FLow chemistry for Isotopic eXchange

Project funding from the EU's Horizon 2020 Program

NEWSLETTER

FLIX Newsletter °2 - May 2022

We are delighted to present the second newsletter of the EU funded project - FLIX. In this issue of the newsletter, we want to present you what we managed to achieve in the last year, what arrangements were made during the 2nd GA and we would like to present our students who work intensively with us and implement the assumptions of the project.

1. THE TWO YEARS OF THE PROJECT ARE BEHIND US

Sophie Feuillastre, Project Coordinator

Christophe Dugave, Deputy Coordinator

How the consortium perceives the last year of work in the project

During the past year, the FLIX project has made significant progresses and partially made up for lost time related to the successive Covid lockdowns in 2020 and 2021. However, differences have been noticed between countries and therefore partners, some of them were forced to completely stop their activities while others continued to work in labs, complicating both the efficacious collaboration and the project coordination. Unexpected changes in management and communication teams also occurred but had fortunately a limited impact on the project follow-up.

The first on-site FLIX meeting originally scheduled in Germany (LIKAT) was finally done by teleconference on December 14th, 2021. Although it allowed the consortium members to discuss about project advances, problems they had to face, possible solutions, future prospects and new objectives, the short webinar revealed to be less stimulating than a face-to-face meeting that facilitates interactions and information exchanges. The FLIX consortium is now expected to gather in Aarhus (Denmark) on September 21 and 22 for a more classical on-site assembly hoping that there will be no limitation for travel and meetings.

What has been achieved

The ultimate outcome of the project is to devise and build a modular and adaptable flow chemistry system for the straightforward and combinable isotopic labelling of complex chemicals and biologics. The 'FLIX machinery' will use a combination of specialized reactor modules operating under continuous flow conditions for the online $^{1}H/^{2}H$, $^{12}C/^{13}C$, $^{14}N/^{15}N$ and methoxy group direct isotope exchanges with an unprecedented efficacy and without any chemical alteration of the molecules.

Although the Covid lockdown delayed FLIX activities, major advances have been achieved for the development of new specific and selective catalysts for the $^{1}H/^{2}H$ and $^{12}C/^{13}C$ exchange reactions applicable on a large variety of compounds. According to the project's spirit, most transformations are carried out on end-use molecules and, when not possible, during the very late stages of molecule synthesis. To date, our efforts were focused on the hydrogen/deuterium ($^{1}H/^{2}H$) exchange and the [$^{12}C/^{13}C$]carbonyl and nitrile exchange through either direct or indirect substitution. In this way, a portfolio of new catalysts and new chemical reactions usable in flow chemistry was developed and is now tested on more complex (multifunctional) molecules.

Presently, the project completion status is estimated to be around 50%.

Key results, milestones and challenges

WP2 (FLIX-CAT: Development and screening of novel catalysts for isotopic exchange)

New heterogeneous, homogeneous catalysts and metallic nanoparticles have been developed by partners. For instance, new iron and manganese catalysts supported on organic polymers were developed by the LIKAT team and allowed HIE on a broad diversity of anilines, phenols and heteroarenes. They have also developed new homogeneous catalytic systems for the labelling of benzyl aldehydes and ketones. The INSA team developed new bimetallic nanoparticles and new heterogeneous catalysts that considerably improve the labelling efficiency of amino acids with deuterium (^{2}H). The CEA team described a new method enabling the efficacious labelling of N-heterocycles, alkylkamines, benzylic scaffolds and pharmaceuticals based on the in situ formation of Rhodium nanoparticles (RhNps).

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The AU Team devised a new strategy for the synthesis of a variety of [13C] labeled esters from the corresponding iodide derivatives using a Nickel pincer and [13C]carbon monoxide and was applied to many examples. They have also developed new hydroformylation strategies towards multi-carbon isotope labelling of pharmaceutical compounds.

In all labs, the optimization of experimental conditions was carried out in parallel for the adaptation of methods to the real conditions for the translation to flow chemistry.

