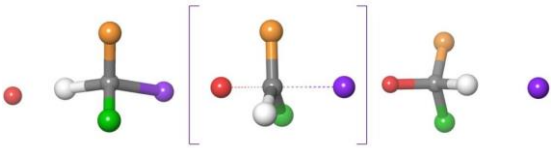
13th Paul Walden Symposium

September 14th-15th, 2023

Program and abstracts



Riga, Latvia

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Poster awards by

Paul Walden 13th Symposium on Organic Chemistry

We have the great pleasure of inviting you to the 13th Paul Walden Symposium on Organic Chemistry, which is hosted by the Latvian Institute of Organic Synthesis (LIOS) and Riga Technical University (RTU).

Paul Walden (Pauls Valdens) was an expert in three 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 2023, the recipient of the Paul Walden medal is Prof. Olafs Daugulis from the University of Houston, USA. His research interests are synthetic organic and organometallic methodology.

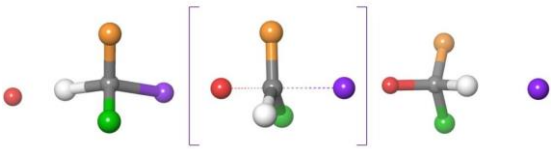
The goal of this Conference is to bring together scientists, scholars, and students from universities, research institutes, and industry across the Baltic States. The traditional format of the Walden Symposium comprises plenary lectures by renowned organic chemists and a poster session, where students communicate their research.

In addition, two oral presentations are offered by the best Latvian PhD students. Furthermore, this year, we will uphold all the long-standing traditions of the Walden Symposium, including the student poster competition that commenced 22 years ago. A panel consisting of invited speakers and local professors will determine the recipients of the best poster prizes in the bachelor, master, and PhD categories. We are pleased to announce that this year's best poster prize is generously sponsored by the Ukrainian company Enamine.

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

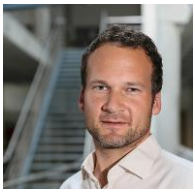
On behalf of the Organizing Committee,
Dr. Peteris Trapencieris
Latvian Institute of Organic Synthesis, Latvia

Program



Program

Thursday, September 14th

9.00		Welcoming remarks Prof. **Edgars Sūna** (Chairman of the Scientific Board, Latvian Institute of Organic Synthesis)
9.10		Presentation of the Paul Walden medal to Prof. Olafs Daugulis (University of Houston, Texas, US) by Prof. **Māris Turks**, Dean of the Faculty of Materials Science and Applied Chemistry (Riga Technical University)
9.30		Prof. **Olafs Daugulis** (University of Houston, US) ***New methods for carbon-hydrogen bond functionalization***
10.20		Prof. **Nicolai Cramer** (Ecole polytechnique fédérale de Lausanne, Switzerland) ***From [ ] to L****
11.10		*Symposium group photo and Coffee break*
11.40		Prof. **Andrew D. Smith** (University of St Andrews, UK) ***Promoting the forbidden: catalytic enantioselective [1,2]-rearrangements***
12.30		Poster pitches (PhD students)
12.45		*Lunch*

14.40 

Prof. **Zoltan Novak** (Eötvös Loránd University, Hungary)
Synthesis of fluoroalkylated derivatives: feedstocks, reagents, catalysis and media

15.30 Poster pitches (PhD students)

15.45 *Coffee break*

16.15 Poster pitches (PhD students)

16.30 

Prof. **Lutz Ackermann** (Georg-August-University Göttingen, Germany)
Metallaelectro-catalyzed bond activation

17.20 Guided tour of the Paul Walden and Wilhelm Ostwald monuments

Friday, September 15th

9.00 

Prof. **Pierangelo Metrangolo** (Politecnico Milano, Italy)
Journey through the World of halogen bonding

9.50 

Prof. **Rebecca Melen** (University of Cardiff, UK)
Group 13 Lewis acids for synthesis and catalysis

10.40 *Coffee break*

11.00 

PhD **Renāte Melngaile** (Latvian Institute of Organic Synthesis, Latvia)
Development of fluoromethylene transfer reagents

11.30 

PhD student **Gļebs Jeršovs** (Latvian Institute of Organic Synthesis, Riga, Latvia)
Sulfur-selective alkylation of sulfinamides

12.00 *Lunch*

13.00 Poster session & *Coffee break*

15.20 

Prof. **Paolo Melchiorre** (University of Bologna, Italy)
Photochemistry & organocatalysis: new radical opportunities

16.10 Poster awards and closing remarks

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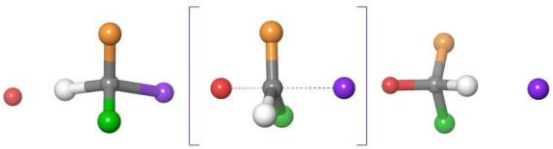

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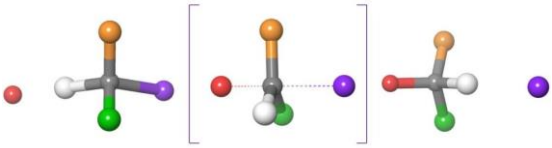
Plenary lectures



PL-1

New methods for carbon-hydrogen bond functionalization

Olafs Daugulis

University of Houston, USA
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This talk will describe the ongoing work in our group that has led to the development of new directing groups for carbon-hydrogen bond functionalization under palladium, cobalt, and copper catalysis. Furthermore, we will report on recent developments showing the use of copper(I)-sandwich complexes in non-directed sp^3 C-H bond functionalization which proceeds *via* carbene intermediates.

PL-2

From [ ] to L*

Nicolai Cramer

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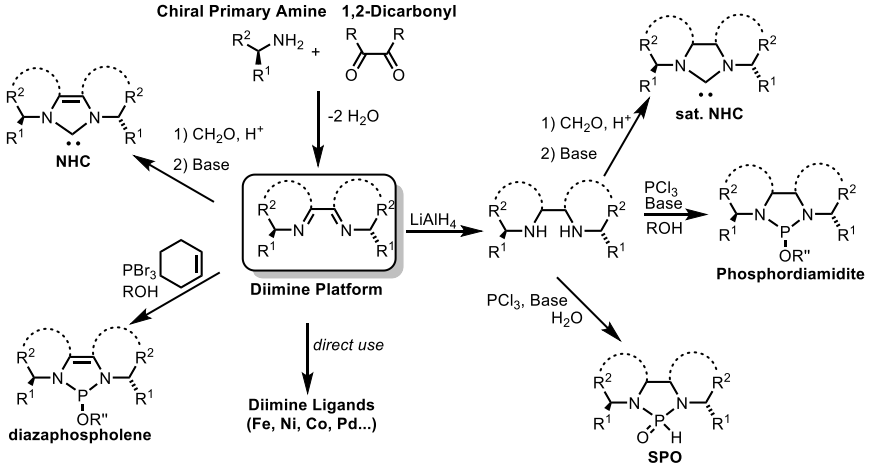
Advances in organic chemistry are of importance for modern society and synthesizing tailored molecules in high purity is critical for many industries. Of particular relevance for enantioselective catalysis is the efficient and streamlined access of to robust chiral ligands. Moreover, the design and development of novel enabling ligands systems is vital for success and represents one of our central research goals. In this respect, diimines are a versatile platform. These compound class is easily accessed from dicarbonyls and chiral primary amines by simple condensation chemistry. It then can be rapidly elaborated into a variety of enabling chiral ligands and catalysts. My presentation will cover some of our progress in diimine iron-catalyzed enantioselective transformation, the application of chiral NHC*-nickel catalyzed C-H bond functionalizations and the development of challenging transformation enabled by DAPs as main-group catalyst.



PL-3

Promoting the forbidden: catalytic enantioselective [1,2]-rearrangements

Andrew D. Smith

EaStCHEM, School of Chemistry, University of St Andrews, UK
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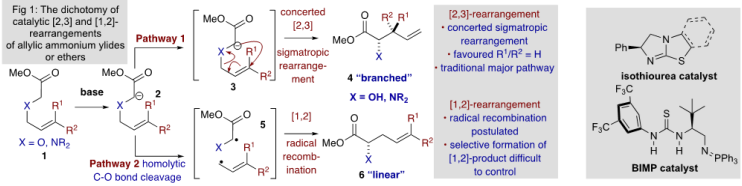
Stereoselective [2,3]-sigmatropic rearrangements have great utility in organic synthesis.[1] In particular, their ability to form carbon-carbon bonds with high diastereo- and enantiocontrol through well-defined and predictable transition states under mild reaction conditions makes these processes attractive for the synthesis of complex targets. In this context, the [2,3]-sigmatropic rearrangement of allylic ethers or allylic ammonium ylides 1 allows the preparation of bespoke α-functionalised stereodefined "branched" alcohol or amine derivatives 4 (Fig 1, Pathway 1). This process is well described in the literature with a concerted pathway *via* 3 predicted through orbital symmetry constraints. However, an alternative reaction pathway, that of the corresponding [1,2]- rearrangement, leads to the alternative "linear" product. As a concerted mechanism for a [1,2]-rearrangement is thermally-disallowed based on orbital symmetry, the generally accepted mechanism of this transformation is proposed to proceed through initial deprotonation, followed by homolytic C−O bond cleavage to generate a diradical pair 5, which undergoes radical-radical recombination to form the new bond and generate 6 (Pathway 2).[2] This di-radical pathway has been contentiously debated for decades; subtle changes in electronic and steric structure of the substrate is known to bias either the [1,2]- or [2,3]-rearrangement pathway, often leading to uncontrolled formation of both products. Irrespective of the mechanistic pathway there is extremely limited precedent (no examples to date) of the catalytic enantioselective [1,2]-rearrangements of allylic ethers or ammonium ylides. This talk will demonstrate the generation of methodology for the selective promotion of catalytic enantioselective [1,2]-variants of these processes using BIMP organocatalysts and isothioureas, as well as mechanistic studies of these reactions.



