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Swiss Chemical Society

ALFRED WERNER FUND

MASTER'S STUDENT SCHOLARSHIPS

In this report, the Alfred Werner Scholars' class of 2021–2023 present their Master Thesis research projects. There are eleven scholars of this class who completed their studies earlier this year. One scholar is expected to complete his studies by the end of the year, as he was doing an internship during his Master studies. For the same reason, we have one report of a student of the class of 2020–2022.

The Alfred Werner Fund of the SCS Foundation, established in 2013, supports Master degree studies for excellent students from foreign countries in Chemistry or Biochemistry at a Swiss University or at a Federal Institute of Technology. The Foundation offers scholarships in the amount of CHF 30'000 for international students nominated by the Swiss partner universities.

ETH zürich · EPFL · Universität Basel · UNI FR Université de Fribourg Universität Freiburg · Université de Genève · Université de Neuchâtel unine · u b Universität Bern · University of Zurich[UZH]

The scholarship program is supported by the Swiss chemical and pharmaceutical industry, below, and a number of private donors.

arxada · dsm-firmenich · Givaudan · MERCK · NOVARTIS · syngenta · Roche

So far, more than eighty scholarships have been granted to students from over 30 countries, most of them continuing their career in Switzerland. To learn more about the Alfred Werner Scholars, please visit the Gallery of alumni at https://foundation.scg.ch/scholarships/scholar-gallery or download the Alfred Werner Program Impact Report 2013–2021 from the same Web site.

Alfred Werner Fund Master's Scholarships 2023–2025

The Allocation Committee of the Alfred Werner Fund, consisting of representatives from the program supporting companies and the partner universities, granted stipends to the following international students:

Lucas Paul Grobon, EPFL
McGill University, Canada
Yingjain Li, EPFL
Sun Yat-sen University, China
Den Martymianov, ETHZ
Kharkiv National University, Ukraine, to ETHZ
Polina Foteva, University of Geneva
University of St Andrews, United Kingdom
Pan Relid Coll, University of Geneva
University of Barcelona, Spain

Alfred Werner Fund Master's Scholarships 2021–2023

Seyedmohamadjavad Chabok
Nationality: *Iran*
Bachelor at: *Sharif University of Technology, Tehran, Iran*
Master at: *EPFL*
Master thesis supervisor: *Prof. Kevin Sivula*

$FASnI_3$ Thin Film Crystallization: Insights from Photonic Processing and New Additive Engineering

In the following work, we demonstrated a scalable method for the rapid production of $FASnI_3$ thin films for the first time by employing the Flash IR annealing (FIRA) method. Next, we studied the effect of additive engineering on the crystal growth of $FASnI_3$ through the judicious choice of two new additives, varying their interaction strength with Sn^{2+}. Our work further hints toward a careful selection of additives because unknown mechanisms, possibly complexation, can interfere with the additive effect on the crystal growth process.

Formamidinium tin iodide ($FASnI_3$) is a member of the tin-based perovskite group that has gained increasing attention as an alternative to its lead counterpart due to environmental considerations. The main obstacles for the commercialization of $FASnI_3$ are its stability and its rapid crystallization, resulting in vacancy and defect formation in the structure.

Moreover, the lab-scale production of perovskite materials relies on the conventional antisolvent (AS) method, wherein a separate solvent is dripped on the wet substrate to trigger crystallization of the perovskite layer. The AS method entails prolonged processes (hours) employing toxic organic solvents, which are unrecoverable from the process. The AS method is neither environmentally friendly nor scalable for global scale production of perovskites.

My thesis addressed two central challenges in tin-based perovskites: scalable preparation and controlling crystallization.

Firstly, we demonstrated a scalable method for the rapid production of $FASnI_3$ thin films for the first time by employing the Flash IR annealing (FIRA) method. Notably, the FIRA method not only eliminates the use of toxic halogenated solvents but also slashes preparation time from hours to mere seconds, rendering it scalable and commercially viable.

Principally, in FIRA, the substrates are exposed to highly intense infrared radiation that triggers the crystallization (Fig. 1). Only the fluorine-doped tin oxide (FTO) layer absorbs the IR radiation because glass and the perovskite precursor solution are transparent to the IR radiation. This rapid temperature increase enables quick (seconds) and indirect annealing and preparation of the perovskite thin films.[3] Through optimization of FIRA process parameters, *i.e.* pulse time and precursor solution concentration, we obtained uniform and pinhole-free $FASnI_3$ films on a NiO_x-coated substrate.

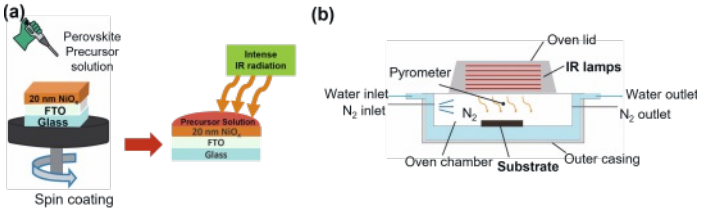

Fig. 1. a) FIRA operation, b) schematic of FIRA chamber.

Next, we turned our attention to addressing the challenge of rapid crystallization. Additive engineering is utilized to improve the power conversion efficiency of $FASnI_3$ films; a record of 14% is achieved with trimethylthiourea as the additive.[4] Our work focused on additive engineering and $FASnI_3$ crystallization. Through the judicious choice of two novel additives (DA and MDA, Fig. 2a), we varied the interaction strength of the additives with Sn^{2+} to provide insights into the additive-based crystallization control. We hypothesized that the additive with stronger interaction with Sn^{2+} should retard the crystallization more effectively.

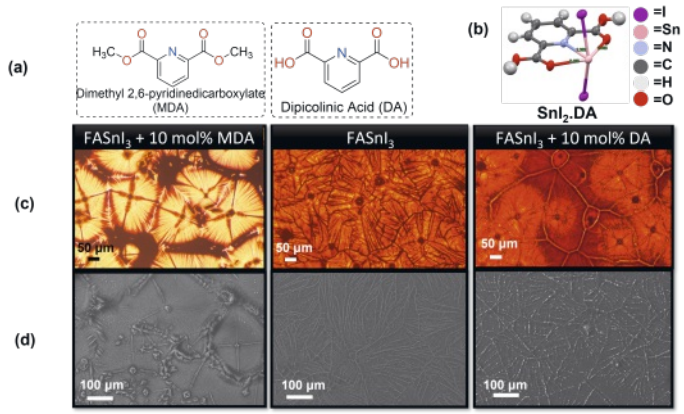

Fig. 2. a) Chemical structure of the additives. b) Single-crystal structure of SnI_2.DA complex in solid state. c) Optical transmission microscopy images of the films. d) Scanning electron microscopy images of the films.

We discovered that while DA has a stronger interaction with Sn^{2+} in the precursor solution, MDA retarded the crystal growth process more effectively than DA, in contrast to our theory.

With these contrasting results, we hypothesized that DA is removed from the crystal growth medium through the SnI_2.DA complex. Due to the absence of the complexation, we suggested that MDA remained in the crystallization medium, resulting in its more substantial effect on the crystal growth process.

Further characterization methods were utilized to study the crystallinity and photophysical properties of the films. Neither DA nor MDA enhanced the photoluminescence quantum yield (PLQY) or charge carrier lifetime compared to the control films ($FASnI_3$). DA and MDA additives may not be suitable for photovoltaic applications in tin-based perovskites.

Our work calls for attention in choosing additives since unknown mechanisms, possibly complexation, can prevent the additive from functioning expectedly. We imagine providing more insights into choosing additives in the future by studying a range of additives with different interaction strengths with $FASnI_3$.

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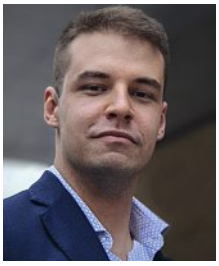
[2] S. Ghosh, S. Mishra, T. Singh, *Adv. Mater. Interf.* **2020**, *7*, 2000950, https://doi.org/10.1002/admi.202000950.
[3] S. Sánchez, A. Hagfeldt, in 'Perovskite Solar Cells', Eds. M. Grätzel, S. Ahmad, S. Kazim, John Wiley & Sons, Ltd, **2021,** pp. 33–89, https://doi.org/10.1002/9783527825790.ch2.
[4] Z. Zhu, X, Jiang, D. Yu, N. Yu, Z. Ning, Q. Mi, *ACS Energy Lett.* **2022**, *7*, 2079, https://doi.org/10.1021/acsenergylett.2c00776.

