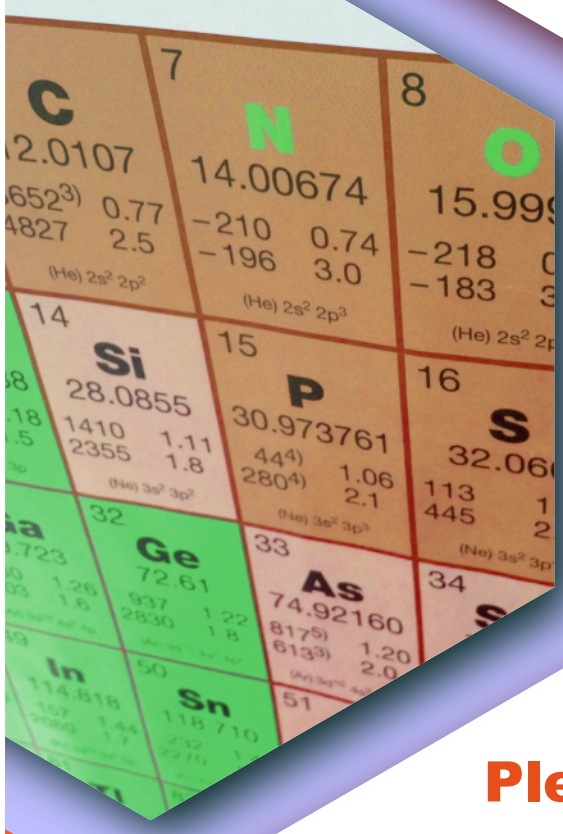
Register now!

March 12th & 13th 2026

Lunteren

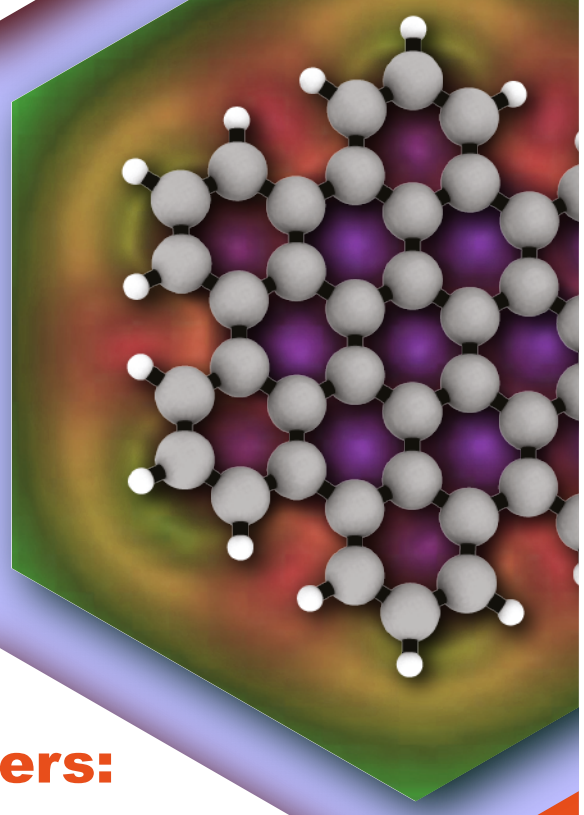
Dutch Symposium on Organic Chemistry



SOC

Organic Chemistry Division

KNCV



Plenary

Varinder Aggarwal
University of Bristol

Jeffrey Bode
ETH Zürich

Antonio Echavarren
ICIQ

Speakers:

Géraldine Masson
CNRS

Dirk Trauner
University of Pennsylvania

Danila Branca
IRBM

Alois Fürstner
Max-Planck-Institut
für Kohlenforschung

PhD & postdoc lectures!

Parallel sessions on both days to showcase your research!

Register & more info:
soc.kncv.nl

Program Thursday March 12th 2026

09:00	***Welcome & Coffee in FIRE***	
10:00	***Opening by Eelco Ruijter***	
	Keynote I *in AIR*	
10:05	**Varinder Aggarwal (University of Bristol, UK)** *Synthesis in a Boron World*	
	Parallel session I *in AIR* Chair: Eelco Ruijter	**Parallel session II *in WATER*** Chair: Kim Bonger
10:55	**Ivo Kruisheer (VU)** *Prize-Winning Route to IschnocybineA*	**Wiert Kolkman (RU)** *Targeted photodynamic therapy for the treatment of congenital hyperinsulinism*
11:15	**Jonas Djossou (UvA)** *Radical Disconnection as Gateway to Diverse Aminomethylation Reactivity*	**Dominik Schauenburg (UM)** *Dynamic Covalent Chemistry for Life-Like Materials: From Reversible Bonds to Regenerative Function*
11:35	**Job Gieling (UCLouvain, BE)** *Scalable and Sustainable Mechanochemical Deracemisation by Resonant Acoustic Mixing*	**Paul Wienecke (RUG)** *SAR and Target Identification Studies on 1-TbAd - a Nucleosidic Virulence Factor of Mycobacterium tuberculosis*
11:55	***Lunch in FIRE & ALV (ALV in WATER; starts at 12:30)***	
	Keynote II *in AIR* Chair: Kim Bonger	

13:00	**Danila Branca (IRBM, IT)** *Evolution Towards Clinical Candidate MK-0616: Next Generation Oral Tricyclic Peptide PCSK9 Inhibitors for LDL-Lowering and Coronary Heart Diseases*	
	Parallel session III *in AIR* Chair: Fedor Miloserdov	**Parallel session IV *in WATER*** Chair: Leendert van den Bos
13:50	**Frank de Kleijne (RU)** *Anchimeric assistance of acyl neighboring groups as stereodirecting strategy in synthesis: What can we learn from glycoscience?*	**Dmitrii Nagornîi (UvA)** *Flow-Enabled, Modular Access to α,α-Difluoromethylene Amines*
14:10	**Zezhong Dong (UvA)** *Macrocycle quinone rotaxanes as integrated proton-coupled electron transfer platforms*	**Giulia Brioschi (UNMI, IT)** *Synthesis of bioactive stilbenoid metabolites and derivatives as potential antimicrobial agents*
14:30	**Baptiste Roure (RUG)** *A Strongly Oxidizing Dicationic Photocatalyst for the Direct Amination of Arenes*	**R. Okawa (VU)** *Application of the Ugi reaction to post-translational modifications in the mRNA display*
14:50	***Coffee/Tea***	
	Keynote III & IV *in AIR* Chair: Cati Ferrer	
15:20	**Antonio Echavarren (ICIQ, ES)** *Molecular Gymnastics through Gold–Carbene Chemistry*	
16:05	***Junior PI Lecture:*** **Mathijs F.J. Mabesoone (RU)** *Data-driven Discovery of General Design-Rules for Peptide Surfactants*	

16:25 **Géraldine Masson (CNRS, F)**

Chiral Brønsted Acid–Driven Enantio- and Regioselective Transformations of Polyunsaturated Systems toward Complex Molecular Architectures

17:00 ***Posters & Drinks in FIRE***

18:30 ***Dinner in the Restaurant***

20:00 **Socialising & Borrel *in FIRE***

Program Friday March 13th 2026

Keynote V *in AIR*
Chair: Fedor Miloserdov

09:00 **Alois Fürstner (Max-Planck-Institut für Kohlenforschung, DE)**

On the Pluripotent Triple Bond

	Parallel session V *in AIR* Chair: Fedor Miloserdov	**Parallel session VI *in WATER*** Chair: Kevin Neumann
09:50	**Daan Hoogers (UL)** *How Electronic and Steric Effects in Acceptor Alcohols Shape SN1- and SN2-type Glycosylation Reactions*	**Brendan Horst (VU)** *Efficient Synthesis of the Novel Anti-Malarial Drug Ganaplacide*
10:10	**Soma P. Rudi (UvA)** *S,O-ligand enabled meta C-H halogenation of anisole derivatives via palladium/norbornene catalysis*	**Phillip Yesley (RU)** *Site-Selective Ligand Selection by Mutational Profiling for Covalent RNA Targeting*
10:30	**Diego Meneses (UM)** *Dual Nickel/Photoredox Catalysis Enables Isocyanide Insertion Chemistry*	**Peter Fodran (RUG)** *TBA*

10:50 ***Coffee / Tea***

Keynote VI *in AIR*
Chair: Jordy Saya

11:20 **Rienk Eelkema (TUD)**
Ionising radiation generated reaction networks can activate chemotherapeutic drugs

11:50 ***Lecture "EurJOC Best Research Article by Early Career Researcher"***
Lecture by the winner

12:10 ***Junior PI Lecture:*** **Eva J. Meeus (WUR)**
Late-Stage Diversification of Native Tryptophan-containing Peptides and Peptide Drugs through Nitrogen Atom Insertion

12:30 ***Lunch in FIRE***

Keynote VII – IX *in AIR*
Chair: Kevin Neumann

13:30 **Jeffrey Bode (ETH Zürich, CH)**
Synthetic Organic Chemistry for Biologics

14:15 ***Junior PI Lecture:*** **Danny Broere (UU)**
Old Dogs with New Metal-Ligand Cooperative Tricks

14:35 ***Dirk Trauner (University of Pennsylvania, US)***
The Art of Picking a Target Molecule

15:20 ***SOC Prizes for best oral and poster presentations***

15:30 ***Closing followed by drinks***

Partners of DSOC

Oral abstracts

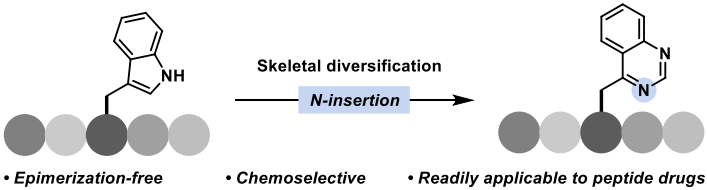
Late-Stage Diversification of Native Tryptophan-containing Peptides and Peptide Drugs through Nitrogen Atom Insertion

Eva J. Meeus‡[a,b], Ann-Sophie K. Paschke‡[b], Magoti A. Masota[c], Florin Hoffmann[b], Nathalie M. Grob[c]*, Bill Morandi[b]*

a, Laboratory of Organic Chemistry, Wageningen University, The Netherlands
b, Laboratorium für Organische Chemie, ETH Zürich, Switzerland,
c, Institute of Pharmaceutical Sciences, ETH Zürich, Switzerland.

* Presenting and corresponding authors:
emeeus@ethz.ch; grobn@ethz.ch; morandib@ethz.ch

Synthetic methods that allow for the direct modification of a molecule's core skeleton have recently undergone a renaissance.[1, 2] As an alternative to traditional orthogonal syntheses, these methods offer a straightforward strategy for scaffold diversification with minimal effort, supporting the advancement of drug discovery as novel late-stage diversification tools.[3] Although the utility of such methods has been demonstrated for the late-stage diversification of several pharmaceuticals, their full potential remains largely untapped.[4] Hence, we set out to extend scaffold diversification through atom insertion to previously unexplored drug modalities: peptide drugs. In this work, we demonstrate the epimerization-free, chemoselective late-stage diversification of tryptophan-containing native peptides through nitrogen atom insertion in solution.[5] The direct application of this rapid and straightforward method to structurally complex peptide drugs underscores the broader potential of atom insertion reactions in drug discovery beyond small molecules.



References

1. R. Sharma, M. Arisawa, S. Takizawa, M. S. H. Salem, *Org. Chem. Front.* **2025**, *12*, 1633–1670.
2. J. Jurczyk, J. Woo, S. F. Kim, B. D. Dherange, R. Sarpong, M. D. Levin, *Nat. Synth.* **2022**, *1*, 352–364.
3. E.-Q. Li, C. W. Lindsley, J. Chang, B. Yu, *J. Med. Chem.* **2024**, *67*, 13509–13511.
4. S. R. Williams, J. C. Vantourout, *Chimia* **2024**, *78*, 446–448.
5. A.-S. K. Paschke, E. J. Meeus, M. A. Masota, F. Hoffmann, N. M. Grob, B. Morandi, *J. Am. Chem. Soc.* **2026**, *148*, 55–60.

Scalable and Sustainable Mechanochemical Deracemisation by Resonant Acoustic Mixing

Job Gieling,[a†] Guillaume Wery,[a†] Zoer El Kaderi,[a] Leeroy Hendrickx,[b,c] Thomas Wiegand,[b,c] Carsten Bolm,[d] Tom Leyssens[a] and Daniel M. Baier[a]

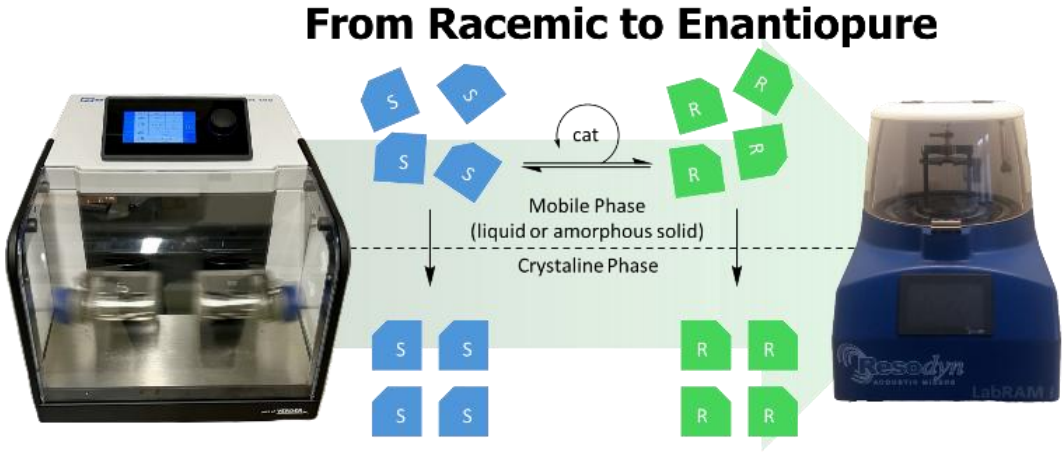
[a] *Department of Molecular Chemistry, Materials and Catalysis; Institute of Condensed Matter and Nanosciences; Université Catholique de Louvain; Place Louis Pasteur, 1 bte L4.01.06, 1348 Louvain-La-Neuve (Belgium)*

[b] *Max Planck Institute for Chemical Energy Conversion; Stiftstrasse, 34-36, 45470 Mülheim an der Ruhr (Germany)*

[c] *Institute of Technical and Macromolecular Chemistry; RWTH Aachen University, Worringerweg 2, 52074 Aachen (Germany)*

[d] *Institut für Organische Chemie; RWTH Aachen University; Landoltweg, 1, 52074 Aachen (Germany)*

job.gieling@uclouvain.be



Resonant Acoustic Mixing (RAM) is introduced as a solvent-minimised, scalable approach to deracemisation, achieving enantiomeric excesses of up to 91%.[1] This study systematically explores the impact of processing parameters, particularly the nature and quantity of liquid additives, on the outcome of deracemisation of imines, revealing RAM's robustness and reproducibility. RAM enables seamless 5-fold upscaling, delivering near-gram-scale deracemisation with minimal solvent use ($\eta = 0.02$) without the need for milling media. This renders RAM as a highly promising green chemistry approach to deracemisation and enantiopure products.

Notably, a racemic mixture was deracemised to 73% ee in 1.5 hours without the need for chiral reagents, showing enhanced efficiency compared to ball-milling and solvent-based deracemisation approaches. Mechanochemical deracemisation by RAM is a significant advancement, compared to classical and ball milling methods. offering a faster, waste-minimising and scalable method.[2,3] This enables a pathway to large-scale deracemisation processes and enantiopure products while reducing waste.

1 J. Gieling, G. Wery, Z. El Kaderi, L. Hendrickx, T. Wiegand, C. Bolm, T. Leyssens, D.M. Baier, *manuscript under review*.

2 W. L. Noorduin, T. Izumi, A. Millemaggi, M. Leeman, H. Meekes, W. J. P. Van Enckevort, R. M. Kellogg, B. Kaptein, E. Vlieg and D. G. Blackmond, *J. Am. Chem. Soc.*, 2008, **130**, 1158–1159.

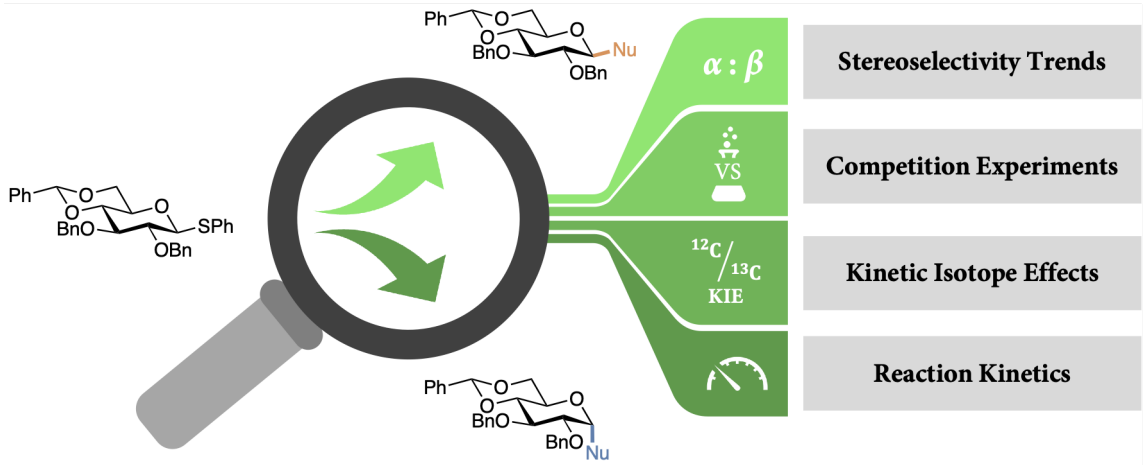
3 J. Gieling, G. Wéry, C. Lopes, J. de Meester, C. Brandel, Y. Cartigny, T. Leyssens and D. M. Baier, *Chem. – Eur. J.*, 2025, **31**, e202404120.

How Electronic and Steric Effects in Acceptor Alcohols Shape S_N1- and S_N2-type Glycosylation Reactions

Daan Hoogers[a], Koen N.A. van de Vrande[a], Dennis van der Meij[a], Wouter A. Remmerswaal[a], Gijsbert A. van der Marel[a], Jeroen D. C. Codée[a]

[a] Leiden Institute of Chemistry, Einsteinweg 55, 2333 CC Leiden, The Netherlands.

The stereochemistry of glycosidic bonds dictates glycan structure and function. Therefore, their selective introduction is crucial in the synthesis of oligosaccharides. This study systematically maps the influence of electronic and steric properties of alcohol acceptors on the glycosylation mechanism of the 4,6-*O*-benzylidene glucosyl donor, which has been shown to engage in glycosylation reactions spanning the whole breath of the S_N1-S_N2 reaction continuum. Using kinetic isotope effects (KIE), competition experiments and the determination of stereoselectivity as a function of acceptor concentration, we have quantified the influence of electronic and steric effects in the acceptor on the stereochemical outcome of the glycosylation reaction. In this way, we were able to pinpoint the mechanism on the S_N1-S_N2 continuum. Our findings reveal that α-glycosides can originate from S_N1- and S_N2 pathways, while the β-products are always generated through an S_N2-like mechanism. Sterically hindered and electron poor acceptors favor the S_N1-like pathway, and the stereoselectivity of the reaction can be controlled, in part, by adjusting the concentration of the acceptor.