The development and exploitation of new isotopic sources, which could be more secure and easier to use especially at a preparative scale, have also been studied.

WP3 (FLIX-BOX: Continuous Labeling Machine)

The use of flow reactor modules has started to prove its potency compared to batch operations thanks to the work performed by CEA, University of Amsterdam and Cominnex teams, first and encouraging results have been obtained for the $^{1}H/^{2}H$ and $^{12}C/^{13}C$ exchange reactions of Csp2-H and Csp3-H bonds.

WP4 (Proof of concept and applications)

Model compounds of biological interest were labeled with ^{2}H and ^{13}C using flow chemistry demonstrating the potential of FLIX for isotope exchange in terms of efficiency, specificity and selectivity.

Plans for the next year

The research of new catalysts by our consortium has led to the devise of new strategies and the development of new tools for the specific and selective introduction of deuterium and carbon-13 either in end-use molecules or in the late-stage of their synthesis, thus demonstrating that this approach is by far more efficacious in terms of time, costs and consumption of chemicals (and therefore less polluting). During the next year of the project implementation, a particular effort will be done for the design of nitrogen and methoxy groups exchanges, challenging goals which have been poorly studied to date.

However, FLIX has a sufficient portfolio of catalysts and reactions for isotope exchange and has now reached the stage of applications to more complex molecules displaying biological activities in order to validate the main FLIX concept.

On the other hand, adaptation of catalysts to the particular needs of flow chemistry and requirements specifications of FLIX-CAT modules and FLIX-MACHINE is also currently a great concern to us.

The development of the FLIX-MACHINE is also undergoing but has been strongly impacted by the sanitary crisis. A major effort will be done in order to catch up with the schedule.

2. Second General Assembly

Due to the Covid-19 pandemic-related restrictions and obligation to keep sanitary distancing, the FLIX second General Assembly was done by videoconference using Microsoft Teams on 14th December. It gathered all FLIX partners from their respective countries during half a day, in order to exchange about the progress in scientific and technical aspects, but also to present the work done in management and communication.

All partners reminded their objectives, briefly summarized previous results and exposed their main outcomes from the second period. A particular attention was attributed to Work Packages 2 (FLIX-CAT: Development and screening of novel catalysts for isotopic exchange), 3 (FLIX-BOX: Continuous labelling machine) and 4 (Proof of concept and applications).

The overall project output exposed during this meeting showed that the FLIX project was running in accordance with the research plan in an excellent cooperative spirit. Finally, the originality and quality of results was also underlined by the Advisory Board.

3. Students in the FLIX project

FLIX project involves 7 partners from academia and industry who gather their complementary expertise in this unique project. The FLIX project is also young recruiters who joined the project and carry out tasks together with the project partners. In this newsletter, we would like to introduce them.

Kevin Tatoueix

I am a second year PhD student at the CEA of Paris-Saclay. I graduated in chemistry from the INP-ENSIACET engineering school in Toulouse (France) in 2020. I also hold a master degree in organic chemistry from the Sorbonne University in Paris.

During my work at the CEA, I developed interest in isotope labelling especially in flow conditions. What I find exciting in flow chemistry is that it involves both my chemistry and engineering skills I earned from my education.

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I believe that flow chemistry could bring the Isotope Exchange to another level making it even more scalable and attractive to fulfil the need for stable isotopically labelled compounds.

The aim of my work is to develop new methodologies for the synthesis of deuterated compounds. This includes the exploration of innovative catalytic systems and the implementation of H/D exchange in flow reactors.

The participation in the FLIX project offers a great opportunity for meeting various chemists and sharing science via active collaboration since the consortium involves many types of expertise.

Rouan Pauline

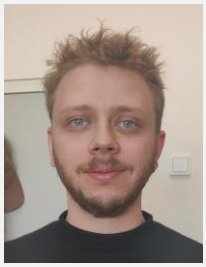
I am currently a PhD student at Toulouse Biotechnology Institute (TBI) on the INSA Toulouse campus. I work on the Flix project on the metabolism of microorganisms. I studied biochemistry, biology and microbiology at the Paul Sabatier University in Toulouse, until I obtained a master in Structural and Functional Biochemistry.