Future Plans

I will soon start my PhD studies on liquid metals for catalysis at EPFL under the supervision of Prof. Raffaella Buonsanti. I would like to express my gratitude to the Swiss Chemical Society Foundation and the Alfred Werner Scholarship for their support.



Bratislav Dačević
Nationality: *Serbia*
Bachelor at: *University of Belgrade*
Master at: *University of Basel*
Master thesis supervisor: *Prof. Thomas R. Ward*

Towards a Novel Artificial Metalloenzyme Platform Based on a Thiamine-dependent Enzyme

Inspired by gold(I) N-heterocyclic carbene complexes, we synthesized and characterized an artificial metallocofactor, isosteric to gold(I)-thiamine, and used it to catalyze a hydroamination reaction. However, the attempt to incorporate it into thiamine-dependent enzymes resulted in significant deactivation due to the presence of reduced cysteines. Different strategies were pursued to eliminate cysteine reactivity, but despite the absence of thiols, a notable decrease in catalytic activity was still observed. Nevertheless, it was shown that the metallocofactor is stable in the presence of a cysteine-free thiamine-dependent enzymes, leaving hope for the advancement of the activity.

Artificial metalloenzymes are hybrid catalysts that result from combining an abiotic metal cofactor with a protein. These systems seek to achieve high activity and selectivity for unnatural reactions by exploiting the effect of the second and third coordination spheres.[1] One approach to construct an artificial metalloenzyme is to coordinate an existing organic cofactor to a metal center; an example of such a natural cofactor is thiamine pyrophosphate (TPP). Appealingly, the thiazolium fragment of TPP represents an N-heterocyclic carbene (NHC), a ligand class extensively used in transition metal complexes for various catalytic applications.

Hilvert *et al.*[2] initially proposed an idea of making the TPP-metal complex. The linear geometry of gold(I) NHC complexes and their potential in homogeneous electrophilic catalysis inspired us to pursue a similar strategy. Many attempts to synthesize the TPP gold(I) complex were unsuccessful, so a new isosteric thiamine analog (PT) was obtained. Subsequently, a phosphorylated metallocofactor (AuPTdP) was synthesized and characterized, showing good stability and solubility. AuPTdP was tested as a catalyst in an intramolecular hydroamination reaction giving indole as a product (Fig. 1). It was tested both free and in the presence of Pyruvate decarboxylase (PDC) from *Zymomonas mobilis*.

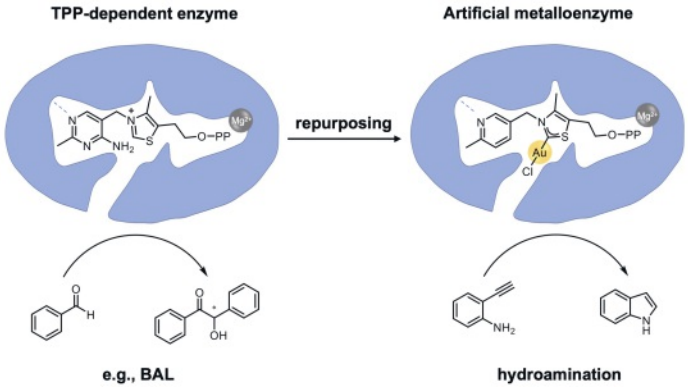


Fig. 1. Repurposed TPP-dependent enzyme with AuPTdP artificial metallocofactor; proposed hydroamination reaction.

The activity of the metallocofactor was expected to increase through the incorporation in the TPP-dependent enzyme, which was not the case. The question then was how an enzyme deactivates the gold(I) complex. Considering strong interactions between thiols and gold, control experiments confirmed that proteins with reduced cysteine residues destroyed the catalytic activity of AuPTdP.

Cyclohexane-1,2-dione hydrolase (CDH) from *Azoarcus sp.* has only three cysteine residues; hence, it was engineered to a cysteine-free TPP-dependent enzyme. No improved activity compared to the free AuPTdP was seen with the single mutants, but with one of the double mutants (CDH 13; Fig. 2.) there was a 4.5-fold increase in activity compared to the presence of the wild type. Surprisingly, activity was lower with the cysteine-free triple mutant, compared to CDH 13.

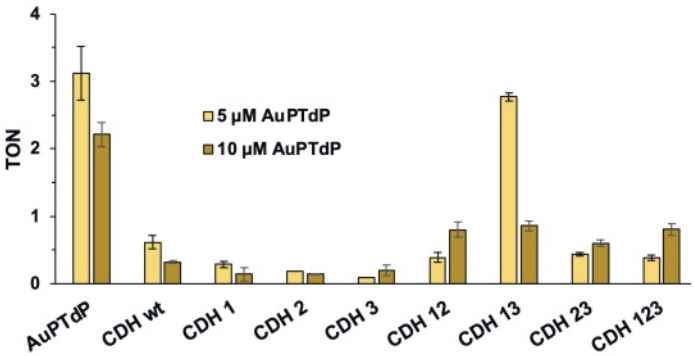


Fig. 2. Catalytic activity (TON) of AuPTdP in the presence of different CDH mutants (5 µM); mutations: C77S (1), C260S (2), and C428S (3).

The most straightforward strategy was testing wild-type TPP-dependent enzymes without cysteines. Surprisingly, the metallocofactor activity in the cysteine-free protein's presence was still lower than that of the complex alone. It was concluded that an unspecific interaction deactivates gold(I) cofactor, whilst the gold-NHC bond remains intact.

Despite all the challenges, once the artificial enzyme is developed, the ultimate goal remains to target demanding gold(I)-catalyzed transformations and improve their regio- and stereoselectivity.

[1] B. J. Bloomer, D. S. Clark, J. F. Hartwig, *Biochemistry* **2023**, *62*, 221, https://doi.org/10.1021/acs.biochem.1c00829.
[2] C. Dince, PhD thesis, ETH Zurich, **2015**, https://doi.org/10.3929/ethz-a-010566904.

Future Plans

After successfully defending my MSc thesis at the University of Basel, I started my PhD studies at the University of Groningen in the Netherlands. I was happy to join the research group of Prof. Gerard Roelfes as a MetRaZymes MSCA doctoral candidate. My PhD research is focused on the design of artificial metalloenzymes for the biocatalysis of radical reactions.

Liliana Gálvez-Vázquez
Nationality: *Mexico*
Bachelor at: *Benemérita Universidad Autónoma de Puebla*
Master at: *University of Bern*
Master thesis supervisor: *Prof. Dr. Peter Broekmann*

Method Development for Corrosion Inhibitor Screening

Controlled removal of material (etching) from metal surfaces is a relevant procedure for microchip manufacturing in the semiconductors industry. One of the main approaches to achieve this metal removal involves the use of additives in chemical and electrochemical wet etching processes. Herein, we introduce three novel and complementary approaches that provide insights into characteristic features of wet chemical and electrochemical etching.

Corrosion manifested by the deterioration of metals through chemical or electrochemical interactions with the environment is most of the time considered a non-desirable phenomenon.[1] However, corrosion brought about by wet etching[2] can be very useful in the semiconductor industry to achieve clean particle-free and low roughness metal surfaces.[3] One way to suppress the damage on metal wafer surfaces induced by wet etching techniques involves the use of additives that act as corrosion inhibitors. Such additives are used to slow down or suppress metal corrosion while keeping surface smoothness. Due to the high quality of the metal surfaces achieved, these additive-assisted approaches are considered among the most useful methods to avoid uncontrollable corrosion.[4]

The goal of this master's thesis work, which was carried out in a collaboration with our industrial partners at BASF, was the method development for cheap and quick additive screening based on electrochemical and chemical etching that enabled the identification of best corrosion inhibitors. Furthermore, advanced characterization procedures were introduced that revealed the influence of the applied process parameters on important surface properties associated with metal corrosion (amount of removed metal, removal rate, surface roughness, texture, and homogeneity).

Electrochemical etching was carried out by means of linear sweep voltammetry that enabled additive ranking regarding their inhibition capabilities on two relevant metals, namely molybdenum and tungsten.

