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April 4th & 5th 2024

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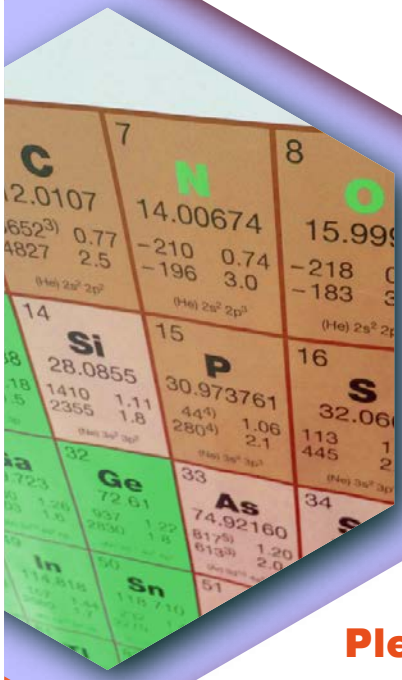
Dutch Symposium on Organic Chemistry



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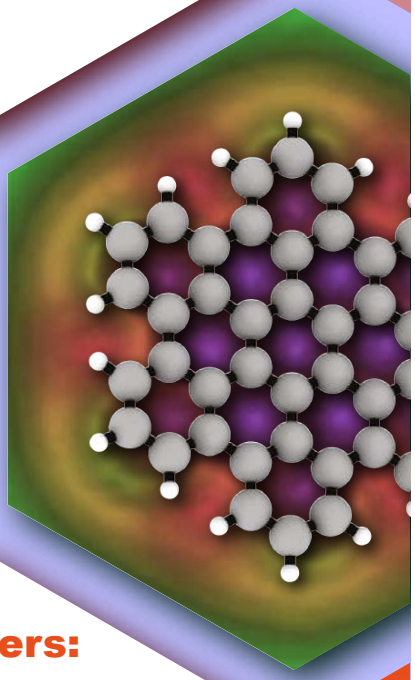

Plenary

Alison Wendtlandt
MIT

Andrea Rentmeister
University of Munich

Ryan Gilmour
University of Münster

Mark Ford
Bayer Crop Science

Speakers:

David Craik
University of Queensland

David Leigh
University of Manchester

Daniele Leonori
Aachen University

Timothy Noël
University of Amsterdam

PhD & postdoc lectures!

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11:20	**Frank de Kleijne (RU) - O-03** *Studying reaction mechanisms using NMR spectroscopy: the glycosylation reaction*	**Juncheng Liu (TUD) - O-06** *Organochlorides Mediate Oxidation Reactions Induced by Low Dose Ionizing Radiation*
11:40	**Markus Kwakernaak (TUD) - O-04** *Perylene dianhydride hydrogels obtained from highly accessible perylene-3,4,9,10-tetracarboxylic diamic acids precursors*	**Ru Jiang (RUG) - O-07** *Artificial Metalloenzymes Catalyzed Preparative Scale Syntheses of Pharmaceutically Relevant γ-Aminobutyric Acid Derivatives*
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15:25	**David Craik (University of Queensland)** *Discovery and applications of cyclotides in agriculture and medicine*	
16:10	**SOC Prizes for best oral and poster presentations**	
16:20	**Closing followed by drinks**	

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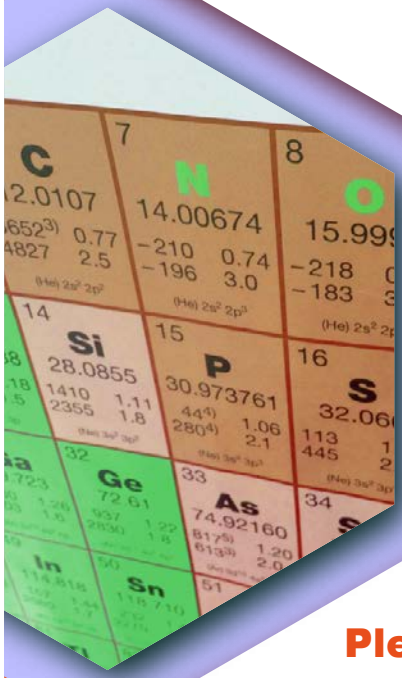

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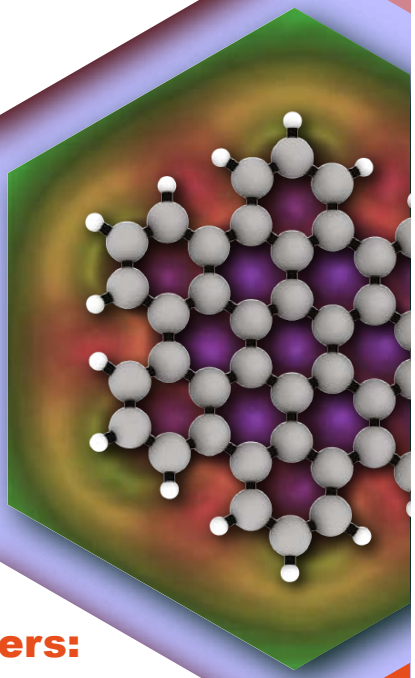

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PhD & postdoc lectures!

ORAL PRESENTATIONS

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O-01

Shedding Light on Hidden Protein Marks - a novel Photochemical approach to Unveil Lysine Crotonylation (Kcr)

Westerveld, M.[a], Jones, O.[a], Aidukas, D.[a], Besermenij, K.[a], Petracca, R.[a]*

[a]*Chemical Biology and Drug Discovery (CBDD), Department of Pharmaceutical Sciences, Utrecht University, the Netherlands*

Background: Lysine crotonylation (Kcr) is a newly discovered post-translational modification (PTM) occurring on both histone and non-histone proteins.[1] Like other PTMs, Kcr plays a crucial role in cellular regulation and appears to be implicated in various diseases, including cancer and heart failure.[2] However, the study of Kcr has been limited by the lack of specific chemical tools for its in-depth investigation.
Objective: This research study aims to develop PhotoCrot, a novel light-mediated chemical method, designed to selectively ligate and characterize therapeutically relevant Kcr proteins (Figure 1).
Methods: We use a radical-mediated thiol-ene *click* (TEC)[3,4] reaction to selectively ligate the α,β-unsaturated bond of the crotonyl moiety with a thiol-containing chemical probe. Short peptides and model recombinant proteins are obtained by selectively installing the crotonyl group on Lys residues using a crotonylated Lys as a building block in an automated peptide synthesizer and by amber codon suppression,[5] respectively. The chemical probe is equipped with a *tag* to facilitate the visualization and retrieval of the desired proteins post-ligation. Subsequent proteomics studies are conducted to identify the crotonylated proteins.
Results: Initially, the TEC reaction was optimized using a Kcr-containing model peptide and Glutathione (GSH) as the thiol component. After extensive optimization, the desired thioether ligated product could be obtained with excellent yield (>98%) in short times (10 min). Crotonylated peptides and model recombinant proteins were employed as standards to design the proteomics experiments, leading to the successful identification of Kcr modified peptides. Preliminary results of the ligation reaction, when applied to a recombinant Kcr protein, are both positive and promising.
Conclusion: The establishment of this photochemical approach represents a significant advancement in the study of Kcr PTMs. The method's specificity and efficiency pave the way for a comprehensive understanding of Kcr's biological significance and its implications in disease, potentially uncovering new therapeutic targets and biomarkers for cancer and cardiovascular diseases.

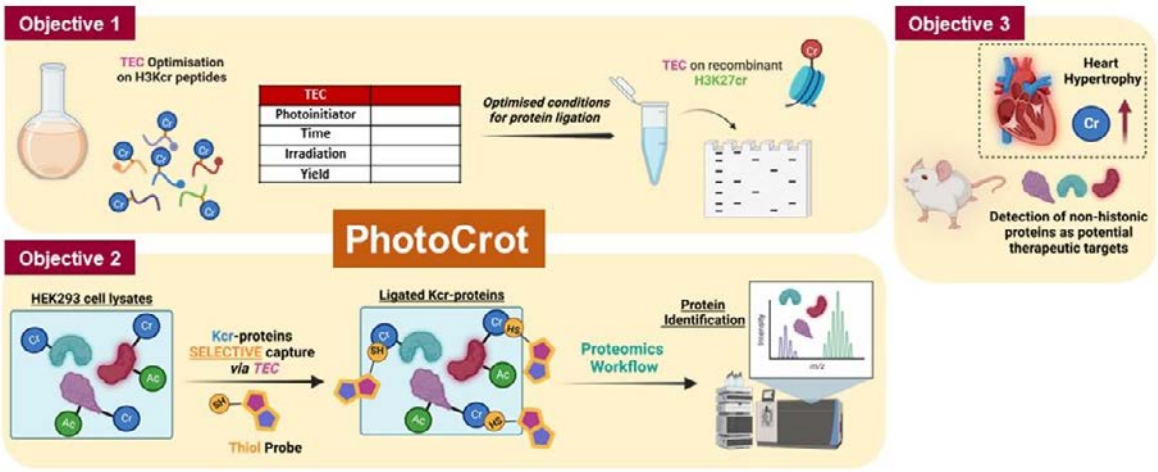

Figure 1. *General scheme of project objectives*

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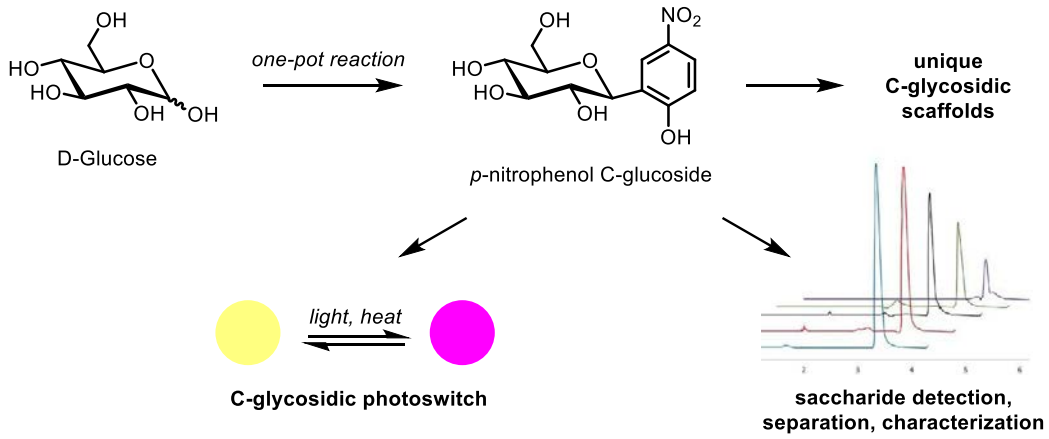
O-02 A one-pot and protecting group-free synthesis of *p*-nitrophenol C-glycosides and its applications

Daan Bunt, A.J. Minnaard, University of Groningen

In plants, polyphenolic compounds (*e.g.* flavonoids) are often equipped with sugar molecules to increase their solubility, change their biological activity, or influence their compartmentalization and translocation.[1] These sugars are usually attached to oxygen atoms, which produces O-glycosides. However, much more rarely, the sugar is attached to a carbon atom, providing a C-glycoside. Compared to the O-glycosidic bond, the C-glycosidic bond is significantly more inert, acid resistant, and is not a substrate for glycosidase enzymes. Hence, C-glycosidic compounds have attracted attention as synthetic targets in academia and in the pharmaceutical industry. Synthetically, C-glycosides are most commonly made via Lewis acid-catalyzed chemical glycosylations and Fries rearrangements, or via organometallic cross-coupling reactions, which require extensive protection and manipulation of the starting materials, while the yields of such reactions are often moderate.[2]

In this lecture, I will discuss how we developed a one-pot procedure, which can be used to make *p*-nitrophenol C-glycosides directly from unprotected saccharides in close to quantitative yields. This method gives easy access to an unprecedented C-glycosidic scaffold on a wide range of mono-, di- and oligosaccharides.



In addition, I will show how we utilized this one-pot procedure in several surprising applications: 1) to produce novel, uniquely substituted aromatic C-glycosides from a broad scope of saccharides, 2) in the development of C-glycosidic photoswitches with improved water solubility, and 3) to contribute to the long-standing challenge of separation and detection of unprotected saccharides.

References

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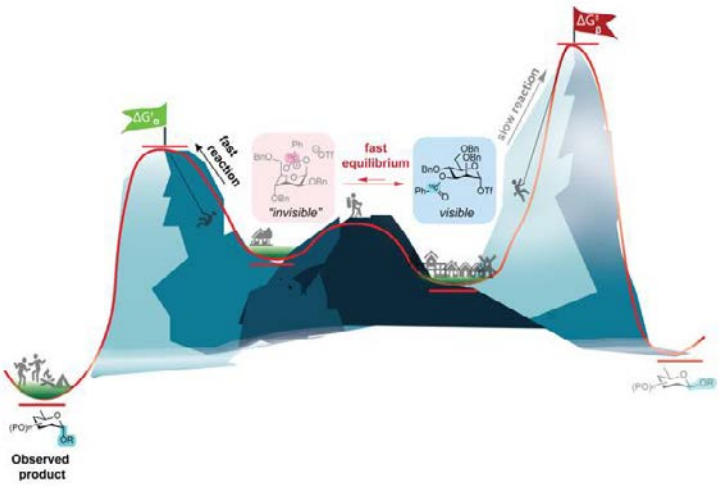
[2] Y. Yang, B. Yu, *Chem. Rev.* **2017**, *117*, 12281–12356.

O-03

Studying reaction mechanisms using NMR spectroscopy: the glycosylation reaction

By: Frank de Kleijne
Institute: Radboud University Nijmegen
PI's: Dr. Thomas Boltje and Dr. Paul White
Co-authors: Floor ter Braak, Peter Moons, Hidde Elferink, Sam Moons, Dimitrios Piperoudis, Bart Bijleveld, Sybren Corver, Kas Houthuijs, Hero Almizori, Giel Berden, Jonathan Martens, Jos Oomens, Paul White, and Thomas Boltje



The stereoselective introduction of glycosidic bonds (glycosylation) is one of the main challenges in the chemical synthesis of carbohydrates. Glycosylation reaction mechanisms are difficult to control because in many cases the exact reactive species driving product formation cannot be detected and the product outcome cannot be explained by the primary observable reaction intermediate. In these cases, reactions are expected to take place via other low-abundance reaction intermediates that are in rapid equilibrium with the primary reaction intermediate via a Curtin-Hammett scenario. Despite this principle being well-known in organic synthesis, mechanistic studies investigating this model in glycosylation reactions are complicated by the challenge of detecting the extremely short-lived reactive species responsible for product formation.

Herein,[1-3] we report the utilization of the chemical equilibrium between low abundance reaction intermediates and the stable, readily observed α-glycosyl triflate intermediate in order to infer the structure of the former species by employing exchange NMR. Using this technique, we enabled the detection of reaction intermediates such as β-glycosyl triflates and glycosyl dioxanium ions. This demonstrates the power of exchange NMR to unravel reaction mechanisms as we aim to build a catalogue of kinetic parameters allowing for the understanding and the eventual prediction of glycosylation reactions.

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[2] De Kleijne, F. F. J.‡; ter Braak, F‡.; Piperoudis, D.; Moons, P. H.; Moons, S. J.; Elferink, H.; White, P. B.; Boltje, T. J. Detection and Characterization of Rapidly Equilibrating Glycosylation Reaction Intermediates Using Exchange NMR. J. Am. Chem. Soc. 2023, 145, 26190
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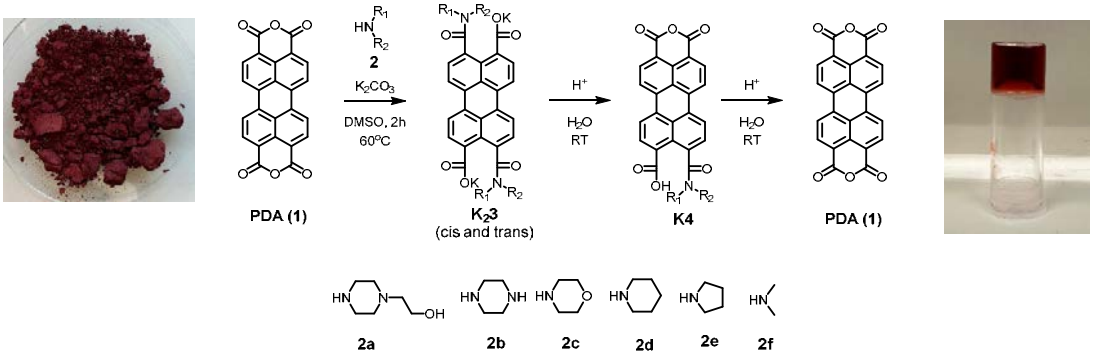
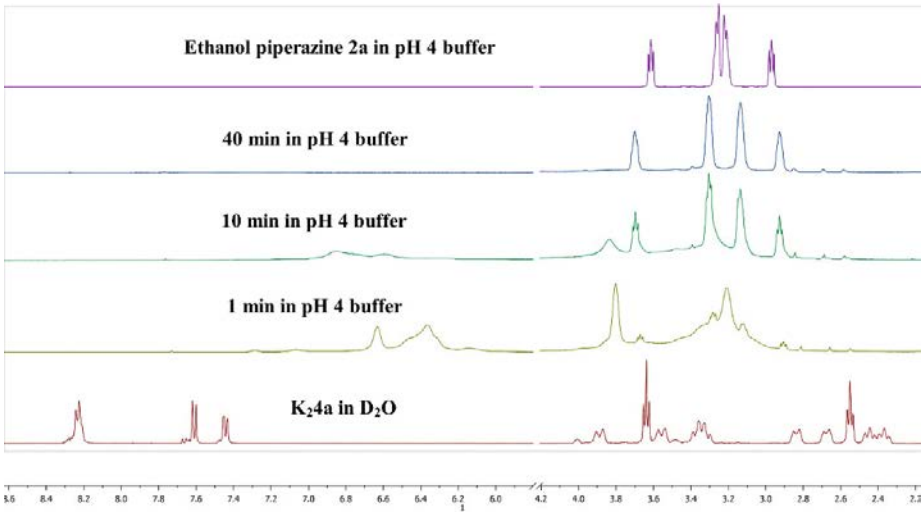
O-04 Perylene dianhydride hydrogels obtained from highly accessible perylene-3,4,9,10-tetracarboxylic diamic acids precursors.

