Department of Chemistry- *Postgraduate Conference* 2026

The University of Manchester (UK) | 18-19 June 2026

# 2026 Chemistry PGR CONFERENCE

# *Programme*

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## Thursday 18th June

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|---|---|---|
| 08:45 - 09:15 | **Welcome with Coffee** | **Chemistry Concourse** |
| 09:15 - 09:45 | **Opening Remarks**- Prof. Martin Attfield | **LTG.51** |
| 09:45 - 10:45 | **PGR Talks** - Morning Session<br>see *pages* 5-7 *for full programme* | **LT G.51-G.53-G.54** |
| *from 10:45* | **Break** | |
| 11:05 - 12:05 | **PGR Talks**- Morning Session Continued<br>see *pages* 5-7 *for full programme* | **LT G.51-G.53-G.54** |
| *from 12:05* | **Lunch + Poster Session**<br>see *pages* 10-11 *for poster board a/location* | **Schuster Building**<br>***JBB Theatre*** |
| 14:00 - 15:30 | **PGR Talks** -Afternoon Session<br>see *pages* 5-7 *for full programme* | **LT G.51-G.53-G.54** |
| *from 15:45* | **Tea and Coffee** | **Chemistry Concourse** |

## Friday 19th June

| | | |
|---|---|---|
| 08:45 - 09:30 | **Welcome with Coffee** | **Chemistry Concourse** |
| 09:30 - 10:30 | **PGR Talks** - Morning Session<br>see *page 8-9 for full programme* | **LT G.51-G.53-G.54** |
| *from 10:30* | **Break** | |
| 10:50 - 12:00 | **PGR Talks**- Morning Session Continued<br>see *page 8-9 for full programme* | **LT G.51-G.53-G.54** |
| *from 12:00* | **Lunch + Poster Session**<br>see *pages 12-13 for poster board a/location* | **Schuster Building**<br>***JBB Theatre*** |
| 14:00 - 15:30 | **PGR Talks** -Afternoon Session<br>see *page* 8-9 *for full programme* | **LT G.51-G.53-G.54** |
| *from 15:30* | **Coffee Break** | **Chemistry Concourse** |
| 16:00-16:30 | **Closing Remarks** - Prof. David Procter<br>*PCR Prizes Announcement* | **LTG.51** |
| *from 16:30* | **Wine Reception** | **Chemistry Concourse** |

## Thursday 18th June

### *Thursday 78th* - LT G.51

***Chair:* Dr Raphael Johnson**

| | | | |
|---|---|---|---|
| 9:45 | Daniel Corman | PHYS | Achieving uniform and strong in situ NMR sample illumination in cryogenic probes |
| 10:00 | Karthik Kumaran Saravanan | PHYS | Understanding electrochemical behaviour at unconventional liquid/liquid interfaces through charge transfer and electrodeposition |
| 10:15 | Sittipong Kaewmorakot | PHYS | Electrowetting on Carbon electrodes |
| 10:30 | Prithvi Moharana | PHYS | Investigating the Structural Dynamics of the XRCC4-SUMO Protein System Using Electron Paramagnetic Resonance {EPR) Spectroscopy and Molecular Modelling |
| | **Break - *Next Chair:* Dr Joseph Flitcroft** | | |
| 11:05 | Jaiming Chung | CAT | CHQuant: A Protocol For Quantifying Conformational Sampling with Convex Hulls |
| 11:20 | Toby Thompson | CAT | Electron and Nuclear Spin Dynamics of Lanthanide Complexes in Solution |
| 11.35 | Reece Marsden | CAT | A Deflation Algorithm for the Global Optimisation of EPR Spectra |
| 11.50 | James O'Brien | CAT | Application of $\sigma$-hole Interactions Within Organocatalysis |
| | **Lunch + Poster Session - *Next Chair:* Dr Khaled Parvez** | | |
| 14.00 | Carletta Wong | MAT | Electrical and Thermal Transport in Printed Graphene Thin Films with Tuneable Seebeck Coefficient |
| 14.15 | Ivan Myring | MAT | Discovery Tools for Polymers to Extract and Stabilise Membrane Proteins |
| 14.30 | Juliana Morell | MAT | Direct Writing of Nanoscale Semiconductors from Single-Source Precursors |
| 14.45 | Saurav Kalluvadi Veetil | MAT | Direct imaging elucidates ionic memory in two-dimensional nanochannels |

## *Thursday 78th* - LT G.53

***Chair:*** **Dr Hikaru Ishikura**

| | | | |
|---|---|---|---|
| 9:45 | **Lukas Marrow** | **ORG** | Macroscopic contraction of a gel by an enhanced molecular motor |
| 10:00 | **Ethan Lim** | **ORG** | (Aza)-Michael Addition of Aliphatic Amines and Enolates to Aryl Alkenes via Organobase Catalysis |
| 10:15 | **Ron Verdijk** | **ORG** | Deep Learning Reveals the Structure of Kinetic Degeneracy in Catalytic Mechanisms |
| 10:30 | **Orla Conboy** | **ORG** | Thiophene to N-Heteroarene Conversion |
| | | | **Break -** ***Next Chair:*** **Dr Mengjiao Wu** |
| 11.05 | **Xiaotian Xie** | **ORG** | Synthesis of Chondroitin Sulfate-Related Oligosaccharides Fragment Precursors |
| 11.20 | **Lauren Holder** | **ORG** | Synthesis of a Small Molecule Library to Explore New Inhibitory Prospects for Pathogenic Fungi |
| 11.35 | **Affe Conboy** | **ORG** | Skeletal Editing of Pyridines Through Ring Opening |
| 11.50 | **Joaquin Baixeras Buye** | **ORG** | Photolytic proofreading of diastereoselectivity during chemically fuelled rotaxane assembly |
| | | | **Lunch + Poster Session -** ***Next Chair:*** **Dr Felix Hernandez Culebras** |
| 14.00 | **Muze Li** | **ORG** | 7,4-Ester Migration Mediated by Samarium Diiodide and Light |
| 14.15 | **Jannik Schiess!** | **ORG** | Influence of Substituent Effects on a Catalysis-Driven Molecular Single-Bond Rotary Motor |
| 14.30 | **Jacob Roberts** | **ORG** | Chemical Synthesis of Fluorinated Carbocyclic Nucleoside Analogues from the Chiral Pool |
| 14.45 | **Michael Wong** | **ORG** | Stereoselective Ruthenium-Catalysed meta-C(sp')-H Alkylation with $\alpha$-halocarbonyls |
| 15.00 | **Ruth Garner** | **ORG** | Phosphorus(V)-based red light photoredox catalysis |
| 15.15 | **Emily Cramp** | **ORG** | Inverted metal-free active template synthesis of rotaxanes via axle-mediated rotaxination |

## *Thursday 78th* - LT G.54

***Chair:*** **Dr Thomas King**

| | | | |
|---|---|---|---|
| 09:45 | Sophie Wulf | BIO | Biocatalytic cascade synthesis of $\beta$-methyl-branched-amino-acids |
| 10.00 | Thomas Hoare | BIO | Are Tags Always Benign? Disordered Tags Unfold GFP in Electrospray Droplets |
| 10.15 | Ho Fung Mack | BIO | Replacing chromatography with ice-affinity for protein purification using a genetically encoded Crye-Tag |
| 10.30 | Faisal Ciwa | BIO | Bioengineered Spider Silk Mimetics and the Means to Spin them |
| | **Break - *Next Chair:* Dr Akalabya Bissoyi** | | |
| 11.05 | Tiasa Biswas | BIO | Structural Understanding of Novel Fungal Terpene Synthases/Cyclases |
| 11.20 | Elena Rongione | BIO | A Ru-P4S0 analogue: Preparation and strategies for decarbonylation |
| 11.35 | Aitor Carneiro | BIO | Chemoproteomic Profiling of Small Molecule Phenotypic Hits to Investigate Cancer Mechanisms |
| 11.50 | Alexandru Ilie | BIO | DMSO and Serum-free Cryopreservation of T-Cells in Vials and Multiwell plates enabled by Glycerol-Osmoprotectant Formulation |
| | **Lunch + Poster Session - *Next Chair:* Dr Emily Radley** | | |
| 14.00 | Bhumishree Dehury | BIO | Development and characterization of a biosensor for 2,S-furandicarboxylic acid in Pseudomonas putida |
| 14.15 | Emily Rushworth | BIO | Enzymatic activation of sulfur heteroaromatics facilitates downstream enantioselective cross-coupling reactions |
| 14.30 | Kevin Hamdani | BIO | Characterisation of Isolated Reductase Domains from a Panel of Self-Sufficient Thermostable Cytochromes P4S0 |
| 14.45 | Carly Masonheimer | BIO | Enzymatic Metal-Hydrogen Atom Transfer with a Cobalt Protoporphyrin Cofactor |
| 15.00 | Harry Spacey | BIO | Design and Engineering of Light-Activated Enzymes for Chemical Production |

## Friday 19th June

### *Friday 19th* - LT G.51

***Chair:* Dr Jinge You**

| | | | |
|---|---|---|---|
| 9.30 | Thomas Duddles | MAT | Synthesis of Novel Members of the Al MIL-S3 Solid Solution Series, AlFx(OH)l-x(bdc), Displaying Incrementally Modified Flexing Behaviour and Hydrophobicity |
| 9.45 | Yashoda Abeykoon | MAT | Crystallization of Elusive Form II Paracetamol onto Edible Substrates by Gas Blow Coating |
| 10.00 | Robbie Clark | MAT | Beyond Activity: Defining Catalyst Sustainability in Depolymerisation Systems |
| 10.15 | Cigdem Oral | MAT | Using Biomimetic Ice-Binding Polymers to Control Cryogel Architecture and Mechanical Behaviour |

**Break - *Next Chair:* Dr Ben Reant**

| | | | |
|---|---|---|---|
| 10.50 | Volkan Yasakci | INO | A Novel Design of Immuno-PET Imaging Agent: Using Copper-isotopes for Nanoparticles and Radiolabelled Biospecifics |
| 11.05 | Jodie Glasgow | INO | Synthesis of lanthanide-based silica chelates for molecular upconversion |
| 11.20 | Heather Partlow | INO | An Investigation of Catalytic and Stoichiometric Stepwise Conversion of N, to $NH_3$ Mediated by a Uranium Complex |
| 11.35 | Wang Te | INO | Kinetic separation of $C_3H_6$ from $C_3HJC_3H_8$ Bearing a Zn-MOF |
| 11.50 | Cameron Deakin | INO | f-Element Cyclooctatetraenide Sandwich Complexes |

**Lunch + Poster Session - *Next Chair:* Dr Elliott Nunn**

| | | | |
|---|---|---|---|
| 14.00 | Rebecca Sheppard | INO | Towards the Isolation of a Novel Actinide Metallacyclopropyne |
| 14.15 | Zhu Yuxiang | INO | Stepwise Filling during Efficient Low-Pressure $NO_2$ Adsorption in an Aluminium Metal-Organic Frameworks |
| 14.30 | Gao Yan | INO | Synthesis and DFT calculation of a Uranium Imidazo Carbene Complex |
| 14.45 | Boyang Zhang | INO | Modified Zeolites for Ethane/Ethylene Separation |
| 15.00 | Lucy McKay | INO | Effect of Ligand Methylation on Diastereoisomerism of M4L6 Tetrahedra |
| 15.15 | Benjamin Moore | INO | Optimisation of overall CO, photoreduction over cerium-based MOFs |

## *Friday 19th* - LT G.53

**Chair: Dr Pol Martfnez-Balart**

| | | | |
|---|---|---|---|
| 9:15 | **Daniel Couto** | **ORG** | Reading and Writing Stereochemical Information Encoded in a Molecular Track |
| 9.30 | **Tom Harris** | **ORG** | Organic Salt-Catalysed Nucleophilic Ami nation |
| 9.45 | **Ali Najmi** | **ORG** | Mechanochemistry for the C-H Trifluoromethylation of (Hetero)Arenes |
| 10.00 | **George Bilionis** | **ORG** | Conversion of Alkynes to $\beta$-Keto Nitriles via Photoactivation of an Isoxazole-Triarylamine Electron Donor-Acceptor Complex |
| 10.15 | **Victoria Jiang** | **ORG** | Hydrogen-Bonding in Benzylic Amide Macrocycle-Diamide-[2]Rotaxanes |

**Break - *Next Chair:* Dr Jaime Klein**

| | | | |
|---|---|---|---|
| 10.50 | **Christopher Otun** | **BIO** | Exploiting Enzyme Reversibility for Selective Deuteration in Heavy Drug Synthesis |
| 11.05 | **Zhuoyun Chen** | **BIO** | Long-term kinetics dictated by Active-Inactive Conformational Dynamics Underlie Class D $\beta$-Lactamase Hydrolysis of Carbapenem |
| 11.20 | **Liam Beardmore** | **BIO** | Reversible Functionalisation of Synthetic Cellulosic Oligosaccharides |
| 11.35 | **Minhui Zhu** | **BIO** | Development of a Quantitative MRM assay from Skin Swabs Rich in Sebum to Diagnose Parkinson's Disease |
| 11.50 | **Marta Dolinska** | **BIO** | Electrochemical Control of Multi-Enzyme Cascades in Electro-Biosynthesis and Sensing |

**Lunch + Poster Session - *Next Chair:* Dr Lloyd Murphy**

| | | | |
|---|---|---|---|
| 14.00 | **Madeline Lombardo** | **BIO** | CRISPR-Casl3a for rapid, point-of-care genotyping in pharmacogenomics |
| 14.15 | **Kelly Zhou** | **BIO** | Exploring the evolvability of de nova hydrolases featuring a catalytic triad |
| 14.30 | **Smruti Biswal** | **BIO** | Modelling Sq gains in aggressive prostate cancer through synthetic genome engineering |
| 14.45 | **DongxuYuan** | **BIO** | CYP723 Mediates Stepwise Oxidation of C4-Methyl Groups in Mycobacterial Sterol Catabolism |
| 15.00 | **Annette Egerstrom** | **BIO** | Biocatalytic approaches for the synthesis of 3'- protected nucleotides |
| 15.15 | **Hari Newnham** | **BIO** | Hybrid Native Ion Mobility - Mass Spectrometry Methods for Enhanced Protein Characterisation and Increased Automation & Throughput |

## *Thursday 18th June*

| No | Presenter | Section | Poster Title |
|---|---|---|---|
| | **Samarth Pratap Singh** | **BIO** | Engineering Alditol Oxidases for Broad-Scope Oxidation of Rare Polyols |
| 2 | **Ruichen Zhang** | **INO** | Development of an Advanced In-Situ Gas-Loading System for the Structural Study of Porous Materials on WISH |
| 3 | **Kaysa Sekhavati** | **MAT** | Synthesis of [7]-helicene diimide with an extended backbone: Optical, Chiroptical and Electronic studies |
| 4 | **Maria Kolyagina** | **ORG** | Photochemical Hydroarylation of Enamides using Aryl Sulfonium Salts: A Modular Synthesis of Arylethylamines |
| 5 | **Francis Gallois** | **BIO** | Photophysical investigation of a visible light 2+2 cyclase |
| 6 | **Shruti Goel** | **MAT** | Chemoenzymatic Synthesis ofSialylated Polymer-tethered Nanoparticles |
| 7 | **Yuting Chen** | **INO** | Upcycling waste to value-added with hetero-atomic MFI zeolites |
| 8 | **Kacper Kulikowski** | **PHYS** | Evaluating the mobility-size-shape relationship of nanosized ions across sizepressure scales in Ion Mobility Spectrometry (IMS) |
| 9 | **Adam Lehchilli** | **ORG** | Allosteric Regulation of a Chemically Fuelled Rotary Molecular Motor through Bipyridine-Pt(II) Complexation |
| 10 | **Agne Sabaliauskyte** | **BIO** | Investigating USP7 Dynamics and Binding Interfaces with Solution NMR to Guide Cancer Drug Discovery |
| 11 | **Hannah Knight** | **INO** | Synthesis, Structure and Reactivity of Iron Carbonyl Complexes |
| 12 | **Samuel Ericson** | **CAT** | PolyRapid: Automated High-Throughput Screening of Polymers Using a Computational Workflow |
| 13 | **Jessica Steele** | **CAT** | A High-throughput screening of the Composition Effects on Thermodynamic and Structural Properties in styrene-butadiene Rubber Compounds |
| 14 | **Anson Fong** | **ORG** | Oxadiazolones as precursors to N-arylcarbamimidate esters |
| 15 | **Qiutong Lin** | **BIO** | Biocatalytic SNAr with Nitroalkanes Enables Access to Chiral $\alpha$-Tertiary Amine Precursor |
| 16 | **Isabelle Nebel** | **PHYS** | Control of the Local Environment Enables Sustainable Methanol Production from CO2 |
| 17 | **Yulia Sorokina** | **MAT** | Aerosol Jet-printing of Water-based and Biocompatible Graphene Inks |

| | | | |
|---|---|---|---|
| 18 | **Ashish Choudhary** | **BIO** | Production of cryopreserved rapid viral diagnostics |
| 19 | **Ben Hillman** | **ORG** | Connective Isomerization of Pyrimidines to Pyridines via Unactivated Ring Opening |
| 20 | **Mor Tsfania** | **INO** | Molecular Qugates: Building Tunable Light-switchable Multi-Qubit Architectures |
| 21 | **ZixuanXue** | **PHYS** | Pure shift 7D TOCSY with high sensitivity |
| 22 | **Saverio Canu** | **PHYS** | Optimising Rapid Scan EPR for the kinetic study of light-induced processes |
| 23 | **Jay Johnson** | **BIO** | Making cells into factories: New metalloenzyme radical catalysts for in vivo synthesis monitored by whole cell EPR |
| 24 | **Noorah Almulhim** | **ORG** | Smiles-Truce Rearrangements via Carbon Dioxide Radical Anion ($CO_2{}^{\cdot-}$) |
| 25 | **Liangmeng Hao** | **INO** | Coherent Manipulation of Organometallic Ti (III) and Hf (III) Molecular Spin Qubits |
| 26 | **Thomas Hinson** | **PHYS** | Electrochemical Electrolyte Characterisation for Membrane Free Flow Batteries |
| 27 | **Nilanjan Bhaduri** | **ORG** | Trifluoromethylation of Pyridines through Skeletal Rearrangement |
| 28 | **Warren Ho** | **BIO** | Engineering an essential gene neochromosome in Saccharomyces cerevisiae |
| 29 | **ZhiwuWang** | **MAT** | Thermoelectric properties of clathrates Si45Ge45 and Sn45 |
| 30 | **Iulia Cisu** | **BIO** | Expanding the Scope of Carbohydrate Active P450s for Selective Saccharide Demethylation |
| 31 | **Megan Campbell** | **PHYS** | Investigating the Effects of Non-Steroidal Anti-Inflammatory Drugs on Lipid Metabolism in Prostate Cancer using Multimodal Imaging |
| 32 | **Henry Box** | **BIO** | Structure and Mechanism of PhdC, a Prenylated-Flavin Maturase |
| 33 | **Ahmed Alghizzi** | **INO** | Effect of Mesaconate Linker Modification on MOF-807 $C_2H$J$C_2H_4$ Separation |
| 34 | **RuiyiYang** | **BIO** | Biosensor-Guided Directed Evolution of Silyl Hydrolases for Sustainable Organosilicon Recycling |
| 35 | **Miltiades Angelides** | **CAT** | Towards Optimization of Coarse-Grained Forcefields for Polymers Using Gaussian Processes |
| 36 | **William Chipperfield** | **BIO** | Producing Triacylglycerides for Biofuel from Lignocellulosic Hydrolysate via Yarrowia *lipolytica* |
| 37 | **Aparna Augustine** | **MAT** | Photoinduced dynamically controlled ice binding materials |
| 38 | **Lani Peel** | **BIO** | Optimising FDCA bioproduction using a genetically encoded biosensor |
| 39 | **King Man Leung** | **BIO** | From Structure to Catalysis: Engineering Flavin-Dependent UbiD Biocatalysts from Extremophiles for Sustainable Chemical Transformations |

## Friday 19th June

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| 41 | Chloe Lipinski | BIO | Integration of Synthetic Biology and Chemoenzymatic Approaches towards Diversified Tetrahydroisoquinoline Alkaloids |
| 42 | Shijie Liu | PHYS | Reactor geometry regulates local reaction environment in CO2RR |
| 43 | Samilli Vasconcelos Lima Bulhoes | INO | Activation of CO, by lanthanum tris(cyclopentadienyls |
| 44 | Sophie Kelly | BIO | Electro-enzymatic platforms for CO2 fixation into complex high value chemicals |
| 45 | Olivia Aten | PHYS | From 4D to 2D: Efficient Computation of the Electron Correlation Energies of Atoms in Molecules |
| 46 | Akash Das | BIO | Ruthenium-Based Metalloenzymes for Enantioselective C-H Functionalisation |
| 47 | Gayani Kadukara | MAT | Ultra-Thin MOF-S Crystals Enabled by Gas Blow Coating |
| 48 | Chengzhi Hu | INO | Dinuclear Copper Macrocycle for Selective Electrocatalytic CO,-to-Methane Conversio |
| 49 | Ellie Davies | PHYS | Spin-System Selective 2DJ Spectroscopy |
| 50 | Chung Doan | BIO | Biomimetic cobalt porphyrins towards enzymatic C-H fluorination |
| 51 | Oswald Philipsen | ORG | Force-controlled release of monomers with a rotaxane actuator |
| 52 | Yilin An | BIO | Engineering a De novo enzyme for regioselective pyridone SNAr reactions |
| 53 | Tianrui Ma | INO | Cu(Salen) loaded Zr-BTB MOF for electrical ammonia oxidation to nitrite and nitrate |
| 54 | Cristopher Carr | BIO | Implementing a design, build, test, learn pipeline for the discovery of a silyl hydrolase |
| 55 | Alannah Francis | CAT | The Effect of Dynamic Correlation in Simulation of X-ray Absorption Spectra of Uranyl |
| 56 | Alexander Jones | INO | A Novel Vertex for Metal-Organic Cages |
| 57 | Hamzah Almarhabi | PHYS | Tuning Ion Transport with Gate Voltage |
| 58 | Hannah Partenheimer | BIO | Tandem Biocatalytic Oxidation-Cycloaddition Sequences for the Stereoselective Construction of Benzofused Scaffolds |

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|---|---|---|---|
| 59 | Adel Najafimarghmaleki | CAT | Competitive Retention of Na/Cs in Montmorillonite Interlayers: A Hybrid Molecular Dynamics and Grand Canonical Monte Carlo Study |
| 60 | Shiquan Cao | ORC | Alkoxysulfonium Salt Electron Donor-Acceptor Complexes Enable Metal-Free Carboetherification of Unactivated Alkenes |
| 61 | Natalia Sanchez Castro | BIO | Ultrahigh throughput directed evolution of RNA polymerases for in vitro transcription |
| 62 | Modinat Tijani | INO | Synthesis and Study of a Class 11-111 Uranium Mixed-Valence System |
| 63 | Lea Van Dissel | BIO | Interplatform comparison of Ion Mobility Mass Spectrometry Lipid Characterisation |
| 64 | ZhaoCen | MAT | PFAS Removal Using Metal-Organic Frameworks |
| 65 | Daniel Shenton | BIO | Retuning Nature's Potential by Active Site Engineering and Electrochemical Control |
| 66 | Siska Musiam | ORC | Reactive CMC-Based Materials for Multifunctional Antimicrobial Wound Dressings |
| 67 | Ahmad adel a Babtain | INO | Expanding Lanthanide Redox Chemistry Using Redox-Active Pyridine Diimine Ligands |
| 68 | Ivan Petkov | PHYS | Multiphoton Dipolar Spectroscopy |
| 69 | Michael Yuen | BIO | The Uncatalysed Reduction of Flavins by Nicotinamide Analogues |
| 70 | Maria Petraki | BIO | Expanding the Genetic Code for Precision Antibody Engineering |
| 71 | Orry Mayne | INO | Redox Chemistry off-block complexes with a Simple Diamide Ligand |
| 72 | Jana Frohlich | BIO | Biocatalytic Preparation of Sulfated Phenolic Compounds |
| 73 | Ronak Singha | ORC | Force-controlled capture and release of small molecules with covalent organic cages |
| 74 | Charles Moir | INO | The influence of Sf/6d mixing on uranyl bonding and reactivity |
| 75 | Cameron Evans | BIO | High-throughput characterization and engineering of nucleotide synthases for production of nucleoside analogues |
| 76 | Celine Zurr | BIO | Engineered Enzymes for Bimolecular Nucleophilic Substitutions (SN2) |
| 77 | Chloe Haigh | BIO | Biocatalytic Williamson Ether Synthesis |

# Talk Abstracts

# PGR CONFERENCE

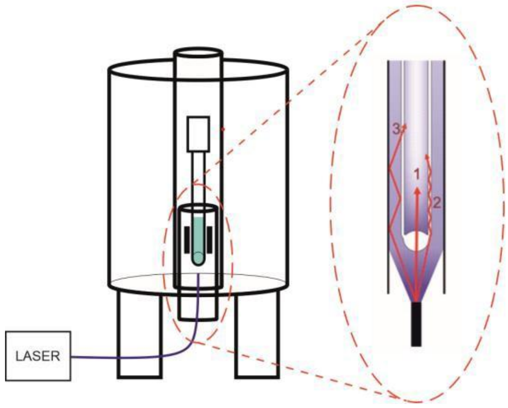
## PHYS

*Section*

# Achieving uniform and strong in situ NMR sample illumination in cryogenic probes

**Daniel Gorman**, Mathias Nilsson, Alexander P. Golovanov

*Department of Chemistry, University of Manchester, Manchester, United Kingdom*




Photochemical and photocatalytic reactions studied in situ by NMR spectroscopy require efficient, uniform sample illumination that is compatible with high optical density samples and high-throughput workflows. Previously it had been suggested that routing optical fibre through a flow accessory port of a cryoprobe allows to illuminate samples from the bottom, enabling automation.[1] While this approach works with samples with low optical density, for highly optically absorbing samples light penetration is severely limited by the large optical path along the sample. Here, we systematically investigate bottom-illumination strategies for light-coupled NMR experiments, examining how light propagation pathways, sample tube geometry, surface treatments, and fibre positioning influence illumination intensity and spatial uniformity.

Using photo-chemically induced dynamic nuclear polarization (photo-CIDNP) as a quantitative, spatially resolved measure of light intensity, we identify three dominant illumination pathways: direct axial transmission through the sample, propagation within tube walls with side scattering, and light transport within the annular gap between the sample tube and probehead bore. Direct axial illumination leads to markedly non-uniform light in optically absorbing samples, whereas redistributing light around the sample and scattering it laterally, using the NMRtorch principle, as earlier suggested by us, significantly improves uniformity.[2] By combining flat-bottom sample tubes, engineered wall etching, and optimised fibre–tube spacing, we achieve near-uniform illumination across the NMR-active volume while maintaining high overall light intensity for a sample with an optical absorbance of 1.7. These results establish practical design principles for robust, automation-compatible illumination setups for light-coupled NMR studies.

## References:

1. Wüster, W. *Magn, Reson.* **2024**, *5*, 61-67
2. Bramham, J.E. *Comms. Chem*, **2022**, *5*, 1-10

# Understanding electrochemical behaviour at unconventional liquid/liquid interfaces through charge transfer and electrodeposition

Karthik Kumaran Saravanan,[1] Robert A. W. Dryfe,[1]
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*karthikkumaran.saravanan@postgrad.manchester.ac.uk*

The Interface between Two Immiscible Electrolyte Solutions (ITIES) is usually constructed with an organic and an aqueous phase and has been studied extensively for more than a century. Despite finding applications in electroanalytical chemistry, electrodeposition of metals and more lately electrosynthesis of free-standing membranes and catalysis, the field is yet to gain traction in mainstream electrochemistry due to lack of industrial scale applications [1-2]. A water-free ITIES is of interest as it can enable interesting chemistries not possible in an aqueous phase enabling new electro synthetic pathways, electrodeposition of non-noble metals and in general broaden the understanding of liquid/liquid interface electrochemistry. Water free Ionic liquid | organic solvent interfaces have been reported by Suzuki, Kucernak's group and Nishi's group, however either they were not focused on understanding the properties of water-free interface or exhibited narrow Polarizable potential Window (PPW) (≤150mV) resulting in their limited ability to study charge transfer reactions at the interface [3-5].

In this work, a new water-free all organic electrochemically polarizable soft interface between Ethylene glycol (EG) and α,α,α Trifluorotoluene (TFT) has been achieved [6]. The partition between EG and organic solvents was first reported by Burton et al. for understanding drug molecule transfer across cell membranes but has never been studied from an electrochemical standpoint. The interface between EG and TFT exhibits a PPW of about 340 mV (Fig1a). This platform enabled quantitative measurements of solvation strength in organic solvents, addressing a key gap in non-aqueous electrochemistry. Electrochemically driven ion transfer and electron transfer have been observed in a water free macro-ITIES for the first time and have also been studied voltammetrically (Fig1b). It was observed that the PPW could be further expanded with controlled water activity in the EG phase. The interface has also been utilized for deposition of gold, palladium and silver at the interface through spontaneous electron transfer. A similar interface was observed with EG and 1,2-dichlorobenzene suggesting EG possibly forms a polarizable interface with the usual organic phases used in conventional ITIES systems.

