryne chemistry. Our approach builds on recent benchmark studies by our group which show that cyclic biaryl hypervalent bromine and chlorine compounds can undergo mild base-mediated aryne formation. The resulting biaryl aryne intermediates can selectively react *in situ* with various arynophiles and C-, N- or O- nucleophiles under metal-free conditions.[1-3]

In this work, we have further explored this unique reactivity of hypervalent Br and Cl compounds as masked arynes to prepare synthetically valuable polyhalogenated biaryl compounds. By employing mild, metal-free conditions and cost-effective reagents, we are able to accomplish highly regioselective (di)halogenations, marking a significant leap in efficiency and opening up new retrosynthetic pathways towards the synthesis of more complex polysubstituted biaryls.

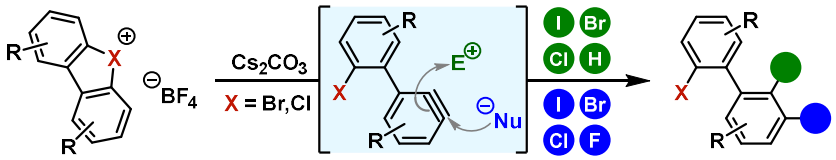

Figure 1. Regioselective (di)halogenation of cyclic biaryl hypervalent bromine and chlorine compounds.

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Late-Stage Peptide Labeling with Near-Infrared Fluorogenic Nitrobenzodiazoles by Manganese-Catalyzed C–H Activation

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Among the vast array of pharmaceutical compounds, peptides have emerged as powerful candidates for drug development.[1] Thus, late-stage diversification of structurally complex amino acids and peptides provides tremendous potential for drug discovery and molecular imaging.[2] Specifically, labeling peptides with fluorescent tags is one of the most important methods for visualizing their mode of operation.[3] Despite major recent advances in the field, direct molecular peptide labeling by C–H activation is largely limited to dyes with relatively short emission wavelengths, leading to high background signals and poor signal-to-noise ratios. In this regards, nitrobenzodiazole (NBD) fluorescent dyes have been identified as powerful labeling tags because of their small size, neutral character, cell permeability and large Stokes shifts.[4,5] Herein, we report on the fluorescent labeling of peptides catalyzed by non-toxic manganese(I) *via* C(sp^2)–H alkenylation[6,7] in chemo- and site-selective manners, providing modular access to novel near-infrared (NIR) nitrobenzodiazole-based peptide fluorogenic probes.[8] This strategy features excellent properties of NBD labeled amino acids and peptides, such as large Stokes shifts, NIR emission wavelengths, and excellent fluorogenicity for real time imaging in live cells.

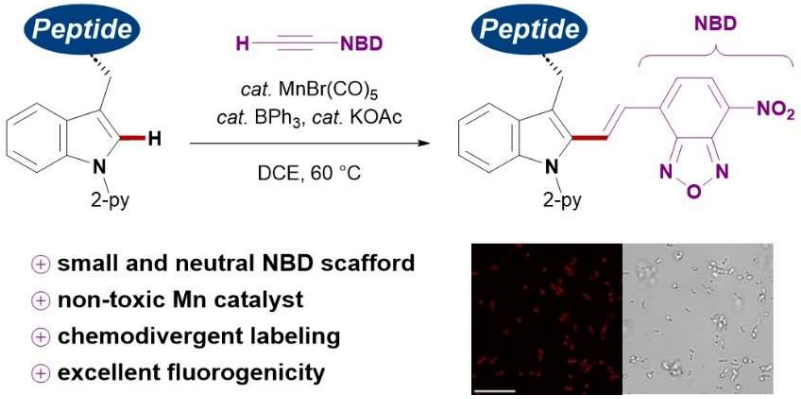

Figure 1. Manganese-catalyzed labeling of tryptophan with NBD fluorescent dye and application for imaging studies.

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Synthesis and Characterization of [N^C^C]Au(III) and [P^N]Au(III) Azido Complexes

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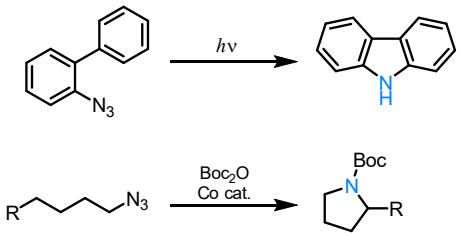
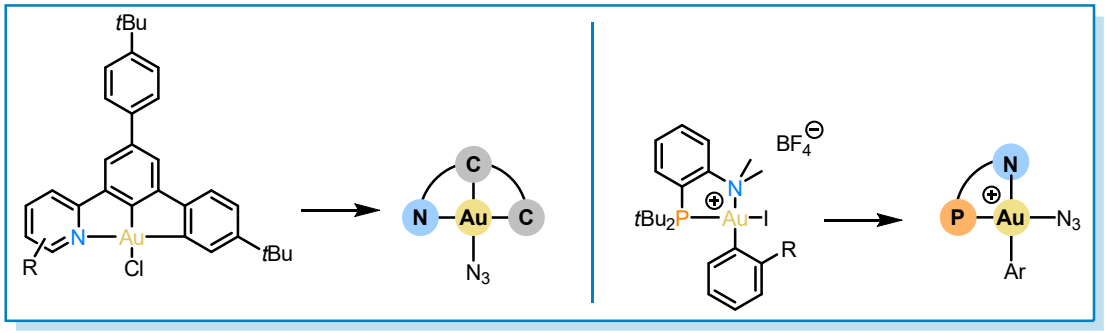
Azides and azido containing compounds are ubiquitous synthons in organic chemistry. Their unique properties (facile extrusion of dinitrogen, nucleophilicity, high reactivity…) make it an outstanding N-atom donor. Since the discovery of the first organic azide in 1864, many organic transformations involving this class of compounds have been developed.[1] Such reactions include alkyne-azide cycloadditions, nucleophilic aminations or C-H aminations (Scheme 1).[2-4]



Scheme 1. Azides in C-H activation

Metallic azides also play an important role in modern chemistry. They exhibit a very rich and diverse coordination chemistry, acting as mono-, di- or even poli-coordinating ligand with a wide variety of transition metals. Moreover, these species can also participate in organic transformations involving the incorporation of N atoms in organic substrates.[5]

In this work, we report the synthesis and characterization of Au(III) azido complexes bearing two different templates; a biscyclometallated [N^C^C] ligand and an hemilabile [P^N] ligand (Scheme 2). The synthesis starts from the corresponding [N^C^C]Au chloride[6] or cationic [P^N]Au iodo[7] complexes, which are transformed into the desired azides in two steps.



Scheme 2. Au(III) azido complexes synthesised in this work

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2-(*o*-Tolyl) Pyridine as Ligand Improves the Efficiency in Ketone Directed *ortho*-Arylation

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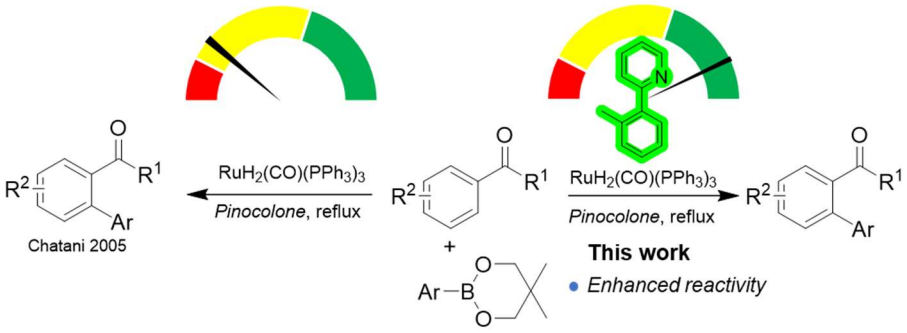
Utilization of directing groups in C-H bond activation has emerged as a prominent strategy for selectively activating specific C-H bond.[1] In this regard, ketones are desireable DGs since they can be transformed into many functional groups and are found in bioactive chemicals and functional materials.[2] Our research focuses on the formation of biaryl complexes using ketone-directed ortho-arylation. Ketone-directed C-H arylation has been described in previous approaches by Murai[3] and other researchers. However, there are limitations to implementing these protocols in the presence of other directing groups. For example, we attempted Chatani's procedure[4] in presence of a competing substrate, namely 2-(o-tolyl)pyridine, but no arylation was observed. In contrast, the presence of only a catalytic amount of 2-(o-tolyl)pyridine increased the efficiency of the ketone-directed reaction. In this work we investigated the role of 2-(o-tolyl)pyridine suggesting that it acts as ligand in ruthenium-catalyzed C-H functionalization.[5-6] Details of reaction optimization and reaction scope will be presented in this contribution.



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Substituting Gaseous Reagents for Solid Alternatives

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The functionalization of short carbohydrate chains is a significant challenge in organic synthesis, primarily due to the low reactivity of alkylhalides and the impractical use of short-chain olefins as alkylating/alkenylating agents. This study is centered on the development of a convenient Heck vinylation protocol that circumvents the need of ethylene gas as a coupling partner. Olefins and especially arylethenes are powerful precursors in organic synthesis used for the synthesis of bioactive compounds as well as polymers. The versatility of the alkene moiety renders them excellent substrates for the construction of more complex molecules. However, conventional methodologies utilize olefins that are gaseous at room temperature or elaborate high pressure equipment, and therefore in this type of transformation, ethylene and other gaseous olefins are often avoided, primarily for practical and safety reasons.

A sustainable and safe approach that can tackle this issue involves the use of solid and easy to handle sources of alkenes and in situ generation of the required reactive coupling partners as illustrated by the use of quaternary ammonium salts as alkenyl sources. [1]The practicality of this method, characterized by its convenience and safety in a one-pot reaction renders it attractive for applications in a research and discovery context.