Another approach was designed to mimic the actual wet chemical etching process that is carried out in the industry for wafer cleaning. The use of inductively coupled plasma mass spectrometry (ICP-MS) allowed us to determine the metal etching rates and the amount of metal that is removed. However, this technique does not enable knowledge of the homogeneity of the removal across the metal sample.

Therefore, as an extension of the wet chemical etching method, a third approach was developed to allow the visualization of removed metal, sample homogeneity and induced sample roughness. This new approach involves the functionalization of metal wafers followed by the manufacture of 'nanomasks' in 2D microarrays of passivated zones through selective exposure to an electron beam (electron beam lithography). Fig. 1 presents a scheme that briefly summarizes the steps of the novel local passivation approach.

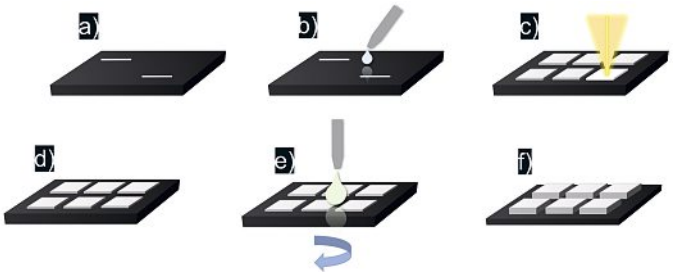


Fig. 1. a) Markers on metal samples. b) Organic treatment. c) Exposure of specific regions to the electron beam (gray areas) promotes surface passivation. The black area represents the area not exposed to the electron beam. d) An array of as prepared nanomasks. e) Nanomasked sample subjected to wet chemical etching. f) Upon chemical etching, only the non-masked sample regions are eroded, whereas the masked areas remain intact.

In conclusion, the development of these methods provides a better understanding of the metal corrosion phenomena, which can be applied to other metallic surfaces (*e.g.* Cu, Co) and requires the use of equipment usually available in many research institutions.

[1] A. Kadhim, A. A. Al-Amiery, R. Alazawi, M. K. S. Al-Ghezi, R. H. Abass, *Int. J. Corros. Scale Inhib.* **2021**, *10*, 54, https://doi.org/10.17675/2305-6894-2021-10-1-3.
[2] O. Cakir, J. *Mater. Process. Technol.* **2008**, *199*, 337, https://doi.org/10.1016/j.jmatprotec.2007.08.012.
[3] W. Kern, K. Reinhardt, 'Handbook of silicon wafer cleaning technology', 3rd Edn, Elsevier, **2018**.
[4] C. G. Dariva, A. F. Galio, 'Corrosion Inhibitors-Principles, Mechanisms and Applications', Eds. M. Aliofkhazraei, Iran, **2014**, pp. 365-375.

Future Plans

First, I would like to thank the Alfred Werner Scholarship and the Swiss Chemical Society for giving me the opportunity to carry out my master's studies at the University of Bern in Switzerland. With this experience, apart from broadening my knowledge, expertise, and capabilities to work in science, I also had the chance to enrich my overview of the world.

In May 2023, after finishing my master's studies with honors, I started my PhD project in the same group. My research topic deals with the electrochemical oxidation of 5-hydroxymethylfurfural, a derivative of biomass to valuable products.

My plans are to successfully finish my PhD studies and after that, I would like to apply all the collected knowledge and expertise in a job related to the chemical industry.

Claire Grigglestone
Nationality: *American*
Bachelor at: *Trinity College – Hartford*
Master at: *University of Zurich*
Master thesis supervisor: *Prof. Dr. Nina Hartrampf*

Studies Toward the Total Synthesis of Lasso Peptide Microcin J25

Lasso peptides are a class of peptidic natural products with a unique 3-dimensional knot-like topology. One well-studied lasso peptide is Microcin J25 (MccJ25), which displays antimicrobial potency against Gram-negative bacteria. MccJ25 consists of 21 amino acids with an N-terminal macrolactam ring, formed via the Glu^{8} sidechain, and is threaded by the C-terminal tail, held in place by bulky sidechain residues. MccJ25 production is limited to biological expression, highly restricting the ability to install noncanonical amino acids and other non-natural moieties. Therefore, our aim is to develop a route toward the total chemical synthesis of MccJ25 utilizing either supramolecular chemistry or preorganization.

Lasso peptides' intrinsic stability, antimicrobial, antiviral, and antitumor activity make them promising therapeutic targets. The first lasso was discovered in 1991, but the lasso topology was not characterized until 2003 – initially they were thought to be branched-cyclic or head-to-tail cyclic peptides. MccJ25 was the first to be characterized by NMR (Fig. 1) and further investigations have proven ion-mobility mass-spectrometry to be an effective method. MccJ25 is exceptionally stable tolerating temperatures up to 121°C, resisting proteolysis, and withstanding pH values as low as 2. MccJ25 exhibits antimicrobial activity against *Salmonella, Shigella flexneri, E. coli,* and *Enterobacter bugandensis.* It binds in the secondary channel of RNA polymerase inhibiting translation and stopping cell growth.[1,2] The chemical synthesis of MccJ25 would enable the design of a peptide library for screening *via* the incorporation of noncanonical amino acids.

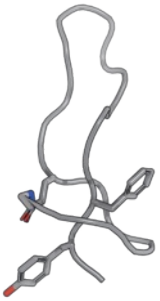


Fig. 1. NMR structure of MccJ25 (PDB: 1Q17).

However, to date, no chemical synthesis has been achieved. Previous efforts have taken inspiration from supramolecular chemistry, particularly the construction of rotaxanes as a lasso peptide is equivalent to a [1]rotaxane. The Bode lab constructed a [1]rotaxane whereby molecular recognition was used to pull a peptide-based motif inside the ring and α-ketoacid-hydroxylamine (KAHA) ligation and native chemical ligation (NCL) were used to graft in sections of lassos (Fig. 2A).[3] The Coutrot lab synthesized a branched-cyclic compound with peptidic motifs and used protonation to cause self-entanglement (Fig. 2B).[4] Meanwhile, the Evans lab followed a similar method to the Bode group but utilized a more peptidic macrocycle with amides capable of hydrogen bonding with the tail (Fig. 2C).[5]

Taking inspiration from these approaches and supramolecular chemistry, our first approach aimed to use a copper-catalyzed azide-alkyne cycloaddition (CuAAC) reaction with a highly peptidic macrocycle to form a [1]rotaxane. Site selective mutations were made in the macrocycle to introduce Cu^{I} coordination motifs. The resulting peptides were tested for their ability to coordinate Cu^{I} and perform in a CuAAC reaction. Unfortunately, none successfully formed a [1]rotaxane, but ongoing investigations are being conducted with more typical CuAAC motifs.

The second approach is based on preorganization. Molecular dynamics simulations were conducted on linear MccJ25 to inves-

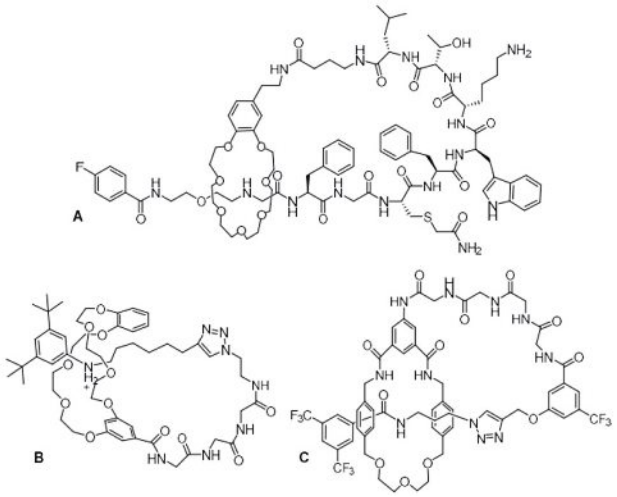


Fig. 2. Lasso peptide inspired [1]rotaxanes previously synthesized by (A) Bode (B) Coutrot (C) Evans.

tigate it's intrinsic preorganization in different solvents. From these studies, it was determined that more structure would need to be introduced into the sequence chemically with the goal of orienting the ring in such a manner that it would close around the tail. Studies are still ongoing.

