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Centre for Synthesis
& Chemical Biology

Recent Advances in Synthesis & Chemical Biology XXII

Symposium
8th December 2023

UCD Village
University College Dublin
Belfield
Dublin
D04 C1P1

"Recent Advances in Synthesis and Chemical Biology XXII"

Friday, 8th December 2023

UCD Village

9.00 am -9.15 am	Opening remarks – **Professor Helen Roche (UCD Vice-President for Research, Impact & Innovation)**
9.15 am - 10.15 am	**Chair: Assistant Professor Eoghan McGarrigle (UCD) – The Thermo Fisher Scientific Lecture** **Professor Jonathan Clayden (University of Bristol, UK)** *"Exploiting Conformational Dynamics: Defluorination, Deracemisation, and Directionality"*
10.15 am - 10.45 am	Coffee/Tea Break + Poster Session (Odd Numbers)
10.45 am - 11.45 am	**Chair: Professor Celine Marmion (RCSI, University of Medicine and Health Sciences) – The Synthesis and Solid State Pharmaceutical Centre (SSPC) Lecture** **Professor Clotilde Policar (Ecole Normale Supérieure-PSL, France)** *"Metal Complexes in Biological Environments: a New Frontier in Inorganic Chemistry — Focus on the Development of Catalytic Antioxidants with Therapeutic Interest"*
11.45am – 1 pm	**Chairs: Assistant Professor Marina Rubini (UCD) and Professor Aidan McDonald (TCD)** **Dáiríne Morgan (UCD**) - *Enantioselective Copper-Catalyzed Alkynylation of Quinolones Using Chiral P,N Ligands;* **Seán McKenna (TCD)** - *Lights, Capture, Extraction! A Photoaffinity Probe for Profiling the Metalloproteome in Live Cells*; **Eilidh Matheson (QUB)** - *Synthesis of Isoprenoid Probes to Explore Coenzyme Q10 and Menaquinone Protein Binding Interactions and for Drug Discovery*; **Dr Bhargava Reddy (UCD)** - *Visible-Light-Induced Difunctionalisation of Alkynes with Arylsulfinates* ; **Dr Bríonna McGorman (DCU)** – *Click Chemistry Based Gene-Targeted Therapeutics*; **Dr Dan Wu (RCSI)** - *Forecasting Vaping Health Risks through Neural Network Model Prediction of Flavour Pyrolysis Reactions*; **Ella Cooper (UCC)** - *The Alkylation of Ketones in Flow*; **Dr Jorge García Lacuna (UCD)** - *Photoexciting Nitroarenes in Flow: From Benzyne Precursors to Nitrosoarenes*.
1 pm - 2 pm	Lunch Break + Poster Session (Odd then Even Numbers)
2 pm - 3 pm	**Chair: Professor Eoin Scanlan (TCD) – The BiOrbic Research Centre Lecture** **Professor Stefan Oscarson (University College Dublin)** *"Towards New Carbohydrate-based Mucolytics, Antibiotics, and Vaccines"*
3 pm – 3.30 pm	Coffee/Tea Break + Poster Session (Even Numbers)
3.30 pm – 4.30 pm	**Chair: Associate Professor Marcus Baumann (UCD) – The Pfizer Lecture** **Professor Edward Anderson (University of Oxford, UK)** *"Taming the Reactivity of Small Ring Hydrocarbons"*
4.30 – 5.30 pm	**Chair: Professor Pat Guiry (UCD)– The Eli Lilly Lecture** **Professor Dale Boger (Scripps Institute, USA)** *"Maxamycins: Redesigned Vancomycins for Resistant Bacteria"*
5.30 pm	Closing Remarks: **Professor Pat Guiry, Director, Centre for Synthesis and Chemical Biology**

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Recent Advances in Synthesis and Chemical Biology XXII
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The Centre for Synthesis and Chemical Biology wishes to thank the following sponsors for supporting this symposium:

Invited Speakers:

Profiles

Professor Jonathan Clayden, University of Bristol, UK

Jonathan Clayden is currently a Full Professor of Chemsitry within the University of Bristol.

He gained his BA in Natural Sciences at Churchill College within the University of Cambridge in 1989. Subsequently, he completed his PhD at the same university under Dr Stuart Warren in 1992. He then moved to the École Normale Supérieure as a Royal Society Western European Research Fellow with Prof Marc Julia.

He returned to the UK as a Lecturer in organic chemistry at the University of Manchester in 2000, before becoming a Full Professor of Chemistry in 2001. He moved from Manchester to the University of Bristol where he is currently.

His and his group's research interests have centred on probing areas related to molecular conformation including asymmetric synthesis, atropisomerism, supramolecular chemistry and organolithium chemistry.

Jonathan has been the recipient of various awards including but not limited to: Merck Award of the Royal Society of Chemistry, Tilden Prize of the Royal Society of Chemistry and he became an Elected Member of the Academia Europaea.

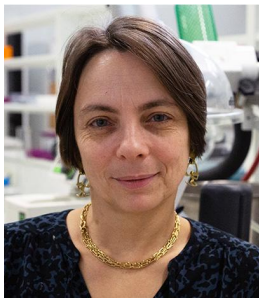
Professor Clotilde Policar (École Normale Supérieure-Paris Sciences et Lettres, France)

Clotilde Policar is a Full Professor of Bioinorganic Chemistry at École Normale Supérieure-Paris Sciences et Lettres.

She was trained in chemistry at École Normale Supérieure Cachan and University of Paris-Sud 11. She obtained her PhD at the same institution under Dr Daniel Mansuy and Dr Isabelle Artaud in bioinorganic chemistry. After completing a Postdoctoral Fellowship with both Dr Sun Un and Dr William Rutherford, she was appointed as an Assistant Professor at what is now École Normale Supérieure-Paris Sciences et Lettres. She became a Full Professor at the same institution in 2008 where she set up a bioinorganic themed group.

Her and her group's research focuses on the study of inorganic compounds in a biological environment and what effects they elicit on biological systems. This has led to the groups continued research into manganese-based anti-oxidants and their development of metal-organic bioprobes (efficiently used as an IR-probe for bioimaging).

Coupled with her impressive research Clotilde has been Dean of the Science Education at École Normale Supérieure since 2020 and has President of the Society of Biological Inorganic Chemistry since 2021.



Professor Stefan Oscarson (University College Dublin, Ireland)

Stefan Oscarson is a Full Professor of Chemical Biology at University College Dublin.

He graduated from Stockholm University with a BSc (Hons) in Chemistry in 1978 and with a PhD from the same university in 1985. He spent a year as a researcher in the Swedish Tobacco Company before joining the Chemistry Department at Stockholm University as an Assistant Professor in 1986. He subsequently became an Associate Professor (1993) and a Full Professor (2000) at the same institution. He spent two years at Göteborg Univeristy before moving to University College Dublin in 2006 where he currently a Full Professor of Chemical Biology.

He and his group's work has primarily been in the area of carbohydrate chemistry and the synthesis of biologically active compounds. In particular focusing on oligosaccharides and glycoconjugates, for use in biological studies. Currently, their work focuses the development of saccharide-based vaccines against microorganisms.

Amongst his notable awards across his career in 2022 Stefan was elected to the Royal Irish Academy and in 2023 he was awarded the NovaUCD Innovation Award for his longstanding collaboration with Professor Stephen Carrington.

Professor Ed Anderson (University of Oxford, UK)

Ed Anderson is a Full Professor and Head of Organic Chemistry at the University of Oxford.

He received his BA at Oxford in 1997 before moving to Cambridge to complete his PhD under Professor Andrew Holmes FRS (graduating 2001). He then moved to Scripps Research Institute in La Jolla, California to undertake a Postdoctoral Fellowship with Professor Erik J. Sorensen (Lindemann Trust). In 2003, he undertook a Junior Research Fellowship at Cambridge with Professor Ian Paterson FRS until 2007. He was then appointed an EPSRC Advanced Research Fellow in Oxford and took up a Lectureship at the University of Oxford before being promoted to Full Professor in 2016. He became Head of Organic Chemistry in 2021.

He and his research group focus on the synthesis of natural products, the treatment of neglected diseases and the development of new synthetic methods, including small ring systems. Accompanying this, the group engages in various interesting collaborations.

Among his list of notable awards includes the 2018/19 Novartis Chemistry Lectureship and the 2020 RSC Bader Award.

Professor Dale L. Boger (Scripps Research Institute, USA)

Dale Bolger is the Richard and Alice Cramer Professor of Organic Chemistry in the Department of Chemistry and the Skaggs Institute for Chemical Biology.

He began his studies by completing a BSc at the University of Kansas in 1975 before completing a PhD with E. J. Corey in 1980. He subsequently returned to the University of Kansas as an Assistant Professor of Medicinal Chemistry until 1985 when he moved to Purdue University, as an Associate Professor of Chemistry. He accepted a Full Professorship in Scripps Research Institute in 1991, a position he still holds today. Between the years of 2012-2018 he acted as Head of the Department of Chemistry at Scripps.

He and his group are renowned for their work in organic synthesis, total synthesis, heterocyclic chemistry, biological mechanistic studies, methodology and medicinal chemistry. They made seminal contributions to the understanding of DNA-agent interactions of naturally occurring antitumor-antibiotics, protein-protein interactions, and discovered new biological targets for various conditions.

As well as being an excellent researcher, Dave has also received various awards, lectureships, fellowships and is a member of various societies and committees. Some recent examples include: ISHC E.C. Taylor Award in Heterocyclic Chemistry (2019), Tetrahedron Prize (2020) and the NIH Merit Award (2018-2026) to name but a few.

Poster Numbers and Titles

P1. BIOINSPIRED CATALYTIC OXIDATIVE C(*SP3*)-H FLUORINATION THROUGH REACTIVE HIGH VALENT COBALT-FLUORIDE INTERMEDIATE

Agnideep Das[a] and Aidan R. McDonald*[a]

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An ongoing interest in oxidizing a wide range of hydrocarbons into functionalized raw materials has attracted researchers' attention of finding highly reactive oxidant. Presently, fluorinated and/or chlorinated hydrocarbons have very broad applications in chemical, pharmaceutical and material industries.[1–3] Currently, fluorination of hydrocarbons requires harsh reaction condition (high temperature and pressure, use of super acids, cracking etc.) or limitation in using of fluorine gas, HF, XeF_2 and hypofluorites. These conditions are often non-selective and generate undesirable chemical waste with energy, financial and environmental cost.[4] However, biological non-heme halogenase enzyme perform oxidative chlorination of hydrocarbons through an iron metal center, which is cheap and naturally abundant. This halogenation reaction proceeds via an iron(IV) reactive intermediate, which acts as the oxidant. Bioinspiration has led many research groups to synthesize earth abundant high valent metal oxidant, but cobalt centric oxidative fluorination is not well investigated so far.[5–7]

Our previous reports evidenced of high valent nickel(III) and iron(IV) fluorides are the reactive oxidant for fluorinating hydrocarbons.[8,9] Both Ni(III) and Fe(IV)-fluorides are capable of rapid fluorination but effective only to weak C-H bonds. Here we investigated a cobalt (II) complex with a tetradentate polyamine ligand scaffold (N,N′-dimethyl-N,N′-bis(2-pyridylmethyl)ethane-1,2-diamine) [BPMEN] that can fluorinate stronger C(*sp3*)-H bonds [BDE_{C-H}> 80 kcal/mol] efficiently reacting with selectcfluor™, an electrophilic fluoride source. Further investigation shows the fluorination reaction is catalytic achieving multiple TON of the product formation. Our current investigation reveals that Co-BPMEN complex follows bioinspired non-heme halogenase enzyme type mechanism with HAT by reactive high valent cobalt to generate alkyl radical followed by XAT.

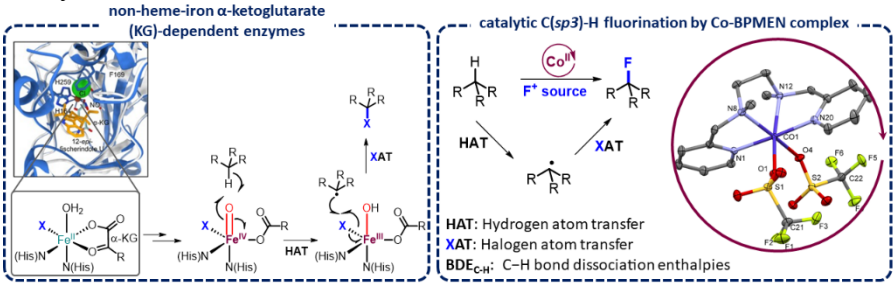

Figure 1: Catalytic radical halogenation mechanism in non-heme-iron α-ketoglutarate (KG)-dependent enzymes (left); bioinspired catalytic fluorination by **Co-BPMEN** complex (right).

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For what's next

P2. DEVELOPMENT OF CONVERGENT BIOCATALYTIC TRANSFORMATIONS FOR THE SYNTHESIS OF COMPLEX ALKALOIDS

Amber Barry and Elaine O'Reilly*
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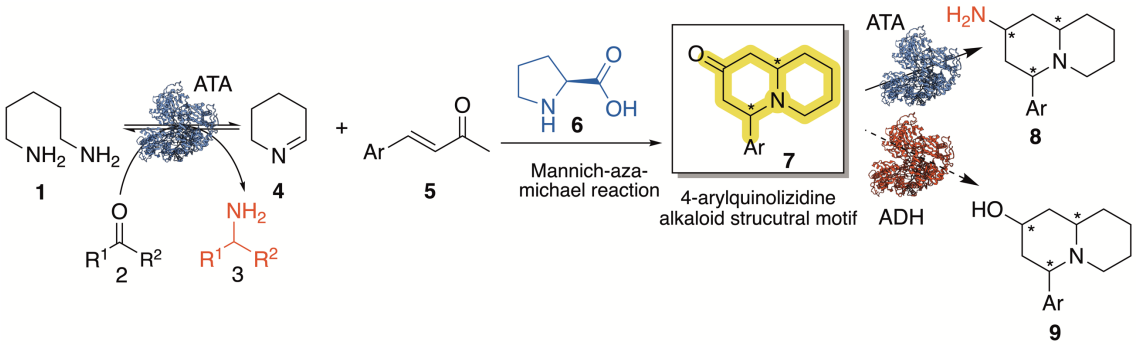
Biocatalysis involves the use of catalytic proteins (enzymes) to perform chemical transformations of simple, cheap, achiral materials into high value, chiral products. Nature uses enzymes, often in cascade approaches, to synthesise important building blocks and to assemble complex natural products. The selectivity of enzymes, their tuneability and compatibility with aqueous solvents, have led to their use in the pharmaceutical and fine chemical industry, offering a more attractive alternative to traditional catalysts and as an important synthetic tool in target retrosynthesis.[1, 2]

Synthetic methodologies accessing natural product *N*-heterocycles structural motifs and their derivatives is of interest to chemists due to their important therapeutic properties.[3] The design of a hybrid bio-organocatalytic cascade was envisaged to enable assembly of complex quinolizidine alkaloid structural scaffolds (**Fig. 1**). The biomimetic cascade approach is initiated by a transaminase catalysed transformation of cadaverine **1** into the reactive imine, Δ^1-piperideine **4**,[4] which can subsequently undergo an L-proline **6** facilitated Mannich-*aza*-Mannich reaction, with an aryl enone **5**, forming the 4-arylquinolizidine-2-one scaffold **7**,[5] a key structural intermediate

in the cascade. The alkaloid **7** has the potential to be further derivatised using additional enzymes, such as transaminases (ATA) or alcohol dehydrogenases (ADH) to generate the amine **8** or alcohol **9** products respectively, providing a chemical handle to further react.



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P3. RADICAL ACTIVATION OF PROBES IN THE THIOL-ENE LABELING OF DEUBIQUITINATING ENZYMES

André Campaniço[1], Daniel B. Longley[2], Timothy Harrison[2], Joanna F. McGouran[1]
[1] *School of Chemistry, Trinity College Dublin, Trinity Biomedical Sciences Institute, 152-160 Pearse St., Dublin 2, Ireland.* [2]*The Patrick G. Johnston Centre for Cancer Research, Queen's University Belfast, Belfast, UK*
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Activity-based probes (ABPs) play an important role in targeting and studying enzymatic activity. More recently, the development of 'inducible' ABPs whose activation can be controlled by exogenous agents has become increasingly relevant, recurring to UV or chemical agents to trigger enzyme labelling.[1] A ubiquitin-based probe with an inert allyl warhead was developed to target deubiquitinating enzymes (DUBs), using radical chemistry to catalyse its activation and binding to the active-site cysteine.[2] 2,2-dimethoxy-2-phenylacetophenone (DPAP) was initially used as the radical initiator, requiring the use of UV and a limiting degassing step.
We now report different ways of activating this bio-orthogonal thiol-ene coupling, with new and innovative initiators, recurring to UV, visible light or chemical activation (Figure 1). Irgacure 2959, 9-mesityl-10-methylacridinium perchlorate (Mes-Acr$^+$) and manganese (III) acetate ($Mn(OAc)_3$) were used to initiate the coupling, generating more effective and milder activating conditions. This is the first time these initiators are used to catalyse thiol-ene couplings in protein-protein interactions and the first report of Mes-Acr$^+$ and $Mn(OAc)_3$ being used in the thiol-ene reaction. Furthermore, we also report the first modifications to the alkene warhead and its preliminary impacts on probe activity and selectivity towards USP7, a very promising DUB in future cancer therapy. DUBs are important regulators of protein degradation and their dysregulation has been associated with known disease states like cancer, inflammatory disorders and neurodegenerative diseases.[3]

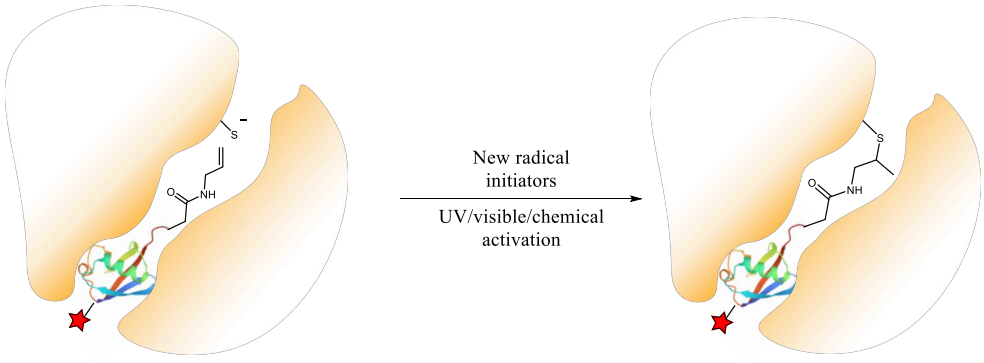

Figure 1. Radical activation of the thiol-ene labelling of DUBs.