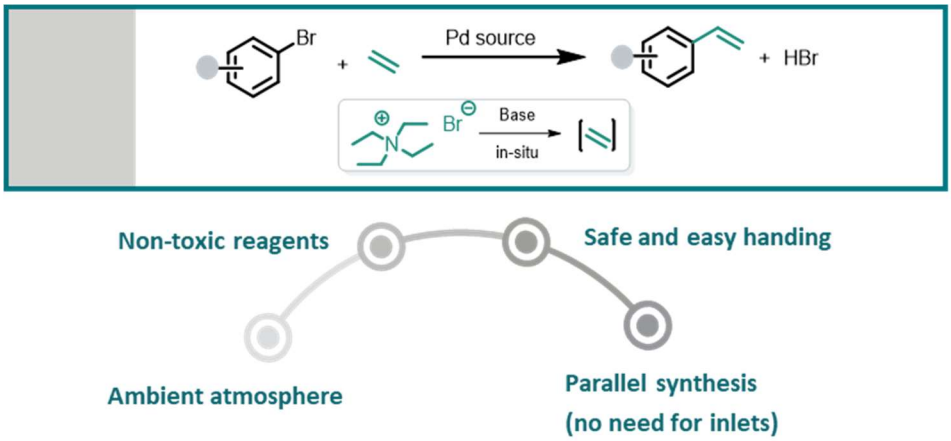

Figure 1. Mizoroki-Heck coupling using tetraethylammonium salt as ethylene precursor.

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Selective C–H Activation of Terpenes

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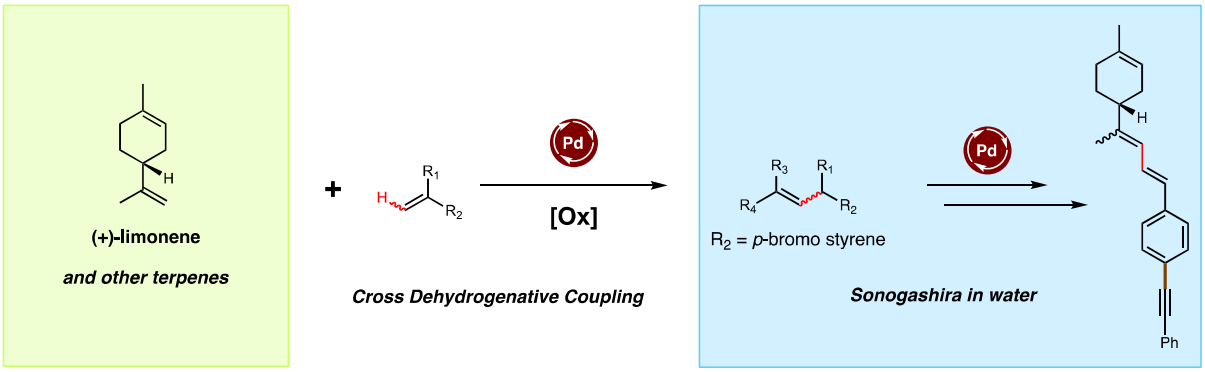
By combining the use of biomass-derived starting materials and step-economy through C–H activation, chemists can achieve more sustainability. Furthermore, if there is to be a significant shift to renewables, then, we must develop new approaches that can be easily adopted and simply "dropped-in" to existing processes. In particular, terpenes stand out as useful starting materials, providing a low-cost and distinct biorenewable platform for selective upgrading to synthetically valuable synthons or more complex natural products. Readily available as a by-product of the citrus juice industry, or produced biotechnologically by yeasts, limonene is the cheapest monoterpene. In this study, we have developed the first Pd(II)-catalyzed C(sp^2)–H / C(sp^2)–H coupling of limonene with several unsaturated partners. Notably, the reaction exhibited exclusive regioselectivity for both reactants, targeting solely the exocyclic unsaturation of limonene. Furthermore, other terpenes incorporating an isoprenyl function alongside an endocyclic alkene, could be successfully reacted, too. DFT computations provided results in accord with the observed selectivity. To further underscore the utility of this C–H activation based catalytic decoration of limonene, we successfully conducted a large-scale Sonogashira reaction under micellar conditions using a C–H/C–H coupled product as a starting substrate. Our future work will focus on developing this C(sp^2)–H / C(sp^2)–H coupling in water, exploring additional selective post-functionalization strategies, and investigating new selective catalytic C–H functionalizations of terpenes.



Scheme 1. Dehydrogenative Cross coupling between terpenes and alkenes followed by Sonogashira coupling under micellar regime.

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Copper(II) Coordination Polymers Driven by 3,4-Pyridinedicarboxylic Acid: Synthesis, Crystal Structures, and Catalytic Behavior in Allylic Oxidation of α-Pinene

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Terpenes are very abundant natural products and useful substrates for the synthesis of diverse value-added organic molecules for cosmetic, fragrance, and pharma industry. Although various catalytic systems were developed for the oxidation of terpenes, these catalysts often incorporate expensive metals and are unrecoverable in many cases. Hence, there is a demand for more efficient and sustainable catalysts.

In this work, two new isostructural 2D coordination polymers were synthesized via self-assembly method and fully characterized. The products were formulated as $\{[Cu_2(pdc)_2(H_2mdea)(H_2O)_2]\cdot 2H_2O\}_n$ (Cu-mdea) and $\{[Cu_2(pdc)_2(H_3tipa)(H_2O)_2]\cdot 4H_2O\}_n$ (Cu-tipa) {H_2pdc, 3,4-pyridinedicarboxylic acid; H_2mdea, methyldiethanolamine; H_3tipa, triisopropanolamine}. The 2D structures revealed 4-connected nets with the **sql** topology type made by 5-coordinated copper(II) units $\{CuO_3N_2\}$ and μ_3-pdc^{2-} linkers (Figure 1). Both compounds were explored as heterogeneous catalysts for the oxidation of α-pinene as a model and abundant terpene substrate, to produce value-added C–H functionalized products, namely 4-*tert*-butilperoxy-2-pinene and verbenone. Catalytic studies were carried out in a small batch reactor (2 mL) at atmospheric pressure with *tert*-butylhydroperoxide as oxidant. Both Cu-mdea and Cu-tipa catalyze the allylic oxidation of α-pinene and display similar efficiency. Under optimized conditions (~93% of α-pinene conversion), 4-*tert*-butylperoxy-2-pinene (42%) and verbenone (25%) were obtained as major products. PXRD and FTIR analyses revealed that both catalysts are stable and can be recovered after catalytic tests. These findings highlight the potential of these coordination polymers as catalysts for the oxidation of α-pinene. In addition, the synthesis scale-up for Cu-mdea and Cu-tipa to reactor level (500 mL) is feasible. Further tests and optimization studies are in progress.

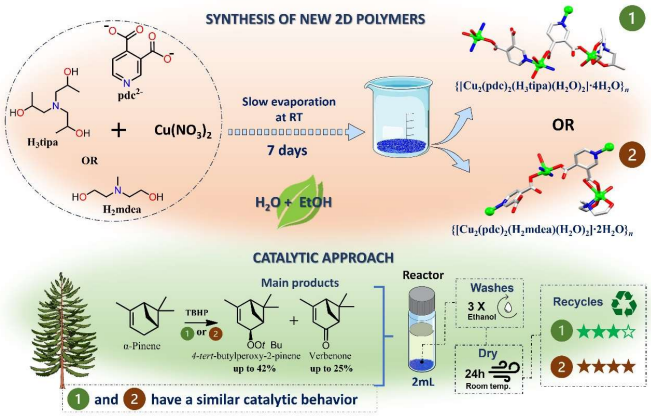

Figure 1. Synthesis of Cu-mdea and Cu-tipa and their catalytic application.

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Electrocatalytic Formal C(sp²)–H Alkylation: Nickel-Catalyzed Cross-Electrophile Coupling with Arylsulfonium Salts

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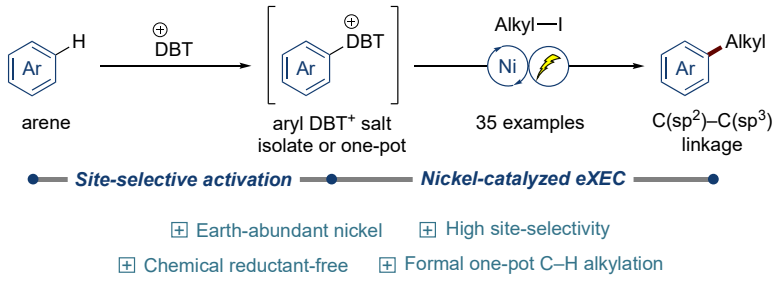
Installing sp³-hybridized carbons into aromatic scaffolds is one of the promising strategies to improve the rate of clinical success in drug discovery.[1] Although conventional cross-coupling reactions with organometallic reagents are highly selective to forge such three-dimensional molecules, there has been increasing demand for more sustainable methods with commercially available substrates. Herein, we present a novel cross-electrophile coupling strategy to install aliphatic chains into aromatic scaffolds via the formation of arylsulfonium salts[2–10] derived from non-prefunctionalized arenes. Various C(sp²)–H bonds can be selectively alkylated under cost-effective nickel catalysis.[11] Furthermore, the reaction harnesses electricity as a reductant, mitigating issues associated with chemical reductants.[12] Notably, one-pot alkylation is viable, highlighting the robustness and practicality of our method.



Scheme 1. Electrocatalytic formal C(sp²)–H alkylation via the formation of arylsulfonium salts. DBT: dibenzothiophene.

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Gold-Catalyzed 1,2-Aryl Shift and Double Alkyne Benzannulation

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The polycyclic aromatic hydrocarbons (PAHs) and their nitrogen-doped analogues have attracted significant attention from the scientific community recently.[1] Alkyne benzannulation or intramolecular hydroarylation of alkynes[2,3] is one among the key reactions which are employed to assemble these dyes. We have demonstrated the tandem intramolecular hydroarylation of alkynes accompanied by a 1,2-aryl shift by exploiting the unique electron-rich character of 1,4-dihydropyrrolo[3,2-*b*] pyrrole scaffold. We found that the hydroarylation of alkynes occurs at the already occupied positions 2 and 5 leading to a 1,2-aryl shift. Interestingly, the reaction proceeds only in the presence of cationic gold catalyst, and it leads to heretofore unknown π-expanded, centrosymmetric pyrrolo[3,2-*b*]pyrroles (Figure 1).