Dynamic Covalent Chemistry for Life-Like Materials: From Reversible Bonds to Regenerative Function

Dr. Dominik Schauenburg, Assistant professor at Department of Instructive Biomaterials Engineering

Institute for Technology-Inspired Regenerative Medicine, Maastricht University,

dominik.schauenburg@maastrichtuniversity.nl

Non-covalent interactions govern the structure and function of many biomolecules, including DNA base pairing, protein folding, ligand–receptor recognition, and membrane organization. From an organic chemistry perspective, dynamic covalent chemistries (DCCs) provide a powerful synthetic framework of reversible bond-forming reactions, enabling molecular systems to reorganize under thermodynamic control.

Inspired by biological regulation, we develop organic synthetic tools based on multi-stimuli-responsive dynamic covalent reactions that respond to endogenous triggers (e.g., redox environment, pH, enzymatic activity) as well as exogenous inputs (e.g., temperature, light, or small-molecule effectors).[1] Central to our approach is the design and synthesis of novel dynamic covalent motifs, with particular emphasis on the reversible conjugation between boronic acids and salicylhydroxamates. These underexplored functional groups form highly chemoselective adducts under neutral aqueous conditions and undergo controlled dissociation in response to mild oxidative stress or pH changes.[2,3]

We employ modern organic synthesis and chemoselective ligation strategies to integrate these motifs into a range of molecular scaffolds, including the synthesis of novel unnatural amino acids, peptide building blocks, and functional monomers. These units are subsequently incorporated into proteins, polysaccharides, and fully synthetic polymer architectures. The boronic acid–salicylhydroxamate system is further combined with established dynamic covalent reactions—such as hydrazone and oxime formation, disulfide exchange, (thio)ester chemistry, Michael additions, and reversible Diels–Alder reactions—to construct complex, adaptive molecular networks.[4]

By advancing organic reaction design at the interface of dynamic covalent chemistry and biomolecular synthesis, this work demonstrates how fundamental organic chemistry principles can be leveraged to create responsive and reconfigurable molecular systems, with downstream applications in functional materials and regenerative medicine.

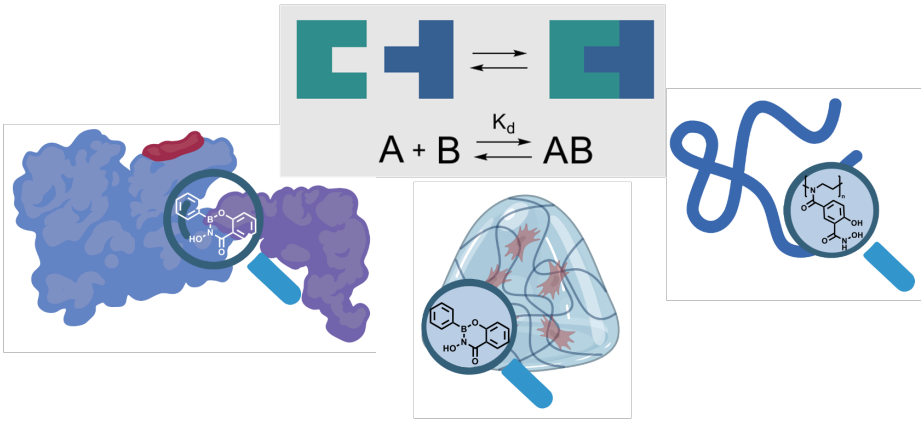


Figure 1. Principle of dynamic covalent interactions with defined dissociation constants (K_d) reflecting reversible binding affinity, and incorporation of salicylhydroxamate–boronic acid motifs into proteins, hydrogels, and synthetic polymers.

References:

1. Rowan, S. J. et al., (2002), Angewandte Chemie International Edition, 41, 898–952
2. Schauenburg, D. et al., (2024), Angewandte Chemie, 136, e202314143
3. Raabe, M. et al., (2022), Macromolecular Bioscience 22.2, 2100299
4. Schauenburg, D. & Weil, T., (2023), Advanced Science 2303396

IONISING RADIATION GENERATED REACTION NETWORKS CAN ACTIVATE CHEMOTHERAPEUTIC DRUGS

Juncheng Liu, Bing Xu, Mark A. R. de Geus, Antonia G. Denkova, Rienk Eelkema

Delft University of Technology, Delft, the Netherlands
E-mail: r.eelkema@tudelft.nl

Keywords: chemical reaction networks, systems chemistry, caged drugs, ionizing radiation

The effectiveness of chemotherapy is often limited by systemic toxicity, which constrains dosing and leads to severe side effects.[1] A promising yet underexplored strategy is to exploit ionizing radiation, already a cornerstone of cancer therapy, not only for its direct tumor-damaging effects but also as a precise, external trigger for the controlled activation of chemotherapeutic drugs.[2]

Clinically relevant doses of ionizing radiation induce water radiolysis, generating a transient network of reactive oxygen species (ROS) that can be harnessed for local drug activation.[3] During radiotherapy, the radiolysis of water produces highly reactive intermediates such as hydrated electrons and hydroxyl radicals. These species can drive secondary chemical processes, including oxidation, bond cleavage, and uncaging reactions, which in turn can trigger nanocarrier disassembly and drug activation.[2-4]

We recently discovered that alkyl chloride additives can enhance these processes by selectively reacting with hydrated electrons generated during water radiolysis under therapeutic X-ray or γ-ray exposure.[5] This reaction produces a strongly oxidizing species capable of initiating efficient bond cleavage. Building on this concept, we have now demonstrated prodrug activation[6] and release from polymer nanocarriers[7] in complex biological environments, including 3D tumor models.

---

[1] N.M. Kuderer, A. Desai, M.B. Lustberg, G.H. Lyman. Mitigating Acute Chemotherapy-Associated Adverse Events in Patients with Cancer. *Nat. Rev. Clin. Oncol.* **2022**, *19*, 681–697.

[2] a) Y. Cao, J. Si, M. Zheng, Q. Zhou, Z. Ge. X-Ray-Responsive Prodrugs and Polymeric Nanocarriers for Multimodal Cancer Therapy. *Chem. Commun.* **2023**, *59*, 8323–8331. b) H. Liu, J. Zhao, Y. Xue, J. Zhang, H. Bai, S. Pan, B. Peng, L. Li, N.H. Voelcker. X-Ray-Induced Drug Release for Cancer Therapy. *Angew. Chem. Int. Ed.* **2023**, *62*, e202306100. c) C. Wang, Z. Zhang, Z. Liu. Radiotherapy-Activated Prodrug: Past, Present and Beyond. *ACS Cent. Sci.* **2025**, *11*, 1306–1320.

[3] J. Liu, A.G. Denkova, R. Eelkema, The role of ionizing radiation-initiated reactions in targeted activation of chemotherapeutics. *Nat. Rev. Chem.* **2026**, *10*, 72-87.

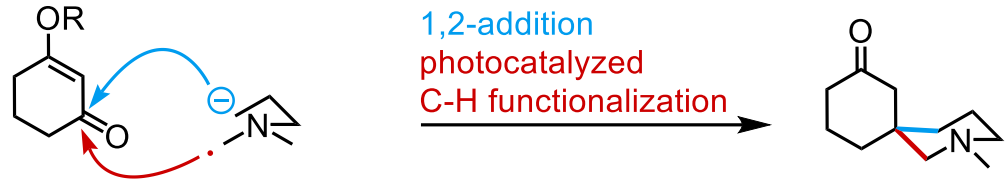
[4] Q. Fu, S. Shen, P. Sun, Z. Gu, Y. Bai, X. Wang, Z. Liu. Bioorthogonal Chemistry for Prodrug Activation in Vivo. *Chem. Soc. Rev.* **2023**, *52*, 7737–7772.

[5] J. Liu, T.G. Brevé, B. Xu, P.-L. Hagedoorn, A.G. Denkova, R. Eelkema. Organochlorides Mediate Oxidation Reactions Induced by Low Dose Ionizing Radiation. *CCS Chem.* **2024**, *6*, 1712–1720.

[6] a) J. Liu, B. Xu, A.G. Denkova, R. Eelkema, Organochloride mediated prodrug activation induced by ionizing radiation, *Chem. Sci.,* **2026**, *17*, 1752–1760
. b) J. Liu, B. Xu, E. Uslamin, E. Pidko, A.G. Denkova, R. Eelkema, Reaction network analysis of organochloride mediated oxidation induced by ionizing radiation, ChemRXiv 2025 10.26434/chemrxiv-2025-cq53z

[7] J. Liu, I. Piergentili, B. Xu, A.G. Denkova, R. Eelkema. Alkyl Chloride-Functionalized Polymers Mediate Oxidation of Thioethers Initiated by Ionizing Radiation. *ACS Appl. Polym. Mater.* **2025**, *7*, 3835–3841.

Spirocycles are important building blocks in medicinal chemistry and modern drug development.[1] Their incorporation into biologically active compounds can lead to improvement of the key properties. However, their synthesis can be tedious, requiring multiple steps. We have developed a synthesis of spirocyclic piperidines with the spiroatom in β-position and demonstrate the scope on 30 differently substituted products. Reactions tolerate functional groups such as halogens, esters and CF_3. The products were obtained in 48-99% yields and in many cases as single diastereomers. Furthermore, we show the versatility of the products with 8 different transformations including reductive amination, Suzuki and Buchwald-Hartwig couplings. Application of the presented strategy to the existing targets such as KRAS inhibitor intermediates leads to a drastic reduction in necessary synthetic steps.



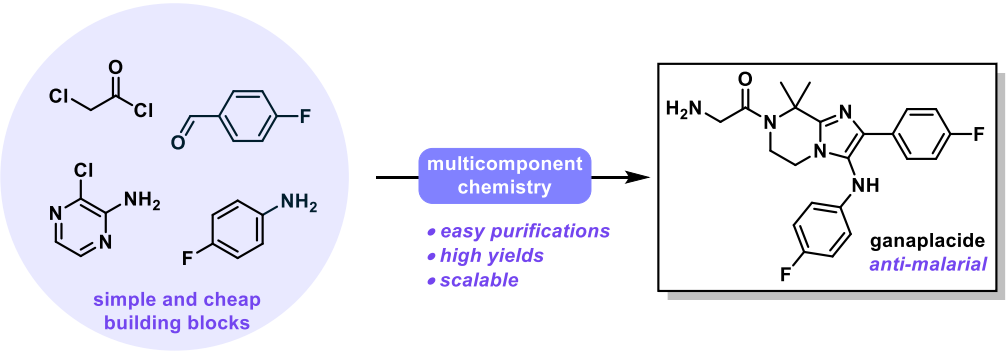
✔ 30 examples ✔ good to excellent yields ✔ up to 100% atom economy

Efficient Synthesis of the Novel Anti-Malarial Drug Ganaplacide

Brendan Horst[1] Tess H. Stepek[1], Liv A. N. Aggernæs[1] and Eelco Ruijter[1]

[1]*Amsterdam Institute of Molecular and Life Sciences, VU Amsterdam, Amsterdam, The Netherlands*

Malaria is a neglected tropical disease that cause about 600 000 deaths each year, mainly on the African continent.[1] As the effective treatment of malaria has stagnated in the past years due to drug resistance, the discovery of new drugs has high urgency. Developed by Novartis, KAF156 (also known as *ganaplacide*) is a new type of anti-malarial of the imidazolopiperazine class that recently successfully completed phase II and phase III clinical trials.[2]



The current route to ganaplacide has several drawbacks, including late-stage palladium-catalyzed cross-coupling reaction. We present a new, short, and efficient route towards this drug involving the rapid and efficient construction of its imidazolopiperazine core using multicomponent chemistry.[3] This process uses only simple and cheap building blocks and produces minimal waste. Furthermore, the synthesis relies on clean, high-yielding steps that require only minimal purification effort, making it viable for industrial upscaling. Additionally, we are exploring how our route can be used for ganaplacide analogues.

References

[1] *World malaria report 2024, WHO.*

[2] a) Chatterjee *et al. J. Med. Chem.* **2012**, *55*, 4244–4273. b) Chatterjee *et al.* U.S. Patent US2013/0281403 A1, Oct. 24, 2013. c) Ogutu *et al. Lancet* **2023**, *23*. 1051-1061.d) *Nat. Biotechnol.*, **2025**, *42*, 1895.

[3] a) Kysil *et al. Eur. J. Org. Chem.* **2010**, *2010*, 1525–1543. b) Zhang *et al. J. Org. Chem.* **2024**, *89*, 18227–18234.

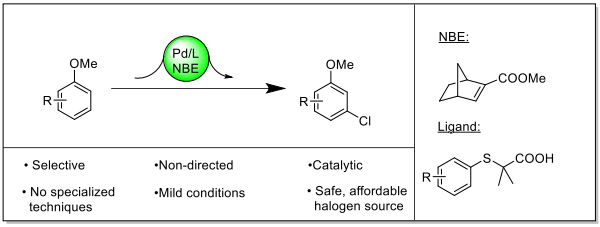
S,O-ligand enabled meta C-H halogenation of anisole derivatives via palladium/norbornene catalysis

Soma P. Rudi

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

s.p.rudi@uva.nl

The halogenation of electron rich aryls is a staple in every organic chemists toolbox. To date a plethora of different methods has been developed for the selective halogenation of the activated ortho and para positions of electron rich aromatics; many of them operating under mild conditions, and with a high functional group tolerance. In contrast, halogenation of the electronically disfavoured meta position is usually achieved via synthetic workarounds, or employ chelating directing groups turning a simple aromatic halogenation into a multistep synthetic adventure.



We have developed a non-directed palladium catalysed *meta* chlorination method using a norbornene mediator, and a custom S,O-ligand optimized *via* DFT calculations and rational ligand design. The reaction uses a safe and affordable halogen source, mild conditions, and it can be performed in any organic lab without requiring specialized equipment or techniques. Palladium/norbornene cooperative catalysis has been reported in a number of C-H functionalizations including arylations, olefinations, and various di-functionalizations. Yet, the scope of these reactions remains limited, and not all functionalities can be installed directly via *meta* C-H functionalization strategies. By halogenating the *meta* position, a wide array of further transformations can be made possible in a more step economic manner, and under conditions that are compatible with highly functionalized precursors. Lastly, chlorinated moieties are omnipresent in pharmaceuticals where a single chlorine atom can enhance the activity of a compound with up to 100 000 fold, similarly to the well-known 'magic methyl' effect, making this method relevant for medicinal chemists.

References

1 Hang Shi, Peng Wang, Shin Suzuki, Marcus E. Farmer, and Jin-Quan Yu *J. Am. Chem. Soc.* **2016** *138* (45), 14876-14879

2 V. Sukowski, M. van Borselen, S. Mathew, B. de Bruin, M. Á. Fernández-Ibáñez, *Angew. Chem. Int. Ed.* **2024**, 63, e202317741.

3 Debora Chiodi and Yoshihiro Ishihara *J.Med.Chem* **2023** *66* (8), 5305-5331

Site-Selective Ligand Selection by Mutational Profiling for Covalent RNA Targeting

Presenter: Phillip Yesley

Abstract

To facilitate the design of RNA-targeted covalent probes we report a bottom-up, structure-informed approach using mutational profiling. We designed a compact library of covalent probes based on the scaffold of Ribocil, a selective inhibitor targeting the bacterial FMN riboswitch and screened them against the FMN riboswitch aptamer from *Fusobacterium nucleatum*, *Bacillus subtilis*, *Escherichia coli*, and *Staphylococcus aureus*. This yielded Covacil, a highly base-selective probe that covalently modifies the FMN riboswitch aptamer at low micromolar concentrations, within 10 minutes. We validate the site-selectivity and covalency of the probe by competitive photo-affinity labelling and mass-spectrometry. When compared to non-targeted covalent probes, Covacil displayed >1,000-fold increased selectivity toward a specific base within the FMN riboswitch aptamer. Finally, we apply Covacil to total RNA and demonstrate that it maintains its base-selective reactivity for the FMN riboswitch within the entire transcriptome.

Targeted photodynamic therapy for the treatment of congenital hyperinsulinism

Wiert Kolkman[ab*], Manon Gloudemans[a], Cathelijne Frielink[a], Floris Rutjes[b], Martin Gotthardt[a], Fritz Andreae[c], Sanne van Lith[a], Dennis Löwik[b]

a, Radboudumc, Department of Medical Imaging, Geert Grooteplein Zuid 10, Nijmegen, Netherlands
*wiert.kolkman@radboudumc.nl
b, Radboud University, Institute for Molecules and Materials, Heyendaalseweg 135, Nijmegen, Netherlands
c, piCHEM Forschungs- und Entwicklungs GmbH, Parkring 3, 8074 Grambach, Austria

Abstract

Congenital hyperinsulinism (CHI) is a rare disease in newborns and infants characterized by inappropriate insulin hypersecretion (overproduction) from pancreatic beta-cells, leading to recurrent and potentially life-threatening hypoglycaemia (low blood sugar).[1] At present, curative treatment options are lacking, and current interventions are highly invasive, resulting in substantial morbidity. This project aims to develop a novel, minimally invasive, therapeutic approach for CHI using targeted photodynamic therapy (tPDT) (Figure 1).

At the core of tPDT are photosensitizers, molecules that generate cytotoxic reactive oxygen species (ROS) upon activation by light of a specific wavelength. High treatment selectivity is achieved via two mechanisms: (1) use of a targeting ligand and (2) local irradiation. The choice of targeting ligand is Exendin, as it selectively binds beta cells expressing the glucagon-like peptide-1 receptor (GLP-1R).[2]

We synthesized Exendin[*]-based tPDT constructs by conjugation to photosensitizer IRDye® 700DX[†]. Two types of Exendin were used: Exendin-4 and Exendin-9-39, a GLP-1R receptor agonist and antagonist, respectively. Each peptide was used in its native form as well as functionalized with a DTPA-chelator to enable radiolabelling for biodistribution studies, leading to four different tPDT compounds. Both *in vitro* and *in vivo* results demonstrate promising effectivity, characterized by efficient ROS production, nanomolar binding affinity for the receptor (IC_{50} = 40-50 nM for Ex-700DX constructs and 110-120 nM for DTPA-Ex-700DX constructs), and GLP-1R selective uptake in a tumour mouse model (2-3 %IA/g).