Markus C. Kwakernaak, Marijn Koel, Peter J.L. van den Berg, Erik M. Kelder and Wolter F. Jager



Perylene amic acid salts (**$K_2$3**) represent a new class of perylene-based hydrogelators, which form hydrogels by a unique protonation-hydrolysis mechanism. Hydrogel formation by this mechanism has been observed for a large number of perylene amic acid salts and their ester analogues, in which amides are substituted by esters.

A series of perylene diamic acid (PDAA) salts derived from cyclic secondary amines were synthesized to study the gelation in detail. Slow protonation with glucono-d-lactone or an acidic buffer will changes the color of the solution to deep red and after a few hours, hydrogels are formed. The gelation process was investigated using time-dependent UV-VIS and ^{1}H-NMR spectroscopy, rheology measurements and cryo-TEM imaging. In the NMR measurements of the gelation of compound **$K_2$3a**, the gelation process is demonstrated by the disappearance of the aromatic protons, and the amic acid hydrolysis is proven by the formtion ethanol piperazine.



In the proposed gelation mechanism, the PDAA is slowly protonated, which initiates π-π stacking of hydrophobic amic acids. Subsequently, the slower hydrolysis reaction will produce anhydrides that have a planar geometry. This will enhance the π-π stacking, which will make the stacks more rigid and the hydrogel stronger. Typical hydrogels have critical gel concentrations (CGCs) of 10^{-5} M and exhibit storage moduli around 500 Pa at 1 mM.

Reference:

Room temperature synthesis of perylene diimides facilitated by high amic acid solubility. Markus C. Kwakernaak, Marijn Koel, Peter J. L. van den Berg, Erik M. Kelder and Wolter F. Jager. *Org. Chem. Frontiers*, **2022**, 9, 1481-1492.

O-05 Chiral Sulfonimidoyl Fluorides as Potent, Enantioselective Inhibitors of Chymotrypsin

Dieuwertje E. Streefkerk, Jordi F. Keijzer, Joy Lunsonga, Linde Swillens, Nina Hutten, Johannes A.M. Damen, Bauke, Albada, Han Zuilhof
Laboratory of Organic Chemistry, Wageningen University.

We present a novel class of chiral sulfonimidoyl fluorides as enantioselective inhibitors of α-chymotrypsin. After screening a library of 16 racemic sulfonimidoyl fluorides for their inhibitory potential for this serine protease, the five best performing inhibitors were enantiomerically separated and IC_{50} values of the enantiomers were determined. Not only did we find enantioselective inhibition, the most potent derivatives were >25 times more active than the established serine protease inhibitor PMSF. Furthermore, tryptic digestion and MS analysis revealed covalent modification of the active site serine, and molecular docking simulations corroborated the determined IC_{50}-values.

O-06 Organochlorides Mediate Oxidation Reactions Induced by Low Dose Ionizing Radiation

Juncheng Liu[1], Tobias G. Brevé[2], Bing Xu[1], Peter-Leon Hagedoorn[3], Antonia G. Denkova[1]* and Rienk Eelkema[2]*
[1] Department of Radiation Science and Technology, Delft University of Technology, Mekelweg 15, Delft 2629 JB.
[2] Department of Chemical Engineering, Delft University of Technology, van der Maasweg 9, Delft 2629 HZ.
[3] Department of Biotechnology, Delft University of Technology, van der Maasweg 9, Delft 2629 HZ.
*Corresponding Authors: Antonia G. Denkova and Rienk Eelkema, Email: A.G.Denkova@tudelft.nl; R.Eelkema@tudelft.nl

The controlled release of drugs using local ionizing radiation presents a promising approach for targeted cancer treatment, particularly when applied in concurrent radio-chemotherapy. In these approaches, radiation-generated reactive species often play an important role. However, the reactive species that can be used to trigger release have low yield and lack selectivity. Here, we demonstrate the generation of highly oxidative species when aqueous solutions containing low concentrations of organochlorides (such as chloroform) are irradiated with ionizing radiation at therapeutically relevant doses. These reactive species were identified as peroxyl radicals, which formed in a reaction cascade between organochlorides and aqueous electrons. We employed stilbene-based probes to investigate the oxidation process, showing double bond oxidation and cleavage. To translate this reactivity into a radiation-sensitive material, we have synthesized a micelle forming amphiphilic block copolymer that has stilbene as the linker between two blocks. Upon exposure to ionizing radiation, the oxidation of stilbene led to the cleavage of the polymer, which induces the dissociation of the block-copolymer micelles and the release of loaded drugs.

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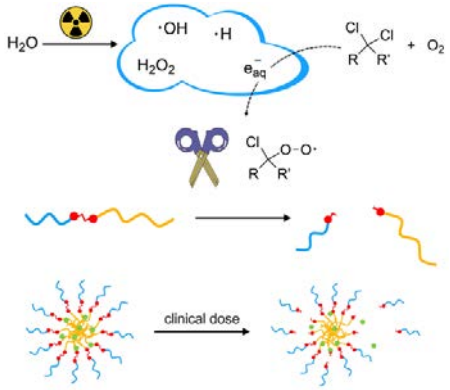

This work has been accepted by CCS Chemistry, https://doi.org/10.31635/ccschem.024.202303794

O-07

Artificial Metalloenzymes Catalyzed Preparative Scale Syntheses of Pharmaceutically Relevant γ-Aminobutyric Acid Derivatives

Ru Jiang[1,2], Fabrizio Casilli[1], Friso Aalbers[1] and Gerard Roelfes[1,2]

[1]Stratingh Institute for Chemistry, University of Groningen, Nijenborgh 4, 9747 AG, Groningen, the Netherlands. [2]E-mail: r.jiang@rug.nl; j.g.roelfes@rug.nl

To combine the attractive features of transition metal catalysis and biocatalysis, artificial enzymes, which consist of abiological catalytic moieties incorporated into protein scaffolds, have emerged as a promising strategy to realize non-natural reactions in biocatalysis.[1] LmrR, a small, homodimeric protein that contains a large hydrophobic pore at its dimer interface, is a privileged scaffold for artificial metalloenzyme (ArM) design.[2] Here, we incorporated the metal binding unnatural amino acid bipyridine alanine (BpyAla) into the protein scaffold LmrR through *in vivo* stop codon suppression[3] and created a proficient and stereoselective artificial metalloenzyme (LmrR_XBpy) for catalytic asymmetric Michael addition of 2-acetyl azaarenes to nitroalkenes (15 examples, up to >99% yield, 99 ± 0% ee) (**Fig 1**). In our design, 2-acetyl azaarene **1** is activated by the new created [Cu-Bpy] site to form the enolate, whereas the aryl substituted nitroalkene **2** is the Michael acceptor, which is bound by the tryptophan residues (W96 and W96') *via* π-stacking interactions, to give the addition product **3**. This provides a new and green synthetic route to the preparative scale syntheses of pharmaceutically relevant γ-aminobutyric acid derivatives.

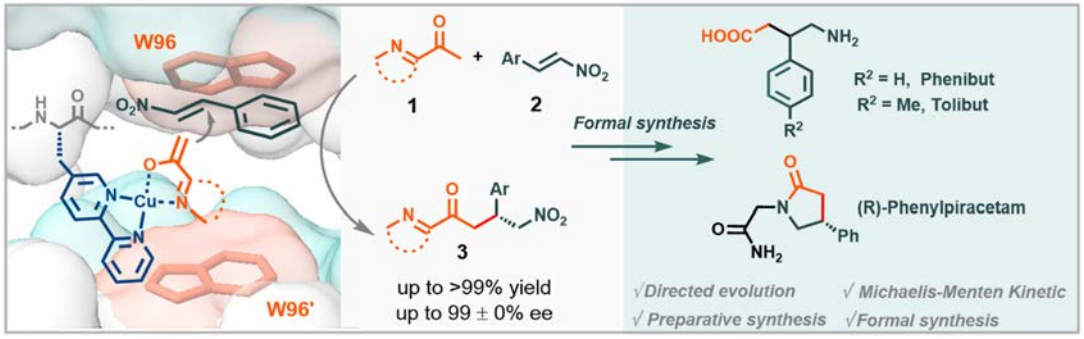

Fig. 1 Artificial metalloenzymes catalyzed preparative scale syntheses of pharmaceutically relevant γ-aminobutyric acid derivatives

Key words: artificial metalloenzyme, copper catalysis, Michael addition, enantioselectivity, preparative syntheses

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3. (a) Wang, L.; Brock, A.; Herberich B.; Schultz, P. G. *Science* **2001**, *292*, 498. (b) Drienovská, I.; Rioz-Martínez, A.; Draksharapu, A.; Roelfes, G. *Chem. Sci.* **2015**, *6*, 770.

O-08 Chemical proteomic platforms for diversifying drug mechanism of action.

Madeline E. Kavanagh, Benjamin D. Horning, Matthew P. Patricelli, Benjamin F. Cravatt

Chemical proteomic platforms are a powerful way to identify small molecule-protein interactions in living systems. These target-agnostic, binding-based assays have the potential to both drastically expand the 'target space' for drug development, and excitingly, to reveal novel mechanisms of action that can be exploited to modulate proteins with greater precision. This presentation will highlight recent examples of small molecules with unconventional mechanisms of action that have been discovered using chemical proteomics, including an allosteric inhibitor of the important immune-oncology target JAK1.[1] These mechanistically differentiated probes are providing us with an unprecedented ability to study biology, and to develop safer, more effective therapeutics.

[1]*Nat Chem Biol, 2022, 18, 1388*

O-09

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d.verdoorn@maastrichtuniversity.nl
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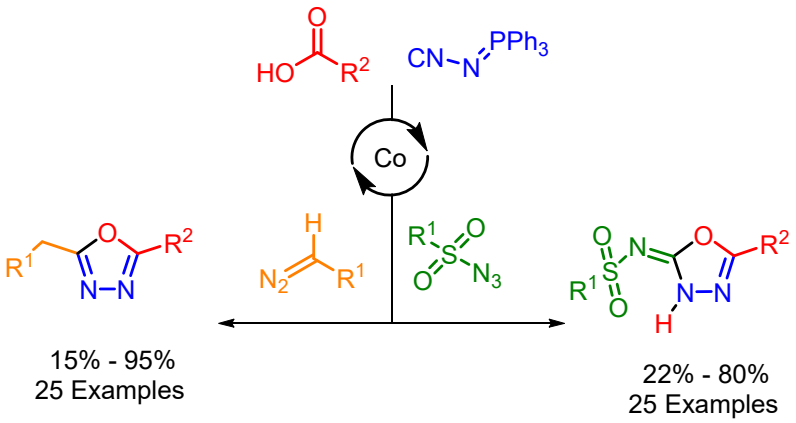
Title: "Co(II) mediated synthesis of 1,3,4-oxadiazole scaffolds"

Key words: nitrene transfer, carbene transfer, *N*- isocyaniminotriphenylphosphorane

Abstract: Multicomponent reactions (MCRs) are highly desired synthetic tools to synthesize complex molecules from simple building blocks, in a single step[1]. A class of C1 building blocks that can be applied in MCR chemistry are isocyanides. Isocyanides possess unique reactivity that allows the possibility for late-stage structural diversification[2]. In addition, the combination of isocyanides with transition-metal (TM) chemistry catalysis has gained much attention in the past decade as an alternative for carbonylation chemistry. During this research we present a Co (II) system that gives access to different 1,3,4-oxadiazole scaffolds[3] in a single step. This research consists of both a nitrene and carbene transfer to *N*- isocyaniminotriphenylphosphorane with a subsequent *aza*-Wittig. The reaction shows a wide tolerance for functional groups, especially in the carbene transfer. General reactions presented in Scheme 1.



Scheme 1: General reactions

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O-10 From identification of reactive intermediates and side products through mass spectrometry to new reaction development

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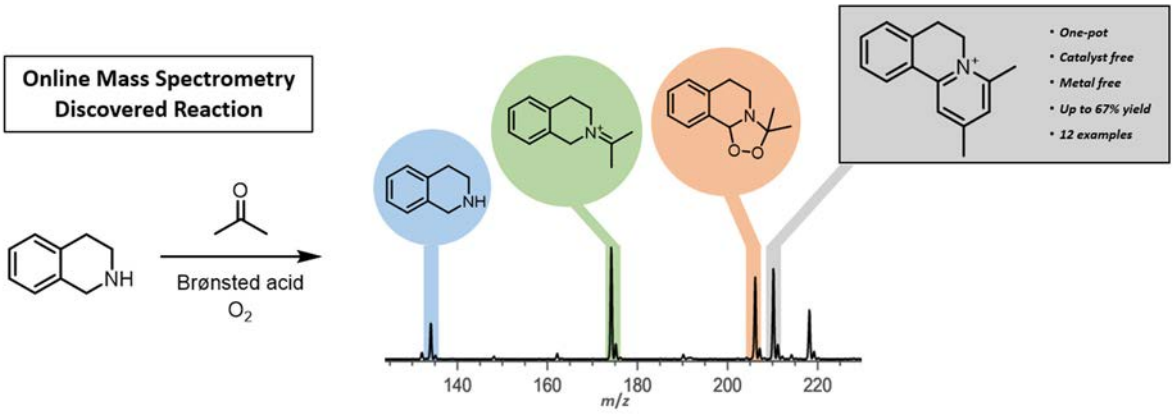
J. Mehara, J. Roithová, Institute for Molecules and Materials, Radboud University Nijmegen

The discovery of new transformations and reaction pathways drives the development of the field of synthetic organic chemistry. While the main goal of synthetic chemists is to obtain maximum yield of a desired product with minimal side product formation, meticulous characterization of the latter as well as any accompanying reactive intermediates might result in serendipitous discoveries of new reaction pathways, alternative mechanisms and new products.

Herein, we will present how we use online mass spectrometry to discover new transformations. After identifying an unknown side product formed in negligible amounts during our studies on the organocatalytic Mannich reaction, thorough online analysis of the reaction intermediates led to the discovery of a new reaction, namely catalyst-free cross dehydrogenative coupling of tetrahydroisoquinoline with acetone, yielding a tricyclic pyridinium compound. Having identified the structure of the side product, we were able to develop a general methodology that provides its exclusive formation. Mechanistic studies gave further inside into the nature of the transformation.



O-11 Chemical Synthesis of Sulfotyrosine-Containing Plant Peptide Hormones

Jasper W. van de Sande, Dieuwertje E. Streefkerk, Richard G.H. Immink, Martijn Fiers, Bauke Albada

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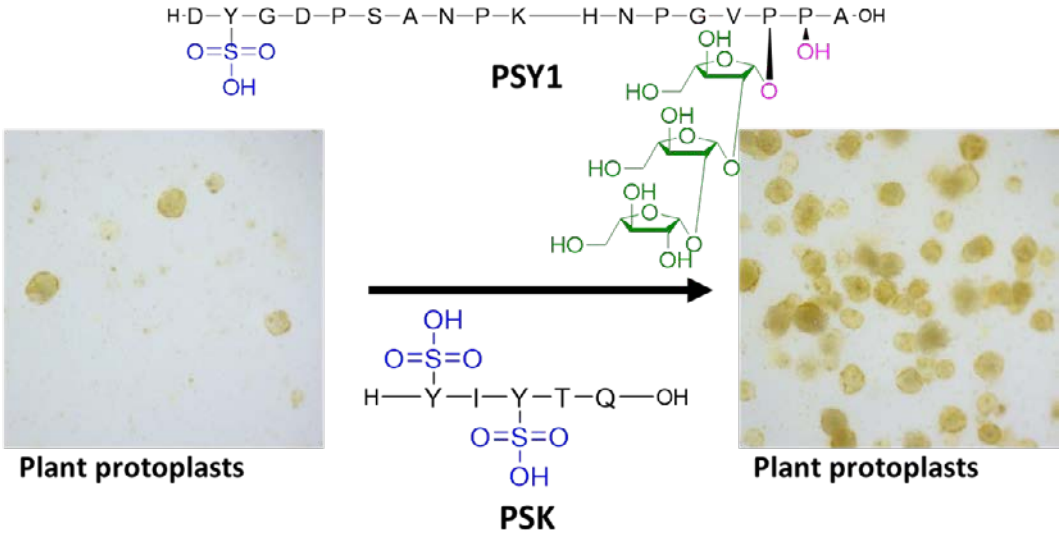

Plant peptide hormones (PPHs) are bioactive, naturally occurring peptides that contain at least one single sulfotyrosine Post-Translational Modification (PTM). Examples of such important plant regulatory hormones are 'phytosulfokine' (PSK) and 'plant peptide containing sulfated tyrosine 1' (PSY1). Both PPHs act as growth factor in *Arabidopsis thaliana* plant species and significantly improves the efficiency of cellular proliferation in plant cell culture, a process known as regeneration. As multiple *Brassica* plant species are recalcitrant, they are unable to withstand or even survive stress conditions, they require artificially generated PPHs to boost regeneration.