I realized 2 internships on the study of the mycomembrane of mycobacterium smegmatis at the IPBS in Toulouse. After the master I did a 3 months internship in a veterinary laboratory to do PCR tests for covid-19. I then worked one year as an engineer in my current team at TBI.

For the FLIX project, I work on the incorporation of stable isotopes (D2) on amino acids, in collaboration with the LPCNO (G.Mencia and B.Chaudret).

It is Dr. Guy Lippens (NMR team at TBI), my thesis supervisor, who allowed me to work on the FLIX project.

Hans Christian Dahl Hammershøj



PhD student at the Department of Nanoscience, Aarhus University. Holds a M.Sc. in Chemistry with speciality in organic chemistry and transition metal catalysis.

Tasks on the project concerns the development of novel labelling reagents and their use for late-stage labelling techniques. Concerning this, we have so far procured a method for obtaining labelled N-alkylamines, via the hydroformylation of labelled volatile alkenes with labelled syngas and subsequent reductive amination. The above method is both expanded towards carbon-13 and deuterium labelling.

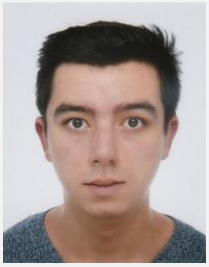
Looking forward, we aim to use labelled acetylene for procuring labelled acetylin groups.

Haraldur Gunnar Gudmundsson

I come from the land of ice and snow. From the midnight sun where the hot springs flow (Iceland). After completing my bachelor's degree from the University of Iceland, I moved to Oxford, UK to commence my PhD under the tutelage of Ed Andersson. There I worked on the development of cyclic siloxanes and their utilisation in Hiyama cross-coupling with specific application towards natural product synthesis. After finishing my PhD, I stayed on in the group for two more years as a postdoctoral researcher working on the synthesis and structural validation of the 51-membered macrolide nature compound stambomycin D. Currently, I am a postdoctoral researcher with Troels Skrydstrup at Aarhus University, Denmark, where I work on the development of novel isotope sources and their application in pharmaceutical synthesis and other bioactive molecules. I enjoy hanging out with friends and family, cooking, and am easily persuaded for the occasional pint at the local pub.

Postdoctoral researcher on the development of novel isotope sources and their application in pharmaceuticals synthesis and other bioactive molecules of interest.

Florian Bourriquen



Born in 1995 in Paris, France, studied chemistry at the University of Rennes 1. After a stay at F. Hoffmann-La Roche, Basel, Switzerland in 2018 focused on cross-coupling reactions, he conducted his master's thesis in 2019 at Sanofi, Vitry-sur-Seine, France, developing potential drug candidates. In 2020, he joined the group of Prof. Matthias Beller at the Leibniz-Institute for Catalysis, Germany.

In the FLIX project, my tasks are to develop new catalysts for deuterium labelling and apply them for the labelling of model substrates as well as compounds of interest such as pharmaceuticals. A priority is given to methodologies based on non-noble metals.

The participation in the FLIX project gives me the opportunity to learn and develop skills on a valuable topic as well as taking part in a large consortium with renowned experts of this field.

Gabriel Mencia Berlinches

Born in 1992 and I obtained my PhD. in chemistry at the University of Alcala (Spain), under the supervision of professors Rafael Gomez and Jesus Cano. During this period, I studied dendritic systems for biomedical applications. Nowadays, I am a post-doc researcher at LPCNO (Toulouse). My actual research domain, under the context of FLIX project, consists on the synthesis of metal nanoparticles as catalysts in the hydrogen isotope exchange reaction.

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Sara Kopf

Sara studied chemistry at the University of Heidelberg, Germany and the University of Cambridge, U.K. She carried out her master's thesis at Boehringer Ingelheim, Biberach, Germany, looking into the applicability of phosphorus-containing functional groups as bioisosteres in medicinal chemistry. Sara moved on to develop a photochemical bioconjugation reaction in the group of Prof. Paolo Melchiorre at ICIQ, Tarragona, Spain, for one year before joining the group of Prof. Matthias Beller at LIKAT, Rostock, Germany as a Ph.D. student in April 2020. Since then, she has been working on the development of new methodologies for hydrogen isotope exchange.