References:

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[2] N. C. Taylor, G. Hessman, H. B. Kramer, J. F. McGouran, *Chem. Sci.* 2020, *11*, 2967.
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P4. A NEW PARADIGM FOR THE ASYMMETRIC DIELS-ALDER REACTION

Patrick J. Guiry and Aoibheann O' Connor
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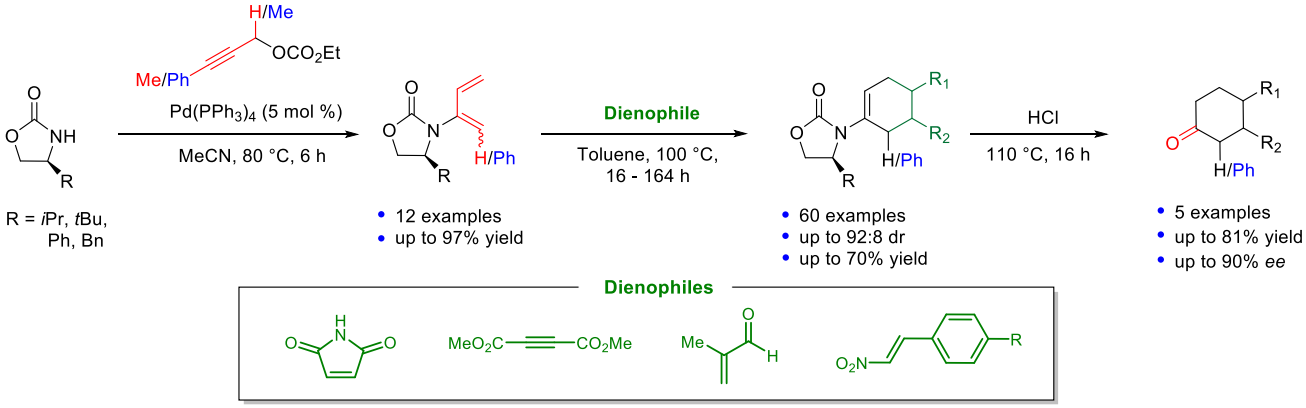
The Diels–Alder (DA) reaction has been intensively developed and refined to become one of the most powerful carbon–carbon bond forming methods in organic chemistry.[1][2][3] The asymmetric variation of the DA reaction was first investigated more than 50 years ago, and continues to see further development in the 21st century. Reportedly, the least investigated approach to the asymmetric DA reaction is the development and subsequent use of chiral dienes, as opposed to chiral catalysts and/or dienophiles.[4] The application of a chirally modified diene, as well as dienes containing an amido or amino group, in total synthesis is lacking in the literature.[5]

A catalytic method to prepare a library of chiral 2-amido-1,3- and 2-amido-1-phenyl-1,3-dienes from a range of oxazolidinones is reported. This palladium-catalysed carbon-nitrogen bond-forming reaction provides the corresponding chiral amido-dienes in moderate to excellent yields (12 examples, up to 97% yield). The resulting chiral amido-dienes are employed as novel dienes in DA reactions (60 examples, up to 70% yield, up to 92:8 dr). Hydrolysis of the DA products to cleave the oxazolidinone chiral auxiliary reveals a range of chiral cyclic ketones (5 examples, up to 81% yield, up to 90% ee) with XRD analysis providing key structural insights and confirming their stereochemistry.



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[3] L. Stenke, B. Nasman-Glaser, J. A. Lindgren, in *Proc. 7th Int. Conf. Prostaglandins, Florence*, **1990**, 7.
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P5. CONTINUOUS FLOW SYNTHESIS OF AZAHETEROCYCLES

Marcus Baumann and Ruairi Crawford

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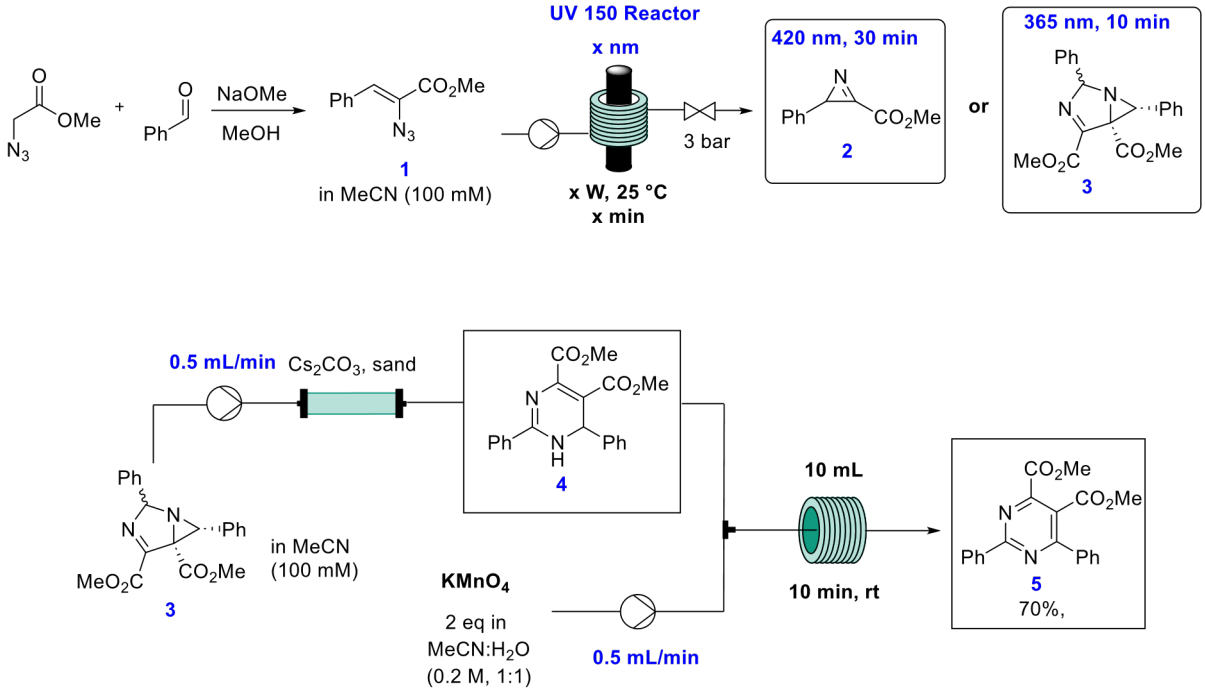
Over the last decade continuous flow chemistry has turned into a powerful tool in organic chemistry due to numerous benefits providing faster and safer reactions. [1]
Herein, we demonstrate the synthesis of azaheterocycles *via* the safe consumption of vinyl azides (**1**) under photoflow conditions. A trend was seen for the synthesis of electronically similar 2*H*-azirines (**2**) which required LEDs between 400-450 nm based on their UV-Vis characteristics. A photochemical flow process was exploited to synthesise a broad range of 1,3-diazabicyclo[3.1.0]hex-3-ene-4,5-dicarboxylate (**3**) by using 365 nm LED. These 1,3diazabicyclo[3.1.0]hex-3-ene-4,5-dicarboxylate were employed in a telescoped process to yield 1,6-dihydropyrmidines (**4**) by Cs_2CO_3 tautomerisation and pyrimidines (**5**) by a $KMnO_4$ oxidation in good to excellent yields. Ortho-substituted 1,3-diazabicyclo[3.1.0]hex-3-ene-4,5dicarboxylate (**3**) were not compatible with the telescoped process due to long reaction times requiring batch conditions. Overall, this process demonstrates the power of flow chemistry to provide access to drug-like molecules in a quick turnaround.



References :

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P6. EXPANDING THE SCOPE OF TRANSAMINASE-TRIGGERED AZA-MICHAEL CHEMISTRY FOR THE SYNTHESIS OF HIGH-VALUE TARGETS

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The pyrrolidine scaffold is commonly found in natural products,[1] synthetic drugs,[2] and organocatalysts.[1] We propose a transaminase (ATA)-triggered intramolecular aza-Michael reaction (IMAMR), where a simple prochiral ketoenone undergoes regio- and stereo-selective amination to form a chiral secondary amine that spontaneously cyclises, affording disubstituted pyrrolidines (**Figure 1**). This work expands the scope of the biocatalytic intramolecular aza-Michael chemistry that has been previously reported by our group to synthesise 2,6-disubstituted piperidines[3] and cyclic β-enaminones.[4] The small ketoenone panel was converted to their corresponding chiral pyrrolidine products using commercially available ATAs. While the transamination reactions are highly selective, the spontaneous IMAMR results in the formation of diastereoisomers that were isolated as inseparable mixtures. Further chemoenzymatic steps are being investigated to isolate an enantio-enriched pyrrolidine product after the transamination reaction.

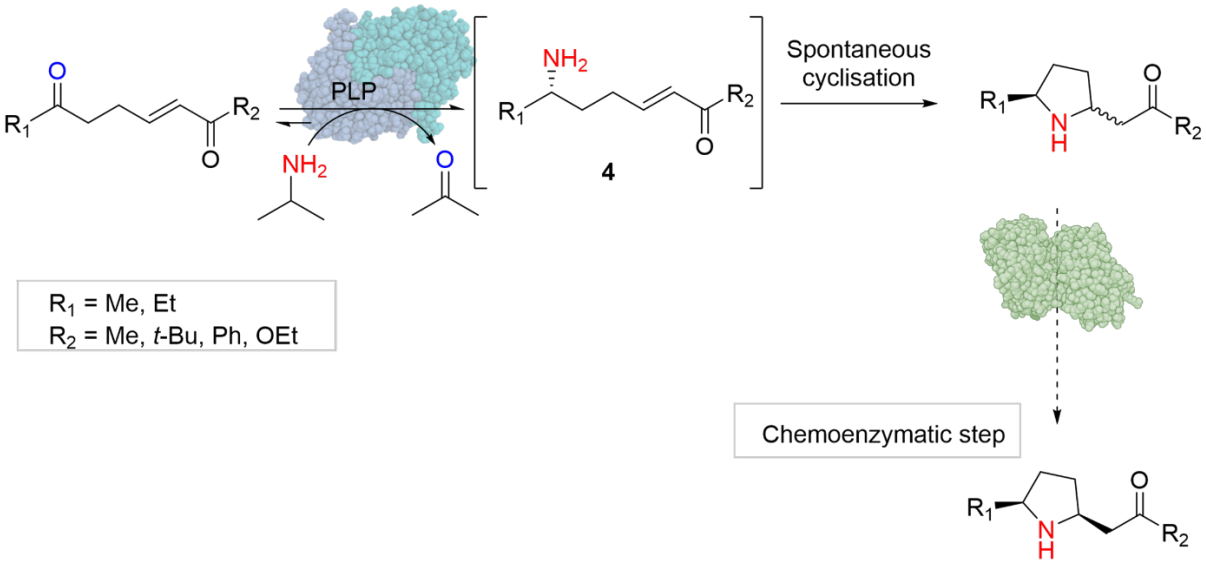

Figure 1. The transaminase-triggered aza-Michael reaction for the formation of disubstituted pyrrolidines followed by a further chemoenzymatic step to isolate an enantio-enriched product.

References:

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P7. DEVELOPMENT OF CHEMICAL PROBES TO STUDY A NOVEL ANTIBIOTIC TARGET

Brad R. Baker,[a] Coilín Boland, [b] Martin Caffrey, [b] and Stephen A. Cochrane*[a]
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[b]*Trinity Biomedical Science Institute, Trinity College Dublin*
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The rapid emergence of multidrug resistant bacteria is one of the biggest challenges facing our generation. Antimicrobial resistant bacteria currently cause 50,000 deaths per annum in the United States and Europe and are projected to cause 10 million additional deaths per year, as well as costing the global economy over $100 trillion, by 2050.[1] Therefore, there is an urgent need for new antimicrobial compounds that target novel biochemical pathways.

Gram-positive bacteria contain a membrane-embedded lipid called undecaprenol. This lipid is phosphorylated by the enzyme undecaprenol kinase (UdpK), yielding undecaprenyl phosphate, a molecular carrier used to transport important polysaccharides (in the form of glycolipids) across the cytoplasmic membrane.[2] These glycolipids are then used as building blocks for essential glycopolymers and glycoproteins, including teichoic acid, peptidoglycan and lipopolysaccharide.[3] UdpK has been linked to bacterial adaption and resilience to environmental applied stressors, and it's over-expression provides resistance to the antibiotic bacitracin.[4,5] Suppression of gene expression has been shown to result in bacterial stunted growth, apoptosis and the restoration of bacitracin efficacy. To develop UdpK inhibitors, a high-throughput assay is required. Existing coupled enzyme assays that monitor kinase activity through NADH consumption are not sufficient as extra experiments need to be performed to prove that inhibition of the kinase is occurring and not of inhibition of another enzyme in the system (e.g., pyruvate kinase or lactate dehydrogenase).

This project aims to develop a novel high-throughput UdpK assay using fluorescence detection methods. Previously, peptides containing a SOX group have been used in the analytical assay of protein kinases.[6,7] In the proposed assay, UdpK-mediated phosphorylation of the terminal primary alcohol on a SOX-modified lipid will result in internal interactions in which the substance can detect its own phosphorylation. To develop an optimal UdpK probe, we are synthesizing a library of SOX-modified lipids, wherein chain length, branching and/or degrees of unsaturation are varied.

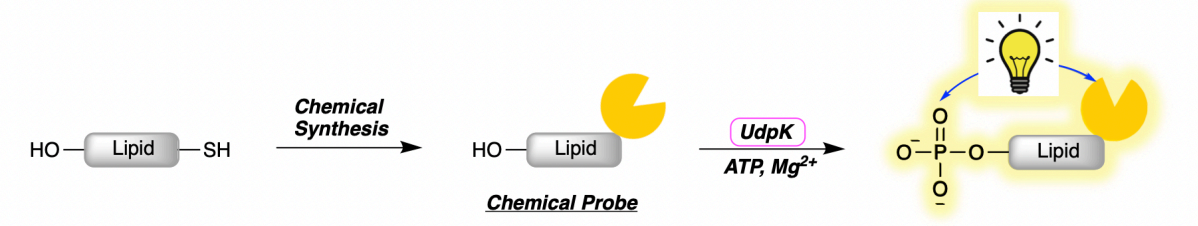

Figure 1: Structure of the SOX group containing probe and the proposed mechanism of the lipid kinase probe.

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P8. UTILISATION OF WASTE PRODUCTS FOR CONSTRUCTION OF ALKENES AND OTHER HIGH VALUE SYNTHETIC TARGETS

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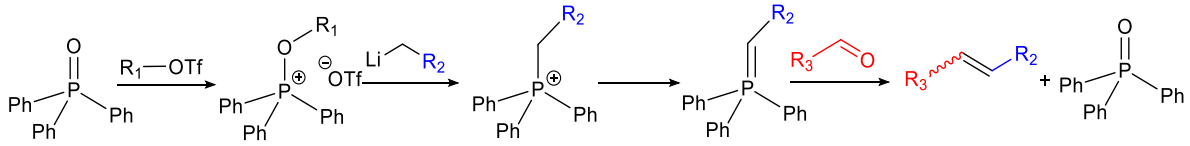
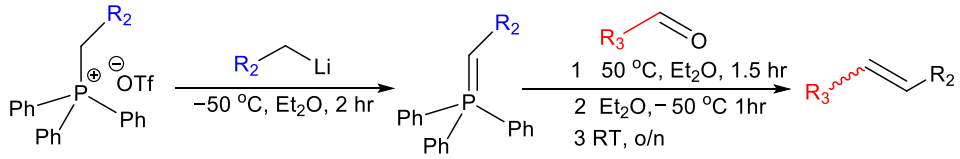
The Wittig reaction[1] is a type of chemical reaction in organic chemistry in which an aldehyde or ketone can be transformed into an alkene starting from a phosphonium ylide. A common application of this reaction is to introduce a carbon-carbon double bond. Although this reaction is widely used in organic chemistry, it has a few drawbacks. It generates phosphine oxide as a waste material, which also makes purification of the product difficult. This results in poor atom economy and large amounts of waste production, and requires large amounts of resource use, especially during purification of the products.[2] This project aims to develop methods for conducting the Wittig reaction using only catalytic amounts of thr phosphorus reagent by enabling the ylide starting material for the Wittig reaction to be regenerated from the phosphine oxide by-product. This would solve the waste generation problem while also increasing the atom economy of the Wittig reaction. In this cycle, phosphine oxide is converted first into alkoxy phosphonium salt, which is then converted into the phosphonium ylide by reacting with an alkyl lithium.

Herein we show that the by-product for the Wittig reaction can be used as a starting material for



subsequent Wittig reactions. Thus far in my project, conditions have been developed that enable Wittig reactions to be conducted using stoichiometric amounts of phosphine oxide as starting material, and a small set of alkene products have been synthesised and isolated using this methodology. This stoichiometric methodology is valuable in its own right in that it enables re-utilisation of what is otherwise a waste product, and also demonstrates the proof of principle that Wittig reactions using phosphine oxide as a catalyst should be possible. The reactions generally show moderate *E*-stereoselectivity, which is expected for Wittig reactions conducted in the presence of lithium cation. In these reactions, phosphine oxide was formed as a waste product, however it can be re-used to convert aldehydes into alkenes, creating a cycle. This will get us closer to atomic economy and greenness.[3]



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P9. TUMOUR RESPONSIVE SYSTEMS FOR TARGETED DRUG DELIVERY

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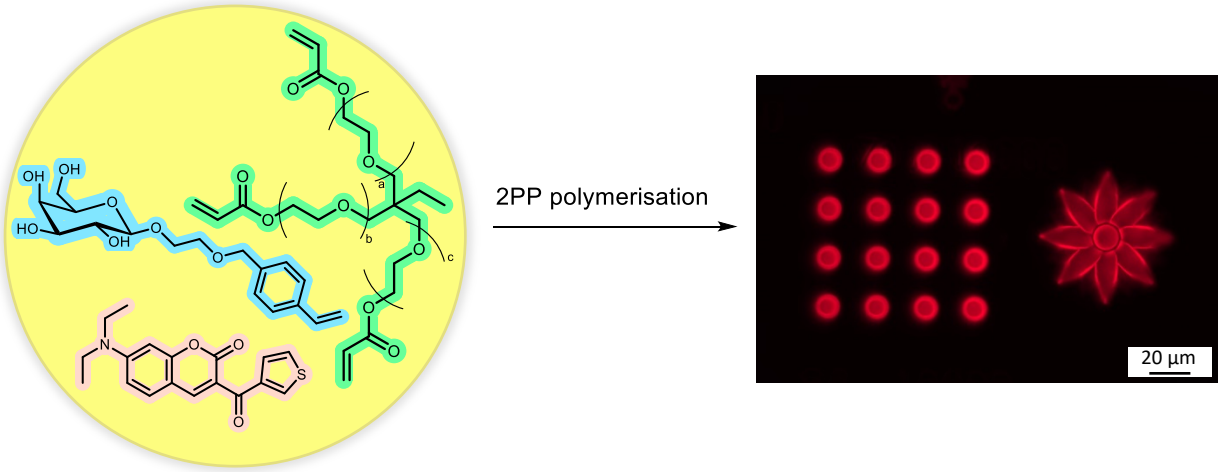
Current treatments used in cancer chemotherapy are limited due to their narrow therapeutic window and low cancer-cell specificity, making the development of targeted drug delivery platforms an urgent research challenge.[1] β-glucuronidase and β-galactosidase are overexpressed in a range of tumour types, compared to relatively minimal expression levels in healthy cells.[2] These glycosidases can therefore be exploited for the specific activation of prodrugs in the tumour microenvironment in enzyme activatable drug delivery platforms, facilitating improved selectivity and efficacy of chemotherapeutics.[3]

Polymer-based drug delivery systems represent a growing class of targeted therapeutics. Specifically, polymeric hydrogels which undergo hydrophilicity and swelling changes in response to external stimuli can be used in the controlled release of loaded drugs.[4] Here, we describe the synthesis of monomers bearing glucuronic acid and galactose moieties and their subsequent polymerisation via two-photon polymerisation (2PP), suitable for incorporation into enzyme responsive systems including a tumour-responsive selective drug delivery platform.