[1] K. J. Rosengren, A. Blond, C. Afonso, J. C. Tablet, S. Rebuffat, D. J. Craik, *Biochem*. **2004**, *43*, 4696, https://doi.org/10.1021/bi0361261.

[2] H. Yu, Y. Wang, X, Zeng, S. Cai, G. Wang, L. Liu, S. Haung, N. Li, X. Ding, Q. Song, S. Qiao, *FASEB J*. **2020**, *34*, 1018, https://doi.org/10.1096/fj.201901717r.

[3] F. Saito, J. W. Bode, *Chem. Sci*. **2017**, *8*, 2878, https://doi.org/10.1039/C7SC00021A.

[4] C. Clavel, K. Fournel-Marotte, F. Coutrot, *Molecules* **2013**, *18*, 11553, https://doi.org/10.1002/chem.201203597.

[5] M. J. Young, G. R. Akien, N. H. Evans, *Org. Biomol. Chem*. **2020**, *18*, 5203, https://doi.org/10.1039/d0ob01190h.

Future Plans

I will continue my research in the Hartrampf group while pursuing a PhD. My projects will focus on late-stage functionalization and peptidic natural product synthesis. Thank you to the Alfred Werner Foundation for enabling me to study at UZH and explore a new field of chemistry.

Jana Lukic
Nationality: *Serbia*
Bachelor at: *Faculty of Technology and Metallurgy, University of Belgrade*
Master at: *EPF Lausanne*
Master thesis supervisor: *Marie Jones, Prof. François Maréchal*

Investigating Technical Pathways towards a Circular Bio-plastic Industry

Increasingly visible effects of climate change and growing trends in consumption are calling for efficient, fossil-independent processes to enable the sustainable production of functional materials. Packaging plastic is an example of highly functional, single-use products of which 96% ends up in the environment as waste.[1] Furthermore, with its fossil sourcing, plastic industry is expected to contribute 15% to the overall greenhouse gas emissions in 2025.[2] The idea of this project is to explore emerging chemo-catalytic routes converting renewable biomass into sustainable polymers[3] and their subsequent recycling routes in closing the carbon balance across the value chain.[4]

Novel polymers have been recently developed (PEF and PHX in Fig. 1) that aim at preserving the native biomass structure to a higher extent throughout processing, as compared to PET production.[5] Fewer steps from biomass to the product induce savings in terms of mass and energy, milder operating conditions and offer the potential for economic and environmental advantage.

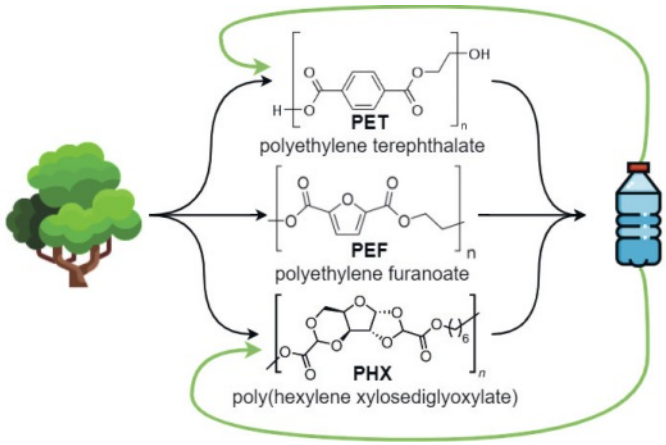


Fig. 1. Bio-polymer alternatives to PET.

The tradeoff between retrofitting the biomass structure to petroleum-based polymers (such as PET) in well-established industrial processes and producing novel polymers with higher efficiencies in emerging, un-optimized processes is assessed in this work. This is done by rigorously modeling all the processes involved based on the industrial practice and patents reported. Mass and energy performances of the processes are compared using mixed-integer linear programming minimization algorithm. Furthermore, by including all the bio-polymer production alternatives and adding the necessary waste treatment units, carbon capture and utilities, the operation of an integrated bio-refinery is assessed. The optimum in terms of environmental impact, production costs and the dependency on electricity and natural gas are sought for.

Detailed scenario analysis and optimization results justify the development of novel processes with higher biomass utilization efficiencies by effectively reducing global warming potential with an increase in production costs. The importance of chemical recycling in reducing the negative environmental implications is emphasized as it contributes to creating a close-loop production and offsets the demand on the virgin biomass feedstock. Unique solutions arising from the interconnection of processes with energy saving technologies and waste treatment units emphasize the importance of following the integrated approach in representing cost-competitive and carbon-neutral bio-refining operation.

[1] J. G. Rosenboom, R. Langer, G. Traverso, *Nat. Rev. Mater*. **2022**, *7*, 117, https://doi.org/10.1038/s41578-021-00407-8.

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[4] L. Manker, G. R. Dick, A. Demongeot, M. A. Hedou, C. Rayroud, T. Rambert, M. J. Jones, I. Sulaeva, M. Vieli, Y. Leterrier, A. Potthast, F. Maréchal, H.-A. Klok, J. S. Luterbacher, *Nat. Chem*. **2023**, *14*, 976, https://doi.org/10.1038/s41557-022-00974-5.

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Future Plans

Following this project, I am eager to continue working in the field of sustainable material production, either through a PhD or working in the industry. I wish to keep developing technical and transversal skills to accelerate the de-carbonization of the chemical industry, and beyond.

Eibhlin Meade
Nationality: *Ireland*
Bachelor at: *University College Dublin*
Master at: *Universität Basel*
Master thesis supervisor: *Prof. Murielle Delley*

Tuning Earth-Abundant Inorganic Materials for Hydrotreating Catalysis

The ever-increasing global energy demand as well as depleting fossil fuel reserves means that using high efficiency fuels is more important than ever. Hydrotreating is an essential process in the upgrading of petroleum-based and biomass-derived fuels. However, these processes rely on rare noble metal catalysts. Previous work has shown that earth-abundant inorganic materials are promising alternatives. Tuning their properties as hydrotreating catalysts is therefore a key aspect to optimizing these materials.

According, to the International Energy Agency, the global energy demand is projected to increase by 1% annually reaching 178,899 terawatt hours in 2022.[1] While renewable energies such as solar and wind energy are promising alternatives, the facilities for such sources are currently insufficient to meet growing demands.[2] The challenge then remains of how to minimize environmental damages and maximize the energy output from sources we currently have.

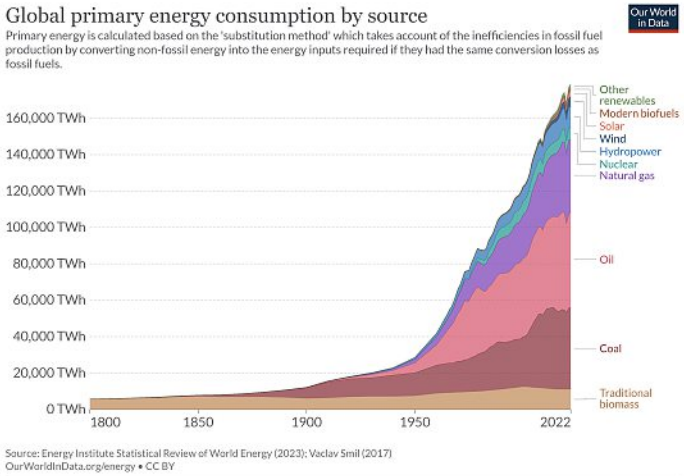

Fig. 1. Global primary energy consumption by source in terawatt hours (TWh) over time (years). Reprinted with permission from the ourworldindata.org, 2022.[1]

Hydrotreating is an essential part of this process. In industry, hydrotreating is a crucial step in petroleum processing as it refines crude petroleum and removes greenhouse gas impurities such as SO_x and NO_x.[3] Hydrotreating also supports the synthesis of biomass derived fuels or 'biofuels' which are a promising solution to ameliorate the limitations of other renewables such as wind, hydroelectric and solar.[4] Such renewable sources face intermittent supplies and storage difficulties.

For these hydrotreating applications, highly active and stable catalysts are required. Commonly, noble metal catalysts such as Ru, Rh, Pd, Pt are employed in hydrotreating reactions.[5] The disadvantages of the high price and low earth abundance of noble metals means that there is growing interest in sustainable and highly active alternatives. Earth-abundant inorganic materials have shown great promise as a more sustainable and highly versatile alternative for hydrotreating reactions.[4,6] However, further improvement of their catalytic properties is needed for their actual implementation in chemical processes.