As a PhD student, Sara's tasks in the FLIX project are the development of hydrogen isotope exchange reactions. For that purpose, she plans and executes reactions in the lab and analyses the results.

Fabian Raymenants

Fabian studied Bioscience engineering at the KU Leuven in Belgium, where he obtained his masters in 2017. After gaining industrial experience with Janssen Pharmaceuticals, Inc., he returned to academia in 2020 to start his PhD in flow chemistry in the Noël Research Group. He is currently working at the University of Amsterdam on the Horizon 2020 project FLIX, applying flow technology to isotopic exchange in organic molecules.

Tasks in project: As a PhD student in the FLIX project, I search for ways to combine flow technology with organic chemistry to perform isotopic labeling. For example, I study photochemical carbonylations with gaseous CO by combining a gas- and liquid stream together inside a flow setup. This segmented flow is then irradiated with a high-intensity light source, which enables chemical reactions to occur between organic substrates in the liquid phase and the gaseous reagent. This method will later be applied to ^{13}CO gas, to incorporate a label into the substrates. If we successfully finish this project, we will also look for ways to incorporate a ^{2}H- or a ^{15}N-label into organic molecules by using continuous-flow technology.

Ádám Mészáros

Ádám Mészáros performed his studies at Budapest University of Technology and Economics as a pharmaceutical engineer. He did his thesis work for B.Sc. in the research group of Zoltán Novák in the field of sequential Sonogashira reaction, and in Servier Research Institute for Medicinal Chemistry for his M.Sc. thesis in the field of foldamer terminal building blocks' synthesis. During his PhD, he worked under Zoltán Novák on synthesis of (2-trifluoromethyl)aziridines using hypervalent iodonium compounds. Currently he is working at X-Chem Inc. in the field of H/D exchange reactions using heterogeneous catalysts under flow conditions (FLIX project).

Ádám is focusing on the development of H/D exchange reactions using heterogeneous catalysts under flow conditions. Ádám has developed a method using nickel catalysis to prepare deuterium labelled heterocycles, including APIs. Currently, Ádám and his co-workers are focusing on wrapping up this subproject by publishing the results.

During FLIX project, I collected a deeper understanding of flow chemistry and how I can effectively translate batch conditions to continuous flow technology. Catalytic H/D exchange reactions are an exciting part of organic chemistry, and utilization of heterogeneous catalysis offers a cheaper and more viable option for that.

Alexandre Labiche

After a general chemistry bachelor degree at the University of Rouen-Normandie in 2017, I successfully obtained my master "Organic Chemistry for Living Systems" in 2019, at the same University. During these years and thanks to several internships, in particular once done is the Daniele Leonori's group at the University of Manchester, I investigated greener possibilities to do chemistry using photochemistry. In the same vein, I started, in 2020, a PhD position at Paris-Saclay CEA in the "Molecular Labeling and Bio-Organic Chemistry Unit", leading by Dr. Frederic Taran. My PhD, directed by Dr. Davide Audisio, is about the development of new methodologies to give access to radiolabeled organic compounds, especially using carbon isotopes (carbon-13 and carbon-14). FLIX (FLow chemistry for Isotopic eXchange), which is the funding of my PhD, allows me to study the radiolabeling of organic compounds using continuous flow chemistry and especially the Carbon Isotope Exchange (CIE).