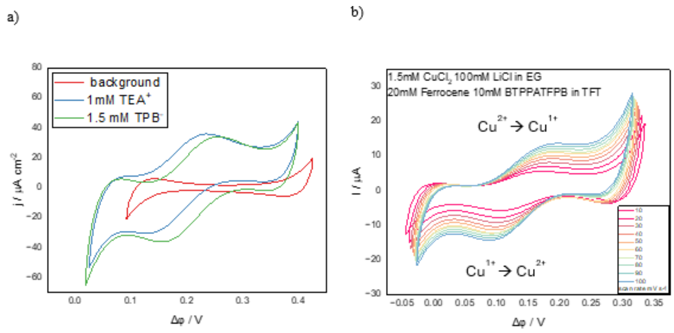


*Fig. 1: a) Cyclic Voltammograms of interface between 100mM LiCl in EG and 10mM BTPPATFPB in TFT (red CV), Ion transfer voltammogram of $TEA^+$ (blue) and $TPB^-$ (green) at the EG | TFT interface. Scan rate=50mV $s^{-1}$. b) Voltammogram showing $Cu^{2+}$ / $Cu^+$ ET at EG | TFT interface.*

## References:

[1] A. Uehara, T. Hashimoto, R. A. W. Dryfe, *Electrochimica Acta* **2014**, *118*, 26-32.
[2] A. Gamero-Quijano, G. Herzog, P. Peljo, M. D. Scanlon, *Current Opinion in Electrochemistry* **2023**, *38*, 101212.
[3] N. E. A. Cousens, A. R. Kucernak, *Electrochemistry Communications* **2013**, *31*, 63-66.
[4] Y. Kuroyama, N. Nishi, T. Sakka, *Journal of Electroanalytical Chemistry* **2021**, *881*, 114959.
[5] M. Suzuki, *Journal of Electroanalytical Chemistry* **1994**, *372*, 39-48.
[6] K. K. Saravanan, R. A. W. Dryfe, *Electrochimica Acta* **2026**, *548*, 147861.

## Electrowetting on Carbon electrodes

**Sittipong Kaewmorakot**,[a,b] Robert A. W. Dryfe.[a,b]

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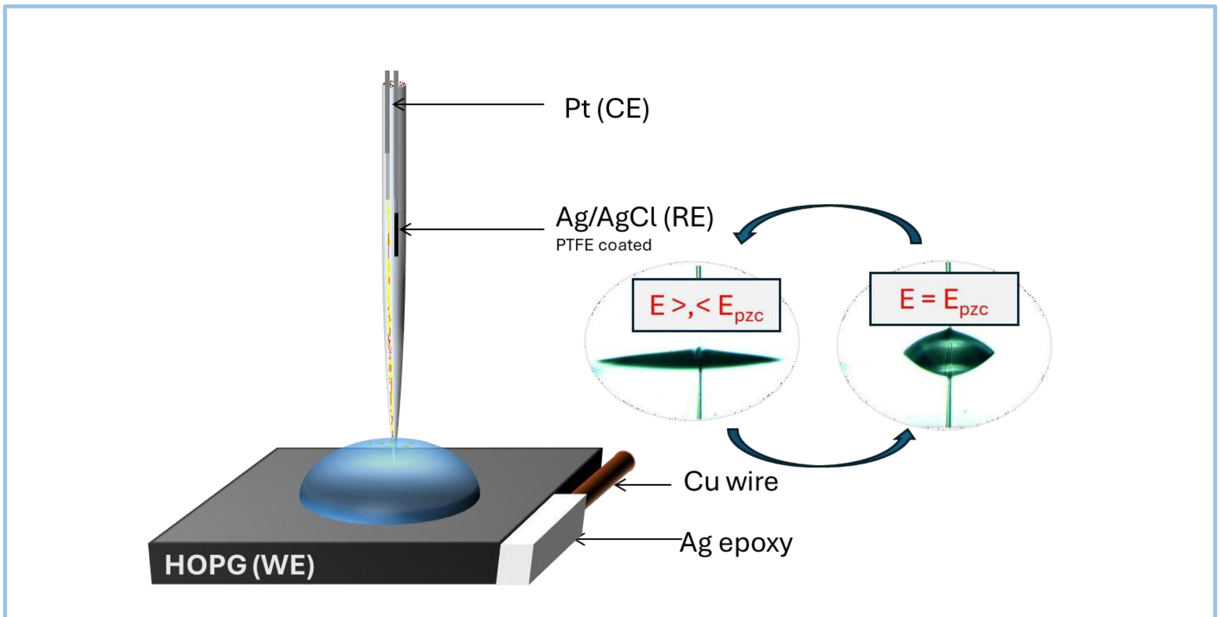
Electrowetting behaviour – the dependence of electrolytes wettability under applied potential bias – is widely used for manipulating the liquids on surfaces. The electrowetting effect underlines a number of applications from optics[1], energy storage[2], to microfluidics[3]. Here, we studied electrowetting directly on different carbon surfaces including highly oriented pyrolytic graphite (HOPG)[4], glassy carbon (GC)[5], boron doped diamond (BDD), and graphene. Water-in-salt electrolytes have been used in order to prevent the electrochemical reactions at interface. Most of carbon surfaces showed the strong adsorption of cations due to significant electrowetting response on negative polarization. However, anions adsorption was observed on HOPG surface. Interestingly, HOPG was also the only substrate that exhibit fully reversible change in electrowetting.

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# Investigating the Structural Dynamics of the XRCC4-SUMO Protein System Using Electron Paramagnetic Resonance (EPR) Spectroscopy and Molecular Modelling

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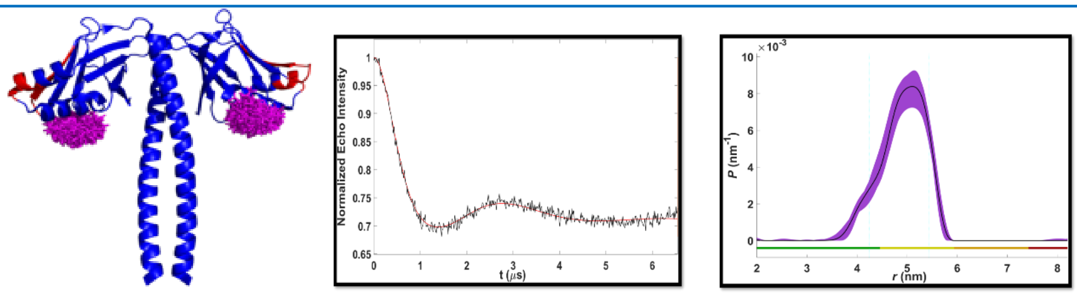
DNA double-stranded breaks (DSBs) are critical forms of DNA damage that, if unrepaired, can lead to cell death, mutations, and cancer [1]. XRCC4 plays a key role in DSB repair via non-homologous end joining (NHEJ) as a homodimeric protein, regulated by small ubiquitin-like modifier (SUMO) chains. These can bind non-covalently or be covalently attached to XRCC4, both potentially enhancing the efficiency of the repair process [2]. Understanding how SUMO modulates XRCC4's structure is key to uncovering regulatory mechanisms in DNA repair. We utilized Pulsed Dipolar Spectroscopy (PDS), specifically Double Electron–Electron Resonance (DEER), to investigate structural changes within the XRCC4 dimer upon SUMO binding. Site-directed spin labels positioned at different XRCC4 domains enabled detection of domain-specific conformational changes, while spin labelling of SUMO provided information on its spatial orientation relative to XRCC4 and validated NMR-derived interaction models. To further validate these models and account for spin-label flexibility, molecular dynamics (MD) simulations of nitroxide spin-labelled systems were performed, and MD-derived distance distributions were compared with experimental DEER measurements. Initial DEER measurements, supported by MMM/HADDOCK predictions and MD simulations, suggest that the XRCC4 dimer retains overall structural integrity upon SUMO binding, with no significant conformational rearrangements observed across the three investigated domains. These findings provide insight into the structural dynamics of the XRCC4–SUMO protein complex and contribute to a broader understanding of regulatory mechanisms involved in DNA repair.




(A) (B) (C)

***Figure 1: Spin labelling and DEER measurements of XRCC4 K72C variant. A)*** *K72C labelled with MTSSL;* ***B)*** *Q-band DEER time trace K72C;* ***C)*** *DEER data for K72C*

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# Talk Abstracts

# PGR CONFERENCE

## CAT

*Section*

# CHQuant: A Protocol For Quantifying Conformational Sampling with Convex Hulls

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## Abstract

Conformational sampling is a key component of the workflow behind any machine learning force field. Existing methods for assessing the coverage of a conformational space can be ambiguous, reference-dependent, and qualitative due to their reliance on visual perception. In this work, we propose CHQuant, a protocol designed to quantify the extent of conformational space coverage. This approach is based on the observation that the movement of atoms defines point clouds that can be characterized by the volumes of the corresponding convex hulls. By applying our method to several small molecules and conformational sampling methods, we show that convex hull volumes behave according to chemical intuition at an atomic, functional group, and molecular level. Therefore, convex hull volumes are useful measures that can be used to compare different sampling methods or data sets. Among many applications, the CHQuant approach monitors the sampling achieved by any molecular dynamics sampler and compares existing conformational databases of the same system.

**Keywords:** Convex hull, conformation space coverage, sub-sampling

# Electron and Nuclear Spin Dynamics of Lanthanide Complexes in Solution

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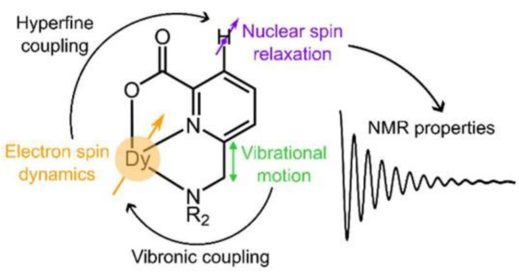
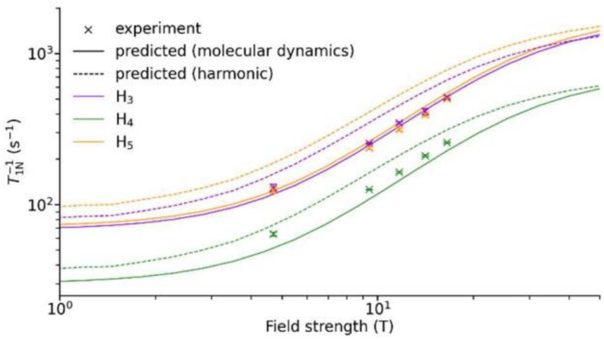
Spin dynamics are essential to the use of lanthanide complexes as contrast agents in magnetic resonance imaging. The PARASHIFT probes, a new, non-gadolinium-based class of agent that can measure both temperature and pH, use the acceleration of nuclear spin relaxation caused by the electron spin to improve their inherently poor signal intensities.[1] However, this process – the paramagnetic relaxation enhancement (PRE) – is poorly understood in solution-phase metal complexes with significant spin-orbit coupling. This is partially because the standard assumptions used to derive equations describing relaxation are invalid for the electron spin. While approximate simulations have been used instead, the complicated behaviour of the ligand field that drives the electron spin dynamics has often necessitated simple models with fitted parameters.[2] We seek to replace these with a fully *ab initio* calculation of the PRE, using simulations of the electron spin as a function of time. The ligand field is generated using CASSCF-SO calculations performed at every step of an *ab initio* molecular dynamics trajectory, allowing a calculation of the PRE that is in extremely good agreement with experiment. The electron spin dynamics are shown to deviate qualitatively from the predictions of the often used, but strictly invalid, Solomon-Bloembergen-Morgan theory. Nuclear relaxation rates are calculated as the sum of two contributions,[3] confirming that the PRE is dominated by the electron spin dynamics at low field, but by rotational motion at high field. This methodology is extremely computationally expensive; to alleviate this, we also investigate simulations driven by a complex's harmonic normal modes. Despite the crudeness of this approach, it displays better than order of magnitude agreement with experiment. The molecular motions that are responsible for the ligand field's time dependence are identified as low frequency (< 300 $cm^{-1}$) modes that regularly undergo large distortions at room temperature.

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# A Deflation Algorithm for the Global Optimisation of EPR Spectra

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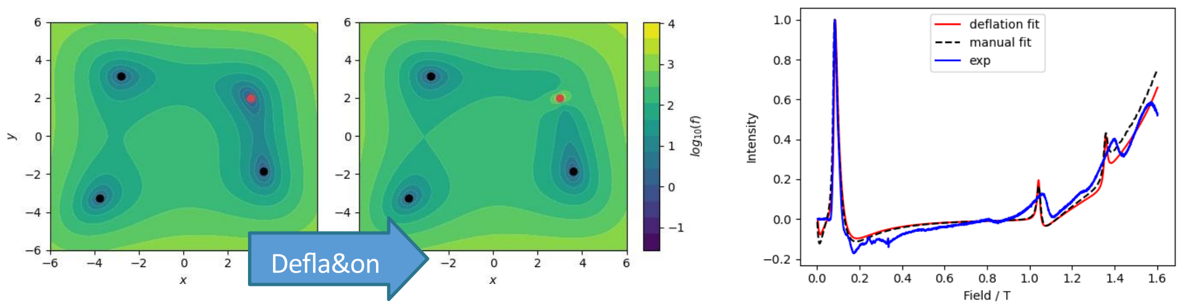
Electron Paramagnetic Resonance (EPR) is a powerful tool in characterization of magnetic properties of compounds. Low energy experimental frequencies used in the technique make it ideal for studying weak interactions, such as exchange coupling between lanthanide centres.[1,2] Characteristic parameters are extracted from experimental spectra *via* fitting to a model spin Hamiltonian. Fitting can be a long and tedious process of varying free and fixed parameters and requires navigation of a high-dimensional error space containing many local minima. So, how can we remove the need for multiple fitting rounds and confirm our fitted solution is the global minimum?

Deflation is a robust and systematic method to find multiple optima of a given function.[3] When an optimum is found it is 'deflated' out of the function with the deflation operator, producing a singularity and preventing repeat convergence. This new 'deflated' function is used for the next optimization round, and the process is repeated until all optima are found. In previous work deflation has been applied in a Gauss-Newton based optimisation algorithm for the fitting of inelastic neutron scattering spectra.[4] We have implemented a deflation algorithm for fitting EPR spectra into our spin Hamiltonian package PHI.[5] From tests with both toy-models and experimental data; our algorithm can locate many local minima spanning the entire parameter space allowing for confirmation of the global minimum, can handle fitting many parameters at once reducing, if not fully eliminating, the need to manually vary fixed parameters across multiple fitting instances and is able to reproduce similar quality fits in much shorter timescales.

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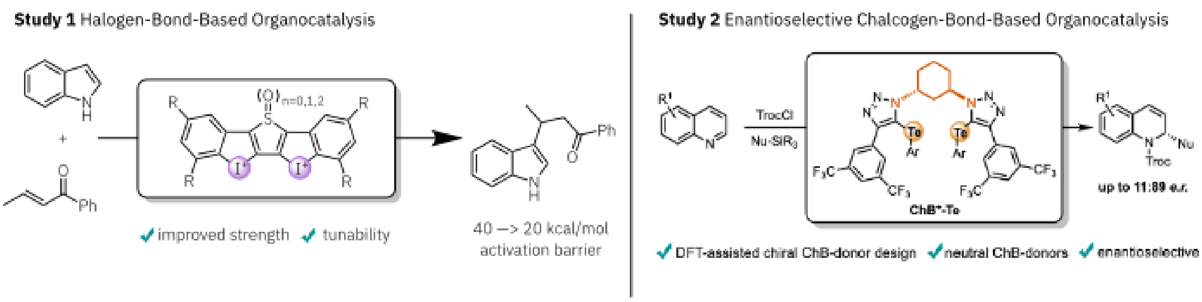
# Application of σ-hole Interactions Within Organocatalysis

**James O'Brien**, Dr. Cristina Trujillo

The area of **organocatalysis** has seen the development of a significant variety of catalyst classes such as covalent catalysts, and hydrogen-bond-based (HB) catalysts. Recent developments within the field have seen the successful implementation of σ-hole-based interactions for noncovalent catalysis. These developments have seen the birth of various novel classes such as **halogen-bond-based (XB)** and **chalcogen-bond-based (ChB)**. The novel developments of such catalysts require increased care for design, due to additional constraints which arise from the physical properties of the σ-hole relative to hydrogen bonds. As such, **computational chemistry** can be leveraged to develop key insights for catalyst development, turning initial physical constraints of the σ-hole to instead allow for additional **substrate specificity** and **catalyst tunability**.[1]

Recent studies from Huber *et al.* introduced **bidentate hypervalent iodine catalysts**, for **XB-mediated organocatalysis**.[2] Expanding upon this work, our research computationally investigated the tunability and improved Lewis-basicity of these systems, resulting in significant improvements of their catalytic strength through various modifications of the original scaffold. These novel catalysts were assessed using density-functional theory (DFT), allowing for the calculation and comparison of reaction barriers for a Michael-addition reaction, ultimately providing meaningful data on of various modification sites and functional groups for this class of catalyst, enabling more careful and rational catalyst design.[3]

Furthermore, whilst XB-based organocatalysts have been recently employed for **enantioselective catalysis**, the employment of ChB remains an unexplored due to greatly increased complexity relative to XB-based catalysis, and HB-based catalysis. To gain further insight into experimentally obtained enantioselective **ChB-based organocatalysts**, the structural space occupied by the catalysts under study were investigated through conformational analyses. The results of which identified the importance of **structural flexibility** of these systems for enantioselective purposes, with a specific focus on the availability of an **internal binding pocket** for introducing a significant chiral environment to the substrate. Using these results, the most promising catalyst was further modified to improve the Lewis-basicity of the actively binding σ-holes to further improve substrate binding within the identified **chiral pocket**, resulting in further increased enantioselectivity, and proving to be the **first class of successful enantioselective ChB-based organocatalysts**.[4]

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# Talk Abstracts

# PGR CONFERENCE

## MAT

*Section*

# Electrical and Thermal Transport in Printed Graphene Thin Films with Tuneable Seebeck Coefficient

**Carletta Wong**,[a] Khaled Parvez,[a] Andrey Kretinin,[b,c] Cinzia Casiraghi,[a]

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Thin films made by the assembly of solution processed two-dimensional (2D) materials are attractive for many applications, including thermal management, as they can be easily produced using low cost and simple fabrication methods, such as inkjet printing, virtually onto any substrate [1-3]. While the literature reports many studies on the thermal properties of single crystal 2D materials, studies on the thermal properties of printed thin films are limited [4]. Furthermore, there is currently very little knowledge on the fundamentals of thermal transport in disordered networks of graphene nanosheets [5], thus it is crucial to study in detail properties such as the thermal conductivity and Seebeck coefficient of graphene printed films.

This work provides a systematic analysis of the thermal properties of printed graphene films. In this study, graphene dispersions were prepared by liquid phase exfoliation (LPE) and electrochemical exfoliation (ECE) using a printable water-based solvent [1], and subsequently printed onto SiN membranes to produce graphene films. A single measurement run on a Thin Film Analyser (TFA) operating under vacuum and at temperatures between 103 K to 523 K was used to extract a range of thermal and electrical properties of the films. In particular, we show that the Seebeck coefficient of graphene films can be made tuneable by using different chemical exfoliation methods, exfoliation conditions and annealing temperatures. These findings provide an insight into the fundamental parameters which govern the thermal transport in graphene thin films, showing opportunities for thermoelectric applications and potential in enabling 2D material-based solutions for thermal management applications.

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# Discovery Tools for Polymers to Extract and Stabilise Membrane Proteins

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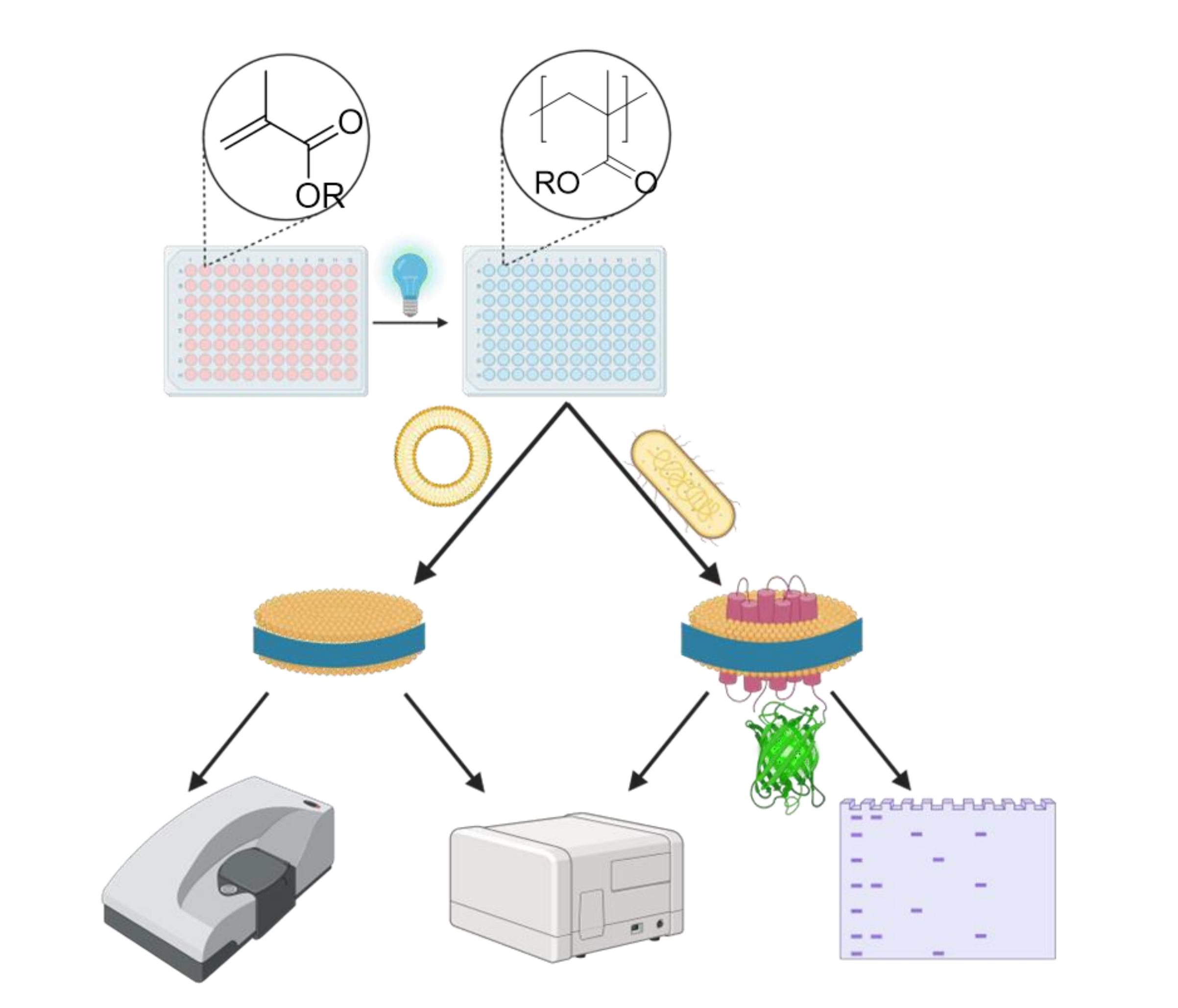
Membrane proteins play essential roles in medicine and biology, including as receptors or ion channels.(*1*) They are the target of many drugs but their study is complicated by the requirement to extract and stabilise the (insoluble) transmembrane domain.(*2*) Conventional detergents compromise protein stability, which lead to the development of polymeric alternatives, such as styrene-maleic acid (SMA), which convert membranes to discoidal nanoparticles (nanodiscs).(*3*) However poor tolerance to divalent cations or low pH, and strong UV absorbance limit the applications for which SMA is suitable.(*4*) Structure-function relationships are still missing meaning some trial and error is used when deploying these polymers.

To address this, we have developed a high-throughput synthetic methodology and testing pipeline. Xanthate-supported photoiniferter polymerisation (XPI) in 96-well plates has been used to obtain a library of methacrylate co-polymers to screen.(*5*) XPI was selected to achieve polymerisation to high conversion without degassing, using visible light, and in the absence of free photocatalysts which can interfere with downstream assays.

The library was first assessed using model membranes, and many of the polymers could efficiently convert large (>100 nm) vesicles to small (<20 nm) particles, the size range of typical nanodiscs, with increased lipid packing density, again typical of nanodiscs. Screening the polymers for tolerance to divalent cations and $[H^+]$ showed some polymers tolerated concentrations an order of magnitude higher than SMA. Finally the library was applied to extract membranes of *E. coli* overexpressing a fluorescently labelled membrane protein (KcsA-KV1.3-sfGFP). This revealed hot-spots for polymers which significantly outperform SMA and the conventional detergent dodecyl maltoside.

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# Direct Writing of Nanoscale Semiconductors from Single-Source Precursors

**Juliana Morell**,[a] Milad Nonahal,[a] Atta ul Haq,[a] Grigore A. Timco,[a,b] Avantika Hasija,[a] Ilya Strashnov,[a] David J. Lewis,[b]* and Richard E. P. Winpenny[a]*

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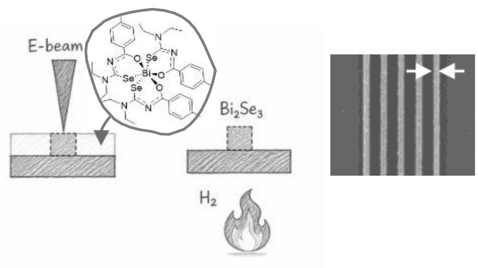
Two-dimensional (2D) metal chalcogenides have gained attention in recent years for their exotic optoelectronic properties. Bismuth(III) selenide ($Bi_2Se_3$) has drawn attention as a topological insulator (TI). Current fabrication methods for $Bi_2Se_3$ can be complex and device integration at the nanoscale is limited. In this work the direct writing of nanoscale 2D bismuth selenide structures is reported using electron-beam lithography using a single-source precursor as a negative-tone resist. The precursor was synthesised from bismuth nitrate and a selenourea ligand in mild conditions. Characterization of the resulting bismuth selenourea complex was performed using elemental analysis, single crystal X-ray diffraction, NMR spectroscopy, and thermogravimetric analysis (TGA). Annealing the precursor in a 5% $H_2$/Ar atmosphere gave $Bi_2Se_3$ as polycrystalline nanosheets confirmed via TEM and energy-dispersive X-ray spectroscopy (EDS). Thin films of the precursor, formed by spin coating, were patterned with an electron-beam, forming polycrystalline $Bi_2Se_3$ nanostructures that retain their geometry after annealing in 5% $H_2$/Ar. Characterization of the nanostructures with SEM, EDS, and TEM reveal bismuth selenide nanocrystals of <100 nm dimension, which can be easily localized based on e-beam pattern design. The versatility of pattern design also means that bismuth selenide nanostructures in varying shapes, sizes, and thicknesses can be precisely positioned, further enabling their functional applications. Direct writing of bismuth selenide by electron beam lithography offers a facile synthesis of a topological insulator with the potential for simplistic device integration by on-chip preparation.



# Direct imaging elucidates ionic memory in two-dimensional nanochannels

**Kalluvadi Veetil Saurav[a,b*]**, Nathan Ronceray[c*], Baptiste Coquinot[d], Agustin D. Pizarro[c], Ashok Keerthi[a,b,f], Theo Emmerich[c,e,#], Aleksandra Radenovic[c,g,#], Boya Radha[b,f,h#]

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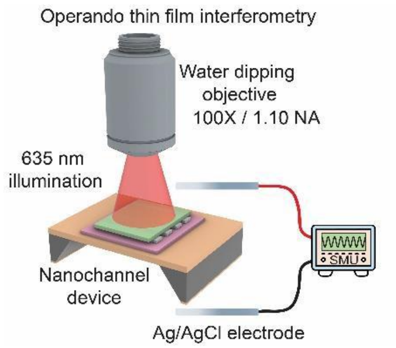
Nanofluidic memristors promise brain-inspired information processing with ions, yet their microscopic origin remains debated. So far, ionic memory has been attributed to ion-specific interactions, dynamic wetting, chemical reactions or mechanical deformations, yet typically without direct experimental evidence. Here, by combining operando interferometric imaging with electrokinetic measurements, we directly visualize voltage-induced blistering of the confining walls of two-dimensional (2D) nanochannels, as key origin of memristive hysteresis. We identify two distinct classes of blisters: unidirectional, driven by electrostatic forces on surface charges, and bidirectional, arising from osmotic pressure due to concentration polarization. This mechanistic framework explains device evolution and device-to-device variability and reframes stochastic blistering as a functional design element. Our results constitute a direct proof of electromechanical coupling as a robust pathway to ionic memory in 2D nanochannels and open routes toward high-performance ionic memristors and electrically actuated nanofluidic valves.