The goal of my project was to understand and tune the surface chemistry of earth-abundant inorganic material for improved hydrotreating catalysis. For this, I synthesized such materials, chemically modified their surface, and subsequently tested both the as-prepared and the modified materials in a catalytic hydrotreating reaction. Investigation of the efficiency and selectivity of surface modified catalysts provided valuable insight into the surface chemistry of these promising catalyst materials and could lead to development of more efficient earth-abundant hydrotreating catalysts.

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Future Plans

I would like to thank the Alfred Werner Foundation which has allowed me to carry out my studies in Switzerland. After successfully defending my MSc thesis project, I will be starting as a research scientist with Echion Technologies in Cambridge (UK), working on high performance battery materials for a greener future.

Giorgi Meshvildishvili
Nationality: *Georgian*
Bachelor at: *San Diego State University Georgia*
Master at: *University of Geneva*
Research Project Supervisor: *Prof. Gérard Hopfgartner*

Atmospheric Pressure Photoionization Tandem Mass Spectrometry for Qualitative Analysis of Metabolites

Atmospheric pressure photoionization (APPI) is the least abundant among the atmospheric pressure ionization techniques such as ESI (Electrospray Ionization) and APCI (Atmospheric pressure chemical ionization). Dopant assisted APPI is able to produce radical cation species that provides much more informative product ion spectra rather than protonated one under ESI.

My research was dedicated to investigating steroids and vitamin D compounds under APPI tandem mass spectrometry. Even though radical cations were not the dominant ions for all of the analytes, the formation was observed for every compound. In some cases, isotopic distribution overlapped target ion species that made it difficult to obtain a clear spectrum for the compounds,

however differential mobility spectrometry helped us to separate co-eluted peaks by adding the additional parameter as compensation voltage (Fig. 1).

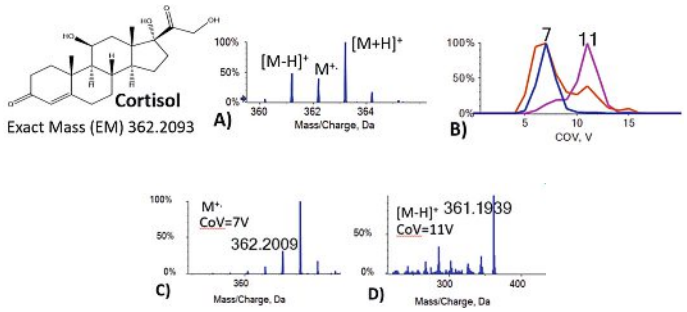

Fig. 1. **A**) MS[1] spectrum of Cortisol. **B)** Compensation voltage (CoV profile for $M^{+\cdot}$ (blue), $[M-H]^+$ (pink) and $[M+H]^+$ (orange). **C)** and **D)** are MS[1] spectra for chosen ion species at the distinctive CoV.

Product ion scan of radical cation gave us the possibility to differentiate epimers and regioisomers (*e.g.* epimers – testosterone and epitestosterone, regioisomers – 7-dehydroxy cholesterol and 24-dehydroxy cholesterol) from each other by their distinctive MS/MS spectra, which provided different peak intensity ratio for analytes (Fig. 2).

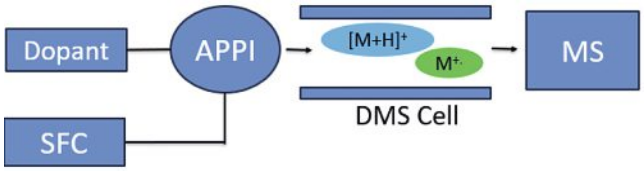

Fig. 2. Instrumental set-up for the experiments.

Moreover, supercritical fluid chromatography has been coupled with APPI-MS and successfully applied to form radical cations of vitamin D and metabolites.

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Future Plans

I would like to express my limitless gratitude to the Alfred Werner Scholarship Program for giving me the opportunity for such an extraordinary studying experience. After successful completion of my master's thesis, I decided to explore the chemical industry and started a six-month complementary master's at DSM-Firmenich in their analytical chemistry department. However, I'm still in the process of choosing my future career path. Academia and industry are interesting and full of challenges that make them both attractive to me.

Alfred Werner Fund: Master's Scholarships 2020–2022

Dieu Khanh An Nguyen
Nationality: *Vietnamese*
Bachelor at: *University of Strasbourg (France)*
Master at: *University of Geneva*
Master thesis supervisors: *Dr. S. Constant, Dr. S. Huang, Dr. B. Boda (Epithelix), Prof. S. Hoogendoorn (University of Geneva)*

Development of an *in vitro* Co-culture Model between Alveolar Epithelium and Parenchymal Fibroblasts to Study Pulmonary Fibrosis and Related Treatments

Idiopathic pulmonary fibrosis (IPF) is a chronic lung disease characterized by accumulating scar tissue and excessive extracellular matrix (ECM) deposition, which impairs gas exchange and ultimately leads to respiratory failure. Despite two FDA-approved drugs (Nintedanib and Pirfenidone) on the market, the disease remains fatal.[1] The lack of effective treatment against IPF can be partially attributed to our poor understanding of the pathomechanism of IPF, hence difficulties in choosing molecular targets. To better study IPF and enhance drug screening effectiveness, human cell-based in vitro models have become increasingly popular. In this study, we present the development of an in vitro co-culture model using alveolar epithelium (AlveolAir™) and primary human parenchymal fibroblasts to study IPF and related treatments (Nintedanib).

AlveolAir™ (AL) is an *in vitro* model of the human alveolar epithelium, recently developed by Epithelix. In this model, pneumocytes are cultured at the air–liquid interface on the apical side of a Transwell insert, which allows epithelial maturation, while primary human endothelial cells are cultured on the basolateral side (Fig. 1, left).

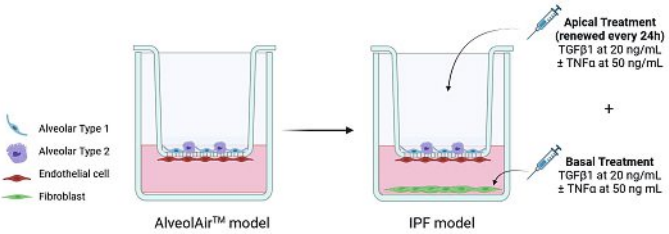

Fig. 1. The AlveolAir™ model (left) was employed for the assembly of the IPF co-culture model (right). TGF-β1 was used as the main fibrosis inducer, with or without TNF-α over 72 h.

To assemble the IPF model, we seeded primary human fibroblasts at the bottom culture wells and placed AL inserts on top (Fig. 1, right). Transforming growth factor β1 (TGF-β1) was selected as the main fibrosis inducer, with or without inflammatory cytokine tumor necrosis α (TNF-α). The stimuli were added in the apical side (renewed every 24 h) and in the basal compartment (single dose) over a 72 h period. Nintedanib was tested to evaluate the model's response to antifibrotic drugs.

We evaluated the model by its ability to recapitulate key events of IPF, particularly fibroblast-to-myofibroblast transition (FMT), epithelial-to-mesenchymal transition (EMT), accompanied by enhanced expressions of ECM proteins, matrix metalloproteinases (MMPs) and other soluble fibrotic markers (Fig. 2).

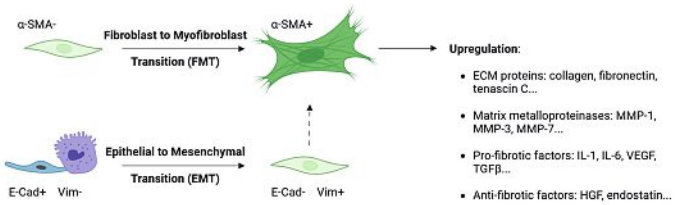

Fig. 2. Key events of IPF with respective biomarkers.