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PL-4

Synthesis of fluoroalkylated derivatives: feedstocks, reagents, catalysis and media

Zoltán Novák

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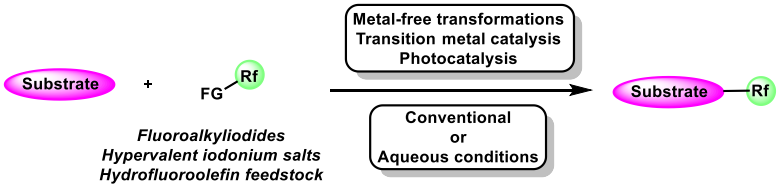
In our research group, we developed versatile synthetic procedures for the introduction of fluoroalkyl groups into various molecular structures. To achieve the functionalizations, we used different types of reagents which are able to transfer fluoroalkyl and fluoroalkenyl groups to the selected substrates. The significant part of our research focusses to the design of novel hypervalent iodonium species which are excellent electrophilic reagents for metal free transformations. With their utilization, we prepared aziridines and fluoroalkyl amines. The iodonium reagents are also suitable for metal catalyzed C-H activation reactions, and we utilized them for the fluoroalkylation and alkenylation of aromatic systems.



In our current research, we showed that fluorinated industrial feedstock materials such as HFO-gases are excellent fluoroalkyl sources for organic chemistry, and based on these materials we developed several transformations to synthesize novel fluorinated compounds. Additionally, we demonstrated that biosurfactants are suitable for aqueous organic transformations of fluorinated compounds, and ensures sustainable media for catalytic processes.

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PL-5

Metallaelectro-catalyzed bond activations

Lutz Ackermann

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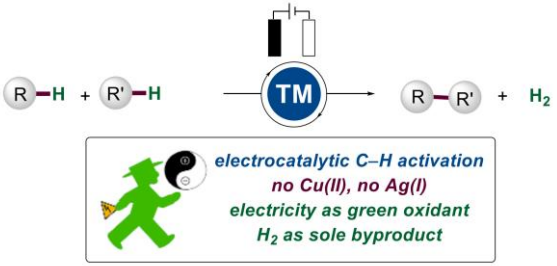
Oxidative C–H activation has emerged as an increasingly powerful tool in molecular syntheses.[1] Despite major progress towards atom and step economy, these transformations largely rely on precious metal catalysts and stoichiometric amounts of toxic metal oxidants, compromising the overall sustainability of the C–H activation strategy. In contrast, employing electrooxidation *in lieu* of reactive chemical oxidants prevents undesired waste formation through oxidant economy and offers efficient use of renewable energies from sustainable sources for chemical bond formation.[2] Inexpensive Earth-abundant 3d metal[3] cobalt a electrocatalysis set the stage for molecular syntheses at a unique level of resource economy. Our studies towards metallaelectrocatalytic C–H and C–C activation, data science[4] and enantioselective[5] electrocatalysis will be discussed, with a topical focus on sustainable base metals.



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PL-6

A journey through the World of halogen bonding

Pierangelo Metrangolo

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In recent years, halogen bonding has grown from a scientific curiosity to one of the most interesting noncovalent interactions for constructing supramolecular assemblies.[1] According to the recently proposed IUPAC provisional recommendation,[2] "A halogen bond occurs when there is evidence of a net attractive interaction between an electrophilic region associated with a halogen atom in a molecular entity and a nucleophilic region in another, or the same, molecular entity". This definition acknowledges the qualitative analogy between halogen bonding and the ubiquitous hydrogen bonding.

In this lecture, I will survey my 20 years of research, starting from small molecule crystal engineering and arriving to the relevant implications of in-vivo halogenation mechanisms.[3]

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PL-7

Group 13 Lewis acids for synthesis and catalysis

Rebecca L. Melen

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As main group chemistry, in particular boron chemistry, has expanded and developed over the past 20 years, one reagent has risen to prominence as well. Tris(pentafluorophenyl)borane, $B(C_6F_5)_3$, (commonly known as BCF) has demonstrated extensive applications in a wide variety of chemistry, including borylations, hydrogenations, hydrosilylations, frustrated Lewis pair chemistry, Lewis acid catalysis and more.[1] The high Lewis acidity of $B(C_6F_5)_3$ is achieved from the electronic effects of its three C_6F_5 rings, rendering it a versatile reagent for a great number of reactions. The talk will show our recent uses of Lewis acidic boranes in organic synthesis and catalysis.[2] This will include the use of boron Lewis acids for reactions with alkenes and alkynes, C-H functionalisation, and in radical chemistry.[3]

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PL-8

Development of fluoromethylene transfer reagents

Renāte Melngaile

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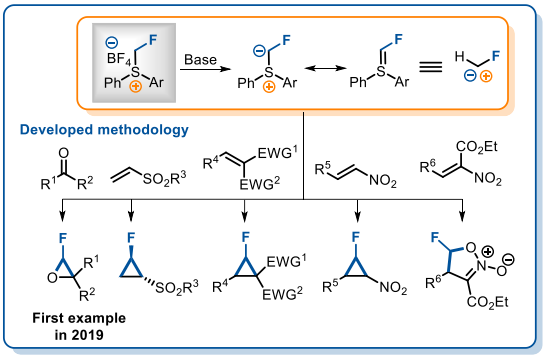
The development of safe and environmentally friendly reagents for the introduction of fluorine into organic compounds is an important challenge and significant research direction in organic chemistry.[1] In the literature, special attention has been devoted to the development of monofluorinated building blocks, which could offer alternative to the direct fluorination, however, there is a lack of reagents capable efficiently introducing monofluoromethylene synthon into a target structure.[2]

Our group has demonstrated for the first time the synthetic application of sulfur fluoromethylide, which was successfully generated from diarylfluoromethylsulfonium salt. When the ylide intermediate reacted with aldehydes and ketones, monofluorinated epoxides were successfully formed.[3] We have further expanded the use of fluoromethylide in fluoromethylene group transfer reactions with activated alkenes, giving the opportunity to obtain valuable fluorinated building blocks.



Scheme 1. Synthetic application of *in situ* generated sulfur fluoromethylide.

Supervisor: Dr. sc. nat. Jānis Veliks

Acknowledgements: This research was funded by the Latvian Council of Science project LZP-2019/1-0258, the European Social Fund within Project No. 8.2.2.0/20/I/008 and Latvian Institute of Organic Synthesis Student grant (IG-2023-01).

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PL-9

Sulfur-selective alkylation of sulfinamides

Glebs Jersovs, Dzonatans Melgalvis, Matiss Bojars

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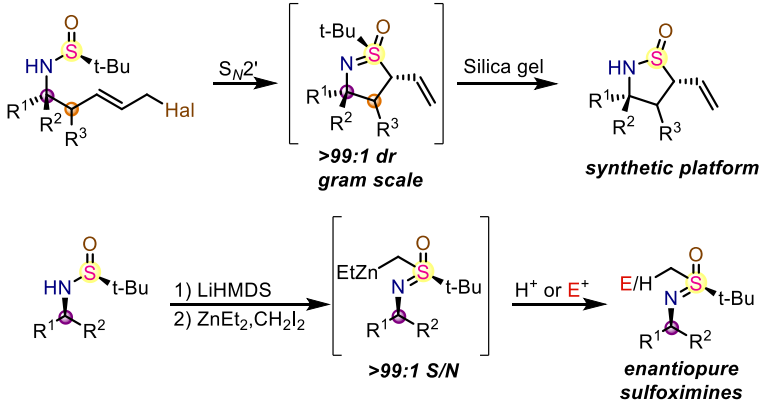
N-Alkylation of readily accessible Ellman's sulfinamide derivatives has become a routine step in preparation of enantiopure amines.[1] On the other hand, rarely exploited nucleophilic character of the *S*-atom in *tert*-butyl sulfinamides can also be used both in inter- and intramolecular transformations. We recently developed a regio- and stereospecific *5-exo-trig* cyclization[2] that allows for facile preparation of diverse cyclic sulfinamides. The latter are convenient enantiopure building blocks for medicinal chemistry owing to ample opportunities for derivatization.

Herein we demonstrate that the alkylation selectivity can be completely shifted to the *S*-atom by employing a zinc carbenoid electrophile. Notably, the transformation produces an unsymmetrical diorganozinc species allowing for further functionalization of the obtained sulfoximine.



Scheme 1. Sulfur selective alkylation of sulfinamides.

Supervisor: Dr. chem. Edgars Suna

Acknowledgements: This project was funded by the Latvian Council of Science; project LZP-2021/1-0578.

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PL-10

Photochemistry & organocatalysis: new radical opportunities

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The chemical reactivity of electronically excited molecules differs fundamentally from that in the ground state. This is the underlying reactivity concept of photochemistry,[1] which has traditionally allowed the development of unique chemical transformations not achievable *via* conventional ground-state pathways. For example, an excited-state molecule is both a better electron-donor (i.e. a better reductant) and electron-acceptor (i.e. a better oxidant) than in the ground state. This explains why the light excitation of organic molecules can unlock unconventional reactivity manifolds.

In this context, our laboratory has been exploring the potential of some organocatalytic intermediates to directly reach an electronically excited state upon visible-light absorption to then switch on novel catalytic functions that are unavailable to ground-state organocatalysis.[2] Studying the mechanism[3] of these photochemical approaches allowed us to expand the synthetic possibilities offered by the excited-state reactivity of organocatalytic intermediates and to develop enantioselective radical processes.[4]

Acknowledgements: This work was financially supported by the Institute of Chemical research of Catalonia (ICIQ, Tarragona) *via* the 'Strategic Funds Call 2021', the University of Bologna, and Agencia Estatal de Investigación (PID2019-106278GB-I00).