We show the chemical synthesis of glycopeptide PSY1, disulfated PSK, and a PSK-like peptide library. PSY1 was obtained after stereoselective total synthesis of β-1,2-linked L-arabinosylated Fmoc-protected hydroxyproline building blocks, and subsequently incorporation into the PPH together with a sulfated tyrosine and hydroxyproline residue. The PSK-like peptide library included N-terminal modifications, amino acid substitutions, incorporation of diastereomers, and backbone N-methylation. Insertion of the latter required solution-phase synthesis of the proper building block prior to solid-phase peptide synthesis.

The biological activity of the synthesized PPHs was assessed in the regeneration capacity of *Brassica oleracea* cells (protoplasts). Most PSK analogues did not affect the regeneration capacity as compared to PSK. However, 2-allo-Ile PSK and 4-Nme-Thr PSK showed increased activity in protoplast regeneration when compared with that of the native peptide. These findings indicated that introducing small chemical modifications in the PPH provides opportunities for inducing protoplast regeneration in recalcitrant species.

O-12

Development of electrophilic probes for the profiling of ligandable arginines in the bacterial proteome

Marnix G. Roseboom, Stephan M. Hacker

Leiden University

Covalent inhibitors are making a comeback in medicinal chemistry and chemical biology due to the growing understanding of electrophilic reactivity towards nucleophilic residues. While traditional therapeutics reversibly bind to their biological targets, covalent inhibitors form a strong covalent bond, enhancing the inhibiting effect. This mechanism is relevant in many antibiotics and is becoming increasingly important due to bacterial antibiotic resistance. Of all residues, cysteine is mostly targeted by covalent inhibition for due to its high nucleophilicity. However, cysteine is relatively uncommon in many proteomes, meaning that many potential drug target sites remain untargetable. Arginine is a more common amino acid and displays a plethora of biologically relevant functions such as ins protein interactions, enzyme functions and protein structure, making it an attractive drug target. However, targeting arginine is more challenging, which is why our research focuses on discovering novel electrophiles binding to this residue.

In this work, we synthesized numerous chemical probes with varying chemotypes and screened them on methicillin-resistant *Staphylococcus aureus* lysate. 1,2-diketoamides emerged as the most suitable chemotype for targeting arginines and a set of 4 additional tailored probes containing this electrophile were developed. These were utilized to profile arginine residues proteome-wide using an activity-based protein profiling workflow, allowing global mapping of >15,000 arginines as well as study of arginine reactivity. This technology will enable the proteome-wide profiling of the target engagement and selectivity of arginine-directed covalent protein ligands and, thereby, contribute to the development of novel covalent inhibitors.

O-13 Metal-free C(sp³)–C(sp³) bond formation using arylsulfonyl hydrazones in photocatalysis

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Historically, alkyl-alkyl couplings have been challenging to accomplish, but in recent years significant progress has been achieved using transition-metal catalysis.[1] Particularly, nickel-mediated cross-electrophile (XEC) coupling has emerged as a potent strategy for constructing C(sp³)–C(sp³) bonds, utilizing various native and bench-stable aliphatic coupling entities. Nevertheless the exploitation of ubiquitous functional groups such as aldehydes as coupling partner via a reductive deoxygenative pathway remains, to our knowledge, underdeveloped. Thus the design of an approach, that enables the direct coupling of sp² and sp³ electrophiles, such as aldehydes and largely present C(sp³)–H bonds or carboxylic acids, would represent an attractive strategy in the cross-electrophile coupling domain. To realize this goal, we were drawn to arylsulfonyl hydrazones, which are considered activated form of aldehydes due to their propensity to undergo radical addition, ultimately yielding deoxygenated, cross-coupled products upon thermal decomposition of alkylated hydrazide intermediates.[2] The use of cheap organic photoredox catalysts (PC) to promote the formation of the carbon radical would make the all process metal-free.

In this work, we demonstrated the realization of such strategy to forge C(sp³)–C(sp³) bonds from easily accessible arylsulfonyl hydrazones and abundant C(sp³)–H or carboxylic acid donors via a two-step synthetic strategy, comprising a first photocatalytic event (Hydron Atom Transfer or Single Electron Transfer) and a subsequent fragmentation reaction.[3,4] This chemistry was applied to the synthesis of various homo-benzylic ethers, arylethylamines and β-aminoacids. Furthermore, this method was implemented for a safe C1 homologation of carboxylic acids.

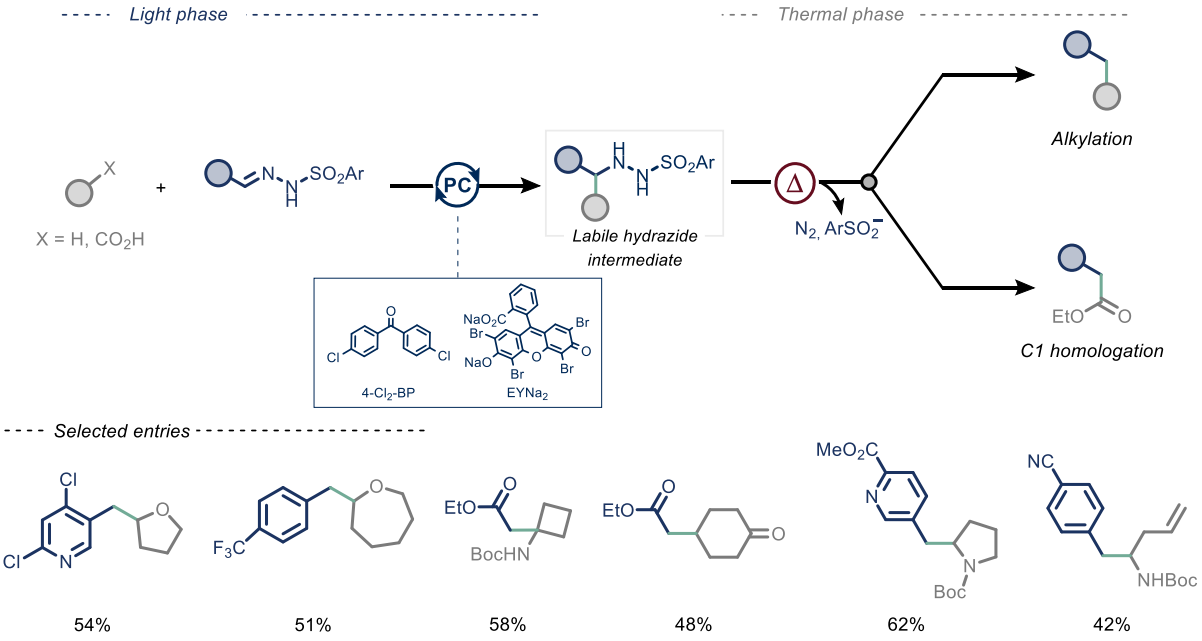

Figure 1 Our metal-free strategy to forge C(sp³)–C(sp³) bonds using arylsulfonyl hydrazones as radical acceptors.

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O-14 Shining light on tryptamine-derived isocyanides: access to constrained spirocylic scaffolds

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Dearomatization of indoles through a charge transfer complex constitutes a powerful tool for synthesizing three-dimensional constrained structures.[1-4] However, the implementation of this strategy for the dearomatization of tryptamine-derived isocyanides to generate spirocyclic scaffolds remains underdeveloped. In this work, we have demonstrated the ability of tryptamine-derived isocyanides to form aggregates at higher concentration, enabling a single electron transfer step to generate carbon-based-radical intermediates. Optical, HRMS and computational studies have elucidated key aspects associated with the photophysical properties of tryptamine-derived isocyanides. The developed protocol is operationally simple, robust and demonstrates a novel approach to generate conformationally constrained spirocyclic scaffolds, compounds with high demand in various fields, including drug discovery.

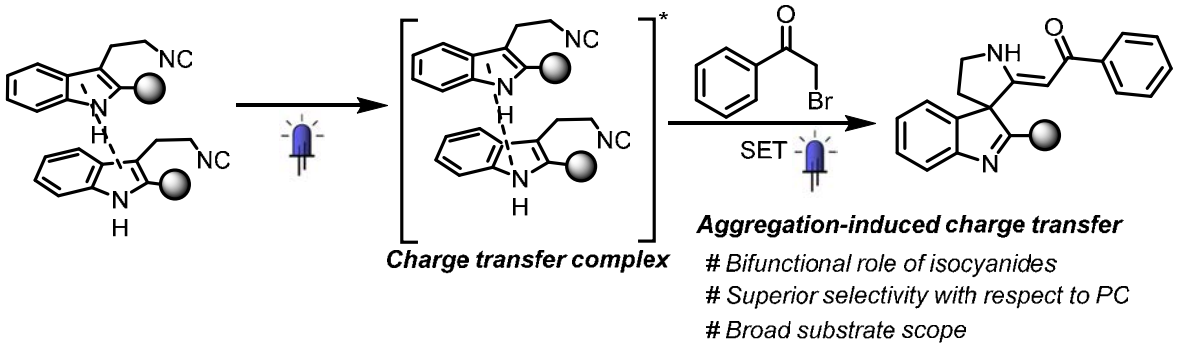

Figure 1. Visible light-mediated synthesis of spiroindolenines employing tryptamine-derived isocyanides.

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O-15

Total synthesis of Acidobacterial tetraether lipid-*br*GDGT Ia and its stereochemical analysis

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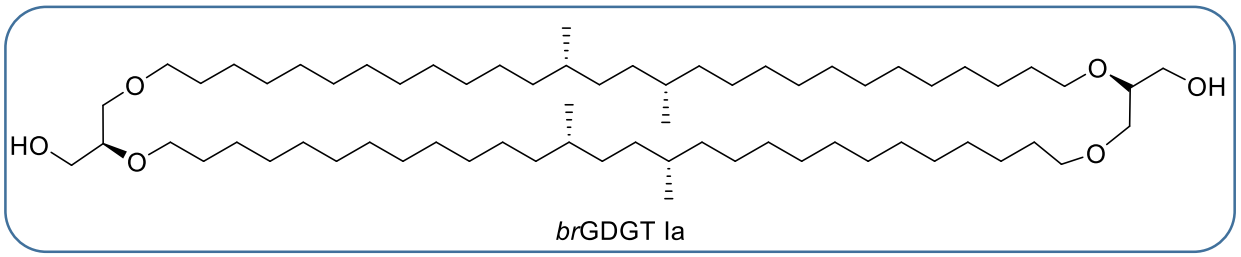

*br*GDGT Ia

Acidobacteria comprise one of the globally distributed and highly diverse phyla of the domain *Bacteria*. Membranes of these bacteria contain characteristic lipids that are considered to have survived Deep time owing to their resistance to degradation, thus playing an important role in the study of origin and sustenance of life on earth. The lipid content of these microorganisms is mainly comprised of glycerol dialkyl glycerol tetraethers (GDGTs) where the hydrocarbon chains are attached through ether bond to the glycerol backbone unlike the usual ester bond. These lipids also have methyl branches (and cyclopentane rings in some cases) but not as regular as in archaea that have isoprenoidal structure. Therefore, they are called as *br*GDGTs (*branched* GDGT).

Till date there has been no syntheses of *br*GDGTs and also the stereochemistry of the methyl branches of these lipids is undetermined. This work presents the first total synthesis of one of the *br*GDGTs i.e.*br*GDGT Ia achieved over 21 steps. Along with the total synthesis we have also determined the *syn* stereochemistry of the methyl branches after comparing with the derivatives obtained from the natural lipid.

The talk will focus on the whole synthesis of the lipid including the challenges faced. Also, I will show how the comparison was carried out for the conclusion on the stereochemistry.

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O-16 *From Shrimp to Aromatics:* Substituted anilides from chitin-based 3-acetamido-furfural

Cornelis H. M. van der Loo,[1] J. P. Kaniraj,[1] Ting Wang,[4] J. O. P. Broekman,[4] Mark L. G. Borst,[2] Kees Pouwer,[2] André Heeres,[3] Peter J. Deuss [3] and Adriaan J. Minnaard [1]

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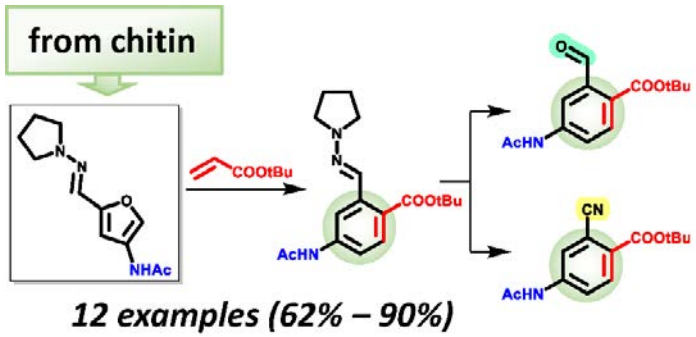
Abstract

The synthesis of aromatic compounds from biomass-derived furans is a key strategy in the pursuit of a sustainable economy. Within this field, a Diels-Alder/aromatization cascade reaction with chitin-based furans is emerging as a powerful tool for the synthesis of nitrogen-containing aromatics. In my talk I will discuss the synthesis of chitin-based 3-acetamido-furfural (3A5F) and its conversion into an array of di- and tri-substituted anilides in good to high yields (62-90%) via a hydrazone mediated Diels-Alder/aromatization sequence. We discovered that the addition of acetic anhydride significantly expanded the dienophile scope and improved yields. Moreover, replacing the typically used dimethyl hydrazone with its pyrrolidine analogue, shortened reaction times and further increased yields. The hydrazone auxiliary was readily converted into either an aldehyde or a nitrile group, thereby providing a plethora of functionalized anilides.



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O-17 Laura Maria Jansen

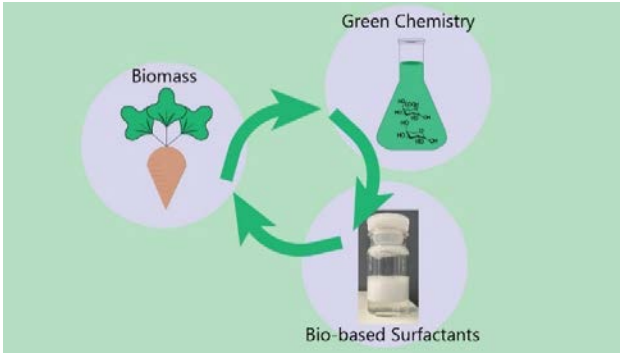
Synthesis and Performance of Bio-based Surfactants Prepared by the One-Pot Reductive Amination of L-Arabinose and D-Galacturonic Acid

Published article: https://doi.org/10.1021/acssuschemeng.3c03753

We developed a method for the synthesis of Bio-based surfactants derived from sugar beet pulp (SBP) monosaccharides, L-Ara and D-GalA. The hydrophilic nature of monosaccharides enables their application as the polar headgroup for the synthesis of bio-based surfactants. Surfactants have the ability to reduce the surface tension and are therefore essential ingredients in the cosmetic, detergent, and chemical industries. The surfactants were prepared via one-pot reductive amination, allowing the introduction of different alkyl chain lengths and methyl modifications. Optimal reaction conditions were established to achieve high yields and easy purification. The synthesized surfactants including the tertiary amines exhibited desirable properties, including solubility, foamability, and reduction of surface tension. Notably, the surfactants derived from D-GalA demonstrated better solubility and foam performance compared to those derived from L-Ara. In addition, these surfactants exhibited surface tension and critical micelle concentration (CMC) comparable to those of the commercial surfactant sodium lauryl ether sulfate (SLES). Furthermore, the biodegradable surfactant GalA1.8 displayed excellent emulsifying properties and low skin irritation potential. The L-Ara surfactant with a short chain, Ara1.6 has potential as a hydrotrope and wetting agent. These findings suggest that bio-based surfactants derived from SBP monosaccharides have promising properties for various applications.

Research in the group of Thomas Boltje, Department of Synthetic Organic Chemistry, Institute for Molecules and Materials, Radboud University.

In my PhD we are in collaboration with Cosun RD&I, my students also worked partly on this project, and the microbiology department did the biodegradability tests.