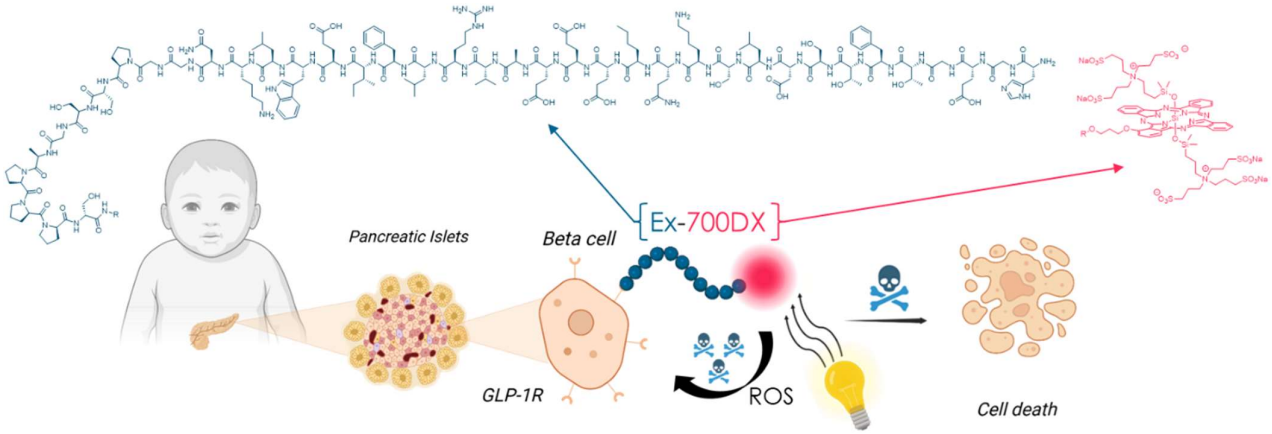


Figure 1 Schematic representation of tPDT by Exendin-700DX (Ex-700DX) in patients with CHI

References

1. Lord, K. *et al*. Clinical Presentation and Management of Children With Diffuse and Focal Hyperinsulinism: A Review of 223 Cases. *J. Clin. Endocrinol. Metab.* **98**, E1786–E1789 (2013).
2. Boss, M. *et al.* ^{68} Ga-NODAGA-Exendin-4 PET/CT Improves the Detection of Focal Congenital Hyperinsulinism. *J. Nucl. Med.* **63**, 310–315 (2022).

[*] Provided by piCHEM
[†] Provided by Rakuten Medical

Macrocycle quinone rotaxanes as integrated proton-coupled electron transfer platforms

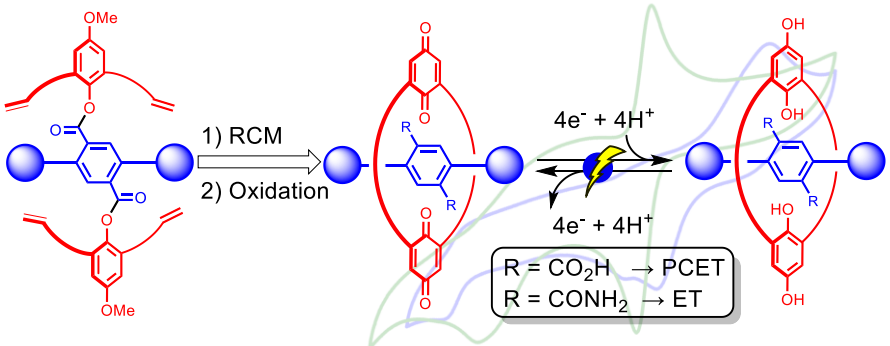
Zezhong Dong, Maartje C. van Rijn, Simon Mathew, Milo D. Cornelissen, Joost J. N. Koning, Nick Westerveld, Steen I. Jørgensen, Sonja Pullen*, and Jan H. van Maarseveen*

Van 't Hoff Institute for Molecular Science (HIMS),

University of Amsterdam,

Science Park 904, 1098 XH Amsterdam, The Netherlands

ABSTRACT: Quinones play a central role in biological redox chains by mediating proton-coupled electron transfer (PCET); however, translating this functionality into well-defined synthetic architectures remains challenging. Here, we report quinone-based rotaxanes in which mechanical interlocking is employed to integrate a quinone macrocycle with a functional thread in a spatially preorganized manner. Central to this work is a covalent prerotaxane approach, enabling oxidative liberation of the mechanically interlocked architecture by converting the macrocycle into a p-benzoquinone with concomitant unveiling proximal proton-donating functionalities on the thread. Electrochemical studies reveal that the resulting diacid rotaxane exhibits pronounced anodic shifts and quasi-reversible reduction behavior consistent with PCET, arising from the enforced proximity of proton-donating sites to the quinone units. In contrast, an amide-containing rotaxane—prepared as a PCET-disfavored control—displays redox responses dominated by electron transfer. These findings demonstrate that mechanical interlocking provides an effective molecular strategy for establishing quinone-based rotaxanes as versatile platforms for biomimetic redox mediation and, more broadly, for controlling coupled electron–proton processes within functional molecular architectures.



Macrocycle Quinone Rotaxane

Synthesis of bioactive stilbenoid metabolites and derivatives as potential antimicrobial agents

Giulia Brioschi, Francesca Annunziata, Salvatore Princiotto, Martina Letizia Contente, Andrea Kunova, Piera Anna Martino, Andrea Pinto, Sabrina Dallavalle, and Gigliola Borgonovo

Department of Food, Environmental and Nutritional Science, University of Milan, via Celoria 2, 20133-Milan, Italy
E-mail: giulia.brioschi2@unmi.it

Stilbenoids are a class of non-flavonoid polyphenols characterized by two phenyl rings linked through a central ethylene bridge. Among them, resveratrol is the most extensively investigated and is naturally present in grapes, berries, and derived products such as wine, as well as in agro-industrial residues and by-products [1]. Following oral administration, resveratrol has been associated with a wide range of significant in vivo bioactivities. However, its rapid and extensive metabolism results in low detectable levels of the parent compound in plasma and tissues, suggesting that its metabolites may play a key role in mediating the observed biological effects [2]. Among stilbenoids, pterostilbene and deoxyrhapontigenin have also attracted scientific interest due to their potential health benefits in a One Health perspective.

A versatile synthetic approach has been developed to attain a collection of stilbenoid metabolites and derivatives in sufficient amounts for biological evaluation and systematic SAR studies. The collection was designed by combining modifications associated with phase I metabolism (i.e. reduction of the double bond, dehydroxylation and methylation of the phenolic hydroxyl groups). The synthesized compounds have been tested for their antimicrobial properties against a representative and benchmark panel of Gram-positive and Gram-negative bacteria and relevant phytopathogenic fungi (*P. oryzae*, *B. cinerea*, and *F. culmorum*). The obtained results showed moderate activity against the selected bacterial strains; on the other hand, several compounds showed remarkable antifungal potential, with over 50% inhibition of the mycelial growth at 200 μM. At 50 μM, most compounds effectively inhibited spore germination and appressorium formation (a specialized dome-shaped infection structure). Moreover, two compounds inhibited appressorium formation even at 10 μM.

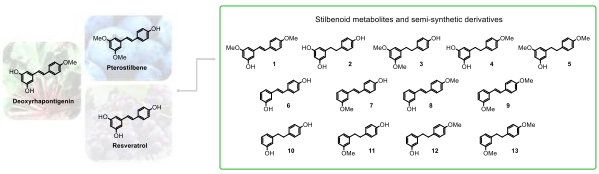


Figure 1: Chemical structures of synthesized stilbenoid metabolites and derivatives.

[1] L. M. Mattio, S. Dallavalle , L. Musso, R. Filardi, L. Franzetti, L. Pellegrino, P. D'Incecco, D. Mora, A. Pinto, and S. Arioli, *Scientific Reports* (2019**)**, 9, 19525.
[2] F. Li, Y. Han, X. Wu, X. Cao, Z. Gao, Y. Sun, M. Wang, H. Xiao, *Frontiers in Nutrition*, (2022), 9:912591

This investigation is partially supported by National Recovery and Resilience Plan (NRRP), Mission4 Component 2 Investment 1.3 -Call for tender No. 341 of 15/03/2022 of Italian Ministry of University and Research funded by the European Union–NextGenerationEU, in the frame of the project: Research and innovation network on food and nutrition Sustainability, Safety and Security (ON Foods)

Dual Nickel/Photoredox Catalysis Enables Isocyanide Insertion Chemistry

Diego Meneses *, Austine Voigt , Prabhat Ranjan , Jordy Saya , Romano V.A. Orru

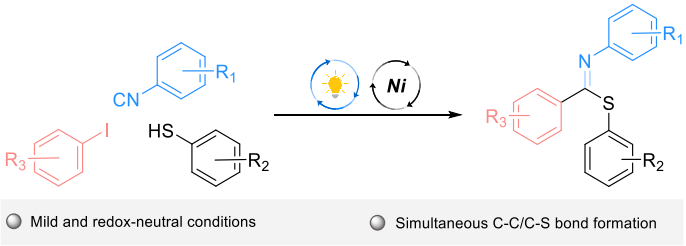
a: Aachen-Maastricht Institute for Biobased Materials (AMIBM) Maastricht Universiteit, Urmonderbaan 22, 6167 RD Geleen (The Netherlands)

* diego.menesessanchez@maastrichtuniversity.nl

Isocyanides are versatile C1 building-blocks that play a central role in multicomponent reactions (MCRs), often serving as safer surrogates for toxic CO. While their combination with palladium catalysis is well established, strategies involving the use of earth-abundant base metals remains underexplored.[1] This is due to their lack of redox flexibility or their strong reactivity in low valent oxidation states, which has been solved by external driving forces like photocatalysis.

Inspired by the recent nickel/photoredox dual catalytic strategies for cross-coupling reactions[2], we developed the unprecedented direct synthesis of thioimidates from readily available isocyanides, aryl Iodides and thiols. This is particulary challenging, since the isocyanide insertion needs to compete with other cross-coupling pathways (thermally driven charge transfer, EDA complexes, radical coupling)

This work establishes a new platform that merges photoredox and nickel catalysis, thereby expanding the synthetic utility of isocyanides in sustainable MCR chemistry.



References

1. Orru, R. V. A., et al., *Angew. Chem. Int. Ed*. **2020**, *132* (2), 548–566.
2. König, B., et al., *Nature* **2023**, *619* (7968), 87–93.

Anchimeric assistance of acyl neighboring groups as stereodirecting strategy in synthesis: What can we learn from glycoscience?

Frank F. J. de Kleijne[1] and Thomas J. Boltje[1]
[1]*Institute for molecules and materials Radboud University, The Netherlands*

Neighboring group participation (NGP) is a well-known concept in organic synthesis to modulate the reactivity of a molecule.[1] A famous example of a molecule that experiences high reactivity due to NGP is mustard gas. Another example of NGP is acyl participation (Figure 1, panel A). This type of NGP is useful for stereoselective synthesis. Typically, acyl NGP implies having a 1,2-relationship from participating to electrophilic side leading to transient five membered ring intermediates. In this work we ask ourselves the question: would participation from more remote positions such as in a 1,3-relationship be feasible to afford six membered ring intermediates (Figure 1, panel B)?

To answer this questions we turn our attention to glycoscience where C-2 acyl participation is commonly employed to prepare 1,2-*trans* glycosidic linkages (Figure 1, panel C).[2] For decades participation of acyl groups at C-3, C-4, and C-6 has been proposed but its existence remained heavily debated (Figure 1 panel D).[3] Only recently has direct experimental evidence become available for this phenomenon.[4,5,6] Herein we present our findings and report factors that enable 'remote' acyl NGP in order to predict if 'remote' acyl NGP would be feasible beyond the realm of glycoscience.

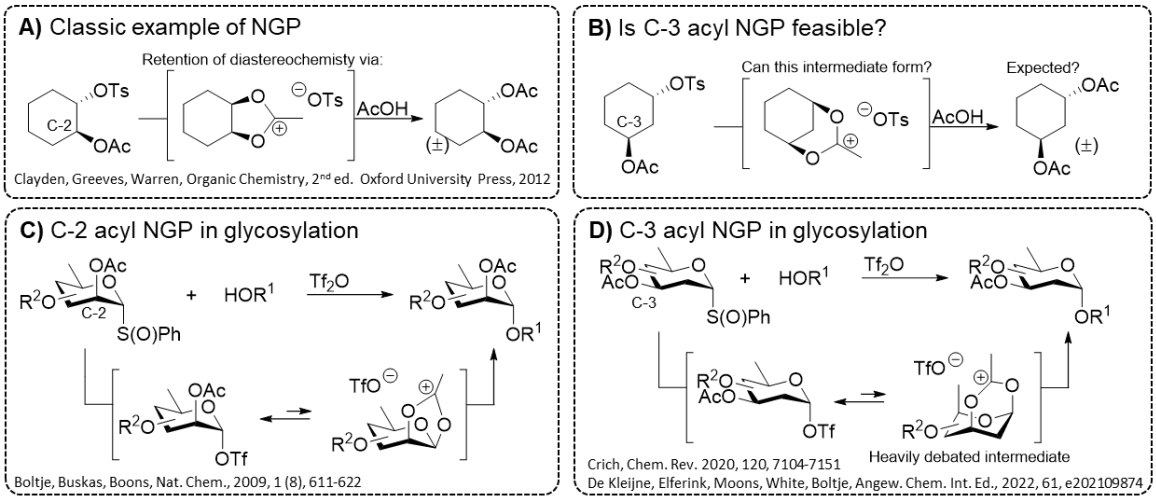


Figure 1: A) Classic example of C-2 acyl NGP, **B)** Illustration of C-3 acyl NGP, **C)** Example of C-2 acyl NGP in glycosylation, **D)** Example of C-3 acyl NGP in glycosylation.

References

[1] Clayden, J.; Greeves, N.; Warren, S., Organic chemistry. Second ed.; Oxford University Press: 2012.

[2] Boltje, T. J.; Buskas, T.; Boons, G.-J., Nat. Chem., 2009, 1 (8), 611-622.

[3] Hettikankanamalage, A. A.; Lassfolk, R.; Ekholm, F. S.; Leino, R.; Crich, D., Chem. Rev, 2020, 120 (15), 7104-7151.

[4] de Kleijne, F. F. J.; Elferink, H.; Moons, S. J.; White, P. B.; Boltje, T. J.,. Angew. Chem. Int. Ed. 2022, 61 (6), e202109874.

[5] de Kleijne, F. F. J.; Moons, P. H.; Ter Braak, F.; Almizori, H. R.; Jakobs, L. J.; Houthuijs, K. J.; Berden, G.; Martens, J.; Oomens, J.; Rutjes, F. P.; White, P. B.; Boltje, T. J., J. Am. Chem. Soc., 2025, 147 (1), 932-944.

[6] Moons, P. H., Ter Braak F., De Kleijne, F. F. J., Bijleveld, B., Corver, S. J. R., Houthuijs, K. J., Almizori, H. R., Berden, G., Martens, J., Oomens, J., White, P. B., Boltje, T. J., Nat. Commun., 2024, 15, 2257.

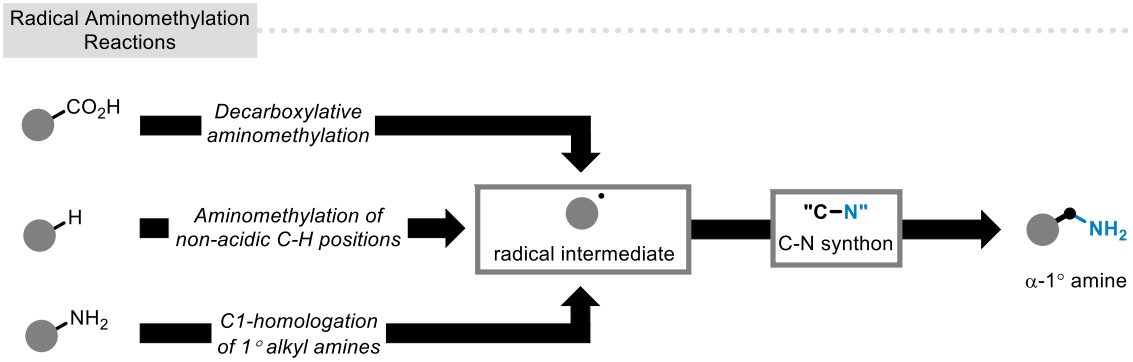
[7] De Kleijne, F. F. J., Ter Braak, F., Piperoudis, D., Moons, P. H., Moons, S. J., Elferink, H., White, P. B., Botlje, T. J., J. Am. Chem. Soc., 2023, 145, 48, 26190-26201

Radical Disconnection as Gateway to Diverse Aminomethylation Reactivity

Jonas Djossou, Timothy Noël*

Flow Chemistry Group, van 't Hoff Institute for Molecular Sciences, University of Amsterdam, Amsterdam, The Netherlands.

Abstract – The aminomethyl group constitutes an essential motif across natural products, pharmaceuticals and agrochemicals,[1] yet classical polar approaches for its introduction often rely on redox- and step-intensive sequences that can limit efficiency.[2,3] In contrast, radical approaches offer the possibility to generate reactive open-shell species in mild fashion.[4] Provided, that the downstream processes after radical generation occur in tightly orchestrated fashion, efficient and mild access to the valuable aminomethyl function could be realized. By careful reaction design with emphasis on the nature of radical precursors and appropriate sources of the aminomethyl unit, a suite of novel aminomethylation reactions has been developed. By-passing reductive processes, the direct photochemical decarboxylation of amino acids enables the single-step conversion into vicinal diamines,[5] whereas light-mediated hydrogen atom transfer facilitates the aminomethylation of non-acidic C-H positions in contrast to the conventional Mannich-Reaction. Eventually, a direct deaminative C1-homologation of alkylamines is achieved in radical fashion, showcasing the transformative potential of radical disconnections.



References

[1] J. R. Cabrero-Antonino, R. Adam, M. Beller, "Catalytic Reductive N-Alkylations Using CO2 and Carboxylic Acid Derivatives: Recent Progress and Developments" *Angewandte Chemie International Edition* **2019**, *58*, 12820–12838.

[2] M. Yan, J. C. Lo, J. T. Edwards, P. S. Baran, "Radicals: Reactive Intermediates with Translational Potential" *J. Am. Chem. Soc.* **2016**, *138*, 12692–12714.

[3] G. A. Molander, I. Shin, "Synthesis and Suzuki–Miyaura Cross-Coupling Reactions of Potassium Boc-Protected Aminomethyltrifluoroborate with Aryl and Hetaryl Halides" *Org. Lett.* **2011**, *13*, 3956–3959.

[4] J. M. Smith, S. J. Harwood, P. S. Baran, "Radical Retrosynthesis" *Acc. Chem. Res.* **2018**, *51*, 1807–1817.

[5] J. Djossou, F. Pasca, M. Akdeniz, S. Bonciolini, A. Pulcinella, O. Bayley, M. Johansson, M. Colella, R. Luisi, T. Noel, "Radical Disconnection Logic Enables Direct Conversion of α-Amino Acids into Differentiated Vicinal Diamines" *ChemRxiv* **2025**, DOI 10.26434/chemrxiv-2025-l7skx.