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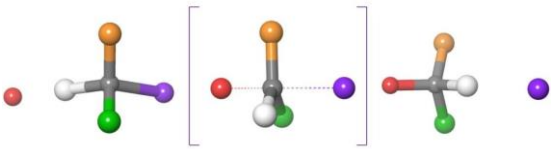
Posters



B-1

Synthesis and application of pentacyclic triterpenoid phosphonates

Rihards Lācis, Elza Fedorovska, Vladislavs Kroškins

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Natural pentacyclic triterpenoids are important secondary metabolites which have attracted interest due to the wide range of their biological activities such as antitumor,[1] antidiabetic[2] and antiviral activities.[3] Oleanolic, ursolic acids and betulin, are the most recognizable compounds of this branch, which are isolated from various plants. However, the medicinal application of these natural products are hindered by their extremely low water solubility and thus – low bioavailability.[4] One option to overcome this limitation is introduction of polar anionic functional groups such as phosphates and sulfates, which, however, are prone to hydrolysis.

Here we describe the synthesis of novel anionic triterpenoid phosphonates, which bear methylene-bridged phosphonate side chains. The latter are suitable for both the enhanced water solubility and complexing / salt formation with metal ions like Ca^{2+}, which is important for their further applications as bioactive additives to various calcium phosphate-based biomaterials.

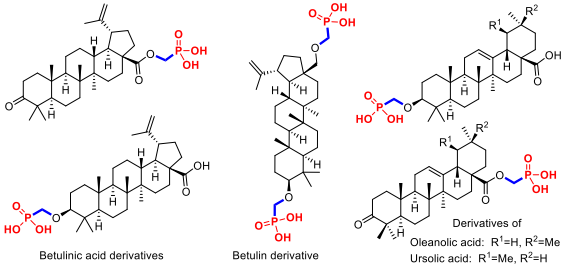

Figure 1. Desired target compounds.

Supervisors: Dr. chem. Jevgenija Lugiņina, Dr. chem. Māris Turks

Acknowledgements: This work has been supported by the State Research Program of Latvia" BioMedPharm". *Dr.* Ö. Demir and *Dr. sc. ing.* D. Loča are acknowledged for the cell viability tests.

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B-2

Ether-functionalized imidazolium ionic liquids

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Ionic liquids (ILs) are ambient-temperature liquid salts composed entirely of ions. The combination of organic cations and inorganic anions allows for the creation of ILs with desirable physical properties such as low melting points, tunable viscosities, increased electrochemical stability, and relatively high ionic conductivity. The first known IL was reported by the Latvian chemist Paul Walden in 1914.[1]

Fluorinated anions produce ILs of low melting points and viscosities, and high electrochemical stability. Ether functionalization has demonstrated to significantly reduce pure IL viscosities and densities.[2]

In this work, we have developed multigram synthetic routes to novel PEG-monomeric and PEG-dimeric imidazolium ILs based on bis-(trifluoromethanesulfonyl)imide $[NTf_2]^-$ anion (Figure 1) for energy storage applications. Density and viscosity analysis has been carried out using rolling ball viscometry and vibrating tube densimetry.

To understand the role of connectivity between the PEG chain and the ionic core, the linker length in cations has been varied from one (**1, 2, 3**) to two (**4**) carbon atoms. To facilitate cooperative interactions of the two chains with plausible solute ions, the chains have been placed in a parallel (1,2-substituted) fashion (**3**). Controls (1,3-substituted) have also been prepared (**1, 2, 3**).

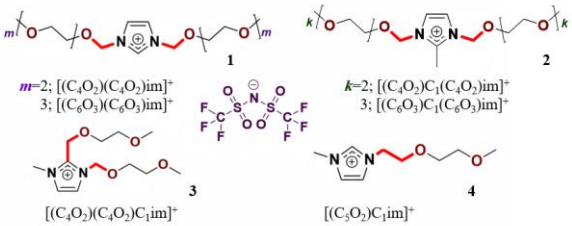

Figure 1. Structures of the cations of intermediates and $[NTf_2]^-$ ILs prepared.

Supervisor: Dr. chem. Eduards Bakis

Acknowledgements: This work was supported by the Latvian Council of Science (Grant No. lzp-2020/1-0391).

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B-3

Sulfonyl group dance for the synthesis of 4-azido-6,7-dimethoxy-2-sulfonylquinazolines

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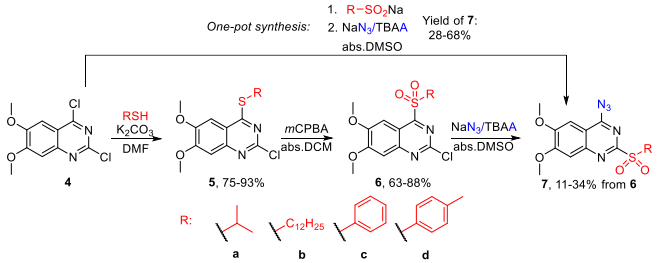
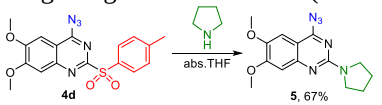
Quinazoline derivatives employ a wide range of biological activities. Modified quinazolines are widely used as anticancer, antiviral, and α1-blocker drugs.[1]

We have adapted the sulfonyl group dance, first characterized in the purine class,[2] to the quinazoline core, and obtained 4-azido-6,7-dimethoxy-2-sulfonylquinazoline derivatives **4** from the commercially available 2,4-dichloro-6,7-dimethoxyquinazoline **1** *via* two different synthetic pathways (Scheme 1).



Scheme 1. Synthetic approach toward 4-azido-6,7-dimethoxy-2-sulfonylquinazolines **4**.

The sulfonyl moiety at the C2 position of **4** inverses the reactivity of the quinazoline core in S_NAr reactions, allowing for selective C2 modification, which in literature is mainly done through ring closure reactions (Scheme 2).[3]



Scheme 2. Synthesis of 4-azido-6,7-dimethoxy-2-(pyrrolidin-1-yl)quinazoline **5**.

Supervisor: Dr. chem. Irina Novosjolova

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

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B-4

Synthetic application of monofluorocyclopropylsulfinate

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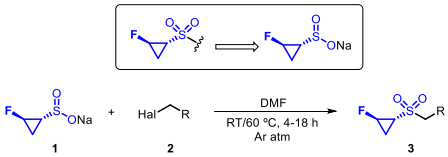
Fluoroalkyl containing compounds (e.g. $–CF_3$, $–CF_2H$, $–CFH_2$) are of high significance in research of pharmaceuticals,[1] agrochemicals[2] and advanced materials[3] as fluoroalkyl groups can alter physiochemical properties of a molecule, for example, metabolic stability and bioavailability.[4] Specifically, *Langlois* reagent ($NaSO_2CF_3$) has been used in a variety of trifluoromethylation reactions[5] as a $–CF_3$ source. Monofluorocyclopropyl group is an intriguing moiety with potential application in medicinal chemistry, therefore, monofluorocyclopropylsulfinate **1**, being similar to *Langlois* reagent, could be an attractive, yet little explored, source of this moiety in fluorine chemistry.

We demonstrate that using monofluorocyclopropylsufinate **1** significantly expands the potential application of our group's developed approach to monofluorocyclopropylsulfones **3** using the Johnson-Corey-Chaykovsky reaction,[6] since now not only aromatic, but also aliphatic monofluorocyclopropylsulfones **3** can be obtained.

Herein, we report a simple one step synthesis of monofluorocyclopropylsulfones **3** by reacting monofluorocyclopropylsulfinates **1** with primary or secondary alkyl halides **2**.



Scheme 1. Synthetic application of monofluorocyclopropylsulfinate **1**.

Supervisors: Ph. D. Renāte Melngaile, Dr. sc. nat. Jānis Veliks

Acknowledgements: Financial support by the European Social Fund project No 8.2.2.0/20/I/008, Latvian Institute of Organic Synthesis Student grant (IG-2023-01).

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M-1

Design of S and Se containing nucleophilic catalysts

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Pyridine and its derivatives are often used as effective nucleophilic catalysts for reactions such as the Baylis-Hillman reaction, acyl group transfer reactions, and others. A noteworthy example is DMAP which is a widely known acylation reaction catalyst. Alcohol acylation reactions can also be catalyzed by isochalcogenurea derivatives which exhibit a 1,5-O···Ch interaction in the acylated intermediates.[1] Similar chalcogen bonding interactions haven`t been investigated in DMAP-type catalysts.

In this research chalcogen containing DMAP-type catalysts were synthesized. Activities of the newly obtained catalysts were determined by performing an acylation reaction of a sterically hindered secondary alcohol (Figure 1). Experiments show that introducing a substituent at the *C*-2 position significantly decreases the catalytic activity which was expected and has been previously reported.[2] Importantly, it was observed that the activity of sulfur-containing catalysts increases with increasing electron donating ability of the *C*-4 substituent of pyridine, but the opposite trend was observed for selenium-containing catalysts.

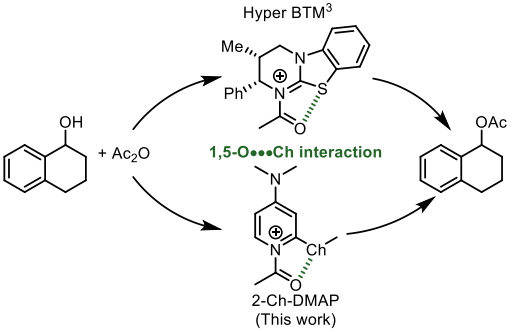

Figure 1. Acylation of a sterically hindered 2° alcohol using Lewis base catalysis.

Supervisor: Dr. chem. Artis Kinēns

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M-2

Elaborating the new route toward Phragmalin methanoindene cage key intermediate

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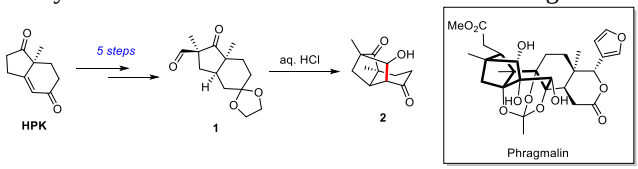
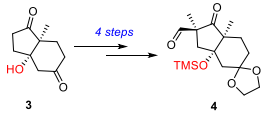
Phragmalin-type limonoids stand out as intricate natural compounds, showcasing a diverse array of biological activities including anti-cancer, anti-bacterial, and anti-inflammatory properties.[1] These compounds feature an unconventional octahydro-*1H*-2,4-methanoindene cage structure (Scheme 1). To construct this scaffold, the Hajos-Parrish ketone (HPK) has been chosen as the readily available starting material for the synthesis of the key intermediate **1**. Subsequently, through the strategic aldol reaction (Scheme 1), aldehyde **1** can be transformed into the distinctive cage framework.[2]



Scheme 1. Structure of phragmalin and synthetic pathway toward the scaffold **2**.