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# Synthesis of Novel Members of the Al MIL-53 Solid Solution Series, $AlF_x(OH)_{1-x}(bdc)$, Displaying Incrementally Modified Flexing Behaviour and Hydrophobicity

**Thomas Duddles**[a], Kho Zhi Quan[b], Ruichen Zhang[a], Dukula De Alwis Jayasinghe[a], Martin Schröder[a], Sihai Yang[a], Alexander Eggeman[b], Daniel Lee[c], Martin Attfield[a]

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Al MIL-53, Al(OH)(bdc) ($bdc^{2-}$ - 1,4-benzendicarboxylate), is a flexible 3D MOF that undergoes reversible breathing transitions between narrow-pore (np) and large-pore (lp) phases via intermediate-pore (int) phases (see Fig. 1a). [1] It's built from 1D chains of $Al(OH)_2O_4$ octahedra (see Fig. 1b) linked by $bdc^{2-}$ and exists in its hydrated int·$H_2O$ phase in moist air (see Fig. 1c). Substitution of $\mu_2$-$OH^-$ for $\mu_2$-$F^-$ in the $M(OH)_2O_4$ octahedra affords AlF(bdc), a hydrophobic and rigid lp framework. [2,3] Here, we present the synthesis and properties of members of the solid-solution series $AlF_x(OH)_{1-x}(bdc)$ (x = 0.3-0.9), which display flexibility intermediate between that of Al(OH)(bdc) and AlF(bdc). $AlF_{0.3\text{-}0.9}(OH)_{0.7\text{-}0.1}(bdc)$ frameworks were synthesised using stoichiometric mixtures of $AlF_3$ and $Al(NO_3)_3{\cdot}9H_2O$ in amidic solvents. $AlF_{0.7\text{-}0.9}(OH)_{0.3\text{-}0.1}(bdc)$ adopts the same rigid lp phase reported for AlF(bdc). $AlF_{0.3\text{-}0.5}(OH)_{0.7\text{-}0.5}(bdc)$, whilst primarily adopting this phase feature a small phase fraction of int·$H_2O$ phase. This indicates a restoration of framework flexibility in this material. $^{19}F$ solid-state NMR shows different degrees of homogeneity in the fluoride distribution across the series of samples. In $AlF_{0.7}(OH)_{0.3}(bdc)$, all $\mu_2$-$F^-$ sites are contained within hydrophobic inflexible framework. In $AlF_{0.3}(OH)_{0.7}(bdc)$ 1/3 of $\mu_2$-$F^-$ species exist in more hydrophilic domains, whilst the remaining 2/3 are contained within hydrophobic domains. This inhomogeneous fluoride distribution, with the least fluoride contained within hydrophilic regions, is believed to be responsible for the inhomogeneous flexible behaviour observed in the lower fluoride content samples. Thermodiffraction performed on the int·$H_2O$ phases in $AlF_{0.3\text{-}0.5}(OH)_{0.7\text{-}0.5}(bdc)$ shows them to become destabilised with respect to higher temperatures as bulk $\mu_2$-$F^-$ is increased. $H_2O$ isotherms show that this flexible material readily forms int·$H_2O$ phases, but that rigid lp remains dehydrated until a threshold partial pressure is met and pore-filling occurs.

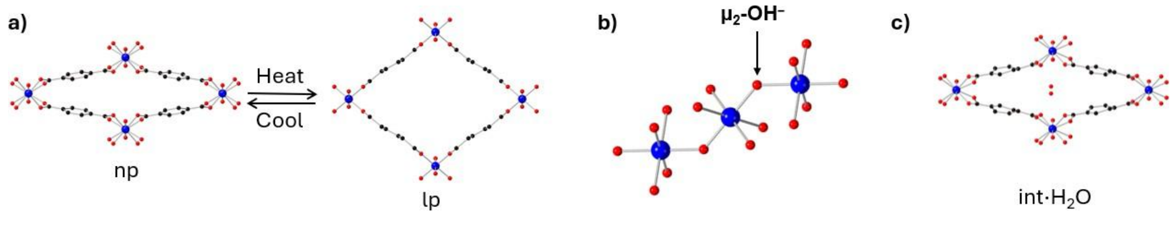


**Figure 1. a)** Crystal structures of np and lp Al MIL-53. **b**) Trans-corner sharing $Al(OH)_2O_4$ octahedra. **c)** Crystal structure of int·$H_2O$ Al MIL-53. Blue = Al, Black = Carbon, O = Oxygen.

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# Crystallization of Elusive Form II Paracetamol onto Edible Substrates by Gas Blow Coating

**Yashoda Abeykoon[1], Gayani Kadukara[1], Adam Hill[1], Alvin J. Walisinghe[1], Emanuele Poliani[1], Thomas Vetter[2], Michael W. Anderson[1,3], Jincheng Tong[1], Cinzia Casiraghi[1]**

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*3 Department of Chemical Engineering and Analytical Sciences, University of Manchester, Manchester, UK.*

Controlling polymorphism during crystallization remains one of the foremost challenges in crystal engineering, owing to the complex interplay between thermodynamics, kinetics, and molecular self-assembly pathways that governs solid-state formation. This challenge is particularly critical for active pharmaceutical ingredients (APIs), with paracetamol (PCM) being a paradigmatic example of this problem: crystallization of its Form II remains exceptionally challenging because both thermodynamic driving forces and classical nucleation pathways strongly favour crystallization of PCM Form I. Here, we introduce a crystallization strategy (the gas blow coating) that enables direct polymorph control beyond the constraints of conventional approaches, based on the decoupling of the nucleation dynamics from equilibrium crystallization conditions by molecular confinement into an ultra-thin puddle.[1]

Here we demonstrate the gas blow coating of the ‘elusive’ pure form II PCM over large areas with well controlled needle-like morphology, without using any additive, stable for at least 30 days. Under optimized conditions, we demonstrate that Form II PCM can be crystallized directly by blow-coating onto edible substrates, exemplified here by gelatine, a widely used pharmaceutical excipient. The desired API polymorph is thus directly produced onto an ingestible carrier, eliminating conventional downstream steps such as granulation, blending with excipients, and tablet compression, hence reducing energy use, solvent consumption, equipment footprint, and material losses per dose. The resulting high surface-area coating, together with a uniform mass loading per unit area, promotes rapid dissolution and offers a straightforward route to reproducible dosing and improved bioavailability, hence leading not only to a transformative way drugs are manufactured, but also how they get consumed, by enabling dose customization.[2]

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# Beyond Activity: Defining Catalyst Sustainability in Depolymerisation Systems

**Robbie Clark**,[a] Dr. Ciaran Lahive,[a] , Prof. Michael Greaney[b], Prof. Michael Shaver[a]

*a.* The University of Manchester, Department of Materials | *b.* The University of Manchester, Department of Chemistry

Plastic waste is a growing problem, with significant impacts on the wellbeing of humans, our environments and the climate. Recycling technologies are pressingly being developed to address these challenges. Chemical depolymerisation – reverting polymers to monomers – offers a promising way to treat plastic waste.[1] Monomers produced can be repolymerised into new plastics, reducing emissions and the consumption of resources. Polyesters, one of the most researched classes of depolymerisable polymers, have many catalytic systems that successfully break them down. A key example is the alcoholysis of poly(ethylene terephthalate) (PET), a prevalent packaging polymer with approx. 25 million tonnes produced annually as of 2019.[2] A variety of different catalysts can significantly speed up and lower the energy inputs of PET alcoholysis. This raises a challenge: which catalysts minimise the environmental impacts of the depolymerisation process itself? With the global-scale consumption of PET, reducing the impacts of this system could be consequential. As of yet, there is a disconnect between efforts to improve catalyst efficiency whilst also evaluating sustainability.

This project seeks to join up kinetic assessments of organocatalysts with their environmental impacts, and the constraints of scaling up. Kinetic parameters are derived for a set of catalysts, and these are paired with life cycle assessments of their syntheses, modelled at plant-scale. By combining efficiency and environmental impact, this project attempts to screen for optimal depolymerisation catalysts and be a model for chemists and engineers seeking to use analytical methods like life cycle assessment and process modelling.

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# Using Biomimetic Ice-Binding Polymers to Control Cryogel Architecture and Mechanical Behaviour

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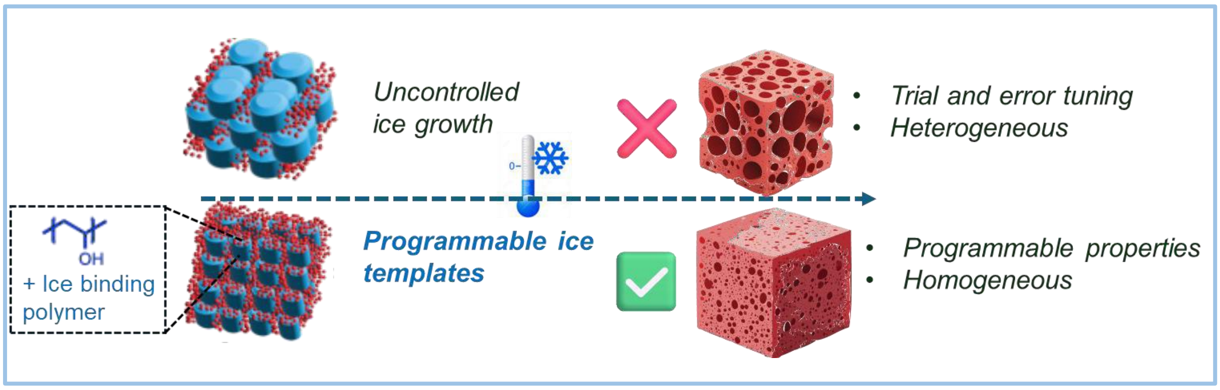
Cryogels are porous materials whose internal structure is defined by ice crystals acting as sacrificial templates during polymerisation, producing interconnected macroporous networks [1]. Their versatility has made them attractive candidates for applications ranging from tissue engineering and drug delivery to water filtration and chromatographic separations. Conventionally, tuning pore dimensions and the resulting mechanical response requires systematic adjustment of monomer composition, freezing conditions, and other processing parameters, which is empirical and time-consuming [2].

This work presents a biomimetic strategy for rationally engineering cryogel architecture by directly controlling ice crystal growth before and during gelation. Drawing inspiration from ice-binding proteins found in cold-adapted organisms, we employ ice-binding polymers to prescribe the dimensions of the ice template. Poly(vinyl alcohol) (PVA) was selected as the ice-binding agent owing to its commercial availability, ease of chemical modification, and inherent resistance to denaturation, which is a notable practical advantage over its protein counterparts [3].

Using N,N-dimethylacrylamide (DMAA) as a model monomer system, we show that systematically varying PVA concentration provides direct, predictable control over pore size. This, in turn, allows a suite of material properties, including stiffness, swelling behaviour, and viscoelastic response, to be programmed in a linked and coherent fashion. The approach is experimentally straightforward and offers a sustainable route to porous material fabrication, opening new design possibilities for next generation cryogel systems.

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# Talk Abstracts

# PGR CONFERENCE

## ORG

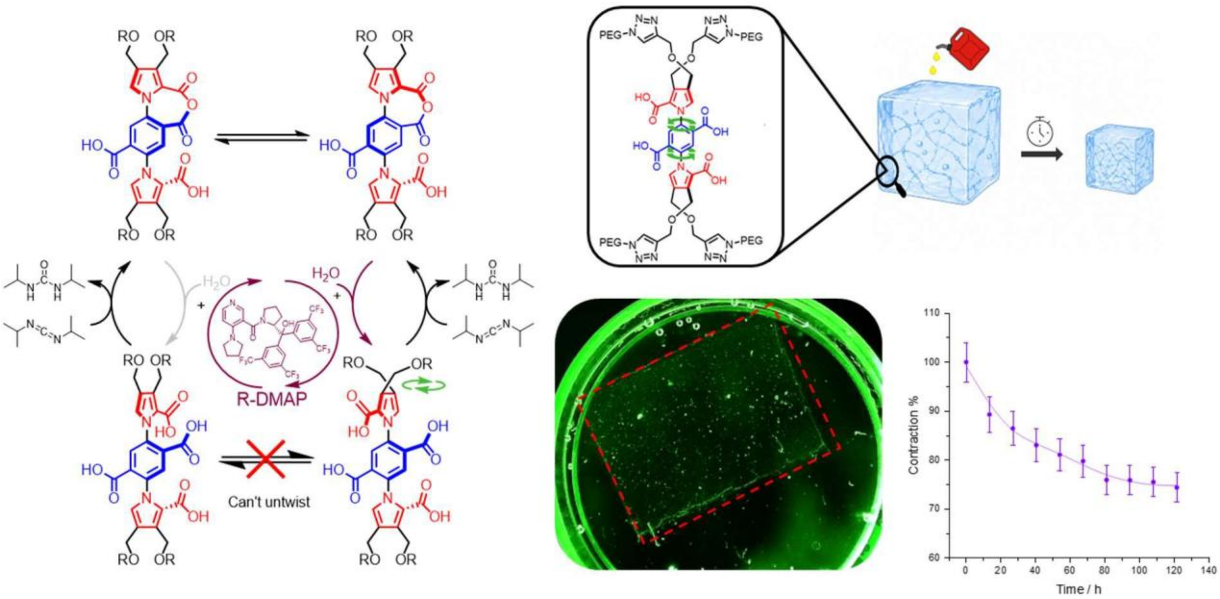
## *Section*

# Macroscopic contraction of a gel by an enhanced molecular motor

**Lukas Marrow,**[a] Peng-Lai Wang,[a] David Leigh[a,b]

*a.* University of Manchester, Manchester, United Kingdom | *b.* East China Normal University, Shanghai, China

Chemically fuelled molecular motors have previously been used to induce contraction in poly(ethylene glycol)-based hydrogels by expending a chemical fuel; however, improving the speed and efficiency of these systems remains a significant challenge. Here, a dual molecular motor crosslinker, bearing two rotors on a single stator, was developed based on earlier studies showing enhanced rotational rates and efficiency compared to a single-rotor motor. The crosslinker was accessed in eight steps, substantially shortening the synthetic route compared with the previously reported single-motor crosslinker. The dual motor was shown to catalyse carbodiimide fuel hydration more rapidly than the analogous single-motor system. Incorporation of the crosslinker into poly(ethylene glycol)-based gels via CuAAC polymerisation produced contractile materials that exhibited contraction rates comparable to previously reported single-motor gels. Variation of fuelling conditions gave insight into the contraction mechanism, suggesting a ratchet-like mechanism driven by chemically fuelled motor rotation. In addition, the versatility of the crosslinker was explored through preliminary studies of alternative applications, including microgel actuators and surface chemistry modification. Together, these results demonstrate the potential of dual molecular motors as versatile components for responsive and adaptive soft materials.

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# (Aza)-Michael Addition of Aliphatic Amines and Enolates to Aryl Alkenes via Organobase Catalysis

**Ethan Lim,**[a] Bradley Cooper,[a] Jonathan Da Luz,[a] Thomas Harris,[a] Abby Sutton,[a] James Douglas,[a,b] Cristina Trujillo,[a] Michael James[a]

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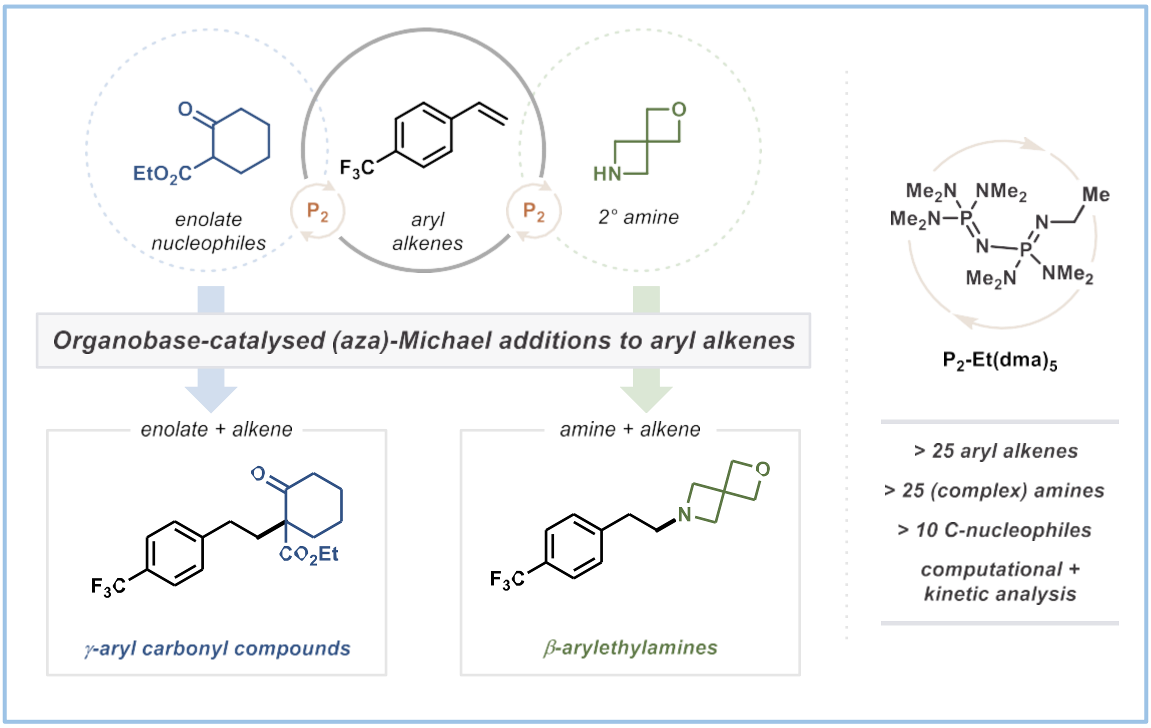


While classical Michael additions efficiently functionalise strongly polarised alkenes, nucleophilic additions to less polarised alkenes remains challenging without resorting to the use of transition-metal catalysis or harsh basic conditions which limit functional group tolerance.[1] This talk will describe an organobase-catalysed method for the addition of secondary amine nucleophiles to minimally polarised alkene electrophiles, forming valuable β-(hetero)arylethylamines.[2] The developed conditions were also applicable to challenging Michael addition reactions with enolate nucleophiles, providing facile access to all-carbon substituted quaternary centres and precursors to unnatural amino acids.

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# Deep Learning Reveals the Structure of Kinetic Degeneracy in Catalytic Mechanisms

**Ron Verdijk**,[a] Jordi Burés,[a,b] Igor Larrosa[a]

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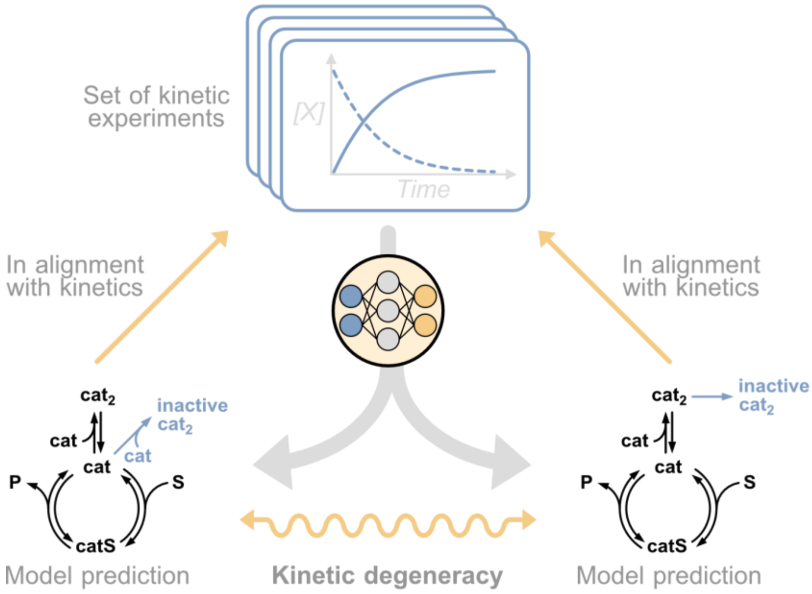


Mechanistic inference from kinetic data commonly assumes that distinct mechanistic features produce distinct kinetic signatures. In practice, this assumption often fails since different elementary-step combinations can generate indistinguishable sets of concentration-time profiles, creating kinetic degeneracy and preventing reliable mechanistic assignment. Although machine-learning approaches can classify kinetic data against libraries of fully defined mechanisms[1], their scope has remained too narrow to interrogate this problem systematically. Here we report a deep-learning framework spanning 438 catalytic reaction mechanisms, more than an order of magnitude larger in scope than previous models. This expanded mechanistic space enables the mapping and quantification of kinetic degeneracy across mechanisms. We find that ambiguity is highly structured and strongly feature-dependent: activation features are generally associated with more distinctive kinetic signatures, whereas deactivation features account for much of the observed overlap in kinetic space. Several dominant degeneracy modes recur, including cases in which bimolecular deactivation and unimolecular loss from pre-associated catalytic species become kinetically indistinguishable. Even under idealized conditions, some ambiguities persist, revealing fundamental limits to the mechanistic information contained in a set of experiment's concentration-time data. Our results show that kinetic data often delimit a kinetically distinguishable mechanism class rather than a unique mechanism, and provide a framework for assessing mechanistic distinguishability and identifying when orthogonal measurements are required.

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# Thiophene to N-Heteroarene Conversion

**Órla Conboy**,[a] Scott O'Brien,[a] Andy Yen,[b] Jordan Berreur,[a] David J. Procter.[a]

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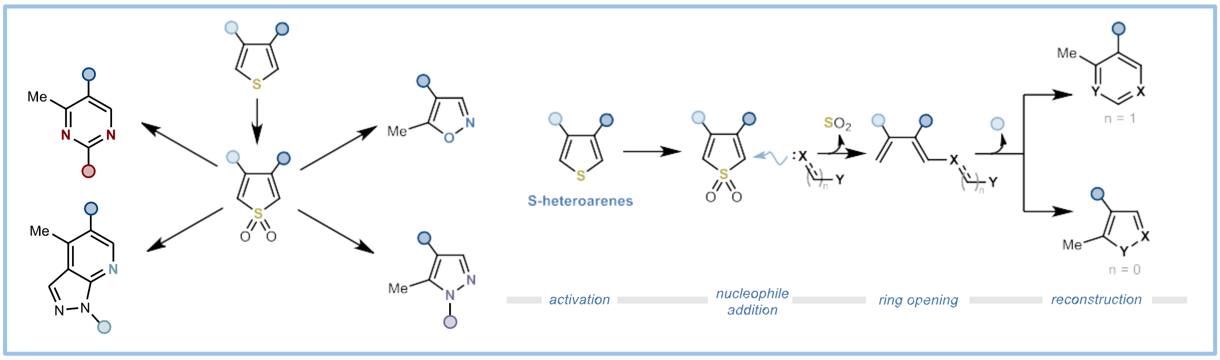
Heteroarenes are prevalent structural motifs in pharmaceuticals, functional materials, and catalysts, creating strong demand for methods that enable their efficient construction and manipulation. Recently, heteroaromatic scaffold editing has emerged as a powerful tool for interconverting between heteroarene classes.[1] Such transformations can provide new retrosynthetic disconnections and accelerate analogue generation for drug discovery. However, despite the abundance of thiophenes and related sulfur heteroarenes, thiophene-to-heteroarene interconversion remains an unmet challenge.

Building on our work on the activation of sulfur heteroaromatics through *S*-oxidation to enable Pummerer-type reactivity,[2,3] we demonstrate that oxidation can reprogramme the intrinsic reactivity of thiophenes to unlock skeletal remodelling pathways. Oxidation to the corresponding *S*,*S*-dioxides disrupts aromatic stabilisation and inverts the polarity of the heterocycle, enabling nucleophile-triggered ring opening – an editing strategy typically confined to *N*-heteroarenes.[4] Subsequent cyclisation, accompanied by extrusion of $SO_2$ and a skeletal carbon atom, reconstructs the heteroaromatic core to access structurally diverse *N*-heteroarene frameworks. Experimental and computational studies support a distinct mechanism whereby nucleophile-promoted $SO_2$ extrusion generates diene intermediates that cyclise through divergent pathways to form either five- or six-membered heterocycles, depending on the nucleophile. This work extends the design principles of nucleophile-triggered skeletal editing beyond N-heteroaromatic substrates and establishes oxidation-enabled ring opening and remodelling as a strategy for the transformation of sulfur heteroarenes.

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# Synthesis of Chondroitin Sulfate-Related Oligosaccharides Fragment Precursors

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Insert here your abstract (~250 words, please do not exceed one page)

Chondroitin sulfate (CS) is a highly sulfated glycosaminoglycan (GAG) composed of repeating disaccharide units of *N*-acetylgalactosamine (GalNAc) and glucuronic acid (GlcA). CS can interact with a variety of proteins and has potential therapeutic effects on a variety of diseases (e.g., cancer, coronary artery disease, osteoarthritis, etc.). Since GAGs are structurally complex and highly heterogeneous, and the structural requirements for protein binding are not yet clear, it is necessary to provide structurally well-defined saccharides through chemical synthesis of GAG fragment precursors to explore the GAG protein binding properties.

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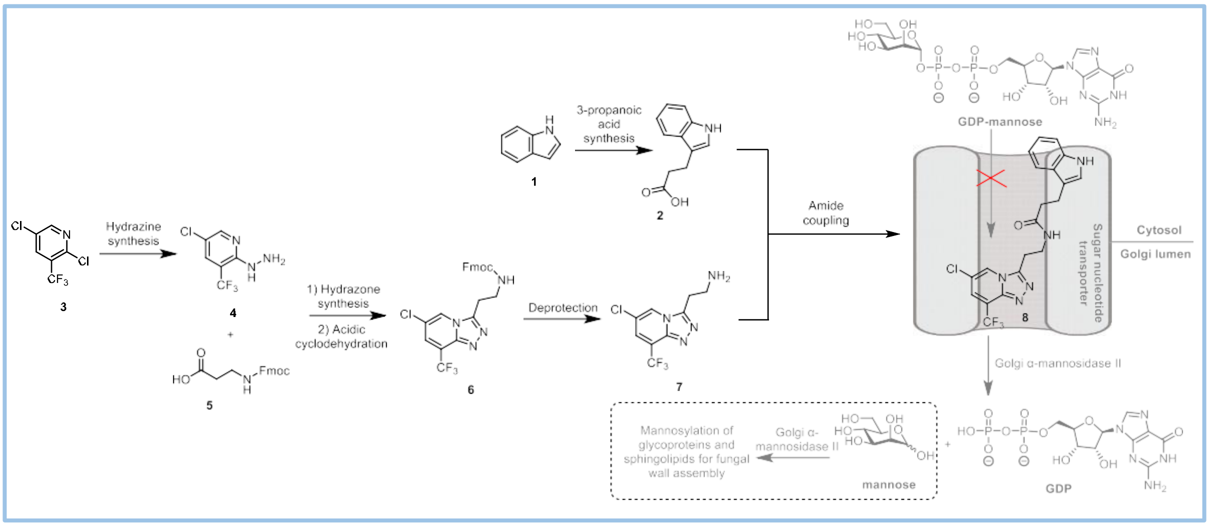
# Synthesis of a Small Molecule Library to Explore New Inhibitory Prospects for Pathogenic Fungi

**Lauren Holder**,[a,b] Johannes Reynisson,[b] Jonathan Reuven,[c] Gavin J. Miller [a]

*a.* Manchester Institute of Biotechnology, Department of Chemistry, University of Manchester, Manchester, M17DN | *b.* School of Chemical and Physical Sciences and School of Pharmacy, Keele University, Staffordshire, ST55BG | *c.* Syngenta, Jealotts Hill Research Station, Bracknell RG426EY



Pathogenic fungal infections cause disruption to the global food chain due to the emergence of resistance to crop fungicides.[1,2] Developments in novel antifungal agents for agricultural use are sparse; only 19 antifungals have been approved as crop health active ingredients since 2010.[2] Fungal cell walls are composed of polysaccharide chains such as chitin, glucans and mannoproteins that are a result of sugar nucleotide-mediated biosynthesis, which themselves are transported into the Golgi by sugar nucleotide transporters.[3-5] Building upon recent structural biology data of a guanosine diphosphate (GDP)-mannose transporter, it was proposed that inhibition of GDP-mannose transport could lead to cell lysis by reducing the supply of mannose required for fungal cell wall biosynthesis. There are numerous residues in the protein binding site which could be targeted by small molecule inhibitors as a novel method to disrupt this transport, which include but are not limited to serine, lysine and tyrosine residues.[6-9] Preliminary biological data and molecular docking studies have led us to the development of a small heterocyclic lead molecule library bearing triazolopyridine and indole moieties connected by a flexible alkyl amide linker. These studies have identified an unoccupied hydrophobic pocket within the binding site which were then explored through structure-activity relationship inhibitor design. Presently, we have developed synthetic routes towards a first series of putative heterocyclic inhibitors, based on an internally identified lead molecule, which provides a pathway towards exploring inhibition of the target protein.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# Skeletal Editing of Pyridines Through Ring Opening

**Aífe Conboy** and Michael F. Greaney

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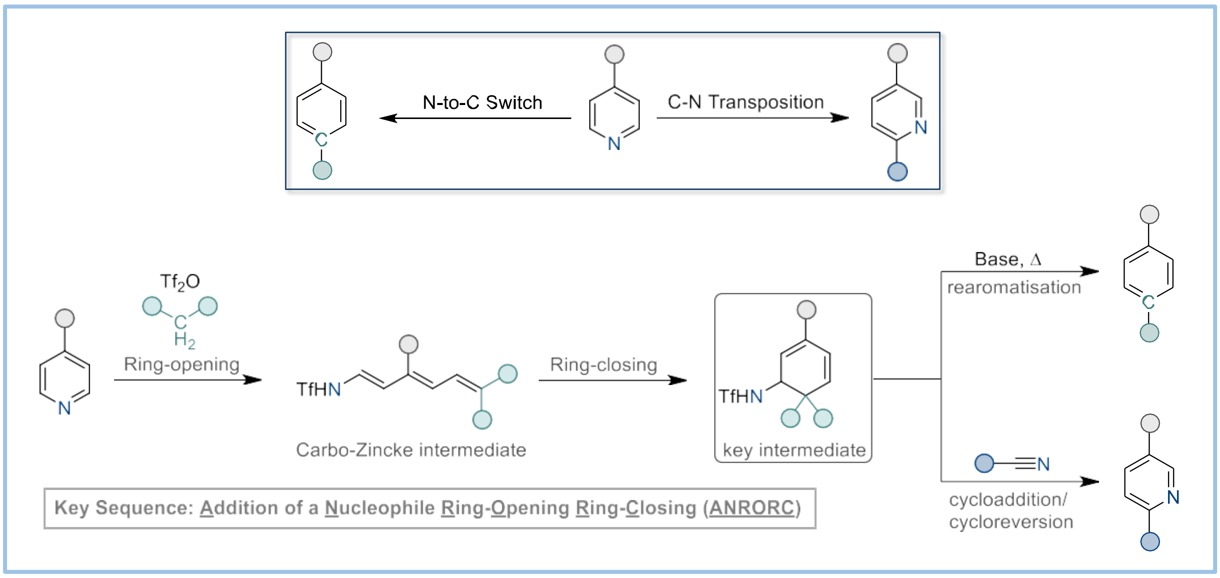
Skeletal editing strategies that enable chemists to insert, delete, or swap individual atoms within the core of molecules have recently emerged as a powerful means to alter molecular frameworks at a fundamental level.[1] The ubiquity of pyridines in pharmaceuticals makes them a prime target for skeletal editing approaches, with such scaffold hopping potentially enabling rapid assessment of structure–activity relationships in drug discovery programs, in addition to inspiring new modes of retrosynthetic thinking.