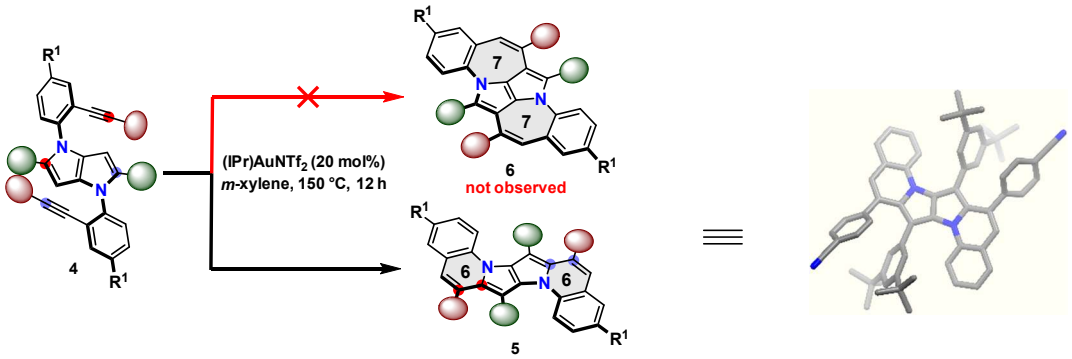

Figure 1. Rapid synthesis of π-extended pyrrolopyrroles **5** through double Au-mediated hydroarylation of alkyne-containing TAPPs **4** accompanied by twofold 1,2-aryl migration.

In addition to discovering the special example of a 1,2-aryl shift, we identified that this reaction is tolerant to many functional groups, in particular those that are viable in the area of optoelectronics. Computational studies of the reaction mechanism revealed that the formation of the six-membered rings accompanied with a 1,2-aryl shift is both kinetically and thermodynamically favorable over plausible formation of products containing 7-membered rings. Steady-state UV/Visible spectroscopy showed that upon photoexcitation, the prepared S-shaped N-doped nanographenes undergo mostly radiative relaxation leading to large fluorescence quantum yields. Their optical properties are rationalized through time-dependent density functional theory calculations. We anticipate that this chemistry will empower the creation of new materials with various functionalities.

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Ruthenium-Catalyzed Aminocarbonylation with Isocyanates through Weak Coordinating Groups

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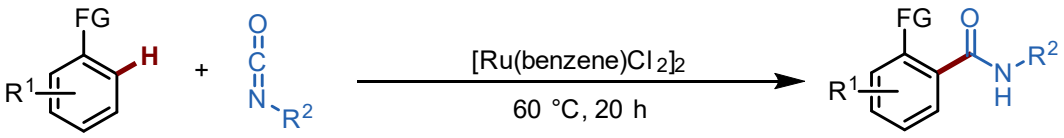
Introducing amide functional group under mild conditions has growing importance owing to the prevalence of such moiety in biologically active molecules.[1] Herein, we disclose a mild protocol for the directed ruthenium-catalyzed C–H aminocarbonylation with isocyanates as the amidating agents developed through high-throughput experimentation (HTE).(Scheme 1)[2] The redox-neutral and base-free reaction is guided by weakly Lewis basic functional groups, including anilides, lactams and carbamates to access anthranilamide derivatives. The synthetic utility of this transformation is reflected by large-scale synthesis and late-stage functionalization.



- HTE enabled fast optimization
- wide range of directing groups including acetanilides, pyrrolidone and carbamate
- mild conditions suitable for late-stage functionalization

Scheme 1. Ruthenium-catalyzed aminocarbonylation with isocyanates.

Acknowledgments: This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No. 860762.

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Air-stable bis-Cyclometallated Iridium Precatalysts for ortho Directed C-H Borylation

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Over last few decades C-H activation has gathered continuous scientific interest and has evolved from early examples using stoichiometric organometallic reagents towards catalytic transformations with new practical applications in industry.[1] Lately cyclometallated complexes have emerged as a new class of catalysts for various C-H functionalizations, and they can be used for late-stage functionalization (LSF) of complex molecules.[2] Among the different C-H functionalization methods C-H borylation has gained particular interest due to the versatility of the organoboron species.[3] Furthermore cyclometallated iridium(III) complexes bearing pyrido-thiophene ligand have been reported for highly selective directed C-H borylation, however their application is hampered by the need of relatively high reaction temperatures.[4]

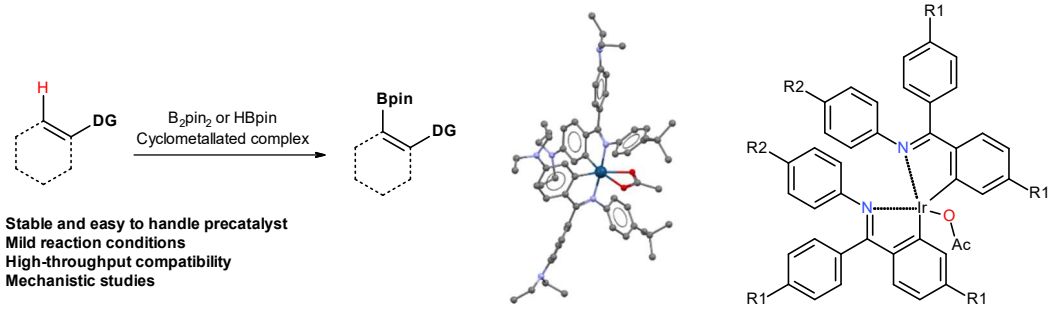

Figure 1. *Ortho*-directed C-H borylation using novel bis-cyclometallated precatalysts.

Here we report the synthesis and application of novel air-stable bis-cyclometallated iridium precatalysts. These precatalysts can be easily prepared from different iridium precursors and display high reactivity in a wide range of organic solvents already at 50 °C temperature. The new complexes exhibit high air stability and directing group selectivity for *ortho* selective C-H borylation of wide range of different molecules including natural products and drug derivatives. Preliminary mechanistic studies suggest the precatalyst first undergoing activation by HBpin and elimination of one of the coordinated imine ligands.

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Surfactant-driven Strategies for Sustainable C–H Activation: Progressing Towards Mild Reaction Conditions

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Considering the development of new reactions and chemical processes, sustainability and minimizing waste generation have become highly significant. With the potential for a ban of several reprotoxic polar aprotic solvents such as DMF and NMP through the REACH regulation, alternatives for such reaction medias are indispensable. In the last decade, micellar conditions in bulk water have emerged as such for several transformation such as cross couplings or amide formations, however only a handful of examples emerged for C–H activations, often under high temperatures.[1]

Our research focuses on the development of mild reaction conditions in water for C–H activations, either through the careful design of additives to commercially available surfactants[2] or through the implementation of novel designer surfactants, able to catalyze C-H activations at ambient temperature.[3] With the installation of ligands at core of our surfactants that have the potential to catalyze the concerted metalation-deprotonation (CMD), we were able to lower the reaction temperature for the ruthenium C–H arylation of ferrocenes from 100°C to 35°C. Remarkable, the simple addition of such ligands to known surfactants provides only moderate performance. Our conditions have shown to tolerate a broad spectrum of functional groups with yields up to 86% and a high chemoselectivity, enabling the late-stage functionalization of active pharmaceutical ingredients and natural products.

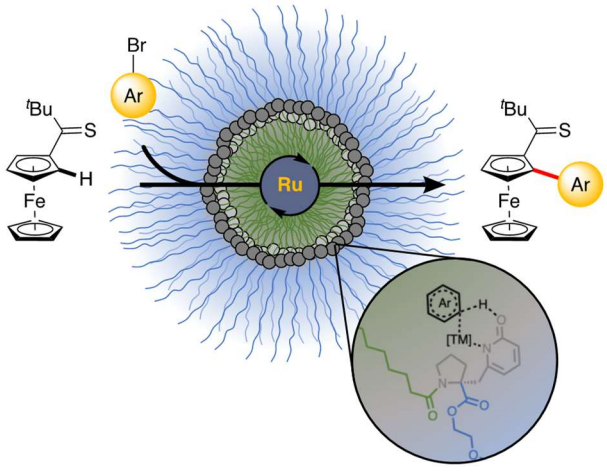

Figure 1. Surfactant enabled C–H under mild reaction conditions.

Acknowledgments: This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No. 860762.

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Deep Look into C-H Arylation of (Poly)Fluorobenzene with 2-Chloropyridine Derivatives: Sustainable Approach and Mechanistic Study

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C-H activation allows the rapid synthesis of a wide range of relevant compounds, for example pharmaceuticals, agrochemicals and functional materials. However, the applicability of this transformation has been limited mainly by the inert nature of the C-H bond. Harsh reaction conditions, long reaction times and high catalyst loading is typically required, making this method very limited to an industrial approach, especially from an economic and environmental point of view. Recently, alternative and more sustainable approaches are developed following the rules of Green Chemistry[1]. Our work focuses on the functionalization of pyridines in C-2 position with fluoroarenes. These motifs are typically used in various fields such as medicinal-, agro- and materials chemistry[2]. The development of a sustainable protocol could be promising for the industrial manufacturing and might lay the basis for alternative synthetic technologies such as flow chemistry or microwave technique[3]. Based on the recent results[4], a protocol with a sustainable approach is highly needed and there is also a lack of exploring the reactivity corresponding to the substituent pattern of the reactants. First, an optimisation has been performed to improve the state-of-the-art method focusing on solvent, catalyst, ligand, temperature and the base resulting in a significant increase in isolated yield up to 85%. Our method benefits from the low amount of catalyst loading, the use of a commercial and cheap ligand and green solvent (Figure 1).

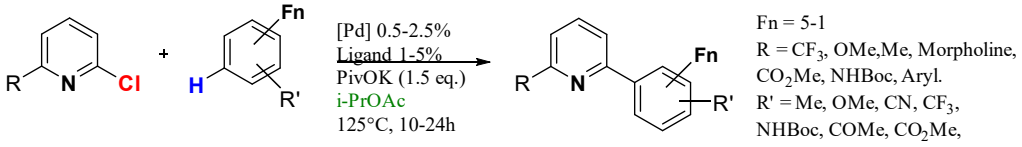

Figure 1. Model reaction under optimized conditions. Palladium and ligand are not indicated for IP rights.

The reaction was then extended and a wide range of substrates (substituted pyridines and fluoroarenes with 3-5 fluorine atoms) were introduced, showing that a substituent in 6-position led a more active and easier substrate to activate (lower loading of catalyst) than without it and tolerating efficiently diverse substituents (e.g. -NHBoc; -CO_2Me; EWD and EDG groups). A DFT computational study of the reaction mechanism will show how the applied conditions influence the transformation. Furthermore, substrates with less than 3 fluorine atoms and post-functionalization of the aromatic fluorines[5] will be explored; showing a wide application of this transformation in different fields of chemistry.

Acknowledgments: This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No. 860762. We would like to express our gratitude to Dr. Peter Fehel for the collaboration and support in the computational study of the reaction.