O-18 β-D-arabinofuranosyl cyclitol aziridines for selective inhibition and in cell fluorescent labeling of GBA2

Rob F. Lammers, Qin Su, Max Louwerse, Max Janssen, Rolf G. Boot, Wendy A. Offen, Gideon J. Davies, Herman S. Overkleeft, Johannes M. F. G. Aerts, Marta Artola

Non-lysosomal glucocerebrosidase (GBA2) is a retaining β-glucosidase belonging to the glycosyl hydrolase family GH116 involved in glucosylceramide metabolism and cellular homeostasis. Although it is known that homozygous mutations in the *GBA1* gene coding for the closely related lysosomal glucocerebrosidase GBA1 causes Gaucher disease, and heterozygous mutations in *GBA1* are a significant risk factor for Parkinson's disease, the relation between GBA2 and these diseases remains poorly understood. Among the GBA2 inhibitors described, Miglustat (Zavesca®), an iminosugar with dual GBA2 (IC_{50} = 200 nM)[1] and glucosylceramide synthase (IC_{50} = 34.4 μM)[2] activity, stands as a clinically approved treatment for Gaucher disease and Niemann-Pick type C and has demonstrated to exhibit anti-inflammatory effects.[3] On the other hand, cyclophellitol-based aziridine activity-based probes (ABPs) have been developed to covalently inhibit all retaining exo-β-glucosidases GBA1, GBA2 and GBA3. GBA3 is a cytosolic glucocerebrosidase which physiological function and pharmacological relevance remain to be elucidated. In an attempt to find the first selective covalent GBA2 inhibitors, we screened our cyclitol aziridine-based ABP library as conformationally restricted cyclitols, armed with an electrophilic warhead suitable to intercept the Koshland double-displacement mechanism of GBA2. To our delight, we found that β-D-arabinofuranosyl cyclitol aziridines are highly selective and covalent GBA2 inhibitors. We harnessed this β-D-arabinofuranosyl cyclitol aziridine scaffold to develop new selective probes for visualizing GBA2 using confocal microscopy in cellular environments. By comparing the reactivity of alkyl- and acyl-functionalized aziridines in β-D-arabinofuranosyl cyclitols and connecting these to lipophilic aglycons, a strategy known to enhance the affinity of iminosugars towards GBA2,[4] we generated several potent and selective mechanism-based GBA2 inhibitors. In summary, the new research tools presented herein hold promise for advancing our understanding of this enigmatic enzyme and exploring potential clinical applications.

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O-19

Regiodivergent Site-Selective Electrochemical Oxidation of Glycosides

Marios Kidonakis, Augustin Villotet, Ruben Andringa, Martin D. Witte, Sebastian B. Beil, Adriaan J. Minnaard

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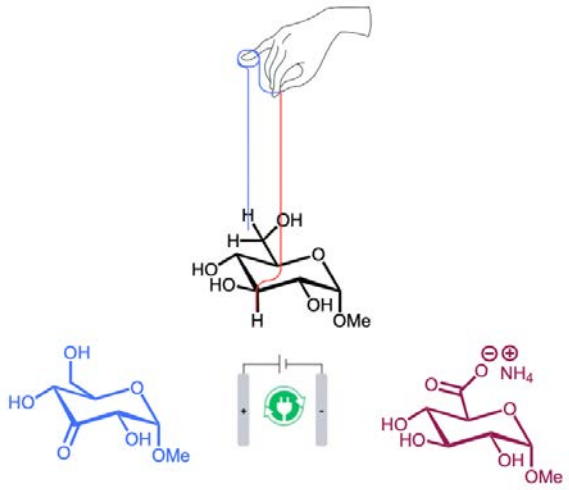
Site-selective modification of carbohydrates provides derivatives or even rare sugars, which are of special interest in pharmaceutical science and related disciplines.[1] Among the existing strategies, electrochemistry serves as a sustainable and inexpensive way to achieve this goal.

In this study we present a regio-divergent electrochemical strategy for the selective oxidation of pyranosides. Under constant current electrolysis, quinuclidine (Qu) mediates oxidation on the C3-OH in excellent selectivity, serving as a versatile alternative to Pd-catalyzed and photochemical C3-oxidation.[2] By switching the mediator to TEMPO and in the presence of aqueous ammonia as the electrolyte, oxidation takes place exclusively on the C6 position. In the latter case, the resulting ammonium uronic salts are delivered in quantitative yields just after lyophilization of the crude reaction mixture.[3]



Scheme 1: Regiodivergent Electrochemical Oxidation of Methyl-a-D-Glycopyranoside.

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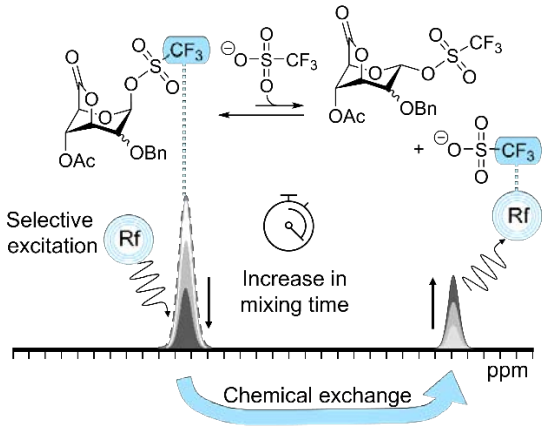
O-20

To β or not to β: Defining the Glycosylation Mechanism of Uronic Acid Lactones in the Solution-phase

Peter H. Moons, Frank F.J. de Kleijne, Hero R. Almizori, Luuk J.H. Jakobs, Floor ter Braak, Floris P.J.T. Rutjes, Paul B. White, and Thomas J. Boltje

The glycosylation reaction is the most important reaction in carbohydrate chemistry, yet attaining complete stereocontrol in this reaction remains challenging. Its complex nature is defined by the highly-reactive intermediates that form upon activation of a glycosyl donor. Characterizing these elusive intermediates is key in understanding how the reaction works and thus essential in Previously, we established that C-4 acetyl 6,3-mannuronic acid lactone is an effective donor for the stereoselective incorporation of mannuronic acids.[1] We showed that the C-4 acetyl group can participate in the gas-phase, thus forming an elusive dioxepanium ion intermediate, which plausibly explained the stereoselectivity of this reaction. Herein, we demonstrate that its excellent β-selectivity can in fact be attributed to another reactive intermediate in the solution-phase using nuclear magnetic resonance (NMR) spectroscopy. We established that this is a low-abundant equatorial glycosyl triflate and determined the exchange kinetics kinetics using exchange spectroscopy (EXSY) NMR[2] and chemical exchange saturation transfer (CEST) NMR.[3,4] Finally, we studied the reaction kinetics of 6,3-uronic acid lactones using variable-temperature (VT) NMR. These results demonstrate the power of NMR in elucidating elusive reactive intermediates and show that the glycosylation behavior of uronic acids is different in the solution-phase than in the gas-phase.



Acknowledgements
This work was supported by a VIDI grant (192.070) awarded to T.J. Boltje.

Keywords: Glycosylation • Stereoselectivity • EXSY NMR • CEST NMR • Glycosyl triflates • Uronic acid lactones • Kinetics

References:

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O-21

Click'n Lock: Dynamic Chemistry for Peptide Modifications and Cyclization

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Tetrazines are known for their rapid and chemoselective reactivity towards dienophiles via the inverse electron-demand Diels–Alder (IEDDA) cycloaddition. This work is focused on tetrazine reactivity beyond IEDDA. Thiomethyltetrazines can undergo a fully traceless click reaction with thiols under physiological conditions, which we call tetrazine-thiol exchange (TeTEx). [1] We employed TeTEx for the chemoselective and reversible modification of peptides. The inherent reactivity of tetrazines towards IEDDA with dienophiles made it possible to "lock" the clicked structure, hence the term Click'n Lock. We then went on to apply our newly found click transformation in the rapid cyclization of peptides in the absence of activation reagents or protecting group reshuffling.[2] We aim to apply these chemistries in the development of activity-based probes and modification of larger biomolecular scaffolds.

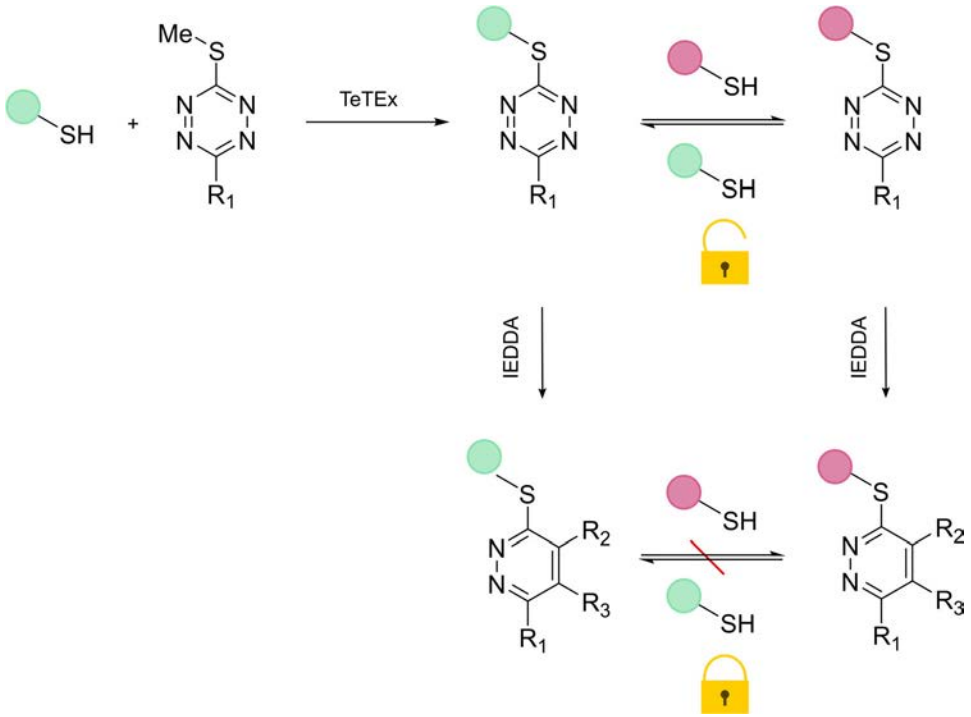

Figure 1. Click'n Lock. Thiomethyltetrazine click reaction with thiol (TeTEx), followed by a dynamic transClick reaction with a different thiol. IEDDA results to the stable pyridazine structure.

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O-22

C-Terminal Peptide Modification: Merging the Passerini Reaction with Chemo-Enzymatic Synthesis

Jay Hanssens[1], Sam van Dun[2], Tessa H.G. Lokate[1], Vincent Reinartz[1], Leendert J. van den Bos[2], Romano V.A. Orru[1], Jordy M. Saya*[1]

Aachen-Maastricht Institute for Biobased Materials at Maastricht University, Urmonderbaan 22, 6167RD Geleen, Netherlands

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Abstract

Peptides and proteins play a vital role in various areas of high societal and scientific relevance today, including catalysis and medical treatments. The increasing need for peptide products stimulates constant scientific efforts to develop novel synthetic strategies for their manufacture. While recombinant production of peptides is a viable route, solid-phase peptide synthesis (SPPS) remains a widely adopted technique. However, it remains limited in the size of the synthesizable peptides and is very atom inefficient, rendering it non-sustainable. As a result, ligation strategies were introduced to facilitate the synthesis of longer peptide chains. Enzymatic/biochemical ligation approaches, experiencing rapid advances over the past decades, have gained popularity as complementary methods to more traditional chemical ligations. In our research, we developed a novel ligation approach that combines the Passerini multicomponent reaction and chemo-enzymatic peptide synthesis (CEPS), facilitating the extension of peptide chains obtained via chemical synthesis.[1,2] The Passerini reaction utilizes aqueous acidic buffer conditions to establish chemoselectivity for the carboxylic acids, while the subsequent enzymatic ligation selectively targets the formed C-terminal substrates. We functionalized a diverse set of pentapeptides utilizing numerous isocyanide and carbonyl compounds and successfully performed subsequent ligations. This combined multicomponent chemoenzymatic method therefore represents a valuable novel technology for future research requiring site-selective C-terminal modification of peptides/proteins. We intend to apply this fundamental methodology to the synthesis of peptide and protein materials, providing a more versatile and sustainable approach to protein production.

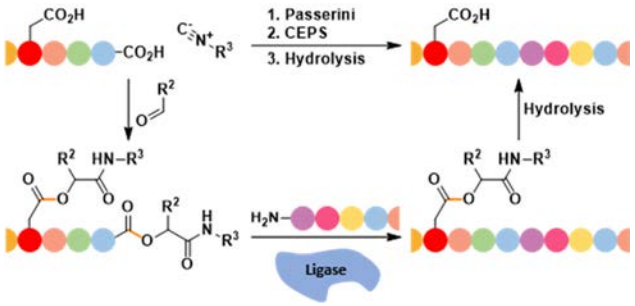

Figure 1. *Novel Passerini-CEPS-hydrolysis strategy for the functionalization of peptide C-termini.*

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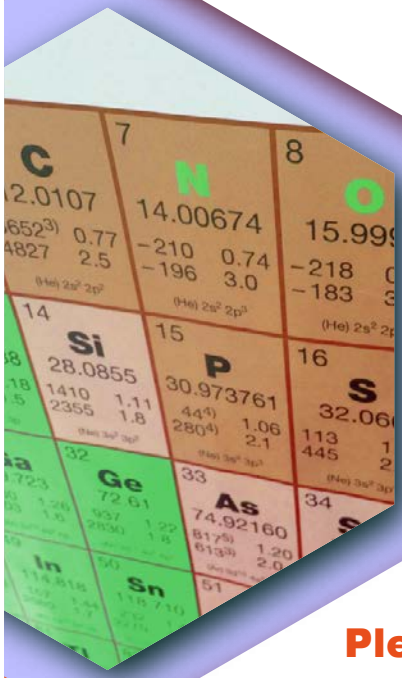

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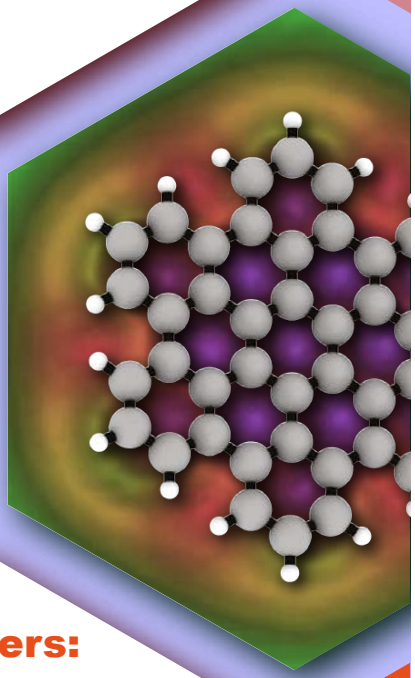

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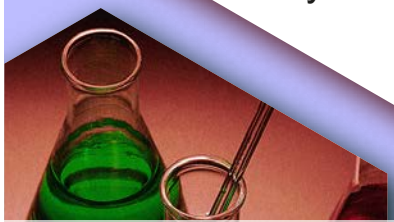

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POSTER PRESENTATIONS

P-01

Synthesis of a Library of a Oligomeric Lignin Models

Eman Abdelraheem[1], Fedor Miloserdov[1], Tom Ewing[2], Gijs van Erven[2,3]

1. *Laboratory of Organic Chemistry, Wageningen University, Wageningen, the Netherlands*
2. *Wageningen Food & Biobased Research, Wageningen University, Wageningen, The Netherlands*
3. *Laboratory of Food Chemistry, Wageningen University, Wageningen, the Netherlands*

Email: Eman.abdelraheem@wur.nl

Abstract:

Lignin is the most abundant aromatic substance in nature and holds great potential for valorization in the biobased economy. The predominant structural feature of the lignin biopolymer is a complex network of methoxylated aromatic subunits linked through various etherand C-C bonds. Studying and developing strategies for the catalytic modification and selective conversion of the lignin polymer into value-added chemicals and materials hence, heavily relies on appropriate structural lignin model compounds including dimers, trimers, and small oligomers. Therefore, access to different model compounds containing specific subunits and β-O-4, β-5 or β-β linkage motifs is crucial and targeted at here, ultimately aiming to build a structural library. We report a protocol for photoredox oxidative [3+2] cycloadditions of phenols and alkenes applicable to the modular synthesis of a large family of β-5 lignin oligomers, and present insight into the further development of this platform for synthesizing other structurally relevant oligomeric models.

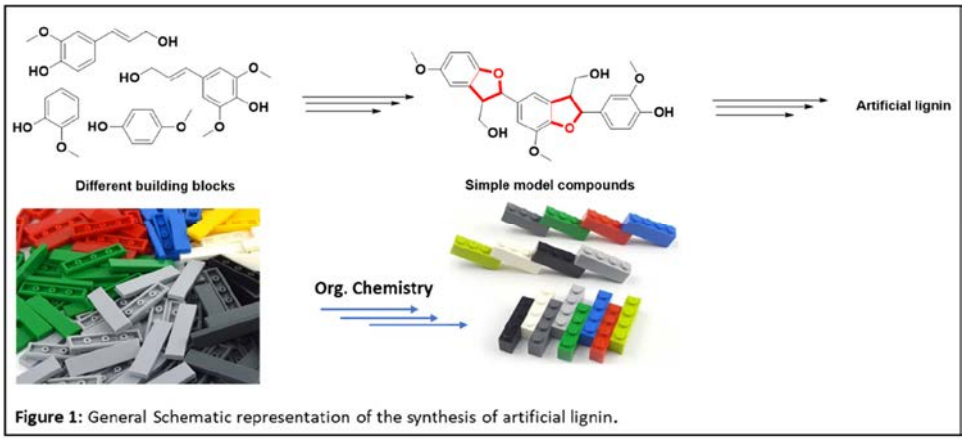


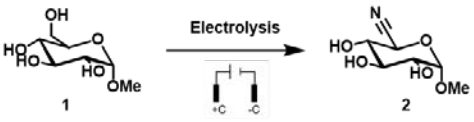
Figure 1: General Schematic representation of the synthesis of artificial lignin.