Dutch Symposium on Organic Chemistry 2026

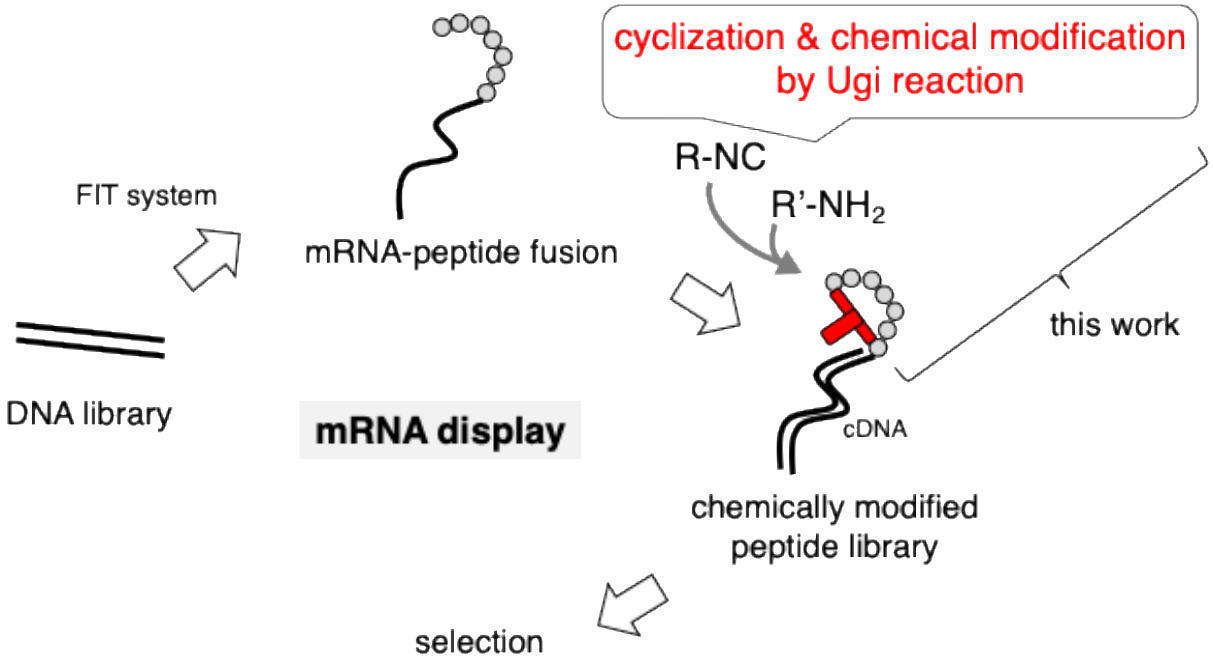
Application of the Ugi reaction to post-translational modifications in the mRNA display

R. Okawa, S. A. K. Jongkees*

Chemistry and Pharmaceutical Sciences
Vrije Universiteit Amsterdam,
O|2 building O2-03W11, de Boelelaan 1108, 1081 HZ Amsterdam
**E-mail: s.a.k.jongkees@vu.nl*

The Ugi multicomponent reaction has attracted considerable attention due to its broad applicability across fields such as medicinal chemistry and chemical biology. One particularly promising area of research is the integration of the Ugi reaction[1)] into mRNA display technology[2)]. mRNA display is a robust method that enables the encoding of peptides while preserving their sequence information, thereby facilitating the selection of high-affinity binders to target proteins. Incorporating the Ugi reaction into this framework enables facile generation of highly diverse peptide libraries containing unnatural functional groups. This novel approach has the potential to enhance the efficiency of mRNA display and promote innovation in therapeutic development.

In this study, we explored the application of the Ugi reaction to 6- to 11-mer peptides as a strategy for constructing novel peptide libraries. Specifically, we aimed to achieve head-to-tail cyclization and the simultaneous introduction of unnatural functionalities via the Ugi reaction. We first investigated the scope of compatible peptides and substrates. In addition, we conducted stability tests of mRNA–DNA complexes under the reaction conditions, and demonstrated that the Ugi reaction system could be applied to peptides translated from DNA templates.



1. Ugi, I. *Angew. Chem., Int. Ed. Engl.* **1962**, *1*, 8.
2. Roberts, R.W.; Szostak, J. W. *Proc. Natl. Acad. Sci. USA* **1997**, *94,* 12297.

A Strongly Oxidizing Dicationic Photocatalyst for the Direct Amination of Arenes

Baptiste Roure,[a†] Alexandra Matei,[a†] Xiaobing Chen,[a] Sebastian B. Beil[a,b] and Ben L. Feringa*[a]

[a] Stratingh Institute for Chemistry, University of Groningen, 9747AG Groningen, the Netherlands. [b] Current address: Max-Planck-Institute for Chemical Energy Conversion, Department for Electrosynthesis, Stiftstraße 34–36, 45470 Mülheim an der Ruhr, Germany. †These authors contributed equally.

The direct introduction of nitrogen-based functionalities onto aromatic rings is crucial, considering the broad applicability of these compounds, particularly in the pharmaceutical industry. Such transformation has become an attractive method to bypass the classical multistep and sequential synthesis of arylamines.(1) Most current new approaches rely on photocatalysis, using a strong photooxidant to generate an arene radical cation *in situ*, which can then be trapped by a nitrogen nucleophile.(2)

In this context, the development of new photocatalysts capable of accessing oxidation potentials greater than +2.5 V has been a thriving field of research in the recent years. For instance, some of the previous methodologies that have been reported involving novel strong photooxidants include: conPET,(3) photoelectrocatalysis(4, 5) and ground-state oxidants.(6–9) Albeit elegant and effective, these approaches required, (a) the use of additives and/or co-oxidants, (b) long reaction times, and (c) *the use of HFIP or TFE as main or exclusive solvent in most of the cases*. Therefore, the main goal of this work was to design an easily accessible and commercially available cationic photocatalyst capable of addressing some of the aforementioned challenges.

Herein, we report the use of a commercially available dicationic organic photocatalyst to achieve this transformation (**Figure 1**). This strategy is applicable to several nitrogen nucleophiles and electron-deficient arenes (scope of 50 examples), features short reaction times, and avoids the use of additives or fluorinated solvents, a common limitation of many previous methodologies (**Figure 1**). Preliminary mechanistic studies (including Stern-Volmer quenching studies, CVs, and KIE experiments) are supporting the initial formation of a nitrogen centered radical cation.

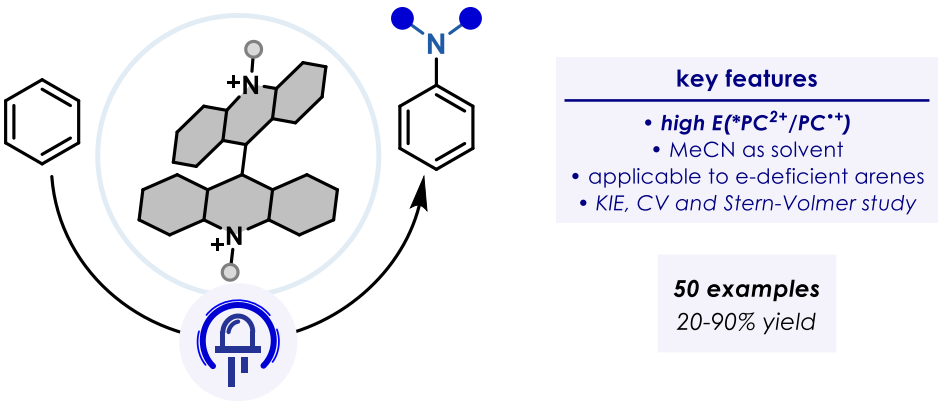


Figure 1. Overall goad of the project and key results.

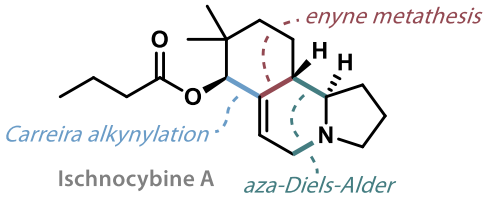
(1) R. Dorel *et al.*, *ACIE* **58**, 17118–17129 (2019); (2) N. A. Romero *et al.*, *Science*. **349**, 1326–1330 (2015); (3) K. Targos *et al.*, *J. Am. Chem. Soc.* **143**, 4125–4132 (2021); (4) H. Huang *et al.*, *Angew. Chem. Int. Ed.* **58**, 13318–13322 (2019); (5) J. Žurauskas *et al.*, *Angew. Chem.* **135**, e202307550 (2023); (6) S. Das *et al.*, *Chem. – Eur. J.* **23**, 18161–18165 (2017); (7) S. C. Sau *et al.*, *J. Am. Chem. Soc.* **146**, 3416–3426 (2024); (8) S. S. Rana *et al.*, *J. Am. Chem. Soc.* **146**, 3603–3608 (2024); (9) P. P. Sen *et al.*, *Org. Lett.* **25**, 1895–1900 (2023)

Prize-Winning Route to Ischnocybine A

Ivo Kruisheer, Aleksandar Mandić, Roan Spiertz, Eelco Ruijter, Thomas Hansen

Synthetic Organic Chemistry & Catalysis, Amsterdam Institute of Molecular and Life Sciences, Vrije Universiteit, Amsterdam, Netherlands

As part of Merck's 6th Compound Challenge, a 48-hour global retrosynthesis competition, we proposed a synthetic route to Ischnocybine A and were awarded first prize.[1] In this talk, I will discuss our approach to the Compound Challenge as well as our subsequent efforts in the laboratory to synthesize Ischnocybine A. Ischnocybine A features a unique 6/6/5 fused ring system bearing three stereogenic centers.[2] Our synthetic strategy relies on an asymmetric organocatalyzed *aza*-Diels-Alder reaction, enyne metathesis and a stereoselective Carreira alkynylation. The proposed route involves six steps and is formally protecting-group-free, underscoring its efficiency and elegance. Moreover, the methodology is sufficiently flexible to be adapted to other members of the Ischnocybine family with only minor modifications, a direction we are currently exploring.



- from *Ischnocybe plicata*
- deoxybuzonamine core
- 6/6/5 fused ring structure
- 3 stereogenic centers
- M_W = 291.44 g mol^{-1}

(1) Seipp, C. A.; Monks, B. M.; Karnysh, I.; Betz, U. A. K. Innovation and Team Spirit: The Magic of Science Competitions Seen through the Lens of the Compound Challenge. *Angew. Chem. Int. Ed.* **2024**, *63* (13). https://doi.org/10.1002/anie.202317338.

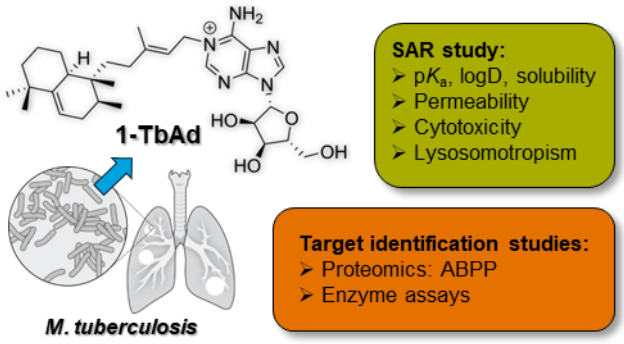
(2) Menegatti, C.; Wood, J. S.; Banks, P.; Knott, K.; Briganti, J. S.; Briganti, A. J.; McNally, S. V. G.; Marek, P. E.; Brown, A. M.; Jones, T. H.; Williamson, R. T.; Mevers, E. Neuromodulating Alkaloids from Millipede Defensive Secretions. *J. Nat. Prod.* **2025**, *88* (1), 110–118. https://doi.org/10.1021/acs.jnatprod.4c01162.

SAR and Target Identification Studies on 1-TbAd - a Nucleosidic Virulence Factor of *Mycobacterium tuberculosis*

Paul Wienecke,[1,*] Anna-Lisa E. Lawrence,[2] Miyer F. Patiño-Ruiz,[3] Sarah L. Stellnberger,[4] Naschla Gasaly,[5] Marek Freindorf,[6] Susan Render,[1] Orestis Stavrinou,[1] Jeffrey Buter,[1] D. Branch Moody,[7] Elfi Kraka,[6] Paul de Vos,[5] Verena Pichler,[4] Bert Poolman,[3] Shumin Tan,[2] Madeline Kavanagh,[8] Adriaan J. Minnaard[1,*]

[1]University of Groningen, Stratingh Institute for Chemistry, Nijenborgh 7, 9747 AG Groningen/Netherlands
[2]Tufts University School of Medicine, Molecular Biology and Microbiology, 150 Harrison Ave, 02111 Boston/USA
[3]University of Groningen, Groningen Biomolecular Sciences and Biotechnology Institute, Nijenborgh 3, 9747 AG Groningen/Netherlands
[4]University of Vienna, Department for Pharmaceutical Chemistry, Althanstraße 14, 1090 Vienna/Austria
[5]University Medical Center Groningen, Department of Pathology and Medical Biology, Hanzeplein 1, 9713 GZ Groningen/Netherlands
[6]Department of Chemistry, Southern Methodist University, 3215 Daniel Avenue, Dallas, TX 75275-0314, USA
[7]Harvard Medical School, Division of Rheumatology, Inflammation and Immunity, Brigham and Women's Hospital, 75 Francis St, 02115 Boston/USA
[8]Leiden University, Leiden Institute of Chemistry (LIC), Einsteinweg 55, 2333 CC Leiden/Netherlands

*e-mail: a.j.minnaard@rug.nl, p.wienecke@rug.nl



1-TbAd is a highly abundant terpene nucleoside from *Mycobacterium tuberculosis*. Because of its chemical properties, it accumulates in the host's macrophages' phagosomes and raises the pH of these usually acidic cell compartments ("lysosomotropism"). Thereby, 1-TbAd inhibits degradative mechanisms and improves nutrient access, facilitating survival of *Mtb* in immune cells. In this study, we aim to better understand how structural elements of 1-TbAd influence its physicochemical properties and how they drive the blocking of phagosomal acidification. A SAR study around 1-TbAd deepens the knowledge on the tuning of lysosomotropism, a feature that can be either desired or undesired in the design of bioactive compounds. Not only 1-TbAd is evaluated as a lead structure, but also these N-1 alkylated adenosine derivatives in general are investigated, a widely neglected compound class. Furthermore, proteomics studies and enzyme assays were conducted to reveal protein targets and explore bioactivities beyond lysosomotropism.

Flow-Enabled, Modular Access to α,α-Difluoromethylene Amines

Dmitrii Nagornîi[1], Pietro Ronco[1,2], Khadijah Anwar[1], Nikolaos Kaplaneris[1], James J. Douglas[3], Timothy Noël[1,*]

[1] Flow Chemistry Group, Van 't Hoff Institute for Molecular Sciences (HIMS), University of Amsterdam, Amsterdam, The Netherlands.

[2] Department of Chemistry, University of Pavia, Viale Taramelli, 27100 Pavia, Italy

[3] Early Chemical Development, Pharmaceutical Sciences R&D, AstraZeneca, Macclesfield, UK.

The α,α-difluoromethylene amine (NCF_2R) motif represents a useful functionality in medicinal chemistry, yet practical and modular methods to access this class of compounds are lacking.[1-3] Here, we report a safe and scalable flow-based strategy for the on-demand generation of NCF_2R anions using a packed-bed microreactor containing caesium fluoride. This protocol enables the late-stage installation of the CF_2 group under mild conditions, avoiding the use of hazardous fluorinating agents and minimizing fluorinated waste. This fully modular strategy features three points of diversification (carboxylic acid, sulfonamide, and electrophile), allowing efficient access to a broad range of α,α-difluoromethylene amines. The method tolerates a variety of functional groups, supports late-stage functionalization of pharmaceutically relevant scaffolds, and is compatible with downstream cross-coupling reactions, demonstrating the robustness of the reaction protocol. This work provides a versatile platform for the streamlined incorporation of NCF_2 motifs, expanding the range of synthetic strategies available in medicinal and fluorine chemistry.

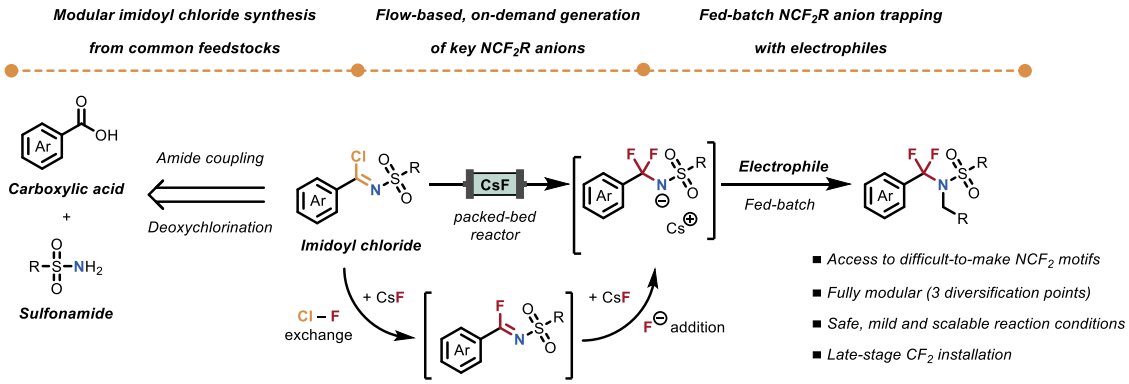


Figure 1. Reaction design: modular and scalable access to NCF_2 motifs using flow-enabled anion generation and fed-batch trapping.

1. Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. Fluorine in medicinal chemistry. *Chem. Soc. Rev.* **2008**, *37* (2), 320-330.
2. Gillis, E. P.; Eastman, K. J.; Hill, M. D.; Donnelly, D. J.; Meanwell, N. A. Applications of Fluorine in Medicinal Chemistry. *J. Med. Chem.* **2015**, *58* (21), 8315-8359.
3. Du, Y., et al. Fluorine in the Pharmaceutical Industry: FDA-Approved Fluorine-Containing Drugs in 2024. *Chem. Eur. J.* **2025**, *31* (25), e202500662.

Title:
A Two-Step Photocatalytic Platform for Rapid Access to sp^3-Rich Spirocyclic Scaffolds in Drug Discovery

Authors:
P.Fodran, R. Mu

Affiliations:
[1] Department of Chemical and Pharmaceutical Biology, Groningen Institute of Pharmaceuticals, Faculty of Science and Engineering, University of Groningen, Antonius Deusinglaan 1, 9713 AV Groningen, The Netherlands

Abstract:
The incorporation of saturated, three-dimensional motifs—particularly spirocycles—has emerged as a powerful strategy to increase the sp^3 character of small-molecule therapeutics, a factor correlated with improved clinical-trial success and market viability (Lovering *et al.*, *Escape from Flatland*, 2009). Despite their promise, the widespread adoption of spirocyclic scaffolds is hampered by multistep syntheses that rely frequently on protecting-group manipulations.

We report a concise, two-step synthetic platform that converts inexpensive, bulk-available feedstock chemicals into a diverse set of spirocyclic building blocks suitable for medicinal-chemistry programs. The cornerstone of the methodology is a visible-light-mediated, photocatalyzed intramolecular Giese addition to enones, proceeding with **100 % atom economy** and under mild conditions that tolerate a broad range of functional groups. Subsequent straightforward functional-group interconversions enable rapid diversification of the spirocyclic core.