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Selective C-H Functionalization at C3, C4 and C5 of furfural and HMF

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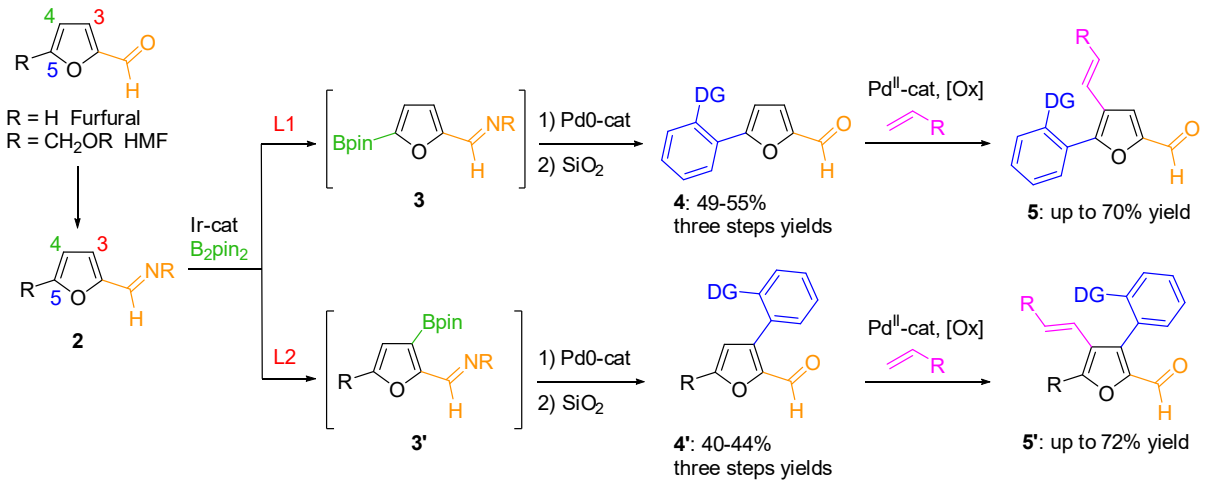
Furfural and 5-hydroxymethylfurfural (HMF) are promising renewable products derived from lignocellulosic biomass, which are raw materials for sustainable production of high value-added chemicals. Their selective functionalization is currently an emerging field and subject of many research efforts.[1] A special quest for stabilizing substituents at C3 and/or C4 positions of furanic platforms is essential to improve chemical and thermal stability of the furanic core. C3–H borylation was only reported on C5-substituted furfural derivatives to overpass the natural selectivity for the C–H bond α to the oxygen atom.[2] We developed a method to achieve a ligand-control selective borylation at C3 or C5 position of non-substituted furfural **1** by transition metal-catalyzed C–H activation exploiting the aldehyde function to install an imine as directing/protecting group. This strategy provide access to borylated reagents (**3** and **3'**) with high versatility that can be used *in situ* as nucleophilic partners in Suzuki-Miyaura cross-coupling reactions affording *ortho* substituted heterobiaryl compounds (**4** and **4'**) after removal of the imine group.

Finally, the installation of a second directing group in *ortho* of the new aryl moiety both in position C5 or C3 open the path for transition-metal-catalyzed C4-H functionalizations, such as Fujiwara-Moritani olefination, with the formation of **5** and **5'** from moderate to good yields. This C3/C4-H functionalization strategy is compatible with the employment of suitably protected HMF as starting material, providing the synthesis of the first example of tetrasubstituted furaldehyde (Scheme 1).



Scheme 1. C5/C4-H or C3/C4-H functionalization of furfural and HMF

Acknowledgments: Biomass 4 Synthtons

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Site-Selective C-H Functionalization of Benzoic Acids Enabled by Non-Covalent Interactions

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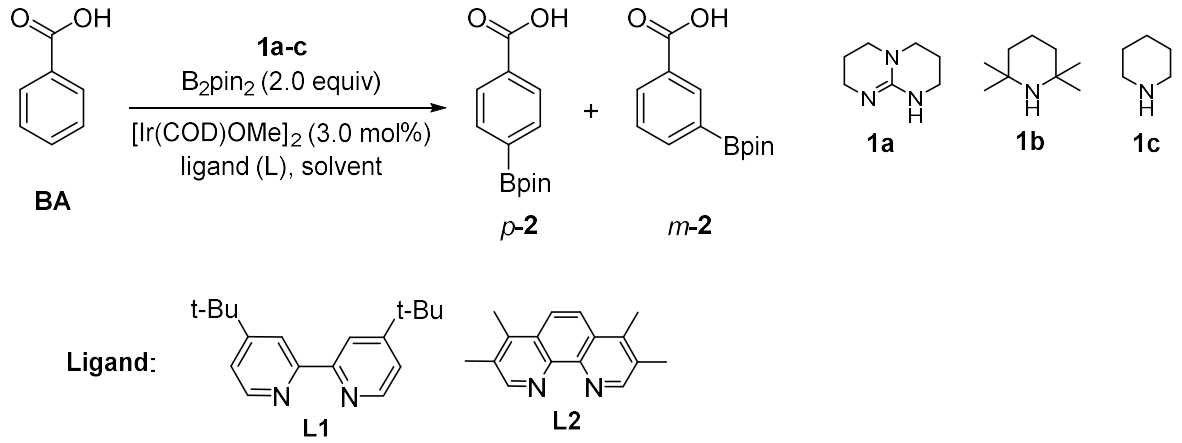
Due to the ubiquity of the carbon-hydrogen bonds (C-H) in organic molecules, their direct functionalization shows promise for streamlining the synthesis of complex scaffolds. However, because of the very high dissociation energy of the C–H bond its direct conversion into C–C or C–heteroatom bond poses a great challenge. Among other transition metal catalyzed C-H transformations the Ir-catalyzed borylation emerged as one of the most exploited reactions due to its mild conditions that allow facile entry into highly valuable synthons.[1] However, despite this transformation has showcased impressive advances there is still an ample potential for further exploration. The regioselectivity issues are perhaps one of the best articulated ones due to the low regiocontrol of the non-directed Ir-catalysis. These issues have been traditionally tackled by the use of covalently bonded directing groups (DG) that allow the positioning of the metal catalyst in a proximity to the desired C-H bond.[2] Though the DG technology is unique in its ability to regioselectively functionalize C-H bonds, these methods are limited by the difficulty to remove such groups after functionalization. Given the aforementioned, herein we report a concept for the para-selective borylation of carboxylic acids that relies on an unreported to date carboxylate-guanidinium noncovalent interaction (Scheme 1). Our strategy is based on the simultaneous non-covalent protecting of the free acid accompanied by steric guidance of the catalyst in a proximity to the *para* position. Up to 80% yield and *para/meta* selectivity of 6:1 have been achieved.



Scheme 1. Ir-catalyzed borylation of benzoic acid in presence of different organic bases.

Acknowledgments: The authors acknowledge the National Scientific Program "VIHREN" (grant КП-06-ДВ-1)

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C-H activation of Unbiased C(sp3)–H Bonds: Gold(I)-Catalyzed Cycloisomerization of 1-Bromoalkynes

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Here, we present a gold(I)-catalyzed C(sp^3)-H functionalization of 1-bromoalkynes without any sort of electronic, or conformational bias.[1,2] Moreover, it doesn't need any directing group.[3] The reaction proceeds regiospecifically and stereospecifically to the corresponding bromocyclopentene derivatives. The latter can be readily modified, comprising an excellent library of diverse 3D scaffolds with very high C(sp^3) fraction (Fsp^3) for medicinal chemistry.[4] In addition, a mechanistic study has shown that the reaction proceeds via a so far unknown mechanism: a concerted [1,5]-H shift / C-C bond formation involving a gold-stabilized vinylcation-like transition state (Figure 1).

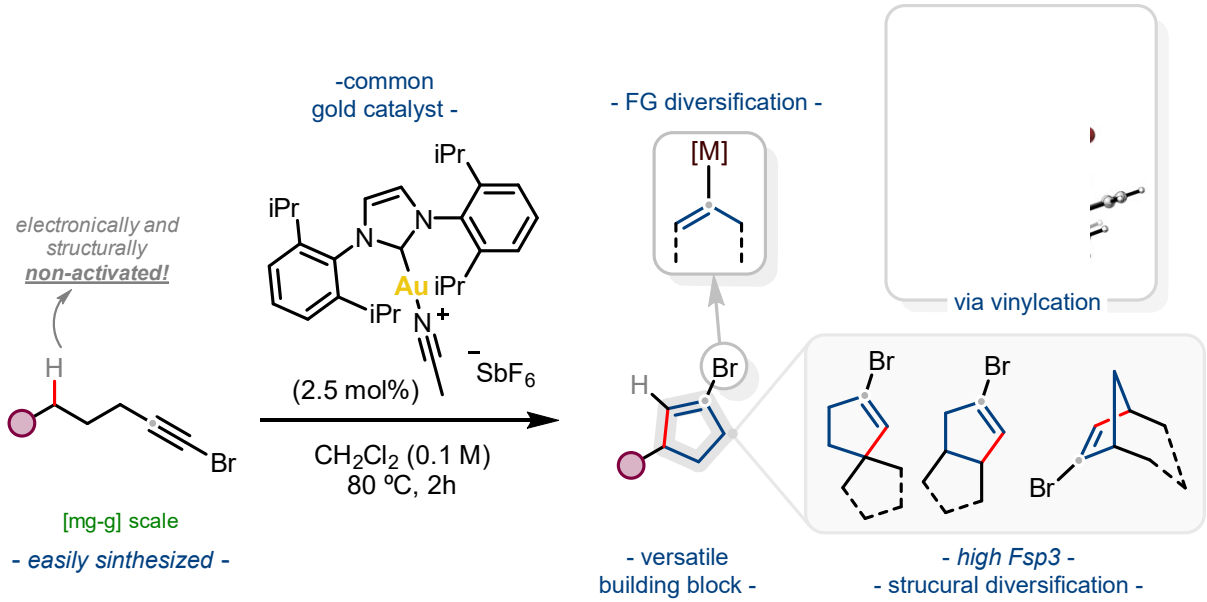

Figure 1. C(sp^3)-H functionalization of 1-bromoalkynes employing a common gold(I) catalyst to form the corresponding bromocyclopentene with a high structural variety via a new transition state vinylcation in gold chemistry.