P-02

One-pot electrochemical conversion of alcohols to nitriles in unprotected carbohydrates

Imke M. A. Bartels, Prathap Kaniraj, Marios Kidonakis, Sebastian B. Beil, Martin D. Witte, and Adriaan J. Minnaard

Carbohydrates are an important class of compounds, as raw materials for industry, in food and feed, but also in biology. They are non-toxic, available on large scale in a pure form, and thus represent interesting bio-based starting materials for the development of new photo-redox and electrochemical reactions. Cyano-functionalized monosaccharides are an interesting class of building blocks. A nitrile is a versatile functional group used in polymers, surfactants and in click chemistry. Furthermore, a nitriles is readily converted to other functional groups such as an acid, aldehyde or amine.[1] However, there are currently not many methods to prepare nitriles from alcohols. The use of expensive transition metal catalysts and harsh conditions is often required, and the application of toxic cyanide extents the carbon chain by one.[2] The electrochemical conversion of an alcohol to a nitrile can contribute to the solution of these issues, as electrochemical conversions requires only mild conditions and can be quite selective. In the last few years, several methods have been developed for the TEMPO-mediated electrochemical ammoxidation of benzyl alcohols to nitriles.[3] Based on the reported literature, we developed a new method for the one-pot electrochemical ammoxidation of unprotected carbohydrates, which is highly selective and reasonably chemoselective.



Entry	Suporting electrolyte	Solvent	NH_3 source	Conversion (%)
1	-	MeCN:H_2O (9:1)	NH_4OAc	23-70
2	-	MeOH	NH_4OAc	-
3	-	H_2O	NH_4OAc	-
4	-	*t*-BuOH:MeCN:H_2O (8:1:1)	NH_4OAc	60
5	-	*t*-BuOH:MeCN:H_2O (8:1:1)	$NH_4CO_2NH_2$	13
6	-	*t*-BuOH:MeCN:H_2O (8:1:1)	NH_4Cl	-
7	-	*t*-BuOH:MeCN:H_2O (8:1:1)	NH_4PF_6	-

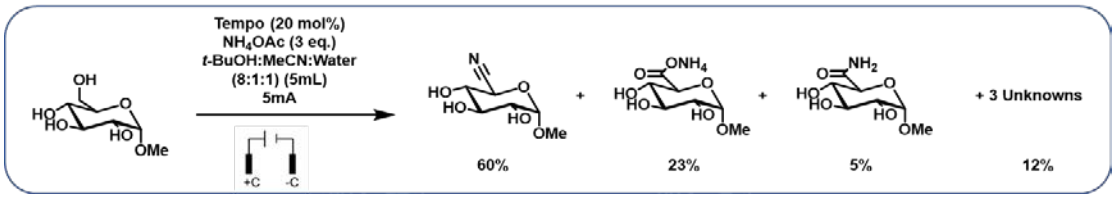


Figure 1: *Optimization of electrolytic conditions.*

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P-03 **Title abstract: Finding personalized IPSC-based medicine for monogenic neurodevelopmental disorders**

Authors
Ellen van den Berg

Abstract:
Neurodevelopment disorders (NDDs) are affecting brain development and function.[1] NDDs usually occur during early stages of development affecting mostly infants, children and adolescents. These disorders are heterogeneous in nature, as different genes and mutations are associated. Current treatments are limited to symptomatic medication that takes no notice of the etiological heterogeneity and may cause severe and unpredictable side effects.[2]

Here, we will present a multi-level strategy termed 'BRAINmodel', focusing on the balance between excitatory and inhibitory inputs (E/I) in the brain. The aim is to develop personalized treatment strategies by linking iPSC-based models, EEG data, and clinical assessments in patients with two types of genetic NDDs, the chromatin-, and SNAREopathies.[3] Chromatinopathies involve mutations affecting proteins responsible for chromatin remodelling and transcriptional regulation,[4] while SNAREopathies are characterized by mutations that disrupt synaptic SNARE function.[5] Our goal is to identify and optimize small organic molecules that are capable of modulating cellular targets that are studied within the BRAINmodel project.

Keywords: Neurodevelopmental disorders; iPSC-based models; EEG; SNAREopathies; Chromatinopathies; Drug discovery and development

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P-04 Navigating through Chemical Space: Exploration Scores for *de Novo* Generated Molecule Clusters

Remco L. van den Broek[1], Valeriia Fil[2], Daniel Svozil[2], Willem Jespers[1], and Gerard J.P. van Westen[1]

[1] Department of Drug Discovery and Safety, Leiden Academic Centre for Drug Research (LACDR), Leiden University, Box 9502, 2300 RA, Leiden, The Netherlands
[2] Laboratory of Informatics and Chemistry, University of Chemistry and Technology Prague, Technická 5, 166 28 Prague 6, Czech Republic

ABSTRACT

Numerous molecular generators have been developed over the last decade to improve the exploration rate of chemical space for the identification of novel hit compounds. Despite the abundance of molecular generators available, their integration within the chemist's toolkit remains limited. Skepticism against the use of molecular generators may be attributed to their tendency to produce highly complex or irrelevant molecules coupled with the absence of fair and understandable benchmarks. Our goal is to provide chemists with a means to select molecular generators based on their efficacy in navigating chemical space. We achieve this by evaluating molecular generators with two scores: 1) their coverage of known drug-like structures, and 2) the chemical relevance of *de novo* generated molecule clusters. The coverage score measures how well the generator explores chemical space, while the relevance score assesses the usefulness of the clusters by evaluating synthesizability and drug-likeness. Together, these scores offer a comprehensive tool to judge both a generator's exploratory ability and the utility of the chemical spaces it explores for discovering new hit compounds.

P-05 **Title**: Elucidating the Impact of CoREST subunit degradation via PROTACs on hematopoiesis and Leukemia Cell Differentiation

Authors: **Lorenzo Cavina**, Saskia Bergevoet, Jeron Venhuizen, Igor Hermens, Bert van der Reijden, Floris P.J.T. Rutjes.

Abstract:

The CoREST complex, a crucial transcriptional coregulatory assembly implicated in chromatin remodeling and gene silencing, encompasses key subunits such as LSD1 (also known as KDM1A, lysine-specific demethylase 1A), HDAC1/2 (Histone deacetylase 1/2), and the transcription factor GFI1 (growth factor independent 1 transcriptional repressor). Its role in modulating histone modification makes it integral to hematopoiesis and, when dysregulated, is associated with leukemia pathogenesis.[1] This study aims to explore the selective degradation of the CoREST subunits using Proteolysis Targeting Chimeras (PROTACs), which, hijacking the ubiquitin-proteasome system, shall promote the endogenous degradation of their respective targets.[2] We present herein PROTACs leveraging small molecule as warheads targeting LSD1 and HDAC1/2, and Nucleic Acid Based PROTACs (NAB-PROTACs) targeting GFI1. We hypothesize that targeted degradation of the separate CoREST components will lead to significant alterations in regulation and function of the whole assembly, potentially affecting chromatin remodeling and gene expression patterns that are essential in leukemia progression. This study not only aims to enhance our understanding of leukemia pathophysiology through epigenetic mechanisms but also seeks to contribute to the development of targeted therapeutic strategies in hematological malignancies by employing PROTACs as a precision tool.

References:

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P-06 FROM INORGANIC PHOSPHATES TO ORGANIC: HOW TO IMPROVE THE PHOSPHORUS INDUSTRY?

Anna Chernysheva[1], C. Lillian Bisschop[1,2], G. Bas De Jong[1], J. Chris Slootweg[1]

[1]Van 't Hoff Institute for Molecular Sciences, University of Amsterdam, Amsterdam, The Netherlands

[2]Faculty of Applied Science and Technology, University of Applied Sciences Leiden, Leiden, The Netherlands

Currently, the phosphorus industry is a complex and energy-consuming process, which involves non-renewable resources, such as phosphate rock (mostly fluorapatite, $Ca_5(PO_4)_3F$) [1]. For example, to make pure organophosphorus compounds with flame-retardant properties, now it is necessary to convert fluorapatite into white phosphorus P_4. The next step includes phosphorus oxidation and the production of halogenated phosphorus compounds, such as PCl_3, PCl_5, etc. Only after this reduction-oxidation cycle, it is possible to obtain desirable organophosphorus compounds [2]. The energy consumption of the described process and the toxicity of the intermediates lead to the need to revise the industrial synthesis of organophosphates.

It is also necessary to consider this problem because of the expected crisis. The population of our planet is growing and this growth should decline only after 60 years [3]. To meet both the growing demand for phosphorus-containing products and to reduce the amount of phosphorus ending up in the environment after use, it is interesting to use wastewater as a renewable source of phosphorus. This approach will also help to avoid such a negative phenomenon as eutrophication – excessive growth of algae on the water surface which is dangerous for fish and other living creatures [4].

It is already known how to make phosphoric acid from the wastewater. But how to obtain valuable organophosphorus compounds from the phosphoric acid avoiding unnecessary reduction-oxidation cycles? The idea of this project is trying to answer that question. In other words, that project aims to find a lost chain between phosphoric acid and organophosphorus compounds.

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P-07

Name: René Dekkers
Employer: Leiden University
Institute: Leiden Institute of Chemistry

Title: Design and synthesis of paramagnetic tags for protein dynamic studies in NMR

Abstract

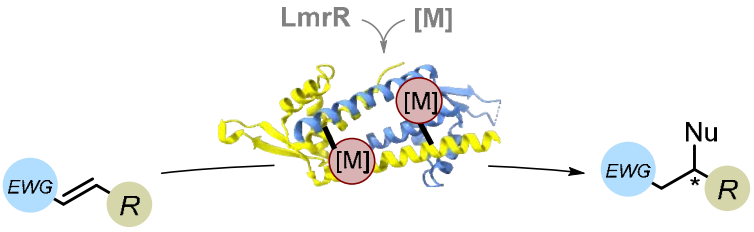
To understand the functioning of macromolecules such as proteins, it is important to study their dynamics. While low energy states (LES) are well-known and extensively studied with commonly used technieques (e.g. crystallography or Cryo-EM), high energy states (HES) are more difficult to observe due to their short time of excistance. Nevertheless, it is hypothesized that HES are crucial for understanding macromolecular functioning. In this project, we aim to study these HES using NMR, making use of paramagnetic effects. These effects are obtained using a paramagnetic metal, wich we introduce by attaching a paramagnetic tag to the protein. One such tag needs to be chemically synthesized after wich the paramagnetic metal can be included upon complexation, followed by covalently binding the tag to a protein. With my poster I would like to present a briefly some background, latest results and future prospects but would like to focus and emphasize the synthesis of these paramagnetic tags.

P-08

Participant: Franco Della Felice

Title: Artificial metalloenzymes with LmrR: towards a transition metal catalyzed enantioselective conjugate addition

Abstract: Artificial metalloenzymes (ARMs), that is, designed enzymes containing a synthetic metal co-factor within a protein framework, locates itself as a promising area of research for the discovery and development of new synthetic transformations. Recently, the group of Roelfes have successfully exploited the use of the lactococcal multidrug resistant regulator (LmrR) as the host protein in a set of different type of reactions in a selective manner, i.e., Diels-Alder reaction, Friedel-Crafts alkylation and conjugate additions, by the introduction of both non-canonical amino acids (ncAAs) and synthetic transition metal complexes.[1] Intrigued in continuing expanding the synthetic utility of LmrR, here we will present our results on the incorporation of ncAAs capable to anchor transition metals and their use in the development of enantioselective conjugate addition reactions.



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P-09

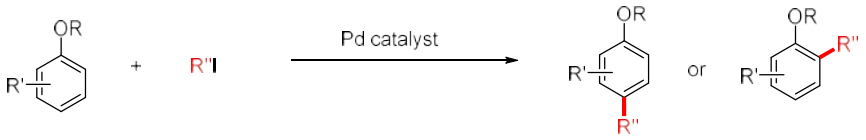
NON DIRECTED C–H ARYLATION OF ELECTRON-RICH ARENES VIA PALLADIUM/S,O-LIGAND CATALYSIS

Ke-zuan Deng, Verena Sukowski and M. Á. Fernández-Ibáñez*

Van 't Hoff Institute for Molecular Sciences, Faculty of Science, University of Amsterdam, Science Park 904, 1098 XH Amsterdam, The Netherlands

Biaryl compounds are one of the most common and versatile skeletons in organic synthesis present in bioactive molecules, synthetic intermediates, functional materials and reagents.[1] Thus, developing efficient methodologies to prepare various biaryl compounds is of great importance. Traditionally, biaryl compounds are synthesized *via* cross coupling, which requires a pre-halogenated starting arenes.[2] On the other hand, C–H arylation is a greener alternative to the cross coupling since no pre-functionalization of the starting arene is required.[3]

Here, we present a novel nondirected C–H arylation of electron-rich arenes via Pd/S,O-ligand catalyst. The reaction proceeds under mild reaction conditions with a broad substrate scope providing the arylated products in good yields. The method is applicable to late-stage functionalization of several pharmaceutical molecules and synthesis of industrially useful starting materials.



R' = EDG/EWG; R'' = aryl.

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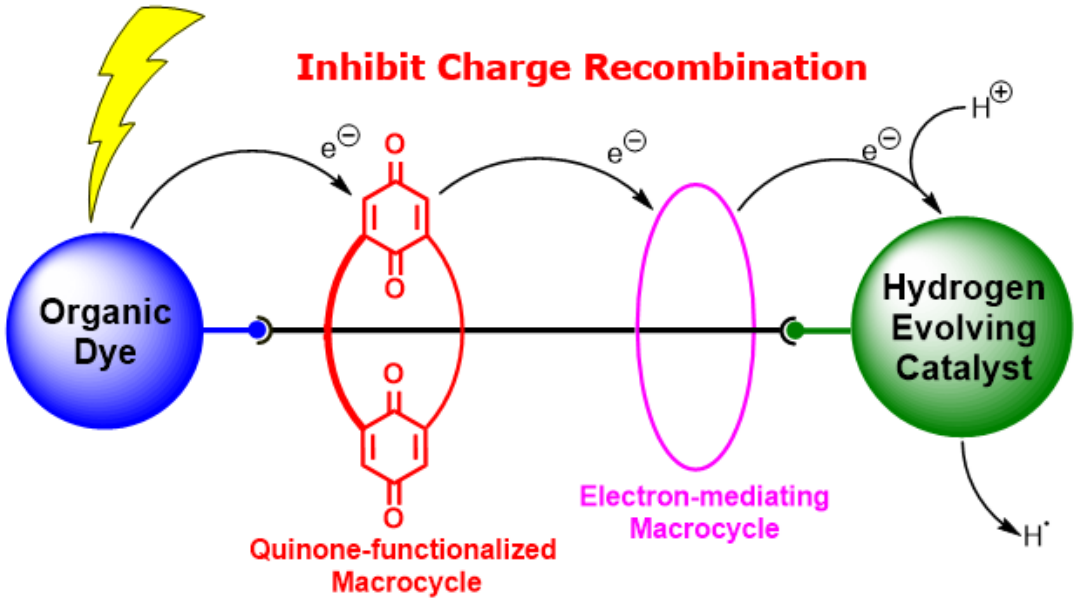
P-10 Hybrid covalent/supramolecular synthesis of [3]rotaxanes as photoactive electron shuttles

Zezhong Dong, Jennifer Munro, Alessandro Mantoani, Nick Westerveld, Simon Mathew and Jan H. van Maarseveen.



Addressing the challenge of electron recombination in artificial photosynthetic devices necessitates innovative solutions. Our proposed strategy involves the integration of redox mediators within the macrocycles of [3]rotaxanes to serve as efficient electron transporters. This approach aims to facilitate unidirectional electron flow from the dye to the hydrogen evolving catalyst, thereby mitigating the issue of rapid recombination. The design encompasses two key components. Firstly, a quinone-functionalized macrocycle, synthesized via covalent templated methodology, offers the unique capability to neutralize negative charges through protonation of the quinone radical anion, thereby enhancing electron transfer efficiency. Complementing this, the second macrocycle, engineered through supramolecular synthesis, features redox-active properties with a lower reduction potential and ensures the unidirectional transport of electrons. By combining these specialized macrocycles within the [3]rotaxane framework, we envision a novel approach to circumvent electron recombination, ultimately advancing the efficacy of artificial photosynthetic systems.