Application of the sequence to a library of **30 structurally varied substrates** demonstrates its robustness and scalability, delivering spirocyclic products that can be further elaborated via standard transformations (oxidation, reduction, cross-coupling, amide formation, reductive amination). This platform therefore provides a practical, atom-economical route to sp^3-rich scaffolds, addressing a key synthetic bottleneck in contemporary drug discovery.

Keywords: sp^3 enrichment, spirocycles, photocatalysis, Giese addition, atom economy, medicinal chemistry.

Poster abstracts

1

Lysine targeting molecular glues for profiling specificity in 14-3-3 PPI stabilization

Tessa Harzing, Galen Miley, Luc Brunsveld
Eindhoven University of Technology

Protein-protein interaction (PPI) stabilization by molecular glues (MG) has been shown to be an alternative strategy for targeting proteins lacking structured binding pockets. Molecular glues are often serendipitously discovered using high throughput fragment screening approaches. We instead aim to gain a mechanistic understanding of PPI stabilization using the 14-3-3 protein and its binding partners as a platform. The binding partners all interact in the same groove on 14-3-3, therefore providing a constant but varied interface to profile 14-3-3 PPI stabilization by molecular glues. This profile can then inform the design of future 14-3-3 PPI molecular glues, by providing information regarding MG specificity.

Previously identified lysine targeting stabilizers containing an aldehyde warhead were used as a starting point. A small library containing variations on one part of the molecule was generated and subsequently assessed on stabilization potential against a 14-3-3 binding partner panel by a fluorescence anisotropy (FA) point screen assay. So far, this assay showed that especially halogen and hydroxy-substituents could stabilize many of the interactions. X-ray crystallography results obtained alongside the FA assay show the potential for formation of weak halogen or hydrogen bonds with residues Ser45 and Asn42 on 14-3-3, explaining the aptitude of these molecular glues in stabilizing the 14-3-3 PPIs.

Subsequently, the most promiscuous substitution patterns were selected and kept constant in the generation of a new library focusing on variations on the next part of the stabilizer. Afterwards, these stabilizers will again be profiled against the same peptide panel. This loop will then be continued across the remaining parts of the stabilizer to create the full 14-3-3 PPI stabilization profile.

2

Building a New Aza-Triptycene Scaffold for Multinuclear Metal Chemistry

Stijn Bronsveld, Luuk Stringer, dr. ing. Daniël L. J. Broere; Organic Chemistry and Catalysis, Institute for Sustainable and Circular Chemistry, Utrecht University, The Netherlands

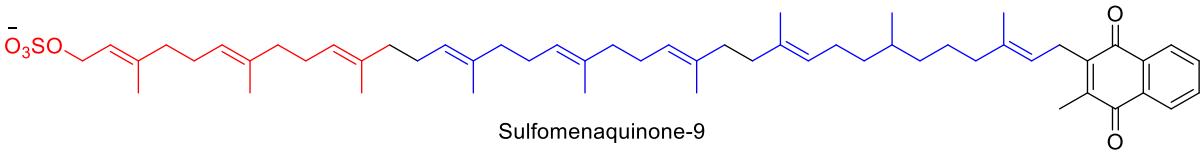
Triptycenes are rigid and symmetric compounds with a well-defined spatial orientation. Incorporation of nitrogen heteroatoms into the triptycene framework is synthetically challenging, but attractive because these nitrogen atoms can serve as metal-binding sites, enabling the formation of multinucleating ligands for transition-metal complexes. Despite synthetic efforts reported in the literature, triptycenes with more than two nitrogen atoms incorporated into the backbone have not yet been described. We evaluated multiple synthetic strategies toward aza-triptycene derivatives. On this poster, we present the first successful synthesis of a triazatriptycene scaffold. This new framework provides a platform for future development of multinuclear transition-metal complexes.

3

Towards the total synthesis of sulfomenaquinone-9

Joey van Looij & Adriaan Minnaard
Stratingh Institute for Chemistry, University of Groningen

Sulfomenaquinone-9 is a sulfated derivative of menaquinone-9 that was isolated from *Mycobacterium tuberculosis* by the group of Bertozzi.[1] Genetic and biochemical studies have linked its biosynthesis to virulence-associated pathways, yet its precise molecular function remains unknown, making sulfomenaquinone-9 a promising target for investigating the mechanisms underlying *M. tuberculosis* pathogenicity.[2]



Sulfomenaquinone-9

In this study, we describe a [3+3+3] assembly strategy that employs two farnesol-derived building blocks and one citronellol-derived building block for the synthesis of an extended prenyl framework. The key step is a Biellmann coupling between suitably functionalized prenyl fragments, which enables formation of the carbon–carbon bonds connecting the individual isoprenoid units. This strategy allows stepwise elongation of the prenyl chain via iterative coupling reactions involving sulfone-activated intermediates and complementary leaving-group-containing partners.

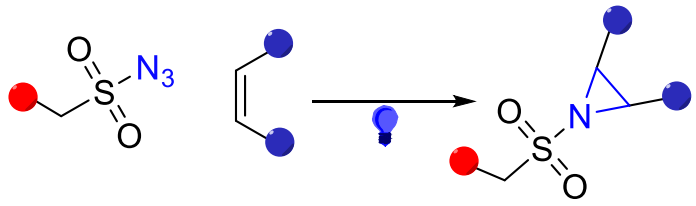
4

NITRENE GENERATION OF ALIPHATIC SULFONYL AZIDES FOR OLEFIN AZIRIDINATION

J. Schoenmakers[1], D.V. Filippov[1], J.D.C. Codée[1], E. Bouwman[1]

[1] *Leiden Institute of Chemistry, Leiden University, Leiden, The Netherlands*

Aziridines, which are three-membered heterocycles consisting of one nitrogen and two carbon atoms, have shown to be useful functional groups both in synthetic intermediates and biologically relevant molecules. In contrast to epoxides, the possibility to functionalize aziridines with a linker makes them particularly useful. However, despite their broad applicability, the synthesis of these moieties is considered a challenge. Therefore, multiple photocatalytic aziridination methodologies have been developed over the past few years. In these reactions, nitrenes are generated by electron or energy transfer from a photosensitizer such as a cyanoarene[1,2] or ruthenium complex[3], to an organic azide or iminoiodinane. However, for the synthesis of sulfonyl aziridines the presence of an aromatic ring, like a tosyl group, showed to be crucial for these types of transformations. Therefore, when a linker on the aziridine needs to be attached, harsh deprotection conditions followed by the attachment of the linker are required. To resolve this, a new aziridination methodology has been developed which allows the synthesis of sulfonyl aziridines with an aliphatic tail. On this aliphatic tail the desired linker, for example an azide or alkyne, can be attached. This allows the synthesis of complex linker attached aziridine for which protection and deprotection steps can be avoided.



References

[1] D. Dam, N.R. Lagerweij, K.M. Janmaat, K. Kok, E. Bouwman, J.D.C. Codée, *JOC.* **2024**, *89.5*, 3251-3258

[2] A.R. Meyer, M.V. Popescu, A. Sau, N.H. Damrauer, R.S. Paton, T.P. Yoon, *ACS Catal.* **2024**, *14.6*, 12310-12317

[3] Y. Guo, C. Pei, R.M. Koenigs, *Nat. Commun.* **2022**, *13.1*, 86

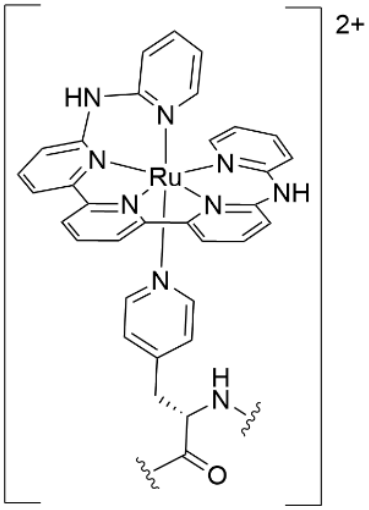
5

Photoactivated chemotherapy with cytotoxic peptide inhibitors

Maarten van Ginkel, Hermen Overkleeft, Sylvestre Bonnet

Chemotherapeutics are often associated with severe side effects hampering the efficacy of anti-cancer treatment. For some solid tumors the therapeutic window is therefore small; poor tumor penetration calls for higher dosages, which are not an option due to the dose limiting side-effects. In this context photoactivated chemotherapy (PACT) shows great promise. When using PACT to widen the therapeutic window, the existing chemotherapeutic molecule is coordinated to a metal complex, reducing the biological activity of the chemotherapeutic. Upon irradiation of this complex the coordination bond is broken, releasing the original drug and restoring its biological activity. This method provides spatiotemporal control over the drugs activity and therefore provides a means of reducing side-effects, as the active drug is only present at the tumor site and the rest of the body is left unharmed.

In this work a potent peptide inhibitor was modified by incorporating a pyridine moiety to allow coordination to a ruthenium baptpy complex (See Figure 1). After successful synthesis and purification of the inhibitor and the corresponding ruthenium complex, UV-Vis experiments demonstrated that the complex undergoes photosubstitution upon irradiation with visible light. Next the activity of the inhibitor was assessed with enzyme activity assay, showing a potency like that of the original chemotherapeutic. In addition, the potency of the complex both in the dark and upon light irradiation was assessed with the same assay, showing a clear increase in potency upon irradiation. Finally, a cell viability assay was performed on the free inhibitor, showing that the free inhibitor is indeed still functioning as chemotherapeutic agent. The same cell viability assay was performed on the complex both in the dark and upon light irradiation, clearly showing a decrease in cell viability upon light irradiation.



$[Ru(baptpy)L]^{2+}$

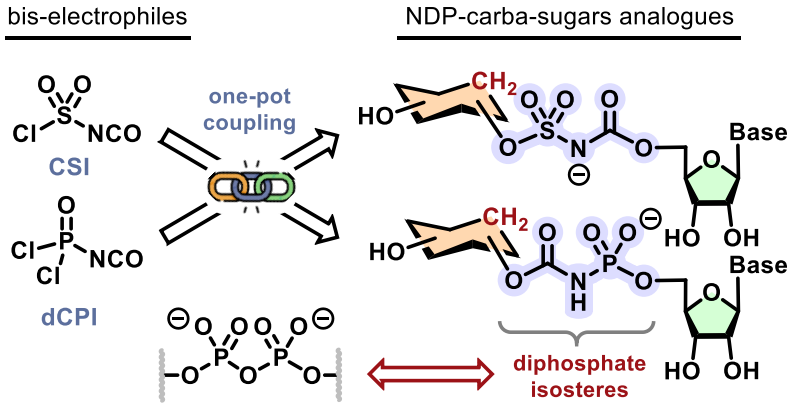
Figure 1: General structure of peptide-based inhibitor bound to the ruthenium baptpy complex.

6

MODULAR SYNTHESIS OF NUCLEOSIDE DIPHOSPHATE SUGAR ANALOGUES USING BIS-ELECTROPHILIC REAGENTS

Roy Steneker[a], Koen J. Rijpkema[a], Dmitri V. Filippov[a], Jeroen D.C. Codée[a], Hermen S. Overkleeft[a]

[a]Leiden Institute of Chemistry, Leiden University, 2333 CC Leiden, The Netherlands



Pyrophosphates, the anhydrides of two phosphoric acid residues, represent a ubiquitous structural motif that plays a dominant role across all kingsdoms of life.[1,2] The chemical behaviour and biological function of pyrophosphates are largely governed by their high negative charge at physiological conditions. While these unique features make them ideally suited for their biological roles, their lability towards chemical and enzymatic hydrolysis, as well as their membrane impermeability, makes this moiety unattractive for incorporation into chemical tools and inhibitors in chemical biology and medicinal chemistry.[3,4] These limitations have driven considerable interest in the development of stabilized, non-hydrolyzable, and in some cases, less-charged pyrophosphate isosteres.[5–10]

We describe a flexible, modular synthesis of nucleoside diphosphate (NDP-) sugar analogues by linking carbasugars and nucleosides with the bis-electrophilic reagents chlorosulfonyl isocyanate (CSI) and dichlorophosphoryl isocyanate (dCPI), introducing sulfonyl- and phosphoryl-carbamate linkages as promising pyrophosphate isosteres, respectively.[11] We demonstrate the versatility of this method through the synthesis of GDP-fucose and UDP-GlcNAc analogues, which may act as glycosyltransferase inhibitors and serve as tools for studying pyrophosphate-binding and -processing enzymes.

References:

1. F. H. Westheimer, *Science*, **1987**, 235, 1173–1178.
2. O. I. Kolodiazhnyi, *Symmetry*, **2021**, 13.
3. E. S. Rudge et al., *RSC Med. Chem.*, **2022**, 13, 375–391.
4. C. S. Rye and J. B. Baell, *Curr. Med. Chem.,* **2005**, 12, 3127-3141.
5. A. K. Dutta, I. Captain and H. J. Jessen, *Top. Curr. Chem. (Z)*, **2017**, 375, 51.
6. V. D. Romanenko and V. P. Kukhar, *Arkivoc*, **2018**, 1–49.
7. S. B. Engelsma et al., *Angew. Chem. Int. Ed.* **2017**, 56, 2955–2959.
8. J. Guo et al., *Org. Lett.* **2024**, 26, 739–744.
9. L. M. Seebald et al., *J. Am. Chem. Soc.* **2024**, 146, 3220–3229.
10. O. Baszczynski et al., *RSC Adv.*, **2020**, 10, 1776–1785.
11. R. Steneker et al., *Org. Lett.* **2026**, 28, 3, 912–916.

7

Synthesis of red light photoswitches – The case of Konrad's azobenzene

Ana Margarida Pereira[1], Vincent Ornelis[1], Kasper Eersels[1], Hanne Diliën[1] and Bart van Grinsven[1].

[1] Department of Sensor Engineering, Faculty of Science and Engineering, Maastricht University, Duboisdomein 30, 6229GT Maastricht, The Netherlands.

E-mail: ana.duartepereira@maastrichtuniversity.nl

Azobenzenes are widely applied as photoswitches in several fields such as material sciences and pharmaceuticals. However, for in vivo applications, light has to be able to reach the azobenzene moiety. It has been shown that red light and ideally near infrared light penetrates deeper within tissue than radiation with shorter wavelengths.[1] In this regard, the work of Konrad *et al*. is worthy to be highlighted because the authors reported on an azobenzene derivative that can be switched to the *cis*-state upon irradiation with 660 nm light yielding a 17:83 *trans*:*cis* ratio, while the *trans*-state can be obtained upon irradiation with blue light (440 nm) yielding a 95:5 *trans*:*cis* ratio. Moreover, the thermal relaxation half-life is 5h at 25 °C in DMSO.[2]

In this work, we have optimized the synthesis of Konrad's azobenzene (**Fig. 1**). Various reaction conditions and purification conditions were tested. For the oxidation condition, we replaced the reported potassium permanganate[2] by N-chlorosuccinimide/DBU[3] which increased the yield from 5% to 22%. Additionally, various reaction temperatures were screened for this reaction, in which it was observed that higher temperatures promote a slight increase in chemical yield (at -78 °C, η=22%/ at -20 °C, η= 25%). In the chlorination reaction, no product was formed when a lower concentration of the starting material was used, therefore unravelling an important effect of the starting material concentration on product formation. Overall, our optimized synthesis protocol allows the synthesis of this interesting azobenzene building block in 14% overall yield on a 200 mg scale.

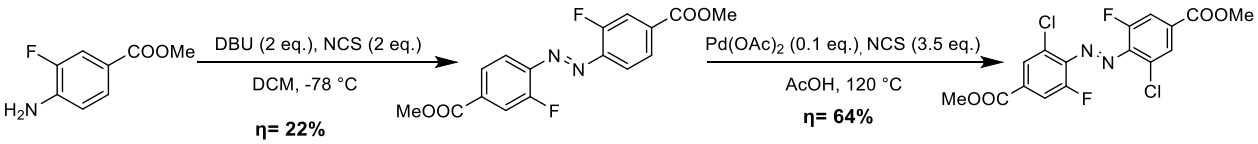


Figure 1. Optimization of Konrad's azobenzene synthesis.

Funding: ZonMw (04510242410025).

Acknowledgement: We would like to thank Evi Timmer who worked on this project for her bachelor thesis.

References:

[1] Y. Shimojo, T. Nishimura, H. Hazama, T. Ozawa, K. Awazy *J. Biomed. Opt.*, **2020**, *25*, 045002.

[2] D. B. Konrad, G. Savasci, L. Allmendinger, D. Trauner, C. Ochsenfeld, A. M. Ali, *J. Am. Chem. Soc.*, **2020**, *142*, 6538.

[3] A. Antoine John, Q. Lin, *J. Org. Chem.*, **2017**, *82*, 9873-9876.

8

Abstract for Poster Dutch symposium on organic chemistry 2026

Wim Nijskens

Title

Development of Covalent Small Molecule NR2F6 Modulators

Authors

W.J.H. Nijskens[1], G.J.M. Oerlemans[1] , V. Valkova[1], E. Klop[1], H.R. Vickory[2], J. Revalde[2], M. Konstantinidou[2], M.R. Arkin[2] & L. Brunsveld[1]

Affiliations

[1]Laboratory of Chemical Biology and Institute for Complex Molecular Systems (ICMS), Department of Biomedical Engineering, Eindhoven University of Technology

[2]Department of Pharmaceutical Chemistry and Small Molecule Discovery Centre, University of California San Francisco

Abstract

NR2F6 is one of the least studied proteins among the nuclear receptor superfamily. As a true orphan receptor, no endogenous ligand has been identified. Furthermore, although a cofactor screening revealed NR2F6 model cofactors (in vitro), endogenous cofactors remain unknown as well. Recently, our group solved the first crystal structure of the NR2F6 ligand binding domain (LBD) in complex with model peptide NSD1 was recently solved (PDB: 8C5L), revealing that the protein acts as a homodimer. Through screening of a covalent library, we found compounds that either inhibit or stabilize the NR2F6/NSD1 interaction through an interaction with a NR2F6 cysteine with low micromolar affinities. These molecules were then optimized after the synthesis of library of molecules. Through mutational studies, the orthosteric cysteine 203 was identified as binding site for the small molecule inhibitors, while the allosteric loop cysteine 316 was found to be the anchor point for the stabilizers.
By optimizing crystal growth, the first ternary (NR2F6/NSD1/stabilizer) crystal structure was elucidated. This showed that the mode of action was due to the stabilization of the homodimerization, rather than inducing new interactions with the protein. Aided by the structural information, we now aim to improve the current small molecule modulators through additional synthetic and crystallographic endeavors.