In this work, the main focus was to install the hydroxy group at the ring junction position in order to construct the methanoindene cage possessing bridgehead alcohol structural motif (Scheme 1). Therefore, the main starting material – HPK was switched to Hajos-Parrish ketol (**3**). Moreover, more efficient new synthetic route toward β-keto aldehyde **4** was developed (Scheme 2). Studies of aldol-type cyclization of compound **4** *en route* to cage structure are in progress.



Scheme 2. The new route toward the key intermediate **4**.

Supervisors: prof. Aigars Jirgensons, Mg. sc. ing. Georgijs Stakanovs

Acknowledgements: This work was supported by ESIF project Nr.1.1.1.2/VIAA/4/20/752. *Dr. chem.* M. Skvorcova for theoretical and practical consultation.

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M-3

Bromination of 2,6-methyl groups of *bis*-1,4-dihydropyridines and bromine nucleophilic substitution

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Due to their unique and extensive biological uses, 1,4-dihydropyridine (1,4-DHP) scaffolds are an important family of pharmacologically active compounds.[1] Several studies have been carried out on the synthesis and properties of 1,4-DHP-containing, liposome-forming, cationic amphiphiles. Some of the 1,4-DHP amphiphiles have shown the ability to introduce plasmid DNA into various cell lines *in vitro*.[2-4]

One of the most important steps in the preparation of synthetic cationic lipids based on the 1,4-DHP structure is the bromination of methyl groups at positions 2 and 6. In this work, by testing four different brominating reagents, the optimal reaction conditions for bromination were found, followed by nucleophilic substitution of bromine with various pyridine derivatives containing electron-donating or electron-withdrawing substituents.

The best reaction conditions for the bromination were found to be the use of pyridinium perbromide in ethyl acetate. These reaction conditions allowed to decrease the reaction time to 30 minutes and increase the yield up to 85%. From the obtained bromides, 11 novel cationic pyridine moieties containing amphiphilic *bis*-1,4-DHP derivatives **1** (Figure 1) were synthesized in 16-80% yields.

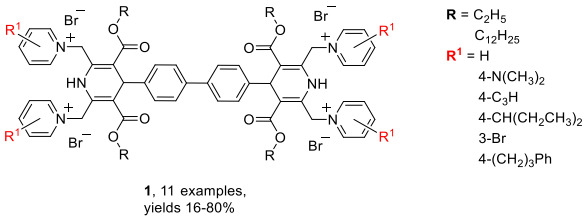

Figure 1. General structure of synthesized *bis*-1,4-DHP amphiphiles.

Supervisor: Dr. pharm. Martiņš Ruciņš

Acknowledgements: This work was funded by the EuroNanoMed3 Project TENTACLES.

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M-4

Synthesis of 1,2-dihydropyridine derivatives and their aromatization

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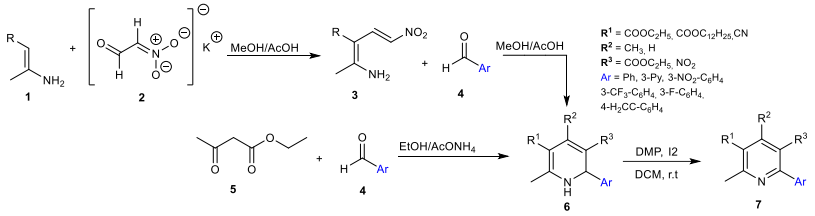
Historically, 1,4-DHPs have received more attention due to their use as antimycobacterial and anticonvulsant agents, along with their role as calcium-channel modulators in treating cardiovascular diseases and exhibiting anti-cancer activity.[1,2] In recent years, drugs such as nifedipine and niguldipine have been found to undergo redox processes, due to the catalysis of cytochrome P-450 in the liver during their metabolism.[3] Therefore, 1,4-DHPs have been more studied, while derivatives of 1,2-DHPs remain largely unexplored thus making them valuable compounds.

In this study, the examination of ten different oxidation methods is undertaken and Dess-Martin periodinane (DMP)/I_2 in dichloromethane at room temperature is identified as the most effective. To study this method eleven 1,2-DHPs **6** were obtained by the cyclization of corresponding nitrodienamines **3** and acetoacetic acid ethyl ester **5** with aldehydes **4** according to previously published procedure.[4] Derivatives of 1,2-DHPs are synthesized with different alkyl chain length at position 3, varying aromatic group at position 6 or alterations of the nitro to ester group at position 5 (Scheme 1).



Scheme 1. Synthesis of 1,2-DHP **6** followed by aromatization to pyridines **7**.

At the end eight new pyridine compounds **7** were obtained in good yields (64−90%). Overall, this study provides valuable insights into the oxidation process of 1,2-DHPs and demonstrates the practicality of employing diverse oxidants.

Supervisor: Dr. chem. Aiva Plotniece

Acknowledgements: This research was funded by the EuroNanoMed3 Project TENTACLES.

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M-5

Hydrosilylation of esters to silyl acetals catalysed by using SilBoRed™ technology

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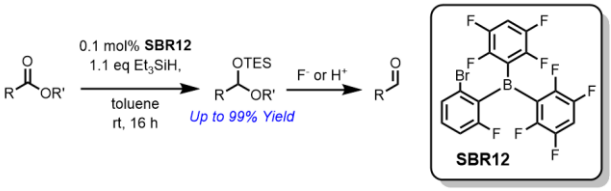
The selective reduction of an ester functional group to the corresponding aldehyde is one of the fundamental reactions in organic chemistry. For this transformation diisobutyl aluminium hydride (DIBAL-H) is a widely used reducing agent which poses a serious risk during the manufacturing due to its pyrophoric nature and additionally cryogenic conditions are needed to reach good selectivity. Moreover, during the process a considerable amount of inorganic waste and flammable gas (isobutane) are being generated. Over the past decades, hydrosilylation has become a powerful tool in organic synthesis. Recently Aldexchem Ltd. has filed a patent application describing polyhalogenated triaryl borane catalysts exhibiting excellent selectivity and conversion in the hydrosilylation of various esters furnishing the corresponding silyl acetals in nearly quantitative yields

Herein we report on the expansion of the substrate scope and the optimization of ester hydrosilylation by using SilBoRed™ technology, as well as the application of the developed methodology in the total synthesis of naturally occurring pheromones.



Scheme 1. Hydrosylilation of esters toward silyl acetals.

Supervisors: Dr. Gints Šmits, Dr. G. Szilvágyi, J. Répási

Acknowledgements: The authors acknowledge AldexChem for The financial support.

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M-6

Synthesis of potential IRE1α inhibitors

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IRE1α is a transmembrane protein located in the endoplasmic reticulum of cells. It is involved in the development of such cancers as breast, prostate, and pancreatic cancer. IRE1α inhibitors might be used to treat these types of cancer. [1]

Most of the currently known IRE1α inhibitors have pharmacodynamic properties inappropriate for clinical use.[1, 2] In this work, a series of 3-substituted aminotriazoles **1a-m** were synthesized as potential IRE1α inhibitors to study their structure-activity relationships with the aim of finding a compound that would exhibit higher activity and selectivity than the IRE1α inhibitors described in literature.

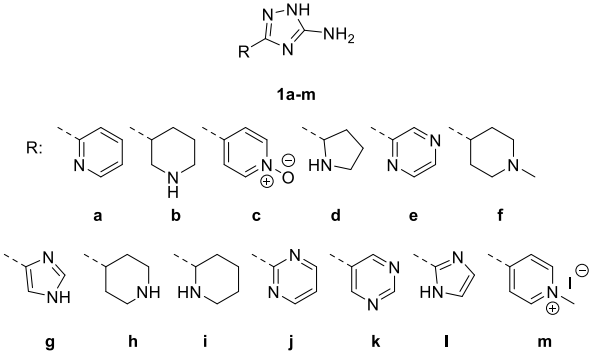

Figure 1. Synthesized 3-substituted aminotriazoles.

A number of other 3-substituted aminoazoles were also synthesized. However, none of these inhibited IRE1α as effectively as the aminotriazoles. Compounds **1d**, **1f**, and **1j** had the greatest ability to inhibit IRE1α out of all the synthesized compounds.

Supervisor: Dr. chem. Igors Kļimenkovs

Acknowledgements: We acknowledge Prof. A. Samali's group (University of Galway) for the activity determination of the synthesized compounds.

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M-7

Palladium catalysed [3+2] cycloaddition of trimethylenemethane to sulfur dioxide

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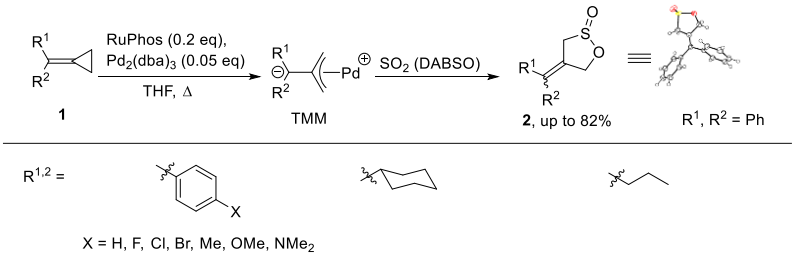
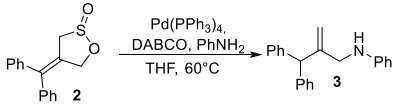
Trimethylenemethane (TMM) is a known intermediate which can be represented as 4 carbon conjugated structure of diradical or zwitterion.[1] TMM has been shown to react with carbonyl-, iminyl-, cyano- groups and C-C double or triple bonds. Also its reaction with CO_2 has been reported previously.[2]



Scheme 1. TMM reaction with SO_2.