P-11

Effect of polifluorinated solvent 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) on the kinetic of Passerini multicomponent reaction

Claudio Ferdeghini,[a] Minghui Wu,[a] Prabhat Ranjan,[a] Chevonne Hagens,[a] Martien A. Wurdemann,[a] Jan Pyschik,[b] Alexander Mitsos,[b] Romano V.A. Orru,[a]* Jordy M. Saya[a]*

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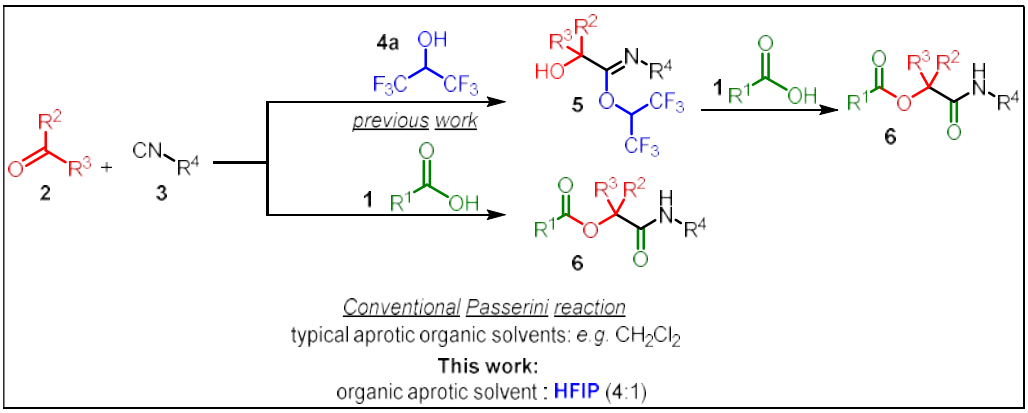
[b] Process Systems Engineering (AVT.SVT), RWTH Aachen University, Forckenbeckstraße 51, 52074, Aachen, Germany

Multicomponent reactions (MCRs) stand as indispensable tools in modern organic synthesis, offering a simplified approach in the synthesis of complex molecules.[1] Among these, the 3-center Passerini reaction (P-3CR) has emerged as a versatile and atom-economical strategy for the synthesis of different classes of compounds.[2] However, the inherent sluggishness of the kinetics of this reaction presents a significant drawback, necessitating innovative approaches for acceleration.

Recent investigations have shed light on a promising solution: the addition of 1,1,1,3,3,3-hexafluoroisopropanol (HFIP, Scheme 1). [3] In fact, due to the acidic properties and very low nucleophilicity, this alternative solvent showed promising results in opposition to the use of other alcoholic solvents, which are typically associated with slower reaction rates due to competitive hydrogen bonding interactions. The observed acceleration suggests a potential role for HFIP in the formation of hydrogen bonds activating carbonylic compounds, thus facilitating the Passerini reaction rate. This phenomenon not only highlights the complexity of solvent effects but also underscores the importance of understanding molecular interactions in reaction mechanisms.

Further exploration of the interplay between HFIP and the reaction components is warranted to elucidate the underlying mechanism driving this rate enhancement phenomenon. Such insights hold the promise of not only optimizing the Passerini reaction but also advancing our understanding of solvent-mediated effects in multicomponent reactions.



Scheme 1. Influence of HFIP in Passerini reaction

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P-12

C-Terminal Peptide Modification: Merging the Passerini Reaction with Chemo-Enzymatic Synthesis

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Abstract

Peptides and proteins play a vital role in various areas of high societal and scientific relevance today, including catalysis and medical treatments. The increasing need for peptide products stimulates constant scientific efforts to develop novel synthetic strategies for their manufacture. While recombinant production of peptides is a viable route, solid-phase peptide synthesis (SPPS) remains a widely adopted technique. However, it remains limited in the size of the synthesizable peptides and is very atom inefficient, rendering it non-sustainable. As a result, ligation strategies were introduced to facilitate the synthesis of longer peptide chains. Enzymatic/biochemical ligation approaches, experiencing rapid advances over the past decades, have gained popularity as complementary methods to more traditional chemical ligations. In our research, we developed a novel ligation approach that combines the Passerini multicomponent reaction and chemo-enzymatic peptide synthesis (CEPS), facilitating the extension of peptide chains obtained via chemical synthesis.[1,2] The Passerini reaction utilizes aqueous acidic buffer conditions to establish chemoselectivity for the carboxylic acids, while the subsequent enzymatic ligation selectively targets the formed C-terminal substrates. We functionalized a diverse set of pentapeptides utilizing numerous isocyanide and carbonyl compounds and successfully performed subsequent ligations. This combined multicomponent chemoenzymatic method therefore represents a valuable novel technology for future research requiring site-selective C-terminal modification of peptides/proteins. We intend to apply this fundamental methodology to the synthesis of peptide and protein materials, providing a more versatile and sustainable approach to protein production.

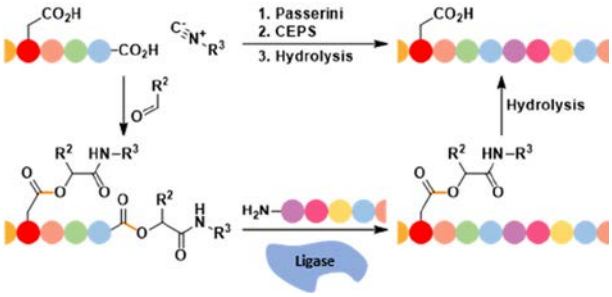

Figure 1. *Novel Passerini-CEPS-hydrolysis strategy for the functionalization of peptide C-termini.*

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P-13 Broad spectrum profiling of RING E3 ligase activity using photoactivatable synthetic ubiquitin probes

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The ubiquitin-proteasome system is crucial in the regulation of cellular protein concentration. The core principle of the system is the transfer of ubiquitin to an available lysine of a substrate protein. After multiple cycles of ubiquitin chain extension, the substrate protein is recognized by the 26S proteasome and will be degraded. The transfer of ubiquitin occurs via the E1-E2-E3 ligase cascade. Dysregulation in this complex system leads to the manifestation of diseases such as cancer and neurodegenerative diseases. Since the E3 ligases mediate the last step of ubiquitin conjugation and primarily determine the substrate specificity, they are the most interesting family of proteins for drug development.
In the past, molecular probes have been developed to study the activity of HECT and RBR E3 ligases, targeting the enzyme's active-site cysteine. RING E3 ligases, which is the largest family of E3 ligases (~600 enzymes encoded), lack this active site cysteine and therefore still lacks effective molecular tools to study their activity. Therefore, we aimed to develop molecular probes with which we can profile RING E3 ligase activity.
These probes mimic the Ub~E2 complex and are able to covalently bind the RING E3 ligases via uv-induced crosslinking. Various ubiquitin probes have been synthesized containing unnatural photo-crosslinking amino acids in varying positions. These ubiquitin peptides have been conjugated to a recombinant E2 ligase, which has its active site cysteine mutated towards a lysine to prevent further transfer of the ubiquitin peptide.
The library of probes has been tested against recombinant RNF23 and multiple probes successfully bound the E3 ligase and can now be used for further proteomics studies. These probes will be of indispensable use for the development of novel treatments targeting RING E3 ligases.

P-14 Abstract Lunteren 2024

Authors details
Mathilde Janssen
Synthetic Organic Chemistry
Under supervision of Prof. Floris Rutjes and Dr. Daniel Blanco-Ania

Title
Synthesis of Cyclobutanes for Fragment-Based Drug Discovery

Abstract

Cyclobutanes offer unique opportunities in medicinal chemistry, because of their distinctive puckered structure [1]. Fragment-based drug discovery (FBDD) has become a well-established approach in medicinal chemistry to generate lead compounds. In current libraries, 3D small-ring fragments, such as cyclobutanes, are underrepresented because of the limited number of ways to synthesize them[2]. Therefore, we set out to synthesize novel FBDD-libraries containing cyclobutane fragments. Previously, various synthesis routes towards substituted cyclobutanes using [2+2] cycloadditions have been described [3]. However, in most cases alkenes with bulky and flat aromatic groups are required for the successful synthesis. As a result, molecules are generated that are not appropriate for FBDD, because of their size (>300 Da) and non-versatile substituents for further library preparation. A non-standard method, like high pressure (10–15 kbar) chemistry provide a unique opportunity to synthesize novel cyclobutane scaffolds using [2+2] cycloadditions. We used various alkenes and allenes with a variety of functional handles to afford 1,2- and 1,3-substituted cyclobutanes. The problems and opportunities of the design and analysis of these libraries will be discussed.

Relevant keywords
Cyclobutanes, [2+2] cycloaddition, fragment-based drug discovery.

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P-15

Synthetic challenges towards a specific modification of (+) -2*R*,3*R*-corynomycolic acid from *Corynebacterium sp*

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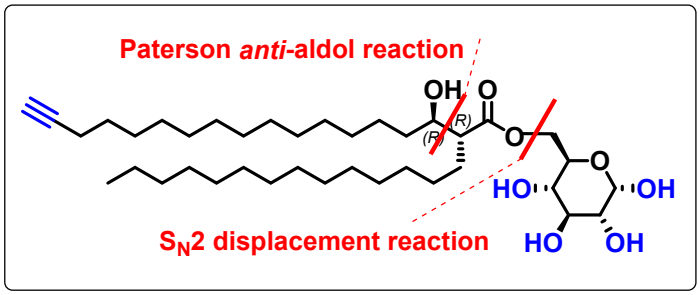
Introduction: Corynebacteriales are an order of Actinobacteria that includes numerous human pathogens, such as the etiologic agents of tuberculosis, leprosy and diphtheria. They are characterized by an atypical cell envelope containing unique high molecular weight α-branched β-hydroxylated fatty acids (C30–90) called mycolic acids[1]. These have been shown to play a critical role in the structure and function of the cell wall. Over the last decade, bio-orthogonal chemical reporters have emerged as valuable tools for detecting bacterial cell surface components *in situ*[2]. Such developments include the study of mycomembrane (MM) components and several trehalose-based probe have been developed allowing the visualization of the MM in live cells through the metabolic labeling approach[2-3]. In this work, we present the design and synthesis of a modified natural coryno mycolic acid with a clickable alkyne unit at the terminus. The specific changes in the original coryno mycolic acid were not so easy to construct. The main challenges we faced during the synthesis are (i) the generation of the anti-stereochemistry between the β-hydroxyl group and the α-chain of the mycolic acid and (ii) achieving a selective mono-6-*O*-esterification of the *glucose* unit without protecting the secondary OH groups.



Notably, a boron-mediated aldol reaction of a chiral ketone, developed by the Paterson group, was key to complete the target compound. Contrary to other famous enantioselective anti-aldol reactions, such as the Masamune and the Fráter–Seebach alkylation which met with failure. In the end, the alkyne based corynomycolic acid was synthesized in 13 steps.

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P-16

The synthesis of fructose-based surfactants

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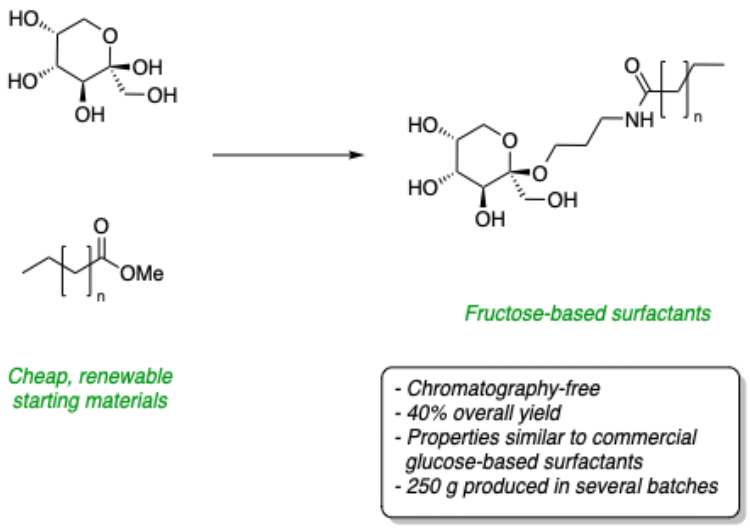
Bio-based surfactants hold an important role in the transition of the chemical industry from starting materials derived from fossils to renewable building blocks[1]. Among these, glucose-based surfactants hold a privileged position, while amphiphiles based on fructose, the second most abundant monosaccharide, are underexplored[2].

We present a scalable synthesis of surfactants from renewable sources: fructose and fatty acid methyl esters (FAMEs)[3]. The HCl-catalysed Fischer glycosylation reaction of fructose and 3-hydroxypropionitrile is aided by reactive crystallisation of a single stereoisomer, which is isolated by filtration in 66% yield. The obtained intermediate is hydrogenated at ambient pressure over Raney nickel to yield 3-aminopropyl fructoside quantitatively. This amine is transformed into the corresponding amide by NaOMe-mediated amidation with a variety of FAMEs. Amphiphilic properties of the obtained amides were evaluated by CMC and Krafft point measurements, as well as a foaming test and were found to be comparable to commercial glucose-based surfactants[3].



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P-17

Design and Synthesis of Covalent Inhibitors for Inverting α-Glucosidases

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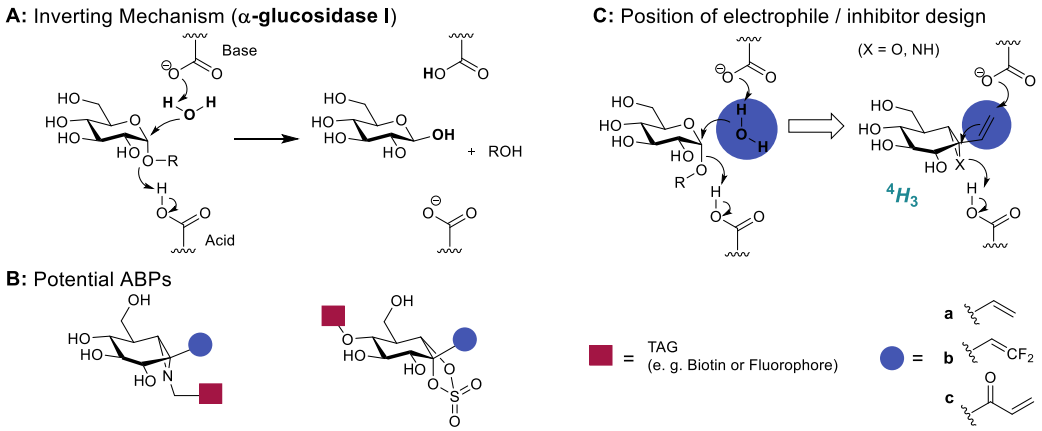
Inverting glycosidases are an important and widespread class of enzymes (Fig. 1 A). As for retaining glycosidases, these enzymes can be promising targets in biomedicine and biotechnology. Inverting α-glucosidases are of particular interest as they play an important role in cellular functions, such as the correct folding of proteins in the endoplasmic reticulum. However, selective inverting α-glucosidase inhibitors are scarce, and chemical probes that selectively report on their activity in biological samples do not exist.

To overcome the absence of inhibitors we sought to apply activity-based protein profiling (ABPP) to this class of enzymes. This powerful method depends heavily on the availability of mechanism-based enzyme inhibitors to develop affinity-based probes (ABPs, Fig. 1B). Herein we present the rational design and synthesis of potential covalently binding inhibitors targeting inverting α-glucosidases. The designs are based on the use of carbaglucose scaffold, carrying an epoxide, mimicking the $^4H_3$ conformation of the natural substrate in the transition state of the hydrolysis reaction. To enable the formation of a covalent bond between the inhibitor and the enzyme, a suitable electrophile is introduced that can take up the space normally occupied by the water molecule involved in the hydrolysis reaction (Fig. 1C). In addition, a specially developed assay was implemented and used for biological evaluation.



Design approach for covalently binding inverting α-glucosidase inhibitors in ABPP.

Acknowledgements.
This project is funded by the European Union. (MSCA Postdoctoral Fellowships to FK, Project 101063551)

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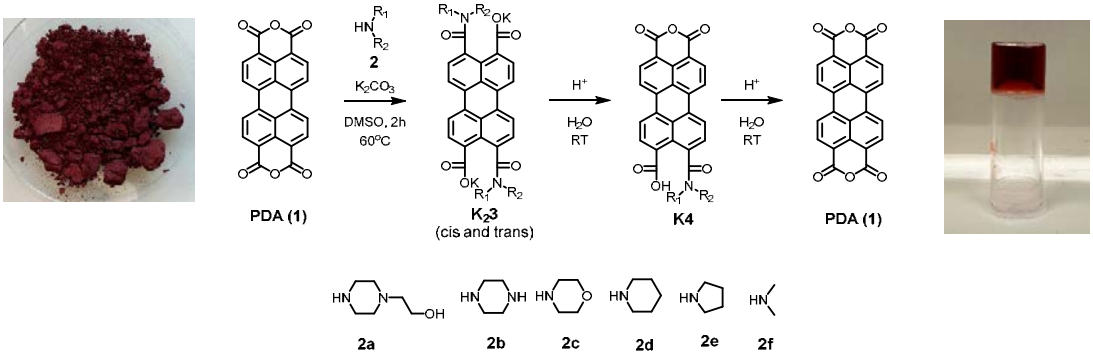
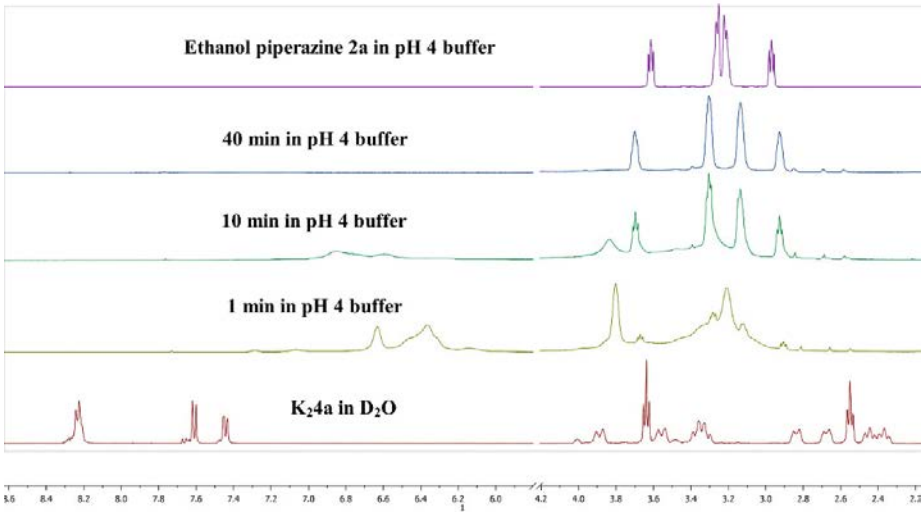
P-18 Perylene dianhydride hydrogels obtained from highly accessible perylene-3,4,9,10-tetracarboxylic diamic acids precursors.

