October 28-29, 2021
Riga, Latvia

12th Paul Walden Symposium on Organic Chemistry

Latvian Institute of Organic Synthesis

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12th Paul Walden Symposium on Organic Chemistry

PROGRAM AND ABSTRACT BOOK

Riga, Latvia
28-29 October, 2021

https://walden.osi.lv/

Paul Walden 12th Symposium on Organic Chemistry

We have a great pleasure of inviting you to the 12th Paul Walden Symposium on Organic chemistry (Walden-2021), which will be hosted by the Latvian Institute of Organic Synthesis (LIOS) and Riga Technical University (RTU). Unfortunately, restrictions of COVID pandemia forced us to change the platform of the Conference to the virtual.

Paul Walden (*Pauls Valdens*) was an expert in 3 different research areas - organic chemistry, electrochemistry and science history. His first scientific results were obtained in Riga under the supervision of Nobel prize winner Professor Wilhelm Ostwald. In 1896 he discovered his famous rule, later called the "Walden inversion". Starting from 1987, RTU awards a Paul Walden medal in chemistry and science history, both beloved Walden's scientific disciplines. In 2021, the recipient of the Paul Walden medal is Dr. Pavel Arsenyan, a selenium chemist from LIOS.

The goal of this Conference is to bring together scientists, scholars, and students from universities, research institutes, and industry across the Baltic States. Traditional format of the Walden Symposium comprises plenary lectures by renowned organic chemists and a poster session, where students communicate their research. In addition, two oral presentations are offered by the best Latvian PhD students. Despite the COVID-related restrictions, we feel committed to maintaining all the established traditions of the Walden Symposium, and especially the students' poster competition that started 20 years ago. This year a virtual poster session will take place during the second day of the Symposium. A jury comprising invited speakers and local professors will award the best poster prize in bachelor, master and PhD categories. This year the best poster prize is sponsored by company Armgate and RTU Institute of Technology of Organic Chemistry.

We wish you a successful and inspiring event with many interesting discussions and debates!

On behalf of Organizing Committee,

Dr. Peteris Trapencieris
Latvian Institute of Organic Synthesis, Latvia

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Selenium in medicinal and material chemistry: a blessing and a curse

Pavel Arsenyan

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Refinery production of selenium worldwide is about 2700 tons annually. 17% of it is used in nutrition and cosmetics, the rest – in the production of various materials. Over the past 20 years, scientific studies have clearly demonstrated that selenium is an irreplaceable microelement with essential properties for human health. Selenium is an active component of GPx, which is an enzyme involved in cell redox homeostasis. Selenium has antioxidant properties and it is crucial in physiological and pathological processes linked to increased reactive oxygen species generation. Selenium is needed for the proper functioning of the immune system, as a key nutrient it inhibits HIV progression to AIDS and decreases a risk of cardiovascular diseases. Indeed, relationships between the level of selenium in the daily diet and the risks of developing various types of cancers have been established. However, the main negative issue about selenium is a narrow range between therapeutic and toxic doses. Selenium-containing compounds used in industry are quite toxic, e.g. LD_{50} of widely used nutrient – sodium selenite – varies from 8.1 to 12.1 mg/kg, which is comparable with potassium cyanide toxicity. In the last decades, introduction of selenium into biologically active molecules have attracted increasing attention. Some compounds exhibit excellent properties as antioxidants, redox modulators, antitumor and antihypertensive agents in preclinical studies. Unfortunately, from thousands of synthesized and studied selenium-containing compounds not a single one has been approved as a drug so far.

Despite the wide use of selenium in the production of different alloys, glass, quantum dots, LEDs, and solar cells, there are only few examples of utilization of organic selenium-containing compounds in OLED technology.

Herein, the development of novel methodologies for the synthesis of fused selenophenes, polyaromatic hydrocarbons, isoselenazolium and indolizinium salts will be discussed with the aim to find the right direction for the future research in the elaboration of drug candidates and smart materials.

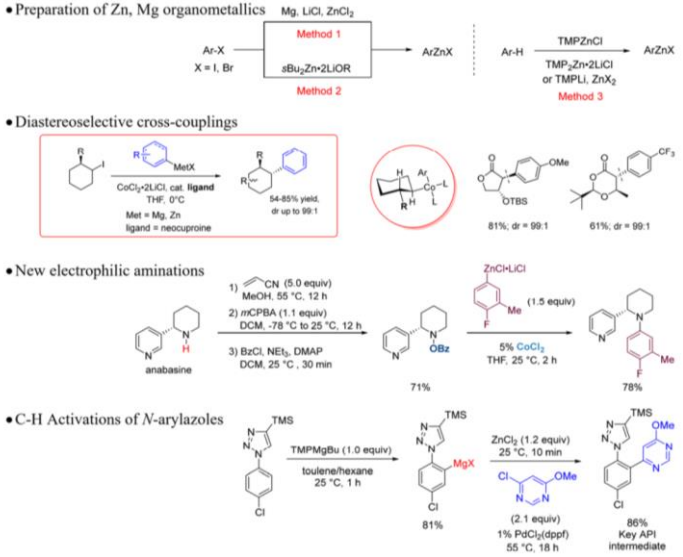
Acknowledgements
Financial support from ERDF project Nr. 1.1.1.1/19/A/016 is gratefully acknowledged.

Stereoselective reactions of lithium organometallics – recent applications in flow organometallic chemistry

Paul Knochel

University Munich, Chemistry Department, Butenandtstr. 5-13 D-81377 Munich, Germany

Transition metal catalyzed cross-couplings and aminations are important tools for the pharmaceutical and agrochemical industries, especially heterocyclic organozinc and –magnesium reagents have proven their utility for these applications. Herein, we will first describe the most important methods for preparing polyfunctional organozinc and organomagnesium reagents and describe their use for performing cobalt-catalyzed cross-couplings and aminations.



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Boring Silicon Chemistry Made Interesting

Martin Oestreich

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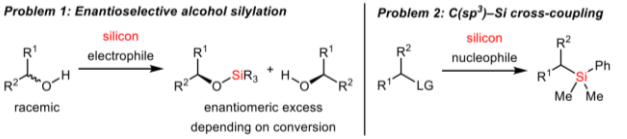
This talk will present solutions to two long-standing problems in silicon chemistry:

- The (dynamic) kinetic resolution of alcohols by enantioselective silylation[1] through transition-metal-catalyzed dehydrogenative Si–O coupling.[2,3]
- The formal transition-metal-catalyzed nucleophilic substitution of C(sp^3)–LG (with LG = leaving group) with silicon (pro)nucleophiles4 by ionic5 or radical mechanisms[6] ...and enantioselective detours.[7]



Scheme 1. Long-standing problems in silicon chemistry.

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The synergistic interplay between catalysis and electrosynthesis

Robert Francke

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To most chemists the term 'electrocatalysis' is known as the facilitation of a heterogeneous electron transfer via a chemical interaction between the electrode and a substrate (A).[1] This chemical interaction can occur either between A and a catalytically active electrode (heterogeneous electrocatalysis, see Figure 1a) or between A and a homogeneous electrocatalyst (see Figure 1b). The opposite case, the utilization of an electrochemical step to catalyze a chemical reaction ('electrochemical catalysis', see Figure 1c), is a much less known but yet a very powerful approach in electrosynthesis.[2] Here, the injection (or removal) of an electron into (or from) A triggers a redox-neutral reaction (e. g. an isomerization) that may otherwise require harsh conditions and/or the use of reagents. Such processes involve the electro-generation of an ionic or radical ionic species, which after a coupled chemical step either undergoes a backward electron exchange with the electrode (ECE^b mechanism) or triggers a chain process in the bulk solution, both leading to formation of product (P). Under these circumstances, sub-stoichiometric amounts of charge are sufficient to achieve a full conversion and conceptionally, the electrons and holes can be understood as being catalysts.

In this contribution, the concepts presented above will be illustrated using examples from our laboratory. The anodic conversion of alcohols to carbonyl compounds mediated by TEMPO-modified polymethacrylates will serve as an example of electrocatalysis.[3,4] The concept of electrochemical catalysis will be discussed by means of the Newman-Kwart rearrangement of *O*-aryl thiocarbamates to the corresponding *S*-aryl compounds, the key-reaction in the three-step synthesis of thiophenols from the corresponding phenols.[5,6]

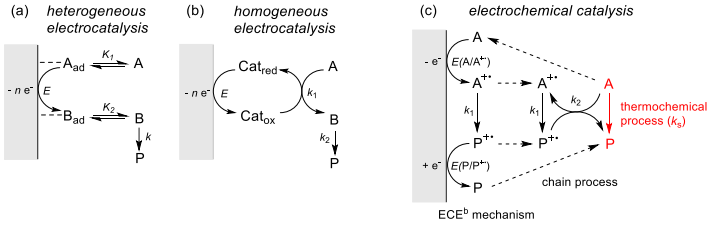

Figure 1. Catalytic approaches in organic electrochemistry.

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Catalytic Asymmetric Group Transfer, Boronate Directed C-H activation & Protein Structure Mimicry

Alan C. Spivey

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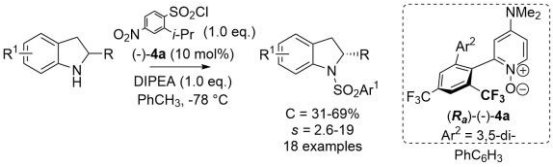
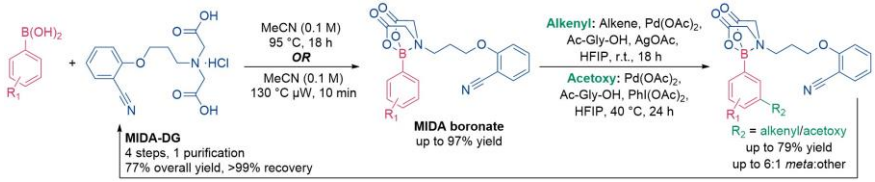
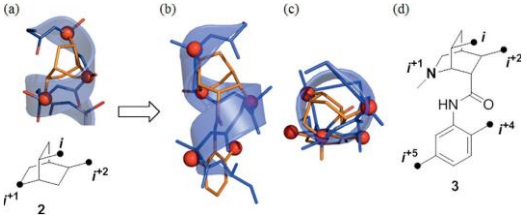
Three areas of research will be presented.
Firstly, a review of Lewis base catalysed acylation, sulfonylation and phosphorylation of alcohols and amines will be presented and the utility of some atropisomeric pyridine and pyridine-*N*-oxide catalysts developed in our labs for promoting examples of this type of transformation presented.