Herein, we unveil novel TMM reactivity towards SO_2. TMM is generated *in situ* from easily attainable methylenecyclopropanes **1** through palladium catalysis, then TMM reacts with dissolved SO_2 yielding γ-sultines **2**.

Investigation of γ-sultine **2** reactivity has shown that these products are bench-stable, but can regenerate TMM through palladium catalysis, reacting with a nucleophile under milder conditions than described in literature.[3]



Scheme 2. TMM regeneration through palladium catalysis.

Supervisor: Dr. chem. Māris Turks

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M-8

Tandem 1,2-silyl shift – friedel–crafts synthetic approach to substituted vinyl chromanes

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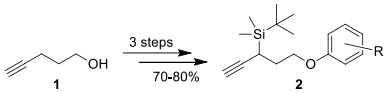
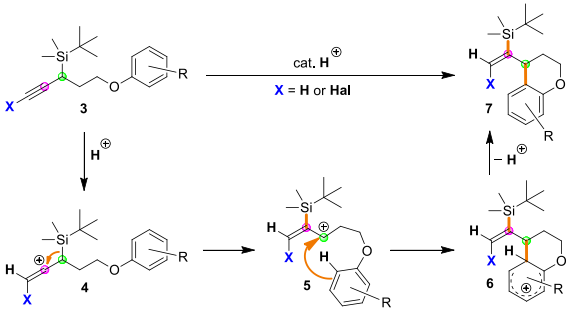
Herein we report a new synthetic route to substituted 4-vinyl chromanes. The key synthetic step involves tandem 1,2-silyl shift – Friedel–Crafts cyclization of propargyl silyl group containing aryl ethers **2**.

Aryl ethers **2** can be obtained from commercially available pent-4-yn-1-ol (**1**) in 3 steps: O-silylation, retro-Brook rearrangement[1] under Schlosser conditions and modified[2] Mitsunobu reaction with corresponding phenols (Scheme 1).



Scheme 1. Synthesis of aryl ethers **2**.

Aryl ethers **3** in the presence of strong Brønsted acids undergo cyclization[3] to yield chrormanes **7** (Scheme 2). In order to increase functionalization of the molecule, terminal alkyne can be easily converted to haloalkyne and employed in same catalytic conditions to yield chromane with *E*-selective alkene side chain.



Scheme 2. Tandem 1,2-silyl shift – Friedel–Crafts cyclization of aryl ethers **3**.

Supervisor: Dr. chem. Māris Turks

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M-9

First total synthesis of (+)-Sitsirikine and (+)-Dihydrositsirikine

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Sitsirikine and Dihydrositsirikine are monoterpenoid indole alkaloids found in leaves of *Vinca rosea* Linn. and first isolated by Barnes and coworkers in 1961 (Figure 1)[1] followed by core structure assignment in 1963 by Brown and Kutney.[2] The stereochemistry of Sitsirikine was finally assessed by Brown and Leonard[3] only in 1979. Sitsirikine exhibits vasorelaxant activity against phenylephrine-induced contraction of rat mesenteric arteries, with EC_{50} values less than 10 μM.[4]

Herein we report the first total synthesis of Sitsirikine and Dihydrositsirikine. The synthesis features a diastereoselective Ireland-Claisen rearrangement furnishing the key piperidine building block which is further incorporated into the octahydroindoloquinolizine employing an oxidative Bishler-Napieralski sequence. The spectral data of the synthetic sample is in good agreement with the literature.[5]

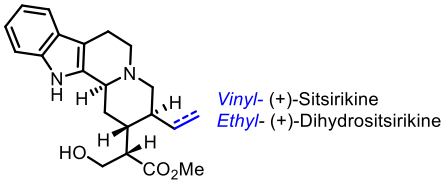

Figure 1. Structures of (+)-Sitsirikine and (+)-Dihydrositsirikine.

Supervisor: Dr. chem. Gints Šmits

Acknowledgments: The authors acknowledge the individual fellowship project of the Latvian Council of Science no. lzp-2020/2-0045 for the financial support.

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D-1

3-Heteroaryl 2-aminopyridine modified triplex-forming peptide nucleic acids

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Replacement of canonical cytosine nucleobase by 2-aminopyridine (M) in peptide nucleic acids (PNA) significantly improved triplex stability of PNA with double-stranded RNA (dsRNA) at physiological pH (Fig. 1A, R = H).[1] π–π stacking between base pairs provides a significant contribution to the DNA double helix stability.[2] Possibly, the strength of PNA-dsRNA triplex may be further improved by increasing the number of π–π interactions in PNA strand by introducing aromatic substituents at 3rd position of M (Fig. 1A, R = heteroaryl). There is enough space for the additional cycle in the major groove according to the molecular dynamics simulations and *ab initio* calculations indicate that π–π stacking will give up to **7** kcal/mol extra stabilizing energy for two cycles.

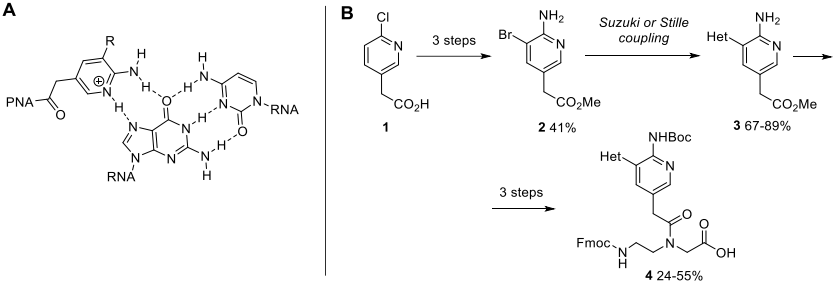

Figure 1. M^+•G-C triplet (A) Synthesis of PNA monomers (B).

To test this hypothesis a series of 3-heteroryl-2-aminopyridine containing monomers **4** were synthesized (Fig. 1B). The key steps were Suzuki or Stille coupling reactions of bromo amino pyridyl acetate **2**. Obtained monomers were incorporated in PNA and binding affinity to dsRNA was measured with UV thermal melting method.

Supervisor: Dr. chem. Mārtiņš Katkevičs

Acknowledgements: This work was supported by Latvian Institute of Organic Synthesis internal student grant IG-2023-08.

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D-2

1,3-Difunctionalization of propargyl silanes for the synthesis of allyl functionalized vinyl silanes

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The β-silicon effect refers to the instrinsic ability of organosilicon compounds to accelerate reactions involving the formation of β-silyl carbenium ions. This can be attributed to either C-Si bond hyperconjugation or formation of cyclic silonium ion. The latter, in the combination with other stabilizing effects, explains the prevalence of reactions proceeding *via* 1,2-silyl migration.[1]

Building upon this concept, herein we report the use of propargyl silane for 1,3-difunctionalization. This involves the introduction of electrophilic halogen species (Br^+, I^+) to induce anti-selective 1,2-silyl migration, resulting in the formation of the reactive allylic cation. The latter can readily engage with nucleophiles present in the system (e.g. solvents like MeOH, DMF+H_2O, AcOH) leading to the generation of *E*-selective allyl functionalized vinyl silanes.[2]

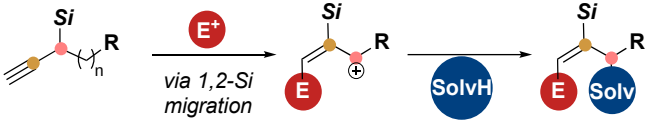

Figure 1. General scheme for electrophile-induced 1,3-difunctionalization of propargyl silanes with a solvent as a nucleophile.

The resulting products feature a continuously functionalized atom triad, that can serve as a building block for further tranformations like Suzuki-Miyaura cross-coupling reactions, C-H activation, electrophilic silicon exchange and Lewis acid-promoted intramolecular cyclization to obtain alkenes with predetermined double-bond geometry or variously substituted indenes.

Supervisor: Dr. chem. Māris Turks

Acknowledgements: This work was supported by European Social Fund within the project no. 8.2.2.0/20/I/008, Riga Technical University doctoral student grant and by the Latvian Council of Science Grant LZP-2023/1-0576.

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D-3

Synthesis and antiradical properties of Meldrum's acid decorated dendrimer

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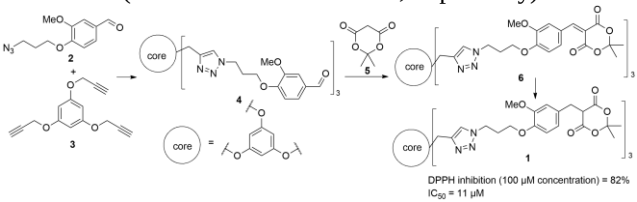
Oxidation processes can cause the degradation of various products, as well as aggravate various diseases. Antioxidants, which inhibit said processes, are often limited by low solubility, stability and bioavailability. Dendrimers can be used to tackle these problems.[1] Additionally, the use of dendrimers can also lead to increased antioxidant activity.[2] Although polyphenols are one of the most widely established group of antioxidants, several antioxidants (both synthetic and natural) contain the 1,3-dicarbonyl moiety.[3] Our group has demonstrated Meldrum`s acid derivatives as outstanding scaffolds for effective antioxidants.[4] Previously, we have constructed small dendrimer structures with short alkyl chain linkers between the core and the surface groups.[5] Herein we have turned to a 1,2,3-triazole linker. The compound **1** was synthesized through a linear synthetic strategy: the 1,3-dipolar cycloaddition reaction between the azide **2** and alkyne **3** (leading to the aldehyde terminated dendrimer **4**), followed by the Knoevenagel condensation and finally reduction of the arylidene compound **6**. The antiradical activity of the target compound **1** was assessed using the DPPH test. This compound demonstrated higher antiradical activity (inhibition at 100 µM concentration = 82%) than such well known commercial antioxidants as BHT and ascorbic acid (inhibition of 16% and 14%, respectively).



Scheme 1. Synthesis and antiradical activity of the dendrimer **1**.