Through immunostaining of FMT marker α-SMA and E-Cad, trans-epithelial electrical resistance (TEER) results, mass spectrometry (MS) analyses of human fibroblasts and pneumocytes, and Multiplex/Luminex quantification of other soluble fibrotic markers, we have found that the presence of inflammation is required for induction of IPF with TGF-β1. We also identified pro-fibrotic markers, notably MMP-3, which were overwhelmingly elevated during IPF induction. The reliable marker of lung fibrosis and its easiness of measurement allows the adaptation of this model for higher throughput screening of antifibrotic drugs. Finally, we also confirmed that Nintedanib (1 μM) only showed partial effectiveness against IPF induced by TGF-β1 alone, which is reflective of clinical results.[1]

Our system is simple to set up, easy to use and gives reproducible results (though validation with other donors is still required). However, we believe that it is a robust first building block towards more elaborated models, integrating alveolar macrophages, for example.

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Future Plans

I would like to send my sincere thanks to the Alfred Werner Fund for their support during my academic journey. I will soon join the Hoogendoorn research group at the University of Geneva as a PhD candidate. My project focuses on the synthesis and evaluation of probes targeting the primary cilium, with an overall objective to develop a chemoenzymatic tagging strategy that can be used to dissect and perturb the biological functions of proteins within the primary cilium in healthy and ciliopathy cell models.

Anamarija Nikoletić
Nationality: *Serbia*
Bachelor at: *University of Belgrade*
Master at: *University of Basel*
Master thesis supervisor: *Prof. Cornelia Palivan*

Synthesis and Self-assembly of Bifunctional Amphiphilic Diblock Copolymers

Achieving precise control over the structure and material properties has been a central goal in the field of synthetic polymer chemistry. Considerable effort has been devoted to developing novel synthetic methodologies for gaining control over molecular weight, dispersity, architecture, and functionality of formed polymers. Using functional initiator and end-group modification, polymers with alkyne and thiol functional groups at the α- and ω-chain end, respectively, were obtained and self-assembly into nano- and microscale vesicles was demonstrated. Polymer functionalization with thiol and alkyne groups offers great opportunities for the creation of more complex polymeric architectures via well-established click chemistry methodologies.

Amphiphilic block copolymers can form a wide range of particle morphologies driven by hydrophobic effect. Aqueous self-assembly of amphiphilic block copolymers into nano- and microscopic assemblies is commonly used in an array of applications ranging from nanoreactors to cell mimicry and drug delivery.[1] Compared to lipid vesicles (liposomes), using vesicles based on amphiphilic polymers offer both improved mechanical and chemical stability, as well as the possibility to tune thickness, permeability, stimuli-responsive behavior and surface functionality.[2] The reach and utility of polymeric vesicles (polymersomes) for biomedical applications can be enhanced when functionalized with targeting ligands such as antibodies, peptides, carbohydrates and small molecules. Conjugating such moieties allows polymersomes to be used for targeted drug delivery, cell imaging or immobilization on surfaces.[3]

Various synthetic strategies can be used to introduce reactive groups to polymersomes. Controlled radical polymerizations such as atom transfer radical polymerization (ATRP) and reversible addition–fragmentation chain-transfer (RAFT) polymerization are a popular way to obtain telechelic polymers because they provide control over both the structure and the molecular weight distribution of the resulting polymers as well as their end-group functionalities (Fig. 1a). Other living polymerizations like cationic ring opening polymerization (CROP) can also be used to obtain polymers with well-defined end-functionalities but with a more limited library of compatible monomers and initiators.

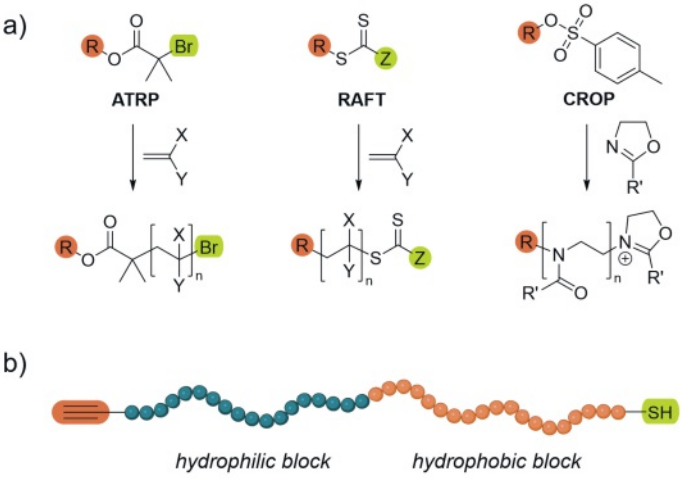

Fig. 1. a) Structure of functional initiators used in different living polymerizations and their polymers. b) Scheme of the bifunctional amphiphilic diblock copolymer.

In our work, we synthesized different functionalized amphiphilic diblock copolymers using CROP, ATRP and RAFT polymerizations. By utilizing functional initiators and end-group modification, we introduced alkyne, azide, thiol, hydroxyl and carboxyl end-groups to polymer chains. We developed a strategy for the synthesis of bifunctional amphiphilic diblock copolymers with alkyne and thiol end-groups (Fig. 1b), offering the opportunity for further modification using orthogonal CuAAC and thiol-ene click chemistry. The applicability of synthesized polymers in the CuAAC and thiol-ene reactions was demonstrated through reactions with different azides and alkenes, respectively.

Self-assembly into polymersomes was demonstrated using the solvent switch method (Fig. 2a), while giant unilameral vesicles (GUVs) were produced using double emulsion microfluidics

(Fig. 2b). The current work in our group is focused on the development of functionalized stimuli-responsive polymer vesicles for biomedical applications.

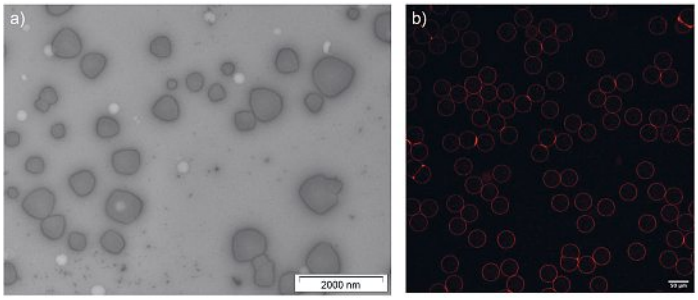

Fig. 2. A) TEM image of polymersomes formed by solvent switch method and b) CLSM image of GUVs formed by double emulsion microfluidics stained with Bodipy 630/650 dye.

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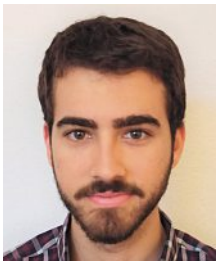
Future Plans

I have started my PhD studies as part of the Swiss Nanoscience Institute (SNI) PhD School, working in groups of Prof. Oya Tagit (FHNW, School of Life Sciences) and Prof. Cornelia Palivan (University of Basel). During my PhD I'll continue my work on block copolymers synthesis and self-assembly with the goal of developing multi-compartment nanofactories for on-site and on-demand drug synthesis and delivery. I am very grateful for the Alfred Werner Scholarship for giving me the opportunity to pursue my master's studies in Switzerland.



Tomas Rodriguez Gil
Nationality: *Spain*
Bachelor at: *University of Seville*
Master at: *University of Geneva and EPFL*
Master thesis supervisor: *Prof. Sascha Hoogendoorn*

Synthesis and Biological Evaluation of Proteolysis Targeting Chimeras for the Hedgehog Signaling Pathway

The Hedgehog pathway is a crucial signaling cascade in embryonic development and cancer where Smoothened, a membrane protein, plays a key role. The existence of Proteolysis Targeting Chimeras (PROTACs) degrading relevant members of this pathway would be of great help in basic research and could open the door to future therapeutic tools based on the same approach. In this project, novel PROTACs making use of cyclopamine, a natural product binding to Smoothened, were synthesized utilizing two different types of E3 ligase ligands: hydroxythalidomide and VHL peptide. Preliminary Smoothened binding studies on one analog, however, showed ineffective binding to the target, and so optimization of the construct will be necessary.

Throughout the evolution of the metazoans, only a handful of signaling pathways have consistently remained present across many different phyla, among them the Hedgehog (Hh) signaling pathway.[1] In humans, it is no surprise that alterations of such a finely tuned interplay of proteins lead to a variety of malformations in embryos[2] and cancers in adults.[3] Recent findings further suggest a relevant role of the pathway in Alzheimer's and Parkinson's disease,[4,5] altogether making research in the field of Hh signaling of the uttermost interest. However, many of its key aspects remain poorly understood to this day, and in order to elucidate them, chemical and biological tools capable of selectively impairing its components prove to be extremely useful.