Secondly, some work we have carried out to develop modified MIDA boronate ligands to allow directed *meta*-CH activation of aryl boronate derivatives will be described.



Thirdly, studies directed at the development of a novel scaffold for the modular synthesis of five residue alpha-helix mimetics and their use for the development of leads for protein-protein interaction antagonists in the cancer area will be described.



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Photoinduced Assembly of C–N and C– Bonds

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Photoinduced Assembly of C–N Bonds. The first part of the presentation will illustrate the work my group has carried exploring the reactivity of nitrogen radicals for the assembly of C–N bonds. This includes C–H amination of aromatics,[1] olefin diamination[2] and dehydrogenative aniline synthesis.[3] This will include a discussion of the key mechanistic aspects related to the reactivity of nitrogen radicals as well as their synthetic implications.

Photoinduced Assembly of C–C Bonds. The second part of the talk will discuss the development of an alternative strategy for C-radical formation from alkyl and aryl halides.[4] This will illustrate the unique ability of α-aminoalkyl radicals to undergo halogen-transfer reactions and how this can be used in synthetic chemistry.

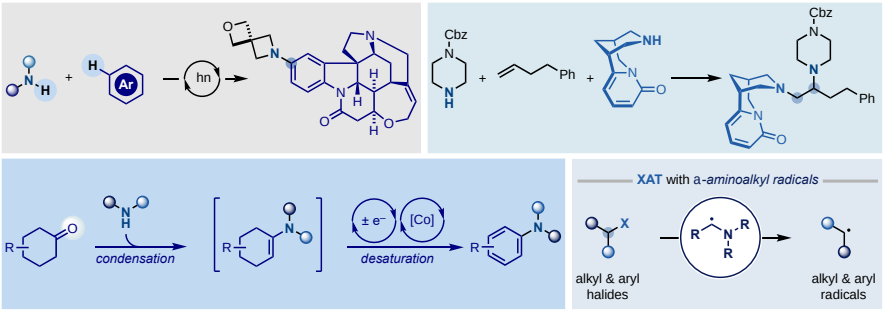

Figure 1.

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Recent Developments in Low Pressure Carbonylations

Troels Skrydstrup

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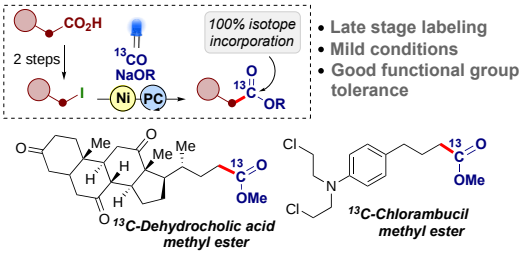
Carbonylation reactions rank as one of the most selective and efficient chemical processes for the introduction of oxygen containing functionality into organic substrates. Transition metal complexes play a key role in promoting such transformations with carbon monoxide. In this talk, I provide a short overview on how carbonylation chemistry can be exploited for the efficient late-stage introduction of carbon isotopes into pharmaceutically relevant molecules, a mandatory process for carrying out drug metabolism and pharmacokinetic (DMPK) studies.[1–5] Furthermore, I will elaborate on recent efforts to extend this chemistry to a molecular surgery strategy for extruding an embedded carbon atom within the drug's framework, followed by its replacement with another carbon isotope via a sequence of C–C bond cleaving and bond forming events.[6]



Scheme 1. Nickel-mediated alkoxycarbonylation for complete carbon isotope replacement.

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Late Stage Fluorination with Metal Alkali Fluoride

Véronique Gouverneur

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Our research on late-stage fluorination is aimed at enhancing our fundamental understanding of fluoride reactivity, populating the toolbox of reactions for the synthesis of fluorochemicals, transforming ^{18}F-radiochemistry, and allowing access to PET ^{18}F-labelled radiotracers for diagnostic and drug discovery. A recent research avenue includes the development of bio-inspired urea organocatalysts for enantioselective fluorination with metal alkali fluoride, the safest and most cost-effective fluorine source. This lecture will focus on this aspect of our programme with a focus on the chemistry of CsF and KF.

STUDENT PRESENTATIONS

Light-driven modifications of Cys and Sec containing peptides

Sindija Lapčinska

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Late-stage modification of peptides attracts high attention from medicinal chemists. Conjugation is an attractive approach for enhancing the properties of peptides. Notably, 30% of peptides that have entered clinical development in the last decade are conjugates. On the other hand, photocatalysis is an efficient and sustainable route to achieve chemoselective bioconjugation under mild and biocompatible conditions. Furthermore, peptides with cysteine (Cys) or selenocysteine (Sec) residues are convenient targets for selective modification.

An efficient method for functionalization of short protected and unprotected selenocystine-peptides was developed using visible light-initiated reaction.[1] The protocol is based on the generation of a selenium radical via visible light-initiated reaction in the presence of organic dye. The selenium radical is further oxidized to an electrophile and trapped by *N*-heterocycles, providing respective Sec-containing indoles and azaindoles in good to high yields. Notably, intramolecular indole selenylation was performed providing Sec-containing indole-based macrocycles.

Additionally, 4-substituted coumarins and quinolinones were able to trap the selenyl electrophile providing 3-selenyl substituted heterocycles in good yields. Analogously, various thiols, including Cys peptides, were efficiently employed for synthesis of 3-sulfenyl coumarins and quinolinones under light irradiation. Importantly, the reaction proceeded also under sunlight in comparable yields.

Last but not least, a straightforward method for preparation of Se–S bond-containing peptides was developed utilizing visible light-initiated reaction.[2] Significantly, unprotected peptides with "sensitive" amino acids showed excellent tolerance under chosen conditions. Furthermore, we demonstrated that Se–S bond-containing substrate is oxidation sensitive linker with potential application in biocompatible materials.

Supervisor: Dr. chem. P. Arsenyan

Acknowledgements
Financial support from Latvian Institute of Organic Synthesis is gratefully acknowledged (IG-2021-01).

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Cobalt Catalyzed C-H bond functionalization

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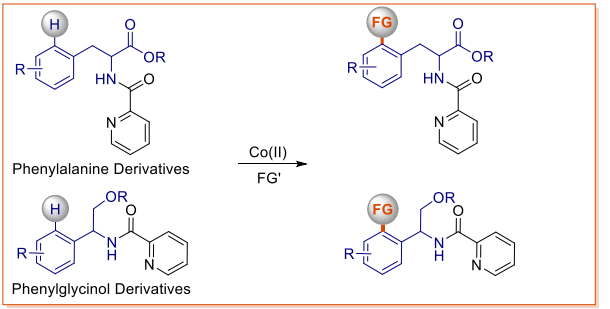
Over the past few decades, transition metal catalyzed C-H functionalization reactions have been immensely investigated due to their ability to functionalize relatively unreactive C-H bonds whilst simplifying synthetic schemes thus making the synthetic pathway more economical. Third row transition metals (Fe, Co, Ni) have displayed a rapid increase in applicability in C-H functionalization reactions, having similar or even better reactivity than precious metal (Pd, Ru, Rh) catalysts. In particular, simple cobalt salts in combination with directing group and oxidant have shown great potential in C-H functionalization methodology, allowing to construct C-C, C-N, C-S or C-Hal bonds.[1] Our work is dedicated to the development of Co-catalyzed, picolinamide directed C-H functionalization methodology of amino acid and amino alcohol derivatives (scheme 1.).



Scheme 1. C-H functionalization of phenylalanine and phenylglycinol derivatives

Supervisor: Dr. chem. L.Grigrojeva

Acknowledgements
This work is financially supported by LIOS grant IG-2019-05, ERDF project No. 1.1.1.5/17/A/004 and Latvian Council of Science, project [Cobalt catalyzed C-H bond functionalization], project no. lzp-2019/1-0220.

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POSTERS

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D-1

Benzoxaphosphepine 2-Oxides as Potential Carbonic Anhydrase Inhibitors

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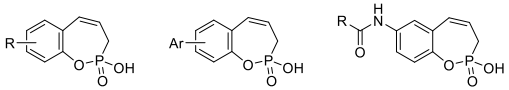
Carbonic anhydrases (CAs, EC 4.2.1.1) are a superfamily of metalloenzymes present across all kingdoms of life, as they catalyze reversible carbon dioxide hydration.[1] CAs were discovered in 1933, and since then they have been extensively studied. Today, inhibition of the CAs has pharmacological applications in many fields, such as anticancer agents, antiglaucoma, diuretics, antibacterial, anti-infectives, and many more. In last two decades CAs have been identified as a drug target.[1,2]

Recently in our research group, we designed and synthesized benzoxaphosphepine 2-oxides **1**. These compounds demonstrated good inhibitory activity and selectivity of tumor-associated hCA IX and hCA XII.

To better understand the structure–activity relationship (SAR), benzoxa-phosphepine 2-oxide aryl derivatives **2** were synthesized using Suzuki–Miyaura cross-coupling. A series of benzoxaphosphepine 2-oxide acylamino derivatives **3** were synthesized to extend compound library.



1 **2** **3**

R = H, Hal, EDG, EWG

Figure 1. Structures of synthesized compounds.