Supervisor: Dr. chem. Inese Mieriņa

Acknowledgements: This work was supported by Riga Technical university (project No. ZM-2021/15)

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D-4

Synthesis of a cyclen containing purine derivative as a potential photo-catalyst

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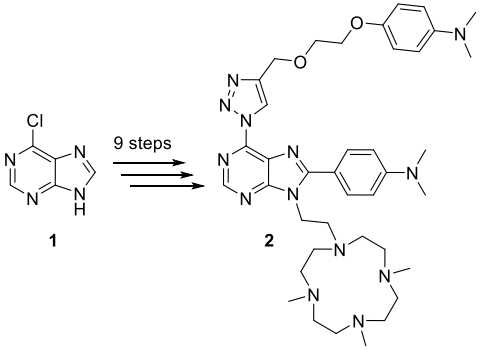
Fluorescent purine derivatives can be used in analytics as a metal ion[1] and pH sensors.[2] They also can be used as photo-catalysts.[3]

Target purine derivative **2** was designed as a potential system for photo-catalysis. For the synthesis of **2**, derivatization of *C*(6), *C*(8) and *N*(9) positions of 6-chloropurine (**1**) is required. Several synthetic pathways were designed and have been tested. In the end, target compound **2** was obtained in 9 steps, using the combinations of S_NAr, S_N2, CuAAC, C-C metal catalyzed coupling, alkylation and Mitsunobu reactions (Scheme 1).



Scheme 1. Starting material **1** and target compound **2**.

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

Acknowledgements: The authors thank MEPS co-project LV-LT-TW/2022/9 for financial support. A.B. thanks the European Social fund within project Nr. 8.2.2.0/20/l/008 and Riga Technical University.

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D-5

Indole synthesis *via* C(sp^2)-H bond functionalization of amino acids

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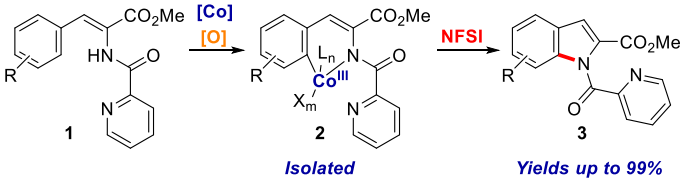
Nowadays the field of third-row transition metal-catalyzed C-H bond functionalization is being extensively studied as an attractive and cheaper alternative to noble metal catalysts, and the directed C-H bond functionalization methodology using transition metal catalysis has proven itself as a valuable organic synthesis tool.[1,2] As a result, in the last couple of decades this approach has been widely exploited in fields of medical chemistry, material sciences, total synthesis and organic synthesis, mainly due to its step- and atom- economical nature.[3]

Our current work is devoted to the development of cobalt-catalyzed picolinamide-directed C(sp^2)-H bond functionalization of amino acid derivatives. Starting from α,β-unsaturated phenylalanine derivatives **1** we were able to synthesize different C-H activated Co(III) complexes **2** (Scheme 1). Moreover, using *N*-fluorobenzenesulfonimide, indole **3** derivatives can be obtained in very good yields.



Scheme 1. Indole **3** derivative synthesis *via* cobalt catalysis.

Supervisor: Dr. chem. Liene Grigorjeva

Acknowledgements: This research is funded by the Latvian Institute of Organic synthesis internal grant Nr. IG-2023-05.

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D-6

Electrochemical cleavage and subsequent oxyfluorination of cyclopropane *C-C* bond

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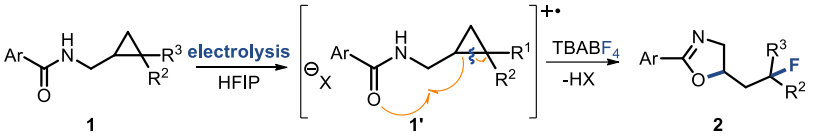
Fluorination reactions are very important in medicinal chemistry.[1] Introduction of a fluorine atom into a molecule can affect the conformation, pKa, intrinsic potency, membrane permeability, metabolic stability, and more.[1]

Tetrafluoroborate anion is an uncommonly employed fluorinating agent, due to it being weakly nucleophilic. In electrosynthesis tetrafluoroborate is widely used as an inert electrolyte, however, there are several examples where electrochemical fluorination has been achieved with tetrafluoroborate as a fluorine source.[2-4]



Scheme 1. Electrochemical cleavage of cyclopropane **1** *C-C* bond, followed by oxyfluorination to form oxazoline **2**.

In this work, we have developed a method where electrochemically activated amide group in compound **1** induces the cleavage of cyclopropane *C-C* bond, followed by fluorine atom transfer from tetrafluoroborate (Scheme 1). As a result, monofluorinated oxazolines **2** are formed, which can be used as precursors for monofluorinated amino alcohols.

Supervisor: Dr. chem. Aigars Jirgensons

Acknowledgements: This work was supported by a student grant from Latvian Institute of Organic Synthesis (IG-2023-07).

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D-7

Probing of irreversible covalent warheads for plasmodium serine protease SUB1 inhibitors

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Malaria is a life-threatening disease caused by the *Plasmodium* parasite which is responsible for over 600 000 deaths annually.[1] Due to a widespread resistance of plasmodium strains to available chemotherapeutics new anti-malarials with novel modes of action are urgently needed. The *Plasmodium* parasite is a single-celled organism which infects and replicates in the human red blood cells. Escape from the red cell *via* process called egress is triggered by an essential subtilisin-like serine protease SUB1 which renders this enzyme as a perspective anti-malarial drug target.

Boronic acid **1** is known to have an inhibitory effect of SUB1 by forming covalent reversible bond with catalytic site serine of the enzyme.[2] In our follow up studies, the boronic acid moiety in peptidomimetic inhibitors has been replaced by other warheads able to form covalent irreversible bonds[3] with the serine residue of SUB1. Here we present the synthesis of a small library of structures which have the potential to be effective SUB1 inhibitors (Figure 1).

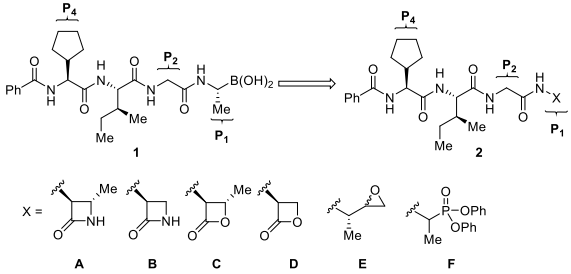

Figure 1. Potential peptidiomimetic SUB1 inhibitors comprising covalent warheads.

Supervisor: Dr. chem. Aigars Jirgensons, Dr. Elina Lidumniece

Acknowledgements: This work is funded by Latvian Council of Science (lzp-2020/1-0327).

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D-8

Ring-opening cross-coupling of cyclopropanols with electrophilic alkenes *via* photoinduced charge transfer facilitated by decatungstate catalyst

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A unique property of cyclopropanols to form photoactive Electron Donor-Acceptor (EDA) complexes with electron-deficient olefins was applied for the synthesis of functionalized ketones through the cleavage of the cyclopropanol ring. In the developed method, the reaction rate of the transformation was drastically increased in the presence of tetrabutylammonium decatungstate (TBADT). Through comprehensive mechanistic study, it was demonstrated that TBADT facilitates the electron transfer between the substrates, enabling the reaction even in cases where an EDA complex cannot be formed. Such behavior of the decatungstate photocatalyst remains largely unexploited since its known synthetic applications are mostly focused on C–H functionalization The described transformations proceed under mild conditions and do not require stoichiometric oxidants. The generality and robustness of the developed method have been validated on a broad scope of cyclopropanol and alkene substrates, delivering the corresponding adducts in up to 92% yield. Successful scale up under continuous flow conditions has also been demonstrated.[1]

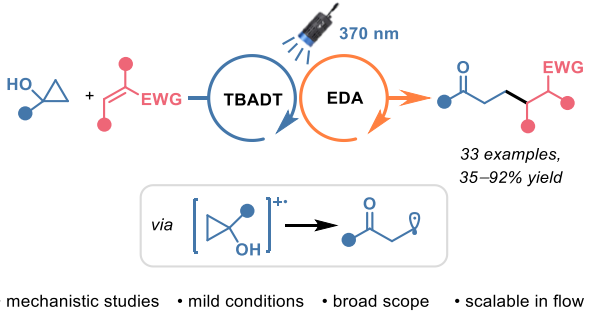

Figure 1. Outline of this work.

Supervisor: Dr. Maksim Ošeka

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D-9

Electrophile induced 1,2-silyl migration in propargyl silanes: a pathway towards saturated heterocycles

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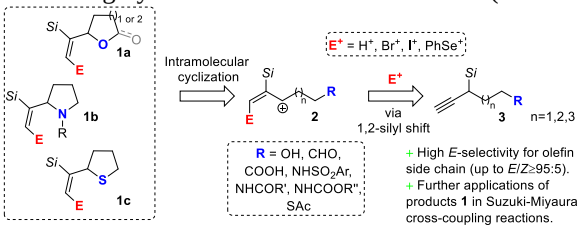
Small saturated heterocycles, namely tetrahydrofuran, pyrrolidine and thiolane derivatives, remain important targets in organic synthesis and drug design due to their prevalence as structural units in pharmaceuticals.[1]

One of the generally used strategies towards the synthesis of saturated heterocycles is intramolecular carbon-heteroatom bond formation, often requiring transition-metal catalysis in order to *in situ* generate the C(δ^+) species, which is later trapped by an internal nucleophile.[2] Alternatively, as a continuation to our previous work,[3] we explored the possibility of generating stabilized carbocations *via* electrophilic activation of propargyl silanes. Electrophiles, such as H^+, Br^+, I^+ and RSe^+ readily added to the alkyne moiety in propargyl silanes **3**, forming intermediate vinyl cations. Rapid 1,2-silyl migration yielded stabilized allylic cations **2**, which were trapped by various internal *O*-, *N*- and *S*-nucleophiles, forming saturated heterocycles **1a-c** with highly stereodefined olefin side chain (Scheme 1).[4]



Scheme 1. Saturated heterocycle synthesis from propargyl silanes.