Proteolysis targeting chimeras (PROTACs) are heterobifunctional molecules designed *ad hoc* to degrade a given protein of interest (POI) *via* the ubiquitin-proteasome system (UPS).[6] In the native UPS, proteins that must be degraded are tagged with ubiquitin by means of an E3 ligase and then processed by the proteasome. PROTACs hijack this system by forming a ternary complex with the ligase and the POI, which forces the former to act specifically on the latter (Fig. 1). Once the POI is tagged and eventually degraded, the PROTAC is regenerated and may start the cycle again, thus behaving in a catalytic manner.

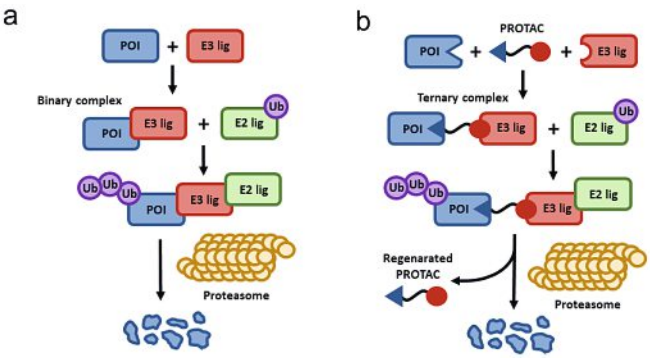


Fig. 1. Comparison between the regular functioning of the UPS (a) and the version altered by a PROTAC (b).

In this project, we designed and successfully synthesized two different PROTACs (Fig. 2) targeting Smoothened (SMO), a central component of the Hh pathway. Cyclopamine, a natural product, was used as the ligand for SMO, whereas thalidomide, target-

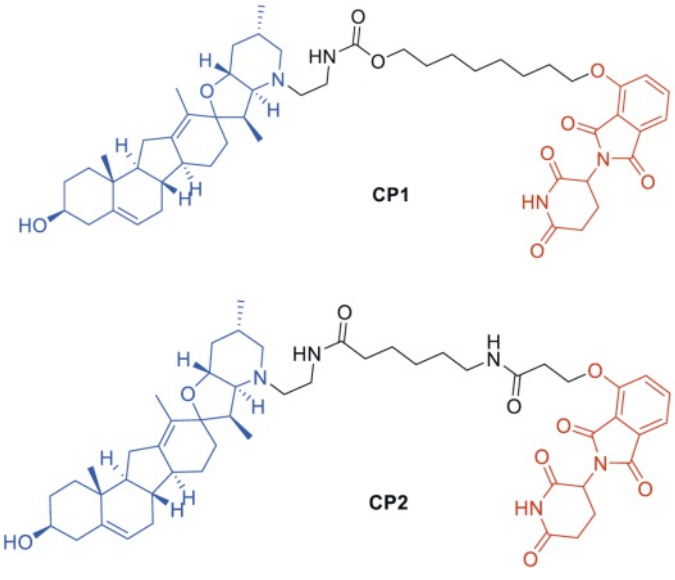


Fig. 2. CP1 and CP2, the two PROTACs that were synthesized making use of cyclopamine (in blue) as a ligand for SMO and thalidomide (in red) as a ligand for the E3 ligase cereblon

ing cereblon, was used as the E3 ligase ligand for the Cyclopamine Probes (CPs).

The synthesis of a third PROTAC (CP3) making use of VHL peptide instead of thalidomide was attempted, but could not be successfully completed within the timeframe of the thesis.

The synthesis of CP1 and CP2 was based on that of BODIPY-cyclopamine (a heterobifunctional fluorescent probe with great affinity for SMO),[7,8] with a functionalized version of cyclopamine being used as the starting point to generate the CPs by coupling it with the different linkers and finally with the E3 ligase ligand. Substitution reactions were employed for linker attachment, since a previous click-chemistry approach yielded ineffective PROTACs – probably due to the bulkiness and rigidity that the triazole group implied for the linker. The successful formation of the two CPs was confirmed by both NMR and LC-MS, but only CP1 could be purified at quantities high enough for biological testing to be properly carried out.

As the primary biological test for the newly created probe, we used a competition assay (similar to a displacement assay). For this, HEK293 cells transiently expressing SMO were incubated with both BODIPY-cyclopamine and CP1 at the same time. Fluorescence was then measured using flow cytometry for different concentrations of CP1 at a fixed BODIPY-cyclopamine concentration. Since the fluorescence observed on the cells is proportional to the amount of BODIPY-cyclopamine bound to them, and this fluorescence can only diminish if another binder replaces BODIPY-cyclopamine, a decrease in fluorescence with increasing concentrations of CP1 would suggest some level of affinity of CP1 for SMO. However, we found that CP1 was unable to bind SMO – an absolute prerequisite for it to be able to function as a SMO degrader.

In conclusion, even though it was not possible to accomplish the goal of synthesizing a functional PROTAC capable of degrading SMO, we obtained valuable insights that may be used to continue pursuing this objective. Furthermore, we managed to optimize the synthetic route towards cyclopamine analogs, which will undoubtedly save future researchers precious time.

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Future Plans

After graduating, I started an internship at Hoffmann-La Roche, where I am currently working. In the future, I would like to continue growing professionally in the Swiss pharmaceutical sector and ideally be able to combine scientific research and project management. None of this would have been possible without the help of the SCS Foundation, to whom I am deeply grateful.

Uroš Stojiljković
Nationality: *Serbia*
Bachelor at: *University of Belgrade*
Master at: *University of Basel*
Master thesis supervisor: *Prof. Dr. Olivier Baudoin*

Iridium(III)-catalyzed Directed C(sp^3)–H Amidation for the Synthesis of Chiral 1,2-Diamines

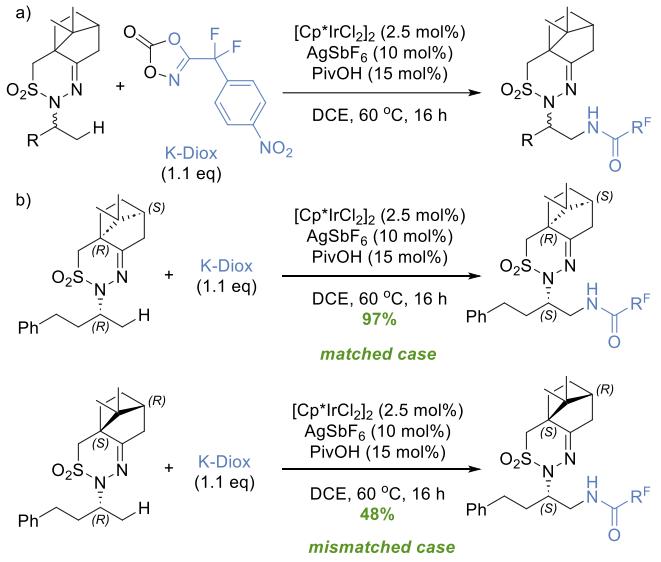
Chiral 1,2-diamines are ubiquitous structural motifs among pharmaceuticals, natural products, ligands for transition metal-catalyzed reactions, and organocatalysts. However, the construction of chiral 1,2-diamine motifs remains a challenging task. To address this, we developed a directed iridium(III)-catalyzed intermolecular C(sp^3)–H amidation reaction that furnishes scalemic 1,2-diamines upon cleavage of the directing group.[1] This method relies on the design of a novel, cheap, and cleavable directing group derived from camphorsulfonic acid. Mechanistic studies provided insights into the observed reactivity difference between pairs of diastereomeric substrates.

Chiral 1,2-diamine backbone is a prevalent and privileged scaffold among biologically active natural products and pharmaceuticals.[2] Furthermore, this structural motif has received much attention in transition metal-based asymmetric catalysis and organocatalysis. Concerning their high value, vicinal diamines have been subjected to a myriad of synthetic studies in the past.