We have developed skeletal editing reactions of pyridines through a nucleophilic addition ring-opening ring-closing (ANRORC) sequence.[2,3] Addition of an appropriate soft carbon nucleophile, such as malonate, facilitates ring opening of an *in situ* activated pyridine to generate a carbo-Zincke intermediate. Subsequent ring closure forms our key cyclohexadiene intermediate. Simple heating of this carbocycle results in rearomatisation to give benzene products, enabling the development of a pyridine N-to-C switch in a one-pot protocol that has been demonstrated on a range of pyridines, including biologically active examples, in up to 99% yield. Alternatively, reaction with dienophiles allows the same cyclohexadiene intermediate to be leveraged for other skeletal editing transformations of pyridines through cycloaddition/cycloreversion (CACR) reactions. We have demonstrated transposition of the pyridine nitrogen from the 4- to the 3-position through CACR of the cyclohexadiene with a nitrile dienophile, as well as other atom-pair switches through the use of alternative dienophiles.

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# Photolytic proofreading of diastereoselectivity during chemically fuelled rotaxane assembly

**Joaquin Baixeras Buye[1‡], Lukas Marrow[1‡], Amina Sakho[1], Enzo Oliveiri[2], David A. Leigh[1,3*]**

*[1] Department of Chemistry, University of Manchester, Manchester M13 9PL, UK*

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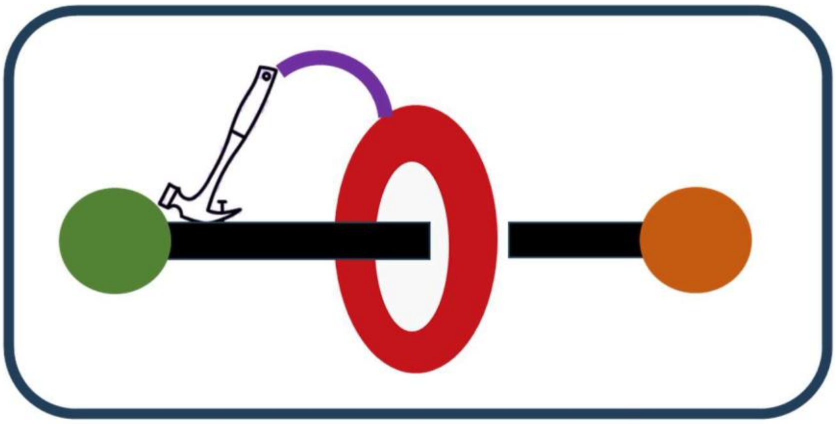
*[3] School of Chemistry and Molecular Engineering, East China Normal University, 200062 Shanghai, China.*

*‡ Both authors contributed equally.*

Biological molecular machines reduce error rates during replication, transcription and translation through kinetic proofreading, in which nucleoside triphosphate hydrolysis supplies the energy for error correction. Inspired by this principle, we report a chemical system that uses photolytic proofreading to control the ratio of facial isomers obtained during rotaxane synthesis. Metal-free active template synthesis of a crown ether rotaxane initially gives a 40:60 mixture of two facial stereoisomers. The crown ether was designed so that one isomer photocleaves 3.7× faster than the other under 420 nm irradiation, allowing selective removal of the less photostable isomer and increasing the diastereomeric ratio at the cost of some yield. Photolytic cleavage of the rotaxane cleanly regenerates the starting components. When irradiation is applied during rotaxane formation, newly formed rotaxane selectively photocleaves, and the liberated components can re-form rotaxane in situ by consuming a chemical fuel, 4-nitrophenyl carbonate. This cycle gives the system repeated opportunities to form the preferred diastereomer. When both synthesis and photolysis occur simultaneously, a chemically driven non-equilibrium quasi-steady state enriched in the more photostable isomer develops, with a d.r. of 1.6:1, compared to 0.6:1 in the absence of photolysis. This system operates as an information-ratchet, which couples efficient synthesis biased towards the undesired isomer with stereoselective photolysis to autonomously correct threading orientation. As a result, rotaxane can be obtained in higher diastereomeric ratio and yield than is possible through synthesis alone. These findings show how proofreading can be applied to diastereoselective error correction in molecular design, expanding the design space and application of small-molecule machinery.



# 1,4-Ester Migration Mediated by Samarium Diiodide and Light

**Muze Li[a],** Zhiping Wang[a], Nico Spreckelmeyer[a], Song Yu[a], Ciro Romano[a], Nikolas Kaltsoyannis[b], and David Procter[b]

*a.* Affiliation 1 | *b.* Affiliation 2

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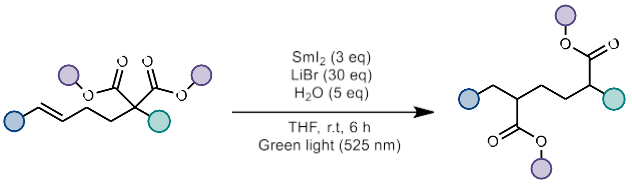
*$SmI_2$ has become a significant reagent in organic synthesis since its introduction in 1977. Over the past 40 years, it has been applied to a wide range of reductions involving various functional groups and in carbon-carbon bond formation. Additionally, different additives, such as HMPA, water, and lithium bromide, have been used to modulate the reduction potential of $SmI_2$, enabling a broader range of reactions that proceed with good yields and diastereoselectivity.*

*In 2022, Procter and co-workers reported an unusual SmI2-mediated 1,4-migration of an ester group, in which an acyclic ester radical was generated, and underwent by a 5-exo-trig cyclization and fragmentation to form the desired product. However, this work was limited to lactone systems and required the use of large amounts of the toxic additive HMPA.*

*In this project, we explored 1,4-ester migration using a malonate system, replacing HMPA with lithium bromide and light irradiation, which are cheaper and safer activators for synthetic applications.*

*This report outlines the optimization of the reaction conditions, presents preliminary data on the 1,4-ester migration, details the scope expansion, and describes the synthetic sequences used to prepare the substrates.*

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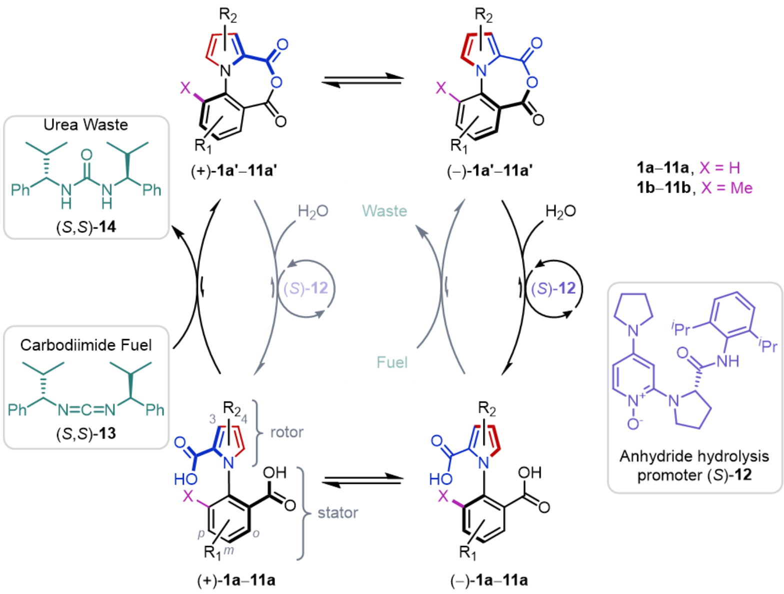
# Influence of Substituent Effects on a Catalysis-Driven Molecular Single-Bond Rotary Motor

**Jannik L. Schiessl**, Alexander Betts, Victoria Y. Jiang, Owen Veck, David A. Leigh*.

Biological systems maintain the out-of-equilibrium conditions required for life through molecular machines such as ATPase,[1] which rotates unidirectionally via a catalysis-driven information ratchet mechanism. Inspired by nature, our group recently developed an analogous synthetic small molecular rotary molecular motor that catalyses a carbodiimide hydration reaction. The anisotropy introduced in the system by using chiral reagents, the carbodiimide (fuel) and the hydrolysis promoter, results in the motor rotating with a directionality of 3:1.[2] This bias can be further improved to 24:1 by altering the structures of carbodiimide and hydrolysis promoter.[3] Besides directionality, additional parameters such as rotational speed, stall torque, and fuel efficiency further define the overall performance of molecular motors and constitute their key performance indicators (KPIs).

In this work, we investigate how electronic and steric substituent effects modulate the performance of a single-bond rotary molecular motor. A series of molecular motors and motor analogues bearing electron-withdrawing (nitro) and electron-donating (methoxy) groups were synthesized, and their KPIs quantified and compared. This structure-performance analysis reveals how substitution patterns govern motor behaviour and identifies the motifs that achieve the highest performance. The insights obtained in this project provide design principles for catalysis-driven molecular motors and lay the groundwork for their future application.

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|---|---|---|---|---|---|---|---|---|---|---|---|
| $R_1$ | H | *p*-OMe | *p*-$NO_2$ | *m*-OMe | *m*-$NO_2$ | *o*-OMe | *o*-$NO_2$ | H | H | H | *p*-OMe |
| $R_2$ | H | H | H | H | H | H | H | 3-$NO_2$ | 4-OMe | 4-$NO_2$ | 4-$NO_2$ |

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# Chemical Synthesis of Fluorinated Carbocyclic Nucleoside Analogues from the Chiral Pool

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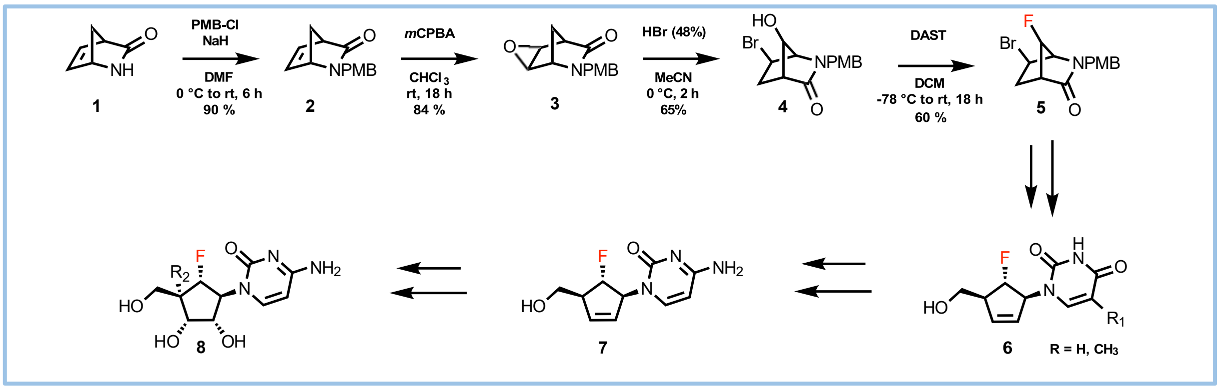
*a.* University of Manchester *b.* Keele University *c.* Riboscience LLC

Nucleoside analogues (NA's) are an established class of therapeutics for the treatment of viral infections and cancer.[1,2] Generally, this is due to their ability to act as potent inhibitors of DNA and RNA replication. Unfortunately, because of their mode of action and lack of selectivity NA's exhibit significant adverse side effects, limiting the dose which can safely be tolerated by patients. Therefore, the search for new NA's with improved activity, selectivity, and toxicity profiles remains of significant interest.[3] Carbocyclic nucleosides, in which the furanosyl oxygen is replaced with carbon, have been shown as a key scaffold with increased metabolic stability, observed in the approved drugs abacavir and entecavir which are used to treat HIV and Hepatitis B, respectively.[3] Furthermore, carbocyclic nucleosides can be modified to incorporate fluorine, which has been shown to be beneficial to lipophilicity, bioavailability, and binding affinity.[5] Important examples here include 6´-mono and 6´6´-difluorinated NA's;[6] a 6´,6´-difluorinated adenosine analogue displayed antiviral activity against MERS, ZIKA and Chikugunya viruses.[7] Supported by this promising bioactivity, we sought to develop a novel methodology to synthesise 6´-modified NA's (Scheme 1). The method originates from Vince lactam **1** through to an epoxide (**3)**, which enables a key intramolecular rearrangement and affords alcohol **4**. Hydroxyl intermediate **4** then undergoes deoxyfluorination to fluoride **5** which presents a scaffold to access new 6´-modified NA's (**6**-**8**), including 4´ modifications, to be investigated for their biological activity.

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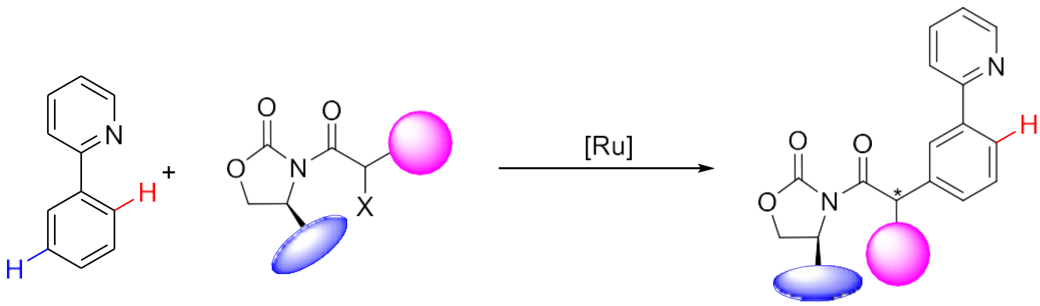
# Stereoselective Ruthenium-Catalysed meta-C(sp2)–H Alkylation with α-halocarbonyls

**Michael Wong**,[a] Aitor Carneiro,[a] Pablo Domingo-Legarda,[a] Prof Igor Larrosa[a]

*a.* University of Manchester

Transition metal-catalysed C(sp$^2$)-H functionalisation have been risen in complex molecule synthesis and late-stage derivatisation due to its reliability and availability towards various transformations with designated regioselectivity.[1] While stereoselective *ortho*-functionalisation has been well-documented with several metal catalysts in combination with bespoke asymmetric ligand systems, direct approaches to stereoselective distal functionalisation remains challenging. In the decent decade, ruthenium catalysts have demonstrated their unique reactivity of undergoing direct *meta*-C(sp$^2$)-H functionalisation with tertiary alkyl halides and α-halocarbonyl motifs. Yet, the stereoselective modification of such transformation has not yet been reported and it will benefit the pharmaceutical community as it may broaden the chemical space for late-stage drug derivatisation with more tailoring stereochemistry.

Chiral oxazolidinones, also known as Evans' chiral auxiliaries, with their extensive application in asymmetric synthesis,[2] have come into our vision. With the chiral oxazolidinone-furnished α-haloamindes as the alkylating agent, we speculated that the aforementioned transformation could be achieved by incorporating the substrate stereogenic control into the precedent ruthenium *meta*-selective alkylation protocol.[3] Very recently, a prototype reaction has been successfully developed, giving the *meta*-alkylated arene product with good yield and diastereoselectivity (up to 74%, dr = 17:1). Preliminary results and reaction optimisation towards the diastereoselective reactions will be demonstrated in this presentation.

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# Phosphorus(V)-based red light photoredox catalysis

**Ruth A. Garner**,[a] Tim Renningholtz,[a] Rayyan Miah,[a] Anastazja Wika,[a] Nicholas Kerry,[a] Elliott Nunn,[a] Adam Brookfield,[b] Lubomir Loci,[b] Alice Bowen,[b] Cristina Trujillo,[a] Louise Natrajan,[a] Aaron D. Trowbridge,[a*]

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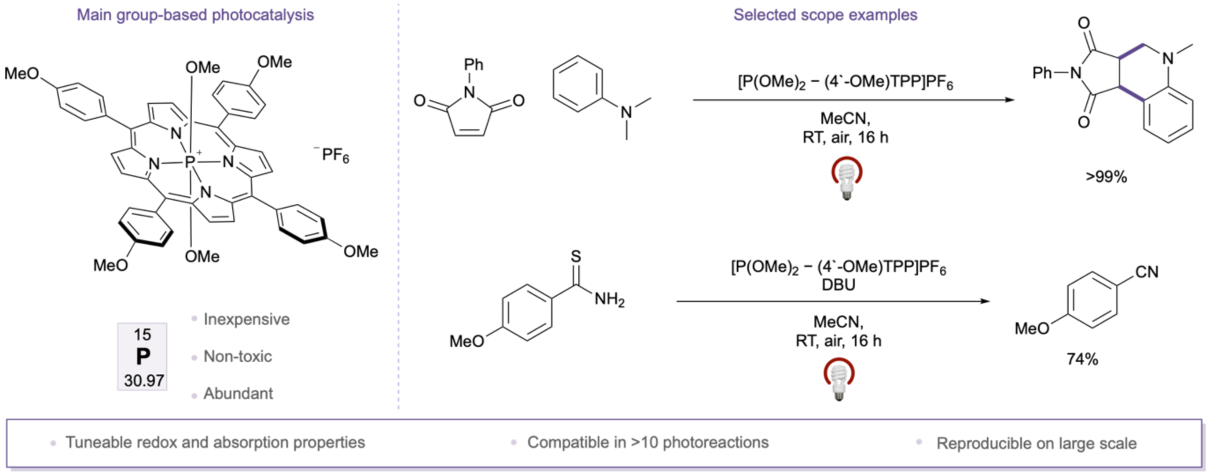


Over the last decade, photoredox catalysis has emerged at the forefront of organic chemistry, enabling previously intractable and highly sought-after synthetic transformations to occur under milder conditions.[1] Despite this, most photocatalysts absorb high energy light and rely on the use of rare-earth metals or bespoke synthesis, rendering them unsustainable and difficult to scale, which has impacted their wider application. A desirable solution to these challenges is to opt for lower energy red light to promote photoredox reactions, which has deeper light penetration allowing for consistent and reproducible results on scale, whilst inhibiting side reactions.[2] However, the dearth of suitable red light-absorbing structures and use of rare-earth metals has significantly hampered progress within the field.[3] The use of main group elements in photocatalysts is a desirable solution to these limitations, however, remains surprisingly limited despite their low cost, widespread abundance and variable oxidation states. To this end, we have designed and synthesised a series of phosphorus-centred porphyrins, exemplifying the first example of phosphorus(V)–mediated–photoredox catalysis under red light irradiation. By tuning the electronics of the phosphorus(V) centre through modulation of the porphyrin ring and axial ligand substituents, we have unlocked a red light active photocatalyst that can be applied in a range of photochemical reactions, with yields matching or surpassing those of traditional based photocatalysts. Additionally, interrogation of the excited state through computational modelling and analytical studies provides vital information of the behaviour of electron transfer and photophysical pathway of the P(V)-porphyrins. Finally, a reproducible electrochemical method for the synthesis and isolation of a novel phosphorus-porphyrin radical has been developed and applied in single electron reductions to gain valuable mechanistic insight.

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# Inverted metal-free active template synthesis of rotaxanes via axle-mediated rotaxination

**Emily Cramp**,[a] Jiankang Zhong,[a] Axel Troncossi,[a] Enzo Olivieri,[a] Chuan Guo,[a] Patrick Zwick,[a] George F. S. Whitehead,[a] and David A. Leigh[a, b]

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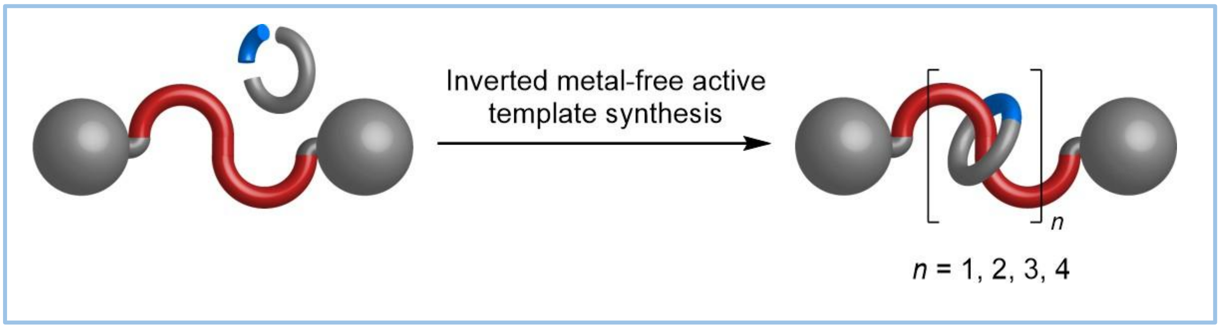
Active template synthesis of rotaxanes accelerates an axle-forming reaction through a macrocycle, using either a coordinated metal ion or appropriately arranged functional groups. This research builds upon previously published metal-free active template syntheses[1-3], by inverting the oligo(ethylene glycol) (OEG) and amide components.

Here, we report a rotaxination strategy in which an OEG thread both accelerates amide bond formation and promotes macrocyclization around itself. Rotaxane formation is promoted by hydrogen bonding interactions that stabilise the macrocyclization transition state while the OEG chain is positioned within a forming macrocycle.

By transposing the usual roles played by the ring and axle in active template synthesis, the approach obviates the need for permanent structural motifs in the macrocycle, generating [2]rotaxanes in up to 70% yield from simple building blocks.

Longer chains enable the iterative synthesis of [n]rotaxanes with as many as four macrocycles on an octa(ethylene glycol) thread. X-Ray crystallography of a [5]rotaxane shows a helical stack of threaded macrocycles, stabilised by $\pi$-stacking and bifurcated C-H…O…H-N hydrogen bonding between the rings.

Skeletal editing to delete the newly formed amides affords minimalist rotaxanes consisting of an OEG axle threaded through a cyclohydrocarbon.

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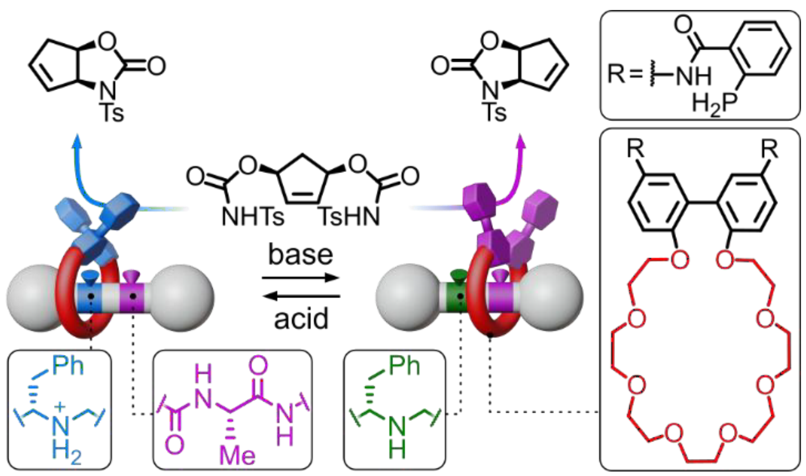
# Reading and Writing Stereochemical Information Encoded in a Molecular Track

**Daniel P. Couto**,[a] Félix Hernández-Culebras,[a]

Daniel J. Tetlow,[a] David A. Leigh* [a,b]

*a.* University of Manchester | *b.* East China Normal University

At the core of biology's most sophisticated information-processing systems lies the reading of chiral-encoded molecular information and its expression into chemical outcomes. To date, synthetic molecular machines that similarly translate encoded stereochemical information remain elusive. Here, we report switchable rotaxane molecular shuttles that couple co-conformational motion with controllable conformational dynamics to read, reconfigure and write chiral information. In these systems, acid–base inputs shuttle a stereodynamic macrocycle between two differently encoded stations on a molecular thread, placing it in distinct local chiral environments. Rapid shuttling contrasts with slower atropisomer equilibration about the macrocycle biaryl axis, enabling time-resolved monitoring of handedness inversion by NMR and circular dichroism spectroscopy. Using a phosphine-bearing macrocycle the stereochemical state encoded in the thread is transduced into the enantioselectivity of a palladium-catalysed allylic substitution, allowing divergent stereochemical outcomes to be programmed into the molecular track. These findings demonstrate how mechanically interlocked architectures can serve as platforms for storing, relaying and expressing molecular information, offering a foundation for programmable asymmetric catalysis, chiral sensing, and molecular machines capable of dynamic stereochemical information processing.