Supervisor: Dr. chem. R. Žalubovskis

Acknowledgements
We thank professor C. T. Supuran for the determination of CA inhibition. This project was funded by Latvian Institute of Organic Synthesis internal student grant IG-2021-09.

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D-2

Reactivity Investigation of Propargyl Silanes with Various Electrophyles

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Stabilizing properties of β-silicon effect have been known to facilitate reactions of unsaturated systems involving the formation of β-silyl carbenium ion.[1] Stabilization is achieved by either vertical - hyperconjugation or non-vertical - formation of cyclic silonium ion. Formation of the latter in the combination with other stabilizing effects explains why many reactions involving β-silyl carbenium ion tend to undergo 1,2-silyl shift.[2]

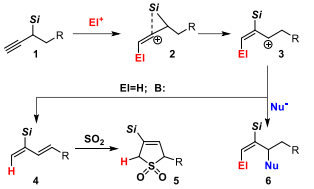

Figure 1. Mechanism and transformations of propargyl silanes

Herein, we report the use of liquid sulfur dioxide for the transformation of propargyl silanes **1** as a highly polar and Lewis acidic reaction media. This offers possibility to use weaker Bronsted acids like BzOH, TsOH compared to solvents like DCM. Generated silyl dienes are trapped *in situ* with SO_2 in cheletropic reaction forming corresponding silylsulfolenes **5.**[3]

To expand this concept further, other electrophiles have been used to activate propargyl silane moiety to obtain intermediate **3**. The latter can react with various nucleophiles to obtain compounds **6**.

Supervisor: Dr. chem. M. Turks

Acknowledgements

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D-3

Synthesis and Photophysical Properties of C-C Bonded Triazole-Purine Conjugates

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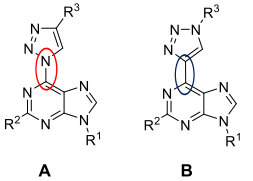
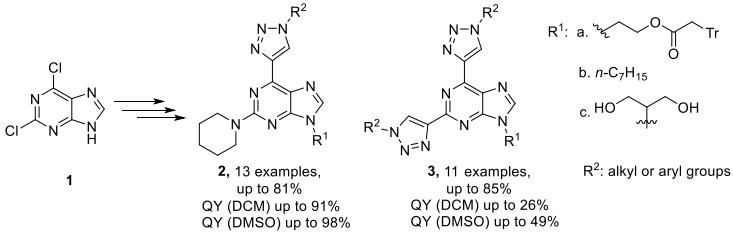
Earlier, our group reported the synthesis and photophysical properties of C-N bonded 6-(1*H*-1,2,3-triazol-1-yl)-9*H*-purine derivatives **A** (Scheme 1).[1,2] In this work we synthesized C-C bonded 6-(1*H*-1,2,3-triazol-4-yl)-9*H*-purine derivatives **B**. Such compounds possess enhanced stability due to C-C bond connection of 1,2,3-triazole to the purine ring, thus this triazole cannot act as a leaving group.



Scheme 1. C-N and C-C bonded triazolylpurine structures.

Target compounds **2-3** were synthesized from 2,6-dichloropurine **1**, using the sequence of Mitsunobu, Sonogashira, CuAAC and S_NAr reactions (Scheme 2). Further, photophysical properties of obtained compounds have been studied. Quantum yields reached up to 91% in DCM and 98% in DMSO solutions.



Scheme 2. General structures of target products **2-3**.

Supervisor: Dr. chem. I. Novosjolova

Acknowledgements
Dr. phys. K. Traskovskis is acknowledged for photophysical measurements.
This work was supported by the Latvian Council of Science grant No LZP-2020/1-0348.

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D-4

Process Optimization of the Synthesis of UAMC-00050, a Novel uPA Inhibitor

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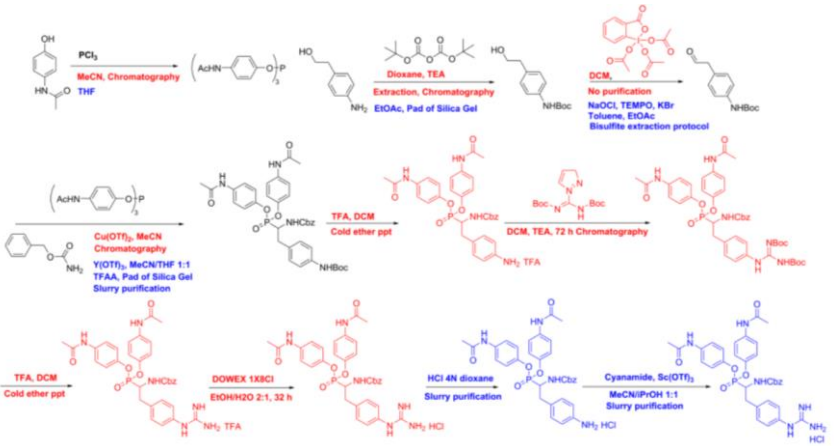
The α-aminophosphonate UAMC-00050, a newly developed trypsin-like serine protease inhibitor, has shown promising results for the treatment of dry eye syndrome and ocular inflammation.1 A laboratory-scale synthetic route was initially developed at the University of Antwerp. Preparation of larger amounts of UAMC-00050, required in the advanced steps of the project, proved to be difficult, due to the usage of environmentally unfriendly solvents and hazardous reagents. A new process was developed with greener alternatives and less toxic reagents. Every reaction was investigated to obtain the maximum yield, all the flash chromatography were replaced with silica pad filtration and slurry purifications. The overall yield was increased from 7% of the discovered route to 32% of the process development route. Scheme



Scheme 1. Process development for the candidate drug UAMC-00050, in red the old drug discovery procedure, in blue the optimized procedure.

Supervisor: Dr. chem. K.Shubin

Acknowledgements
This work has received funding from the European Union's Horizon 2020 research and innovation program under the Marie Skłodowska-Curie grant agreement No 765608.

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D-5

Electrosynthesis of *α,β*-Unsaturated Esters from Furfurylated Ethylene Glycols and Amino Alcohols

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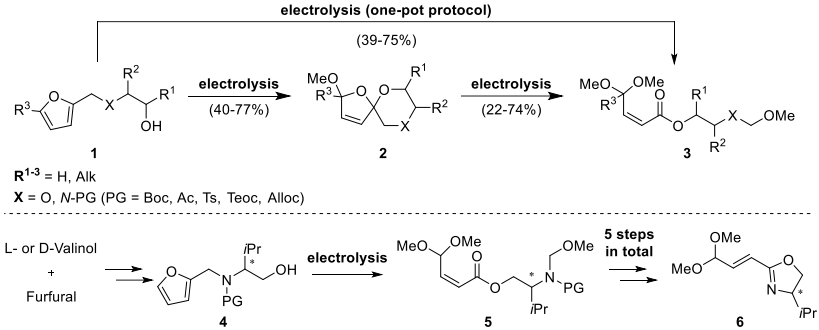
Biomass derived furanoics, easily accessible in bulk amounts, are versatile starting materials to obtain a range of chemicals with an application in material science, drug discovery and agriculture.[1]

Electrochemical methods have already been demonstrated as useful tools for valorization of biomass-derived compounds.[2] Furanoics are particularly suitable for electrochemical transformations due to the low oxidation potential of the furan ring which allows selective oxidation in the presence of other functional groups.

The aim of this work was to develop an electrochemical method to transform furan derived alcohols **1** into spirocycles **2** and unsaturated esters **3** (Scheme 1, top).[3] We have also developed synthesis of enantio-enriched oxazolines **6**, derived from electrochemically obtained esters **5** (Scheme 1, bottom).



Scheme 1. Electrochemical transformations of alcohols **1** (top) and synthesis of oxazolines **6** (bottom).

Supervisors: Dr. chem. A. Jirgensons, Mg. chem. A. Lielpētere

Acknowledgements

This work was supported by student grants from Latvian Institute of Organic Synthesis (IG-2020-05 and IG-2021-03).

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D-6

Functionalization of 1*N*-Protected Tetrazoles by deprotonation with turbo Grignard Reagent

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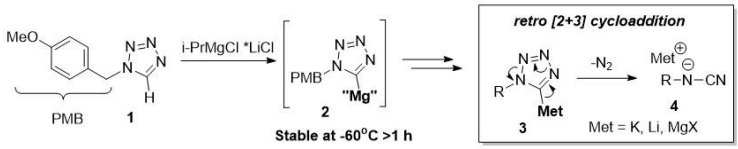
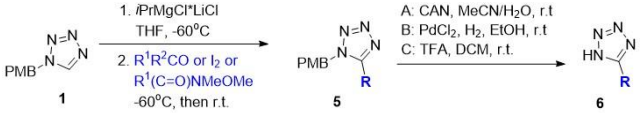
Tetrazoles do not exist in nature; however, the tetrazole motif is an important substructure that finds application in several fields such as pharmacology, biochemistry, and materials. Consequently, several methods for the synthesis of tetrazoles have been developed. Among them, C-H functionalization of tetrazoles via metallation is an attractive approach. This, however, suffers from low stability of metallated intermediate **3** (Scheme 1) which undergoes rapid retro [2+3] cycloaddition to cyanamide **4**.

In this work, we report C-H deprotonation of 1*N*-PMB protected tetrazole **1** with turbo-Grignard reagent (Scheme 1). This provides a metallated intermediate **2** with increased stability that overcomes the retro [2+3] cycloaddition problem.



Scheme 1.

The application of the metallated tetrazole **2** was demonstrated by the reaction with electrophiles such as aldehydes, ketones, Weinreb amides and iodine.



Scheme 2.

Deprotection of selected reaction products **5** was achieved utilizing three different methods, providing unprotected tetrazoles **6** (Scheme 2).

Supervisor: Dr. chem. A.Jirgensons

Acknowledgements
EU H2020 Marie Curie Skłodowska ETN program, project INTEGRATE (grant number 642620).