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P10. VISIBLE-LIGHT-INDUCED DIFUNCTIONALISATION OF ALKYNES WITH ARYLSULFINATES

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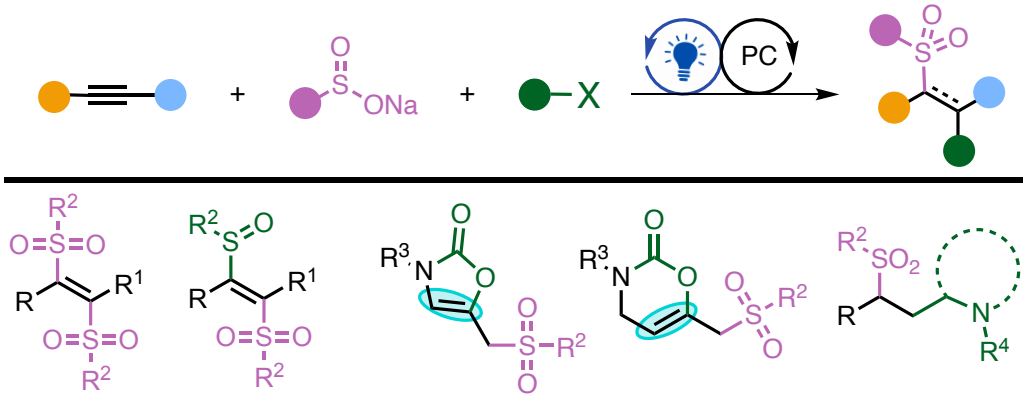
Organosulfur compounds are attractive scaffolds because of their numerous applications in medicinal chemistry, agrochemicals, material science and organic chemistry. Among them, sulfones are an important class of organosulfur molecules and versatile synthons in organic chemistry.[1] Furthermore, sulfur is found more frequently than fluorine in drug molecules and recently alkyl/vinyl sulfones have been found to act as radical precursors in synthetic organic chemistry. Due to their importance in various fields, many synthetic strategies were developed to synthesise sulfone-containing molecules.[2] Among them, radical sulfonylation is one of the most efficient approaches to access functionalized sulfones with high step- and atom- economy.[3] Recently, visible light-promoted reactions has played a promising role in organic synthesis because of demonstrated complex bond constructions under mild reaction conditions and visible light is environmentally benign.[4] In this context, in the present project we focus on the radical difunctionalisation of the alkynes under photochemical conditions to access highly functionalised sulfones. We will present our recently developed visible-light-induced difunctionalisation of alkynes with arylsulfinates under ambient conditions.[5]



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P11. THIOL-YNE MEDIATED CYCLISATION OF OXYTOCIN AND CARBETOCIN ANALOGUES

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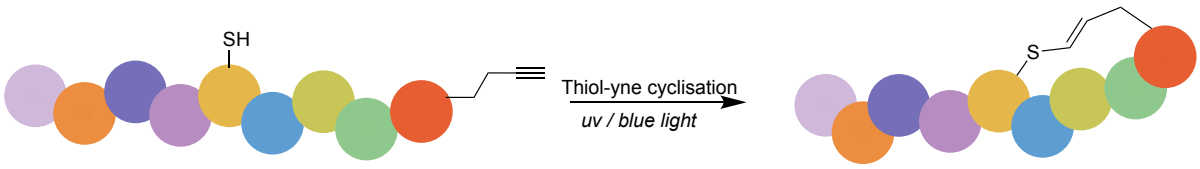
Peptide based biomolecules offer significant potential as therapeutics due to their high affinity towards receptors and reliable, cost-efficient synthesis. However, poor membrane permeability and susceptibility to peptidases are some of the drawbacks that prevent their widespread use.[1] These issues can be addressed through stabilisation of peptide sequences through cyclisation and/or replacement of disulfide bonds with more stable linkages. While a number of peptide stapling techniques exist, they often require the synthesis of unnatural amino acids or the use of metal-based catalysts. Light mediated thiyl radical methods are therefore of great benefit as these methods can be carried out under relatively mild, selective conditions and make use of naturally occurring cysteine amino acids. The aim of this work is to explore thiol-yne mediated radical macrocyclization techniques in order to develop a reliable method for peptide stapling and the synthesis of novel peptide therapeutics.[2,3] Furthermore, the formation of a vinyl sulfide provides a beneficial handle for further post-cyclisation functionalization.



The optimised methodology has been used to synthesise a range of analogues of Oxytocin. This cyclic peptide hormone plays important roles in social behaviour and childbirth and has medicinal uses in the latter. However, due to the presence of a disulfide bond, it has a very short half-life of ~3 min in blood.[4] Thus, thiol-yne cyclised variations are expected to possess improved stability. Variations on Carbetocin, a synthetic analogue of Oxytocin have also been synthesised.

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P12. AUTOMATED SYNTHESIS OF MONOSACCHARIDE BUILDING BLOCKS AND APPLICATIONS IN OLIGOSACCHARIDE SYNTHESIS

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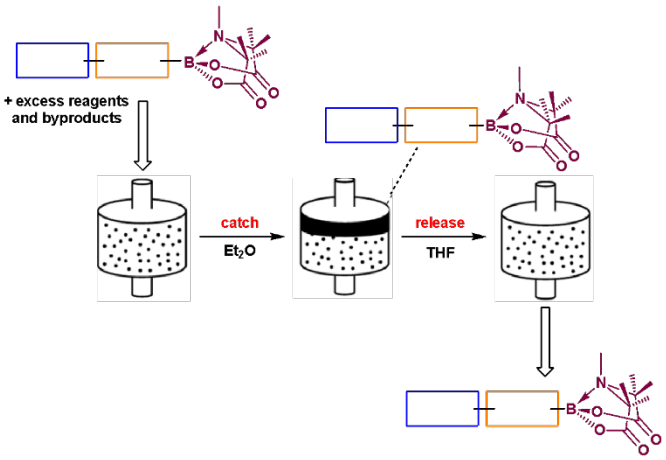
The development of effective techniques for the synthesis of carbohydrates with complex structural organisation is crucial to the discipline of glycoscience. Despite significant progress in the synthesis of oligosaccharides, the synthesis of targets featuring complex glycosidic linkages of monosaccharide building blocks remains a challenge. These compounds are present in a wide range of biologically relevant compounds. While much of the emphasis in the development of automated platforms for carbohydrate synthesis has been on the construction of oligosaccharides, manual syntheses of monosaccharide building blocks can represent up to 90% of the synthetic effort and thus constrain throughput[1]. This is often laborious and time-consuming. Furthermore, excess amounts of glycosyl donor building blocks are frequently used in glycosylations, presenting a pressing need to develop methods to streamline the acquisition of monosaccharides. The aim of this work is to improve the purification of monosaccharides, which is often a bottleneck in the preparation of important carbohydrates. By using a purification tag, TIDA,[2] it is hoped that the process of purifying monosaccharides can be made simpler and more efficient. TIDA-boronate ester tag was synthesized and installed onto a monosaccharide and various protection and deprotection were performed. One of the key findings of this research is that the silica binary affinity properties of the TIDA tag can be extended to monosaccharides bearing a variety of protecting groups. This characteristic proved beneficial during the synthesis of the tagged molecules, as it simplified purification and eliminated the need for arduous column chromatography. As a result, this process is potentially amenable to automation. Additionally, the tagged building blocks can be used to synthesize a trisaccharide in high yield, indicating that the TIDA tag is appropriate for the syn simple oligosaccharides.



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P13. FORECASTING VAPING HEALTH RISKS THROUGH NEURAL NETWORK MODEL PREDICTION OF FLAVOUR PYROLYSIS REACTIONS

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Vaping involves the heating of chemical solutions (e-liquids) to high temperatures prior to lung inhalation.[1,2] A risk exists that these chemicals undergo thermal decomposition to new chemical entities, the composition and health implications of which are largely unknown.[3,4] To address this concern, a graph-convolutional neural network (NN) model was used to predict pyrolysis reactivity of 180 e-liquid chemical flavours.[5,6] The output of this supervised machine learning approach was a dataset of probability ranked pyrolysis transformations and their associated 7,307 products. To refine this dataset, the molecular weight of each NN predicted product was automatically correlated with experimental mass spectrometry (MS) fragmentation data for each flavour chemical. This blending of deep learning methods with experimental MS data identified 1,169 molecular weight matches that prioritized these compounds for further analysis. The average number of discrete matches per flavour between NN predictions and MS fragmentation was 6.4 with 92.8% of flavours having at least one match. Globally harmonized system classifications for NN/MS matches were extracted from PubChem, revealing that 127 acute toxic, 153 health hazard and 225 irritant classifications were predicted. This approach may reveal the longer-term health risks of vaping in advance of clinical diseases emerging in the general population.

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P14. POST TRANSLATIONAL MODIFICATIONS OF HUMAN INTERFERON GAMMA FOR IMPROVED THERAPEUTICS

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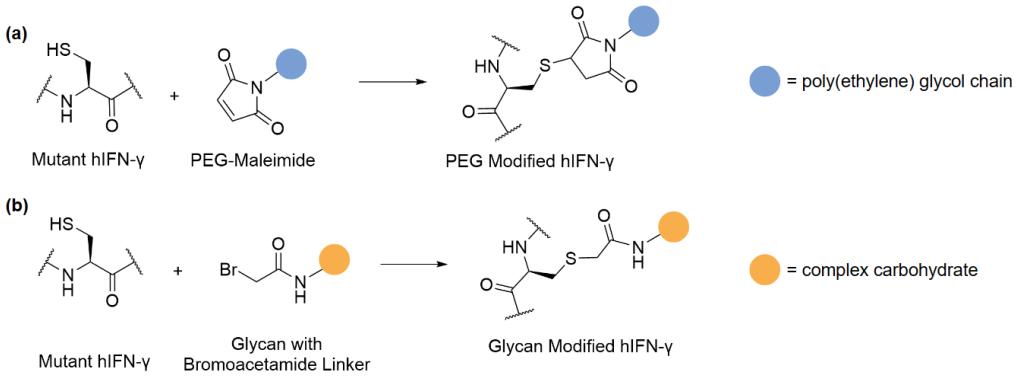
Interferon gamma (IFN-γ) is a pleiotropic cytokine found to play a critical role in the function of immune response.[1] It belongs to the interferons, a group of proteins named for their ability to interfere with viral activity.[2] [3] Human IFN-γ is composed of 143 amino acids with N-glycosylation sites at asparagine residues 25 and 97 (Asn25 and Asn97, respectively).[4] However, the recombinantly expressed un-glycosylated form of this recombinant protein has a short half-life, which is not desirable for therapeutics.[2] PEGylation is a widely used post translational modification technique when modifying peptides and proteins. The use of a poly(ethylene glycol) (PEG) moiety has been used to address the half-life of therapeutic proteins, as the conjugation of the PEG moiety increases the size of the poly-peptide, which reduces renal clearance of drugs.[5] Moreover, glycosylation techniques have also been employed to increase the therapeutic potential of certain proteins. Furthermore, the addition of either a PEG or glycan moiety have been known to increase the stability in solution of proteins. Herein, we aim to improve the stability of recombinantly produced hIFN-γ via the PEGylation and/or glycosylation at its naturally occurring glycosylation sites. Cysteine chemistry will be employed, due to the thiol side chain's unique reactivity.[6] Here, three hIFN-γ variants with cysteine (Cys) in place of Asn25 and Asn97 (Asn25Cys, Asn97Cys and Asn25/97Cys) have been recombinantly produced in *E. coli*. Due to the likeness in size when compared to the naturally occurring glycans of hIFN-γ, a PEG-Maleimide and a nonasaccharide-bromoacetamide of approximately 2 kDa were explored as possible decorations, and the reaction chemistry optimized.[2] As well, a smaller N-Acetylglucosamine (GlcNAc) -bromoacetamide was explored to compare the possible steric hindrance of different decorations (**Figure 1a,b**). The successful coupling reactions were characterized via SDS-Page and Mass Spectrometry.



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P15. DUAL EMISSION AND LIFETIME IMAGE TRACKING FROM THE PLASMA MEMBRANE TO SUBCELLULAR LOCALES

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Variations in pH play essential roles in cellular biology with implications for medical diagnostics and molecular imaging. Novel bio-conjugated, ratiometric pH-responsive BF_2-azadipyrromethene fluorophores with dual emissions at 720 nm (pH > 6) and 790 nm pH < 5) have been developed and their aqueous solution photophysical properties determined. Their dual-emission and fluorescence lifetime characteristics have been exploited to track their spatial and temporal progression from first contact with the plasma membrane to subcellular locales. Their dual-emission *off/on* to *on/off* responses being controlled by a reversible phenol/phenolate interconversion (Figure). Live cell confocal microscopy experiments using *c*RGD, *c*RAD and PEG conjugated fluorophores in the metastatic breast cancer cell line MDA-MB-231 confirmed the usability of the dual emissive properties for imaging. All three derivatives performed as probes capable of real-time continuous imaging of fundamental cellular processes such as plasma membrane interaction, tracking endocytosis, lysosomal accumulation and efflux, over prolonged periods of time without perturbing normal cellular function. Furthermore, fluorescence lifetime imaging microscopy (FLIM) provided valuable insights regarding the fluorophore microenvironments (Figure). Overall, the unique photophysical properties of these fluorophores shows excellent potential as information rich diagnostic probes.

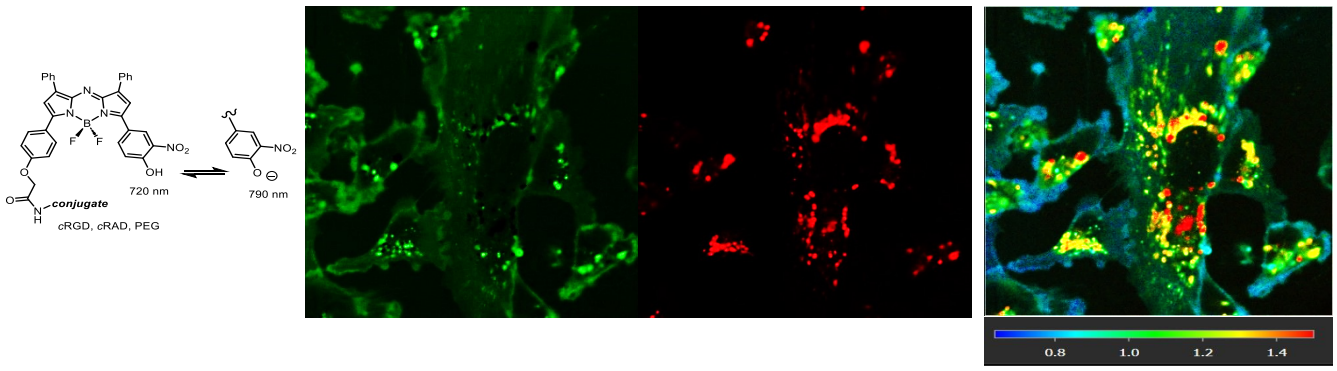

Figure. Dual emission bio-conjugated BF_2-azadipyrromethene fluorophores: structures, wavelength switching mechanism and MDA-MB 231 cell images intensity (left) and lifetime (right).

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P16. NICKEL-CATALYSED ARYLATIVE CYCLISATIONS OF ALKYNE-TETHERED ELECTROPHILES

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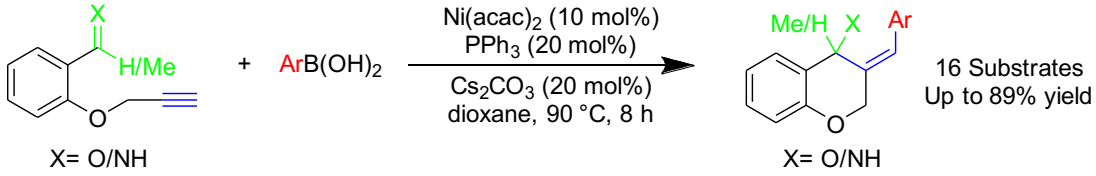
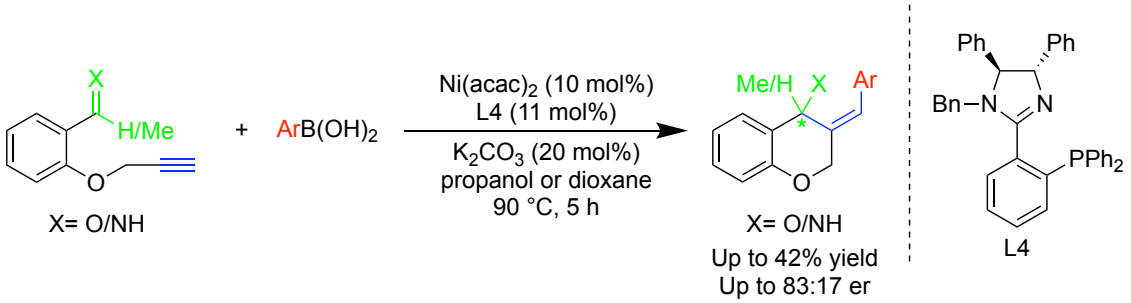
Aryl-metallative cyclisations of alkyne tethered electrophiles are a step-economical manner of synthesising complex molecules that can be of use in both medicinal and synthetic organic chemistry.[1] Within the literature only three examples of *syn*-arylnickelative cyclisations exist.[2-4] This work expands upon some of the initial work from Reddy and co-workers to a new range of electrophiles, namely, ketones and imines, synthesising 16 novel substrates in good to moderate yields of up to 89%.



Enantioselective *anti*-arylnickelative cyclisations have been developed for a broad range of substrates using Phox type P,N ligands.[5] We found that the Phim type P,N ligands are superior at inducing enantioselectivity in the *syn*-arylnickelative cyclisations and in this work we have undertaken initial steps towards development of the first enantioselective version of this reaction.