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Mild Oxidation of Alkanes Catalyzed by Modified Multimetal Layered Double Hydroxides

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Sustainable C-H functionalization is a hot topic encompassing the research areas that span from organic synthesis to organometallic chemistry and catalysis. Although saturated hydrocarbons are widely used as substrates for the synthesis of many chemicals of industrial significance, the involved reactions usually require numerous steps and harsh conditions due to elevated inertness of alkanes. In the context of green chemistry, approaches based on precious metals and/or hazardous solvents and oxidants should be ruled out. Therefore, the search for more sustainable and inexpensive catalytic systems that are capable of activating saturated hydrocarbons under mild conditions represents a challenging objective.[1,2]

Layered Double Hydroxides (LDHs) are 2D compounds with a general structure similar to that of brucite, $Mg(OH)_2$, where some isomorphic substitutions of divalent metal ions by tri- and/or tetra-valent ones take place. A general LDH formula can be written as $[(M_{1-x}M'_x(OH)_2)]^{a+}(X^{n-})_{a/n}\cdot bH_2O$ ($0 < x < 1$), where M and M' are metal cations and A is an anion. Owing to high chemical flexibility, tunable basicity, adsorption capacity, and low-cost, LDHs have been used as catalysts or precursors in many reactions.[3]

Considering the C−H functionalization of alkanes, we propose the use of LDHs as catalytic systems for mild oxidation of alkanes to alcohols and ketones, and in some cases to carboxylic acids. LDHs containing several metal cations have been synthesized by simple methods (coprecipitation at room temperature or hydrothermal) and post-treated with ethanol (Aqueous Miscible Organic Solvent Treatment, AMOST; AMO-LDHs).[4] Hydrogen peroxide has been used as a green oxidant, whereas the main hydrocarbon substrates have been propane and cyclohexane. The tests with ethane and C_5-C_8 cycloalkanes have also been performed. Effects of acid promoter, catalyst amount, and substrate scope on the yield of oxygenates have been assessed.

Characterization of AMO-LDHs by PXRD, FT-IR, TGA, and ICP-OES shows that the compounds are pure (LDH phase) and their formulae can be established. Catalytic tests have revealed a high activity for the samples containing Fe^{3+} or Cu^{2+}. A synergic effect has been observed for the AMO-LDH catalyst combining both iron and copper centers, resulting in total yields of oxygenated products of up to 40% based on alkane substrate, and catalyst turnover numbers (TONs) up to 370. The oxidation of various types of linear (e.g., *n*-heptane) and branched cyclic (adamantane, *cis*- and *trans*-1,2-dimethylcyclohexane) alkanes with H_2O_2 under optimized conditions suggests that the reaction mechanism proceeds via the formation of hydroxyl radicals (through interaction of LDHs with H_2O_2) and alkyl radicals. Catalyst structure – activity correlations, reaction optimization, and effects of different parameters will be showcased.

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Fe(II) and V(III) C-scorpionate Complexes for Homogenous Catalysis in Peroxidative Oxidation of Toluene

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Our aim was to synthesize catalysts based on iron(II) and vanadium(III) featuring C-scorpionate ligands and assess their effectiveness in oxidizing toluene, in alignment with the principles of green chemistry. Benzaldehyde, the primary product of toluene oxidation (Figure 1), holds significant importance as a starting material in the industries of dyes, perfumes, and pharmaceuticals [1].

The iron(II) complexes, namely $[FeCl_2\{HC(pz)_3\}]$ **1** and $Li[FeCl_2\{SO_3C(pz)_3\}]$ **2**, along and the vanadium(III) complex $[VCl_3\{HC(pz)_3\}]$ **3**, were synthesized using established protocols [2]. Comprehensive characterization through Infrared (IR) and Nuclear Magnetic Resonance (NMR) spectroscopies confirmed the identity of all compounds.

We investigated the catalytic potential of **1**-**3** in the peroxidative oxidation of toluene using *tert*-butyl hydroperoxide, employing mild reaction conditions. The study analyzed and discussed various factors, including reaction time, catalyst type and quantity, temperature, and the influence of additives on the process.

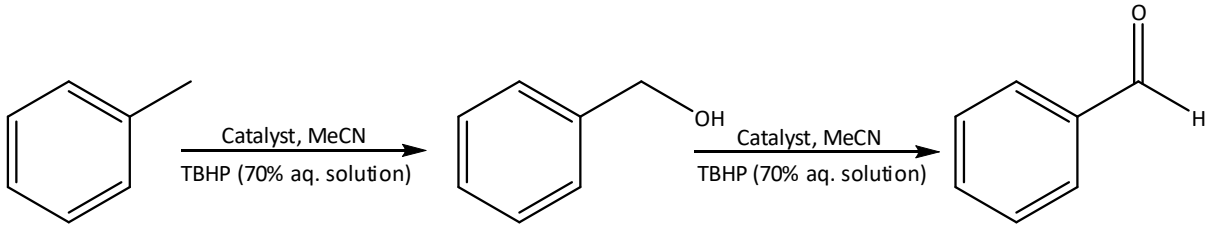

Figure 1. Toluene peroxidative oxidation into benzyl alcohol and benzaldehyde.

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Design of Copper Catalyzed Atropoenantioselective C-N Coupling

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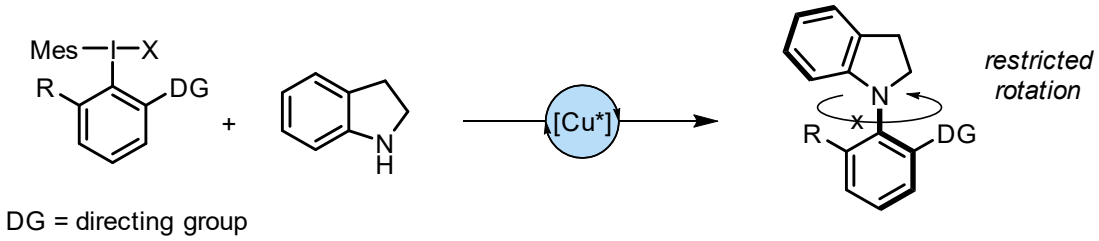
Chirality is an intriguing feature many natural products and numerous bioactive molecules contain stereogenic centers. In particular, C-N axially chiral compounds have been attracting a particular attention of the scientific community as a privileged class of biologically active compounds. Despite this 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 in mild conditions. Thereby, we have recently reported the first example of atroposelective metal catalyzed N-arylation delivering C-N axially chiral compounds.[2,3]

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.



Scheme 1. General scheme for Cu-catalyzed atroposelective coupling

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Biomimetic Ru-catalysed oxidation of C-N and C-O bonds with N_2O or O_2

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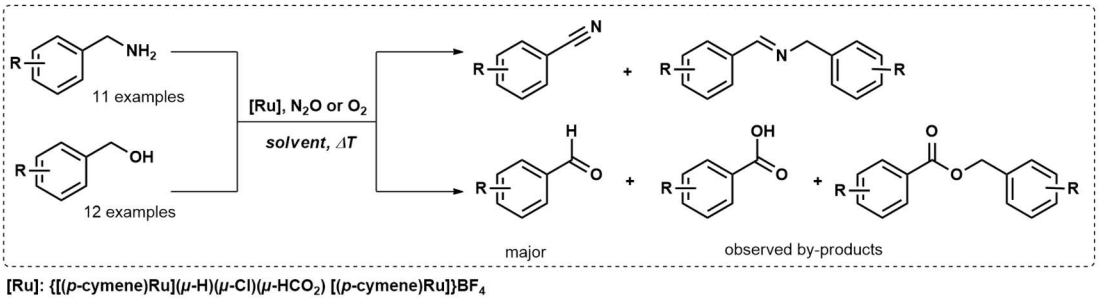
The water-soluble organometallic complex {[(*p*-cymene)Ru](*μ*-H)(*μ*-Cl)(*μ*-HCO_2)[(*p*-cymene)Ru]}BF_4 is known for the evolution of H_2 from aq. formaldehyde acting as biomimetic formaldehyde dehydrogenase.[1-3] In addition, it catalyses i. e. transfer-hydrogenation reactions[4] and deamination of nitriles.[5] Now, we report on the ability to mimic nitrous oxide reductase (N_2OR) and alcohol oxidase.[6-8] This study explores the oxidation of benzylamines to yield benzonitriles and the conversion of benzyl alcohols into benzaldehydes while nitrous oxide simultaneously decompose in presence of hydrogen donating molecules like amines and alcohols (Scheme 1). The selectivities can be controlled by solvents, oxidants and temperature while in general temperatures below 100°C are sufficient to obtain yields and selectivities upto >99% with low catalyst loadings, tolerating various functional groups; the observed by-products are i. e. imines, respectively benzoic acid or benzyl benzoates. Albeit oxygen is known as potent oxidant, the observation that the catalyst can both oxidise alcohols or amines and simultaneously decompose the greenhouse gas nitrous oxide is very interesting. These reactions with an air stable and robust catalyst are easy to carry out and affordable, making them highly practical.

Both benzonitriles and benzaldehydes find diverse applications across various industries. Benzonitriles serve as key components in pesticides, precursors for benzoguanamine resins, and play a crucial role in the synthesis of fluvoxamine, an essential antidepressant.[9] On the other hand, benzaldehyde, known for its characteristic bitter almond odor and taste, serves as a versatile flavoring agent. Additionally, it is widely employed as a denaturant and fragrance in the cosmetic industry.[10] In our ongoing studies, beyond the activation of C-H bonds, we explore the decomposition of the greenhouse gas N_2O, wherein the ruthenium dimer acts as a nitrous oxide reductase (N_2OR).



Scheme 1. Biomimetic oxidation of benzylamines and benzyl alcohols.

Acknowledgments: The authors acknowledge the Fundação para Ciência e Tecnologia (FCT, EXPL/QUI-QOR/1079/2021; 2022.02069.PTDC, UIDB/00100/2020, LA/P/0056/2020), the Deutsche Forschungsgemeinschaft (DFG 411475421) and the Instituto Politécnico de Lisboa (IPL/2023/SMARTCAT_ISEL).