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D-7

Synthetic Approach towards Enantiopure Cyclic Sulfinamides

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N-Alkylation of readily accessible Ellman's sulfinamide derivatives has become a routine step in preparation of enantiopure amines.[1] On the other hand, rarely exploited nucleophilic character of the *S*-atom in *tert*-butyl sulfinamides can be revealed in a serendipitously discovered intramolecular alkylation. Regio- and stereospecificity of this transformation allows for facile preparation of diverse cyclic sulfinamides **3**. The latter are convenient enantiopure building blocks for medicinal chemistry owing to ample opportunities for diversification at the asymmetric *S*-atom and at the olefin site.

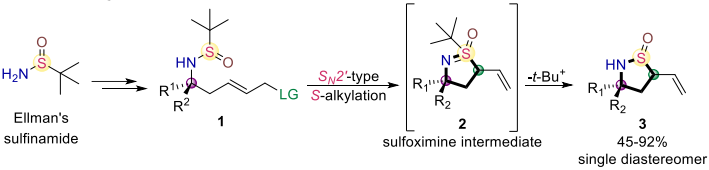

Figure 1. Intramolecular *S*-cyclization of *tert*-butyl sulfinamides **1**

Supervisors: Dr. chem. E. Suna, Dr. chem. P. Donets.

Acknowledgements
We gratefully acknowledge financial support from Latvian Institute of Organic Synthesis (LIOS).

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D-8

C-H Activation of Betulin Analogs

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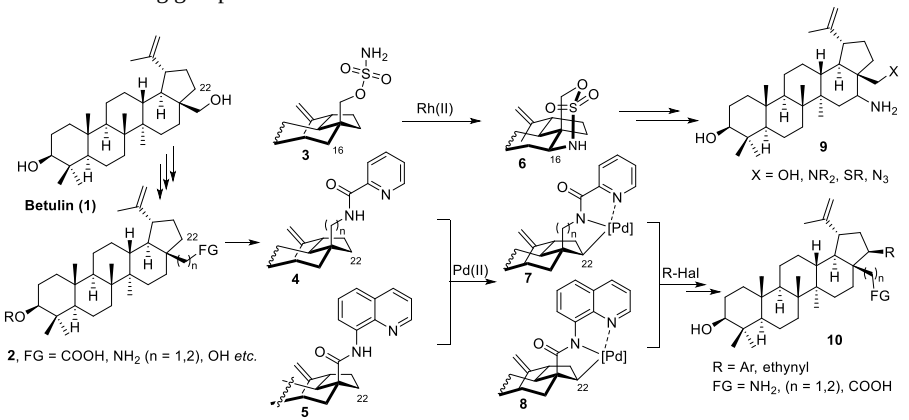
Betulin is pentacyclic triterpenoid natural product that is observed as secondary metabolite in more than 200 different types of plants. Betulin and its derivatives exhibit several important pharmacological properties such as antitumor, anti-inflammatory, antiparasitic, and anti-viral activities.[1] Owing to the success of Bevirimat various research initiatives have been undertaken to evaluate the potency of betulin analogs as different classes of therapeutic agents, and several lead targets have been identified with multiple mechanisms of action for further development. The aim of this work is to discover novel biologically active betulin type compounds by C-H functionalization at C(22) and C(16). For this purpose, precursors bearing different directing groups were obtained.



Scheme 1. Rh(II) and Pd(II) catalyzed C-H activatin routes

8-Sulfamate ester **3** was used for Du Bois γ-C-H bond amination via formation of oxathiazinane **6**.[2] Intermediate **6** can be further converted into differently functionalized compounds **9** through the ring opening reactions. 8-Aminoquinoline amide **5** and picoline amides **4** were combined with aryl halogenides and haloalkynes in the Daugulis C-H activation conditions.[3]

Supervisors: Dr. chem. J. Lugiņina, Dr. chem. M. Turks

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D-9

Cation–π Interactions for high Emission Intensity

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Modern light emitting devices are based on light emitting molecules (luminophores). In an isolated state luminophores can frequently achieve photoluminescence quantum yields (PLQYs) approaching 100%. However, in most applications luminophores are used in the solid state,[1] where intermolecular interactions are inevitable. Additionally, if luminophores do experience intermolecular interactions their light emitting properties are generally weakened, this phenomenon is known as aggregation caused quenching (ACQ).

While the common π–π type intermolecular interactions result in ACQ,[2] we have demonstrated that charged aromatic systems, such as imidazolium salts **1** and pyridinium salts **2**, **3** that feature π^+–π or π^+–π^+ intermolecular interactions displayed higher solid state PLQY than that in diluted solutions. We have provided evidence that intermolecular charge transfer (ICT) is responsible for the observed intense emission in the solid state. Furthermore, the counter ion strongly affects the solid state emissive properties. Accordingly, iodide counter ion displayed the lowest solid state PLQY while perchlorate counter ion displayed the highest PLQY, owing this effect to the π^+–π interaction stabilizing hydrogen bonds. Additionally, π^+–π interaction guided self-assembly of non-emissive pyridinium monomer **3** was achieved in diluted organic solvents, resulting in an ICT type emission and a sensory response. Hence, pyridinium salts display unconventional and useful emissive properties both in the solid state and solution.

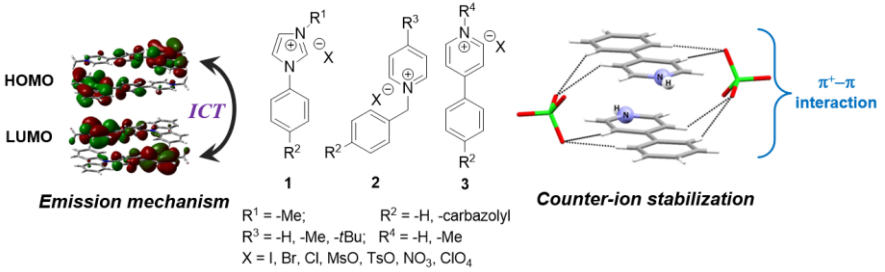

Figure 1. Imidazolium and pyridinium salts **1**–**3**, emission mechanism and counter ion stabilization.

Supervisor: Dr. chem. E. Suna.

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D-10

S_NAr Regioselectivity and Azide-Tetrazole Equilibrium Study in Pyrido[2,3-*d*]pyrimidine

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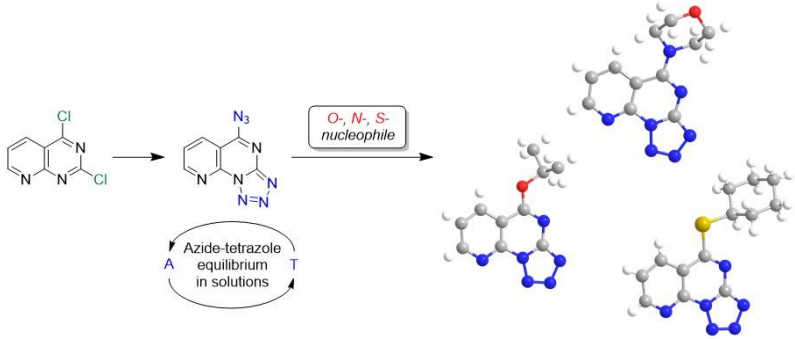
Pyrimidine scaffold is found in many biologically active compounds such as antiviral, antimicrobial and anticancer drugs.[1] Therefore modifications of pyrimidine moiety and new synthesis methods toward modified pyrimidines are continuously developing.

Our group has previously discussed azido group mediated aromatic substitution rearrangements in purines and quinazolines and the importance of azido-tetrazolo equilibrium in diazidopurine.[2] Herein we extend our research to pyrido[2,3-*d*]pyrimidines. S_NAr regioselectivity patterns of the latter *via* different substitution routes (**Scheme 1**) have been explored. Also dynamic azido-tetrazolo equilibrium in various organic solvents is studied in detail and solid state tautomer forms are determined by single crystal X-ray spectroscopy.



Scheme 1. S_NAr regioselectivity in azido-pyridopyrimidines.

Supervisors: Dr. chem. Irina Novosjolova, Dr. chem. Māris Turks

Acknowledgements

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D-11

Peptidic Boronic Acids as Inhibitors of PfSUB1

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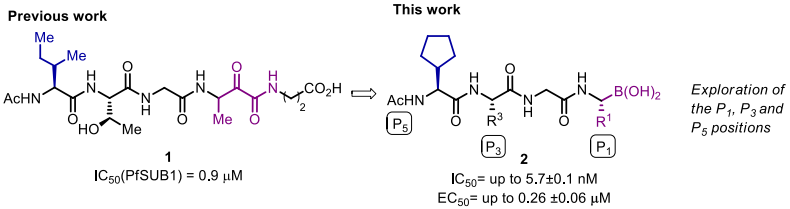
Malarial subtilisin-like serine protease (SUB1) is a multifunctional processing protease with a significant role in egress of newly formed merozoites by activation of a cascade of essential proteolytic events, leading to the rupture of human red blood cell and re-invasion.[1] Therefore, an inhibition of this enzyme can prevent from parasite replication and disease progression.

Previously, we have reported rationally designed peptidic α-ketoamide inhibitor **1** with submicromolar PfSUB1 inhibition potency (scheme 1).[2] However, the compound **1** showed no antimalarial activity in cell assay which was attributed to the low cell permeability.



Scheme 1. Known inhibitors of PfSUB1

This has prompted us to develop the next generation of peptidic PfSUB1 inhibitors **2** with a boronic acid moiety as a covalent warhead. Subsequently, we have discovered substrates **2** with inhibitory potency in nanomolar range. Moreover, compounds show potent parasite growth inhibition in red blood cell assay.[3]

Further investigation of the amino acid residues at P3 and P5 positions and their structure-activity relationship is ongoing.