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P17. SYNTHESIS OF ISOPRENOID PROBES TO EXPLORE COENZYME Q10 AND MENAQUINONE PROTEIN BINDING INTERACTIONS AND FOR DRUG DISCOVERY

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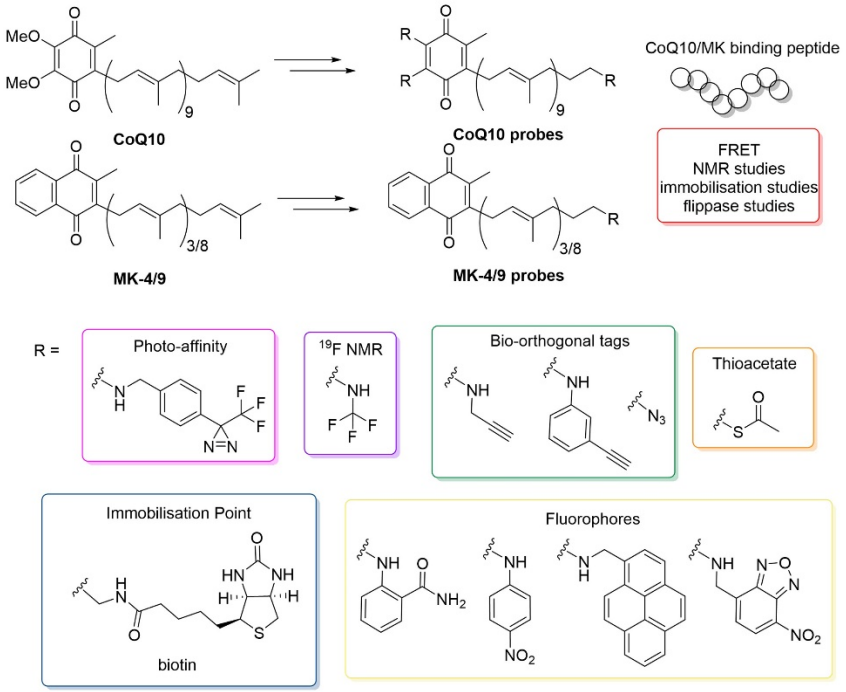
Coenzyme Q10 (CoQ10) is a redox active isoprenoid necessary for human mitochondrial energy production.[1] The equivalent bacterial co-factor, menaquinone (MK), has recently been identified as an antibiotic target.[2] CoQ10 and MK-derived chemical probes would be highly valuable for chemical biology applications. For example, such probes could be utilised for identification of novel inhibitors of CoQ10-binding proteins (e.g. drug targets), to study how known proteins interact with CoQ10 or discover new antibiotics that bind to MK. Both CoQ10 and MK possess a long isoprenyl chain. This is an ideal point to insert useful chemical 'tags' without disrupting the binding interactions and redox chemistry undertaken by the quinone head group. Herein, we report the successful synthesis of CoQ10 and MK4/9 probes, achieved utilising ω-modification chemistry, adapted from previous methodology developed by the Cochrane lab.[3] We have synthesised the binding portion of a known CoQ10 binding protein and a known antibiotic peptide that binds to MK. Work is currently ongoing to use the binding peptides to establish a viable FRET assay, a flippase assay and immobilisation studies to demonstrate the viability and wide applications of these isoprenoid probes.



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P18. AN ELECTROCHEMICAL OXIDATION PRINS-TYPE CYCLISATION SEQUENCE FOR THE CONSTRUCTION OF OXAZINONES VIA *N*-ACYLIMINIUM IONS

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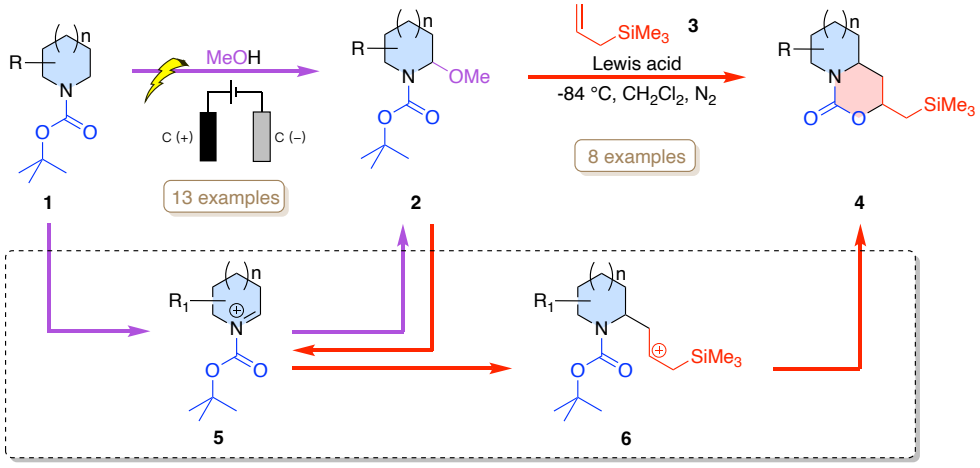
Nitrogen-containing heterocyclics represent one of the privileged structural motifs in synthetic pharmaceuticals and are also widely found in naturally occurring compounds.[1] Among various synthetic strategies for the functionalization of nitrogen-containing compounds, the electrochemical oxidation (also known as Shono oxidation[2,3]) has gained increasing popularity as a powerful and green strategy to selectively and efficiently oxidise a C-H bond in the α position to the nitrogen atom.

In this project (Scheme 1), we perform the electrochemical oxidation using an ElectraSyn device, and then use a Prins-type cyclisation to construct the oxazinone skeleton **4** from a variety of cyclic and acyclic *N*-Boc compounds **1**. Both transformations proceeded via a reactive *N*-acyliminium ion **5**, which can be readily trapped by a variety of nucleophiles. For example, allylsilane **3**, reacts to provide the β-silyl carbocation **6**. The intramolecular interception[4] between the oxygen atom of the Boc group and the β-silyl carbocation then produces the final products **4**. The scope of the sequence to date and its stereochemical outcome will be described, which includes the substituents (R), ring size and acyclic examples. Also included will be the optimisation of the Prins-type cyclisation to form **4**.



Scheme 1. An Electrochemical Oxidation Prins-type Cyclisation Sequence

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P19. NOVEL ROUTES TO PHOSPHONODITHIOATE ANTIVIRALS

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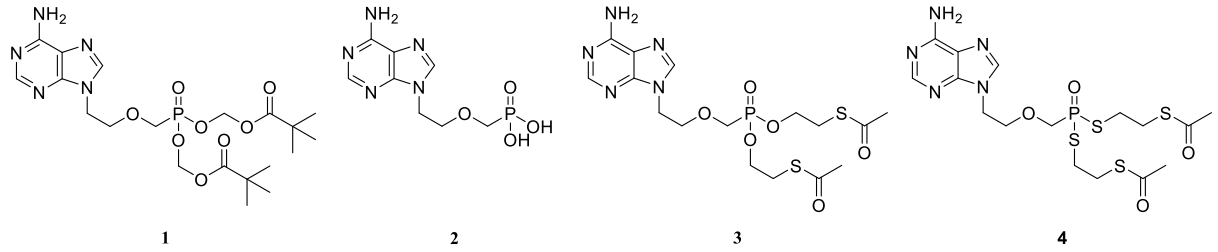
The Human Immunodeficiency Virus (HIV) is the pathological agent responsible for HIV infections. HIV attacks the hosts immune systems helper T cells which express the glycoprotein cluster of differentiation 4 (CD4) on their surface.[1] Gradual failure of the immune system due to the depletion of CD4 cells allows opportunistic infections to thrive where progression of HIV to Acquired Immunodeficiency Syndrome (AIDS) is likely. HIV/AIDS can be fatal. The major challenge in tackling HIV is found in its rapid mutation rate which drives resistance to existing antivirals. While the use of combination therapies has generally proven successful in treating the disease, new effective antiviral agents are continually required to combat future resistance. Nucleoside reverse transcriptase inhibitors (NRTIs) are a class of HIV antivirals which inhibit the enzyme reverse transcriptase. The acyclic nucleoside phosphonates (ANPs) represent a particularly interesting subclass.

Adefovir dipivoxil (**1**) is a well-known ANP prodrug of adefovir (**2**) (Figure 1). The *S*-acetyl thioethyl (SATE) derivative (**3**) of adefovir likewise shows enhanced bioavailability when compared to **2**.[2] This project focuses on the synthesis of novel, sulfur-containing SATE derivative **4**. Existing ANPs such as adefovir dipivoxil (**1**) contain phosphorus-oxygen bonds which are cleaved upon incorporation of the antiviral into the growing viral DNA chain.[3] SATE-derived antiviral **4** incorporates phosphorus-sulfur bonds which are more labile than phosphorus-oxygen bonds. This strategic bioisosteric replacement should allow for more rapid cleavage of the phosphorus-sulfur bonds and faster incorporation of the antiviral agent into the growing DNA chain.[4] Presented here is a summary of our work to date, including a variety of routes explored to reach target compound **4** through both the synthesis of phosphonodithioates and the derivatisation of adefovir (**2**).



1 **2** **3** **4**

Figure 1

References

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P20. PHOSPHINE-MEDIATED REDUCTIVE ETHERIFICATION OF ALDEHYDES

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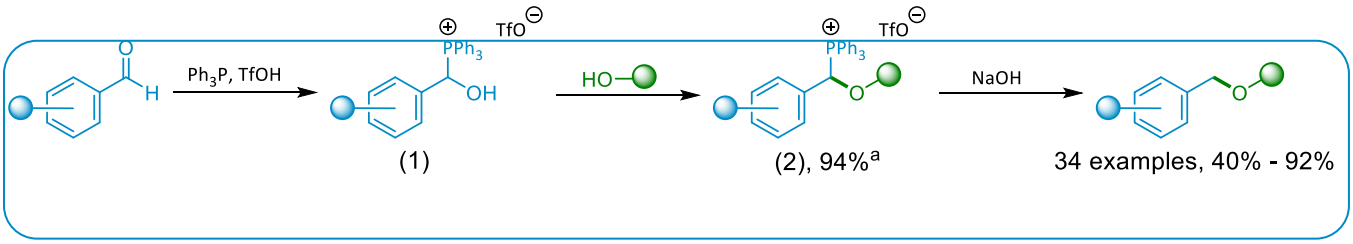
The ether functional group is a common structural feature found in a variety of bioactive compounds including antivirals, antifungals and antimicrobial agents.[1] Tamiflu, an ether-containing antiviral agent used to treat Influenza A and B, generated a market value of $1.1 billion in 2018. Ethers are typically accessed through the Williamson etherification,[2] which involves the reaction of an alkyl halide and an alkoxide to furnish the desired ether. Alkoxymercuration is an alternative strategy which requires toxic mercury reagents and is therefore undesirable. Moreover, in all instances toxic halogenated waste must be carefully removed to avoid contamination.[3,4]



Scheme 1: General scheme for reductive etherification of aldehydes.

The methodology proposed herein, employs an aldehyde as the stoichiometric alkyl source and negates the need for alcohol pre-treatment. Aldehydes are abundant alkyl sources, generally non-toxic and more desirable than alkyl halides[5] and as such, exhibit a variety of improvements on alkyl halides as the stoichiometric alkyl source. It has been found that the key intermediate (1) in the formation of benzyl ethers can be obtained in a simple one step reaction. Subsequent phosphonium salt hydrolysis yields the desired benzyl ethers in up to 92% yield. This methodology provides an alternative means of accessing this ubiquitous functional group, whilst obviating the use of alkyl halides, in a chemoselective manner with high functional group tolerance.

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P21. H–PHOSPHONATE PROMOTED ALCOHOL ACTIVATION: AN ATOM ECONOMIC ROUTE TO ALKYL HALIDE SYNTHESIS

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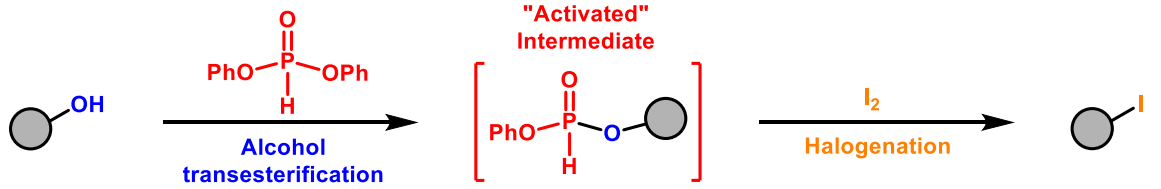
Bimolecular nucleophilic substitution reactions of alcohols are commonly employed in new carbon–carbon and new carbon–heteroatom bond construction.[1] However, achieving S_N2 reaction at an alcohol centre often comes at the cost of atom economy.[2] Current approaches geared towards alcohol substitution often require the use of additional activating agents, creating a reactive alkoxy intermediate susceptible to nucleophilic attack.[2] Consequently, these strategies often generate a super–stoichiometric quantity of waste materials.[2] [3]

This work is centred on enhancing the atom economy of alcohol activation towards halogenation, with respect to halide waste generation. We report a novel H–phosphonate promoted alcohol activation capable of furnishing 1eq. alkyl iodide from 0.5eq. of I_2 **(Scheme 1)**. This renders the methodology halide waste free, as every single iodine atom input into the process is incorporated into the final product. Furthermore, the diphenyl H–phosphonate promoter can be generated *via* a PCl_3 free route,[4] further minimalizing the halogenated waste associated with the overall process. This is an operationally convenient strategy, employing commercially available reagents in a "one-pot/dump and stir" reaction. Added benefits include the potential to enhance the overall process "greenness", as it can also be adapted for use in the bio–renewable solvent *p*–cymene.



Advantages

- **Applicable for 1°, 2° and 3° alcohols**
- **Amenable for use in bio-renewable solvent**
- **Lowest theoretical halide loading**
- **Example application in API synthesis**
- **PCl_3 free promoter**
- **One pot process**

Scheme 1

References:

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P22. THE ASYMMETRIC SYNTHESIS OF QUATERNARY AND TERTIARY STEREOCENTRES IN N-HETEROCYCLES USING DAAA AND DAP

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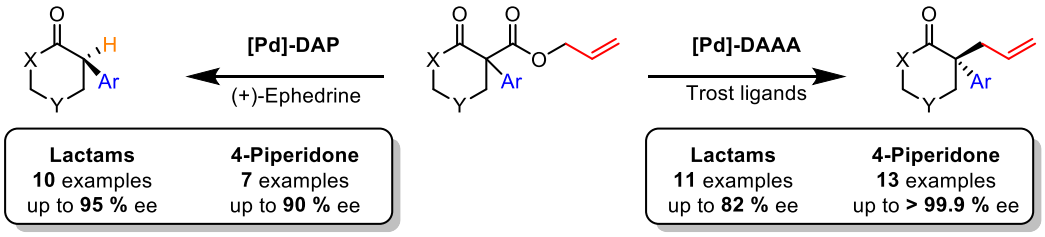
Many natural products and pharmaceuticals possess both quaternary[1] and tertiary[2] α-aryl stereocentres. Allylic groups are a well-studied functional handle that finds excellent use in natural product synthesis and other synthetic applications. Nitrogen-containing heterocycles are ubiquitous in biologically relevant compounds, and as such are common structural motifs in many natural products and pharmaceuticals.[3] Therefore, the study of methods for the highly enantioselective synthesis of α-aryl stereocentres in nitrogen-containing compounds is desirable. These products can be accessed through Pd-catalysed decarboxylative transformations[4,5] such as decarboxylative asymmetric allylic alkylation (**DAAA**) or decarboxylative asymmetric protonation (**DAP**) of lactam and 4-piperidone substrates.



The development and optimisation of DAAA and DAP for the synthesis α-aryl lactams/piperidones will be described. A substrate scope for DAAA of lactams has given 11 examples in up to 82 % ee. A substrate scope for DAAA of 4-piperidones has given 13 examples in up to > 99.9 % ee. A substrate scope for DAP of lactams has given 10 examples in up to 95 % ee. A substrate scope for DAP of 4-piperidones has given 7 examples in up to 90 % ee.

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P23. SYNTHETIC MAGNESIUM TETRAPYRROLE RADICALS FOR MECHANISTIC STUDIES OF PHOTOSYSTEM II

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Magnesium tetrapyrrole derivatives are fundamental to the reactivity of several photosynthetic pigments, most notably the chlorin complex chlorophyll-*a* in P680.[1] The P680 reaction centre consists primarily of 4 chlorophyll-*a* molecules. This give an overall redox potential of 1.1-1.3 V (vs. SHE) whilst isolated chlorophyll-*a in vitro* has only shown potentials around 0.7-0.8 V.[2] Water oxidation reactions typically require extreme conditions and precious metal catalysts to work,[3] yet photosynthesis occurs under ambient conditions. Taking inspiration from biology, elucidating the conditions and the mechanisms which allow chlorophyll to generate such high redox potentials under mild conditions may lead to ground-breaking improvements in oxidation catalysis.

A series of magnesium porphyrin and chlorin surrogates for chlorophyll-*a* are synthesised. The oxidation of these to π-cation radicals is carried out via chemical and electrochemical methods. The radical species are then studied by EPR and UV-Vis spectroscopy to optimise the generation of these. After probing the π-cation radicals, their oxidation reactivity towards phenol substrates is investigated via time-resolved UV-Vis spectroscopy. Our promising initial results are presented here including the synthesis of previously uncharacterised π-cation radicals, optimisation of their synthesis and demonstration of their reactivity towards a range of substrates. Ultimately, we aim to develop our findings into a mechanistic understanding of the influence of the tetrapyrrole ligand on natural oxidation chemistry.

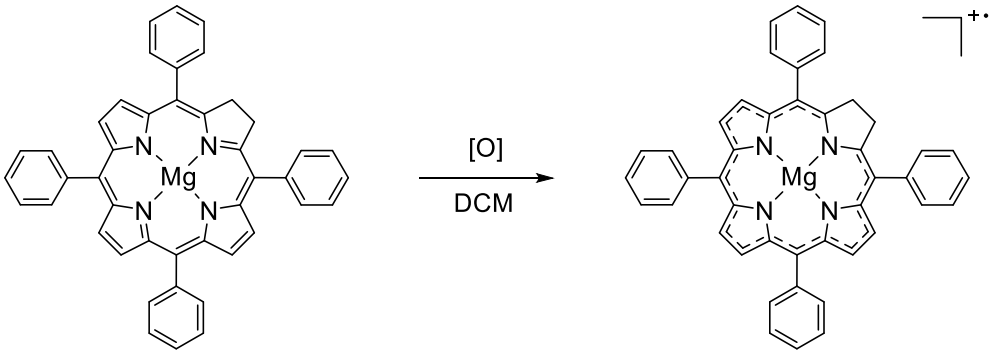

Figure 1: Generation of the π -cation radical of synthetic chlorin complex magnesium tetraphenylchlorin via chemical oxidation.