Recently, transition metal-catalyzed C(sp^3)–H amidation reactions have emerged as a powerful strategy for making C(sp^3)–N bonds. However, only a few precedents of C–H amidation reactions for the synthesis of vicinal diamines were reported. Furthermore, these methods usually occur through an outer-sphere nitrene insertion process, displaying a higher reactivity towards C–H bonds with low bond dissociation energies, as exemplified by Du Bois and coworkers.[3] On the other hand, C–H activation-based methods that occur through an inner-sphere concerted metalation-deprotonation (CMD) mechanism would involve intermolecular C–H amidation of a substrate containing a nitrogen-based directing group. Such a reaction would preferentially target primary and secondary C–H bonds, offering a complementary reactivity to previously reported methods.

Driven by our initial work on the synthesis of 1,2-amino alcohols[4] and motivated by the lack of precedents, we developed a directed iridium-catalyzed C(sp^3)–H amidation for the synthesis of chiral 1,2-diamines (Scheme 1a).[1] This method relies on a recently developed amidating reagent K-diox and cleavable thiadiazine dioxide-based directing group derived from camphorsulfonic acid (CSA). As CSA is inherently a chiral compound, installation of the racemic directing group onto an enantiopure alcohol furnishes two diastereomers of the substrates for the C–H amidation reaction. We were intrigued to discover that, under the same C–H amidation conditions, two diastereomers have drastically different reactivities (Scheme 1b).

Given the difference in the reactivity of two diastereomers, we prepared a range of diastereomerically pure substrates bearing a directing group from enantiopure secondary alcohols and studied their reactivity in the C–H amidation reaction. We were pleased to observe that most matched substrates performed well under optimal conditions, giving corresponding amides in excellent yields. Furthermore, we confirmed the remarkable reactivity difference between matched and mismatched diastereomers when the R substituent was rather bulky or rigid. The reaction showed broad applicability, allowing amidation of substrates bearing various oxygen- and nitrogen-based functional groups. However, it was shown that the reaction outcome strongly depends on the steric hindrance around the directing group, suggesting that steric ef-



Scheme 1. a) Optimal conditions for the developed reaction; b) difference in reactivities of two diastereomeric substrates.

fects have a significant influence on the reactivity. Furthermore, we showed that our methodology efficiently utilizes other amidating reagents and can also be employed for constructing α-tertiary 1,2-diamines under slightly modified reaction conditions.

Intrigued by the difference in reactivities of diastereomeric substrates, we conducted detailed experimental and computational mechanistic investigations of the reaction in hand. A strong primary kinetic isotopic effect indicates that CMD is, in fact, a rate-limiting step. Detailed density functional theory (DFT) studies and non-covalent interaction (NCI) analysis shed light on the observed differences in reactivities of diastereomeric substrates.

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Future Plans

After successfully defending my MSc thesis under the guidance of Prof. Dr. Olivier Baudoin at the University of Basel, I started working at Novartis Institutes for BioMedical Research (NIBR) as a Master's graduate. At Novartis, I work on a drug discovery project in the Diseases of Aging and Regenerative Medicine team. After acquiring some medicinal chemistry experience in the pharmaceutical industry, I will join the Baudoin research group for my PhD studies, where I will work on the development of novel C–H activation reactions.

Marina Teixeira Chagas

Nationality: *Brazil*
Bachelor at: *Federal University of Rio de Janeiro*
Master at: *ETH Zurich*
Master Thesis Supervisor: *Prof. Dr. Gonzalo Guillén Gosálbez*

Enhancing Fischer-Tropsch Electrofuels Production: Reducing Hydrogen Consumption *via* the Boudouard Reaction

Electrofuels are alternative fuels produced from carbon dioxide and electrolytic hydrogen which can contribute to the decarbonization of the transport sector. As studies show that electrolytic hydrogen is the main contributor to their overall cost, reducing its requirement for electrofuels production can lower their cost and consequently make them more economically appealing in comparison to fossil fuels. This study evaluated the potential of the Boudouard reaction in decreasing hydrogen use in the Fischer-Tropsch process when starting from carbon dioxide from direct air capture and electrolytic hydrogen. The economic and environmental impact of Fischer-Tropsch electrofuels was evaluated considering both the reverse water gas shift and the Boudouard reactions as alternatives for the generation of carbon monoxide from carbon dioxide. Biochar was selected as carbon source for the Boudouard reaction, and the process was modeled and optimized in terms of carbon footprint and operating cost, resulting in different flowsheet configurations. Through economic evaluation and life cycle assessment, it was possible to verify that the Boudouard reaction can decrease the hydrogen consumption in the Fischer-Tropsch process.

Climate change mitigation refers to the efforts to limit climate change by avoiding or reducing the emissions of greenhouse gases. This involves initiatives for the reduction in fossil fuel use, widespread electrification, improvement of energy efficiency, and use of alternative fuels.[1,2] In the transport sector, however, which presents the highest dependence on fossil fuels among all sectors and accounted for 37% of CO_2 emissions from end-use sectors in 2021,[3] electrification might be limited, especially for long-distance modes of transport. For this reason, the use of alternative, low-carbon – or, ideally, carbon-neutral – fuels could offer a way to achieve decarbonization.[1,4,5]

Electrofuels are alternative fuels produced from carbon dioxide as main carbon source and hydrogen derived from water electrolysis powered by renewable or zero-carbon energy sources.[6–8] Their production, by the so-called power-to-gas/liquid/fuel technologies, can be divided into two main processes: the hydrogen production by water electrolysis and the fuel production *per se*.[9]

In the electrolysis, electricity is used to split water molecules into hydrogen and oxygen.[6] In the context of decarbonization, low-carbon electricity, from sources such as solar, wind or nuclear, should be used to power electrolysis and, in this case, the hydrogen obtained is denominated green hydrogen.

In fuel synthesis processes, on the other hand, hydrogen and carbon dioxide are combined to form different energy carriers. CO_2 can be used directly, or it can be first reduced to carbon monoxide, in case of reaction pathways such as the Fischer-Tropsch synthesis, which start from CO instead.[10]

The Fischer-Tropsch process is an example of a gas-to-liquid process, which converts synthesis gas ($CO + H_2$), into a mixture of linear and branched hydrocarbons and oxygenated products.[11] Therefore, it requires an initial reaction step to obtain carbon monoxide, and the reverse water gas shift reaction is the usual route to do so, converting CO_2 and H_2 into CO and H_2O. However, it might not be the best alternative.

According to studies, the production cost of electrolytic hydrogen constitutes the largest contribution for the overall cost of electrofuels.[10] This is mainly due to the electricity requirement for its production and the capital costs of the electrolyzer.[12] Be-

cause the reverse water-gas shift reaction converts CO_2 to CO at the expense of H_2 consumption, an alternative route which does not feature hydrogen as reactant might result in a lower overall cost. This is the case of the Boudouard reaction, in which carbon dioxide reacts with solid carbon to produce carbon monoxide. In addition to the cost benefits, this reaction route could also potentially contribute to lower global warming impact of the overall process depending on the source of solid carbon employed. For instance, biochar, which is the carbonaceous solid product obtained from the slow pyrolysis of biomass,[13] presents significant carbon abatement potential[14] and can therefore reduce the overall carbon footprint of the electrofuel production process when selected as carbon source.

This study aimed to evaluate the economic and environmental potential of Fischer-Tropsch electrofuels, considering both the reverse water-gas shift and the Boudouard reactions as possible routes to obtain carbon monoxide from carbon dioxide. Purchase prices for carbon dioxide from direct air capture, green hydrogen and biochar were considered, and the fuel synthesis process was modeled and optimized for both economic and environmental parameters. The goal was to determine whether the Boudouard reaction, due to the theoretical reduction in hydrogen consumption in the process, could be a more advantageous alternative to obtain carbon monoxide for the Fischer-Tropsch process considering the cost of the electrofuels obtained and the carbon footprint of the process.

Additionally, a sensitivity analysis was carried out to shed light on how the cost of green hydrogen, which has the largest contribution, affects the final cost of the electrofuels produced. Furthermore, it was possible to assess their competitiveness in regard to fossil fuels for different cost ranges for hydrogen.

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Future Plans

I am currently finalizing my internship in Process Engineering for Direct Air Capture at Climeworks in Zurich and will be starting soon my PhD at ETH Zürich on the topic of sustainable chemicals and fuels. There, I will explore machine learning for sustainable process design.

I would like to once again express my gratitude to the Alfred Werner Scholarship program for giving me the opportunity to continue my studies in Switzerland.