9

Advancing peptide synthesis by templated ligation

Proteins and peptides play a central role in modern drug discovery. Solid-phase peptide synthesis (SPPS) is a powerful technique for the preparation of synthetic peptides and relies on the stepwise elongation of a peptide chain immobilized on a solid support. However, as peptide length increases, efficient chain elongation becomes increasingly challenging. To overcome these limitations, several chemical ligation strategies—such as native chemical ligation (NCL), Staudinger ligation, and serine/threonine ligation (STL)—have been developed. These approaches allow the assembly of longer peptides from shorter fragments. Despite enabling access to otherwise unattainable targets, many ligation methods suffer from intrinsically slow reaction kinetics. In cases where peptide fragments exhibit poor solubility, reaction rates can become so low that competing side reactions dominate. To address this limitation, we aim to develop a templating strategy in which a fast click reaction brings the reactive termini of two peptide fragments into close proximity. By increasing the effective local concentration of the reacting groups, we expect to accelerate both native chemical ligation (NCL) and serine/threonine ligation (STL). After ligation, the template can be removed to afford the native peptide.

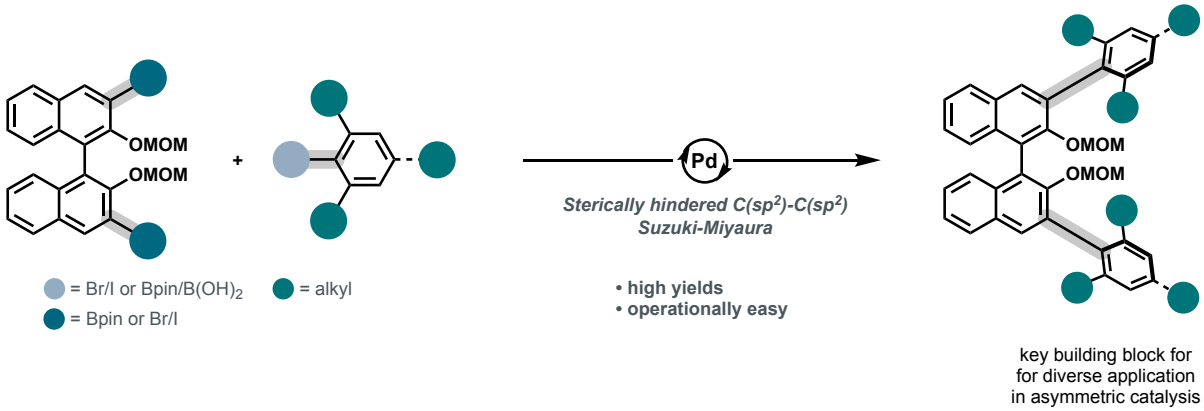
10

Efficient synthesis of 3,3'-sterically hindered BINOL derivatives: a Pd-catalyzed Suzuki-Miyaura approach

Aleksandar Mandić, Eelco Ruijter, Thomas Hansen

Synthetic Organic Chemistry & Catalysis (SOCC), Amsterdam Institute of Molecular and Life Sciences, VU Amsterdam, Amsterdam, the Netherlands

The rapid emergence of transition-metal catalyzed cross-couplings enabled highly efficient access to (hetero)polyaryls, which are core motifs in advanced materials, pharmaceuticals, natural products, and ligands. Among these, 1,1'-bi-2-naphthol (BINOL) derivatives have emerged as privileged chiral scaffolds due to their low cost and high configurational stability, making them one of the pillars upon which asymmetric catalysis stands. However, the synthesis of very sterically encumbered BINOL derivatives, particularly 3,3′-substituted analogues, remains highly challenging and typically relies on Kumada or Negishi couplings[1] that require sensitive organometallic intermediates and multi-step preparations. In contrast, the more user-friendly Suzuki-Miyaura methodology remains largely underexplored in this context due to the insufficient reactivity of hindered coupling partners, often resulting in low conversion. Tapping into the possibilities of using a coordinatively unsaturated Pd(0) intermediate opens up new chemical avenues for such transformations. Here, we systematically evaluate the influence of the palladium source and ligand structure on the formation of 3,3′-coupled BINOLs, identifying catalytic systems that enable high yields with challenging substrates. With this approach, largely popularized TRIP (2,4,6-triisopropylphenyl)[2] BINOL derivative has been successfully made in 72% yield. The developed cross-coupling platform will offer new pathways to the vast diversity of BINOL derivatives to fuel asymmetric catalysis research.



References

(1) Pu, L. Regioselective Functionalization of BINOL *Chem. Rev.* **2024**, *124* (10), 6643–6689.

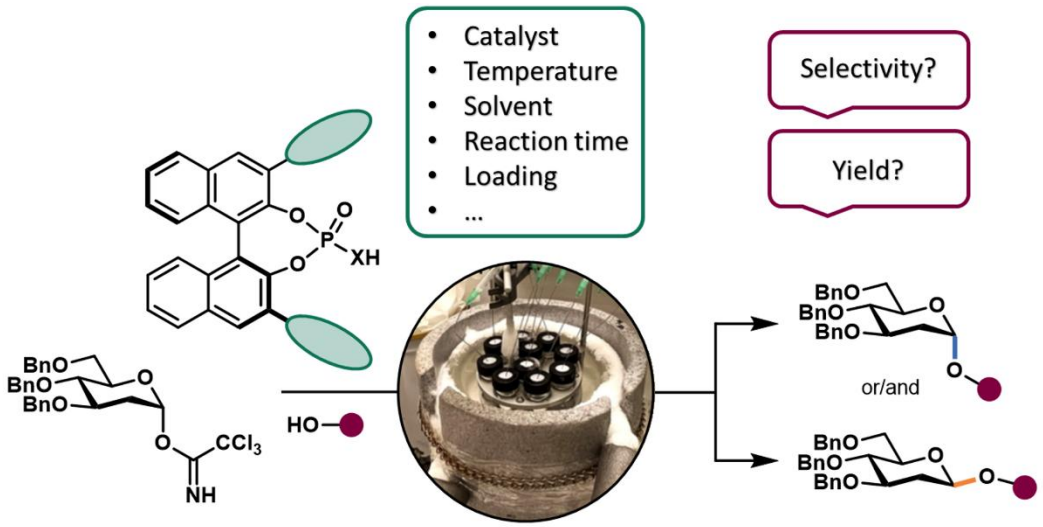
(2) Hoffmann, S.; Seayad, A. M.; List, B. A poweful Brønsted Acid Catalyst for the Organocatalytic Asymmetric Transfer Hydrogenation of Imines. *Angew. Chem. Int. Ed.* **2005**, *44* (45). 7424–7427.

Stereocontrolled Organocatalytic Glycosylations of 2-Deoxy-glycosides

Meizhe Liu, Daan Hoogers, Aleksandar Mandić, Jeroen Codée, Eelco Ruijter, Thomas Hansen

Synthetic Organic Chemistry & Catalysis, Amsterdam Institute of Molecular and Life Sciences, Vrije Universiteit, Amsterdam, Netherlands

The efficient construction of glycosidic linkages for complex carbohydrate synthesis remains a daunting challenge.[1] This is especially true for 2-deoxy-glycoside donors, which are key components of many bacterial glycosides. The missing C2-oxygen substituent prevents conventional stereocontrol strategies such as neighbouring group participation. Over the past decades, numerous strategies have been developed to address this challenge, with catalyst-controlled glycosylations emerging as especially promising.[2] Unfortunately, these approaches often deliver inconsistent results, as stereoselectivity depends on a delicate interplay between the catalyst, the glycosyl donor, and the acceptor's stereochemistry.[3] Here, we systematically investigate a series of organocatalytic glycosylation reactions using a library of chiral phosphoric acids as catalysts. We delineate how catalyst architecture governs both reactivity and selectivity and, through combined experimental and computational studies, identify key reactive intermediates and clarify the underlying catalytic mechanism. Guided by these mechanistic insights, we design organocatalytic glycosylations that provide either stereoisomer on demand.



(1) X. Zhu, R. R. Schmidt, New Principles for Glycoside-Bond Formation. *Angew. Chem. Int. Ed.* **2009**, *48* (11), 1900–1934. **DOI:** 10.1002/anie.200802036.

(2) M. Nielsen, C. M. Pedersen, Catalytic Glycosylations in Oligosaccharide Synthesis. *Chem. Rev.* **2018**, *118* (17), 8285–8358. **DOI:** 10.1021/acs.chemrev.8b00144.

(3) R. Williams, M. C. Galan, Recent Advances in Organocatalytic Glycosylations. *Eur. J. Org. Chem.* **2017**, *2017* (42), 6247–6264. **DOI:** 10.1002/ejoc.201700785.

12

Macrocyclic Molecular Glues for the 14-3-3/ChREBP Interaction: Affinity and Cooperativity in an Inverse Relationship (Merel van den Bosch)

Molecular glues (MGs) stabilize protein-protein interactions (PPIs) by simultaneously binding two or more proteins at their composite interface. Macrocycles present attractive properties as MGs, including large contact surfaces to address the often flat and undefined composite PPI interfaces, but their structure-based design has remained intangible. We have designed peptidomimetic macrocycles capable of enhancing the PPI between 14-3-3 and the carbohydrate response element binding protein (ChREBP), a regulatory transcription factor. Biophysical characterization of these MGs revealed the importance of optimized linker length, displaying a reduced entropic cost compared to the linear counterparts, while preserving key contacts with 14-3-3. Binding assays demonstrated that the macrocycles selectively and cooperatively stabilized the 14-3-3/ChREBP complex, with an intriguing inverse relationship between intrinsic binding affinity to 14-3-3 and cooperativity in PPI stabilization. Ternary co-crystal structures of the macrocycles binding at the composite 14-3-3/ChREBP interface provided a molecular rationale for the affinity and cooperativity differences. Overall, this study highlights structural, kinetic, and thermodynamic features that guide effective macrocyclic MG design and brings forward the crucial interplay of affinity and cooperativity in stabilizing PPIs.

13

Diastereoselective Ugi reactions to synthesize proline-rich (poly)peptides

Felix Boerman

Collagen is known for its unique properties, largely due to its formation into distinct triple helices. These helices result from the folding of three peptide chains (α-chains), each composed of repeating tripeptide units that are predominantly made of proline and hydroxyproline. The unique structure and properties of collagen have led to an increasing demand for its applications across fields, ranging from tissue engineering and wound healing to bioplastics and coatings. Currently, collagen is primarily sourced from animals, a process hampered by challenges including complex extraction methods, the risk of disease transmission, and variability in yield and quality. Synthetically replicating this complex structure remains challenging. To address this, we aim to use diastereoselective Ugi reactions to build the characteristic collagen tripeptide unit. In this approach, commercially available building blocks are paired with biocatalytic desymmetrization of prochiral cyclic amines to generate optically pure chiral imines as Ugi partners. The resulting tripeptides then serve as modules in solid-phase synthesis to assemble medium-sized collagen-mimetic peptides (CMPs). These CMPs reproduce key structural and functional features of natural collagen, enabling detailed studies of triple-helix folding and thermal stability. The imines installed within the CMPs provide stereochemical control and modularity, laying the groundwork for fully synthetic collagen.

Revisiting Ru–BINAP Catalysis: New Reactivity from a Classical Platform

Yifei Zhou, Fedor M. Miloserdov

Hemilabile biarylphosphines can stabilize electronically flexible metal centers while preserving access to distinct catalytic manifolds. [1-3] We investigated the ruthenium–BINAP platform across two oxidation states and found that the ligand supports orthogonal activation modes that can be interconverted and kinetically tuned.

A low-valent complex Ru(BINAP)(PPh_3) behaves as a latent 16-electron Ru(0) fragment:[4] the π-arene interaction suppresses cyclometalation yet allows rapid ligand substitution and activation of C–H, N–H, and even N–Et bonds under mild conditions. These reactions proceed through substrate activation enabled by an electron-rich Ru center. Protonation of related Ru(0)/alkene species generates Ru(II) complex that is capable of asymmetric hydrogenation, revealing a mechanistic continuity between bond activation and catalytic reduction pathways.

We then examined the influence of counteranions on the Ru(II) manifold using a family of Ru(L)($X)_2$ complexes (X = acetate, sulfonates).[5] Replacement of acetate by weakly coordinating sulfonates dramatically accelerates catalyst activation and hydride formation, enabling reliable asymmetric hydrogenation at atmospheric (1 bar) H_2 without pre-pressurization while maintaining enantioselectivity. The rate enhancement correlates with anion coordination strength and reflects a lower barrier to formation of active Ru–hydride species.

Overall, BINAP effectively stabilizes a ruthenium(0/II) center capable of inert-bond activation (Ru(0)) and facile catalytic hydrogenation (Ru(II)). Reactivity is governed not only by oxidation state but also by accessibility of activation pathways, which can be tuned through counteranion identity. This provides a unified strategy for controlling ruthenium catalysis through combined ligand and anion design.

(1) Burgos, C. H.; Barder, T. E.; Huang, X.; Buchwald, S. L. Significantly improved method for the pd-catalyzed coupling of phenols with aryl halides: understanding ligand effects. *Angew. Chem. Int. Ed.* **2006**, *45*, 4321-4326.

(2) Zuccarello, G.; Zanini, M.; Echavarren, A. M. Buchwald-Type Ligands on Gold(I) Catalysis. *Isr. J. Chem.* **2020**, *60*, 360-372.

(3) Newman-Stonebraker, S. H.; Wang, J. Y.; Jeffrey, P. D.; Doyle, A. G. Structure-Reactivity Relationships of Buchwald-Type Phosphines in Nickel-Catalyzed Cross-Couplings. *J. Am. Chem. Soc.* **2022**, *144*, 19635-19648.

(4) Zhou, Y.; Wensink, N. H.; Pécharman, A. F.; Miloserdov, F. M. Synthesis and Reactivity of Ru(BINAP)(PPh_3). *Angew. Chem. Int. Ed.* **2024**, *63*, e202318684.

(5) Zhou, Y.; Vink, P.; Kılınç, I.; Sokolova, O. O.; Miloserdov, F. M. Ruthenium Bis-Sulfonate Complexes: Synthesis and Application in Asymmetric Hydrogenation. *Organometallics* **2025**, *44*, 2630-2635.

Non-Innocent Behavior of Aromatic Isocyanides under Visible Light: A Pathway to Thioformimidates and Dehydroalanine

Minghui Wu,[a] Jay Hanssens,[a] Jordy Saya,[a] Romano Orru,[a] Prabhat Ranjan [a,b]

[a]Aachen-Maastricht Institute for Biobased Materials (AMIBM), Maastricht University, The Netherlands.
[b]UCLouvain, Institut de la Matière Condensée et des Nanosciences (IMCN), Belgium
Email: wu.minghui@maastrichtuniversity.nl

Thioformimidates play an important role in peptide modifications as the protection group [1]. The most common method for the synthesis of thioformimidates involves S-alkylation of thioformamides with aryl or alkyl halides. However, these processes often suffer from several limitations and purification problems due to the instability of thioformamides and limited substrate scope. Alternatively, thioformimidates can also be synthesized from isocyanides and thiols triggered by UV-light or AIBN initiator [2]. Generally, this reaction proceeds with the formation of a thiyl radical in the presence of UV-light or AIBN followed by thiyl radical addition on the isocyanide to generate an α-thioimidoyl radical [3]. This radical can then undergo H-abstraction from thiols to form the final thioformimidates product. Despite the convenience of this method, less attention has been directed to this pathway due to the following reasons: a) the requirement of UV-light; b) poor reaction efficiency; c) the formation of unwanted side products such as 1,1-bisthiolation; d) C-S bond scission of the intermediate α-thioimidoyl radical, leading to the generation of isothiocyanates.

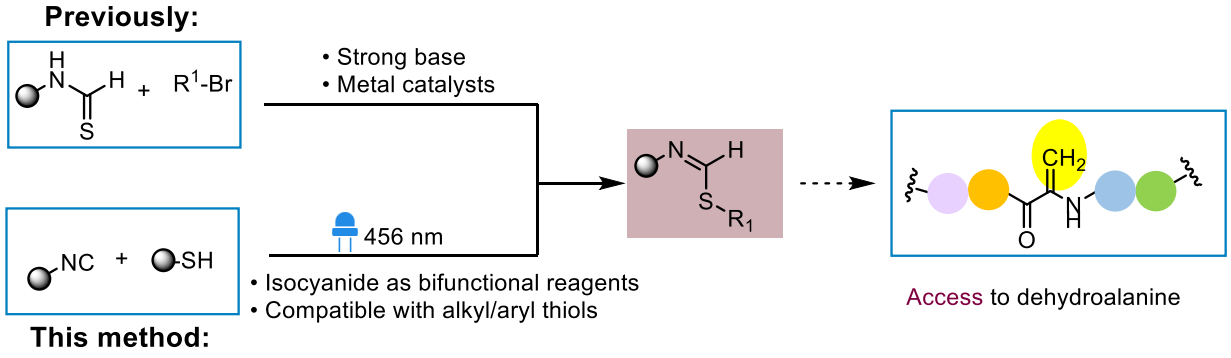


Figure 1. Visible light-mediated synthesis of thioformimidates

Previously, we designed a photocatalyst-free pathway to spirocyclic scaffolds from tryptamine-derived isocyanides by employing blue light [4]. Given the significance of thioformimidates and the current limitations in versatile, sustainable synthetic methods, we focused on developing an innovative, photocatalyst-free, visible-light-driven approach for their synthesis. This study marks a significant advance in the field, as it not only improves existing methods for accessing thioformimidates but also reveals a previously camouflaged role of isocyanides in generation of thiyl radicals.

References

[1] Byerly-Duke, J. and VanVeller, B. *Organic Letters*, **2024**, *26* (7), 1452-1457
[2] Matsubara, Y., nakamura, T., yoshihara, M. and maeshima, T. *Chemical and Pharmaceutical Bulletin*, **1982**, 30 (9), 3389-3391.
[3] Tsuchii, K., Tsuboi Y, Kawaguchi, S., Takahashi, J., Sonoda, N., Nomoto, A. and Ogawa, A. *The Journal of Organic Chemistry*, **2007**, 72 (2), 415-423.
[4] Wu, M. Saya, J.M., Han, P., Walia, R., Pradhan, B., Honing, M., Ranjan, P. and Orru, R.V.A. *Chemical Science*, **2024**, 15, 6867-6873

16

Towards New Chemical Tools to Investigate Carbohydrate Sulfatases

Madouc D. Bergers[a], Charlie Tomlinson[b], Alan Cartmell[b], Zachary W. B. Armstrong[a]

[a]Leiden Institute of Chemistry, Leiden University, 2333 CC Leiden, The Netherlands

[b] Department of Biology, University of York, Heslington, York, YO10 5DD, United Kingdom

Sulfated glycans are found throughout multicellular life, where they play essential roles in cellular integrity, growth, and signaling, and serve as key components of mucins. [1] Mucins are heavily glycosylated proteins that form a protective barrier between host-associated microorganisms and the epithelial surface in the human gut. [2] Alteration or depletion of this barrier is associated with several inflammatory bowel diseases and colonic carcinomas.[3] Recent studies have highlighted the critical role of bacterial carbohydrate sulfatases in mucin degradation.[4] *Bacteroides thetaiotaomicron*, a human gut symbiont, relies on a single sulfatase to metabolize sulfated *O*-glycans in vitro and plays a major role in vivo. Despite the clear importance of carbohydrate sulfatases in the microbial degradation of mucins, chemical tools to study this class of enzymes remain limited. In this work, we present the design and synthesis of chemical tools that enable rapid, sensitive, and facile detection of carbohydrate sulfatases.