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# Organic Salt-Catalysed Nucleophilic Amination

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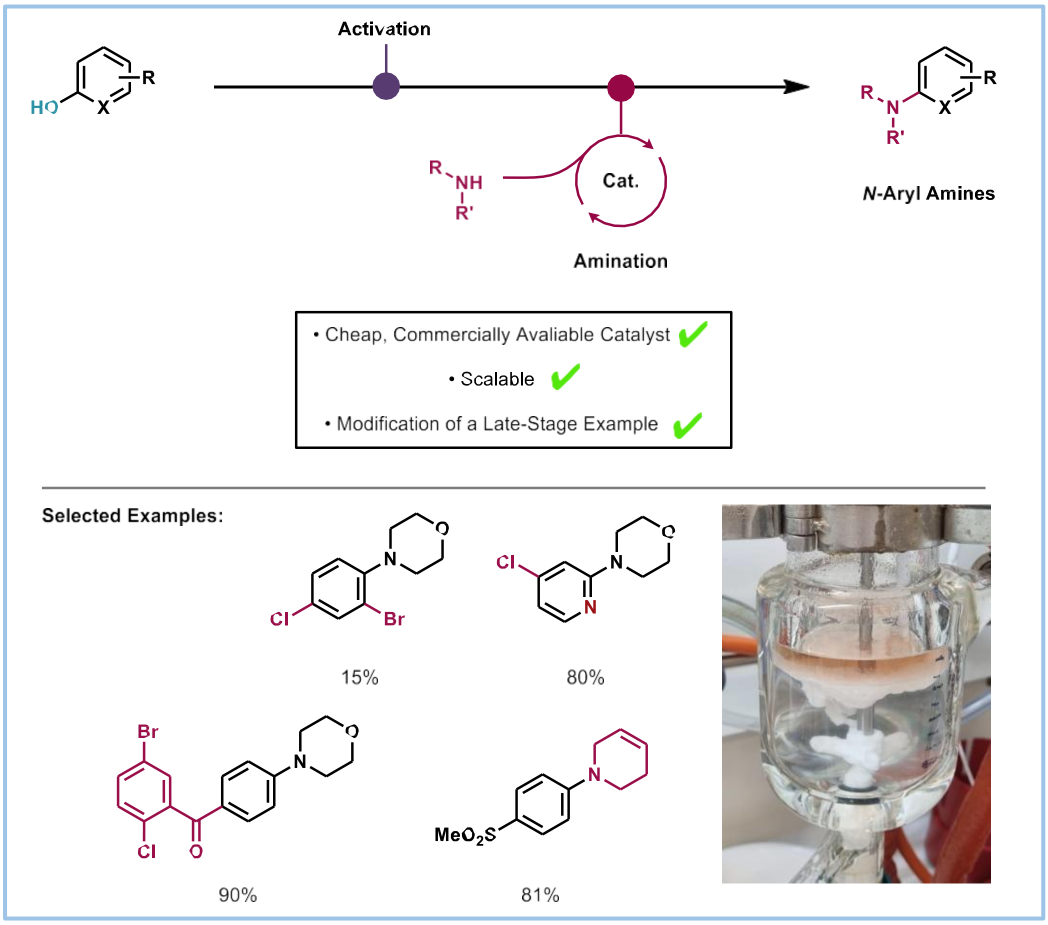
*N*-(Hetero)aryl amines are present in over 40% of drug candidates, yet current methods for their synthesis are hampered by sustainability challenges and harsh reaction conditions.[1,2,3] Phenols are an attractive class of starting materials due to their high availability and biogenicity, making their conversion into medicinally relevant scaffolds desirable. To investigate this challenge, we have discovered that $S_NAr$ reactions can be catalysed by the addition of tetrabutylammonium bromide (TBAB).

Using this strategy, an amination protocol has been developed and applied to 19 substrates, with yields of up to 98%. Scalability has been demonstrated through a 43 mmol reaction that affords the aminated product without the need for column chromatography. Mechanistic studies to elucidate the role of TBAB and the origin of its rate enhancement are ongoing.

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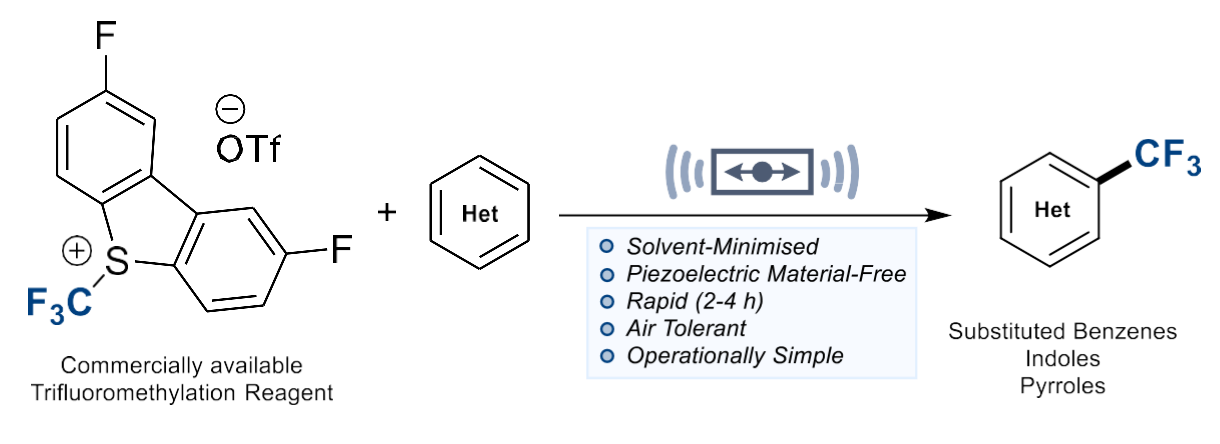
# Mechanochemistry for the C–H Trifluoromethylation of (Hetero)Arenes

**Ali Monteiro Najmi** [a], Dr. Gillian McArthur [a] Professor Igor Larrosa,[a]

The trifluoromethyl (-$CF_3$) group is a privileged motif, featuring in 10-15% of currently marketed pharmaceuticals and 38% of modern crop protection agents. [1] As such, novel methods for installing the -$CF_3$ group which are more efficient and environmentally sustainable are highly desired. Moreover, direct trifluoromethylation of arenes *via* C-H activation allows streamlined synthesis while improving atom economy and decreasing waste by obviating substrate pre-functionalisation. Solution-phase arene C-H trifluoromethylation has been described, but these methods require large amounts of solvent, expensive photocatalysts and/or constant irradiation, or result in over-reaction. [2]

Mechanochemistry has been identified by IUPAC as one of the “Top Ten Emerging Technologies in Chemistry”, offering decreased reaction times, expedited or alternative reactivity, and lower PMI values. Mechanochemical methods for the C-H trifluoromethylation of (hetero)arenes have been reported using either piezoelectric ceramics or biogenic materials. [3,4] In this study, we report an additive-free method for C(*sp*$^2$)-H trifluoromethylation of (hetero)arenes under solvent-minimised ball milling conditions. This method offers short reaction times, operational simplicity and the ability to run the reaction under ambient atmosphere (whereas inert conditions are required for many solution-phase methods). This protocol has so far been extended to electron-rich benzenes, pyrroles, and indoles. Mechanistic elucidation of the reaction is currently underway, along with further exploration of the reaction’s substrate scope. It is envisioned that the reaction may also be applicable to the late-stage functionalisation of complex substrates, encouraging further uptake of mechanochemistry in the chemical community.




Scheme 1: Additive-free Mechanochemical C–H Trifluoromethylation of (Hetero)Arenes

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# Conversion of Alkynes to β-Keto Nitriles via Photoactivation of an Isoxazole-Triarylamine Electron Donor-Acceptor Complex

**George H. Bilionis**,[a] Giacomo E. M. Crisenza[a]

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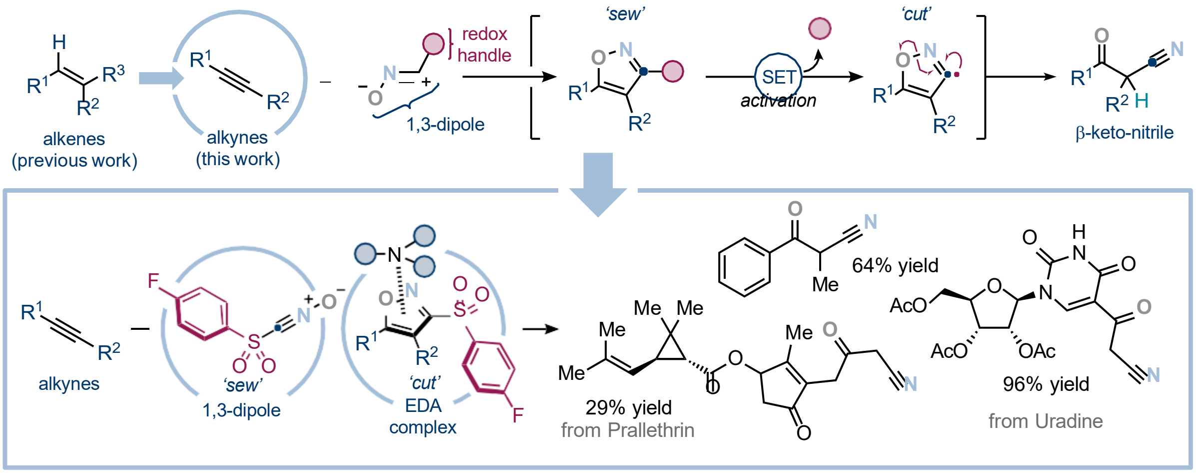
Alkynes, readily available in feedstock and commercial sources, are privileged handles for synthetic building blocks. Due to the high degree of unsaturation across their C≡C bond, they are often exploited to install multiple, distinct functionalities.[1] To achieve this, state-of-the-art approaches rely on transition-metal catalysis [2] and radical cross-coupling reactions.[3] These approaches can be limited by their poor regioselectivity, necessitating the use of biased substrates and a restricted pool of coupling partners.[4]

Seeking to overcome these challenges, we had previously developed a 'Sew & Cut' strategy enabling the stereoselective difunctionalisation of alkenes via a telescoped 1,3-dipolar cycloaddition and electroreductive activation sequence.[5] Building upon this, we sought to expand the range of dipolarophiles to include alkynes. Here, the 'sew' [3+2] cycloaddition step forms isoxazole cycloadducts, which proved to be incompatible with our former electrochemical conditions. To foster selective SET activation, we devised a visible-light-driven strategy enabled by the formation of an EDA complex between the cycloadduct and a triarylamine. Irradiation of the charge-transfer complex triggers the radical fragmentation of the heterocycle, delivering the sought-after keto nitrile products. Our telescoped protocol is broad in scope, enabling the chemo- and regioselective 1,2-oxy-cyanation of simple alkyne hydrocarbons as well as C≡C bonds embedded within complex natural products, agrochemicals, and pharmaceutical agents – thereby rendering the method applicable to both feedstock valorisation and late-stage functionalisation.

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# Hydrogen-Bonding in Benzylic Amide Macrocycle -Diamide [2]Rotaxanes

**Victoria Y. Jiang**,[a] Prodip Howlader,[a] David A. Leigh*,[a,b] Jenny K. Y. Wong[c]

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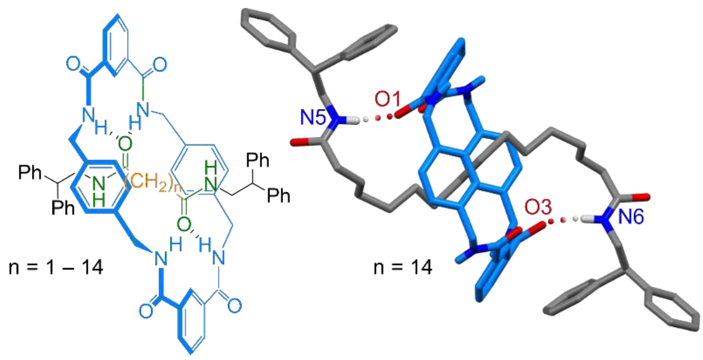
We report on a series of [2]rotaxanes featuring a flexible diamide moiety of different lengths on the axle (Figure 1). The elongated templates were still able to support hydrogen bonding directed benzylic amide macrocyclization,[1] regardless of being significantly structurally different from the optimal fumaramide template,[2] with the yield peaking at 48% before plateauing around 7% as the length of the spacer increased. In the [2]rotaxane with a single carbon spacer between diamides, intramolecular hydrogen bonding within the thread[3] resulted in low yields, and gave rise to an unusual hydrogen-bonding pattern. In longer rotaxanes, the flexibility of the threads gave rise to novel co-conformers, which were identified by $^1$H NMR and X-ray crystallography. While the shielding pattern and corresponding dominant co-conformer in solution remained the same throughout the series, the thermodynamic preference over these translational isomers in the solid-state was observed to be different for rotaxanes at different lengths. This was an unprecedented consequence of increased flexibility in interlocked molecules and may prove useful for the design of future rotaxanes and molecular ratchets.

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# Talk Abstracts

# PGR CONFERENCE

## BIO

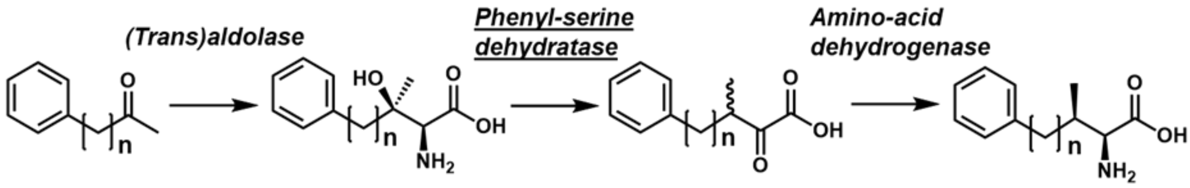
*Section*

# Biocatalytic cascade synthesis of β-methyl-branched-amino-acids

**Sophie Wulf**,[a] Andrew Buller[a]

*a.* University of Manchester, Manchester Institute of Biotechnology

β-methyl-branched-amino-acids are regularly employed in ligand and natural product synthesis. When incorporated into pharmaceuticals, this motif imparts proteolytic stability and enhanced biological activity. Current synthetic routes to these amino-acids require harsh conditions using bespoke chiral ligands. Existing enzymatic approaches to accessing these amino-acids show promise by utilizing dynamic kinetic resolution on achiral α-keto-acids as starting materials to achieve high-yields and diastereoselectivity. However, α-keto-acids require multistep synthesis, and the resulting products are prone to degradation through oxidative decarboxylation.[1] I aim to address this limitation by using accessible and bench stable ketones as starting materials to generate the α-keto-acids in-situ. This intermediate is further reacted to β- methyl-amino-acids in a one-pot cascade. Previous work in our lab has established that L-threonine trans-aldolases, such as ObiH, can produce tertiary-β-hydroxy-amino-acids.[2] We further discovered the phenyl-serine dehydratase, RpicPSDH, can dehydrate these amino-acids [2], converting them to the corresponding α-keto-acid. Herein, I have crystallized a substrate bound RpicPSDH and used this structural information to aid in evolving a phenyl-serine dehydratase for a three-step biocatalytic cascade.

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# Are Tags Always Benign? Disordered Tags Unfold GFP in Electrospray Droplets

**Thomas D. Hoare**[1], Xudong Wang[1], Hanan Messiha[1], Kathleen Cain[1], Xamuel Lund[2], Aurélie Fournet[2], Pau Bernado[2], Perdita Barran[1]

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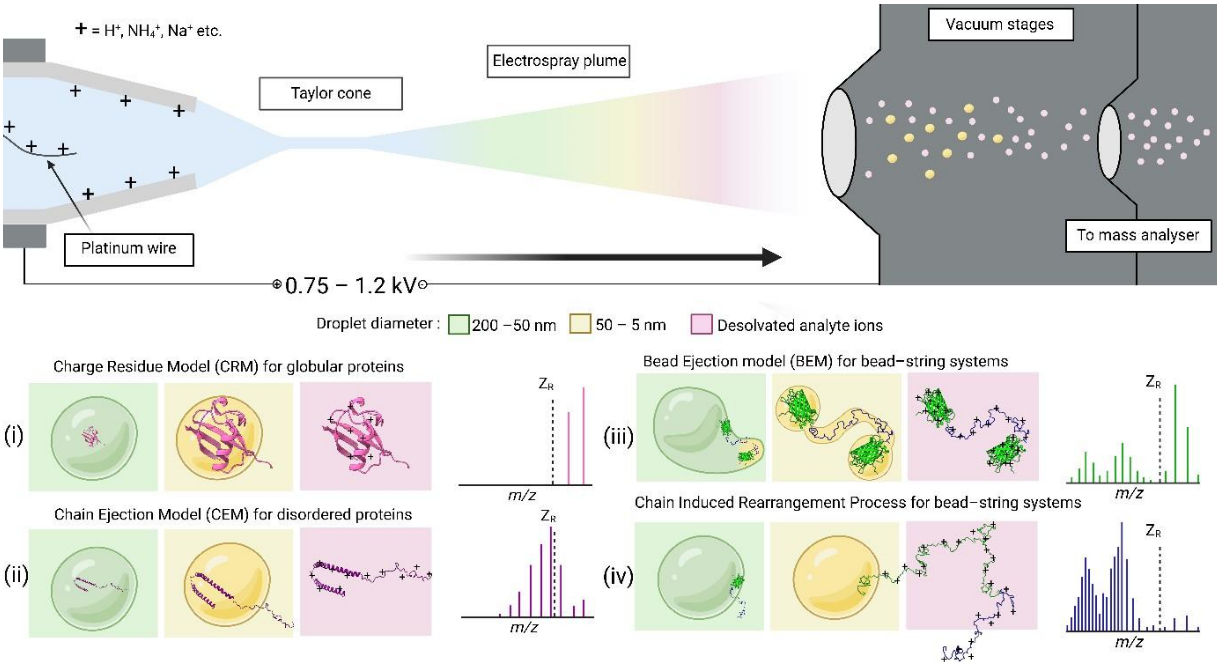


**Nano-electrospray ionisation mass spectrometry (nESI-MS)** is a routine analytical technique used to study the conformational ensembles of proteins. During the nESI process, proteins are initially contained within highly charged droplets (~1 µm in diameter) that shrink through solvent evaporation and Coulomb fission events, ultimately producing gas-phase protein ions for mass spectrometric analysis. When combined with ion mobility measurements, information on the effective size of these ions can also be obtained, providing indirect insights into the solution-phase structural ensemble of a protein system.

Understanding how proteins ionise during nESI is critical, as ionisation processes directly influence the resulting gas-phase ensemble and may therefore bias structural interpretations. Ionisation models have been developed to describe the behaviour of either compact, globular proteins (i) or highly disordered (bio)polymer chains (ii). However, many biologically relevant proteins contain both ordered and disordered regions, and the ionisation behaviour of these hybrid systems remains comparatively poorly understood (iii).

Green Fluorescent Protein (GFP) is a ubiquitous protein used in molecular biology as a fluorescent reporter and is known for its highly stable fold. Here, we present nESI-MS and ion mobility data for a series of GFP-containing constructs incorporating domains with varying degrees of structural order, including Ubiquitin, α-synuclein, and Httex1. While GFP and GFP–Ubiquitin constructs are observed as compact species consistent with retention of the native β-barrel fold, constructs containing intrinsically disordered regions exhibit collision cross sections that can only be explained by the unfolding of the GFP β-barrel. To rationalise this discovery, we propose the **Chain-Induced Rearrangement Process**

**(ChIRP)** model (iv), in which **the coulombically driven extrusion of disordered chains from charged droplets generates sufficient mechanical tension to unfold neighbouring structured domains prior to complete desolvation in nESI-MS**. These findings identify an edge case in which a nominally soft ionisation method can induce protein denaturation and highlight how disordered tags can substantially influence the structural ensembles observed by native mass spectrometry.

# Replacing chromatography with ice-affinity for protein purification using a genetically encoded Cryo-Tag

**Ho Fung Mack,[a] Matthew I. Gibson[a,b*]**

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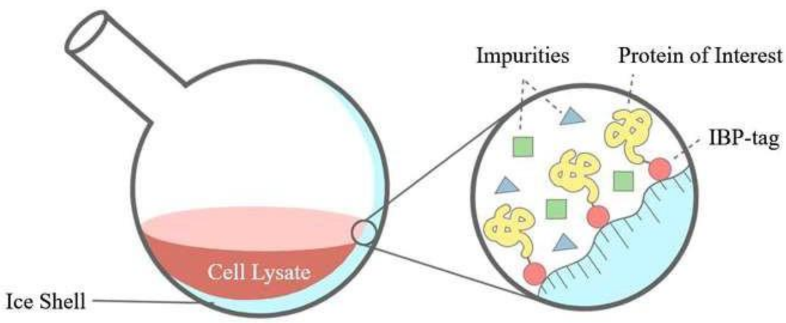
Attention of ice binding proteins (IBPs) was caught because of their unique properties, including ice shaping, thermal hysteresis (TH) and ice recrystallization inhibition (IRI). With those properties, IBPs become one of the promising tools on cryopreservation. Rather than exploring the role of IBPs in cryopreservation, here the use of IBPs as and genetically encodable fusion tag for ice shell purification is proposed, as an alternative to traditional chromatography. In the current study, a 14-amino acid IBP-tag was fused with other protein of interest. Recombinant proteins were successfully purified with a simple and commonly available set-up. Further evaluations were performed to ice-shell purified protein. As a result, proteins retained original structure and activity after ice shell purification. Recombinant proteins also exhibit ice shaping property and IRI activity, which originated from the cryo-tag. The current result implies a potential application of the IBP-tag as a dual functional tag for both cryopreservation and purification of the recombinant protein.

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# Bioengineered Spider Silk Mimetics and the Means to Spin them

**Faisal Giwa**,[a] Jonny Blaker,[a]

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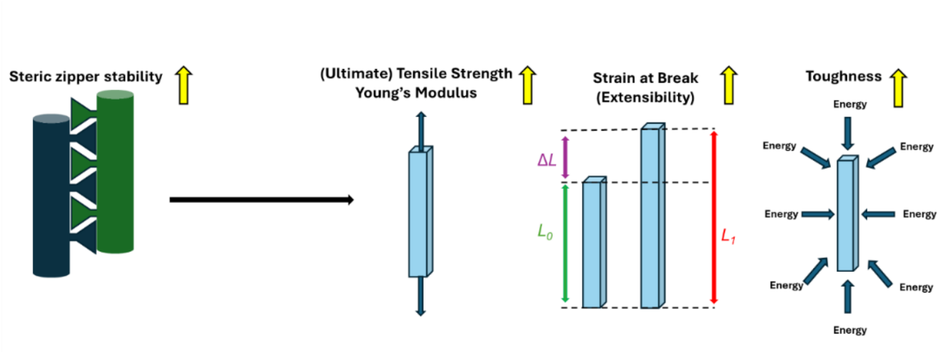
Artificial spider silks perform worse than their natural counterparts due to their reduced molecular weight. However, efforts to increase molecular typically result in the yield of purified protein being heavily reduced. Here we substitute functional motifs in biomimetic spider silks predicted to enhance fiber assembly and monitor how these changes impact common predictors of fiber performance.



## Structural Understanding of Novel Fungal Terpene Synthases/Cyclases

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Terpenes constitute one of the largest and most structurally diverse families of natural products, yet fungal terpene synthases remain far less understood than their plant and bacterial counterparts.
This study investigates novel fungal terpene synthases using an integrated biochemical and structure-guided approach.
Heterologous expression, coupled with GC–MS product profiling, enabled the functional screening of candidate enzymes and the selection of targets based on product complexity, tractability, and structural promise.
Subsequent experimental studies refined cloning and expression strategies, including resolving transposon-associated instability through reconstruction of a key expression construct into a stable pBb-pMVA system. Computational analysis incorporating AlphaFold prediction, homology modelling, and molecular docking was employed to examine active-site architecture, substrate positioning, and catalytic pocket volume. These analyses informed the rational design of twenty-two mutagenesis targets across two terpene synthases.
GC-MS analysis of sequence-verified variants revealed mutation-dependent changes in catalytic activity and product distribution, providing new mechanistic insight into determinants of fungal terpene cyclisation and highlighting residues that influence terpene scaffold formation.

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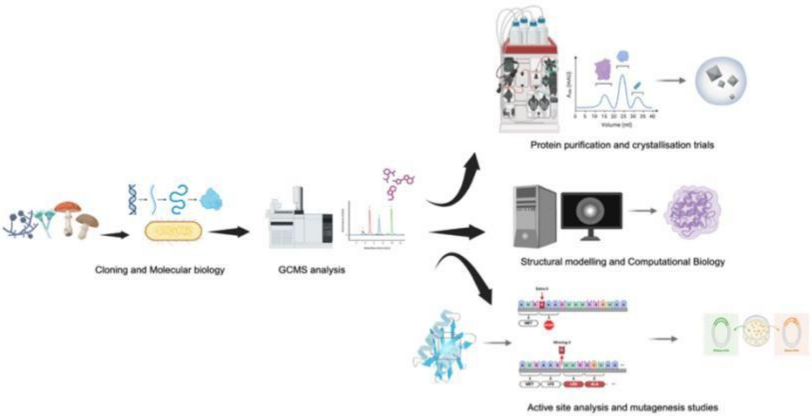


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# A Ru-P450 analogue: Preparation and strategies for decarbonylation

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Cytochromes P450 are well-known monooxygenase enzymes, which catalyse C–H activation *via* direct reaction with $O_2$. The catalytic cycle of P450s involves the formation of a reactive high valent Fe(IV)-oxo species, named Compound I, the key intermediate in the O-atom insertion step.[1] Fundamental insight into the short-lived Compound I species can be generated by substituting the metal centre in P450s to different transition metals.[2] One particularly attractive, but challenging target for this metal-exchange is ruthenium, which has been studied extensively from a theoretical context but never tested experimentally.[3, 4] The focus of this project is the preparation of P450s, where the native Fe-protoporphyrin IX (FePPIX) heme cofactor is substituted by a ruthenium analogue. For this purpose, a library of apo-P450s was constructed to determine which of them could be expressed in high yield and with minimal Fe-contamination. Concomitantly, ruthenium mesoporphyrin IX (RuMPIX) was synthesised.[5] Two separate methods to dissociate metal-bound CO were also established. Through these methods, ruthenium-P450 analogues have been prepared and can now be studied for mechanistic insight.

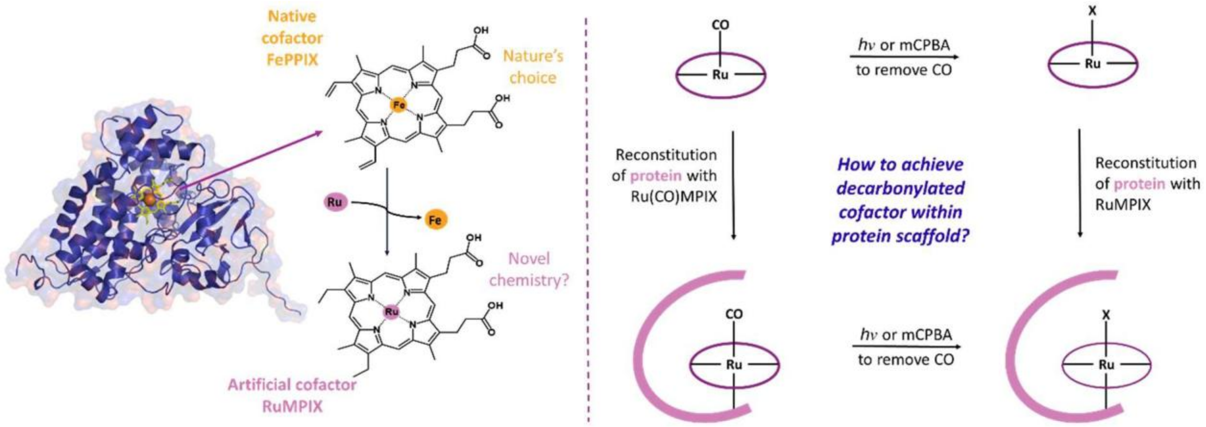


***Figure 1.*** Structure of the heme domain of P450-AX (from *Meinhardsimonia xiamenensis*) with the native heme cofactor (in yellow) incorporated. Highlighted is the Fe centre (in orange), also shown the target RuMPIX (in mauve), on the left. On the right, the methods for the incorporation of decarbonylated RuMPIX in the protein scaffold.

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# Chemoproteomic Profiling of Small Molecule Phenotypic Hits to Investigate Cancer Mechanisms

**Aitor Carneiro**,[a] Hazim Al-Hazmi,[b] Benjamin Foster,[b] Duncan Smith,[c] Sam Butterworth,[d] Christine Schmidt,[b] Igor Larrosa[a]

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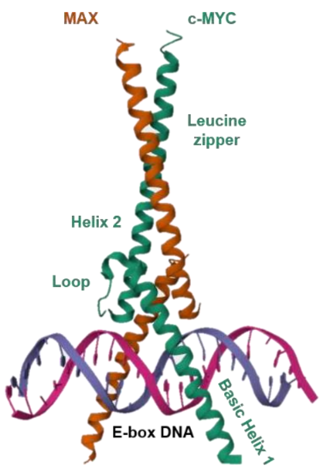
Phenotypic drug discovery (PDD) has recently re-emerged as an ambitious strategy to discover first-in-class drugs and chemical tools to study complex diseases.[1] As opposed to the traditionally predominant target-based drug discovery (TDD), in which establishing a specified protein target enables structure-based drug design campaigns, PDD reverses the process by using an observed compound effect in a biological system as the starting point to study the underlying mechanism of action that explains it. In that context, chemoproteomics workflows are implemented to enable target identification and validation.[2]

In this work, we have identified a covalent small molecule phenotypic hit in neuroblastoma cell lines. This small molecule disrupts the morphology of the treated cells, and it reduces the protein levels of the transcription factor c-Myc – a key regulator in oncology –[3] in a dose-dependent manner. However, we do not observe a direct engagement with c-Myc, which points towards an indirect chemical modulation. We have designed and synthesised various chemical tools – both preserving and deliberately inactivating the phenotype observed – to study the engagement of this chemotype with the proteome in complex cellular environments using chemoproteomics workflows. As a result of this, we have been able to link the phenotypic effects observed to a compound-induced iron-dependent ferroptosis of the cancer cells.[4]

Herein, we present our findings towards the elucidation of the main target and mechanism of action of this small molecule phenotypic hit, as well as a characterisation of the several processes triggered in the studied cancer cells.