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P24. ASYMMETRIC SYNTHESIS OF QUATERNARY A-ARYL STEREOCENTERS IN BENZOFURANONES USING DECARBOXYLATIVE ASYMMETRIC ALLYLIC ALKYLATION

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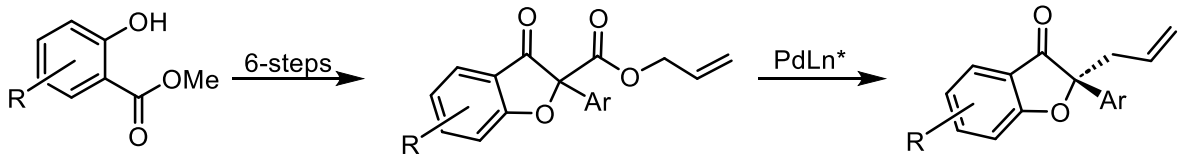
Benzofurans are a common motif found in natural products and biologically active compounds, some of which contain anti-inflammatory and anti-cancer properties. A typical approach to install these structures is to start with the corresponding benzofuranone which can then be converted to the benzofuran by reduction and subsequent dehydration.[1] Quaternary α-aryl stereocenters are found in nature and have been shown to have interesting properties. Recent efforts with the benzofuran/benzofuranone motifs have focused on the installation of aryl groups at the α-position to generate sterically hindered all-carbon quaternary stereocenters in the resulting products and so methodologies to install these are desired.[2]

These products can be accessed from the Pd-catalysed decarboxylative asymmetric allylic alkylation (DAAA) of α-aryl β-keto allyl esters using chiral *P,P*-Trost ligands. This methodology uses mild conditions to generate motifs difficult to access by other means, generating highly desired quaternary stereocenters in an asymmetric fashion. However, the scope of these attempts are typically limited to small alkyl chains or functionalities distant from the reactive centre. The Guiry group has already extended the scope previously to other α-aryl containing substrates via the use of aryl lead reagents to install the bulky groups on the reactive centre of the desired β-keto allyl ester before applying to the DAAA reaction which insofar has observed high reactivities and enantioselectivities.[3]

The development and optimisation of the synthesis of the model substrate is described along with the optimisation of the DAAA reaction for the 5-methoxybenzofuranone analogue which has displayed good yields and enantioselectivities. Additionally, work on the expansion of the substrate scope is also included.



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Grant No. 18/EPSRC-CDT/3582.

P25. RGD PEPTIDE NAPTHALIMIDE CONJUGATES FOR DRUG DELIVERY AND IMAGING THERAPY.

Laura Ramírez Lázaro, Harlei Martin, Thorfinnur Gunnlaugsonn and Eoin. M. Scanlan.

Arginine-Glycine-Aspartic acid (RGD) peptides are well known for targeting the $\alpha_v\beta_3$ integrin, which is highly expressed in tumours. Therefore, drug delivery and diagnosis through cyclic RGD peptides that bind $\alpha_v\beta_3$ integrin in tumours represents a promising strategy. However, these sequences lack chemical groups that enable their facile detection. The incorporation of organic fluorophores into the peptide sequence offers considerable potential as an approach to target cancer cells. Fluorescent cyclic peptides have been used in biological applications from live-cell imaging to *in vivo* detection of cancer.[1]1,8-Naphthalimides are widely utilised fluorophores and dyes due to their excellent photophysical properties. They have high quantum yields, good photostability and large Stokes shifts. A key structural feature of 1,8-Naphthalimides is that they are planar, which makes them well-suited candidates for intercalating DNA, offering potential as anticancer therapeutics. Herein we report the chemical synthesis of RGD-1,8-naphthalimide conjugates as imaging agents and theranostics for cancer. Furthermore, 4-amino-1,8-Napthalimide may be converted into the corresponding Tröger's Base in the presence of TFA and paraformaldehyde. Tröger's Base 1,8-naphthalimide products (TBNaps) are chiral, cleft-shaped heterocyclic fluorophores that can exhibit fast cellular uptake and also function as cellular imaging probes.[2,3] The conjugation of a cyclic RGD peptide with a Napthalimide fluorophore, with further potential to be converted to the Tröger's Base, represents a powerful modality to access probes and drug targeting agents for cancer therapy.

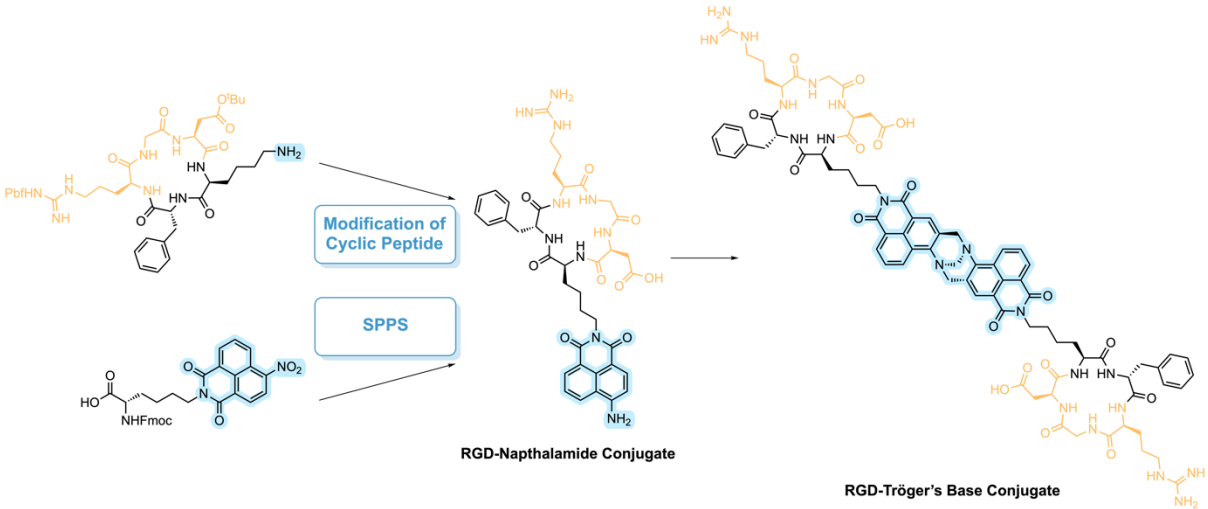

Figure 1. Synthesis of cyclic RGD peptide Napthalimide conjugates.

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P26. MODULAR SYNTHESIS OF BENZOYLPYRIDINES EXPLOITING A CATALYST- FREE REDUCTIVE ARYLATION STRATEGY

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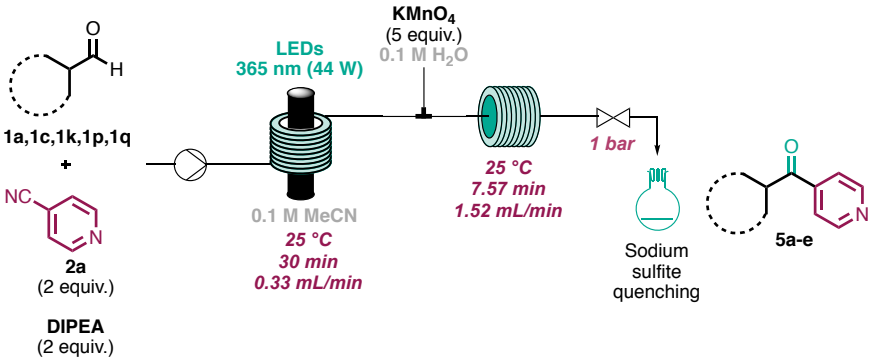
Developments in modern photocatalysis have highlighted the power of Ru- and Ir-based catalysts to bring about a plethora of valuable synthetic processes using visible light.[1] Due to the high cost and potential toxicity, their use in industrial settings is fairly limited. In this context, simple organic molecules with sufficient conjugation continue to play a key role in scaled photochemical reactions and triplet photosensitizers such benzophenone and (thio)xanthone are frequently used examples.[2] While these entities are readily available at low cost, display good solubility and are considered non-harmful, the introduction of electron-donating or -withdrawing substituents that is critical to modify their photophysical properties, commonly necessitates long and inefficient synthesis routes. To address this challenge, we set out to create an expedited route into electronically differentiated bis-aryl ketones that combine electron-rich benzene systems with electron-deficient pyridyl moieties. Continuous flow processing was employed to provide increased scalability, reaction efficiency as well as reproducibility. Our strategy combines a reductive arylation reaction between aryl aldehydes and cyano-pyridines with an oxidation of the resulting secondary alcohol product to yield the desired bis-aryl ketones via a modular route.



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P27. DECIPHERING THE ROLE OF PHOSPHOSERINE IN TAU PROTEIN USING COMPUTATIONAL AND SYNTHETIC APPROACHES

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Neurodegenerative diseases (NDDs) affect millions of people and there are currently insufficient drugs to prevent or treat these conditions. The most common NDD is Alzheimer's disease (AD) and the main symptom is dementia and memory deficit. The causes are still unknown but AD is correlated with alteration of brain cells and proteins such as hyperphosphorylation of Tau. The function of Tau is the assembly and stabilization of microtubules, which help normal neuron functions. In AD, this protein loses that capacity and does not bind microtubules, due to posttranslational modifications such as phosphorylation at a serine residue, which can result in misfolding and consequent aggregation in Neurofibrillary Tangles (NFTs).[1] Aggregation could be triggered by crosslinking of Lys, His or Cys residues to a highly reactive dehydroalanine (Dha) residue, generated by the proximity of Lys and pSer residues.

A Tau protein library has been prepared from the Protein Databank (PDB) and was analysed by a developed Python script to identify proximate Ser and Lys residues. Next, using Pymol's Posttranslational modifications tool (PYTMs), a phosphate group was added to all Ser residues (Fig 1.A). A ranking of 10 structures was obtained based on the Tau PDB: 6HRE structure (Fig.1.B). The stability analysis of these structures was studied with NAMD, a molecular dynamics programme. A peptide fragment was identified and prepared by solid-phase peptide synthesis (SPPS) methods (Fig.1.C). These novel phosphoserine peptides will help to further our understanding on the possible development of Tau aggregation linked to AD and also the role of Tau mutagenesis. The results of our studies to date will be presented.

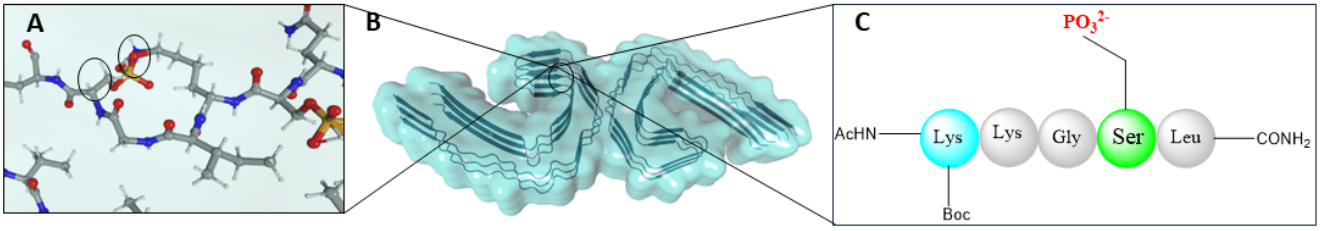

FIGURE 1. A) P-Ser and Lys B) Tau protein, PDB: 6HRE C) Peptide sequence synthetized

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P28. PHOTOEXCITING NITROARENES IN FLOW: FROM BENZYNE PRECURSORS TO NITROSOARENES

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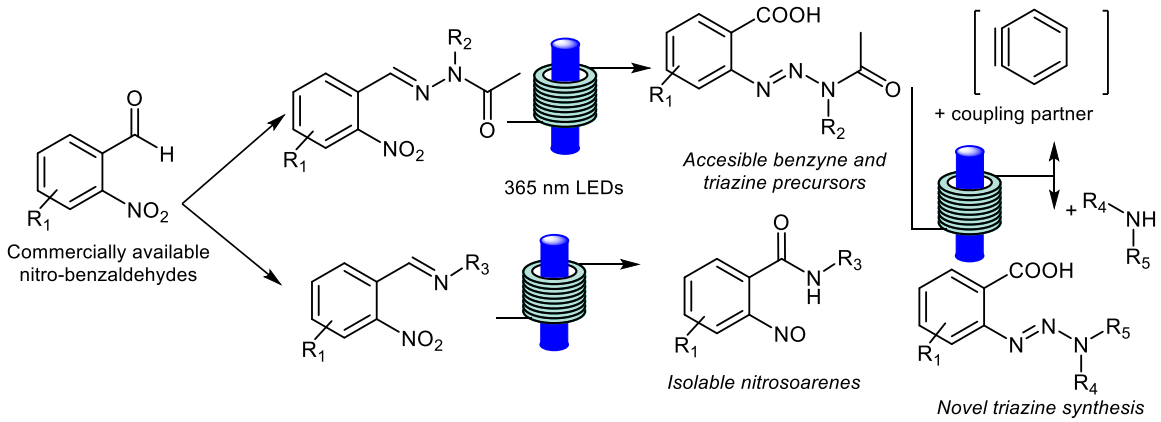
Herein, we present a continuous flow photochemical platform which uses commercially available set-ups and 365 nm light to give access to gram quantities of various target compounds. Continuous flow photochemistry is characterized by sustainable protocols with better yields and high productivity, which are achieved thanks to an efficient and uniform irradiation.[1] Furthermore, other advantages of flow technology involve efficient mixing, the safe use of highly reactive and/or toxic intermediates/reagents, and the possibility of telescoping several reactions.[2]

In recent years, nitroarenes have been exploited as photochemically active compounds towards the generation of relevant heterocycles or as oxygen atom transfer agents.[3] Here, we combine the benefits of using flow photochemistry with the ability to excite these moieties to achieve access to previously difficult-to-access compounds: benzyne precursors and nitrosoarenes.

Firstly, we have developed a photochemical flow process for the generation of benzyne precursors with good yields.[4] These compounds are also tested in flow with different coupling partners to prove benzyne formation. Furthermore, when using these precursors with different secondary amines in flow, a novel triazine formation is reported in good yields. Secondly, a wide range of nitrosoarenes are obtained from related aldimines in good yields with 100% atom economy and without additives needed.[5] Both protocols are tested on gram scale, with intermediate isolation, and further functionalization is also proved.



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P29. SYNTHESIS OF NOVEL BIOISOSTERES OF THE AUTOINDUCER BDSF

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By 2050, 10 million people are expected to die each year as a result of resistant infections.[1] Traditional antibiotics are being rendered increasingly ineffective due as bacterial resistance becomes more widespread. One strategy to combat AMR involves the disruption of native bacterial communication, known as quorum sensing (QS). The diffusible signal factor (DSF) family is a family of QS signals which have been found to increase biofilm formation and virulence in many bacteria e.g. *Pseudomonas aeruginosa* and *Xanthomonas campestris*.[2] DSF (**1**) and *Burkholderia* DSF (BDSF) (**2**) are two important QS signals which are often found in the airways of cystic fibrosis (CF) patients (Figure 1).[3]

Our group has previously demonstrated how *cis*-unsaturated sulfonamides (e.g. **3**) can successfully inhibit QS in DSF-sensitive bacteria.[4] In this project, we have removed the *cis*-unsaturated double bond and generated a diverse library of saturated *N*-acyl sulfonamide isosteres of BDSF (**4**). These compounds will be subsequently tested for their ability to regulate DSF-dependent phenotypes, growth characteristics, biofilm formation and virulence. This will determine the importance of the presence of the *cis*-unsaturated double bond on the QS activities in the selected bacteria.

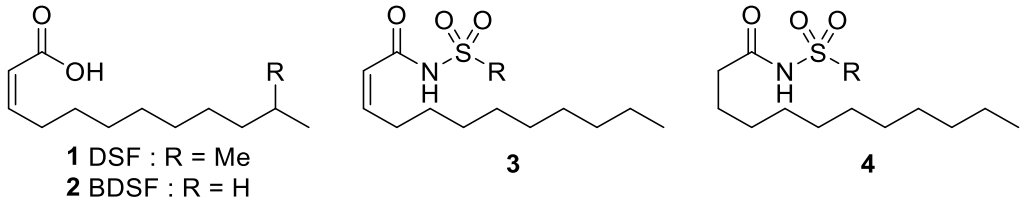

Figure 1

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P30. REGULATE EG AND TA METABOLISM IN PSEUDOMONAS UMSONGENSIS GO16

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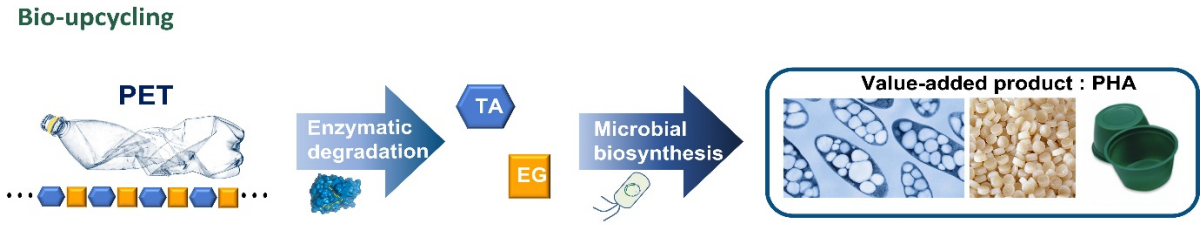
Pseudomonas umsongensis GO16, initially isolated from the soil of a polyethlyene terephthalate (PET) bottle processing plant, exhibits remarkable versatility in utilising various substrates, including PET monomers, terephthalic acid (TA) and ethylene glycol (EG) [1]. Additionally, GO16 possesses genes for synthesising both medium and short-chain length polyhydroxyalkanoates (PHA), making it a promising candidate for upcycling PET waste into bioplastic PHA [2].

While the proof-of-concept for the biotechnological strategy to upcycle PET has been demonstrated [3], enhancing the efficiency of TA and EG metabolism remains a challenge. To address this issue, genetic engineering tools to delete, overexpress and integrate genes were employed. In *P. umsongensis* GO16, TA can be degraded by *tph* genes into protocatechuate (PCA). PCA is metabolised into TCA cycle intermediates through β-ketoadipate pathway. By knocking out *pcaGH* to disable the native PCA ortho-cleavage pathway and introducing the PCA meta-cleavage pathway from *sphingobium sp.* SYK-6, we observed that GO16 could not grow with TA without *pcaGH* genes but recovered its growth when meta-cleavage pathway was adopted. Regarding EG metabolism, a LysR type transcriptional regulator (LTTRs) *ttdR* is located 5'- of the gene for glyoxylate carboligase (*gcl*) was deleted. While the wild-type GO16 can utilise EG as a sole carbon and energy source, the *ttdR* Knockout strain exhibited an inability to grow on EG, highlighting the critical role of *ttdR* in EG metabolism. Furthermore, overexpressing *ttdR* resulted in a 10-hour shorter lag phase and a 1.25-fold higher biomass compared to the control strain when cultivated in 30 mM EG.