References:

[1] Deniaud-Bouët, E., Hardouin, K., Potin, P., Kloareg, B., & Hervé, C. (2017). A review about brown algal cell walls and fucose-containing sulfated polysaccharides: Cell wall context, biomedical properties and key research challenges.

Whitelock, J. M., & Iozzo, R. v. (2005). Heparan sulfate: A complex polymer charged with biological activity. In *Chemical Reviews* (Vol. 105, Issue 7).

Soares Da Costa, D., Reis, R. L., & Pashkuleva, I. (2017). Sulfation of Glycosaminoglycans and Its Implications in Human Health and Disorders. *Annual Review of Biomedical Engineering*, *19*.

[2] Larsson, J. M. H., Karlsson, H., Sjövall, H., & Hansson, G. C. (2009). A complex, but uniform O-glycosylation of the human MUC2 mucin from colonic biopsies analyzed by nanoLC/MSn. *Glycobiology*, 19(7)

[3] Velcich, A., Yang, W. C., Heyer, J., Fragale, A., Nicholas, C., Viani, S., Kucherlapati, R., Lipkin, M., Yang, K., & Augenlicht, L. (2002). Colorectal cancer in mice genetically deficient in the mucin Muc2. *Science*, 295(5560).

Kang, Y., Park, H., Choe, B. H., & Kang, B. (2022). The Role and Function of Mucins and Its Relationship to Inflammatory Bowel Disease. *Frontiers in Medicine* (Vol. 9).

[4] Luis, A. S., Jin, C., Pereira, G. V., Glowacki, R. W. P., Gugel, S. R., Singh, S., Byrne, D. P., Pudlo, N. A., London, J. A., Baslé, A., Reihill, M., Oscarson, S., Eyers, P. A., Czjzek, M., Michel, G., Barbeyron, T., Yates, E. A., Hansson, G. C., Karlsson, N. G., Cartmell, A., Martens, E. C. (2021). A single sulfatase is required to access colonic mucin by a gut bacterium. *Nature*, *598* (7880).

17

Synthesis and Structural Characterization of σ-P/π-arene Ru(0) Complexes

Kathleen Cheasty, Dr. Fedor Miloserdov

Coordination chemistry and homogeneous catalysis rely on the development of effective strategies to stabilizing low-valent transition metal complexes. To this end, herein the synthesis of Ru(0)(P)(L) catalysts are described. Starting from $[Ru(cymene)(Cl_2)]_2$, a typical complex is synthesized by first coordination of the phosphine ligand and subsequent reduction by Zn metal. The high thermal stability and lack of intramolecular C-H activation these complexes is unusual for carbonyl-free phosphine complexes of Ru(0).

These characteristics are the result of the σ-P/π-arene coordination mode of the respective phosphine ligands, which stabilize the complex. It is anticipated that simultaneously as stabilizing the metal center, the σ-P/π-arene ligand also increases its reactivity by its ability to slide from an η^6 coordination mode to an η^4 coordination mode, revealing vacant sites for incoming substrates.

To assess this hypothesis, various Ru(0) complexes were observed by ^{31}P NMR in the presence of various potential substrates, such as styrene, methyl methacrylate, indene and N-ethylpyridin-2-amine, revealing interesting substitution behavior.

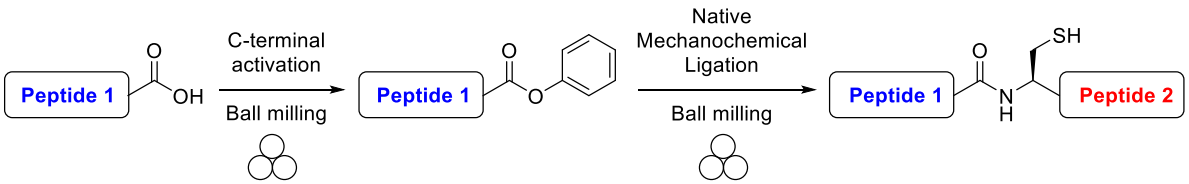
Crystallization efforts of the various Ru(0) complexes are currently ongoing and some experiments for catalytic transformations are being performed.

Reference:

Zhou, Y.; Wensink, N. H.; Pécharman, A.-F.; Miloserdov, F. M. Synthesis and Reactivity of Ruthenium(BINAP)(PPh3). *Angew. Chem. Int. Ed.* **2024**, 63 (14), e202318684.

Native Mechanochemical Ligation

Florian F. ORT,[a], Lukas J.K. Joost,[a] Daniël Blanco Ania,[a] Kevin Neumann,[a] Floris P.J.T. Rutjes[a]
[a] *Synthetic Organic Chemistry, Institute for Molecules and Materials, Radboud University, Nijmegen, The Netherlands*
Florian.ort@ru.nl



Native chemical ligation is the predominant strategy for the chemoselective assembly of large peptides or even proteins, starting from an activated C-terminal fragment and a fragment displaying a N-terminal cysteine. A major challenge in native chemical ligation, and peptide chemistry more broadly, is the limited solubility of peptides, particularly when using hydrophobic fragments. With the emergence of mechanochemistry, an alternative to the conventional solvent based approach has been established. Although mechanochemistry is applicable to a broad range of chemical reactions, mechanochemical native chemical ligation has not yet been reported.

We report the development of native mechanochemical ligation, a peptide ligation methodology using mechanochemistry, that offers a robust approach in which peptide solubility is no longer a limiting factor. Our results show successful chemoselective ligations without any detectable epimerization. In addition, an epimerization-free C-terminal peptide activation[1] was applied using mechanochemistry and embedded into our ligation protocol, further overcoming concerns for epimerization and solubility.

In summary, the application of mechanochemistry for C-terminal activation as well as chemical ligation offers a unique opportunity for overcoming peptide solubility concerns, while expanding the toolbox for modern peptide chemistry.

[1] Popovic, S.; Bieräugel, H.; Detz, R. J.; Kluwer, A. M.; Koole, J. A. A.; Streefkerk, D. E.; Hiemstra, H.; van Maarseveen, J. H., *Chem. Eur. J.* **2013**, *19* (50), 16934-16937.

19

Synthesis of bisenarsan; an organoarsenic metabolite from streptomycetes

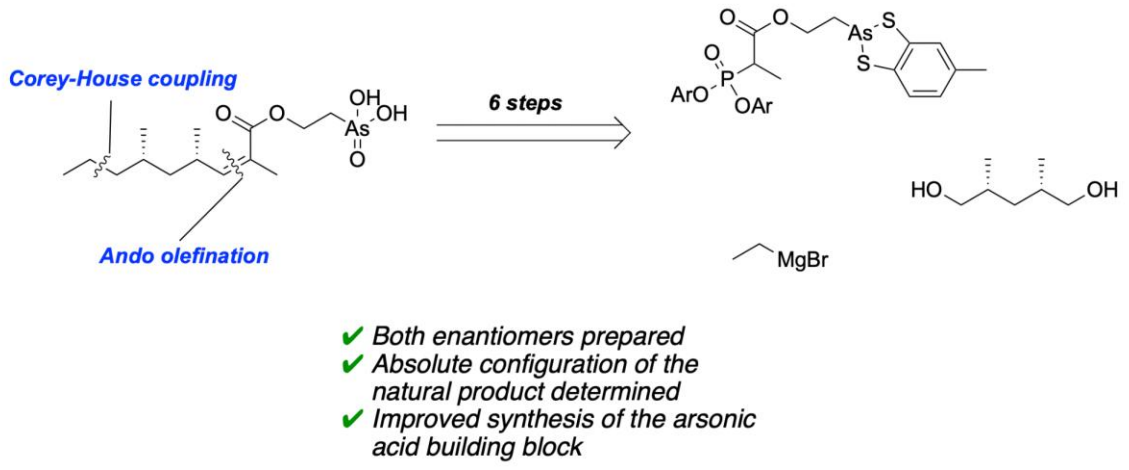
Ihor Kholomieiev, Jeya Prathap Kaniraj, Rafael Tarozo, Adriaan Minnaard

Stratingh Institute for Chemistry, University of Groningen
E-mail: i.kholomieiev@student.rug.nl

As of 2021, over 300 organoarsenic natural products have been identified.[1] Most of these are relatively simple species formed via methylation of inorganic arsenite. However, some of them have more complex structures. For example bisenarsan, the first secondary organoarsenic metabolite isolated from *Streptomyces lividans*, features a (2-hydroxyethyl)arsonic acid subunit, which is unprecedented in nature.[2] The absolute stereochemistry of this natural product was predicted using bioinformatics analysis, but was not confirmed experimentally. The biological role of this compound is also not fully understood.[3]

In this study we synthesized both enantiomers of bisenarsan in 10 and 13 steps (LLS) respectively. The synthesis featured the development of a versatile (2-hydroxyethyl)arsonic acid building block, as well as Corey-House coupling and a highly Z-selective Ando olefination to construct the backbone of the molecule.

By comparing the natural isolate with the synthesized compounds we experimentally determined the absolute stereochemistry of bisenarsan, confirming the prediction made by bioinformatics analysis. We believe that access to synthetic bisenarsan will help further research on the arsenic metabolism of Actinomycetes.



References

[1] **Crit.Rev.Environ.Sci.Technol**. 2021, *52*(21), 3835–3862.

[2] ***Nat. Prod. Rep.***, 2024, Advance Article

[3] **J. Am. Chem. Soc.** 2023, 145, 32, 17863–17871

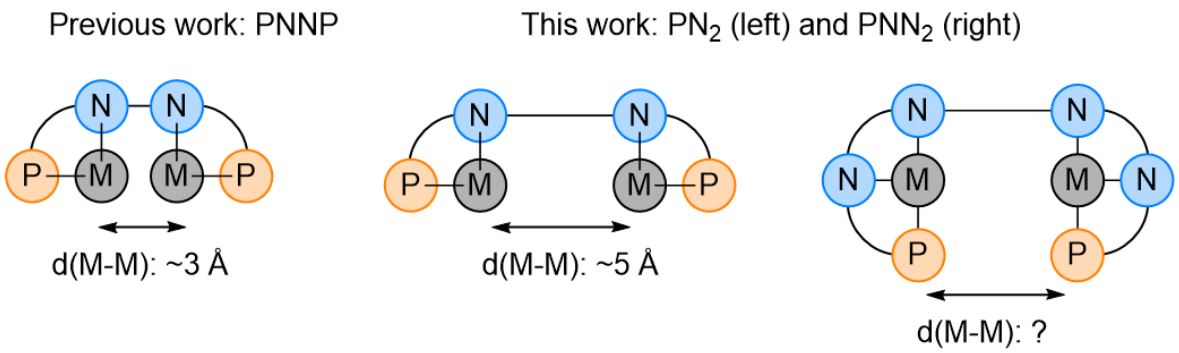
20

Abstract:

Synthesis of Novel Dinucleating Ligands for Long-Range Metal–Metal Interactions Beyond the Bonding Range

In recent years the research in dinuclear metal complexes as homogeneous catalysts has drawn considerable interest. The development of dinucleating ligands has allowed the study of metal-metal interactions and their synergistic effects on catalysis.[1] It is believed that metal-metal cooperativity might play a key role in increasing the catalytic activity and/or selectivity of current homogenous systems. Previous work in our group has focused on the development of naphthyridine-based dinuclear complexes that support short M-M distances (*ca.* 3 Å), allowing for well-defined M-M bonding. Using an 'expanded' pincer ligand with the naphthyridine backbone, dicopper complexes show catalytic dehydrogenation of formic acid.[2] Likewise a similar diruthenium complex allows for the semi-hydrogenation of alkynes,[3] and both catalysts show cooperative metal-ligand and metal-metal cooperation for the catalytic conversion. How changes in the inter-metal distance influence the cooperative effect is underexplored. In this work, we report the synthesis of two novel dinucleating ligands which can facilitate metal-metal distances beyond the M-M bonding range (> 3 Å.). We report the multistep synthesis of a bidentate, dinucleating PN_2 ligand and a tridentate, dinucleating PNN_2 ligand and their coordination chemistry.

Graphical abstract:



References:

[1]: Wang, Q., Brooks, S. H., Liu, T., & Tomson, N. C. (2021). Tuning metal–metal interactions for cooperative small molecule activation. *Chemical Communications*, *57*(23), 2839-2853.

[2]: Bienenmann, R. L., Loyo, A. O., Lutz, M., & Broere, D. L. (2024). Mechanistic Investigation into Copper (I) Hydride Catalyzed Formic Acid Dehydrogenation. *ACS catalysis*, *14*(20), 15599-15608.

[3]: van Beek, C. B., Killian, L., Lutz, M., Weingarth, M., Asundi, A. S., Sarangi, R., ... & Broere, D. L. (2022). E-selective Semi-hydrogenation of Alkynes under Mild Conditions by a Diruthenium Hydride Complex. *Chemistry–A European Journal*, *28*(69), e202202527.

Modular Synthesis of a Library of Lignin Model Compounds

Eman Abdelraheem[a], Tom Ewing[b], Gijs van Erven[b,c,*], Fedor M. Miloserdov[a,*]
[a] *Laboratory of Organic Chemistry, Wageningen University & Research, Wageningen, The Netherlands*
[b] *Wageningen Food & Biobased Research, Wageningen University, Wageningen, The Netherlands*
[c] *Laboratory of Food Chemistry, Wageningen University, Wageningen, The Netherlands*
Eman.Abdelraheem@wur.nl; Fedor.Miloserdov@wur.nl

Lignin is the most abundant natural aromatic resource with huge potential for application in the chemical, pharmaceutical, and materials industries.[1] Despite this potential, lignin is currently heavily underutilized and often burned for energy recovery instead, mainly as a result of its notoriously complex structure.[2] The research in the lignin field is hampered by the lack of structurally representative lignin model compounds (LMCs) that well reflect the different methoxylated aromatic subunits (H, G, S) and various ether and carbon-carbon interunit linkage motifs.

Currently available synthetic routes to such LMCs are labor-intensive and target single molecules. We would argue that a single LMC, no matter how advanced it is, cannot sufficiently represent inherently biodiverse lignin with structures heavily variable depending on its source.

In our work we achieved a modular synthesis of a ***library*** of LMCs consisting of -H-, -G- and -S- subunits linked with β-O-4 and β-5 linkages containing up to five aromatic rings. This was accomplished by using common and readily available TIPS-protected phenolic bromoketoesters as common building blocks (Figure 1). Our modular synthesis enables the effective construction of a library of lignin model compounds, structurally resembling the complexity of native lignin. We are confident that our advanced library of LMCs will ultimately allow to study lignin chemistry in unprecedented detail and are ready to showcase their use in practice.

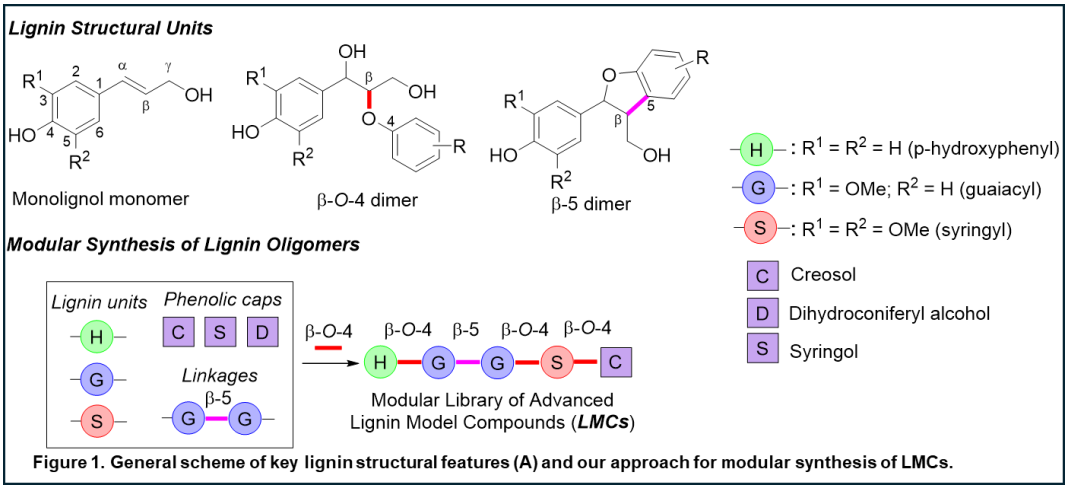


Figure 1. General scheme of key lignin structural features (A) and our approach for modular synthesis of LMCs.

References

(1) C. W. Lahive, P. C. J. Kamer, C. S. Lancefield, P. J. Deuss, *ChemSusChem* **2020**, 13 (17), 4238-4265. DOI: https://doi.org/10.1002/cssc.202000989.

(2) R. Rinaldi, et al. *Angewandte Chemie International Edition* **2016**, *55* (29), 8164-8215. DOI: https://doi.org/10.1002/anie.201510351.

22

Synthesis of pyrrolizidine alkaloid esters for the food safety assessment of lamb's lettuce

Dieuwertje Streefkerk, Leonie Straub, Patrick Mulder, Han Zuilhof, Laura Righetti
Wageningen University and Research

Pyrrolizidine alkaloids (PA) are plant toxins, which are dangerous to human health. PA content in foodstuffs is heavily regulated, using analytical standards to assess the concentration of these dangerous compounds in our food. However, there is an enormous structural diversity of PA's, while only 35 PA's are regulated - mostly because the analytical standards are not available. This leaves a massive knowledge gap in the assessment of food safety.

For lamb's lettuce, we investigated the prevalence of certain retronecine esters and their N-oxides. For some compounds, while differing in HPLC retention time, their high-resolution mass spectra were the same, suggesting sets of isomers. Therefore, by targeted synthesis of the angelic, tiglic and isovaleric esters of retronecine we were able to match the structure with the HPLC peaks and mass spectra. Out of the 12 synthesized compounds, 7 were present in lamb's lettuce. With these compounds in hand, we can now assess prevalence in other foodstuffs and investigate the toxicity of the synthesized retronecine esters.

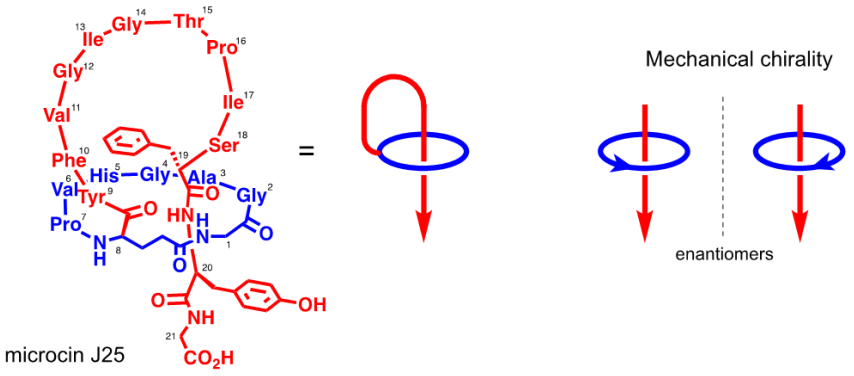
23

DESIGN AND COVALENT SYNTHESIS OF MECHANICAL CHIRAL MOLECULES

Junqiang Liu[1], and Jan H. van Maarseveen[1]

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

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.