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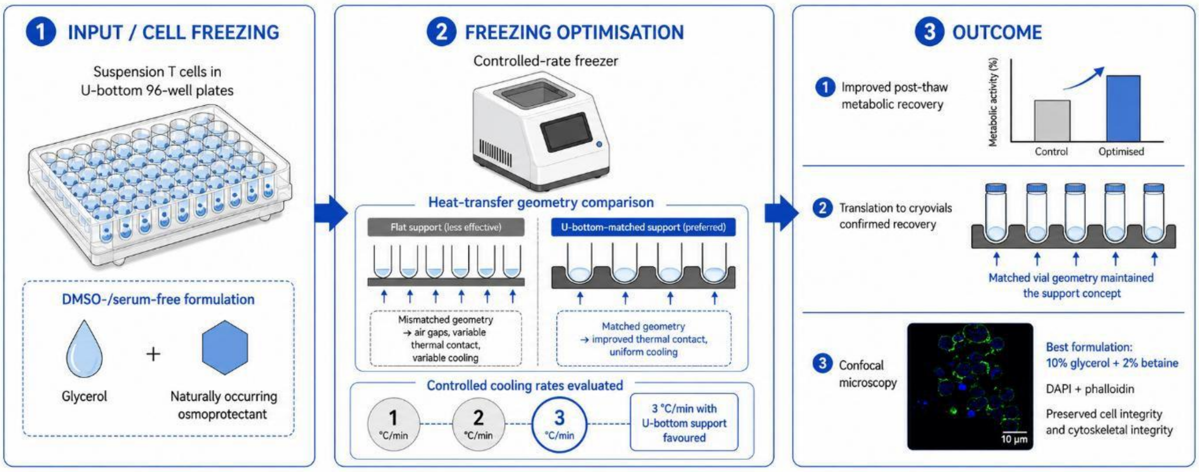
# DMSO and Serum-free Cryopreservation of T-Cells in Vials and Multiwell plates enabled by Glycerol-Osmoprotectant Formulation

**Alexandru Ilie, Akalabya Bissoyi, Cigdem Buse Oral, Qiao Tang, Oliver Grover and Matthew I. Gibson.**

Cryopreservation is pivotal to T-cell screening workflows in immunotherapy discovery, where reliable assay readouts require consistent post-thaw recovery and metabolic function. However, conventional DMSO- and serum-based methods are limited by cytotoxicity and formulation variability, while post-thaw outcomes also depend on cooling rate, sample format, and heat-transfer geometry. Here, we investigated a DMSO- and serum-free cryopreservation strategy based on glycerol and a naturally occurring osmoprotectant, using Jurkat cells as a T-cell model[1]. Initial screening in 96-well U-bottom plates identified a lead glycerol-osmoprotectant formulation under uncontrolled freezing conditions. Subsequent optimisation evaluated controlled cooling at 1, 2, and 3 °C/min using different freezing geometries, followed by storage at −80 °C for 24h before thawing. Flat-contact controlled-rate freezing did not consistently improve post-thaw metabolic activity compared with uncontrolled freezing, although delayed recovery profiles after 72h suggested improved metabolic activity in selected conditions. In contrast, U-bottom shaped freezing geometry led to improved post-thaw metabolic performance, with 3 °C/min emerging as the most favourable freezing rate tested[2]. Translation of formulations, support geometry, and cooling rate into cryovials, followed by one week of storage at −80 °C, confirmed post-thaw viability and recovery by trypan blue exclusion, exceeding the DMSO control under the tested conditions. Differential scanning calorimetry and ice nucleation analyses suggested that the mechanism of action was consistent with mitigation of solution-effects and osmotic stress and not altered ice nucleation[3]. Overall, this work establishes a systematic optimisation for DMSO- and serum-free T-cell cryopreservation, integrating formulation design, cooling rate, and freezing geometry to achieve robust post-thaw recovery.

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# Development and characterization of a biosensor for 2,5-furandicarboxylic acid in *Pseudomonas putida*

**Bhumishree B. Dehury**,[a] Lani Peel [a], Thomas Butterfield [a], Mary Ortmayer [a], Colin Levy [a], Neil Dixon [a]

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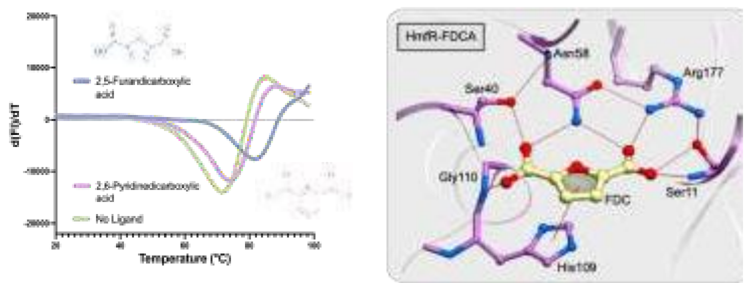
2,5-furandicarboxylic acid, commonly known as FDCA, is an aromatic diacid with potential for replacing petroleum-based polyester plastics with bio-based alternatives at a commercial scale. The biodegradability and renewability of FDCA makes it an attractive precursor to develop high performance bio-based polymers like polyethylene furanoate (PEF) as an alternative to PET plastics. However, the insufficient FDCA production yields remain a limiting factor for large-scale industrial manufacture and development of a biosensor sensitive to FDCA can efficiently screen for the high-performance conditions for bio-based manufacturing processes through real-time monitoring of FDCA production. Here we designed a genetic circuit to establish a FDCA responsive biosensor in *Pseudomonas putida* and subsequently biochemically characterised the associated transcription factor HmfR. Through a bioinformatics-driven approach, we identified and incorporated a transcription factor, HmfR, from *Trinikia symbiotica* into a GFP based reporter system in *P. putida* to screen for sensitivity and specificity against FDCA and its several structural analogues. Thermofluor assay and Isothermal titration calorimetry experiments revealed up to 13 °C of thermal stabilization of HmfR melting temperature and 24.2uM of dissociation constant (Kd) in presence of FDCA respectively, suggesting strong interaction between FDCA and HmfR. Furthermore, the crystal structure of effector binding domain of HmfR showed interaction of FDCA with S11, S40, N58, G110 and R177 and H109 residues. This work demonstrates the development of a biosensor for monitoring FDCA and lays the groundwork for future metabolic engineering strategies aimed at optimizing FDCA bioproduction in microbial hosts.




**A.** Differential Scanning Fluorimetry assay demonstrating a shift in melting temperature ($T_m$) of HmfR after incubation with FDCA. **B.** Crystal structure of HmfR bound to 2,5-FDCA**.**

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# Enzymatic activation of sulfur heteroaromatics facilitates downstream enantioselective cross-coupling reactions

**Emily Q. Rushworth[a,b†], Órla Conboy[a†], Christopher Taylor[a,b], Colin Levy[a,b], Mary Ortmayer[a,b], George F. S. Whitehead[a], Andy Yen[c], Ciro Romano[a], Anthony P. Green[a,b*], David J. Procter[a*]**

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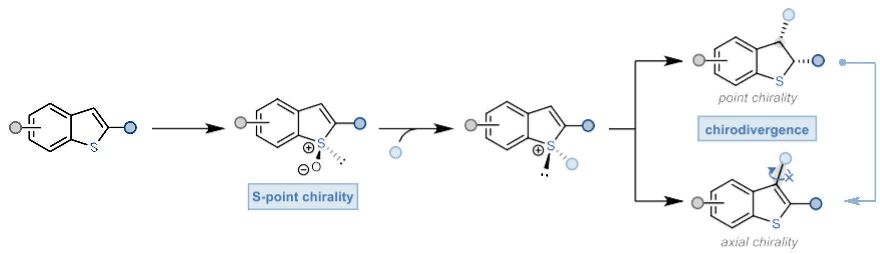
As high value molecules, such as drugs, become more structurally complex, there is an increasing demand for strategies to construct stereogenic elements – such as chiral centres and axes – in an enantiocontrolled fashion. Some methods to access these scaffolds stem from achiral starting materials, which can be utilized in either cross-coupling processes that set a chiral axis, or dearomatization reactions that establish new stereocentres – both of which typically involve the use of transition metal catalysts and/or prefunctionalized substrates. This work establishes a new platform for the enantioselective manipulation of heteroaromatic feedstocks. Enantioselective oxidation of important benzothiophenes using an engineered styrene monooxygenase enzyme furnishes a variety of benzothiophene *S*-oxides in high yield and enantioselectivity. This enzymatic oxidation 'switches on' reactivity and establishes a sulfur-stereocentre that directs the stereochemical course of subsequent cross-coupling reactions with non-prefunctionalized partners.[1,2] Our integrated chemoenzymatic approach serves as a blueprint to unlock the potential of dormant sulfur chirality in important heterocycles to direct stereoselective cross-couplings that expediently deliver diverse enantioenriched products.

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# Characterisation of Isolated Reductase Domains from a Panel of Self-Sufficient Thermostable Cytochromes P450

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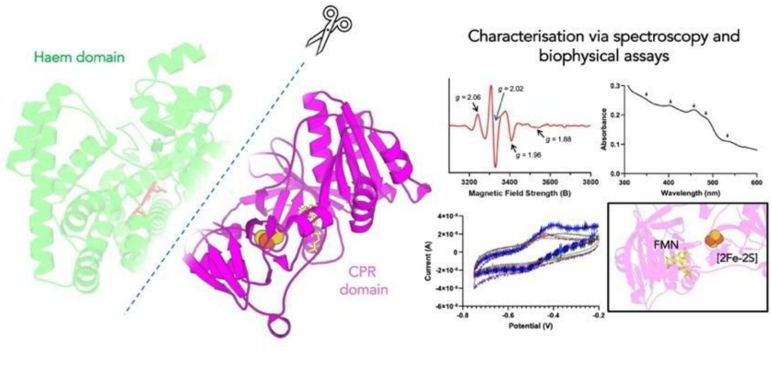
Cytochromes P450 (CYPs) are valuable haem-iron metalloenzymes for industrial biotechnology due to their ability to hydroxylate inert C–H bonds.[1] However, native CYPs often show poor productivity, partly due to inefficient electron transfer needed to drive their catalytic cycle. Self-sufficient P450s, in which haem and reductase (CPR) domains form a single polypeptide (e.g., the CYP116 family), display improved productivity compared to unconnected systems, although detailed structural information remains limited.[2]

In this presentation, we characterise isolated CPR domains from thermostable CYP116B enzymes.[3] These CPRs harbour an FMN and a [2Fe-2S] cluster that mediate electron transfer from NAD(P)H to the haem centre. The domains were successfully expressed and purified, retaining their dual cofactor assembly, as confirmed by spectroscopic methods (EPR, UV-vis) and elemental analyses. All CPRs showed high thermostability (Tm ≥ 50 °C), and redox activity was demonstrated through protein-film electrochemistry.

Comparing hydroxylation using linked versus unlinked haem–reductase constructs revealed that, although the intrinsic redox activity of the CPR domains is unchanged, separating the domains reduces overall P450 catalysis, demonstrating the important role that physical coupling plays for improving electron transfer in self-sufficient systems.[4]

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# Enzymatic Metal–Hydrogen Atom Transfer with a Cobalt Protoporphyrin Cofactor

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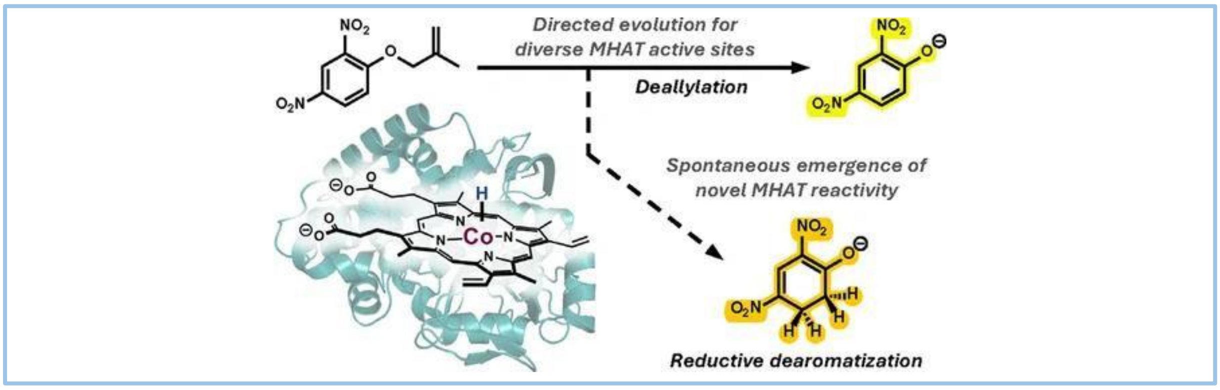
Introduction of unnatural cofactors in biocatalysis may open the door to new reactive enzymatic intermediates, and in turn, new biochemical reactions. Here, we employed a de novo biosynthesized, non-natural cofactor, cobalt protoporphyrin IX (CoPPIX), to generate a mononuclear cobalt hydride in the active site of CYP119, a model P450 enzyme. We show that this cobalt hydride intermediate engages in metal–hydrogen atom transfer (MHAT) reactivity, a well-studied and highly utilized reactivity pattern in synthetic chemistry, but which is not known to operate in Nature. We paired convenient in vivo CoPPIX biosynthesis with a colorimetric screen to enable rapid directed evolution. Thus, we engineered CYP119 for MHAT-mediated deallylation of nitrophenols, with the goal of generating not one prolific catalyst, but a diverse set of MHAT-compatible enzymes. Because many silanes hydrolyse quickly, we additionally sought enzymes that accelerate metal-hydride formation from a more persistent silane. This evolution yielded 80 diverse active site recombinants that catalyse MHAT. Serendipitously, we found many variants reduced the aromatic ring of the colorimetric probe, a reaction not previously known. Detailed mechanistic analysis established this is a radical, MHAT-mediated reductive dearomatization that occurs efficiently under aerobic conditions, albeit on a limited suite of nitrophenyl ethers. These results lay a framework for further engineering and study of biocatalytic MHAT, and the unique role of metal substitution to tune reactivity.

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# Design and Engineering of Light-Activated Enzymes for Chemical Production

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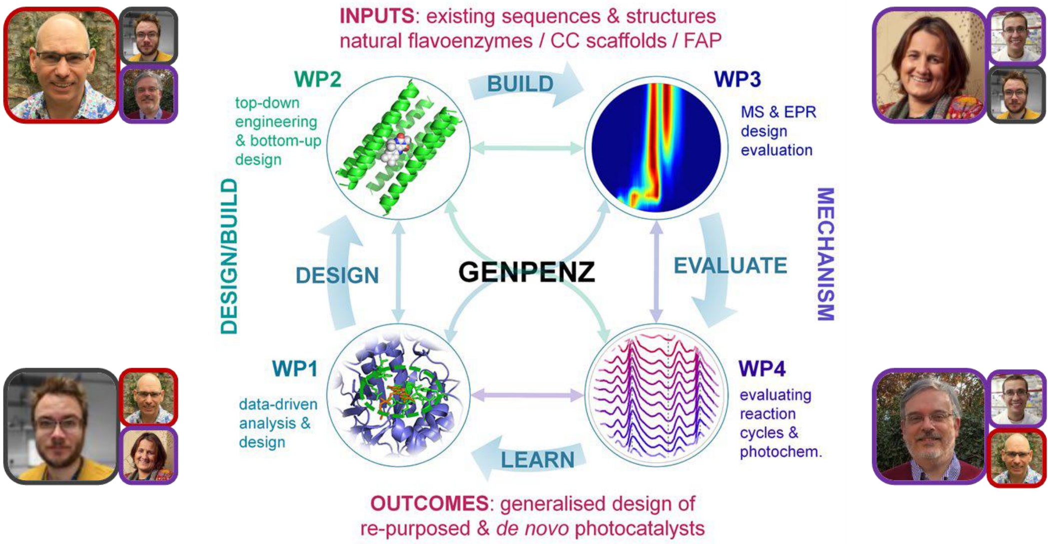
Photoenzymes offer a sustainable route to chemical transformation through the use of light-driven catalysis, yet only a limited number of naturally occurring photoactive flavoproteins have been identified.[1] Here, we seek to expand the known repertoire of photoenzymes by combining machine learning with spectroscopic and activity-based screening to identify and characterise novel photoactive enzymes. A machine learning model was trained using the currently known pool of photoactive flavoproteins and applied to predict potentially photoactive candidate proteins using structural information from the Protein Data Bank. We took forward 79 proteins candidates for expression and fluorescence-based screening to estimate fluorescence lifetimes. For the promising candidates, photophysical properties were further investigated using transient absorbance spectroscopy for accurate quantification of their excited state lifetimes. Photoactivity was evaluated using the model substrate mandelic acid, since free-flavins are able to catalyse light-driven transformations of this compound. We report that multiple non-natural photoenzymes show increased activity for mandelic acid, compared to free-flavin. This project establishes a work-flow for the discovery of previously unrecognised photoactive flavoproteins and provides insights into the structural and photophysical features that govern flavin-based photocatalysis. These findings contribute to the growing field of photoenzymology and may facilitate the development of new biocatalysts for sustainable light-driven synthesis.

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# Exploiting Enzyme Reversibility for Selective Deuteration in Heavy Drug Synthesis

**Christopher Otun**,[a] Francesco Falcioni,[b] Ryan Bragg,[b] Charles Elmore[c] & Jack Rowbotham[a]

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The deuterium kinetic isotope effect (DKIE) can be exploited to increase the therapeutic value of pharmaceuticals which suffer from rapid oxidation or racemisation *in vivo*. By decreasing the rate of these attrition reactions using the DKIE, deuterated drugs can be administered in lower dosages and remain active in the body for longer durations compared to their undeuterated counterparts.[1] Thus, the interest in deuterated pharmaceutical agents has increased substantially in recent years, provoking the development of a range of chemical methods for their synthesis. Biocatalysis is a valuable option for installing deuterium atoms at targeted locations because enzymes are naturally selective and operate in aqueous conditions (enabling deuterium oxide ($^2H_2O$) to be used as the solvent and isotope source).[2] However, hydrogen isotope exchange (HIE) and reductive isotopic labelling methods, which are common in the field of chemocatalysis, are not currently well developed for enzymes. We present new data on the ability of flavoenzymes to catalyse HIE for the synthesis of deuterated reduced nicotinamide cofactors ([4-$^2$H]-NAD(P)H).[3] Moreover, the addition of flavoenzyme into C=N and C=O bond reductase/dehydrogenase-based cofactor recycling systems in $^2H_2O$ facilitates *in situ* (re)generation of [4-$^2$H]-NAD(P)H, providing a facile and selective route to chiral deuterated amines and alcohols for research, diagnostics and therapeutic applications (Figure 1). The commercial availability of the enzymes used in the [4-$^2$H]-NAD(P)H recycling system enables this strategy to be implemented in any standard synthetic chemistry laboratory.

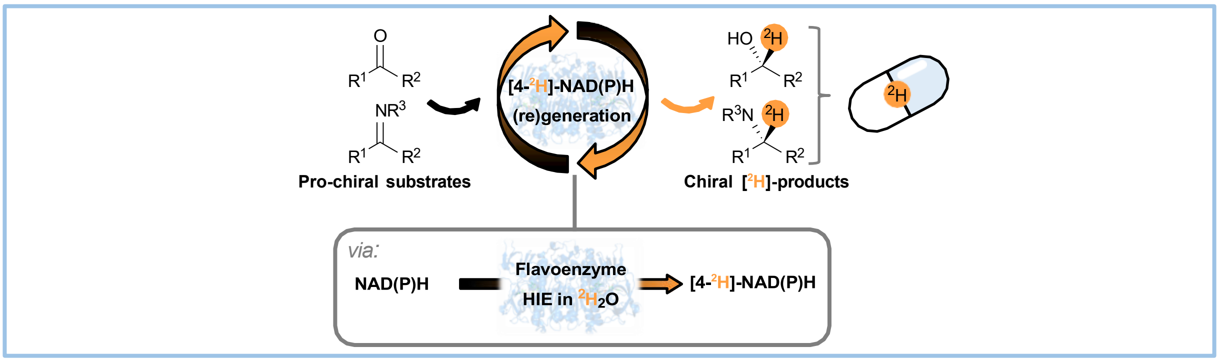


**Figure 1.** Biocatalytic *in situ* (re)generation of [4-$^2$H]-NAD(P)H for the synthesis of chiral deuterated compounds.

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## Long-term kinetics dictated by Active-Inactive Conformational Dynamics Underlie Class D β-Lactamase Hydrolysis of Carbapenem

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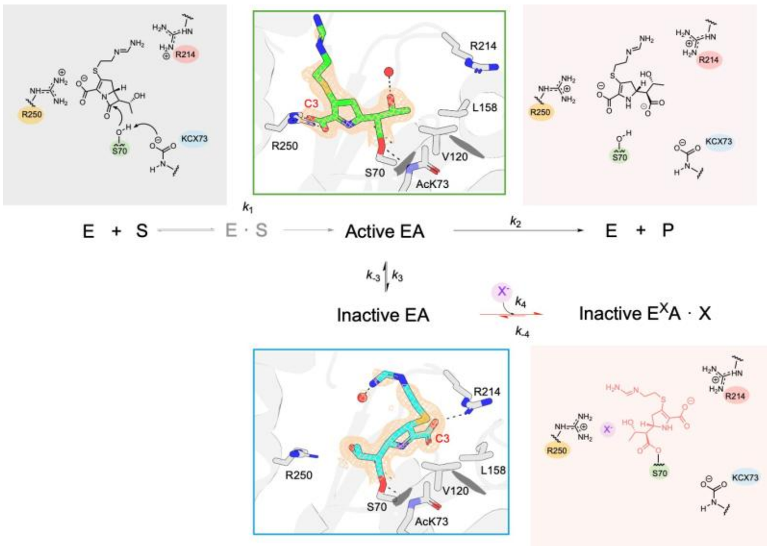
Antibiotic-resistant Enterobacterales producing oxacillinase (OXA)-48-like Class D β-lactamases are associated with high clinical mortality. Chloride ($Cl^-$), a ubiquitous environmental ion, inhibits carbapenem hydrolysis by stabilising an alternative, catalytically "inactive" acyl-intermediate conformation where halide ions bind to the R250 conformational anchor. However, how these conformational ensembles interconvert from a dynamic perspective remains unclear. Here, we combined $^{19}F$ NMR spectroscopy with X-ray crystallography to directly observe the coexistence of catalytically "active" and "inactive" imipenem and oxacillin acyl-enzyme intermediates for OXA-$48_{WT}$ and OXA-$48_{\Delta 214\text{-}217}$. We demonstrate that these intermediates exist in an intrinsic conformational equilibrium that modulates the apparent hydrolytic efficiency of OXA-48. The presence of less-solvated anions stabilises the inactive conformation, shifting the equilibrium toward the inactive state and driving the inhibitory effect. Consequently, $Cl^-$ plays a critical role in determining imipenem minimum inhibitory concentrations (MICs) against OXA-48-producing Klebsiella pneumoniae and Escherichia coli by modulating long-term enzyme kinetics. Furthermore, mutagenesis of the β5-β6 loop, specifically the R214S substitution and R214-P217 deletion, altered this equilibrium by modifying the inactive binding modes of imipenem acyl-enzyme intermediates, accounting for the disparate catalytic activities among OXA-48 variants. Together, our findings demonstrate that the "inactive" acyl-enzyme intermediate is more widespread among OXA-48 variants than previously recognised. This redefines the overall hydrolysis mechanisms among OXA-48-like enzymes, highlighting the critical role of conformational dynamics in carbapenemase function and providing new insights for targeted inhibitor design.

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# Reversible Functionalisation of Synthetic Cellulosic Oligosaccharides

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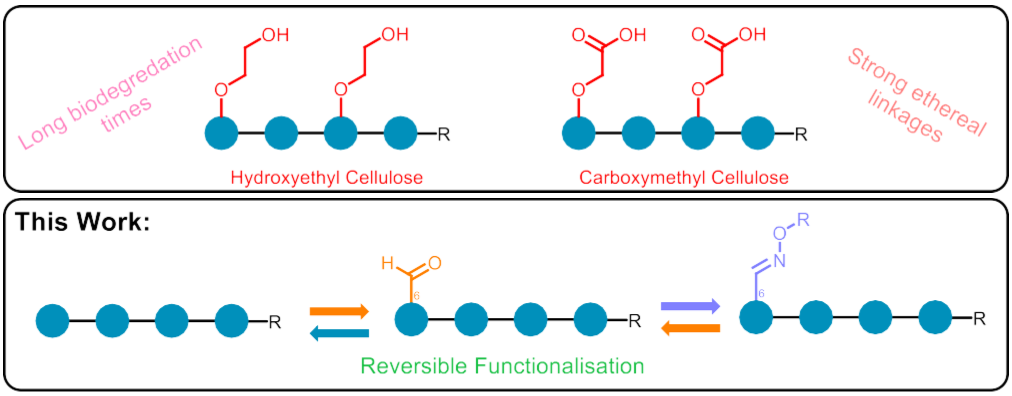
Cellulose is a renewable biopolymer that is industrially modified to confer essential properties. This is apparent in modified hydroxyethyl and carboxymethyl celluloses where etheral hydroxyl group modification is used to improve polymeric properties, such as solubility. However, such ethereal substituents drastically increase biodegradation times compared to unmodified cellulose, due to the strength of the C-O bond [1]. Reversible functional groups in place of ethereal linkages could improve biodegradation prospects for next generation modified celluloses. In this regard, the reaction of aldehydes with hydroxylamines to yield oximes is a reversible process and aldehydes can be introduced at the C6 positions of component glucose units. This has been demonstrated using TEMPO oxidation [2], which requires stochiometric regeneration and is prone to over-oxidation. Alternatively, aldehydes and can be prepared under mild, enzymatic conditions using oxidases and molecular $O_2$ as co-oxidant [3].

This work employs the engineered galactose oxidase (GOase, $F_2$ variant) to explore oxidation of synthetic cellulose oligosaccharides [4]. Firstly, linear β-1,4-linked oligosaccharides containing an aromatic reducing end handle for UV monitoring were synthesised. These materials were then oxidised with GOase $F_2$ at the C6 position of the non-reducing glucose unit, introducing aldehyde moieties for oxime ligation with commercial hydroxylamines. Following isolation and characterisation of modified oligosaccharides, acid catalysis was used to remove the functionality, returning the aldehyde for further re-conjugation or biodegradation.

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# Development of a Quantitative MRM assay from Skin Swabs Rich in Sebum to Diagnose Parkinson's Disease

**Minhui Zhu**,[a] Eleanor Sinclair,[a] Breanna Dixon,[a] Depanjan Sarkar,[a] Michael Morris,[a] Perdita Barran [a]

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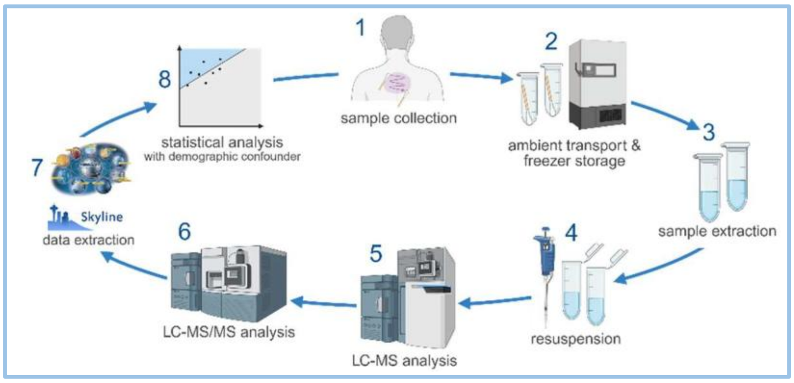
Parkinson's disease (PD) currently lacks an objective diagnostic test beyond clinical assessment of motor symptoms. Skin swab sampling offers a non-invasive and accessible route for biomarker discovery, with practical advantages including simple collection, ambient transport, and compatibility with mass spectrometry. Previous work has shown that swabs collected from sebum-rich areas can distinguish people with PD from controls. [1,2]

Here, data acquired by liquid chromatography-ion mobility-mass spectrometry (LC-IM-MS) on a SELECT SERIES Cyclic IMS (Waters) were analysed and compared with paper spray ionisation (PS)-IM-MS data from the same biological samples. [3] The incorporation of ion mobility offers drift time alongside *m/z* values and retention times, enhancing the distinguishment of complex lipid species. Skin swab samples from 273 participants recruited through the Nose2Diagnose cohort were analysed, including 141 controls, 56 drug naïve (DN) PD and 76 medicated PD. Pooled quality control (QC)-driven batch correction and filtering retained 10,299 reproducible features for univariate and multivariate analyses.

Features differentiating DN from controls were prioritised, while progression-associated e trends were examined in relation to recorded disease duration. Several discriminatory features agreed with previously observed targets from group-specific pooled QC comparison to MS/MS level. Pathway analysis indicated perturbations in lipid-related pathways. Despite the differing selectivity and ionizing efficiency of LC and PS workflows, convergent disease-associated molecular regions were observed, including multiple overlapping signals in the m/z 500-600 range.