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Enhancing Fluorescence via Cyclopalladation: Synthesis of Organometallic 4-Aryliden-5(4H)-Oxazolones

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In recent decades, luminescent organic and organometallic compounds have gained significant attention, particularly for their potential use in organic light-emitting devices (OLEDs).[1] However, luminescent palladacycles have been found to be an exception, as palladation of luminescent ligands often results in a significant decrease in luminescence, unlike iridium and platinum complexes. [2]

In this study, we demonstrate how cyclopalladation can enhance the fluorescent properties of 4-Aryliden-5(4H)-oxazolones by suppressing the hula-twist non-radiative deactivation pathway, as shown in Figure 1 left. This results in fluorescent quantum yields (f) of up to 28% in solution, which is an excellent value for a palladium complex. Additionally, we investigate how the electronic characteristics and position of substituents in the arylidene ring affect the photophysical properties using TD/DFT. Lastly, we employed the automated machine learning workflows of the ROBERT program (Figure 1 right) to discover new luminescent Pd complexes with a modest dataset of 23 points.[3] This digitalized approach enabled us to discover three new luminescent emitters with good QYs from a pool of over 15 potential candidates while conducting a minimal number of experiments.

Overall, our research suggests that cyclopalladation can effectively enhance the luminescent properties of certain compounds and the integration of the ROBERT program allows for the prediction of new candidates, streamlining the process and conserving both time and resources.

ROBERT
AUTOMATED ML PROTOCOLS

Figure 1. Fluorescence amplification by suppression of "hula twist" and ROBERT program.

Acknowledgments: We thank the Spanish Government (Grants PID2019-106394GB-I00, IJC2020-044217-I and PID2022-140159NA-I00, funded by MCIN/AEI/10.13039/ 501100011033) and Gobierno de Aragón-FSE (Spain, groups Química Inorgánica y de los Compuestos Organometálicos E17_23R and Química de Oro y Plata E07_23R) for funding. D.D. thanks Gobierno de Aragón-FSE for a PhD fellowship.

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Self-Assembly of Coordination Polymers and Tetracopper(II) Cores: New Catalysts for Oxidative Functionalization of Saturated Hydrocarbons

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The present study describes a time-dependent self-assembly generation of new copper(II) coordination compounds from an aqueous-medium reaction mixture composed by copper(II) nitrate, H_3bes biobuffer (*N*,*N*-bis(2-hydroxyethyl)-2-aminoethanesulfonic acid), ammonium hydroxide and benzenecarboxylic acid, namely 4-methoxybenzoic (Hfmba) or 4-chlorobenzoic (Hfcba) acid. Two products were isolated from each reaction, namely 1D coordination polymers $[Cu_3(\mu_3\text{-}OH)_2(\mu\text{-fmba})_2(fmba)_2(H_2O)_2]_n$ (**1**) or $[Cu_2(\mu\text{-}OH)_2(\mu\text{-fcba})_2]_n$ (**2**) and discrete tetracopper(II) rings $[Cu_4(\mu\text{-Hbes})_3(\mu\text{-}H_2bes)(\mu\text{-fmba})]\cdot 2H_2O$ (**3**) or $[Cu_4(\mu\text{-Hbes})_3(\mu\text{-}H_2bes)(\mu\text{-fcba})]\cdot 4H_2O$ (**4**), respectively. The compounds were obtained as microcrystalline air-stable solids and characterized by standard methods, including the single-crystal X-ray diffraction.[1] The structures of **1** and **2** feature distinct types of metal-organic chains driven by the μ_3- or μ-OH^- ligands along with the μ-benzenecarboxylate linkers. The structures of **3** and **4** disclose the chair-like Cu_4 rings assembled from four μ-bridging and chelating aminoalcoholate ligands along with μ-benzenecarboxylate moieties.

Catalytic activity of **1**–**4** was investigated in two model reactions, namely (a) the mild oxidation of saturated hydrocarbons with hydrogen peroxide to form alcohols and ketones, and (b) the mild carboxylation of alkanes with carbon monoxide, water and peroxodisulfate to generate carboxylic acids. Effects of different parameters were investigated, including the effect of acid co-catalyst and various selectivity parameters. Apart from notable catalytic activity, this study showcases a novel time-dependent synthetic strategy for the self-assembly of two different Cu(II) compounds from the same reaction mixture.

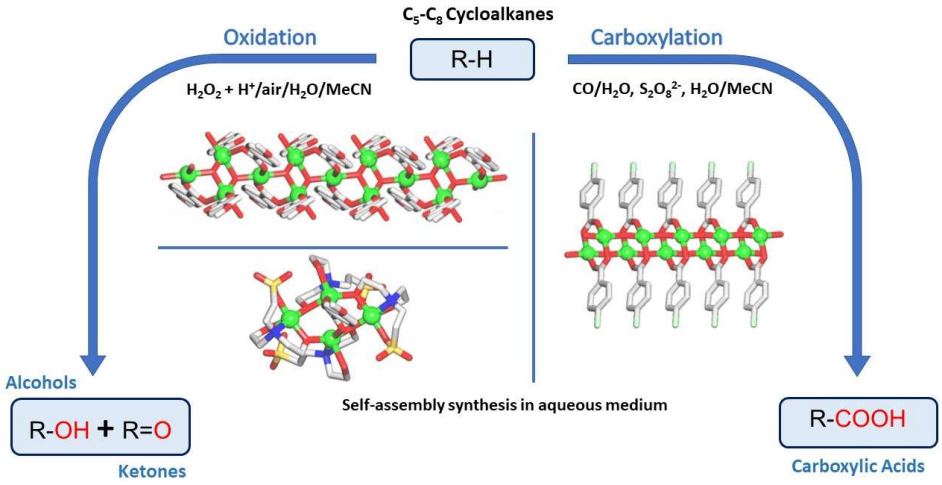

Figure 1. Model Cu-catalyzed oxidation and carboxylation of saturated hydrocarbons.

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Functionalization of Natural Bisquinolizidine Alkaloids

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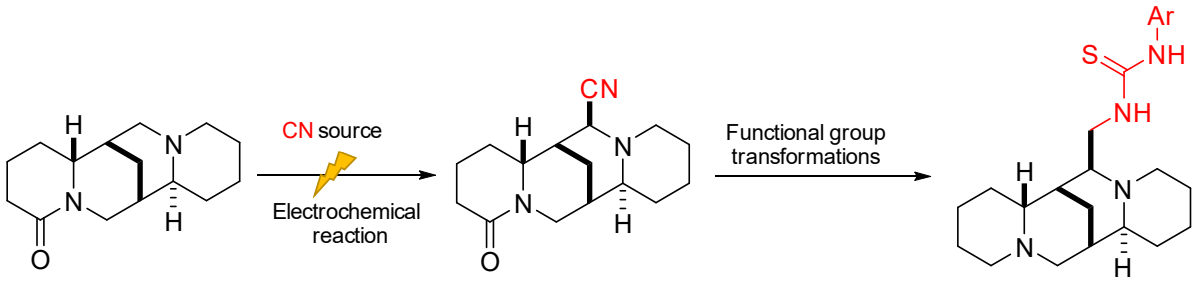
Bisquinolizidine alkaloids (BQAs) are found in several plants of the subfamily Faboideae. Structurally, they contain a chiral bispidine core decorated with fused N-annulated piperidinone or piperidine moieties.[1] BQAs possess a variety of biological activities including oxytoxic, cytotoxic, antipyretic, antiviral, antibacterial and antiarrhythmic properties.[2] An important member of the group is sparteine, which is commonly used as a chiral ligand for various metals in asymmetric synthesis.[3] However, the limited reactive functional groups on sparteine and other BQAs pose a functionalization challenge. Thus, limiting their use in asymmetric catalysis.

Taking advantage of the recent advances in electrochemical organic synthesis, a site selective electrochemical C-H activation of *rac*-lupanine (2-oxo-sparteine) was explored in both batch and flow conditions to afford 17-*rac*-cyanolupanine in moderate yield under mild reaction conditions. The cyanation product was obtained via an in-situ generated iminium intermediate, which was trapped by cyanide in a typical Shono-type oxidation.[4] Subsequent functional group transformations of 17-*rac*-cyanolupanine afforded H-bonding thioureas as value added products (Scheme 1).



Scheme 1. Electrochemical functionalization of *rac*-Lupanine.

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Synthesis of Chiral Ligands and Their Application in Asymmetric C-H Activation

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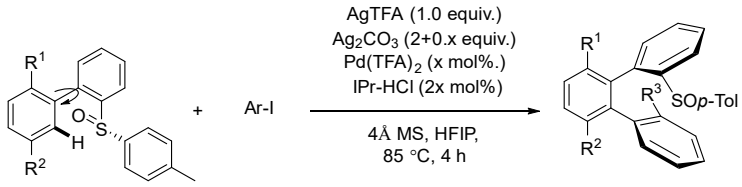
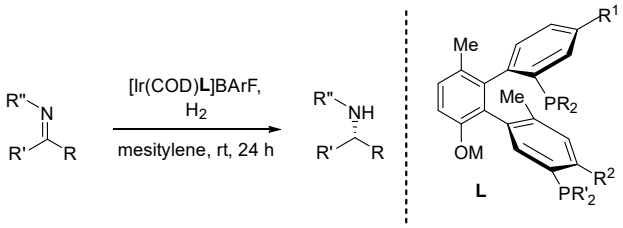
Axial chiral biaryls are key components of some bioactive small molecules, natural products, drugs and advanced materials, which have also been extensively utilized in the field of asymmetric catalysis. In 2018, Wencel-Delord and Colobert. developed a general, step-economic, and unique atroposelective C-H arylation (Scheme 1) delivering unprecedented tetraphenyl scaffolds with two atropoisomeric Ar-Ar axes, and these terphenyls exhibit important structural diversity. In 2023, Wencel-Delord and Colobert reported the synthesis of enantiopure dissymmetrical diphosphines, BiaxPhos ligands and their application in asymmetric hydrogenation of imines (Scheme 2).

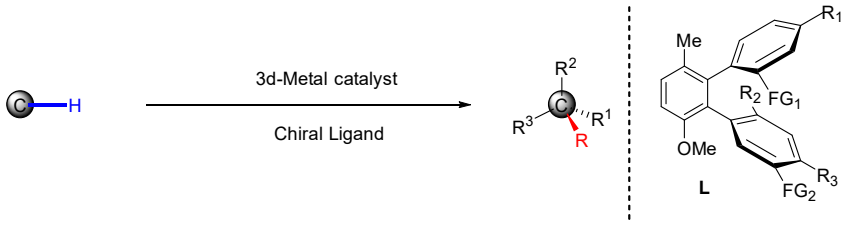


Scheme 1. Atroposelective sp^2 C-H activation



Scheme 2. Asymmetric hydrogenation of imines catalyzed by dissymmetrically substituted diphosphines.