Supervisor: Dr. chem. Māris Turks

Acknowledgements: European Social Fund project Nr. 8.2.2.0/20/I/008, Riga Technical University doctoral student grant and the Latvian Council of Science Grant LZP-2023/1-0576 are kindly acknowledged.

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D-10

C(sp^3)-H arylation of pentacyclic triterpenoids

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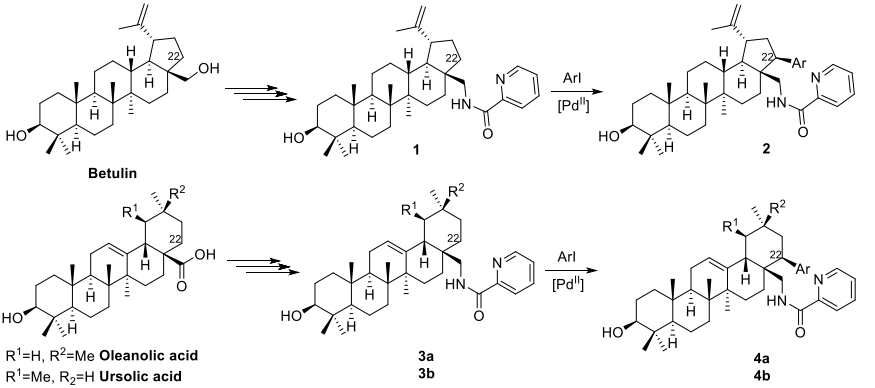
Naturally abundant pentacyclic triterpenoids are significant secondary metabolites which have aroused huge interest by possessing wide range of remarkable biological activities such as antitumor,[1] antidiabetic,[2] anti-inflammatory[3] and antiviral activities[4]. Oleanolic, ursolic acids and betulin, are the most recognizable compounds of this branch, which are isolated from various plants. The aim of this work is to obtain novel triterpenoic derivatives by C-H arylation at C(22). For this purpose, precursors bearing picolinic amide directing groups were synthesized (Scheme 1).



Scheme 1. C-H activation of betulin, oleanolic acid and ursolic acid.

Obtained picolinic amides **1**, **3a**, **3b** were successfully combained with aryl iodides employing Daugulis conditions and C-H arylated products **2**, **4a**, **4b** were obtained.[5]

Supervisor: Dr. chem. Jevgeņija Lugiņina, Dr. chem. Māris Turks

Acknowledgements: We thank the European Social Fund within the project no 8.2.2.0/20/I/008.

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D-11

HFIP-Promoted nucleophilic ring opening of non-activated aziridines under continuous flow conditions

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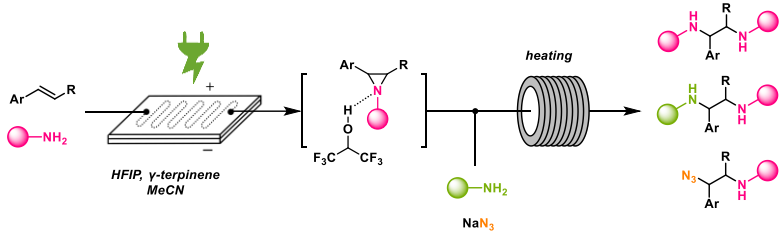
Aziridines, as highly demanded *N*-containing heterocyclic compounds, find extensive application in the synthesis of various drugs and biologically active compounds. The strained structure of the three-membered ring contributes to its heightened reactivity towards nucleophiles. Activated aziridines, in which the nitrogen atom bears an electron-withdrawing group (Ac, Ts, Ns etc.) can be readily subjected to nucleophilic ring opening and reactions of such type have been extensively studied up to this moment. On the contrary, electron-donating groups deactivate aziridine ring towards nucleophilic attack, thus additional activation by acids and higher temperatures as well as prolonged reaction times are required in order to promote the reaction. Recently, the Noël group reported the electrochemical synthesis of non-activated aziridines directly from styrene-type alkenes and primary amines in a flow system.[1] Herein, we report the continuation of this transformation coupled with ring opening with various nucleophiles in flow rendering a telescope process. The excess of hexafluoroisopropanol (HFIP) used in the electrochemical step promotes the ring-opening, while the flow setup enables to perform the reactions under pressure at high temperatures providing β-functionalized amines within minutes timeframe. Moreover, we were able to use explosive compounds under controlled conditions, which demonstrated the safety features of flow chemistry.



Scheme 1: Reaction setup for the synthesis and subsequent ring-opening of non-activated aziridines using continuous flow conditions.

Supervisor: Dr. Maksim Ošeka

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D-12

Synthesis and physical properties of 2,6,8-triazidopurine and 2,4,6,8-tetraazidopyrimido[5,4-*d*]pyrimidine

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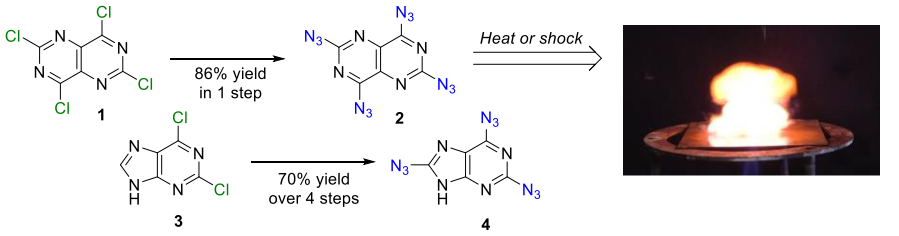
Binary C_xN_y organic compounds are impact-sensitive and possess explosive properties due to the high nitrogen content. The performance of nitrogen-rich compounds is attributed to the high heat of formation. Moreover, the main combustion product of such nitrogen-rich compounds is non-toxic nitrogen gas rather than the CO_2 from oxidation of a carbon backbone as in traditionally used explosives (TNT, RDX). Hence, nitrogen-rich compounds are currently the most promising candidates for the next-generation "green" explosives.[1]

To the best of our knowledge, purine and its homologue - pyrimido[5,4-*d*]pyrimidine have not been used in the synthesis of energetic materials before. However, the nitrogen-rich backbone presents excellent features for application as high energy density materials. Recently, we have designed an approach towards binary C_6N_{16} compound **2** and triazidopurine (**4**) and tested their energetic properties (Scheme 1).[2]



Scheme 1. Synthesis of polyazides **2** and **4**.

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

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D-13

Non-isomeric impurity-induced phosphorescence in carbazole derivatives

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Purely organic phosphorescent materials (phosphors) have recently attracted large interest due to their biocompatibility, low cost and limitless design possibilities.[1] Organic phosphors usually contain extended π-systems with heteroatoms within their structure. Hence, phosphors commonly contain the carbazole **1** subunit. However, recent literature has demonstrated that commercially available **1** contains isomeric impurity (**2**), that induces phosphorescence in carbazole containing luminophores.[2] Herein, we report the synthesis of carbazoles **3b–7b** by the use of Clauson-Kaas cyclization, thus avoiding commercial impurities. Initially, carbazoles **3b–7b** showed phosphorescence, however, after laborious purification, it disappeared. Afterwards a doping study was carried out. When indole derivatives **3c–7c** were used as dopants, no phosphorescence was observed. In contrast, employing benzo[*b*]carbazoles **3d–7d** as dopants led to intense phosphorescence with photoluminescent quantum yields up to 13.9% and emission lifetimes up to 805 ms.

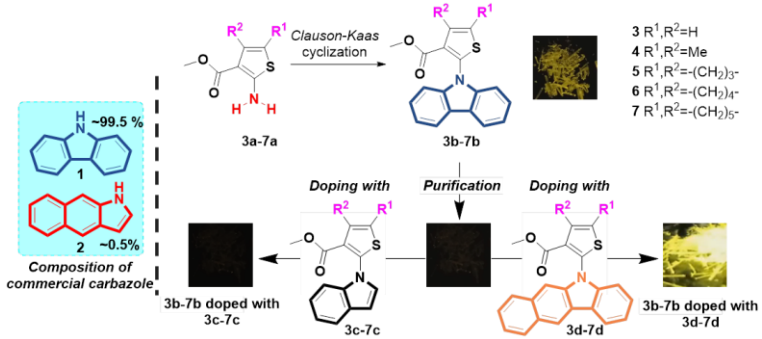

Figure 1. Impurity induced phosphorescence in carbazoles **3b**–**7b**.

Supervisors: Dr. chem. Kaspars Leduskrasts, Dr. chem. Edgars Sūna

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D-14

Mechanochemical synthesis of 5-aminooxazole-4-carbonitriles

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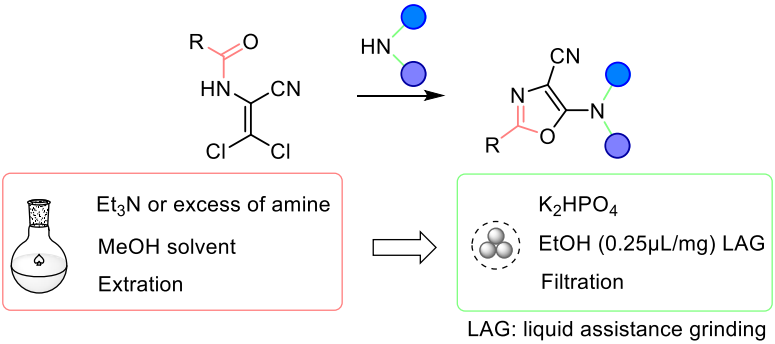
5-Aminooxazoles exhibit noticeable biological activities as inhibitors of human reticulocyte 12/15-lipoxygenase for anti-stroke therapies,[1] inhibitors of Janus kinases (JAK2, TYK2) for treatment of cancer and inflammatory diseases.[2] The primary driving force for the current expansion of solid state methodologies is the pressing need for cleaner, safer and more sustainable chemical transformations.[3] In this work, we present a mechanochemical adaptation of the previously reported solution-state methodology.[4] Organic amine base was replaced to cheap inorganic salt K_2HPO_4, also featuring an operationally simple methodology for performing the reaction with almost no solvents.