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P31. UNDERSTANDING THE BIOLOGICAL DIVERSIFICATION OF CHEMICAL SIGNALLING IN KEYSTONE PATHOGENS FOR DEVELOPMENT OF NEXT GENERATION THERAPEUTICS

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Transcriptional regulators enable microbes to respond to external cues, presenting a tuneable response system involved in antimicrobial resistance, nutrient availability, metabolic reprogramming, quorum sensing signalling and cell-cell communication, efflux, and biotransformation. Recently, two families of transcriptional regulator have emerged with key roles in cell-cell communication and the shaping of microbial community dynamics. Acting as receivers and transducers for distinct chemical languages, members of the LysR- and LuxR-families of transcriptional regulators are now known to play key roles in the pathophysiology of infection.[1-3]

Comparative genomics revealed a wide distribution of LysR-type transcriptional regulators (LTTRs) across the nosocomial pathogen, *Pseudomonas aeruginosa*. PqsR, the receptor for the Pseudomonas quinolone signal and its precursor 4-hydroxy-2-heptylquinoline (**Figure 1**) was found to be amongst the most variable in the dataset. Complementation of the PAO1 *pqsR*-mutant using representative variant PqsR sequences suggests a degree of structural promiscuity within the most variable of LTTRs. Comparative genomics also revealed that this promiscuity of diversification is seen in the LuxR-type transcriptional regulators. Best known as the receptor for the classical quorum sensing acyl homoserine lactone signal, photopyrones have recently emerged as a new chemical language operating through the LuxR system.[4] We show photopyrones and synthetic analogues (**Figure 2**) have anti-biofilm and negative growth impacts on several ESKAPEE and other opportunistic pathogens.[5]

Figure 1

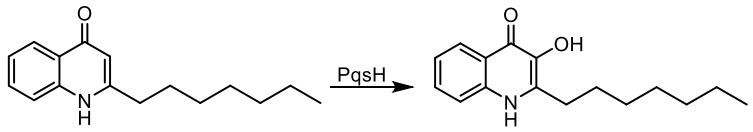
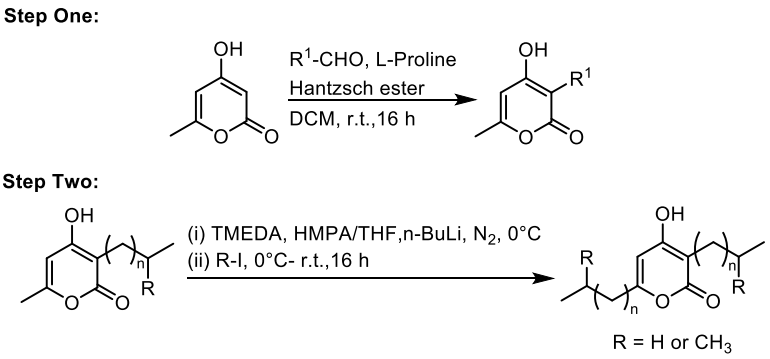


Figure 2



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P32. CONVERSION OF MIXED PLASTIC WASTE TO POLYHYDROXYALKANOATES BY MIXED BACTERIAL CULTURES

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Polyhydroxyalkanoates [PHAs] are a class of biodegradable polyesters with melting and moulding properties similar to thermoplastics, and therefore have a broad range of applications in industrial, agricultural and medical fields. Microbes accumulate PHA as intracellular granules that serve as energy reservoirs under carbon excess and nutrient limiting conditions. Various microbes have been tailored to produce PHA from low-cost substrates.

Converting plastic wastes to PHA is one of the efficient ways to address the existing landfilled waste and reduce future landfilling thereby ensuring a circular economy of plastics. Processes like pyrolysis and enzymatic hydrolysis of mixed plastic waste produce a mixture of aromatic and aliphatic compounds. These monomers can be used as carbon [C] feedstocks for microbial growth [1].

The overall aim of my research is to produce PHA from some of these monomers using mixed bacterial cultures. Various *Pseudomonas* strains were assessed for biomass [as cell dry weight, CDW], PHA production and, C and Nitrogen [N] utilization using the monomers, terephthalic acid, adipic acid and butanediol.

Thus far, mixed cultures with 3 bacterial strains and the above-mentioned monomers were carried out in 1 litre stirred tank bioreactors with various C/N ratios resulting in a maximum volumetric productivity of, 85 mg l^{-1} h^{-1} of biomass and 19.65 mg l^{-1} h^{-1} of PHA. Strategies employed to achieve this result will be discussed.

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P33. MODEL COMPOUNDS FOR THE INVESTIGATION OF ELECTROSTATIC EFFECTS IN PHOTOSYNTHETIC PIGMENTS

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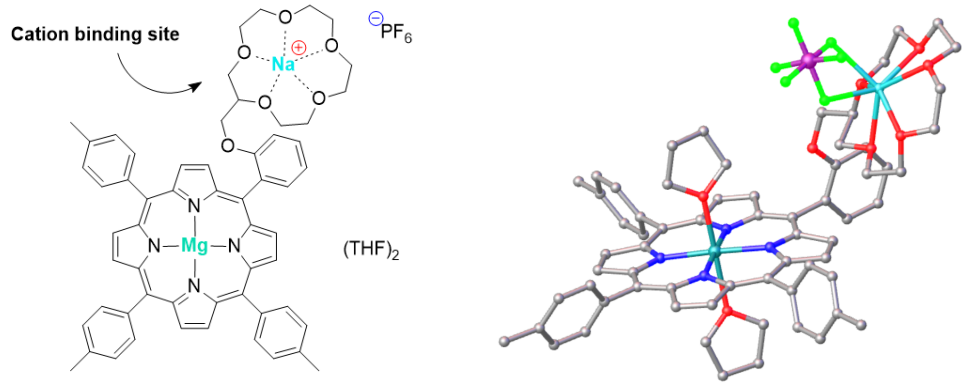
Photosynthetic water oxidation is catalysed by the enzyme Photosystem II (PSII). The reaction is initiated by 1-electron photo-oxidation of a chlorophyll-*a* tetramer named P680. The product is a π-cation radical complex, $P680^+$, with an exceptionally high redox potential of 1.1 - 1.3 V vs SHE. This species drives water oxidation by oxidising the oxygen evolving complex *via* a tyrosine residue.[1] The extreme redox potential of $P680^+$ renders it the most potent oxidant in biology, a fact that is especially interesting considering the comparatively diminished redox potentials of monomeric chlorophyll-*a* and other related photosynthetic pigments (0.45 - 0.78 V vs SHE).[1, 2] The origin of the high redox potential of $P680^+$ is unknown, but a number of proposals have been put forward in the literature, such as: the nature of axial ligands at Mg, the relationship between different chlorophyll molecules in the pigment, and the electrostatic/dielectric environment of the surrounding protein.[3, 4, 5] Uncovering the factors that contribute to the high reactivity of $P680^+$ promises to both improve our understanding of water oxidation in PSII and unearth new design principles for synthetic oxidation catalysts.

This work aims to address the last of the above-listed postulates by demonstrating the impact of electrostatic interactions on the redox and reactivity properties of chlorophyll model compounds. To this end, we have synthesised and characterised novel crown ether-appended Mg-porphyrins, their adducts with redox-inactive metal cations and their 1-electron oxidation products in the presence/absence of bound cations.



Chlorophyll model compound

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P34. STEREOSELECTIVE SYNTHESIS OF α-GALACTOSIDES

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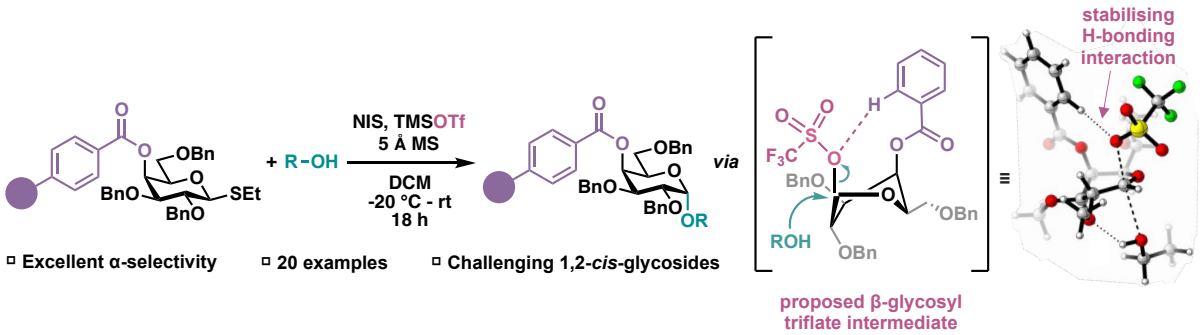
Nature employs carbohydrates as an integral source of structural biodiversity across all organisms. It is understood that the biological properties of these natural products can be fine-tuned *via* alteration of glycosidic patterns, particularly with respect to stereochemistry. Consequently, stereochemical control in glycosylation reactions is a significant objective within the field of carbohydrate chemistry.[1]

This work is concerned with stereochemical control in α-galactosidation reactions. α-Galactoside units are found in many biologically important compounds, for example in cancer-associated mucin-type glycans.[2] However, existing methods for the α-selective synthesis of galactosides that are broadly applicable to a range of galactosyl substrates are limited.[3-6] Thus, further understanding around the stereochemistry of α-galactosidations is required.

This poster will describe a highly α-selective methodology for galactosidation that employs an orthogonal *para*-substituted benzoate protecting group at position four of the galactosyl donor. Computational investigations, a Hammett study on the effect of this benzoyl *para*-substituent and investigation into the influence of acceptor nucleophilicity on glycosylation stereoselectivity have allowed for the proposal of a rationale for the excellent α-stereoselectivity described herein.

The scope of glycosylation has been expanded to accommodate galactosyl-α-1,2-, α-1,3-, α-1,4-, and α-1,6-linkages with exclusive α-selectivities and isolated yields up to 74%. The protecting group tolerance of the methodology is under investigation and includes silyl, benzyl, benzylidene and benzoyl groups thus far. This glycosylation has also been applied to the synthesis of a trisaccharide as well as a derivative of the mucin-type core-8 structure.[7]



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P35. A STRUCTURAL AND FUNCTIONAL MIMIC OF THE P680 DIMER RADICAL CATION

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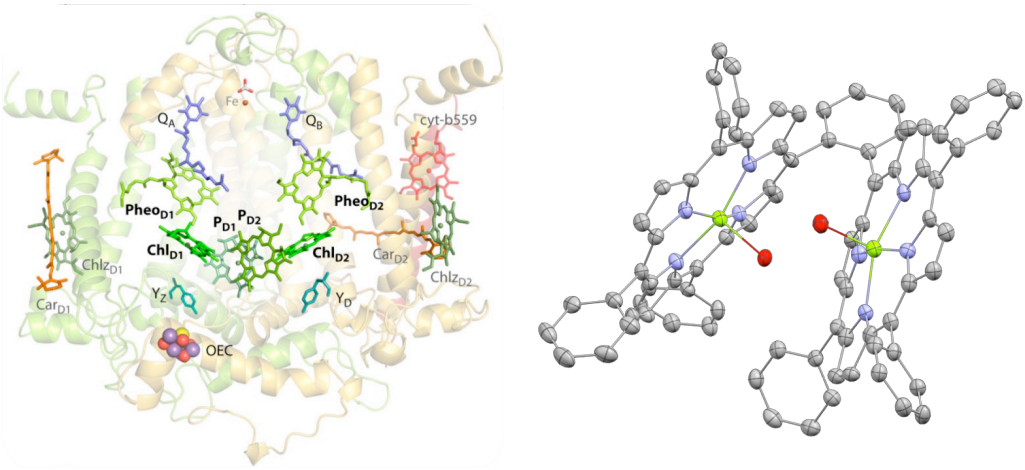
P680, a unique type of chlorophyll a (Chla), serves as photosystem II's main electron donor.[1] According to the PS II X-ray structures, the donor site's D1/D2 core contains four Chla molecules distributed evenly across its center.[2] The central pair of Chl are aligned parallel to each other with a distance of (3.3-3.5 Å), which allows for π-π interaction. However, there is a lack of knowledge regarding $P680^{\bullet+}$, the active oxidant that is considered to be the most potent oxidant in biology. The P680 radical cation has a midpoint potential of ($P680/P680^{\bullet+}$) ≈ 1.1 – 1.3 V vs. SHE.[3] By contrast, the redox potential of Chla has been shown to be 0.78 V vs SHE, whereas the redox potentials of the other well-characterized Chl primary electron donors, P700 and P870, are substantially lower at 0.49 V and 0.45 V vs. SHE, respectively.[4-5] It is unclear how a Chl-based oxidant may achieve such high potentials, and the function of single or multiple Chl units in P680 is still unknown.



Herein, we wish to present the synthesis, characterization and reactivity studies of a structural and functional mimic of the $P680^{\bullet+}$ dimer radical cation. A dimeric magnesium porphyrin has been synthesised to mimic the dimeric core of P680. The dimeric cation radical has been prepared by chemical oxidation from the corresponding Mg-porphyrin dimer. The cation radical was characterized by various spectroscopic methods (EPR, UV-Vis, FTIR, ESI-MS). The reactivity of the generated radical cation towards different phenols have been presented which mimics oxidation of tyrosine by $P680^{\bullet+}$ in PS II.

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P36. BIOCATALYTIC CASCADE SYNTHESIS OF IMINOSUGARS FROM MONOSACCHARIDES

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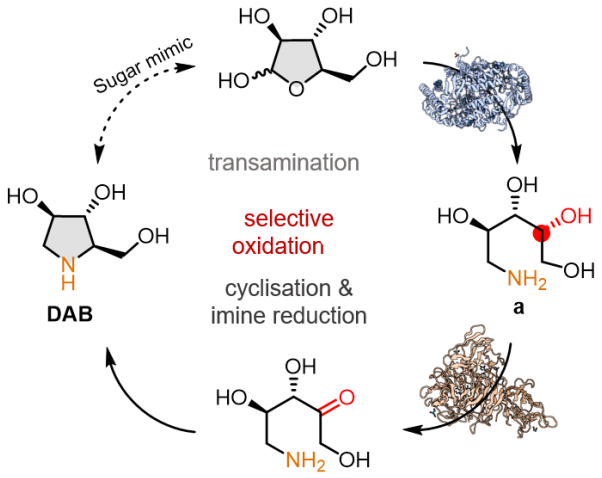
Iminosugars, such as DAB (**1**), are polyhydroxylated alkaloids and sugar mimics, with a nitrogen in the place of the endocyclic oxygen. These naturally occurring compounds are of pharmaceutical importance because they interact with and inhibit carbohydrate processing enzymes, and because of their beneficial drug-like properties.[1] Conventional synthesis of iminosugars from readily available carbohydrates is challenging mainly due to the presence of multiple hydroxyl groups. A key strategy in carbohydrate synthesis has been complex protecting group manipulations in order to perform regioselective functional group manipulations.[2]

Inspired by the reported biosynthetic gene cluster for transformation of fructose-6-phosphate into an iminosugar scaffold,[3] we present a sequential, three step chemo-enzymatic synthesis, whereby minimally protected monosaccharides undergo transamination, selective oxidation, and reduction, *via* transaminase, oxidoreductase, and catalytic hydrogenation steps, respectively.[4-6] Furthermore, we demonstrate novel biocatalytic cascade methodology that can reach iminosugar products in one-pot without workup, and entirely avoid the use of protecting groups.



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For what's next

P37. EXPLORING TOXICANT KETENE RELEASE FROM VITAMIN E ACETATE IN VAPING

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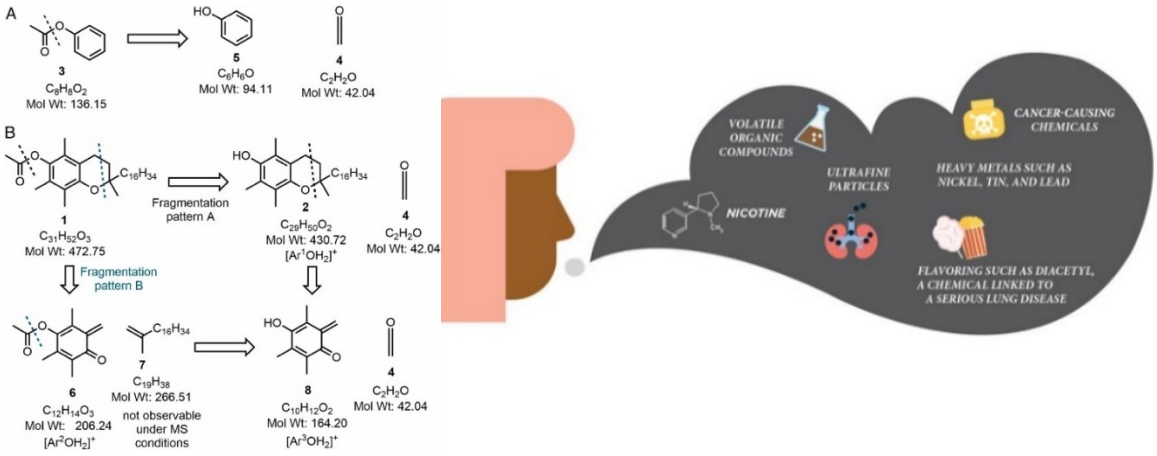
The use e-cigarettes among young people is of growing concern, e-cigarette companies are tailoring marketing campaigns to portray e-cigarettes as being a healthy alternative to smoking with little negative health effects.[1] With the ever-increasing number of flavours available the number of chemical flavourings also increases. Many of these flavourings have not been tested for inhalation toxicity and therefore their long-term biological effects remain unknown. E-cigarette or vaping product use-associated lung injury (EVALI) is a modern phenomenon and a product of e-cigarette use and is characterised by damage to lung tissue resulting in shortness of breath, fever and chills and cough. [2] Patients experiencing symptoms of EVALI including nausea and difficulty breathing will have lung fluid samples taken, Results from these samples in a majority of cases show high levels of Vitamin E acetate (VEA) compared to negligible levels in those who do not vape.[3] We can deduce from these results that there is a strong correlation between the presence of VEA in the patient's lungs and their symptoms.