Supervisor: Dr. chem. A. Jirgensons

Acknowledgements
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D-12

Synthesis of Fluorocyclopropylidenes via Julia-Kocienski Olefination

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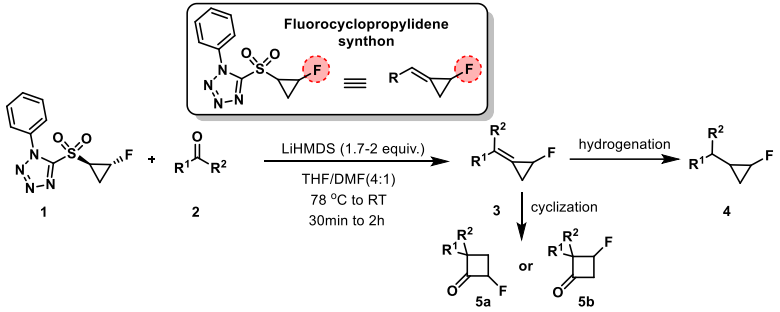
The cyclopropyl fragment and fluorine atom are often presented in the drug molecules because of their ability to modify activity and bioavailability.[1] Although, the combination of these two moieties into fluorocyclopropyl group[2] is less studied, it has been shown to be of great interest for medicinal chemistry applications.[3] Moreover, fluorocyclopropylidene moiety[4] is even less explored despite its potential application[5,6], as concise access to such fluorinated derivatives is missing.

Herein, we report on a new reagent **1** for a straightforward fluorocyclopropylidene group incorporation into aldehydes and ketones. The synthesis of rare[4-6] monofluorocyclopropylidene derivatives **3** via *Julia-Kocienski* olefination reaction using **1** offers further modification options. For example, bioisosteric replacement of *i*-butyl group with fluorocyclopropylmethyl group is an underexplored avenue in medicinal chemistry.



Scheme 1. Synthesis and application of CPD

Supervisor: Dr. sc. nat. J.Veliks

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D-13

Synthesis and Photophysical Properties of Fluorescent Purine-Carbazole Conjugates

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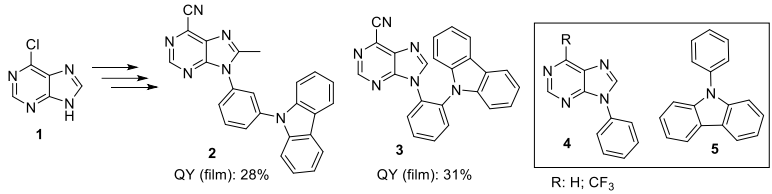
Earlier, we reported the synthesis and photophysical properties of fluorescent 1,2,3-triazolylpurine derivatives[1] and 2-azolylpurines.[2] We continued this work with a synthesis and an investigation of purine-carbazole conjugates, later to study their potential use in OLEDs as emitters or hosts [3]. Now we have modified purine structures with elements, which introduce steric hindrance for achieving optimal emission properties. Structure **2** is modified with a methyl group at purine C(8), which introduces steric hindrance and reduces rotation. In an alternative structure **3** connection between purine and carbazole moieties is made through an *o*-substituted benzene ring, which changes torsion angles between cycles and reduces possible rotation. Different 6-substituted purines **4** are prepared for use together with compound **5** as exciplex systems, which can utilize disconnected donor and acceptor molecules for emission.



Scheme 1. Common starting material **1** and synthesized target compounds **2**, **3** and **4**

Supervisors: Dr. chem. I. Novosjolova, Dr. chem. M. Turks

Acknowledgements
Dr. K. Traskovskis is acknowledged for photophysical measurements.

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D-14

Five-Membered Heterocycles as new Linkers for Potential Transfection Agents - Synthesis and Characterization

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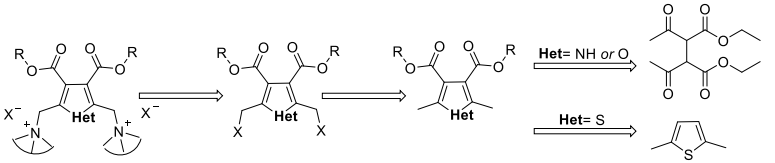
Liposomes and other types of nanoparticles have been extensively studied as innovative materials for the delivery of DNA, RNA, drugs and as different nanoparticles for transmembrane delivery. The structure of cationic lipids is a major factor for their transfection activity. A cationic lipid contains hydrophilic headgroup, a linker and a hydrophobic domain, and each of these structure elements could be modified in various ways. Also, each of these structure elements plays a defined role on biological and physicochemical properties.

This work is more based on study of the role of linker in cationic amphiphilic lipids. In previous studies we have been synthesized amphiphilic lipids with six-membered linkers, respectively, with 1,4-dihydropyridine and pyridine structures.[1] To extend our knowledge about significance of linker between hydrophilic and lipophilic parts we decided to synthesize five-membered analogues. We expect that changing the structure of heterocyclic compound will also result in different properties (both biological and physicochemical).

This work includes the development of synthetic methods to synthesize amphiphilic compounds with furan, thiophene and pyrrole heterocycles as linkers. Retrosynthetic analysis is shown in Scheme 1. Initial data of biological and physicochemical properties shows that synthesized molecules acts as a transfection agents and results are comparable with previously synthesized 1,4-dihydropyridines as well as commercial transfection reagent *TurboFect*.



Scheme 1. Retrosynthetic analysis of cationic amphiphilic lipids with five-membered heterocyclic linker.

Supervisor: Dr. chem. K. Pajuste

Acknowledgements
For financial support (LIOS internal grant IG-2021-07) and for biological studies (Dr. Zajakina group, LBMC).

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D-15

Divergent Semisynthesis of Rumphellaones A-C from β-Caryophyllene

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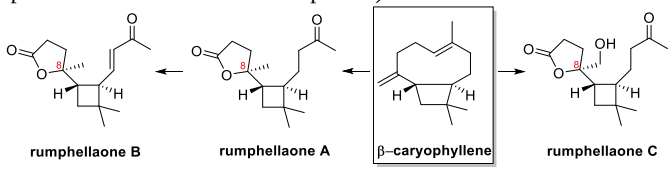
β-Caryophyllene is one of the most abundant sesquiterpenes found in nature, therefore it is available at low price from several commercial sources. The bicyclic structure of β-caryophyllene combined with two stereodefined chiral centers renders this terpene as an attractive renewable source for the access of diverse high value compounds. Our initial research of chemoselective transformations of β-caryophyllene opened an opportunity to develop a concise semisynthetic route (Scheme 1) towards biologically active sesquiterpene lactones (rumphellaones A-C and their C-8 epimers).[1]



Scheme 1. Synthetic route towards rumphellaones.

Rumphellaones A-C are 4,5-*seco*-caryophyllane sesquiterpenoids which were isolated from the gorgonian coral *Rumphella antipathies* and display cytotoxicity against human T-cell lymphoblastic leukemia cells[2] as well as inhibit the generation of superoxide anions and the release of elastase by human neutrophils.[3] Rumphellaone A was synthesized in the shortest reaction sequence reported whereas rumphellaones B and C were obtained for the first time by chemical synthesis.[1] Stereochemical configuration of final products was unambiguously confirmed by single crystal X-ray analysis.[1]

Supervisors: Dr. chem. D. Rasina, Dr. chem. A. Jirgensons.

Acknowledgements
This work is financially supported by ERDF Project no. 1.1.1.2/VIAA/2/18/380. G.S. is supported by LIOS student grant IG-2021-06.

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D-16

Structurally Simplified Diazonamide A Analogs as Anticancer Agents

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Diazonamides are a structurally unique class of secondary metabolites first isolated by Fenical and coworkers from the colonial marine ascidian *Diazona angulata*[1]. The structurally complex Diazonamide A (**1**) was found to be highly cytotoxic anticancer agent (IC_{50} = 57 nM)[2]. Studies conducted by Harran[3] revealed that DZ-2384 (**2**), a structurally simplified analog of **1**, is more potent (IC_{50} = 0.47 nM) and it lacks neurotoxicity at effective doses. However, **2** still remains to be synthetically challenging and its preparation requires many steps with poor overall yield.

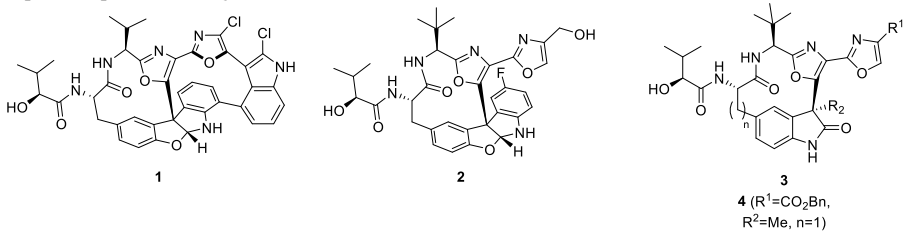

Figure 1. Structures of diazonamide A (**1**), DZ-2384 (**2**) and analogs **3** and **4**

Herein we report the less complex synthesis of oxindole-containing macrocycles **3** using diastereoselective S_NAr-type macrocyclization as the key step. *In vitro* cytotoxicity measurements indicated that analog **4** exhibits nanomolar activity against relevant cancer cell lines making it more cytotoxic than diazonamide A (**1**).

Supervisor: Dr. chem. E. Suna

Acknowledgements
We gratefully acknowledge financial support from European Regional Development Fund (ERDF) and thank *Dr. chem.* Ilona Domraceva for performing *in vitro* experiments.