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4. Meet us

12-16/06/2022	International Symposium on C–H Activation (ISCHA-6), Germany, http://www.ackermann.chemie.uni-goettingen.de/ischa/
19-22/06/2022	14th International Symposium on the Synthesis and Applications of Isotopically Labelled Compounds, Conference, Rayleigh, US, https://web.cvent.com/event/65d76618-d8fd-4df7-b18e-1d0de9c9461b/summary
23/06/2022	Organic Chemistry Lecture Series, Training, University of Münster

5. FLIX publications

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- Minghao Feng, Joao De Oliveira, Antoine Sallustrau, Gianluca Destro, Pierre Thuéry, Sebastien Roy, Thibault Cantat, Charles S. Elmore, Jorg Blankenstein, Frédéric Taran, and Davide Audisio (2021), **Direct Carbon Isotope Exchange of Pharmaceuticals via Reversible Decyanation**, Journal of the American Chemical Society 2021, 143, 15, 5659–5665 https://pubs.acs.org/doi/10.1021/jacs.1c01923
- Marco Lepron, Marion Daniel-Bertrand, Gabriel Mencia, Bruno Chaudret, Sophie Feuillastre, and Grégory Pieters (2021), **Nanocatalyzed Hydrogen Isotope Exchange**, Accounts of Chemical Research 2021, 54, 6, 1465–1480 https://pubs.acs.org/doi/10.1021/acs.accounts.0c00721
- Sara Kopf, Fei Ye, Helfried Neumann, Matthias Beller (2021), **Ruthenium Catalyzed Deuteration of Aromatic Carbonyl Compounds with a Catalytic Transient Directing Group, Chemistry**—A European Journal, 2021, 27, 9768–9773. https://chemistry-europe.onlinelibrary.wiley.com/doi/10.1002/chem.202100468
- Wu Li, Ruiyang Qu, Weiping Liu, Florian Bourriquen, Stephan Bartling, Nils Rockstroh, Kathrin Junge, Matthias Beller (2021), **Copper-catalysed low-temperature water–gas shift reaction for selective deuteration of aryl halides**, Chemical Science, 2021, 12, 14033–14038. https://pubs.rsc.org/en/content/articlelanding/2021/SC/D1SC04259A
- Etienne Levernier, Kevin Tatoueix, Sébastien Garcia-Argote, Viktor Pfeifer, Ralf Kiesling, Edmond Gravel, Sophie Feuillastre, and Grégory Pieters (2022), **Easy-to-Implement Hydrogen Isotope Exchange for the Labeling of N-Heterocycles, Alkylkamines, Benzylic Scaffolds, and Pharmaceuticals**, Journal of the American Chemical Society 2022, 2, 4, 801–808 https://pubs.acs.org/doi/10.1021/jacsau.1c00503
- Alex Talbot, Antoine Sallustrau, Amélie Goudet, Frédéric Taran, Davide Audisio (2022), **Investigation on the Stoichiometry of Carbon Dioxide in Isotope-Exchange Reactions with Phenylacetic Acids**, Synlett 2022, 33, 02, 171-176 https://www.thieme-connect.com/products/ejournals/abstract/10.1055/s-0040-1720447
- Wu Li, Jabor Rabeah, Florian Bourriquen, Dali Yang, Carsten Kreyenschulte, Nils Rockstroh, Henrik Lund, Stephan Bartling, Annette-Enrica Surkus, Kathrin Junge, Angelika Brückner, Aiwen Lei, Matthias Beller (2022), **Scalable and selective deuteration of (hetero)arenes**, Nature Chemistry, 2022, 14, 334–341. https://www.nature.com/articles/s41557-021-00846-4
- Sara Kopf, Jiali Liu, Robert Franke, Haijun Jiao,Helfried Neumann, Matthias Beller (2022), **Base-Mediated Remote Deuteration of N-Heteroarenes – Broad Scope and Mechanism**, European Journal of Organic Chemistry, 2022, e202200204. https://chemistry-europe.onlinelibrary.wiley.com/doi/10.1002/ejoc.202200204

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- Sara Kopf, Florian Bourriquen, Wu Li, Helfried Neumann, Kathrin Junge, and Matthias Beller (2022), **Recent Developments for the Deuterium and Tritium Labeling of Organic Molecules**, Chemical Reviews, 2022, 122, 6634−6718. https://pubs.acs.org/doi/10.1021/acs.chemrev.1c00795
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