In our previous study, VEA has shown to produce highly toxic ketene gas whose effects include skin irritation along with damage to lung tissue.[3] The long-term effects of consistent exposure to this colourless, potent compound remains unknown. With VEA being identified as a ketene source, the number of other potential sources found in e-liquids is unknown. With this in mind our group has begun to map the most common chemical compounds found in e-liquids with the ultimate goal of identifying other sources of ketene gas. With there being 100's if not 1000's of flavouring compounds, to map and screen each one by hand would take a lifetime. Therefore, we will be employing an AI software to map these compounds and allow us to virtually filter out those compounds that would not produce ketenes. Additionally, to these toxic ketenes, pyrolysis reactions undergone by VEA along with other ingredients found in e-liquid can also produce known carcinogens such as benzene as well as toxic alkenes. [4]

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P38. FROM LINEARITY TO CIRCULARITY – CREATING PLATFORM CHEMICALS FROM THIN AIR

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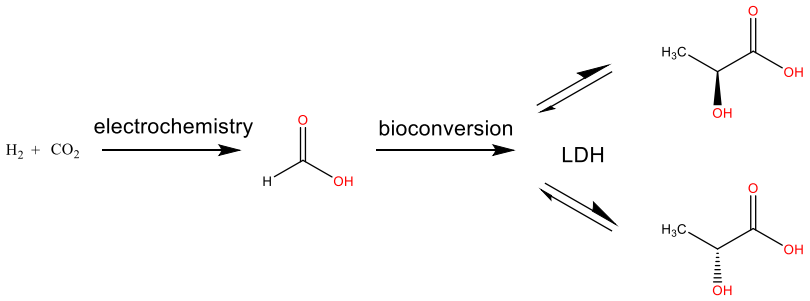
CO_2 is a by-product of many biobased processes like yeast fermentation and a major contributor to climate change. To integrate such processes in a circular (bio-) economy, CO_2 needs to be continuously recycled into the system. To tackle this, CO_2 can be utilised as a feed stock for biotechnological processes. *Cupriavidus necator* H16 fixes CO_2 in the presence of H_2 and can naturally produce the biodegradable plastic polyhydroxybutyrate (PHB) in nutrient limiting conditions[1-2]. The CO_2-proxy formic acid can be used with *C. necator*, as it is easily produced from CO_2 and H_2 in electrochemical processes and has good solubility in water[3].

The aim of this work is to improve growth on formic acid, particularly the maximum growth rate (μ_{max}), and to establish production of lactic acid. Growth improvements were achieved by subjecting *C. necator* to an adaptive laboratory evolution (ALE) campaign in a continuous fermentation. Periodical increases in the dilution rate exhibited evolutionary pressure for faster growing phenotypes. Thereby, a 1.8-fold increase of μ_{max} was achieved compared to the wildtype strain while biomass and PHB yield remained constant. Furthermore, in this project the product scope of *C. necator* on formic acid is to be expanded. Lactic acid can be produced from central metabolites by a lactate dehydrogenase (LDH). Several LDHs have been tested for expression, two of which are now under investigation for *in vitro* and *in vivo* lactic acid production. Current and future work revolves around the metabolic integration of a successful LDH for conversion to lactic acid.



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P39. LIGHTS, CAPTURE, EXTRACTION! A PHOTOAFFINITY PROBE FOR PROFILING THE METALLOPROTEOME IN LIVE CELLS

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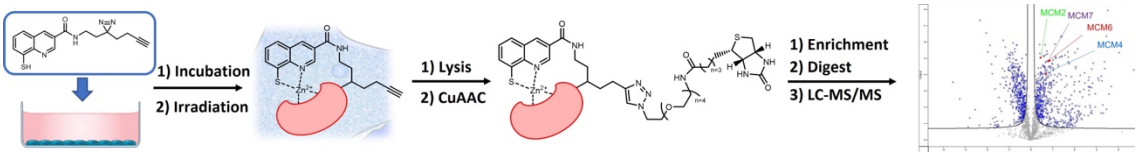
Metal co-factors impart vital structural characteristics and catalytic functions to a wide variety of cellular proteins.[1,2] These metalloproteins are exciting targets for investigation towards the development of novel therapeutics. However, their covalent capture for protein profiling studies can be highly challenging.[3] Here, we describe the design and preparation of a novel affinity-based probe bearing an 8-mercaptoquinoline motif, a privileged ligand able to bind several challenging to engage metalloproteins.[4,5] The probe was equipped with a photolabile diazirine for covalent capture of engaged metalloproteins, while a terminal alkyne was incorporated for enrichment of labelled proteins using copper-catalysed azide-alkyne cycloaddition (CuAAC).[6]

We report the successful synthesis of the probe and subsequent labelling validation experiments using a recombinant zinc-dependent metalloprotein in a competitive and UV dependent manner. This labelling protocol was thereafter translated to enable protein profiling experiments to be performed in live mammalian cells. We established a proteomics workflow for characterising enriched proteins, leading to the identification of several metalloproteins for which no covalent probe had previously been reported. Finally, we determined that a validated metalloprotein-dependent mechanism underlying eukaryotic cell cycle could be disrupted through treatment with the novel probe. This work represents an important contribution to the library of cell-permeable probes with inducible reactivity for profiling a range of therapeutically significant biomolecules.



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P40. DEVELOPMENT OF A REDOX-NEUTRAL WITTIG REACTION CATALYSED BY PHOSPHORUS

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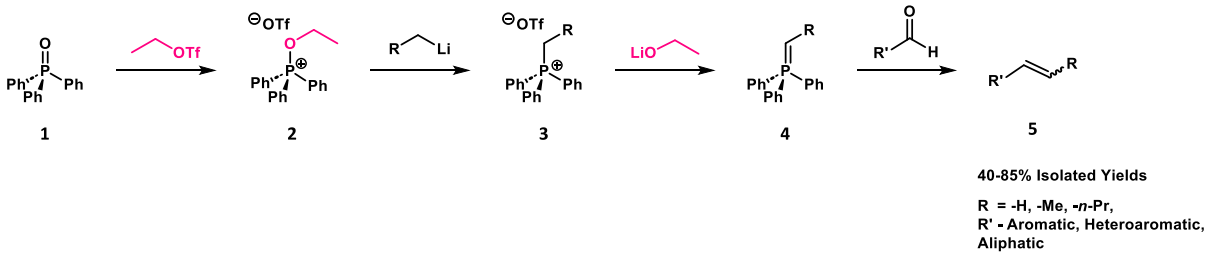
Discovered in 1953 the Wittig reaction remains the cornerstone of olefin synthesis enjoying broad applicability and tolerating a diverse range of functionalities.[1] This reaction generates stoichiometric phosphine oxide waste which is expensive to purify and atom uneconomical.[2]
The ACS green chemistry pharmaceutical roundtable named the Wittig reaction 'one of the top ten key green research areas' sparking interest in developing methodologies for phosphorus-catalysed Wittig reactions. There are already established redox-shuttled,[4-6] electrochemical,[7] and microwave assisted catalytic Wittig reaction.[8] However these approaches do require stoichiometric base and reductant additions diminishing their overall atom economy.
An alternative 'inverse reactivity' approach developed in this project. Using alkyl triflate and alkyllithium reagents, the basis for a new catalytic Wittig reaction has been developed as shown in **Scheme 1.**



Scheme 1: Wittig reaction employing triphenylphosphine oxide 1 as starting material.

With this method triphenylphosphine oxide **1** is alkylated by ethyl triflate to generate ethoxyphosphonium triflate **2**. Displacement of the ethoxy leaving group by alkyllithium reagents forms quaternary phosphonium salts **3** and ethoxide base. The *in situ* generated base deprotonates **3** affording non-stabilised *P*-ylides **4**. Reaction with aldehydes yields alkenes **5** in moderate to good yields (40-85%), triphenylphosphine oxide **1** starting material and simple lithium triflate and ethanol waste products.

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P41. DOUBLE CLICK MACROCYCLIZATION WITH SONDHEIMER DIYNE FOR BIOORTHOGONAL FLUORESCENCE IMAGING

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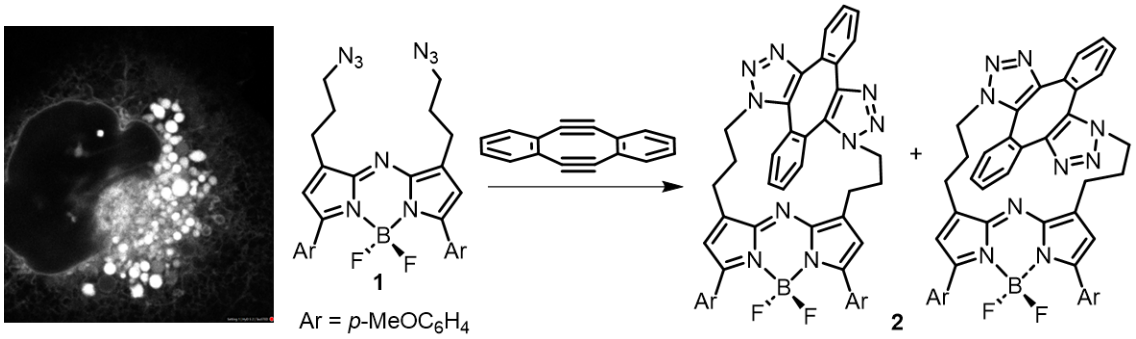
Bioorthogonal fluorescence imaging is an effective way of monitoring dynamic events in sub-cellular compartments in a non-destructive manner. The Sondheimer diyne allows for two sequential 1,3-dipolar cycloadditions under mild conditions without the need for a catalyst.[1] Previous work from the O'Shea research group has shown that this diyne can be used for bioorthogonal imaging in live cells.[2] To expand on these initial findings, the bis-azide substituted BF_2-azadipyrromethene **1** was selected as an attractive candidate for bioorthogonal fluorescence imaging as it would emit in the advantageous near infrared spectral region and has bis-azide functionality allowing for two cycloaddition reactions (Figure). The synthesis of **1** was achieved in 10 steps starting from butan-1,4-diol and 2-bromo-4'-methoxyacetophenone. Photophysical characterization of **1** showed an emission λ_{max} at 677 nm with quantum yield of 0.49 in methanol. The reaction of **1** with Sondheimer diyne gave a mixture of *cis* and *trans* macrocyclization products **2** in excellent yield under mild room temperature conditions (Figure). Preliminary live cell imaging showed that **1** localizes to lipophilic membrane regions and investigations are ongoing to determine its ability to participate in bioorthogonal double click [3+2] cycloadditions in live cells.



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P42. ASYMMETRIC SYNTHESIS OF α-ARYL STEREOCENTRES IN DIHYDROQUINOLINONES *VIA* DAAA AND DAP

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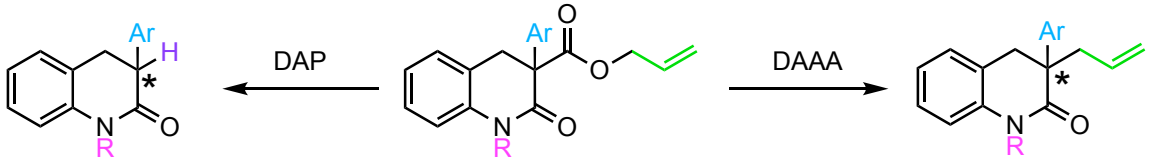
Nitrogen-based heterocycles constitute a significant portion of therapeutic agents in medicinal chemistry and are a prevalent motif in natural products.[1] Many biologically important molecules also contain α-aryl stereocentres. Pd-catalysed decarboxylative asymmetric transformations of α-aryl β-amido allyl esters is an effective route to install these centres. The allylic group is a well-explored functional handle that has many applications in the synthesis of a wide range of structures. Hence, the development of synthetic routes to generate α-allyl, α-aryl stereocentres in nitrogen-containing compounds is highly desirable. Our group has previously applied this decarboxylative catalysis to a range of substrates possessing α-aryl motifs.[2-4]

The synthesis of α-allyl α-aryl quinolinones *via* DAAA is described. A range of substrates were synthesised successfully and transformed to the desired product in high conversions and moderate enantioselectivities. The synthesis of α-aryl quinolinones *via* DAP is also outlined. Optimisation studies with the model substrate are complete and work on expanding the substrate scope has commenced.



up to 100 % conversion
up to 90 % *ee*

up to 98 % conversion
up to 68 % *ee*

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P43. A CLICK CHEMISTRY-DERIVED DINUCLEAR COPPER(II) ARTIFICIAL METALLONUCLEASE

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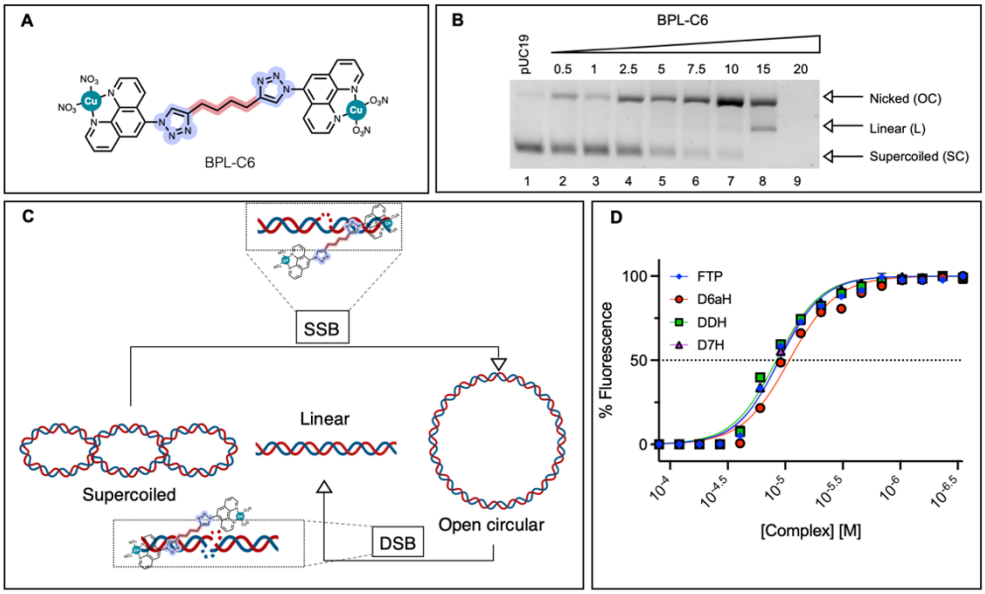
Resistance mechanisms and high toxicity associated with platinum therapeutics has motivated researchers to develop new treatments involving polynuclear metal complexes. One successful example is BBR3464[1], a cationic polynuclear platinum agent capable of long-range crosslinking interactions that circumvent typical 1,2-di-adduct repair processes. Here, we have employed a copper-catalysed azide-alkyne cycloaddition (CuAAC) approach[2,3] to generate a new class of bis-phenanthroline copper(II) complex. These agents were designed to promote long-range DNA cleavage via two distal copper(II) coordinated phenanthroline residues with the aim of overcoming limitations associated with the repair of localized DNA damage. Di-alkynes with varying linker lengths and modifications were selected to enable a DNA damage structure-activity-relationship study from the resultant complexes. From the library of compounds generated, one lead agent called BPL-C6 was identified (**A**). The complex can selectively bind and cleave AT rich DNA from the minor groove and converts supercoiled pUC19 into open circular and linear forms at low micromolar concentrations (**B-D**). BPL-C6 has also shown promising selective anticancer activity and is currently undergoing further investigation by the US National Cancer Institute (NCI).



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P44. STEREOSELECTIVE GLYCOSYLATIONS

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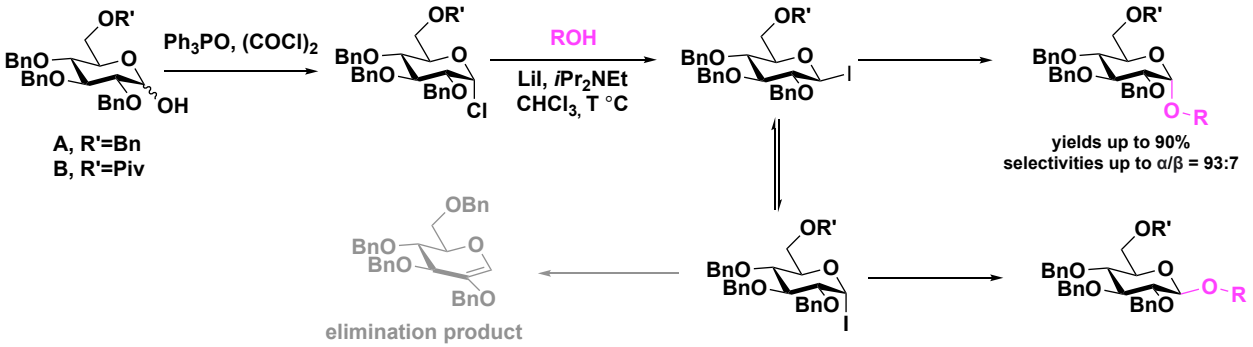
Oligosaccharide synthesis, consisting of multiple glycosylation steps, poses many difficulties with respect to regio- and stereoselectivity [1]. Depending on the reaction conditions, 1,2-*cis* or 1,2-*trans* glycosides can be obtained, of which the former are usually more difficult to synthesize. Previously, the McGarrigle group reported access to 1,2-*cis*-glycosides, by treatement of the glycosyl donor with Denton's catalytic Appel conditions [2], followed by reaction with LiI, iPr_2NEt and the acceptor [3]. This procedure was successufully applied for the stereoselective synthesis of β-mannosides and β-rhamnosides [4].

Herein, this methodology has been applied to the synthesis of α-glucosides. Two donors and six acceptors have been tested (**Scheme 1**). Optimization studies have been carried out to prevent unwanted elimination of the glycosyl iodide intermidiate to form the corresponding glucal side product (**Scheme 1**, grey). Slow addition of base iPr_2NEt was found to limit the formation of the side product, affording an increase in yield by up to 20%, and still with an excellent selectivity of *1/0.08*, *α/β*.

Scheme 1. General scheme for the stereoselective synthesis of α-glucosides.