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M-17

Cobalt-Catalyzed C-H Bond Carbonylation

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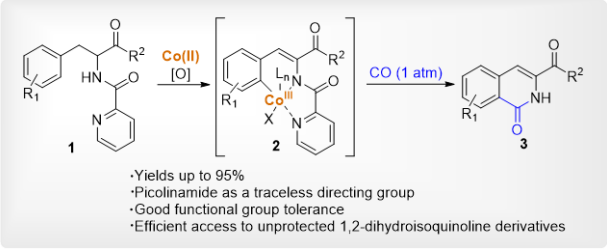
Over the past few decades, transition metal-catalyzed C-H functionalization reactions have been immensely investigated due to their ability to functionalize relatively unreactive C-H bonds. Majority of the results have been achieved using third row transition metals such as Pd, Ru and Rh.[1] Unfortunately, these transition metals are rather expensive and toxic. Cobalt being cheaper and less toxic element than noble metals[2] in combination with directing group and oxidant have shown the great potential in C-H functionalization methodology, allowing to construct C-C, C-N, C-S or C-Hal bonds.[1]

Our work is dedicated to the development of cobalt-catalyzed, traceless picolinamide-directed C-H bond functionalization of amino acid derivatives. During the experiments we found out that phenylalanine derivatives **1** reaction with CO gas leads to formation 1,2-dihydroisoquinoline derivatives **3** in excellent yields.



Scheme 1. Cobalt-catalyzed carbonylation of phenylalanine derivatives **1**.

Supervisors: M. Sc. Ing. Lūkass Lukašēvics, Dr. Chem. Liene Grigorjeva

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M-18

Synthesis of Novel C(3)-Linked Betulin Triazole Conjugates

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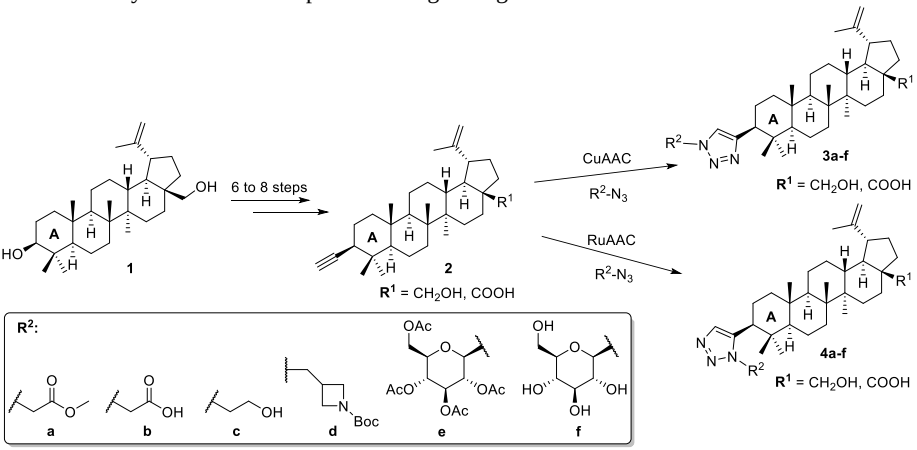
Nowadays medicinal chemistry is focusing on novel drug synthesis based on naturally occurring biologically active compounds and their semi-synthetic analogs. Betulin and its natural analog betulinic acid are lupane type pentacyclic triterpenoids found in many plants, but mostly in outer layer of birch bark (*Betulaceae*, *Betula sp.*). Betulinic acid possesses wide range of antiviral and anticancer activities. Also *in vitro* and *in vivo* studies of synthetically modified triterpenoids showed considerable anticancer activity. Literature studies revealed that nitrogen containing triterpenoid-azole conjugates possesses greater therapeutical properties compared to betulinic acid. We converted betulin to corresponding alkyne via multistep synthesis. Next, copper (I) or ruthenium (II) catalyzed 1,3-dipolar alkyne-azide cycloaddition reaction (CuAAC or RuAAC) yields novel betulin and betulinic acid triazole conjugates, with triazole moiety attached to triterpenoid A ring through C-C bond.



Scheme 1. Synthesis of betulin and betulinic acid triazole conjugates

Supervisors: Senior researcher, *Dr. chem. Jevgeņija Lugiņina*, Prof., *Dr. chem. Māris Turks*

Acknowledgements
This work is supported by Riga Technical University grant No. 04000-1.3-e/15.

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M-19

1,2,3-Triazoles as Leaving Groups in SNAr–Arbuzov Reactions: Synthesis of C6-Phosphonated Purine Derivatives

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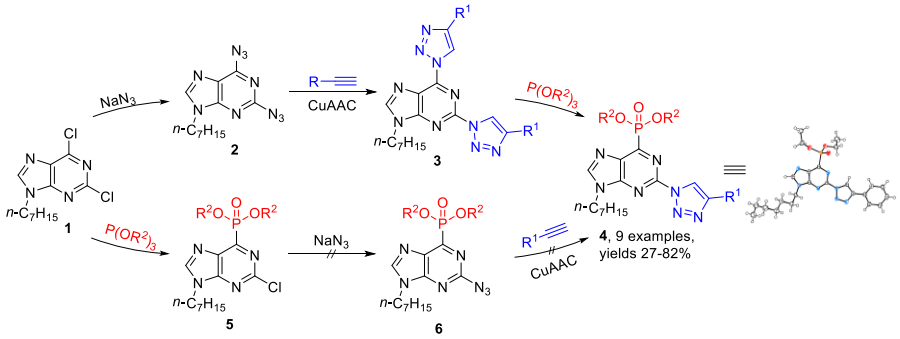
Purine derivatives are widely studied due to their biological activity. They are used as anticancer and antiviral drugs, and as agonists and antagonists of adenosine receptors.[1] In our studies we proved that 1,2,3-triazoles can be used as leaving groups in SNAr reactions with N-, S-, O-, C-nucleophiles.[2-4] In this research we obtained 2,6-bistriazolylpurine derivatives **3** in CuAAC between diazide **2** and different alkyl-/arylalkynes and used them in reactions with phosphites, obtaining 2-triazolylpurine phosphonates **4** in yields up to 82%. Alternative pathway which starts with SNAr-Arbuzov reaction on 2,6-dichloropurine **1**, yields phosphonates **5** and involves next SNAr with NaN_3 and subsequent CuAAC did not give the desired products **4** (Scheme 1). Structure of compound **4** was proved by X-ray analysis (Scheme 1).[5]



Scheme 1. Synthesis of C6 purine phosphonate derivatives **4**.

Supervisor: Dr. chem. I. Novosjolova

Acknowledgements

This work was supported by the Latvian Council of Science grant LZP-2018/2-0037.

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M-20

The Application of 1,2-Silyl Shift in Synthesis of Pyrrolidine Derivatives from Propargylsilanes

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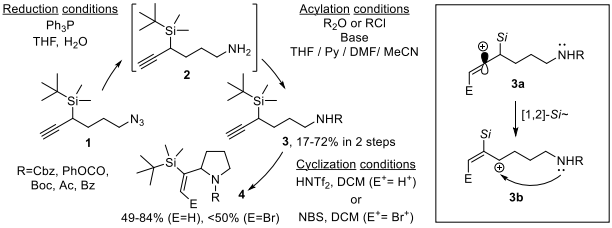
Pyrrolidines are common structural elements in natural products, especially in alkaloids, isolated from plants or microorganisms and exhibiting different biological activities, including antioxidant, anti-inflammatory, antihyperglycemic, antimicrobial, antifungal and anticancer properties.[1] Additionally, pyrrolidine and it's derivatives are often used as transition metal ligands, organocatalysts[2], and chiral controllers in asymmetric synthesis.[1,3]

In this work a new approach towards the synthesis of 2-(1-*tert*-butyldimethylsilyl)vinylpyrrolidines was investigated. By combining Staudinger reduction and subsequent acylation under various conditions, a two-step one-pot process for the synthesis of protected amines **3** from (6-azidohex-1-yn-3-yl)(*tert*-butyl)dimethylsilane (**1**) was designed. Cyclization of propargylsilanes **3** was achieved through electrophilic activation of the alkyne, followed by intramolecular nucleophile attack on the formed carbocation. The proposed intermediates for this transformation are the vinyl carbocation **3a**, which undergoes 1,2-silyl migration, resulting in the more stabilized allylic carbocation **3b**. Finally, an intramolecular nucleophile attacks the formed carbocation **3b**, yielding pyrrolidines **4**.



Scheme 1. Synthesis of 2-(1-*tert*-butyldimethylsilyl)vinylpyrrolidines **4.**

Supervisor: Dr. chem.. M. Turks

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M-21

On-site Molecular Shielding For Efficient Ultra-long Phosphorescence

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Phosphorescence is a type of luminescence in which the emission lifetime is longer than 1μs. Usually, phosphorescence is exhibited by metal containing compounds, but the high toxicity and manufacturing costs as well as low stability limits the use of such materials. Recently to overcome these drawbacks purely organic phosphorescent materials have become popular because of their biocompatibility, low cost, and limitless design possibilities.[1] Unfortunately organic materials rarely display phosphorescence due to slow intersystem crossing (ISC) resulting from deficient spin-orbit coupling (SOC). Materials SOC can be improved by the addition of carbonyl groups, heteroatoms, and heavy atoms, which can lead to an accelerated ISC and improved quantum yield (QY). However, an increase of QY is accompanied with a decrease of the emission lifetime.

Carbazole **1** is well studied in the literature and has a low phosphorescence QY.[3] To improve the QY we synthesized **2** which contains a thiophene fragment instead of benzene. Although a 30-fold increase in phosphorescence QY was observed, the emission lifetime had decreased. Strong intermolecular interactions from the introduced thiophene ring could be responsible for the shorter phosphorescence lifetime, so to test this hypothesis, we designed and synthesized thiophene derivatives **2-5** modified with alkyl substituents.