The aim of our research project is to expand the field of axially chiral tetraphenyl-based ligands, and then evaluate their catalytic activity in asymmetric C-H activation catalyzed by 3d-metal.



Scheme 3. Asymmetric C-H activation catalyzed by 3d metal using axially chiral ligands.

Acknowledgments: We thank the CNRS (Center National de la Recherche Scientifique) and the Ministère de l'éducation Nationale et de la Recherche (France) for financial support. We acknowledge the European Commission for the ERC Starting Grant AlCHIMIE (grant 949804).

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Amide-Functionalized Cu(II) Coordination Polymer: An Efficient Catalyst for the Effective Conversion of Toxic Volatile Organic Compounds

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Three novel coordination polymers (CPs), namely $[Cu(\mu\text{-}1\kappa O,2\kappa N\text{-}L)_2]_n$ (**1**), $[Zn(\mu\text{-}1\kappa O,2\kappa N\text{-}L)_2(H_2O)_2]_n$ (**2**) and $[Cd(\mu\text{-}1\kappa OO',2\kappa N\text{-}L)_2]_n$ (**3**) were synthesized using the 4-(pyrimidin-5-ylcarbamoyl)benzoic acid. The catalytic performances of these CPs were explored in the peroxidative oxidation of Volatile Organic Compounds (VOCs), with toluene and *p*-xylene as model substrates and *tert*-butyl hydroperoxide (*t*-BuOOH) as the oxidant (Figure 1). Notably, **1** exhibited superior catalytic activity in toluene oxidation in water, resulting in a significant 36% total yield. In *p*-xylene oxidation, under diverse conditions, **1** demonstrated maximum efficiency with a remarkable 80% total yield. The research highlights the potential applications of these coordination polymers in developing eco-friendly and efficient catalytic systems for the oxidation of aromatic substrates, emphasizing the copper Cp (**1**) as a promising, environmentally friendly catalyst.

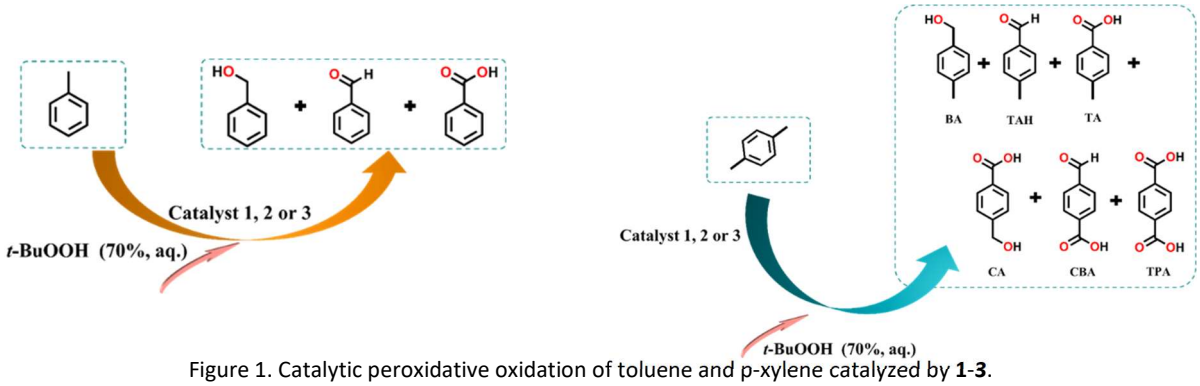

Figure 1. Catalytic peroxidative oxidation of toluene and p-xylene catalyzed by **1**-**3**.

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Functionalization and Biological Evaluation of New Abietane Diterpenoids

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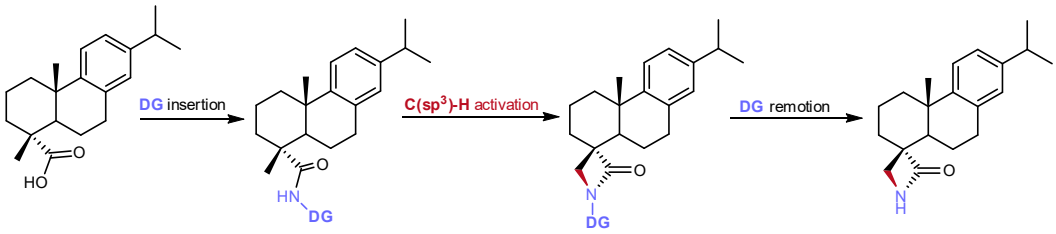
The antibiotic resistance crisis has become a major global problem with the emergence of multidrug-resistant bacteria. To overcome this situation, a faster development of new antibiotics is urgent.[1] Natural products and their derivatives hold an important position as potential medicines. Abietane diterpenoid derivatives are natural products isolated from pine oleoresins.[2] Several members of this family of molecules show interesting biological activities, such as antiviral, antitumor, wound healing, antiulcer, gastroprotective, anxiolytic and antibacterial properties.[2] β-lactam is one of the most relevant classes of antibiotics worldwide.[1] An appealing methodology to obtain β-lactams are through palladium catalyzed C(sp^3)–H bond activation.[3] In the present work, a diverse scope of β-lactam derivatives from dehydroabietic acid were obtained via activation of the C(sp^3)–H bond (Scheme 1). The synthetic methodology envisages the insertion of an amide as directing group, followed by the β-lactam formation. To obtain the free β-lactam, a protocol using ceric ammonium nitrate (CAN) to remove the directing-group was applied. Moreover, the biological activity of new synthesized compounds was tested against different Gram-negative and Gram-positive bacteria strains.



Scheme 1. Synthetic approach to prepare β-lactams from dehydroabietic acid.

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An Electrochemical Oxidation Prins-type Cyclisation Sequence for the Construction of Oxazinones via *N*-Acyliminium Ions

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Nitrogen-containing heterocycles represent one of the privileged structural motifs in synthetic pharmaceuticals and are also widely found in naturally occurring compounds.[1] Among various synthetic strategies for the functionalization of nitrogen-containing compounds, the electrochemical oxidation (also known as Shono oxidation[2,3]) has gained increasing popularity as a powerful and green strategy to selectively and efficiently oxidise a C-H bond in the *α* position to the nitrogen atom.

In this project (Figure 1), we perform the electrochemical oxidation using an ElectraSyn device, and then use a Prins-type cyclisation to construct the oxazinone skeleton **4** from a variety of cyclic and acyclic *N*-Boc compounds **1**. Both transformations proceeded via a reactive *N*-acyliminium ion **5**, which can be readily trapped by a variety of nucleophiles. For example, allylsilane **3**, reacts to provide the β-silyl carbocation **6**. The intramolecular interception[4] of the β-silyl carbocation and the oxygen atom of the Boc group then produces the final products **4**. The scope of the sequence to date and its stereochemical outcome will be described, which includes the substituents (R), ring size and acyclic examples. Also included will be the optimisation of the Prins-type cyclisation to form **4**.

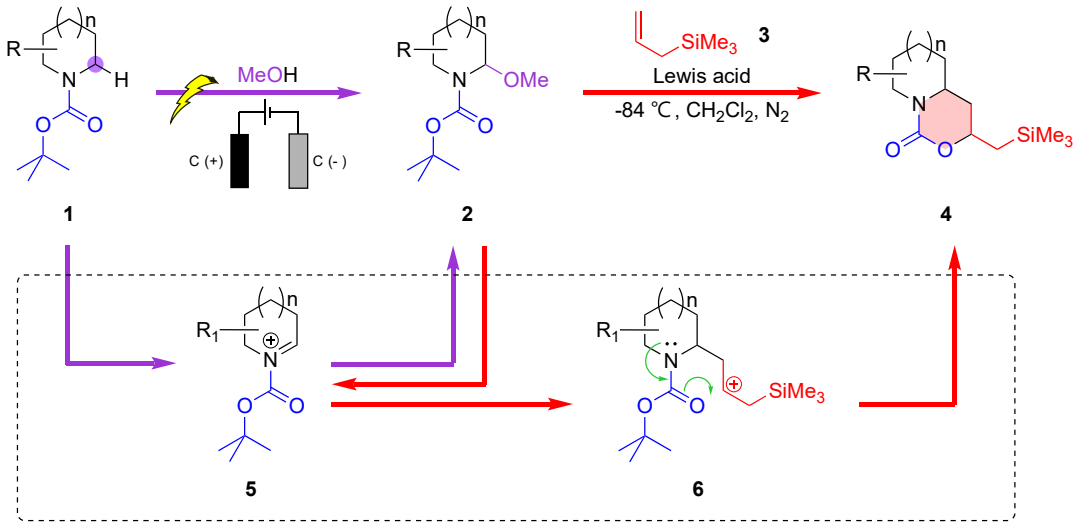

Figure 1. An Electrochemical Oxidation Prins-type Cyclisation Sequence

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Copper(II) and Gold(III) C-scorpionate Complexes as Catalysts for the Selective Oxidation of Toluene

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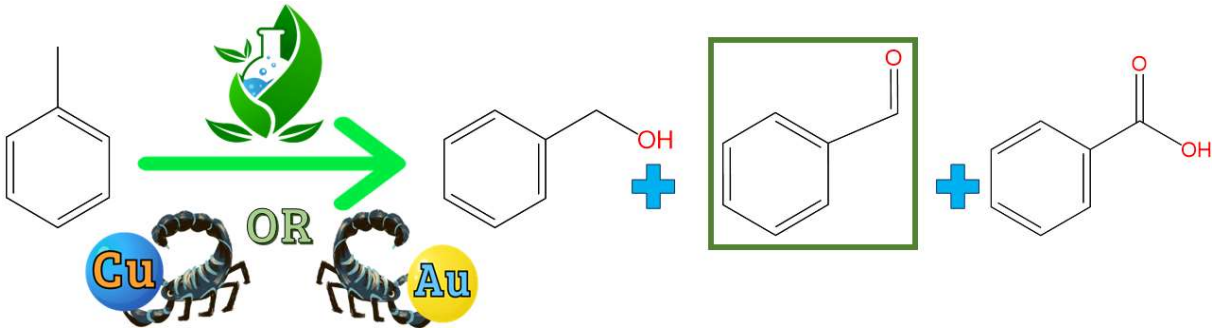
In this study, we assessed the catalytic activity of copper(II) and gold(III) complexes bearing the C-scorpionate ligand, hydrotris(pyrazolyl)methane ($HCpz_3$) [1–4], in the peroxidative oxidation of toluene following the principles of green chemistry. One of the primary and crucial of this reaction is benzaldehyde, holding major importance for the perfume, pharmaceutical, and dye industries.[5]

The catalytic activity of the copper complexes $[\{Cu(CH_3COO)_2\}_3(HCpz_3)_2]\bullet H_2O$ (**1**) $[CuSO_4(HCpz_3)]\bullet 5H_2O$ (**2**) $[Cu(HCpz_3)_2](NO_3)_2$ (**3**) $[CuCl_2(HCpz_3)]\bullet 2H_2O$ (**4**) and the gold complex $[AuCl_2(HCpz_3)]Cl$ (**5**) have been tested (with *tert*-butyl hydroperoxide or hydrogen peroxide) under mild conditions (temperature below 80 °C, green oxidant, solvent-free or green solvents). The influence of various parameters, such as reaction time, amount of catalyst, temperature, presence of additives, and different energy inputs was evaluated and discussed.