Scheme 1. Comparison between conventional solution-based synthesis and mechanochemistry.

Supervisors: Dr. Dzmitry Kananovich, Dr. Oleh Shablykin

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D-15

Multifunctional chiral hydrogen and halogen bond containing catalysts in glycosylation reactions

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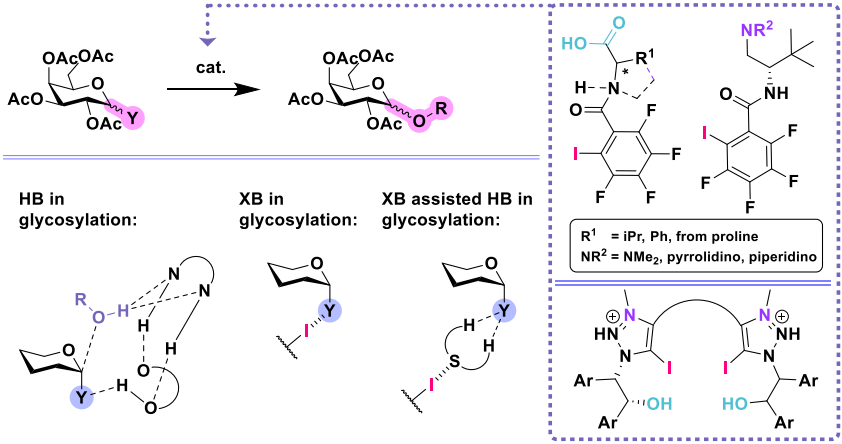
Glycosylation reactions have a 140-year history with many of the original procedures for saccharide synthesis still in use today.[1] Although acid catalysis, hydrogen bond catalysis and organocatalysis are all well-established methods for catalytic glycosylation reactions, halogen bond (XB) catalysis has yet to have been systematically adopted for this type of reaction, outside of a few singular examples.[2] Here, a wide range of chiral bifunctional XB catalysts and organocatalysts were applied to a glycosylation reaction with the aim of attaining anomerically pure sugars. Different donor groups were utilized and the significance of the role of the halogen bond in the formation of the product sugars was assessed.



Scheme 1. Multifunctional chiral hydrogen and halogen bond containing catalysts in glycosylation and different catalaytic mechanisms.

Supervisor: Prof. Tõnis Kanger

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D-16

Greener pharmaceutical synthesis *via* mechanochemical C–N bond formation

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Mechanochemical organic synthesis is a dynamically advancing field that paves the road towards greener and more sustainable chemical industry. Compared to traditional solvent-based syntheses, mechanochemical reactions can offer a superior safety profile and generate less waste.[1] Nevertheless, with the focus on significant application areas like the pharmaceutical industry, it becomes imperative to expand and enhance the existing synthetic methodologies. Specifically, C–N bond-forming reactions stand as pivotal transformations in the synthesis of active pharmaceutical ingredients (APIs), including amides and amines.[2] Here we present our recent achievements that address existing challenges in the field,[3,4] including the protection-group-free amide coupling of hydroxycarboxylic acids and the direct synthesis of amines by nucleophilic substitution of alcohols. Notably, the mechanochemical nucleophilic substitution of chiral secondary alcohols with amines occurs *via* Walden inversion at a stereogenic center (Figure 1). The developed methodologies have been successfully applied for the preparation of bioactive compounds, including the important anticancer drug Imatinib.

Figure 1. Mechanochemical amide coupling and nucleophilic substitution with *N*-nucleophiles in pharmaceutical synthesis. Examples of Walden inversion.

Supervisors: Dr. Dzmitry Kananovich, Prof. Riina Aav

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D-17

Synthesis of new styrylpyridinium dyes and evaluation of the self-assembling and biological properties

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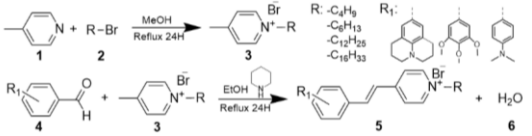
Styrylpyridinium salts are widely studied both as imaging agents for biochemical, biophysical, molecular biology applications due to fluorescent properties[1] and as prospective compounds with biological properties, for example antimicrobial and antifungal activities.[2] The development of new compounds with desirable photophysical properties is a challenge for the researchers working in this field. The aim of the study was synthesis and evaluation of physical, self-assembling and biological properties of new styrylpyridinium derivatives as prospective theragnostic agents.

We synthesized 4-picolinium salts **3** refluxing 4-picoline (**1**) and halogenated alkanes **2** in methanol solution overnight. Styrylpyridinium derivatives **5** were synthesized from the appropriate aldehydes **4** and 4-picolinium salts **3**, reaction mixtures were refluxed for 24h in ethanol solution in the presence of piperidine (Scheme 1). In total we obtained 9 original styrylpyridinium dyes **5** with the yield varying from 24% to 53%.



Scheme 1. Synthetic scheme for preparation styrylpyridinium dyes **5**

Dynamic light scattering method was used for self-assembling estimation; samples were prepared by injection method as aqueous solutions. Styrylpyridinium derivatives with longer alkyl chains at pyridinium nitrogen atom formed homogenous nanoparticles with average diameter in the range 118-597nm depending from compound structure. Cytotoxicity of compounds *in vitro* was assessed by the MTT test on tumor cell lines – HT-1080 and MH-22A and normal mouse fibroblasts NIH3T3. Compounds with longer alkyl chains at pyridinium have high basal toxicity. Fluorescent microscopy was used to analyze cell fluorescence.

Supervisors: Dr. chem. Kārlis Pajuste, Dr. chem. Aiva Plotniece

Acknowledgements: Funded by the Latvian Council of Science project lzp-2021/1-0283; determination of cytotoxicity was performed by Dr. I.Domracheva (LIOS); cell imaging studies were performed by Dr. A.Zajakina's group (BMC).

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D-18

Fluorohalomethylsulfonium salts as a novel fluorohalocarbene source

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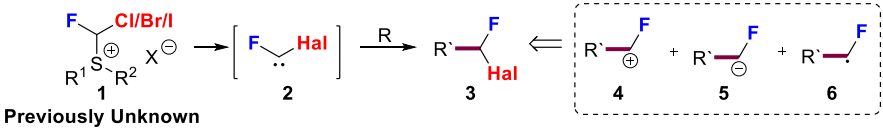
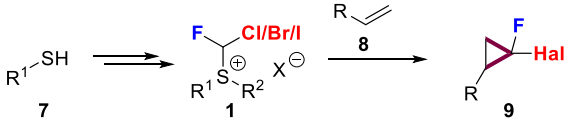
Synthesis of fluoroorganic compounds is of great importance due to their extensive application in medicinal chemistry, agrochemicals and materials.[1] Fluorinated carbene transfer reactions have emerged as efficient method to access highly valuable fluorinated compounds.[2-4] However fluorohalocarbene **2** transfer reactions are significantly less developed. Furthermore, halogen atom can serve as a handle for further functionalization of a molecule. Herein, we presented novel fluorohalocarbene source in form of sulfonium salts **1** (Scheme 1).



Scheme 1. Potential application of fluorohalosulfonium salts.

We have developed synthesis of fluorohalosulfonium salts **1** starting from thiophenol (**7**) and subsequently showed sulfonium salt **1** application for freon free dihalocyclopropanation of unactivated alkenes **8** to access cyclopropanes **9** (Scheme 2).



Scheme 2. Synthesis and application of fluorohalosulfonium salts.

Supervisor: Dr. sc. nat. Jānis Veliks

Acknowledgements: LIOS internal student grant IG-2023-06; European Social Fund within the project «Support for the implementation of doctoral studies at Riga Technical University» No 8.2.2.0/20/I/008; Latvian Council of Science project lzp-2022/1-0335

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D-19

Semisynthesis and structure revision of Linariophyllenes A–C and Rumphellolide H

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Linariophyllenes A–C (**3**–**5**) are sesquiterpenoids, which were isolated from aerial parts of *Evolvulus linaroides*. These natural products demonstrate anti-inflammatory activity by inhibiting the production of NO and pro-inflammatory cytokine IL-1β. Notably, linariophyllene B (**4**) reduced IL-1β level by 93% at 10 μM concentration, exhibiting greater efficacy than the known anti-inflammatory drug dexamethasone (87%).[1]

Intrigued by their biological activity, we designed a stereoselective semisynthetic route (Figure 1) towards linariophyllenes A–C (**3**–**5**) based on the structural similarity with commercially available β-caryophyllene (**1**) and its oxide (**2**). These inexpensive, optically pure, and renewable starting materials are readily available in bulk quantities and were used previously in our studies.[2,3]

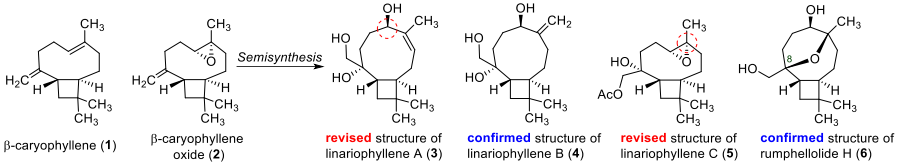

Figure 1. Semisynthesis of linariophyllenes A–C (**3**–**5**) and rumphellolide H (**6**).

Whereas the structure of linariophyllene B (**4**) was confirmed, the structures of linariophyllenes A and C (**3** and **5**) were revised to be the epimers of previously elucidated structures.[1] In parallel, we developed an improved approach toward rumphellolide H (**6**), an anti-inflammatory marine organism-derived tricyclic diol possessing the related framework with an inverted stereocenter at C-8.[4] The structures of final products **3**–**6** were unambiguously confirmed by single-crystal X-ray diffractometry.

Supervisors: Dr. chem. Dace Rasina, Dr. chem. Aigars Jirgensons

Acknowledgements: This work was funded by LIOS internal student grant IG-2023-02.

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