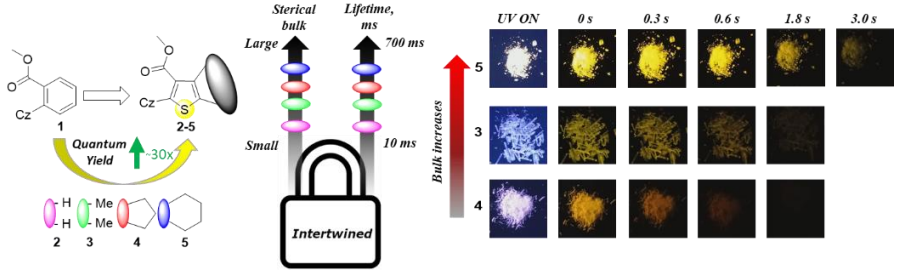

Figure 1. Phosphorescence in compounds **2**–**5**

SupervisorS: Dr. chem. E. Sūna, Ms. chem. K. Leduskrasts

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M-22

Synthesis and Application of Tetrazine Linkers for Chemical Modification of Proteins

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Bioconjugation methods are used for linking one molecule to another where at least one of which is a biomolecule.[1] For instance, tetrazine ligation is a rapid reaction between a tetrazine and a complementary strained dienophile and it is one of the fastest bioconjugation methods known up to date. Reaction proceeds via inverse electron demand Diels-Alder mechanism *(iEDDA)* without the need of catalysts, it is selective and also irreversible due to the loss of nitrogen.[2] Fast reaction rates allow conjugations at very low concentrations which in turn decreases possibility of biomolecule degradation.

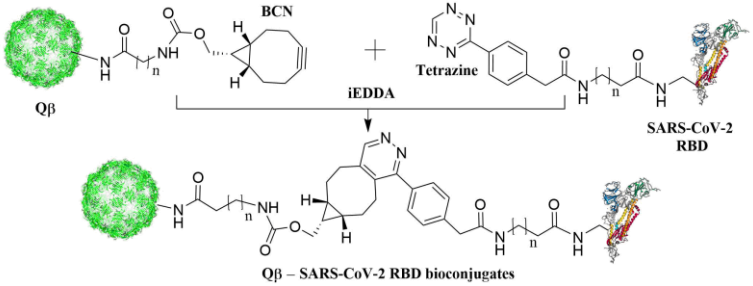

Figure 1. Bioconjugation of modified biomolecules via iEDDA

Herein we report synthesis of linkers containing tetrazine moiety and further attempts of improving linker selectivity for protein modification. Synthesized linkers have also been used for linking SARS-CoV-2 RBD spike protein and Qβ virus-like particles, thus creating a vaccine platform. Bioconjugates were used in mice immunization and preliminary data indicates that the novel Qβ-RBD bioconjugation protocol could be used in a development of SARS-CoV-2 vaccine.

Supervisors: Dr. chem. E. Sūna, MSc. chem. R. Klūga

Acknowledgements
This research was funded by the Latvian Council of Science (VPP-COVID-2020/1-0014).

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M-23

Electrochemical Decarboxylation of *N*-Substituted 2-Aminomalonic Acid Monoesters in intramolecular Hofer-Moest Reaction

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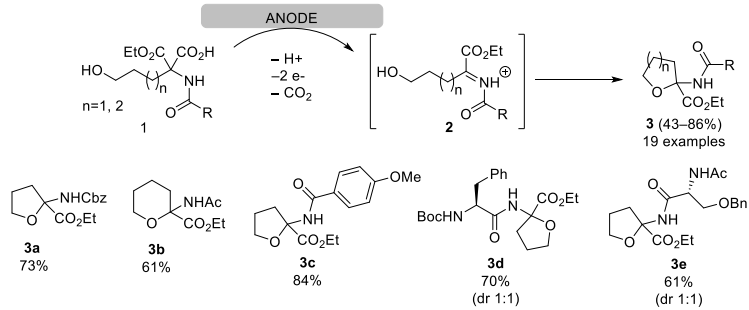
Kolbe reaction is one of the oldest electroorganic reactions, where an alkyl radical is generated upon anodic decarboxylation.[1] In contrast, in Hofer-Moest reaction a carbocation is generated after anodic decarboxylation followed by a reaction with a nucleophilic solvents, alcohols or amines.[2,3]

Malonic acid is an inexpensive and readily available substrate that can be easily functionalized, e.g. by alkylation reactions. Highly functionalized substrates can be obtained even after decarboxylation of the malonate. Hence, malonic acid derivatives are well-suited for electrochemical decarboxylation. Herein we report a previously unreported intramolecular Hofer-Moest reaction of *N*-substituted 2-aminomalonic acid monoesters (Scheme 1). A stabilized cation **2** is formed after anodic decarboxylation of a malonic acid monoester **1** followed by intramolecular cyclization. A quaternary carbon containing tetrahydrofuranes and tetrahydropyranes were obtained in good yields.



Scheme 1. Intramolecular Hofer-Moest reaction of *N*-substituted 2-aminomalonic acid monoesters.

Supervisor: Dr. chem. E. Suna

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M-24

Total Synthesis of the Proposed Structure of Uncarialin A

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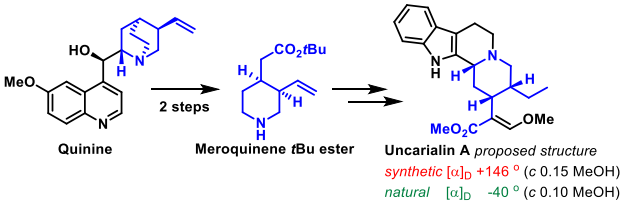
Uncarialin A (**1**) is a monoterpenoid indole alkaloid found in dried hooks of *Uncaria rhynchophylla* and first reported by Ma and coworkers in 2019 (Scheme 1).[1] It is known to inhibit the serotonin 5-HT_{1A} receptor in micromolar level, which is considered as one of the molecular targets for Parkinson's disease treatment. Besides that, it also inhibits the voltage-dependent L-type calcium channels at low micromolar concentrations[2] suggesting potential applications in prevention of cardiovascular diseases. Structurally, uncarialin A (**1**) differs from other naturally occurring *Corynanthe* indole alkaloids with a unique 3*R*,15*R*,20*R* stereochemistry of the chiral centers.

Herein we report the first total synthesis of the proposed structure of uncarialin A employing the readily available quinine as the starting material.[3] The significant spectroscopic differences between the synthetic sample and the literature suggest the originally proposed structure has to be revised. The alternative structures of uncarialin A will be also discussed.



Scheme 1. Application of quinine in the total synthesis of uncarialin A proposed structure.

Supervisor: Dr. chem. G. Šmits

Acknowledgements
The authors acknowledge the individual fellowship project of the Latvian Council of Science Nr. lzp-2020/2-0045 for the financial support.

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M-25

Exploring the Potential of Metal Catalyzed Flouromethylsulfonium Salt Reactions

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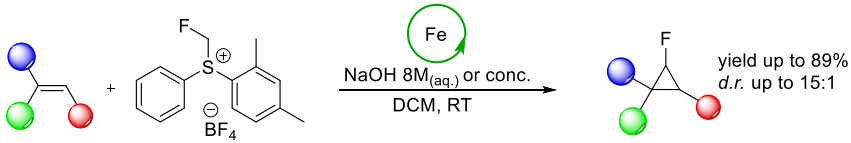
Synthesis of fluorine containing molecules is of great interest due to its unique properties and vast application in pharmaceuticals, agrochemicals and materials.[1]

Fluoromethylsulfonium salts are emerging as synthetic equivalents of flouromethylene synthon.[2] They participate in reactions with nucleophiles,[3] activated alkenes[4, 5] and carbonyl compounds.[6] However, their reactivity in transition metal catalyzed reactions is unexplored. Therefore, it is important to research the potential of metal catalyzed fluoromethylsulfonium salt reactions in order to obtain highly valuable fluorinated molecules.

Herein, we wish to report first fluoromethylene transfer to unactivated alkenes **1** by employing sulfonium salt **2** and earth abundant Fe catalyst (Scheme 1).



Scheme 1. Fluorocylopropanation of unactivated alkenes

The developed method allows fluorocyclopropanation of large variety of alkenes **1** to give otherwise challenging monofluorinated cyclopropanes **3** in moderate to excellent yields.

Supervisor: Dr. sc. nat. J. Veliks

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B-26

Synthesis of 2-Aminoquinazolin-4(3*H*)-one Based Open-Flap Plasmepsin Inhibitors

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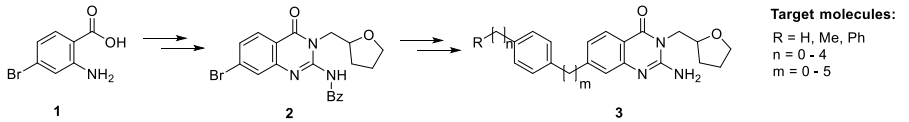
Malaria is a deadly parasitic infection caused by Plasmodium parasites, with *P. falciparum* being the most lethal human pathogen. The widespread resistance against available antimalarial drugs motivates scientists to develop new therapeutic agents targeting the life cycle of the parasite by novel mechanisms of action.

Plasmepsins (plm) are malarial aspartic proteases involved in the degradation of haemoglobin in the erythrocytic stage of the life cycle of parasite and have been proposed as appropriate antimalarial drug targets. Due to the high plm sequence similarity with several human aspartic proteases, e.g. cathepsin D (catD), it is important to design potent plm inhibitors that do not inhibit other proteases. This can be achieved with nonpeptidomimetic inhibitors that bind to the open-flap conformation of the pathogen enzyme.[1]

Current research focuses on structural and dynamic studies of mobile aspartic protease flap loop, with an aim to develop selective open-flap plm inhibitors. Here we present synthesis of known open-flap inhibitors – 2-aminoquinazolin-4(3*H*)-ones[2] **3** with different flap pocket substituents.



Scheme 1. Synthesis of 2-aminoquinazolin-4(3*H*)-ones **3** using building block strategy

Obtained compounds **3** are expected to give information on the role of the aromatic ring in the flap pocket substituent, as it has been identified as a common feature in most of open-flap plm inhibitors.