For targeted translation, precursor/product-ion transitions for prioritised candidates were tested by LC-MS/MS using multiple reaction monitoring (MRM) on a Xevo TQ-XS (Waters). Selected transitions enabled reproducible detection of candidate signals with consistent chromatographic behaviour, providing a focused panel for subsequent validation. This discovery-to-target workflow strengthens the analytical basis for non-invasive skin swab lipid measurements in PD, potentially supporting early diagnosis and monitoring of disease progression.



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# Electrochemical Control of Multi-Enzyme Cascades in Electro-Biosynthesis and Sensing

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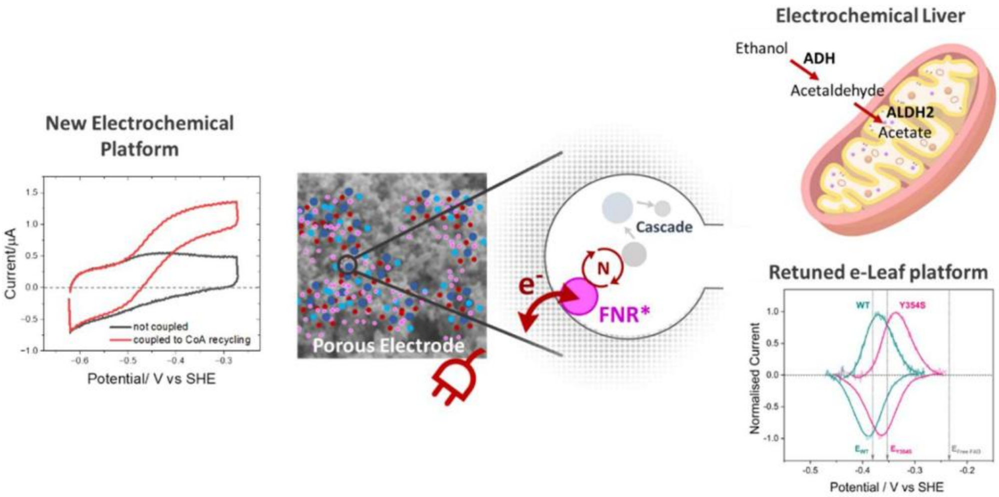
In this project multi-enzyme cascades are controlled electrochemically for discovery in electro-enzymatic multi-step synthesis and for electro-sensing of a human enzymatic pathway.

The Electrochemical Leaf (e-Leaf) is an electrochemical multi-enzyme cascade operating system. It relies on the photosynthetic enzyme, ferredoxin $NADP^+$ reductase (FNR) co-entrapped with cascades in a porous electrode. Through an applied potential, cascades are electrochemically driven via FNR's interconversion of $NADP^+$/NADPH. In this work, an FNR variant (C-terminal tyrosine changed to serine), which swaps the enzyme's cofactor specificity to NADH, extended the e-Leaf's scope.[1-4] An electrochemical characterisation of this variant showed that the tyrosine to serine change retuned the redox potential of the enzyme's bound flavin and altered the overpotential for $NADP^+$ reduction. My current focus is to use this retuned e-Leaf to electrochemically monitor a human liver metabolic cascade – cytoplasmic alcohol dehydrogenase and mitochondrial aldehyde dehydrogenase 2 (ALDH2). The electrode environment mimics the crowded environment of the liver cell, and electrochemical control through FNR makes it possible to study this cascade *in vitro*, including real time monitoring of drug effects on ALDH2 and study of an East-Asian ALDH2 variant.

In a second branch of work, a next-generation electrochemical platform is under development, this time relying on a different electricity-transducing enzyme, pyruvate ferredoxin oxidoreductase (PFOR), for acetyl-CoA recycling. The proof-of-concept has been established: direct electron tunnelling between the electrode and PFOR drives its bidirectional catalysis, and three acetyl-CoA-dependent enzymes have been electrochemically controlled. Electrification of a four-enzyme cascade for synthesis of the natural product, naringenin chalcone, is underway.

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# CRISPR-Cas13a for rapid, point-of-care genotyping in pharmacogenomics

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*a.* Manchester Institute of Biotechnology | *b.* Genome Editing Unit, Faculty of Biology, Medicine and Health | *c.* Department of Chemistry | *d.* NHS Genomic Medicine

Clustered regularly interspaced palindromic repeats (CRISPR)-CRISPR-associated protein (Cas) systems have been utilized in genome engineering and genetic detection through 'programming' of the CRISPR RNA (crRNA) to recognize and degrade foreign nucleic acids complementary in sequence to the crRNA[1,2]. CRISPR-Cas13a is of the Class 2 type VI CRISPR-Cas systems, which are RNA-guided ribonucleases with *trans*-cleavage activity. Binding and cleavage of target RNA that is complementary in sequence to the crRNA activates CRISPR-Cas13a to indiscriminately cleave other RNAs in the area, regardless of sequenceg[1,2]. This dual activity of CRISPR-Cas13 enables the enzyme to act as both the detection mechanism and the signal amplifier in a biosensor with high sensitivity and selectivity for single-nucleotide variants (SNVs)[3]. Clinical implementation of CRISPR-Cas13a-based point-of-care tests (POCTs) will require manufacture of stable, high yield enzyme, and, ideally, use in settings that do not require complex laboratory resources and data processing. This presentation evaluates the feasibility of lyophilizing a CRISPR-Cas13a-based fluorescence assay for use in point-of-care testing of pharmacogenomic variants, specifically targeting the MT-RNR1.1555A>G variant associated with aminoglycoside-induced ototoxicity. These results demonstrate that native LwaCas13a (hereafter Cas13a) loses activity upon lyophilization, whereas fusion with a TwinStrep-SUMO purification tag preserves enzymatic function, enabling for robust *trans*-cleavage after rehydration. The optimized lyophilized CRISPR-Cas13a assay remains stable for up to six months when stored at 4°C or -20°C. Integration with the ISO accredited Genedrive® system confirmed assay compatibility, achieving a limit of detection of 25pg/µL of purified RNA and variant identification within 16 minutes without preamplification steps. The lyophilized CRISPR-Cas13a assay retained high specificity, discriminating single-nucleotide differences with minimal background signal. These findings highlight the potential of lyophilized CRISPR-Cas13a assay as a rapid, sensitive, and deployable diagnostic tool for point-of-care pharmacogenomics, offering a pathway to improve timely clinical decision-making and reduce adverse drug reactions.

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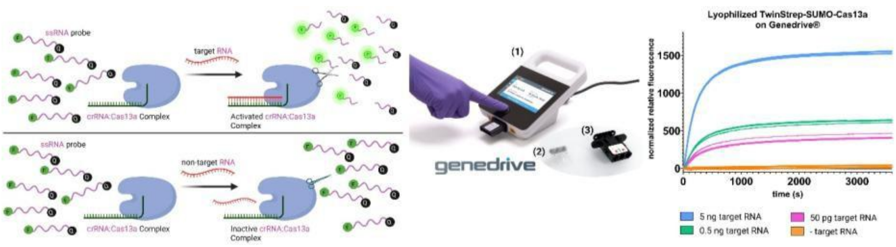


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# Exploring the evolvability of *de novo* hydrolases featuring a catalytic triad

**Kelly Zhou**,[a] Anna Lauko,[b] Sam Pellock,[b] David Baker,[b] Richard Obexer[a]

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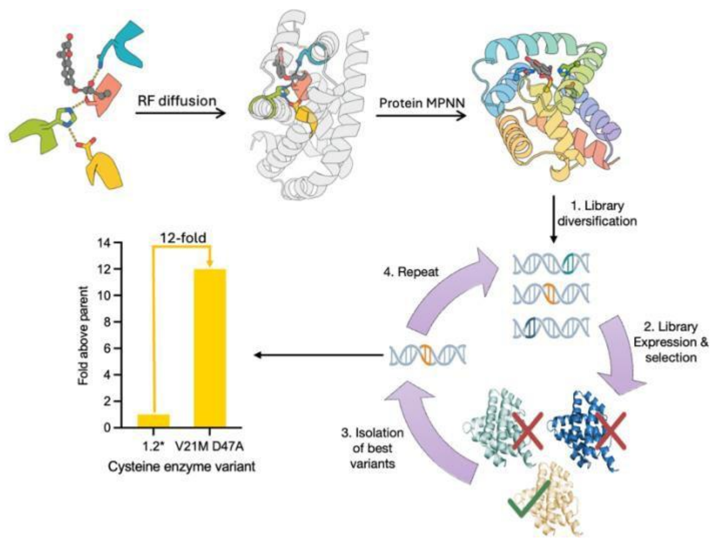
[b]Institute for Protein Design, University of Washington, Seattle, WA, USA.

Enzymes are exceptional catalysts in the chemical industry due to their high-rate accelerations, selectivity and sustainability.[1] However an enzyme is not known for many useful reactions. Recent developments in deep learning-based structure prediction and generative AI have revolutionised enzyme design, leading to *de novo* protein structures with near-atomic precision.[2] These advances further accelerated artificial enzyme design by enabling precise placement of catalytic residues. For the first time enzymes featuring a catalytic triad, a mechanistic motif found in many hydrolytic enzymes, were successfully designed in silico. The resulting enzyme Win1 showed multiple turnovers and a strong dependency on the designed catalytic residues.[3] However, the rate accelerations of Win1 remains far below natural esterases which can approach rates limited by diffusion.[4]

To gain a deeper understanding of the sequence to function relationships of hydrolyses and insights into factors that contribute to efficient catalysis except the mechanistic residues, we use directed evolution to improve the enzyme efficiency of Win1. Specifically, we investigated the divergent evolution of Win1 (ser) and its cysteine counterpart. Over two rounds of multi-well plate-based screening, the catalytic efficiency of Win1 was improved six-fold by introducing four mutations. The cysteine variant showed a two-fold improvement in turnover number from a single mutation. Intriguingly the discovered mutations are exclusive for their respective parent constructs (ser, cys). To further push the limits of evolvability we have established a droplet-based screening approach allowing multiple mutations to be introduced per round of evolution. Our results will provide new fundamental insights into enzyme catalysis and generate valuable data to inform the next generation of designer enzymes.

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# Modelling 8q gains in aggressive prostate cancer through synthetic genome engineering

## Background

Prostate cancer, second in male cancer mortality, displays clinical and genetic heterogeneity. Unlike other tumours where point mutations, insertions and deletions are predominant drivers, metastasis in prostate cancer is primarily driven by large-scale copy number rearrangements such as 8p/10p loss and 8q gain. Yet, the role of 8q or it's encoded genes, in driving metastatic progression is unclear.

Current CRISPR-Cas9 models are limited to single-gene knockouts or genome-integrated cDNA overexpression. Unfortunately, these models do not faithfully mimic changes associated with large-scale native sequences such as 8q gain. Given 8q gain's association with poor prognosis, derivation of an 8q gain model is imperative for understanding disease progression and an exploration of the therapeutic landscape.

## Methods

We harnessed site-specific integration-based genome engineering tools to remodel the 8q amplification step-by-step in 2D primary human prostate epithelial cell (PrECs). *MYC*, present on the 8q24 locus, is a well-characterized oncogene driver implicated in prostate cancer. We, therefore, start by developing cell lines with targeted focal amplification of *MYC* and aim to study the biological consequences of these multi-copy *MYC* cell lines. For this, we have generated a *MYC* minicircle cargo and introduced it into PrECs at an interchromosomal *ACTB* locus as a proof-of-concept.

## Results

By screening single-cell clones using nested PCR, we isolated a clone exhibiting evidence of construct integration. Immunofluorescence analysis confirmed protein-level expression and nuclear localisation of exogenous *MYC.* Ongoing work includes copy number analysis and biochemical characterisation of exogenous *MYC*; followed by exogenous *MYC*-dependent target engagement and resulting differential proliferative phenotypes.

## Conclusion

Overall, we have established a foundation in developing chromosomal 8q gain models in prostate cancer, which are highly germane to the progression and prognosis of the disease. Our approach aids in developing a flexible mammalian synthetic genomics platform to investigate large-scale disease loci in driving aggressiveness in several cancers.

# CYP123 Mediates Stepwise Oxidation of C4-Methyl Groups in Mycobacterial Sterol Catabolism

**Dongxu Yuan** [a], Hannah Ryan [a], Rémi Zallot [b]*, Yi Jin [a]*

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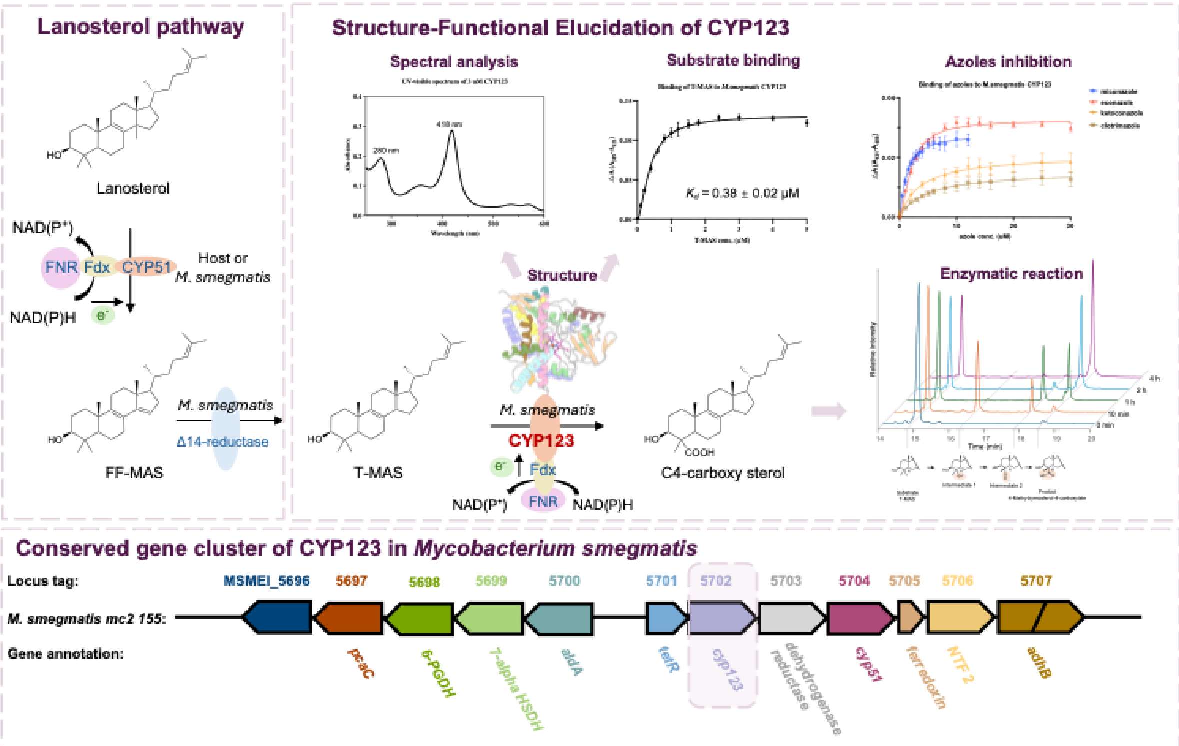
The cytochrome P450 enzyme CYP123 is widely conserved in Mycobacteria and encoded in a genomic region linked to antibiotic resistance and macrophage infection, yet its function remains unresolved. Here, we present the first functional characterisation of CYP123 from *Mycobacterium smegmatis*. The enzyme exhibits canonical P450 spectral properties, binds azole inhibitors with micromolar affinity, and selectively interacts with 14-demethylated sterol intermediates, including FF-MAS and T-MAS, but not lanosterol, cholesterol, cycloartenol, or estrone. Enzymatic assays reveal that CYP123 catalyses a cascade of oxidative transformations: hydroxylation, ketonisation, and carboxylation specifically targeting the alpha carbon at the C4 position of FF-MAS and T-MAS. We propose a metabolic model in which CYP51 and CYP123 collaboratively mediate the initial steps of lanosterol catabolism, a pathway previously underappreciated in Mycobacterium metabolism. Supporting this model, multiple Mycobacterium species utilise lanosterol as a carbon source, while a *M. smegmatis* cyp123 knockout mutant and *M. bovis* BCG, which harbours a natural cyp123 frameshift mutation, exhibit reduced growth on lanosterol as a sole carbon source. This work identifies the CYP51-CYP123 genomic region as critical for lanosterol degradation. Given the essential role of cholesterol catabolism in infection and persistence, our findings provide a foundation for developing therapeutics targeting overall sterol utilisation capabilities.



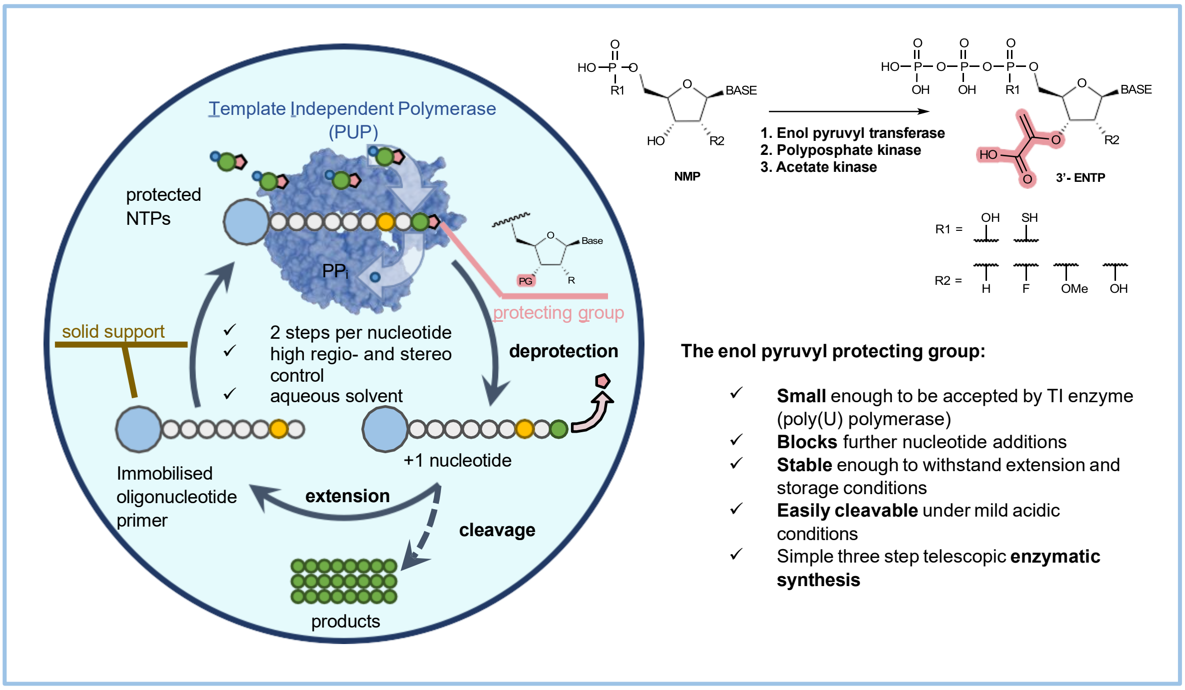
# Biocatalytic approaches for the synthesis of 3'- protected nucleotides

**Annette Egerström**,[a] Florence Hardy,[b] Joe Min,[b] Mark Gainford,[a] Charlotte Griffith,[a] Qinglong Meng,[a] Sasha Derrington,[a] Joel Choo,[a] Richard Obexer,[a] David Baker,[b] Nicholas Turner,[a] Sarah Lovelock[a]

*a.* The University of Manchester | *b.* The University of Washington

Therapeutic oligonucleotides represent a powerful new class of drugs with the potential to treat a broad spectrum of diseases. However, conventional chemical synthesis methods are unlikely to meet future demand, prompting the development of alternative biocatalytic strategies. Among these, template-independent enzymatic oligonucleotide synthesis (TIEOS) offers a promising solution. TIEOS builds oligonucleotides in a stepwise fashion from 3'-protected nucleoside triphosphates (NTPs) using cycles of extension—catalysed by a template independent polymerase—and deprotection. While this method enhances atom and step economy, the preparation of 3'-protected NTPs remains a bottleneck, as it often relies on complex, multi-step chemical syntheses.

To overcome this limitation, we have developed a multi-enzyme cascade that installs a 3'-protecting group onto nucleoside monophosphates (NMPs) using an enol pyruvyl transferase, followed by enzymatic phosphorylation to NTPs using a polyphosphate kinase and acetate kinase. Employing deep learning-based sequence optimisation, we designed a panel of 41 enzyme variants for protecting group installation. Several variants showed enhanced solubility and a broader substrate scope. After several rounds of evolution on the top-performing variant, we can now install the protecting group on the NMPs of all four canonical nucleobases, as well as therapeutically relevant C2' and phosphorothioate modifications. We have shown that the protected NTPs are accepted by a mutant CID1 poly(U) polymerase. Following nucleotide extension, the selected protecting group can be removed under mild acidic conditions. Together, these advances highlight the potential of our biocatalytic platform to provide a robust, sustainable, and cost-effective source of 3'-protected NTP building blocks for TIEOS.



# Hybrid Native Ion Mobility – Mass Spectrometry Methods for Enhanced Protein Characterisation and Increased Automation & Throughput

Proteins are essential biological macromolecules, performing a wide range of functions within living organisms, responsible for structure, catalysis, transport, regulation, defence, movement, storage, and communication. This functional diversity arises from the vast array of possible proteoforms, along with their distinct structures, dynamic behaviours, and accessible conformational landscapes. Despite there being only 20,000 protein encoding genes in the human genome, the number of proteoforms is expanded by non-encoded modifications such as gene splicing and post-translational modifications including glycosylation, phosphorylation and acetylation (amongst a few hundred others).

Characterising proteins is therefore complex, with the chemical composition (primary sequence and post-translational modification identity & position) and higher order structure (3D structure and dynamics) both crucial to understanding function and potential mechanisms of action. Here we present the development of Hybrid Native Ion Mobility – Mass Spectrometry Methods for Enhanced Protein Characterisation and Increased Automation & Throughput, showcasing three key applications: Biopharmaceutical Production, Dynamic Protein Structure Determination and Mechanistic Understanding of Disease.

# Talk Abstracts

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## Section

# A Novel Design of Immuno-PET Imaging Agent: Using Copper-isotopes for Nanoparticles and Radiolabelled Biospecifics

**Volkan Yasakci[a, b], Dipak Babar[a], Aidan Milston[a], Aliaksandr Baidak[a, b] and Frederick Currell[a, b]**

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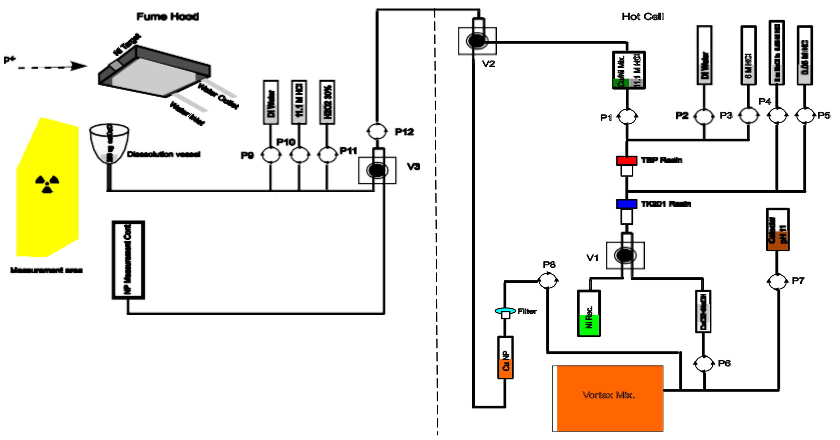
The global rise in cancer incidence has driven continuous advancements in diagnostic and therapeutic radiopharmaceuticals [1-4]. Within this context, the OPTICS (Optimised Production of Theragnostic Isotopes of Copper and Scandium) project aims to implement a fully automated, modular platform for radiopharmaceuticals, including in active nanoparticle form. This work focuses specifically on copper radioisotopes, which are promising theragnostic agents owing to their complementary imaging and therapeutic properties, particularly $^{64}Cu$ ($t_{1/2}$ = 12 h). Natural nickel ($^{nat}Ni$) and enriched $^{64}Ni$ were selected as target materials. Solid nickel targets were dissolved in concentrated HCl with hydrogen peroxide, pH-adjusted to 9 with ammonia, and subjected to electrodeposition at 4.5 V and 50 μA. Irradiation was performed using protons (up to 10 MeV) and alpha particles (up to 15 MeV) for 1-2 hours. Post-irradiation, copper-nickel separation was achieved using Triskem TBP and TK201 resins, which selectively retain copper while allowing nickel to pass through, enabling efficient isolation of the copper fraction in high radiochemical purity.

Table 1. Full process flow chart.




The isolated $^{nat/64}Cu$ was subsequently used for nanoparticle (NP) synthesis via a catechin-mediated oxidation method at 30°C under nitrogen flow for one hour. This approach is particularly advantageous due to its mild conditions, minimal reagent requirements, and rapid completion time. The resulting NPs demonstrated desirable size characteristics, biocompatibility, and environmental friendliness, making them strong candidates for radiopharmaceutical applications. All steps were carried out within a fully automated system comprising the Target Head, Separation Board, and Vortex Mixer, housed within a hot cell.

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# Synthesis of lanthanide-based silica chelates for molecular upconversion

**Jodie Glasgow**,[a] Jessica Lomax,[a] Xinyuan Tu,[a] Patrick Parkinson,[b] *Huanquing Ye,*[b] *Louise Natrajan*[a]

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Upconversion is an anti-Stokes process in which the absorption of multiple low energy photons results in the emission of a photon of higher energy.[1] While there has been much research into the applications of lanthanide doped upconverting nanoparticles, molecular upconversion is an underdeveloped field. This is due to the fact the presence of X-H bonds (X = C, N, O) in the ligand renders molecular systems more susceptible to quenching through non radiative energy transfer.[2] In this contribution we investigate the applicability of using a silica-based framework as a comparatively low phonon ligand for molecular upconversion.3 We report the synthesis and characterisation of two families of silica-based ligands of $Ln^{3+}$ complexes; isobutyl and phenyl POSS ($[Li(THF)]_2Ln(R_7Si_7O_{12})_n$ (R = iBu, Ph) and disiloxanediolates $[\{(Ph_2SiO)_2O\}_2\{Li(THF)\}_2]Ln\{N(SiMe_3)_2\}]$. Our findings show that the POSS silica framework acts to enhance the photophysical properties of the $Sm^{III}$, $Eu^{III}$, $Tb^{III}$, $Nd^{III}$ and $Yb^{III}$ complexes, whilst the $Er^{III}(^{iBu}POSS)_2$ complex is promising candidate for upconverted emission upon near infra-red excitation at 980 nm in solution state at room temperature. The related bidentate disiloxandiolates (Figure 1) also show a similar photophysical enhancement effect and the preliminary upconversion emission of the $Er^{3+}$ derivative will be reported and compared to the larger silica POSS cages.

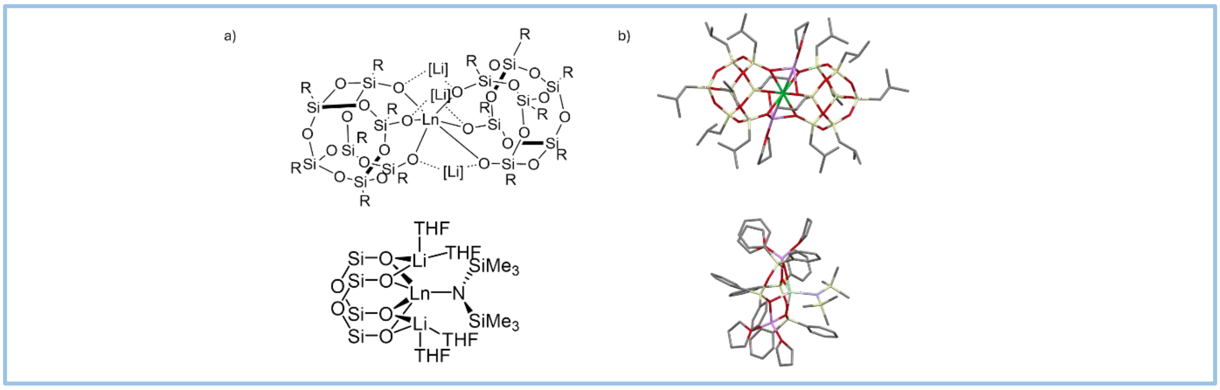


Figure 1. a) Chemical structures of $Ln(^{iBu}POSS)_2$ ($Ln^{3+}$ = Eu, Y, and Er) and Ln(bisdisiloxanediolate) ($Ln^{3+}$ = Nd, Sm, Eu, Er) derivatives synthesised and b) solid state crystal structures of $Y(^{iBu}POSS)_2(THF)_2$ and Nd(bisdisiloxanediolate)

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# Catalytic and stoichiometric stepwise conversion of side-on bound dinitrogen to ammonia mediated by a uranium complex

Mikhail S. Batov,[a] **Heather T. Partlow**,[b] Lucile Chatelain,[a,c] John A. Seed,[b] Rosario Scopellita,[a] Ivica Zivkovic,[d], Ralph W. Adams,[b] Stephen T. Liddle*[b] and Marinella Mazzanti*[a]

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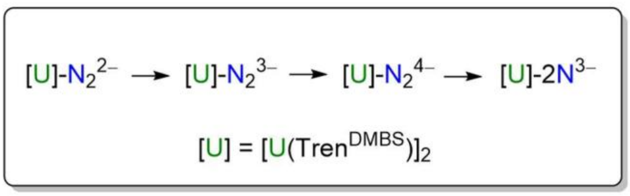
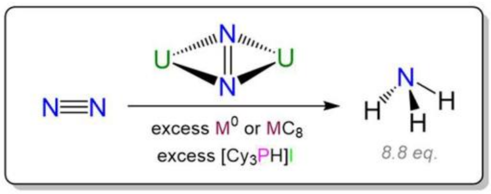
The conversion of chemically inert yet widely abundant dinitrogen, $N_2$, into ammonia, $NH_3$, allows for the synthesis of almost all *N*-containing compounds, both industrially using the Haber-Bosch process, and in the biosphere. The structural determination of the Fe-Mo cofactor, the active site in the nitrogenase enzyme, led to considerable efforts into mechanistic studies using synthetic model chemistry, with the first well-defined system being published by Schrock in 2003, featuring a molecular Mo-triamidoamine catalyst.[1] These systems typically use Mo and Fe due to their biological relevance, despite Haber reporting that U and $UN_x$ materials were effective heterogeneous catalysts for the $N_2$-to-$NH_3$ transformation,[2] prior to the industrialisation of Fe-based ones. This then leaves areas of the periodic table such as early d-block and the f-block underexplored.