References

[1] Luuk Steemers, *Org. Lett*. **2017**,17, 2342-2345

[2] Marvin J. Bayro, *J. Am. Chem. Soc. 2003, 125, 12382-12383*

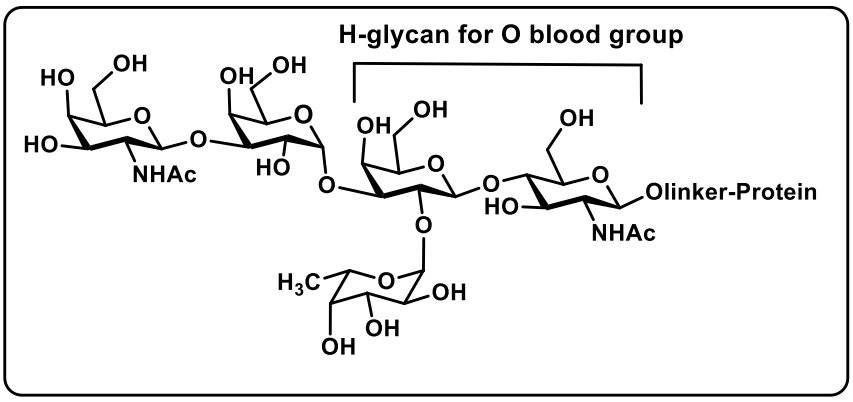
24

Synthesis of the extended B red blood cell glycan

Jochem D.Waard, Mariska Hugen, Samarpita Mahapatra and Marthe Walvoort

University of Groningen, The Netherlands

The ABO blood group antigens represent one of the most significant glycan systems in transfusion medicine. The ABO blood groups are defined by the presence or absence of specific glycans in glycolipids and N-glycoproteins at the RBC surface. A antigens exist not only in their basic form but also has extended structures with additional carbohydrate residues. Similarly, the B antigen has an extended variant (ExtB). Type O blood group, lacks both A and B antigens and thus can theoretically be transfused to recipients of any blood type which makes O-type blood the universal donor. In the present scenario there is shortage of type O blood and this has motivated the search for alternative strategies to ensure blood supply. In recent years significant research has led identification of powerful AB-converting enzymes produced by the human gut bacterium Akkermansia muciniphila where they found key exoglycosidases to cleave AB RBC glycans. The present work is upon the synthesis of glycan part of the extended B red blood cell, further to be used for study of the enzymatic cleavage of the glycan for its conversion to type O blood group glycan and generate monoclonal antibodies against extended B antigens. We plan to synthesize pentasaccharide form of the glycan and attach to a linker that can be further conjugated to a carrier protein. The final product can be used directly for desired biological studies.



References:

1) Storry, J. R.; Olsson, M. L. The ABO Blood Group System Revisited: A Review and Update. *Immunohematology* **2009**, 25 (2), 48–59. https://doi.org/10.21307/immunohematology-2019-231.

2) Jensen, M.; Stenfelt, L.; Ricci Hagman, J.; Pichler, M. J.; Weikum, J.; Nielsen, T. S.; Hult, A.; Morth, J. P.; Olsson, M. L.; Abou Hachem, M. Akkermansia Muciniphila Exoglycosidases Target Extended Blood Group Antigens to Generate ABO-Universal Blood. *Nat Microbiol* **2024**, 9 (5), 1176–1188. https://doi.org/10.1038/s41564-024-01663-4.

Automated Synthesis of Phosphoramidite Ligand Libraries for Asymmetric Catalysis

Lisa Fang, Prof B.L. Feringa

Stratingh Institute for Chemistry, University of Groningen, The Netherlands

Owing to their finely tunable steric and electronic properties, phosphoramidites are highly modular ligands that play a central role in asymmetric catalysis, enabling precise control over enantioselectivity across a broad range of metal-catalyzed transformations.[1] They are straightforward to synthesize and sufficiently stable for handling and storage, making them well-suited for systematic ligand development. However, identifying the optimal ligand for a given reaction remains a time-consuming and empirical process. Recent advances in High-Throughput Experimentation (HTE) have demonstrated its effectiveness in accelerating catalyst discovery and reaction optimization.[2] While HTE has been adopted in industrial research for several decades[3], its implementation within academic laboratories is far from democratized.[4]

In this project, we are developing an automated platform for the parallel synthesis of phosphoramidite ligands. A robust and scalable synthetic procedure has been established and optimized manually, and is being translated to robotic synthesis. The resulting automated workflow enables the rapid generation of structurally diverse ligand libraries with significantly reduced hands-on time and improved reproducibility.

By streamlining phosphoramidite synthesis and facilitating ligand evaluation, this platform aims to accelerate the discovery of high-performance ligands for asymmetric catalysis. More broadly, the combination of modular ligand design and automation opens new opportunities for data-rich catalyst development and lays the groundwork for future closed-loop optimization strategies integrating artificial intelligence and machine learning.

---

[1] Ben L. Feringa, *Accounts of Chemical Research* 33, no. 6 (2000): 346–53; Johannes F. Teichert and Ben L. Feringa, *Angewandte Chemie International Edition* 49, no. 14 (2010): 2486–528.

[2] Eric S. Isbrandt et al., *Angewandte Chemie International Edition* 58, no. 22 (2019): 7180–91; C. Liana Allen et al., *Nature Catalysis* 2, no. 1 (2019): 2–4.

[3] Steven M. Mennen et al., *Organic Process Research & Development* 23, no. 6 (2019): 1213–42; James J. Douglas et al., *ACS Catalysis* 15, no. 7 (2025): 5229–56.

[4] Xisco Caldentey and Eugénie Romero, *Chemistry–Methods* 3, no. 5 (2023): e202200059; Michael Shevlin, *ACS Medicinal Chemistry Letters* 8, no. 6 (2017): 601–7.

Towards Double-Spirocyclic α-Helix Mimetics

Emma K. Schuler*, Florian M. Zielke, Mats Brouwer, Dejeandro Tromp, Dennis W.P.M. Löwik, Daniël Blanco Ania, Floris P.J.T. Rutjes

Radboud University, Institute for Molecules and Materials

*emma.schuler@ru.nl

Protein-protein interactions (PPIs) regulate many essential biological processes, yet they remain an underexplored target class in small-molecule drug discovery due to their typically large, shallow, and dynamic interfaces. In particular, α-helical motifs frequently mediate PPIs, motivating the development of compact, non-peptidic α-helix mimetics capable of reproducing key side-chain vectors while maintaining drug-like properties.[1,2] Within the ASPPIRe project, we explore double-spirocyclic scaffolds as a new class of structurally constrained α-helix mimetics (*Figure 1*).[3] Computational modelling was used to guide the selection of double-spirocyclic frameworks and to assess the influence of linker size and heterocycle composition on three-dimensional shape. To access the targeted scaffolds, several complementary synthetic strategies were explored, including a rearrangement-cyclization cascade, ring-closing metathesis and 2,3-dipolar cycloaddition. These approaches enable the modular construction of rigid, three-dimensional scaffolds equipped with orthogonal functionalization handles. Notably, linker size was found to influence reactivity, motivating the investigation of alternative synthetic routes for specific scaffold classes. Ongoing work focuses on scaffold diversification and library synthesis to enable future SAR studies and screening against biologically relevant PPIs.

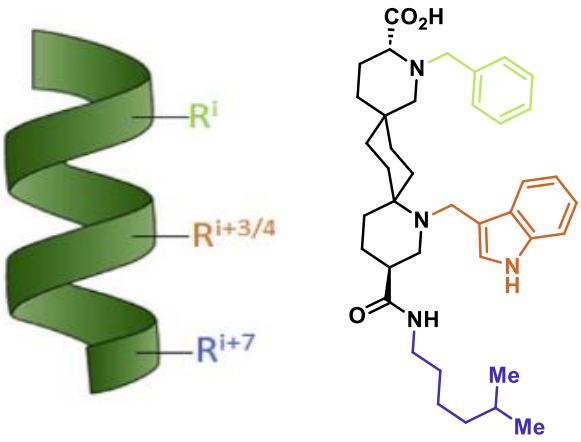


Figure 1. Schematic of an α-helix compared to a substituted double-spiro compound.

1. Arkin, M. R.; Wells J. A. Small-Molecule Inhibitors of Protein-Protein interactions: Progressing towards the Dream. *Nat. Rev. Drug Discov.* **2004**, *3*(4), 301-317.
2. Basse, M. J.; Betzi, S.; Morelli, X.; Roche, P. Toward the Design of Protein-Protein Interaction Inhibitors by Targeting Plastic Hot Spots. *Biochim. Biophys. Acta* **2013**, *1834*(4), 818-829.
3. Hiesinger, K.; Dar'in, D.; Proschak, E.; Krasavin, M. Spirocyclic Scaffolds in Medicinal Chemistry: Recent Progress and Future Directions. *J. Med. Chem*. **2020**, *63*, 10807-10835.

27

Poster DSOC 2026

Maartje Peters, PhD candidate, Wageningen University & Research

Abstract:

Current antibody-based cancer therapies are frequently limited by on-target, off-tumor binding, leading to poor tumor accumulation of the antibody therapies and resulting in a narrow therapeutic window. To improve tumor selectivity, masked antibodies have been developed that remain functionally inactive during circulation and are selectively activated by tumor-associated stimuli. To date, masked antibodies have predominantly been developed through biological engineering strategies. Here, we present a chemistry-based, post-translational masking approach that offers enhanced modularity, precise site control, and greater design flexibility when compared to existing biological methods. Affinity-based masking constructs were already successfully conjugated to antibodies using our established strain-promoted oxidation-controlled ortho-quinone (SPOCQ) click chemistry, and showed promising masking efficiencies. By leveraging chemical conjugation, this strategy enables access to masking designs beyond the constraints of biological encoding and provides a versatile platform to enhance the therapeutic index of antibody-based cancer therapies.

28

Poster Abstract

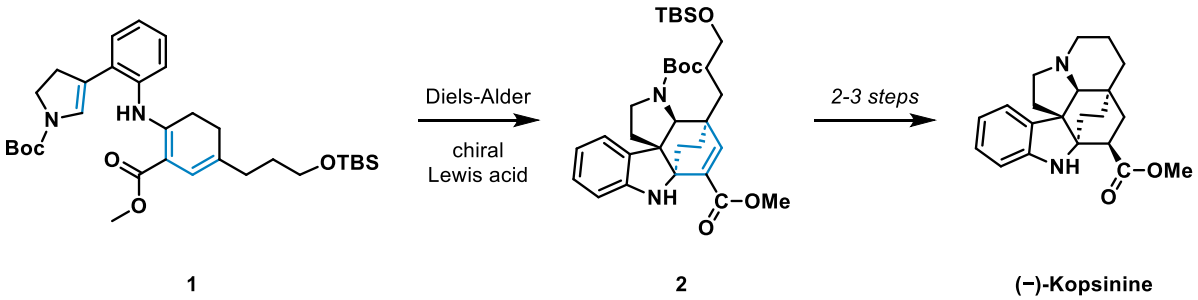
Regio- and Stereoselective Intramolecular Diels Alder

Towards the Total Synthesis of (−)-Kopsinine

Theodora Athanasiadou, Melissa He, Eelco Ruijter*

Department of Chemistry & Pharmaceutical Sciences, Amsterdam Institute for Molecular and Life Sciences, Vrije Universiteit Amsterdam

t.athanasiadou@vu.nl



1 **2** **(−)-Kopsinine**

Monoterpenes indole alkaloids (MIAs) are a large family of natural products isolated from a range of plants, such as *Kopsia*, *Aspidosperma* and *Strychos*. This family of natural products is known for complex structures with fused ring systems, that include the characteristic indole structure, and multiple vicinal quaternary centers. Their biological activity seems to vary from one natural product to another providing a range of applications. (−)-Kopsinine was first isolated from *K. longiflora* by Michael in 1955 and has demonstrated antitussive properties [1]. Its first enantioselective total synthesis was published already in 1985 and, since then, different approaches towards this natural product or similar structural systems have been explored [2]. Some approaches are implementing a radical approach in the later steps or a more biosynthetic approach such as the use of Pictet-Spengler reaction, or even a cascade reaction like Truce-Smiles cascade that was previously developed from our group [3].

Continuing our work in total synthesis of natural products, we envisioned a regio- and stereoselective Intramolecular Diels Alder of substrate **1** towards the synthesis of (−)-Kopsinine. Intramolecular Diels-Alder is a useful synthetic approach commonly found in the total synthesis due to the fact that, when applied to the correct substrate, it can produce high regio- and enantioselective results.

(1) W. Crow, M. Michael, *Aust. J. Chem.* **1955**, *8*, 129-135

(2) P. Magnus, P. Brown, *J. Chem. Soc. Chem. Commun.* **1985**,184-186. https://doi.org/10.1039/C39850000184

(3) B. Horst, D. S. Verdoorn, S. Hennig, G. van der Heijden, E. Ruijter, *Angew. Chem. Int. Ed.* **2022**, *61*, e202210592. https://doi.org/10.1002/anie.202210592

29

Name: Xingchen Ye

Supervisors: Maarten Smulders, Han Zuilhof

Contact: xingchen.ye@wur.nl

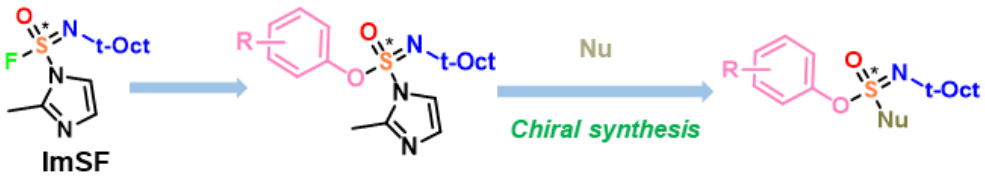
Click chemistry, introduced by Sharpless in 2001, provides a powerful toolbox of high-yielding, modular, and selective reactions for efficient molecular assembly. Among them, SuFEx (Sulfur Fluoride Exchange), developed in 2014, stands out for its ability to form robust sulfur(VI) linkages under mild, metal-free conditions. With excellent functional group tolerance and product stability, SuFEx has found applications in materials science, drug discovery, and beyond.

Building on this foundation, our group recently introduced ImSF, a stable, solid, and user-friendly SOF_4 analog. Importantly, ImSF features a stereogenic sulfur(VI) center, opening new opportunities to access chiral sulfur compounds—a largely underexplored area with significant potential in asymmetric synthesis, molecular recognition, and responsive materials.

This project aims to develop a synthetic platform for enantioenriched sulfurimidates and sulfuramidimidates using ImSF as a chiral sulfur precursor. Key goals include achieving high enantioselectivity, maintaining configurational stability, and exploring solvent-free mechanochemical methods to promote greener synthesis.

In parallel, we will investigate the SuFEx-based polymerization of sulfur(VI) building blocks to construct dynamic covalent networks (DCNs) with advanced properties such as self-healing, recyclability, and stimuli-responsiveness. A variety of analytical techniques (NMR, rheology, DSC, TGA) will be used to assess the structure-property relationships of these dynamic materials.

Ultimately, this work combines the precision of modern click chemistry with sustainable design principles to push the boundaries of functional chiral materials and smart polymeric systems.

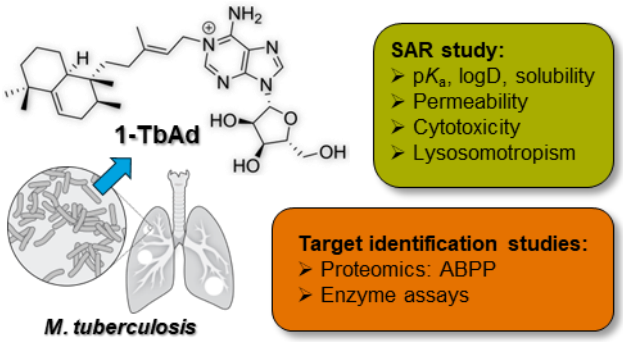


SAR and Target Identification Studies on 1-TbAd - a Nucleosidic Virulence Factor of *Mycobacterium tuberculosis*

Paul Wienecke,[1,*] Anna-Lisa E. Lawrence,[2] Miyer F. Patiño-Ruiz,[3] Sarah L. Stellnberger,[4] Naschla Gasaly,[5] Marek Freindorf,[6] Susan Render,[1] Orestis Stavrinou,[1] Jeffrey Buter,[1] D. Branch Moody,[7] Elfi Kraka,[6] Paul de Vos,[5] Verena Pichler,[4] Bert Poolman,[3] Shumin Tan,[2] Madeline Kavanagh,[8] Adriaan J. Minnaard[1,*]

[1]University of Groningen, Stratingh Institute for Chemistry, Nijenborgh 7, 9747 AG Groningen/Netherlands
[2]Tufts University School of Medicine, Molecular Biology and Microbiology, 150 Harrison Ave, 02111 Boston/USA
[3]University of Groningen, Groningen Biomolecular Sciences and Biotechnology Institute, Nijenborgh 3, 9747 AG Groningen/Netherlands
[4]University of Vienna, Department for Pharmaceutical Chemistry, Althanstraße 14, 1090 Vienna/Austria
[5]University Medical Center Groningen, Department of Pathology and Medical Biology, Hanzeplein 1, 9713 GZ Groningen/Netherlands
[6]Department of Chemistry, Southern Methodist University, 3215 Daniel Avenue, Dallas, TX 75275-0314, USA
[7]Harvard Medical School, Division of Rheumatology, Inflammation and Immunity, Brigham and Women's Hospital, 75 Francis St, 02115 Boston/USA
[8]Leiden University, Leiden Institute of Chemistry (LIC), Einsteinweg 55, 2333 CC Leiden/Netherlands

*e-mail: a.j.minnaard@rug.nl, p.wienecke@rug.nl



1-TbAd is a highly abundant terpene nucleoside from *Mycobacterium tuberculosis*. Because of its chemical properties, it accumulates in the host's macrophages' phagosomes and raises the pH of these usually acidic cell compartments ("lysosomotropism"). Thereby, 1-TbAd inhibits degradative mechanisms and improves nutrient access, facilitating survival of *Mtb* in immune cells. In this study, we aim to better understand how structural elements of 1-TbAd influence its physicochemical properties and how they drive the blocking of phagosomal acidification. A SAR study around 1-TbAd deepens the knowledge on the tuning of lysosomotropism, a feature that can be either desired or undesired in the design of bioactive compounds. Not only 1-TbAd is evaluated as a lead structure, but also these N-1 alkylated adenosine derivatives in general are investigated, a widely neglected compound class. Furthermore, proteomics studies and enzyme assays were conducted to reveal protein targets and explore bioactivities beyond lysosomotropism.