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P45. ACTIVITY BASED PROBES TO REVEAL NEW INSIGHTS INTO P53 DEUBIQUITINATION

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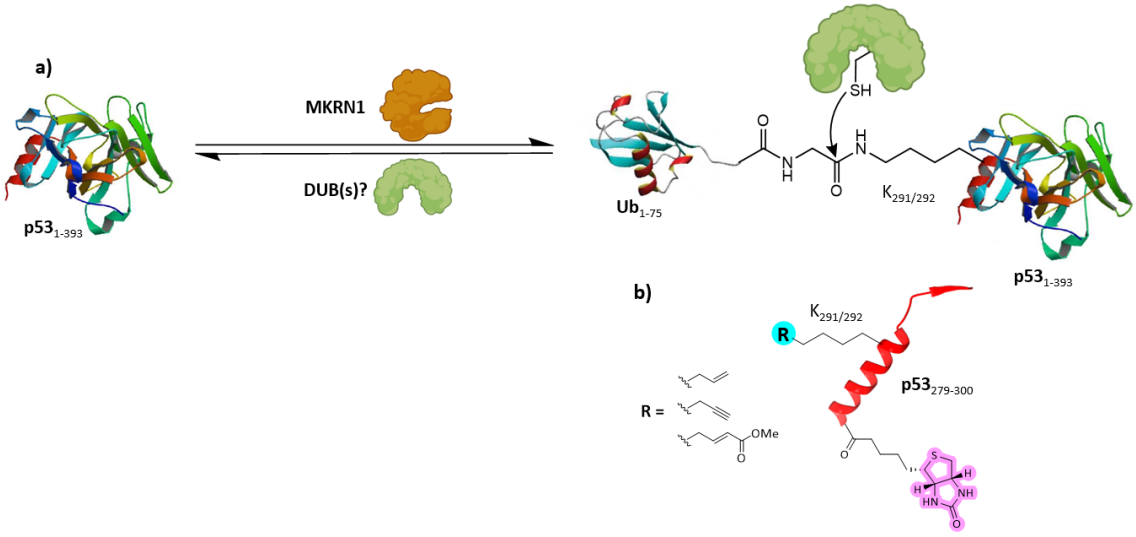
p53 is a highly versatile transcription factor. Its activity is modulated by different Post Translational Modifications (PTMs).[1] In healthy cells, ubiquitination and subsequent degradation by the 26S Proteasome keep p53 basal levels low. However, following stress or DNA damage p53 is saved from proteasomal degradation and activated with a vast array of PTMs, triggering a stress-specific response. In humans, the enzymes responsible for rescuing proteins from proteasomal degradation by removing or editing the ubiquitin tag are a family of proteases called deubiquitinating enzymes (DUBs). With respect to p53, nearly 15 DUBs have been reported to interact with p53, either as positive or negative regulators.[2] However, the DUB (or set of DUBs) responsible for deubiquitination at recently discovered K291/K292 sites has not yet been characterized (**Fig.1a**). To capture this elusive enzyme/s this project aims to synthesize Activity Based Probes (ABPs) that mimic the structure of p53 and feature a reactive handle that is able to covalently modify the DUB interacting with p53.[3] ABPs are useful chemical tools used to characterize new enzymes by capturing their active form in complex cellular environments.[4] In this study, ABPs were generated using a portion of the p53 sequence as a recognition scaffold, in which the key lysines K291/K292 were synthetically modified to incorporate different electrophilic moieties (**Fig.1b**). Following covalent labelling in the DUB active site, a biotin tag allowed for visualization of labelled proteins and their isolation and characterization by proteomic assays. Being designed to target p53 deubiquitination only, this approach aims to discover new functions of DUB enzymes and increase our knowledge on p53 PTMs.



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P46. THE PREPARATION OF DENSELY FUNCTIONALISED CHIRAL PYRROLIDINES BY THE ASYMMETRIC [3+2] CYCLOADDITION REACTION FOR APPLICATION IN ORGANOCATALYSIS

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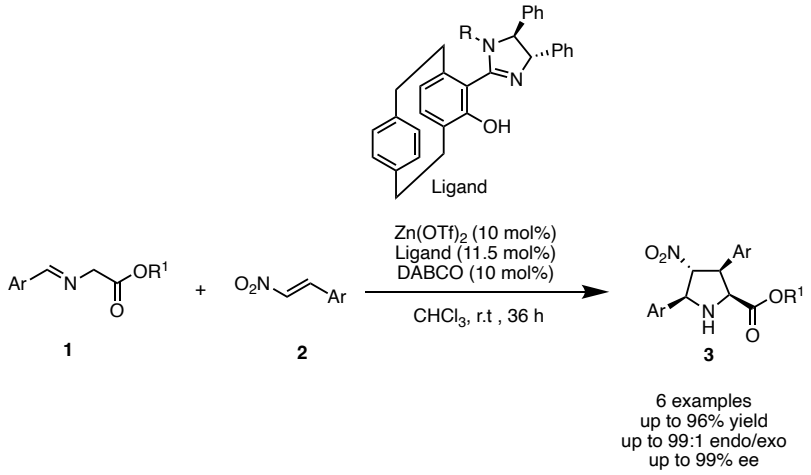
Asymmetric organocatalysis especially pyrrolidine-containing organocatalysts has become an essential part of modern chemistry research,.[1,2] This methodology can also be used to prepare pyrrolidines of medicinal interest.[3]

Recently, the Guiry group has synthesised a novel class of planar chiral N,O [2.2]paracyclophane ligands and applied these ligands in the first example of Zn-catalysed asymmetric [3+2] cycloadditions to furnish pyrrolidines in excellent yields, diastereoselectivity and enantioselectivity.[4] The key objectives of the present investigation was to prepare the UCD-Imphanol class of ligands reported by the Guiry group and expand their scope within the Zn-catalysed asymmetric [3+2] cycloaddition by using different activated dipolarophiles to give a range of densely functionalised pyrrolidines. Presented here is the optimisation steps, where these ligands were shown to perform excellently in the first Zn catalysed [3+2] cycloaddition reaction of azomethine ylides (**1**) and trans-β-nitrostyrenes (**2**). The resulting nitro-pyrrolidines (**3**) were afforded in excellent yields of up to 96%, 1:99 endo/exo ratio and up to 99% ee (Scheme 1) with several examples to date. Future work will apply these ligands in organocatalytic reactions.



Scheme 1: General Scheme of the Zn-catalysed [3+2] cycloaddition of imino esters and trans-β nitrostyrenes using UCD-Imphanol ligands

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P47. CARBON DIOXIDE UTILISATION FOR CONSTRUCTION OF HIGH VALUE CARBOXYL-CONTAINING ORGANIC PRODUCTS

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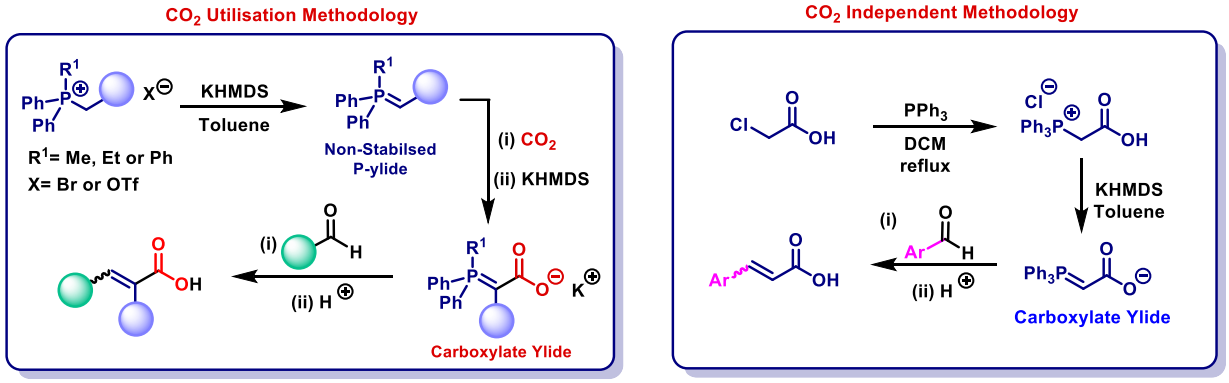
Employing waste products as starting materials for chemical transformations is a key step in addressing the global challenges of sustainable production and consumption. The greenhouse gas CO_2 is perhaps the most significant waste product of the industrialised world.[1] Developing a method for the conversion of a harmful environmental waste product into carboxyl-containing organic products can allow CO_2 to be used as a one-carbon (C1) chemical building block. Phosphonium ylides (P-ylides) have the ability to activate CO_2 into reactive P-ylide CO_2 adducts.[2,3] This activated form of the C1 feedstock can be incorporated into high value carboxyl-containing products and biologically active compounds.

α,β-Unsaturated carboxyl containing organic products are ubiquitous in nature and this structural motif is responsible for the biological activity of many such organic products.[4] It has been found that α,β-unsaturated carboxylic acids can be synthesised using two comparable synthetic routes. The CO_2 utilisation methodology involves the in-situ generated P-ylide activating gaseous CO_2, forming the P-ylide CO_2 adduct. A novel Wittig reaction occurs between the P-ylide CO_2 adduct and aromatic, heterocyclic, and aliphatic aldehydes forming α,β-unsaturated carboxylic acids in moderate to high yields. This telescoped process has shown a high degree of selectivity for the *E*-alkene. This methodology has also been utilized for the synthesis of pharmaceutically relevant organic products.

A route for CO_2 independent generation of the activated P-ylide CO_2 adduct starting with carboxymethyltriphenylphosphonium chloride has also been developed. This novel route can be used to test substrate suitability and reaction conditions independent of the CO_2 utilisation methodology.



Scheme 1: CO_2 Utlilisation Methodology and CO_2 Independent Methodology

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P48. THE DEVELOPMENT OF NOVEL FERROCENYL COMPOUNDS *VIA* ACID-MEDIATED TRANSFORMATIONS AND THE DIASTEREOSELECTIVE SYNTHESIS OF A NOVEL TRICYCLIC INDENE

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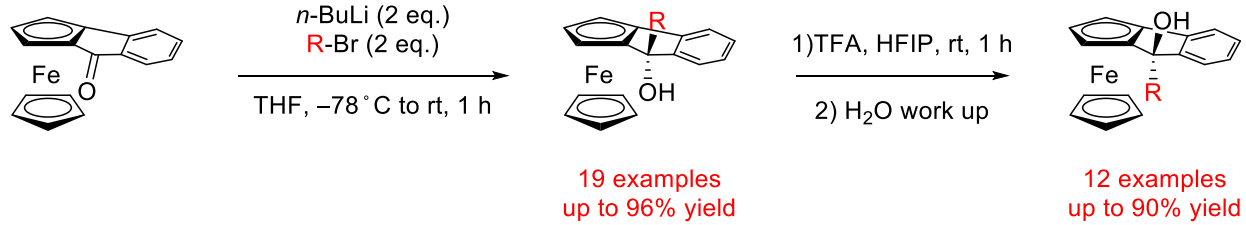
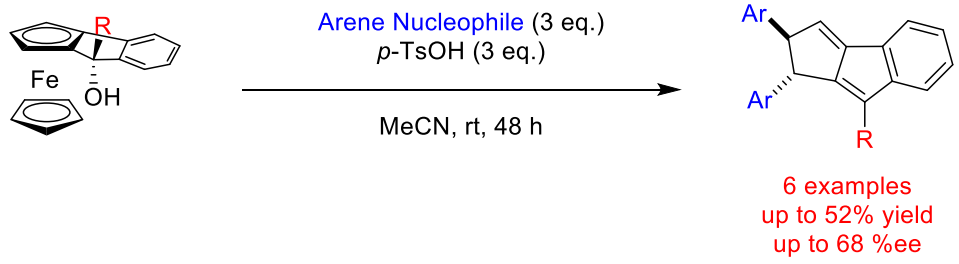
Ferrocene was discovered in 1951 by Kealy and Pauson and has since found uses in asymmetric catalysis, organometallic chemistry, and medicinal chemistry.[1] The Guiry group have previously reported the optimised synthesis of chiral ferrocenyl scaffolds and applied these as ligands in asymmetric catalysis.[2] This project investigates acid-mediated transformations of ferrocenyl alcohols. The reactivity and selectivity of the ferrocenyl monoketone has been exploited in this project for the synthesis of 19 chiral α-ferrocenyl alcohols in high yields of up to 96%. The acid-mediated inversion of the chiral centre at the α-ferrocenyl position was reported in 2020.[3] The scope of this reaction has been further investigated in this project to access 12 inverted chiral alcohols in high yields of up to 90%. Potential uses of the inverted ferrocenyl alcohols are currently under investigation.



A novel tricyclic indene has been synthesised *via* an acid-mediated arylation of ferrocenyl alcohols. A di-C-H-functionalisation of the unactivated cyclopentadienyl ring of the ferrocenyl alcohol results in deprotection of the fulvene and a loss of iron. This is a diastereoselective reaction as only the *trans*- tricyclic indene is observed, and *cis*-addition does not occur. The structure of the tricyclic indenes has been confirmed by X-ray crystallography. Work is ongoing in further exploring the scope and the mechanism of this reaction.



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P49. SYNTHESIS OF TRIARYLSULFONIUM SALTS AND THEIR APPLICATIONS IN ORGANIC SYNTHESIS

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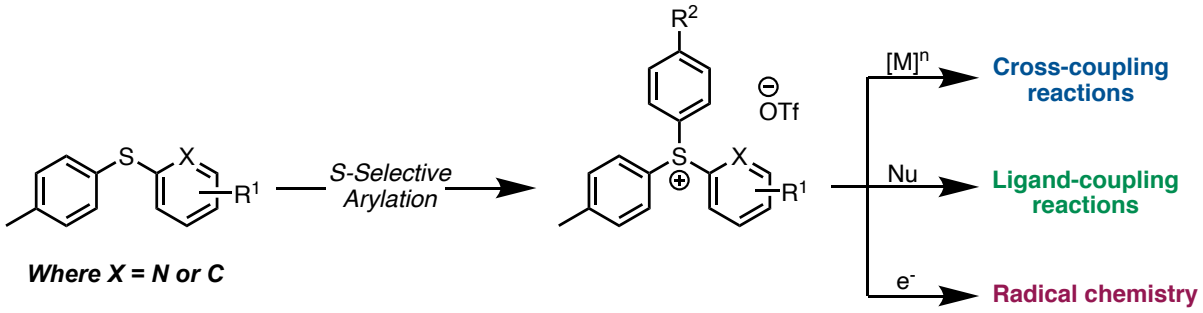
Sulfonium salts are a class of compound finding increased use in organic synthesis, notably in C-C bond formation.[1] Triarylsulfonium salts containing a pyridyl or polyfluorinated aryl ring represent underexplored examples of these salts. 2-Pyridyl and polyfluorinated arylboronic acids undergo rapid protodeboronation under aqueous conditions.[2] As a result these substrates show low reactivity in certain C-C bond forming reactions, such as Suzuki-Miyaura cross-couplings.

Presented here is a general strategy for the synthesis of triarylsulfonium salts containing a 2-pyridyl or polyfluorinated moiety.[3] A range of sulfonium salts showing good functional group and substitution pattern tolerance are shown. The resulting salts were then applied in the transititon metal-free synthesis of biaryls, the utility of which is highlighted by the synthesis of unsymmetrical bipyridine ligands.[4,5] Also presented here is current work on the development of the applications of the polyfluorinated salts in organic synthesis.



Scheme 1. Synthesis of triarylsulfonium salts and their applications in organic synthesis.

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P50. NICKEL CATALYSED MIGITA-LIKE CROSS COUPLING OF GLYCOSYL THIOLS

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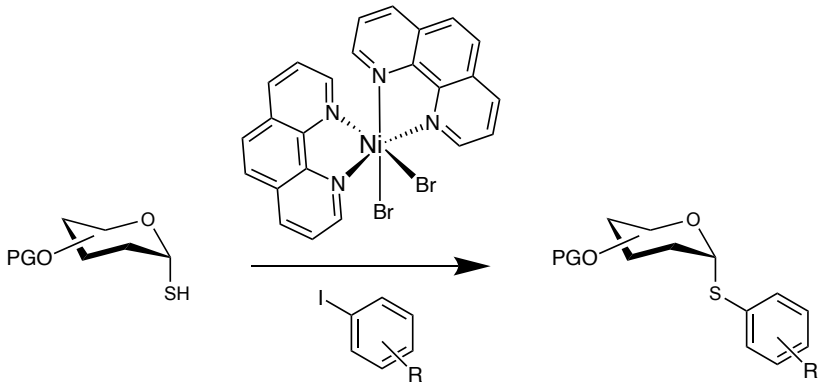
Glycans are a diverse class of molecules with a range of biological roles such as cell signalling and immunity.[1] Their synthesis is crucial in understanding diseases and developing new therapies. Thiosugars, especially 1-thioglycosides, have become ubiquitous in carbohydrate chemistry as glycosyl donors. Their popularity arises from their stability, mild activation, and tuneable reactivity.[2] Thioglycosides are relatively easy to access in the 1,2-*trans* configuration, however the 1,2-*cis* analogues are comparatively challenging. Hence, 1,2-*cis* thiosugars remain underexplored, despite displaying distinct properties compared to their anomers.[3,4] Anomeric configuration is also crucial in the design and synthesis of glycomimetics where the stereochemistry of a glycosidic linkage can determine biological activity.[1] Rather than treating the sugar moiety as an electrophile for synthesis of thioglycosides, we have used glycosyl thiols as a nucleophilic starting material. This way anomeric configuration can be pre-determined, allowing for synthesis of stereochemically defined thioglycosides. We demonstrate the use glycosyl thiols in a Migita-like coupling to synthesise aryl thioglycosides via thiolate generation. By employing a Ni (II) catalyst,[5] this work circumvents the use of expensive and scarce palladium, which is also known to suffer from fouling in the presence of thiolates. A number of aryl thioglycosides have been synthesised in good to high yields, while maintaining the native stereochemistry at the anomeric centre.



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P51. SYNTHETIC STRATEGIES TOWARDS AN EFFICIENT AND MULTIVALENT *CRYPTOCOCCUS NEOFORMANS* VACCINE

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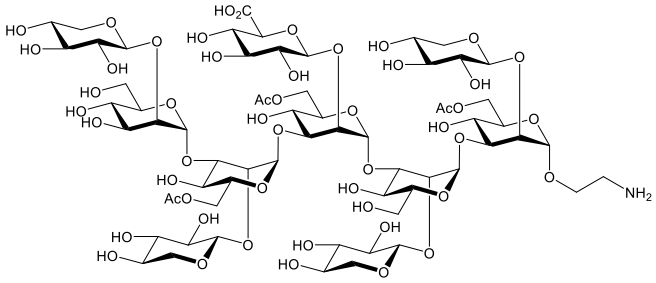
Cryptococcus neoformans is an opportunistic fungal pathogen associated with pneumoniae and acute meningitis. Immunocompromised patients are particularly affected since the pathogen is accounted for 15% of HIV-related deaths worldwide. Lack of efficient and cost-effective treatments, and unevenly distributed diagnosis tools added to it, rank *C. neoformans* first within the critical priority group in the World Health Organization fungal priority pathogens list. [1]

30 years ago, we published the first total synthesis of oligosaccharides mimicking the capsular polysaccharides (CPSs) of the fungus.[2] Theses syntheses have been further developed and optimized throughout the years to facilitate efficient syntheses of numerous glucuronoxylomannan (GXM) structures, representing *C. neoformans'* CPSs. Among them, a decasaccharide (**I**) has been found to be a promising vaccine candidate.[3,4]

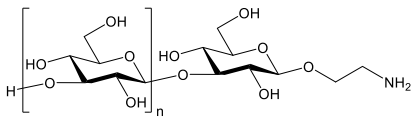
However, GXM are not the only antigenic saccharide structures that can be found within the cell wall of the fungus. Typically, β-1,3-glucans (**II**) are functional linear homopolymers of glucose which have been found of high interest in vaccinal strategies. Namely, their use as potent vaccine adjuvants has been pointed out.[5,6] Their involvement within the design of a novel efficient broad-coverage cryptococcal vaccine is yet to prove.

We present herein a summary of the implemented synthetic strategies to access the GXM decasaccharide (**I**) in one hand and linear β-1,3-glucan structures (**II**) on the other hand.



I

GXM decasaccharide



II

-1,3-glucan

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