Markus C. Kwakernaak, Marijn Koel, Peter J.L. van den Berg, Erik M. Kelder and Wolter F. Jager



Perylene amic acid salts (**$K_2$3**) represent a new class of perylene-based hydrogelators, which form hydrogels by a unique protonation-hydrolysis mechanism. Hydrogel formation by this mechanism has been observed for a large number of perylene amic acid salts and their ester analogues, in which amides are substituted by esters.

A series of perylene diamic acid (PDAA) salts derived from cyclic secondary amines were synthesized to study the gelation in detail. Slow protonation with glucono-d-lactone or an acidic buffer will changes the color of the solution to deep red and after a few hours, hydrogels are formed. The gelation process was investigated using time-dependent UV-VIS and ^{1}H-NMR spectroscopy, rheology measurements and cryo-TEM imaging. In the NMR measurements of the gelation of compound **$K_2$3a**, the gelation process is demonstrated by the disappearance of the aromatic protons, and the amic acid hydrolysis is proven by the formtion ethanol piperazine.



In the proposed gelation mechanism, the PDAA is slowly protonated, which initiates π-π stacking of hydrophobic amic acids. Subsequently, the slower hydrolysis reaction will produce anhydrides that have a planar geometry. This will enhance the π-π stacking, which will make the stacks more rigid and the hydrogel stronger. Typical hydrogels have critical gel concentrations (CGCs) of 10^{-5} M and exhibit storage moduli around 500 Pa at 1 mM.

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Room temperature synthesis of perylene diimides facilitated by high amic acid solubility. Markus C. Kwakernaak, Marijn Koel, Peter J. L. van den Berg, Erik M. Kelder and Wolter F. Jager. *Org. Chem. Frontiers*, **2022**, 9, 1481-1492.

P-19

Site-selective introduction of a gem-chloro-nitroso unit in carbohydrates

Zonghao Lin, Martin Witte, Adriaan J. Minnaard*

Deoxygenative functionalization of ketones is a strategy to convert a keto group into another functional group. Our group disclosed the conversion of a ketone into a chloride, a thiol/thio ether, or a gem dichloro group in unprotected carbohydrates[1]. In the current project, we applied the deoxygenative functionalization of ketones to carbohydrates by site-selective oxidation followed by introducing a gem-chloro-nitroso unit. Gem-chloro-nitroso compounds can be the source of nitrogen oxide radical and are versatile intermediates for the synthesis of various organic compounds, such as gem-chloro-nitro derivatives, gem-dichloro alkanes and cyclization reactions (in particular asymmetric hetero Diels-Alder Reactions)[2]. The gem-chloro-nitroso moiety is formed by chlorination of the corresponding oxime, with t-BuOCl or Cl_2 in dedicated glassware (COware). One peculiar property of gem-chloro-nitroso compounds is their blue color, which is a direct visible proof of their formation. We succeeded in introducing the gem-chloro-nitroso unit in cyclohexanone oxime and protected carbohydrates (Di-isopropylidene-fructopyranose and Di-isopropylidene-glucofuranose) and obtained the final products after purification. Although the gem-chloro-nitroso unit could be installed in unprotected carbohydrates (methyl glucoside and n-butyl glucoside), the compounds are not stable and decompose upon purification. We currently attempt to use the protected carbohydrate-derived gem-chloro-nitroso compounds as chiral reagents in synthesis.

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P-20 Design and covalent synthesis of mechanical chiral molecules

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University of Amsterdam

Abstract

Mechanical chirality is a fascinating molecular physical property that is also found in the natural lasso peptides. This phenomenon appears when two achiral subcomponents incorporating directionality such as the amide bonds in a peptide chain become mechanical interlocked to give rotaxanes or catenanes. An example of mechanical chirality would be a rotaxane composing of an all glycine peptide macrocycle and a thread with two different stoppers. We aim at the stereoselective synthesis of mechanically chiral rotaxanes in order enable in the future the synthesis of optically active lasso peptide analogs.

P-21 Forces exerted by supramolecular polymerization motors

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The study of the processes occurring in living organisms is of fundamental importance and is also a key source of inspiration for the development of new intelligent mater [1,2]. All movement in living organisms is the result of the combined action of dynamic molecules working together to convert chemical energy into orderly activity. Given that the magnitude of the Brownian motion is several orders larger than any mechanical action produced by small molecules, biological molecular machinery operates within large supramolecular assemblies [3].
Molecular mechanisms operating at the level of self-assembly processes are known as polymerization and depolymerization motors [4]. They are capable of exerting pushing and pulling forces and perform useful mechanical tasks at the level of cross-linked polymer networks and at the level of individual fibers [5,6]. Examples of biological polymerization machines that operate on these principles are cellular microtubules and actin filaments [7,8].
Since methods for characterization of life-like systems are necessary for the re-engineering of biological principles of force generations, current project aims to develop a method for qualitative and quantitative assessment of the performance of artificial supramolecular motors using atomic force microscopy (AFM).

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P-22 The synthesis and biological evaluation of 3,4,5-trihydroxylpiperidines and their *N*-derivatives

Qiang Ma, Maria J. Ferraz, Richard J. B. H. N. van den Berg, Hermen S. Overkleeft

1-Deoxynojirimycin (DNJ) is a biologically active natural compound, from which many isomers and derivatives have been studied for their biological potential, including inhibition of the three glucosylceramide processing enzymes, glucosylceramide synthase (GCS), lysosomal glucosylceramidase (GBA) and non-lysosomal glucosylceramidase (GBA2). Recently, there has been reported that the hydroxymethyl group of DNJ is crucial to neither potency nor selectivity of β-glucosidase. On the other hand, the sidechain removal improves the potency on GBA inhibition. With the aim of developing more potent and selective inhibitors of the three glucosylceramide processing enzymes, this project described the synthesis of in total 4 configurational isomers of 3,4,5-trihydroxylpiperidines and their *N*-alkylated derivatives, as well as the biological evaluation. Screening the library against the three glucosylceramide processing enzymes indicates that the hydroxymethyl group is not crucial to their inhibition potency but affects the selectivity toward GCS/GBA2 over GBA. In addition, this inhibition profile confirms that appropriately substituted DL-*glu*/DL-*ido* configured 3,4,5-trihydroxylpiperidines are still effective as dual GCS/GBA2 inhibitors, which have been studied as putative therapeutics for the treatment of the lysosomal storage disorder, Gaucher disease. We believe that our finding here could contribute to the design of next-generation inhibitors of glucosylceramide processing enzymes.

P-23 **Title:** Upgrading agricultural waste: from biobased building block to functional materials

Authors: Claudio Ferdeghini, Lisa Hendrickx and Diego Meneses, Jordy Saya, Romano V.A. Orru

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Group leader: Prof. Dr. Romano V.A. Orru
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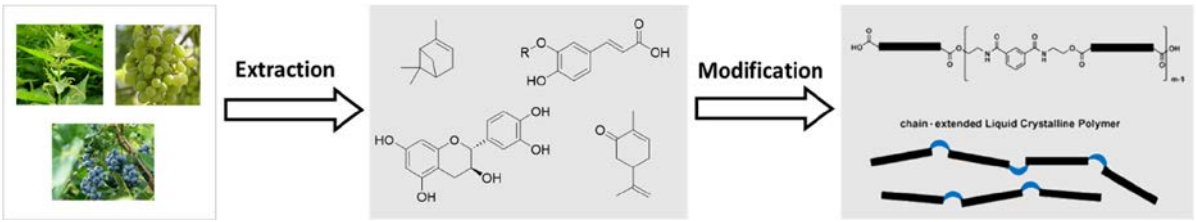
Plants possess a great variety of compounds that had gained interest for humanity. For example, phenolic acids are used for their biological roles as secondary metabolites and from their roles in food quality;[1] terpenes and terpenoids are known as natural building blocks and for their pharmacological properties and flavonols and isoflavonols are important antioxidant compounds, often used as colorants[2]. Due to the interest in extracting those compounds, many different separation techniques have been developed. The highest concentration of those compounds has been found in the fruits of the plants, but what about the other part of the plants? It is possible to convert those parts (pomaces, leaves, roots, branches…) that are classified as "waste" in the cultivation as a valuable source to obtain those compounds? The present work aims to extract compounds from the wasted parts of the plants for their use as monomers in polymerizations or Multicomponent reactions (MCRs) (*Scheme 1*).



Scheme 1: From crops to polymers[4]

This involves the modification of the bio-based building blocks into bifunctional monomers. Once achieved, these modified molecules can be employed in processes such as Passerini polymerization. The utilization of Passerini polymerization offers a distinct advantage as it is a multicomponent reaction.[3] By adjusting a single molecule, we can tailor the properties of resulting polymers, adding a layer of versatility to their applications.

We also plan at using them as starting materials for the development of novel methodology, such as transition-metal-catalyzed isocyanide insertion or the use of phosphonaryl radicals. This includes the use of photocatalysis, electrochemistry and HAT processes.

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P-24 One-pot conversion of alcohols to nitriles in unprotected carbohydrates

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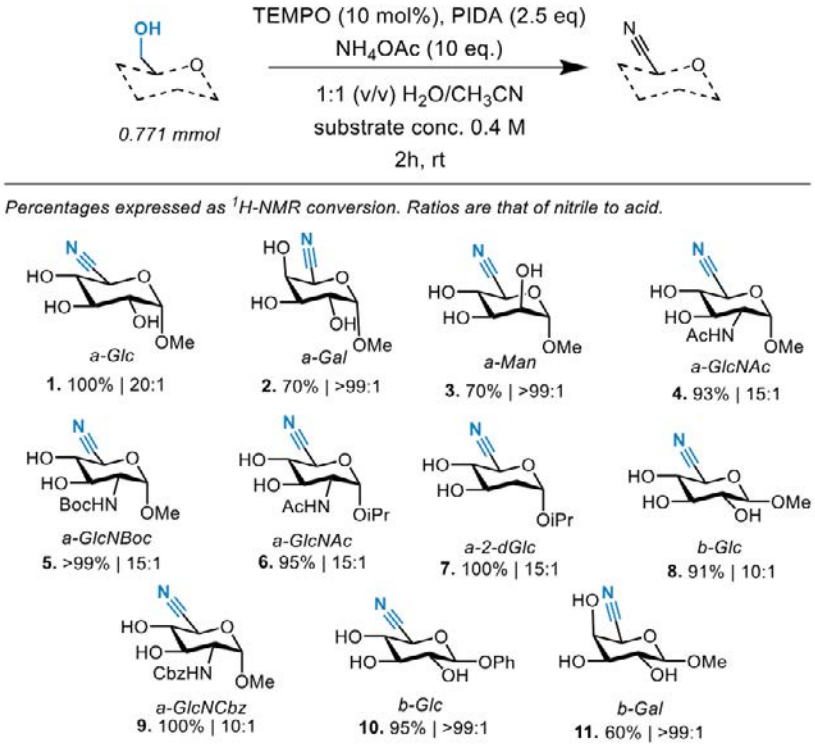
Carbohydrates are a crucial and readily available category of bio-based compounds, and intensively studied also in chemistry. However, a large number of highly similar hydroxy groups coupled with limited solubility in organic solvents, presents persisting challenges in achieving regioselectivity in chemical reactions. In most cases application of various protecting groups is necessary, adding layers of complexity and costs to the process. Up until this point, literature has only reported on the oxidation of the primary hydroxy group in unprotected carbohydrates to the carboxylic acid[1]. Based on available literature we developed a novel method for conversion of primary hydroxyl groups to nitriles in unprotected carbohydrates, using a low-cost, safe and efficient protocol[1,2]. Unlike many alternatives, this method does not rely on transition metal catalysis, but solely uses TEMPO, PIDA and ammonium acetate, providing a valuable modification of the previously reported procedures.[1,2] Introducing a nitrile group into unprotected carbohydrates opens up many opportunities, since nitriles can be directly converted into ketones, acids and amines, which is useful in fields such as click chemistry or surfactants production.[3] The generation of the carboxylic acid side-product was minimised by optimising the reaction conditions. A broad scope of monosaccharide substrates was investigated, resulting in high yields and promising selectivity.



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P-25 Development of electrophilic probes for the profiling of ligandable arginines in the bacterial proteome

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Leiden University

Covalent inhibitors are making a comeback in medicinal chemistry and chemical biology due to the growing understanding of electrophilic reactivity towards nucleophilic residues. While traditional therapeutics reversibly bind to their biological targets, covalent inhibitors form a strong covalent bond, enhancing the inhibiting effect. This mechanism is relevant in many antibiotics and is becoming increasingly important due to bacterial antibiotic resistance. Of all residues, cysteine is mostly targeted by covalent inhibition for due to its high nucleophilicity. However, cysteine is relatively uncommon in many proteomes, meaning that many potential drug target sites remain untargetable. Arginine is a more common amino acid and displays a plethora of biologically relevant functions such as ins protein interactions, enzyme functions and protein structure, making it an attractive drug target. However, targeting arginine is more challenging, which is why our research focuses on discovering novel electrophiles binding to this residue.

In this work, we synthesized numerous chemical probes with varying chemotypes and screened them on methicillin-resistant *Staphylococcus aureus* lysate. 1,2-diketoamides emerged as the most suitable chemotype for targeting arginines and a set of 4 additional tailored probes containing this electrophile were developed. These were utilized to profile arginine residues proteome-wide using an activity-based protein profiling workflow, allowing global mapping of >15,000 arginines as well as study of arginine reactivity. This technology will enable the proteome-wide profiling of the target engagement and selectivity of arginine-directed covalent protein ligands and, thereby, contribute to the development of novel covalent inhibitors.

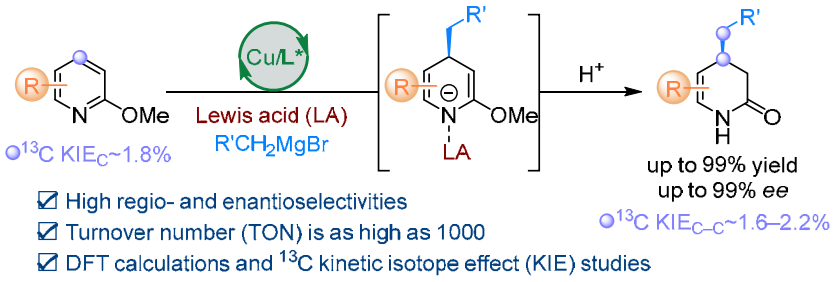
P-26 Catalytic Access to Chiral *δ*-Lactams via Nucleophilic Dearomatizations of Pyridine Derivatives

*Siriphong Somprasong, Marta Castiñeira Reis, and Syuzanna R. Harutyunyan**

Stratingh Institute for Chemistry, University of Groningen, Nijenborgh 4, 9747 AG, Groningen (The Netherlands)

Nitrogen-bearing rings are common features in the molecular structures of modern drugs, with chiral *δ*-lactams being an important subclass due to their known pharmacological properties.[1] Catalytic dearomatization of preactivated pyridinium ion derivatives emerged as a powerful method for the rapid construction of chiral *N*-heterocycles. However, direct catalytic dearomatization of simple pyridine derivatives are scarce and methodologies yielding chiral *δ*-lactams are yet to be developed.