Supervisors: Dr. chem. D. Rasina, Dr. chem. R. Bobrovs

Acknowledgements
This research is funded by the Latvian Council of Science, project "Structural and dynamic studies of aspartic protease flap loop to advance the development of selective plasmepsin inhibitors", project No. lzp-2020/2-0012. D.R. was supported by ERDF Project no. 1.1.1.2/VIAA/2/18/380. R.B. acknowledges ERDF Project no. 1.1.1.2/VIAA/2/18/379 for funding.

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B-27

Synthesis of Enantioenriched Cyanohydrins using Lewis Base Catalysis

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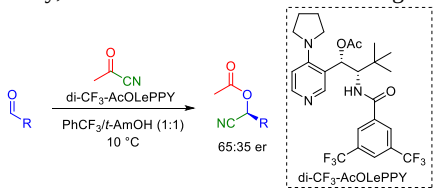
Enantiopure cyanohydrins are valuable building blocks in organic and medicinal chemistry. Both functional groups of cyanohydrins (nitrile and hydroxygroup) can be easily modified giving access to variety of valuable organic compounds such as α-amino acids, α-hydroxy acids, aziridines and others [1].

Herein we present the development of chiral Lewis base catalyzed synthesis of enantioenriched cyanohydrins using aliphatic and aromatic aldehydes. Highest enantiomeric ratio (65:35) was achieved using benzaldehyde and pyruvonitrile in presence of di-CF_3-AcOLePPY catalyst at 10 °C in 1:1 $PhCF_3$:*t*-AmOH solvent mixture. In order to understand and improve the stereoselectivity, mechanism of the reaction is being investigated.



Scheme 1. Synthesis of enantioenriched cyanohydrin.

Supervisor: Dr. chem. Artis Kinēns

Acknowledgement
Financial support from ERDF project No. 1.1.1.2/VIAA/3/19/589 is acknowledged.

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B-28

Synthesis and Reactivity of Imidazolyltetrazole Derivatives *via* Purine Ring Opening

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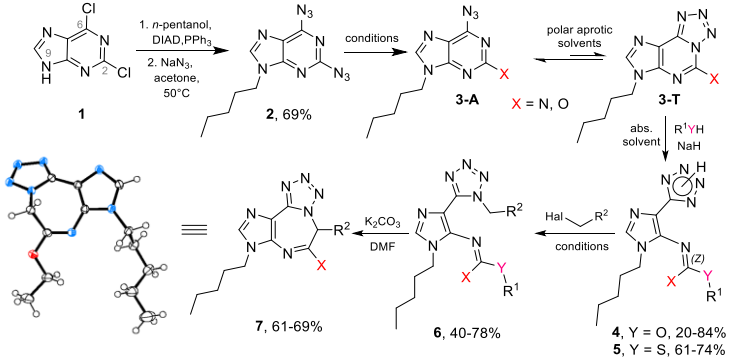
Imidazoles and tetrazoles are important pharmacophores with antibacterial and analgesic activities.[1] The present work focuses on S_NAr reactions of compound **3** with *O*- and *S*-nucleophiles. Compounds **3** exist in azido-tetrazole tautomeric equilibrium (Scheme 1) the extent of which is influenced by solvent, temperature and nearby electron-donating/electron-withdrawing groups.[2] The reactivity of ring opened products can further be explored by alkylating tetrazole ring and *in situ* creating tetrazolo fused 1,4-diazepine derivatives **7** (Scheme 1).



Scheme 1. Synthesis and reactivity of imidazolyltetrazole derivatives

Supervisors: Dr. chem. Irina Novosjolova, Dr. chem. Māris Turks.

Acknowledgements

Dr. phys. A. Mishnev for X-ray analysis.
This work was supported by the Latvian Council of Science grant No LZP-2020/1-0348.

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B-29

Synthesis of 2-Thio-6-triazolyl-7-deazapurine Derivatives

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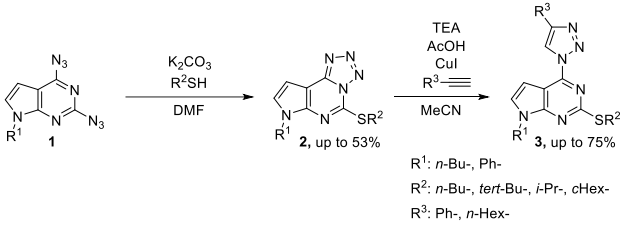
7-Deazapurine (pyrrolo[2,3-*d*]pyrimidine) derivatives are broadly studied as important chemicals due to their potential applications as antitumor and antiviral medicine.[1] It is known that S_NAr reactions between diazidodeazapurine and *N*-nucleophiles give corresponding 2-amino conjugates.[2] By using analogues conditions and performing S_NAr reactions with *S*-nucleophiles – thiosubstituted tetrazolodeazapurine derivatives **2** were obtained in yields up to 53% and then used in subsequent CuAAC with different alkynes yielding triazolyldeazapurine derivatives **3** in yields up to 75%. (**Scheme 1**). Additionally, regioselectivity and structure of compound **2** was proven by X-ray analysis (**Figure 1**).



Scheme 1. Synthetic route to 6-triazolyl-7-deazapurine **3** conjugates.

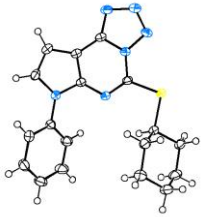


Figure 1. X-ray structure of 5-(cyclohexylthio)-7-phenyl-7*H*-pyrrolo[3,2-*e*]tetrazolo[1,5-*c*]pyrimidine.

Supervisors: Mg. sc. ing. K. Leškovskis, Dr. chem. I. Novosjolova, Dr. chem. M. Turks.

Acknowledgements
Dr. phys. A. Mishnev for X-ray analysis.
This work is supported by the Latvian Council of Science grant No LZP-2020/1-0348.

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B-30

Development of Synthesis Pathways for the Octahydro-1*H*-2,4-methanoindene Scaffold

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The octahydro-1*H*-2,4-methanoindene (**1**) scaffold is present in various limonoid natural products, such as phragmalin, xyloccensins and others.[1] Limonoid natural products exhibit a wide range of pharmacological properties, including anti-HIV, antibiotic, anti-cancer, anti-malarial, and anti-viral activities,[2] therefore, are of high synthetic interest. Some methods for the construction of the scaffold **1** are known.[3,4] However, the total syntheses of phragmalin-type limonoids have not been performed yet. As a part of total synthesis project of Libiguin A, we explore a pathway for a stereodefined assembly of scaffold **1** with a substitution pattern beneficial for further functionalisation.

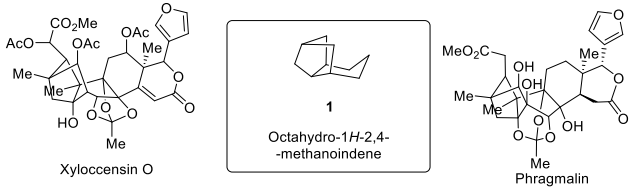
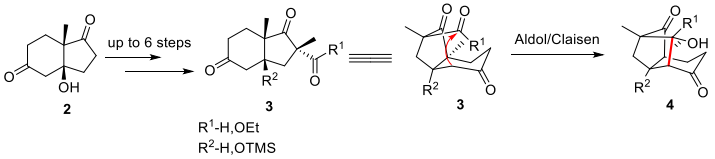


Figure 1. Selected limonoid natural products and scaffold **1**.

The pathway (Scheme 1) involves the modification of the Hajos-Parrish ketol (**2**) to obtain compounds **3** in 5-6 steps, depending on the substituents. Furthermore, compounds **3** will be subjected to Aldol/Claisen type condensations in attempts to yield the octahydro-1*H*-2,4-methanoindene scaffold **4**.



Scheme 1. Synthesis pathway and concept of the envisaged scaffold formation.

Supervisors: Dr. chem. J. Becica, Dr. chem. A. Jirgensons.

Acknowledgements
Project is supported by ESIF project Nr.1.1.1.2/VIAA/4/20/752.

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B-31

Synthesis of Purine Based Organoselenium Compounds

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The importance of modified purine bases and purine nucleosides in medicine, biochemistry and biology is well recognized. Additionally, the interest in the organoselenium compounds has increased in the last two decades due to their various biological activities. The combination of purine scaffold with selenium moieties can lead to the compounds with interesting properties.[1] Here we report the synthesis of 2-chloro-6-selanylpurine (**2-4**) and 2-triazolyl-6-selanylpurine (**6**) derivatives.

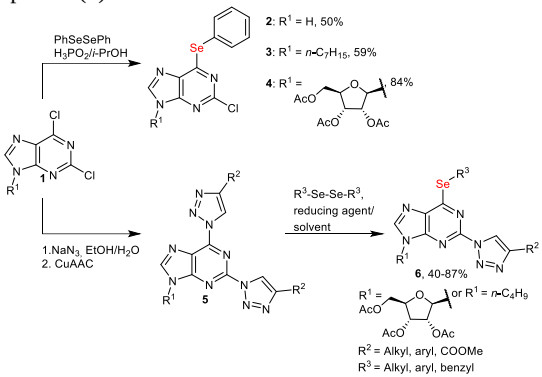

Figure 1. Synthesis of 2-chloro-6-selanylpurine (**2-4**) and 2-triazolyl-6-selanylpurine (**6**) derivatives.

Earlier we demonstrated that 1,2,3-triazole moiety at C(6) position of purine is a good leaving group in S_NAr reactions with *N*-, *S*-, *O*-, *C*- and *P*-nucleophiles.[2] In this study we extended the range of nucleophiles with selenols. The synthetic routes to 6-selanyl-2-triazolylpurine nucleosides and 2-chloro-6-selanylpurines will be discussed.

Supervisors: Dr. chem. I. Novosjolova, Dr. chem. Ē. Bizdēna

Acknowledgements
This work was supported by the Latvian Council of Science grant No. LZP-2020/1-0348.

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