Subsequently, copper(II) complexes were supported over HZMS-5 and HZMS-5AB (the latter treated with an acid/base) using two distinct impregnation methods (wet and wetness). The catalytic performance of the supported catalysts was tested under optimized conditions.



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Unexpected Formation of Asymmetric [C,N,N'] Tridentate Iminopyrrolyl Alkyl-Ni(II) Complexes via Intramolecular C-H Activation

Cláudia A. Figueira,[1] Patrícia S. Lopes,[1] Clara S. B. Gomes,[1,2] Joselaine C. S. Gomes,[1] Ricardo Meyreles,[1] Luís F. Veiros,[1] Pedro T. Gomes[1]

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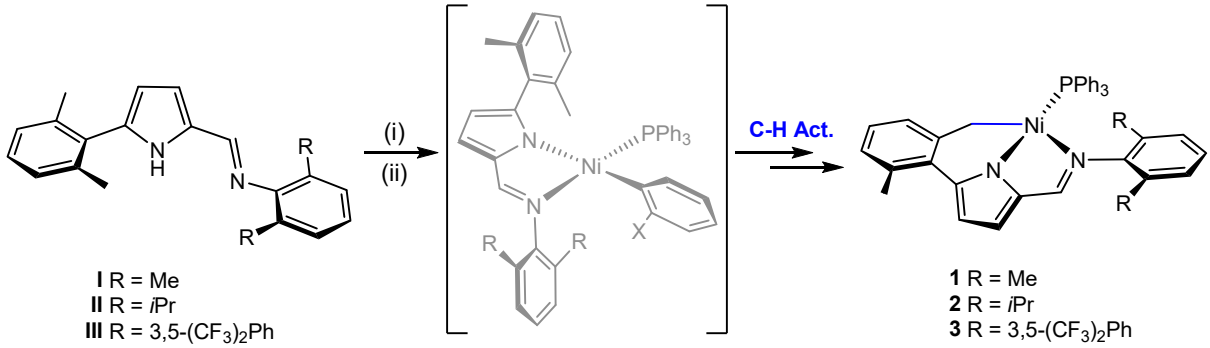
While developing a family of bidentate aryl-nickel(II) phosphine complexes with different 5-aryl-2-(N-aryl)formiminopyrrolyl ligand precursors,[1,2] we found that in some specific cases, instead of the expected bidentate species, the final products were new asymmetric [*CNN'*] tridentate complexes (Scheme 1). When ligand precursors of the type 5-(2,6-$Me_2(C_6H_3)$)-2-(N-2,6-$R(C_6H_3)$)formiminopyrrole (R = Me, *i*Pr, 3,5-(CF_3)Ph) were used, containing *ortho*-methyl substituents on the 5-substituted ring, after the ligand coordination to the nickel center, a subsequent intramolecular C-H activation reaction occurred between one of the referred *ortho*-methyl groups and the metal center, with the formation of a new Ni-C bond, originating a new metallacycle. This C-H activation reaction was then fully explored by NMR spectroscopy and the mechanism analyzed by DFT calculations. To the best of our knowledge, although already reported, intramolecular C-H activation reactions involving the formation of tridentate [*CNN'*] (or similar) ligands in late transition metal complexes, analogous to the present case, were scarcely found in the literature.[3,4]



Scheme 1. Formation of the tridentate [*CNN'*] Ni complexes *via* intramolecular C-H activation: (i) NaH, THF, - H_2; (ii) *trans*-[Ni(*o*-C_6H_4X)$(PPh_3)_2Cl$] (X = H, Cl), toluene, - NaCl, - PPh_3, - C_6H_5X.

The new tridentate compounds were then systematically synthesized, fully characterized, and tested as aluminum-free catalysts for the polymerization of ethylene. Remarkably, the tridentate catalyst systems displayed considerably higher catalytic activities in the polymerization of ethylene than those obtained with the iminopyrrolyl aryl-nickel(II) bidentate catalysts. The polyethylene products obtained were dense viscous oils, with molecular weights of 3000–20000 g/mol, and overall high branching values in the range of 90-130 branches/1000C atoms, consistent with hyperbranched microstructures.

Acknowledgments: The authors want to acknowledge Fundação para a Ciência e Tecnologia (FCT) to finance the Research Unit CQE (projects UIDB/00100/2020 and UIDP/00100/2020), the Associate Laboratory IMS (project LA/P/0056/2020) and the Research Unit and Associate Laboratory LAQV (projects UIDB/50006/2020, UIDP/50006/2020 and LA/P/0008/2020).

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Copper Corrole Derivatives as Bioinspired Catalysts in Mild Oxidative Functionalization of Alkanes

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The development of new bioinspired catalytic systems that are efficient in the mild oxidative transformation of alkanes remains an attractive research direction in the area of homogeneous catalysis.[1] In the current study, copper corrole complexes are synthesized, fully characterized, and evaluated as catalysts in the oxidative transformation of cycloalkanes under mild conditions. The new copper complexes of 5,10,15-*tris*(pentafluorophenyl)corrole bearing one hydroxyethoxy unit are obtained from the controlled nucleophilic substitution of one *para* fluorine atom with ethylene glycol. The model catalytic processes that are studied include: (i) the oxidation of cycloalkanes with H_2O_2 into a mixture of cyclic ketones and alcohols, and (ii) the carboxylation of cycloalkanes in a $CO/S_2O_8^{2-}/H_2O$ system to generate cycloalkane carboxylic acids as main products. Both model reactions occur under mild conditions (50−60 °C). The selectivity features, substrate and oxidant scope, and the effects of various reaction parameters are evaluated.

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H/D Exchange in a Ruthenium Complex Supported by a P,N Ligand

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[Ru(PH^{t}Bu$_2$)(P^{t}Bu$_2$Py)(H)(Cl)], **1**, was unexpectedly formed when 2-(di-*tert*-butylphosphaneyl)pyridine,[1] **L1**, was mixed with [{Ru(COD)Cl$_2$}$_x$], in the presence of NEt$_3$ and H$_2$, by an unprecedent cleavage of a P-C bond and concomitant formation of new P-H and C-H bonds[2] (Fig. 1).

While investigating the mechanism of this reaction, we studied by ^{31}P{^{1}H} and ^{2}H NMR the reaction of complex **1** with D$_2$ in the presence of a base (Scheme 1). NMR data is consistent with the presence of a Ru-D bond as well as a P-D bond and the deuteration of the pyridyl fragment (**1-D**). Efforts are underway to understand this reaction.

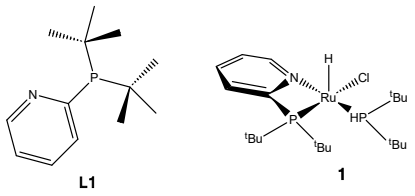
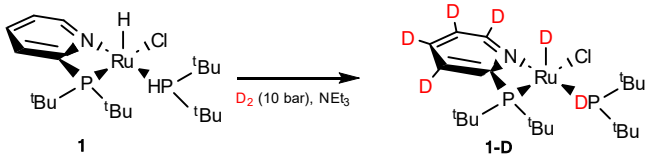


Figure 1. Ligand **L1** and Complex **1**



Scheme 1. Deuteration of complex **1**

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Novel Nucleoside Analogs Containing D-Glucopyranuronamide Units Endowed with Antiproliferative Effects in Cancer Cells

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The development of molecules containing D-glucuronamide moieties is a promising approach in the search for new carbohydrate-based bioactive compounds, given the variety of biological activities reported for both natural or synthetic derivatives containing this glycosyl unit, including antimicrobial or anticancer effects.[1]

The synthesis of glucuronamide derivatives also enables structural variations in a *gluco*-configured template, which is an important aspect for bioactivity tuning, namely at C-6, through N-substitution with various kinds of moieties, and at C-1, using typical methodologies for anomeric functionalization.

In the context of our ongoing interest in the search for new synthetic bioactive D-glucuronamide-containing compounds, and encouraged by our previous findings showing the anticancer profile of *N*-dodecyl glucuronamide-based nucleosides,[2,3] in this communication we disclose the synthesis of novel D-glucopyranuronamide-derived nucleosides comprising *N*-propargyl or *N*-dodecyl substituents and an anomerically-*N*-linked nitrogeneous heteroaromatic system, namely a purine, uracil or a 1,2,3-triazole moiety (Figure 1). The synthesized molecules include [*N*-(glucuronamidyl)triazolyl]methyl phosphonates, glucuronamide-based (purinyl)methyl triazole nucleosides or related purine or uracil nucleosides. D-Glucofuranuronolactone was used as precursor in the synthetic pathways which included key steps as amidation, furanose to pyranose isomerization, anomeric azidation, azide-alkyne 1,3-dipolar cycloaddition, Arbuzov reaction or nucleobase N-glycosylation.

Biological evaluation revealed the significant antiproliferative activities of some nucleosides in breast cancer and leukemia cell lines, turning them promising “hits” for further studies.

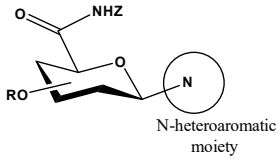

Figure 1 - General structures of the synthesized nucleosides

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