Herein, we describe a highly efficient strategy for the enantioselective C4-dearomatization of unreactive methoxypyridine derivatives, allowing direct access to nearly enantiopure δ-lactams with yields up to 99%. This methodology involves a reactivity enhancement of the pyridine core via Lewis acid activation, the use of readily available Grignard reagents, and a copper(I)-chiral diphosphine ligand as catalyst. Molecular modelling in combination with experimental ^{13}C KIE measurements shed light on the stereochemistry control and the rate-determining step of the reaction.[2]



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P-27

Stereoselective access to bicyclic scaffolds using one-pot Cu-Pd tandem catalysis involving conjugate addition and allylic alkylation

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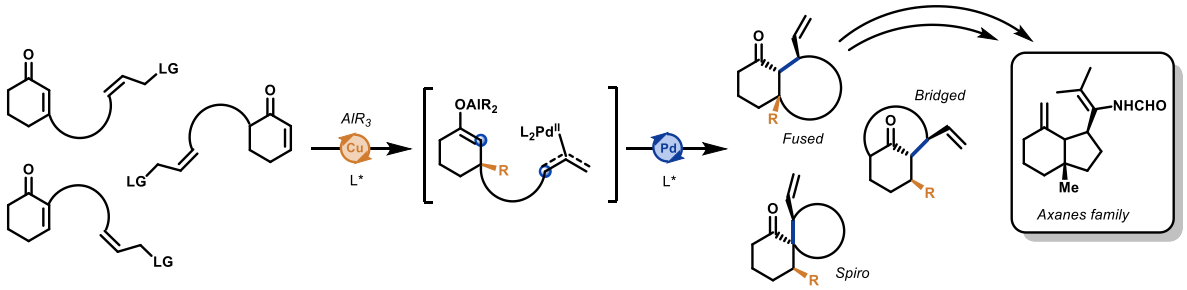
Tandem catalysis refers to a process where two or more closely coupled catalytic steps occur sequentially in one synthetic operation, without isolating intermediates between steps.[1] Each catalytic step produces an intermediate that serves as the substrate for the next one, allowing for the efficient formation of multiple bonds and stereogenic centers in one single procedure. Such strategy has garnered significant attention in recent years due to its capacity to streamline complex reactions and improve both the economics and the environmental acceptability of a process.[2]

Modern transition metal catalysis offers unique opportunities for the chemo-, regio-, and stereoselective construction of new covalent bonds. Notably, the Cu-catalyzed conjugate addition of nucleophiles to cyclic enones generates a metal enolate intermediate which makes it suitable for tandem catalysis in combination with Pd-catalyzed asymmetric allylic alkylation.[3] While the amalgamation of these two independent reactions in an intermolecular fashion has already been reported, no example of an intramolecular version has yet been developed.[4–6]

Our strategy is thus based on the enantioselective Cu-catalyzed conjugate addition of organoaluminium reagents to cyclic enones bearing a tethered chain containing an allylic functionality for subsequent intramolecular asymmetric Pd-catalyzed allylic alkylation. Depending on the position and the length of the tethered chain, bridged, fused, and spirocyclic scaffolds of different ring sizes can be obtained. Moreover, all the stereoisomers of each product are accessible by simply switching the combination of absolute configuration of the ligands. Lastly, many of these bicyclic scaffolds being present in nature, the strategy could be applied to the synthesis of biologically active natural products such as axanes.[7]



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P-28

New synthetic strategies towards 2,8-disubstituted isoanthrazolines

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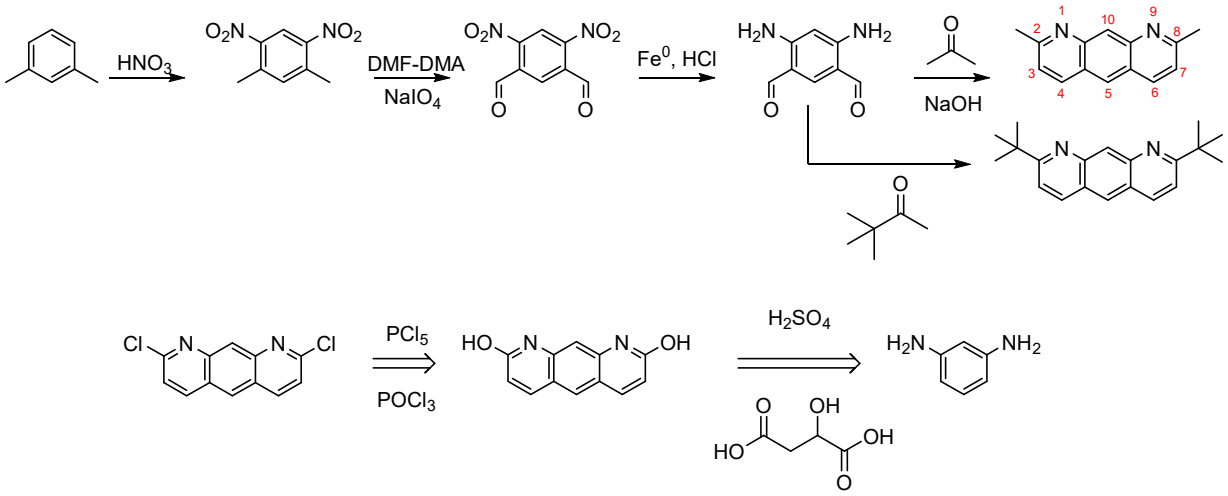
Functionalized isoanthrazolines are common moieties in various facets of organic chemistry, including polymer chemistry, organic semiconductors, and medicine.[1] Usually, 2,8-difunctionalization of isoanthrazolines is achieved *via* the Friedländer reaction between a ketone and 4,6-diaminoisophthalaldehyde (Scheme 1),[2] comprising an aldol condensation followed by a condensation reaction between the aniline moiety and the ketone. To achieve regioselective 2,8-difunctionalization without the 3,7-substituted byproducts, the ketone used in the Friedländer synthesis must either be symmetric (e.g. acetone) or have a quaternary substituent (e.g. pinacolone, Scheme 1). Additionally, some strongly electrophilic ketones such as 2-acetylimidazole or α-halocarbonyls cannot be used in the Friedländer synthesis due to competition with nucleophilic substitution reactions involving the amines.

For applications in coordination chemistry, we are interested in developing new synthetic routes towards 2,8-difunctionalized isoanthrazolines. This poster will discuss our recent efforts, such as the synthesis of 2,8-dichloroisoanthrazoline, which is hypothesized to be amenable to functionalization through nucleophilic aromatic substitution.



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P-29 A structure based design approach to efficiently identify novel SMO antagonist chemotypes

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[1]: Philipps-University Marburg; [2]: University of Oxford

The smoothened receptor (SMO) plays a significant role in embryonic development through the hedgehog signalling pathway, where aberrant stimulation in a later life stage is associated with a variety of cancers [1,2]. Multiple clinically approved antagonists have been developed to target SMO, but these suffer from resistance mutations and/or adverse effects [3,4]. Utilizing a structure based design approach we have identified three novel chemotypes to antagonize SMO with potencies in the low micromolar range. In total 69 compounds identified by virtual screening were assayed in four assaying rounds with hit rates of 27% and 69% during hit identification. Furthermore, members of two of the identified chemotypes show resistance to the D473G^{6x54} resistance mutation similar to SANT-1, indicating their lead optimization potential. Hence, this study shows a successful application of structure based design for the development of novel SMO antagonist chemotypes.

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P-30 Photoswitchable tools for RNA targeting

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The translation process involves the synthesis of proteins by RNA molecules occurring in the ribosomes of cells, which ensures the well-being of cells, its proliferation and its growth among other processes. Lately, it has been studied that controlling of translation (ON/OFF) can affect the properties of certain biological processes of cells.[1] However, control of translation has not been studied for Microglia (neuron type of cell), which is involved in the immune system and associated to diseases such as Alzheimer's and Parkinson's.[2] Moreover, it is suggested that such control in microglial translation would give a better insight into Microglia's functioning. To achieve this task, it is pivotal to identify and target microglial RNA fragments that are involved in protein translation and can also be susceptible to translation inhibition. Hence, we aim to develop a photoswitchable oligonucleotide scaffold for microglial RNA targeting (Figure1), where one state can maximize oligonucleotide-RNA interactions (ON state), while upon light-irradiation such interactions will be minimized (OFF state).For this poster presentation, we will detail new synthetic routes towards functionalized diazocines, conceptually show how smaller units (nucleosides) can be attached, and show how its functionalization affects the photoisomerization properties of the system.

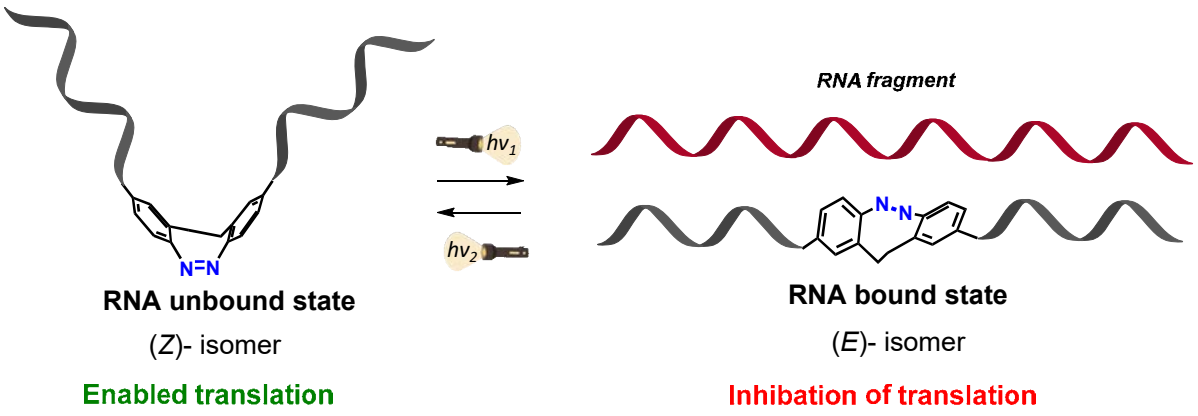

Figure 1. Schematic representation of control of translation using a photoswitchable tool for RNA targeting.

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P-31

Synthesis and Reactivity of Ru(BINAP)(PPh_3)

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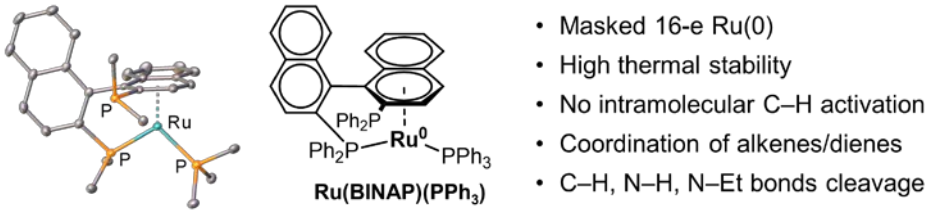

Abstract

Effective strategies for stabilizing low-valent transition metal complexes are important for coordination chemistry and homogeneous catalysis.[1] While Ru(0) complexes have attracted significant attention due to the outstanding propensity of Ru(0) atoms to activate C–H bonds, they suffered from poor stability towards intramolecular C–H activation.[2] Current strategies for stabilizing Ru(0) atoms are limited, impeding the practical applications of Ru(0) catalysis.[3] Herein, we introduce the study of the synthesis and reactivity of Ru(BINAP)(PPh_3).[4] The Ru(0) atom center of Ru(BINAP)(PPh_3) is unprecedentedly stabilized by the P,η^6-arene coordinating BINAP ligand, showing exceptional stability towards heating and a notable absence of intramolecular C–H activation. Ru(BINAP)(PPh_3) not only coordinates small molecules such as styrene derivatives and acrylate esters via PPh_3 substitution, but also activates various bonds including C–H, N–H, and even inert N–Et of the incoming molecules. This study on Ru(BINAP)(PPh_3) gives novel insight into Ru(0) stabilization approaches while maintaining a high specific reactivity potentially useful for catalytic applications. BINAP and similar ligands with a tethered phosphine-naphthalene moiety provide a promising avenue into enantioselective Ru(0) catalysis, and studies aimed at this objective are currently underway within our group.

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P-32

Synthesis of C-5 Modified Kdo Analogues to Study and Perturb Bacterial LPS Biosynthesis

Zeynep Su Ziylan[1], Imke Bartels[1], Dirk-Jan Scheffers[2], Marthe Walvoort[1]

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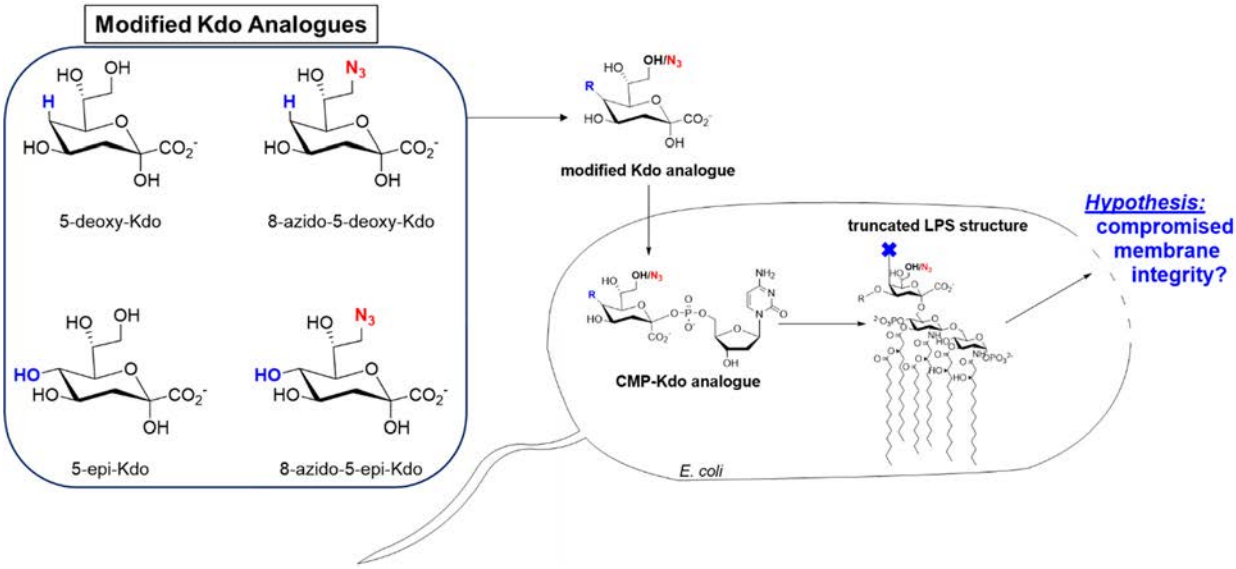
Lipopolysaccharides (LPS) play an important role in the Gram-negative bacterial cell envelope by maintaining cellular integrity and generally function as the first defense layer against environmental stress.[1,2] 3-Deoxy-D-*manno*-oct-2-ulosonic acid (Kdo) is a highly conserved monosaccharide that resides in the inner core region of LPS and links the lipid A region to the extending polysaccharide chain through the hydroxyl group on its C-5 position.[3]

Due to its crucial role in LPS integrity, we hypothesized that metabolically incorporated Kdo analogues modified on the C-5 position would impair LPS synthesis and therefore lead to a reduced cellular membrane integrity. To test this, we successfully synthesized four Kdo analogues, 5-deoxy-Kdo, 5-*epi*-Kdo, 8-azido-5-deoxy-Kdo, 8-azido-5-*epi*-Kdo, and incubated *E. coli* strains in the presence of these analogues to investigate their influence on LPS production and labeling. Interestingly, while 5-deoxy-Kdo and 8-azido-5-deoxy-Kdo did not show any impact on the LPS structure, 8-azido-5-epi-Kdo showed successful labeling on cell membrane LPS. In this study, we present our findings on the extent of LPS labeling using the azide-containing Kdo analogues, impact on the LPS production in *E. coli* strains and the future prospects of our findings.



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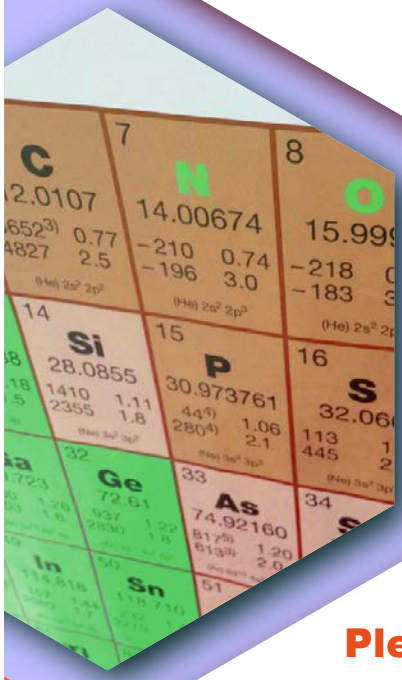

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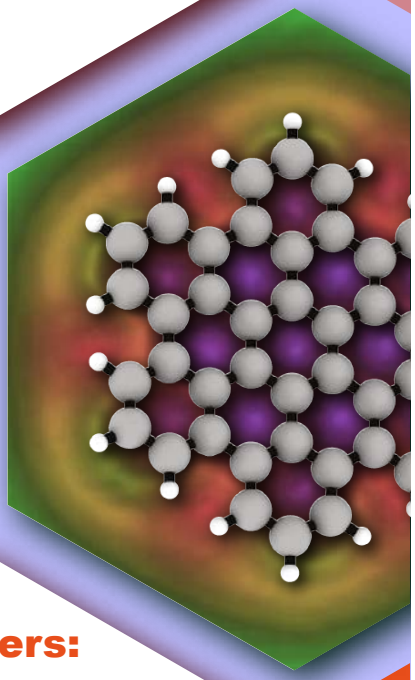

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