Using the Liddle group's prior experience with a Ti triamidoamine complex that is capable of catalysing the transformation of $N_2$ into $NH_3$ under ambient conditions,[3] the previously reported $[(Tren^{DMBS}U)_2N_2]$ was targeted as a potential candidate to catalyse the fixation of $N_2$. This structure features a side-on bound $N_2$, which has long been thought to inhibit any catalytic activity from occurring. This talk reports our recent investigations of the redox reactivity of this complex, its success in catalytic trials and subsequent preliminary mechanistic findings.




*Stepwise reduction*




*Catalytic $NH_3$ formation*

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# Kinetic Separation of $C_3H_6$ and $C_3H_8$ in a Microporous Metal-organic Framework

## Abstract

The development of sorbent materials to promote adsorptive separation of $C_3H_6/C_3H_8$ is an important and challenging task. Here, we report the kinetic separation of $C_3H_6$ and $C_3H_8$ in a robust metal-organic framework, $\{Zn_2(Atz)_2(CO_3)\}$ (HAtz = 3-amino-1,2,4-triazole). This material features *S*-shape channels with an aperture size of 5.1 Å, effectively capturing $C_3H_6$ over $C_3H_8$ with a low isosteric heat of adsorption ($Q_{st}$) of 23.6 kJ mol$^{-1}$. Specifically, the adsorption capacities of $C_3H_6$ and $C_3H_8$ at 298 K and 1 bar are 2.45 and 1.40 mmol g$^{-1}$, respectively. Studies of adsorption kinetics revealed effective diffusion coefficients ($D'$) of $1.32 \times 10^{-3}$ s$^{-1}$ for $C_3H_6$ and $2.35 \times 10^{-6}$ s$^{-1}$ for $C_3H_8$ at 298 K and 100 mbar, resulting in a kinetic selectivity of 562. Breakthrough experiments for an equimolar mixture of $C_3H_6/C_3H_8$ confirmed the efficient and recyclable separation performance in $\{Zn_2(Atz)_2(CO_3)\}$. Solid-state nuclear magnetic resonance, *in situ* single-crystal diffraction, neutron powder diffraction, and calculations have been employed to elucidate the adsorption mechanism and collectively corroborate the preferential affinity for $C_3H_6$ within the pore.

# f-Element Cyclooctatetraenide Sandwich Complexes

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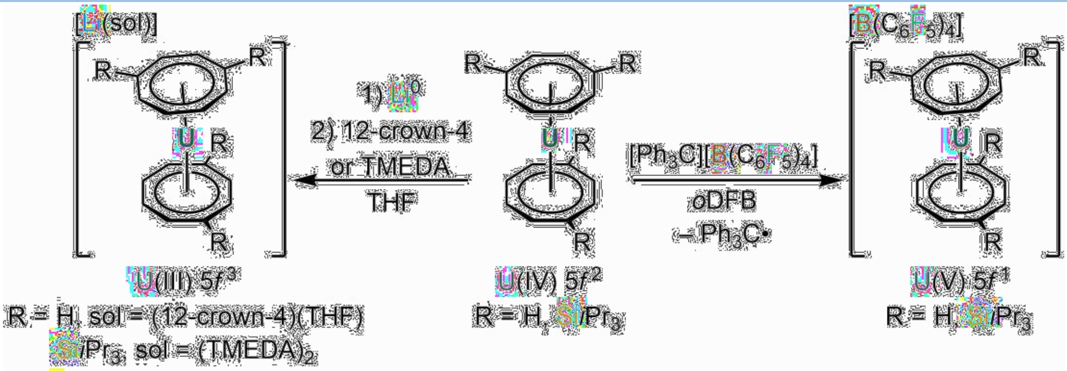
Sandwich complexes feature a metal ion coordinated to two planar aromatic organic rings; ferrocene is the archetypal transition-metal example.[1,2] Actinocenes are actinide analogues, and the first example – uranocene – was named for its similarity to ferrocene.[3] Actinocenes serve as touchstones for evaluating 5f-derived bonding and actinide covalency, and understanding their electronic structure shaped the field of actinide chemistry in much the same way as ferrocene influenced d-block organometallic chemistry.

Despite the centrality of uranocene in developing our understanding of actinide electronic structure, the one-electron-oxidized uranocenium cation, $[U^{V}(COT)^{2}]^{+}$, the equivalent of the ferrocenium cation $[Fe^{III}(Cp)_2]^{+}$, has not been isolated. Electrochemical oxidation of uranocene has been described as irreversible, yielding poorly defined products.[7-9]

In this work we discuss isolation of the parent uranocenium cation, $[U^{V}(COT)_2]^{+}$, and a substituted analogue, $[U^{V}(COT^{\dagger\dagger})_2]^{+}$ ($COT^{\dagger\dagger}$ = $\{C_8H_6\text{-}1,4\text{-}(SiiPr_3)_2\}^{2-}$), as crystalline room-temperature stable borate salts and compare the electronic structure, bonding and reactivity.

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# Towards the Isolation of a Novel Actinide Metallacyclopropyne

**Rebecca F. Sheppard**,[a] John A. Seed,[a] Ashley J. Wooles,[a] Steve T. Liddle.[a,*]

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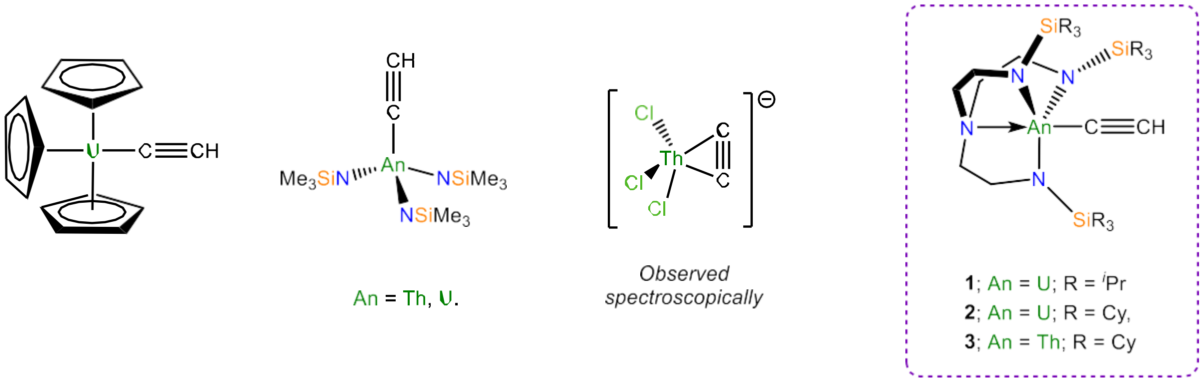
Metal-acetylide complexes have drawn increasing interest for their use in catalysis,[1–4] as well as providing a platform to develop a fundamental knowledge of metal-ligand bonding through electronic structure investigations.[5-9] However, despite significant advancements within the *d*-block metals, the synthesis of molecular terminal actinide-acetylide complexes remains limited to only three examples (**Fig. 1A**).[10,11] In addition, though spectroscopically observed, there are no structurally characterised examples of a primary metallacyclopropyne complex, {M($\eta^2$-C≡C)} for *any* metal (**Fig. 1B**) due to the electron rich, highly strained and extremely reactive nature of this motif.[12]

Herein, we report the synthesis and characterisation of a new family of terminal actinide-acetylide complexes, namely Tren$^{R}$An-CCH (Tren = {N($CH_2CH_2NH_2$)$_3$}, **1**; An = U, R = Si$^i$Pr$_3$, **2**; An = U, R = SiCy$_3$, **3**; An = Th, R = SiCy$_3$) (**Fig. 1C**) as potential precursors towards the isolation of an actinide metallacyclopropyne complex {An($\eta^2$-C≡C)}. Investigations into the subsequent deprotonation of these complexes results in the formation of highly reactive and unstable species, leading to the cleavage of bonds within the triamidoamine ligand framework. We also report the exploration into their redox chemistry with results highlighting the challenges in stabilising this elusive, highly nucleophilic metallacycle motif.




**A** **B** **C:** This work

**Figure 1.** (**A**) Previously reported terminal actinide acetylide complexes; (**B**) Thorium metallcyclopropyne fragment observed *via* mass spectrometry; (**C**) This work: Tren supported actinide acetylide complexes.

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# Stepwise Filling during Efficient Low-Pressure $NO_2$ Adsorption in an Aluminium Metal-Organic Frameworks

**Yuxiang Zhu**[a,b], Martin Schröder [a], Sihai Yang[a] and Floriana Tuna[a,b]

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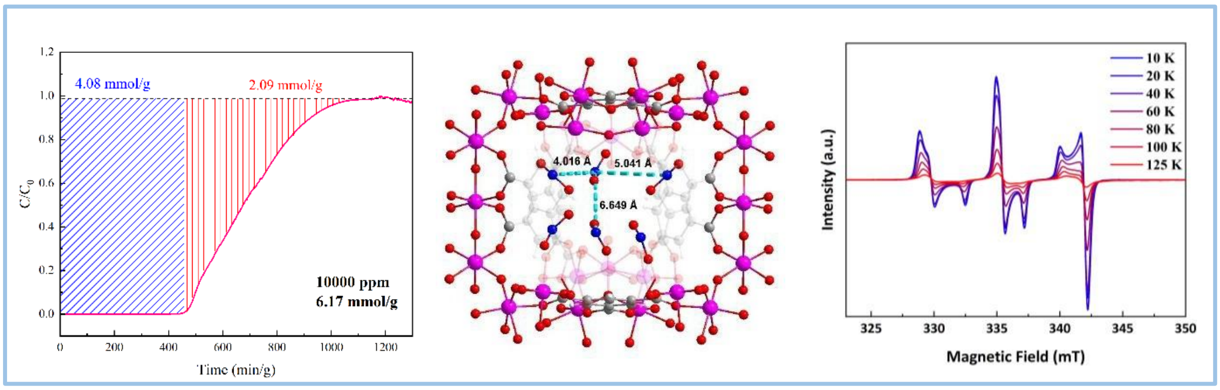
*b.* **Photon Science Institute, University of Manchester, Manchester, M13 9PL, UK**

Metal–organic frameworks (MOFs) are emerging adsorbents for the capture of corrosive air pollutants, but resolving the molecular adsorption sequence of radical gases such as nitrogen dioxide ($NO_2$) remains challenging. Here we report efficient low-pressure $NO_2$ adsorption and stepwise filling in MIL-96(Al), a robust aluminium-based framework containing multiple cage environments connected by small pore windows. MIL-96(Al) retains crystallinity after prolonged exposure to pure $NO_2$ and exhibits a high dynamic uptake of 6.12 mmol $g^{-1}$ at 298 K under a flow of 10000 ppm $NO_2$, corresponding to an equivalent partial pressure of ca. 10 mbar. The adsorption domains and chemical identity of adsorbed $NO_2$ were established by in situ synchrotron X-ray diffraction, in situ FTIR spectroscopy, and continuous-wave EPR spectroscopy, confirming reversible occupation of multiple cage-based sites by framework-confined monomeric $NO_2$ radicals. Pressure-dependent CW-EPR confirms an increasing population of confined $NO_2$ radicals, while loading-dependent pulsed-EPR relaxation measurements show nearly unchanged $T_1$ and $T_2$ values. The preservation of the local relaxation environment despite increased $NO_2$ uptake indicates that additional $NO_2$ molecules occupy separate cage-based adsorption domains rather than accumulating around pre-adsorbed $NO_2$, supporting a stepwise filling process. To the best of our knowledge, this work represents the first use of pulsed-EPR spin relaxation time as a local probe to distinguish host–guest and guest–guest interactions in a radical-gas-loaded porous framework, providing a new strategy for resolving adsorption-site occupation and local structure in MOF adsorbents.

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# Synthesis and DFT calculation of a Uranium Imidazo Carbene Complex

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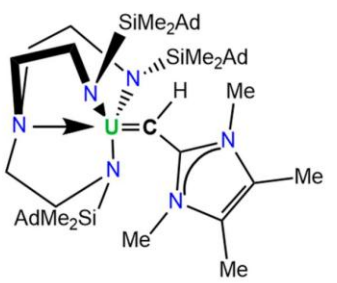
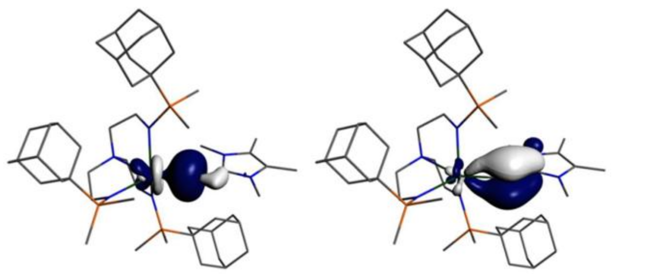
The uranium(IV) imidazolin-2-ylidene carbene complex $Tren^{DMAS}U(IV){=}CHC_7H_{12}N_2$ (Tren= triamidoamine[1], DMAS = $SiMe_2Ad$) has been investigated using Density Functional Theory (DFT). Geometry optimizations were performed without symmetry constraints using the BP86 generalized gradient approximation (GGA) functional and a TZP/ZORA all-electron basis set as implemented in the ADF program.[2] Quantum Theory of Atoms in Molecules (QTAIM) analysis[3] reveals a bond critical point (BCP) electron density (ρ) of 0.1 and a bond ellipticity (ε) of 0.32, indicating that the U=C bond in $Tren^{DMAS}U(IV){=}CHC_7H_{12}N_2$ possesses polarized covalent character. Natural Localized Molecular Orbital (NLMO) analysis provides evidence that both the 5f and 6d orbitals of uranium participate in bonding, with the 5f orbitals playing a dominant role. These computational results offer valuable insight into the design of synthetic strategies to experimentally realize this structure and verify the theoretical predictions. Additionally, this study enhances our understanding of new possibilities for uranium–carbene coordination, highlights the synthesis of the uranium carbene complex $Tren^{DMAS}U(IV){=}CHC_7H_{12}N_2$ without the use of traditional stabilizing elements such as phosphorus, aiming to explore the intrinsic nature of the U=C double bond and potentially establish the first example of such a complex free from conventional stabilization.




$Tren^{DMAS}U(IV){=}CHC_7H_{12}N_2$



Natural Localised Molecular Orbital (NLMO) Analysis for U=C bonds

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# Modified Zeolites for Ethane/Ethylene Separation

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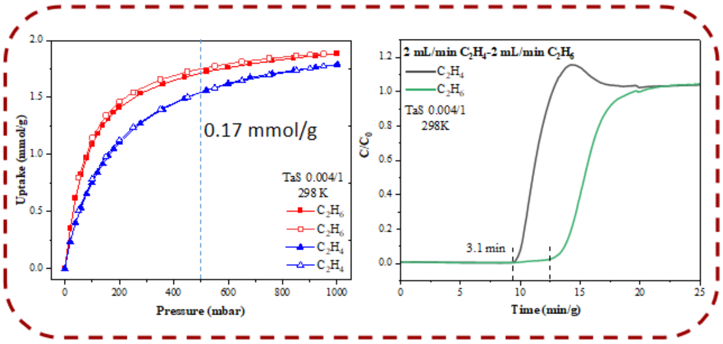
The efficient separation of ethane ($C_2H_6$) and ethylene ($C_2H_4$) is an industrially important yet highly challenging task due to their similar physicochemical properties. Conventional cryogenic distillation remains energy-intensive, prompting the exploration of alternative separation techniques under ambient conditions.[1] In this work, the Ta-doped MFI-type zeolite samples with different Al/Si and Ta/Si ratios were synthesised via hydrothermal methods to investigate their separation performance for $C_2H_6/C_2H_4$ mixtures. The ratios were confirmed by ICP-OES, and the crystallinity of the samples was confirmed by powder X-ray diffraction (PXRD). Nitrogen adsorption isotherms were measured to determine BET surface areas. Gas adsorption capacities for ethane and ethylene were evaluated using gravimetric and volumetric sorption techniques. IAST selectivity values were calculated based on the adsorption isotherms, and dynamic breakthrough experiments were performed under ambient conditions. The IR spectrum was used to confirm the strength of the interactions between the zeolite framework and the guest molecule. Among the tested materials, Ta-incorporated zeolite TaS (Ta/Si = 0.004/1) largest retention time difference for $C_2H_6/C_2H_4$ separation. These results demonstrate the potential of tantalum-modified MFI zeolites for efficient light hydrocarbon separations.

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# Effect of Ligand Methylation on Diastereoisomerism of $M_4L_6$ tetrahedra

**Lucy J Mckay**,[a] George F S Whitehead,[a] Harriet M Simmonds,[a] Imogen A Riddell[a]

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Metal-organic cages (MOCs) are the thermodynamically favoured product of self-assembly of organic ligands and metal ions. MOCs have recently found applications in catalysis, sensing and separation. For the archetypically tetrahedral $M_4L_6$ MOC, incorporating bis-bidentate pyridyl imine based ligands, each metal ion is octahedrally coordinated and thus possesses either Δ or Λ chirality.[1] In solution, this gives rise to three potential MOC diastereoisomers with T (ΔΔΔΔ/ ΛΛΛΛ), $C_3$ (ΔΔΔΛ/ ΛΛΛΔ) and $S_4$ (ΔΔΛΛ) symmetry.[1] The distribution of these isomers may be effected by host guest binding or functionalization of the organic ligand.[2]

Self-assembly of 2,6-bis(4-aminophenyl)naphthalene ($L_1$), 2-pyridine carbaldehyde and iron(II) triflimide have previously been reported to yield a 13:49:38 ratio of T, $C_3$ and $S_4$ cages.[3] Two novel, structurally-related diamines ($L_2$ and $L_3$) have been synthesised and self-assembly was attempted with 2-pyridinecarbaldehyde and iron(II) bis(trifluoromethyl sulfonyl)imide (Figure 1). Reaction products were characterised via $^1$H NMR, mass spectrometry, DOSY and where possible SC-XRD. Results indicate that complexation of $L_2$ yielded a single species with an $M_4L_4$ composition. In contrast, $L_3$ yields an $M_4L_6$ tetrahedron. Investigations into the influence of increasing steric bulk in the 3- position of the diamine ligand and the effect of the identity of the metal ion, on diastereoisomerism are ongoing.

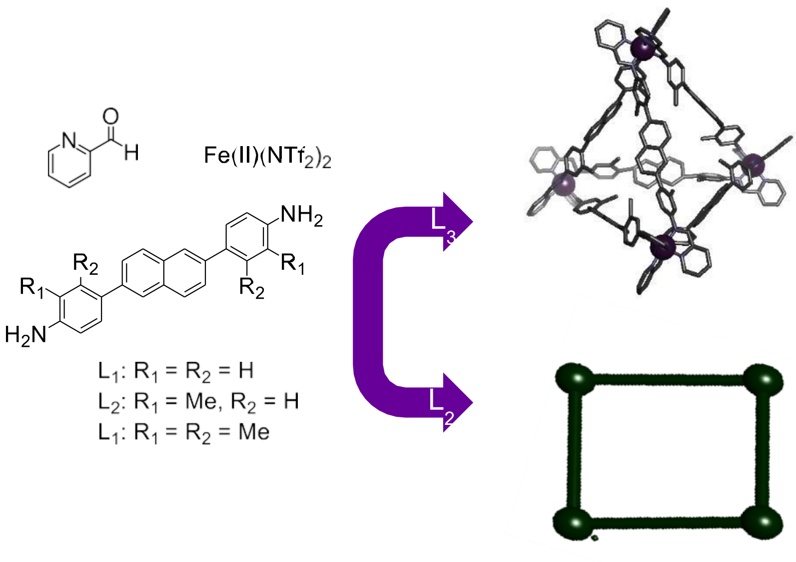


Figure 1: Self-assembly of iron(II) bis(trifluromethyl sulfonyl) imide, 2- pyridinecarboxaldehyde and $L_2$ and $L_3$

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**Optimisation of overall CO2 photoreduction over cerium-based metal-organic frameworks**

Photoreduction of CO2 coupled with water oxidation is a promising approach to generate solar fuels. Herein, we report the optimisation of overall photoreduction of CO2 over four isostructural CeIV-based metal–organic frameworks in which the π-electron count of the organic backbone is systematically increased from 6 to 14. Optical measurements reveal that increasing the π-electron count concurrently narrows the bandgap and enhances the lifetime of excited-state through greater delocalisation of the excited state across the extended π-system. This further results in notably increased photocatalytic performance: MFM-621 with 14 π-electron count exhibits a 14-fold enhancement in reactivity compared with Ce-UiO-66 with 6 π-electron count. The catalytic mechanism has been elucidated through a combination of operando X-ray absorption spectroscopy, synchrotron X-ray powder diffraction and in situ diffuse reflectance infrared Fourier transform spectroscopy, which confirmed the reduction of CeIV centres, followed by coordination of adsorbed CO2 molecules. This design strategy enables the modulation of dynamics of excited-state to promote overall photoreduction of CO2 activity.

# 2026 Chemistry PGR CONFERENCE

# Poster Abstracts

# 2026 Chemistry PGR CONFERENCE

## Posters

## 1 ▶ 77

# Poster Engineering Alditol Oxidases for Broad-Scope Oxidation of Rare Polyols

**Samarth P. Singh**, Claire M. Morely, David Garmeson, Robert A. Field, Jack Rowbotham

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Selective oxidation is a key transformation for converting abundant carbohydrates into higher-value derivatives. Achieving selective oxidation remains challenging because carbohydrates are highly functionalised molecules containing multiple, chemically similar hydroxyl groups.[1] Chemical oxidants typically show poor selectivity, whereas enzymes can offer tight stereo- and regio- selectivity. Alditol oxidases (AldOx) are attractive biocatalysts due to their preference for C-1 oxidation, yet their substrate scope and potential for altering selectivity remains underexplored. [2,3] This work examines AldOx as a platform for selective alditol oxidation. Enzyme libraries and substrate panels were expanded to include functionalised alditols, rare $C_6$–$C_7$ polyols, amino-alditols, and selected aromatic polyols. Mutagenesis campaigns were conducted to probe the enzyme's functional group tolerance and selectivity. In parallel, sequence-based mining was used to identify AldOx homologues with the potential to exhibit alternative regioselectivity.[4] Together, these studies provide initial insights into the substrate scope and evolvability of AldOx for achieving different regio- and stereoselective oxidations of polyols, enabling future access to rare sugars.

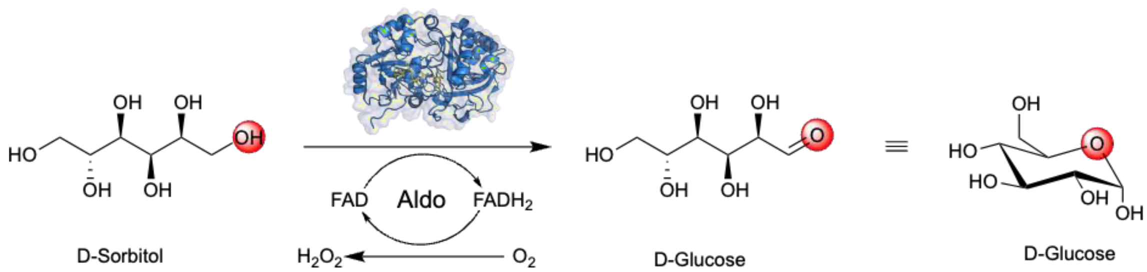


**Figure 1.** Selective C-1 oxidation of D-Sorbitol to D-Glucose by Alditol oxidase.

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# Development of an Advanced In-Situ Gas-Loading System for the Structural Study of Porous Materials on WISH

**Ruichen Zhang**,[a,b] Pascal Manuel,[b] Sihai Yang,[a] Martin Schröder [a]

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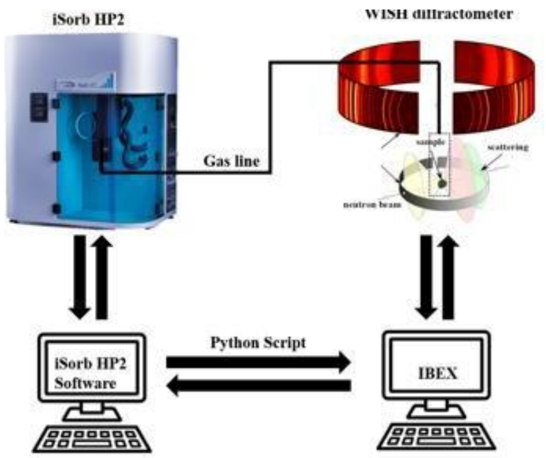
Insert here your abstract (~250 words, please do not exceed one page)

**Precise control over gas loading is critical for resolving the structural dynamics of guest molecules within porous frameworks. We plan deploy the newly integrated iSorb HP2 volumetric analyzer, on WISH replacing the legacy manual gas panel. The iSorb system provides precise, automated gas dosing and dead-volume calibration up to 100 bar across a wide thermal window (15–550 K). Crucially, its integration with the ISIS IBEX system enables the simultaneous collection of high-resolution neutron powder diffraction data and gas adsorption isotherms.**

**This advanced in-situ setup is essential for investigating complex, multi-stage adsorption mechanisms within a hierarchical metal-organic framework (MOF)featuring three chemically distinct cages. We hypothesize that these multi-type cages undergo concomitant occupancy and significant molecular rearrangement before reaching a thermodynamic steady state during gas sorption. To test this, we will execute a targeted dosing-cooling-measurement cycle. This approach will allow us to map the real-time spatial rearrangement of guest molecules, providing the definitive structural evidence needed to move beyond simplified, in-sequence pore-filling models in gas sorption science.**

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# Synthesis of [7]-helicene diimide with an extended backbone: Optical, Chiroptical and Electronic studies

**Kaysa Sekhavati,[1], Vikas Sharma,[1], David Preston,[1] Artemijs Krimovs,[2] Anmol Thanai,[1] George Whitehead,[1] Robert Pal [2] and Ashok Keerthi* [1]**
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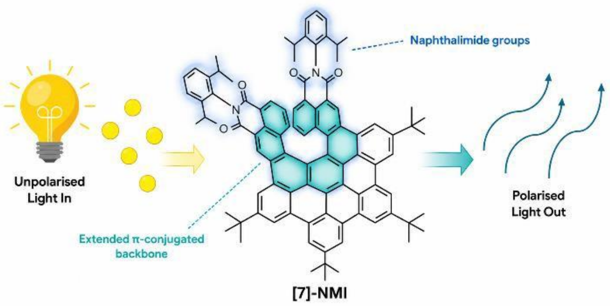
Helicene-based compounds have emerged as promising platforms for chiroptical applications, including circularly polarized luminescence (CPL) and circular dichroism (CD), with potential uses in asymmetric catalysis, liquid crystals, Organic Light-Emitting Diodes (OLEDs), and self-assembled nanomaterials.[1] However, pristine helicenes typically suffer from low fluorescence quantum yields, which limit their chiroptical dissymmetry factors ($g_{abs}$ and $g_{lum}$).[1,2] Functionalization with naphthalimide groups is particularly appealing because these moieties exhibit high fluorescence quantum yields, red-shifted absorption, low-lying frontier molecular orbitals, and n-type redox behaviour.[1] Incorporating such groups can help overcome the commonly observed low emissivity of chiral nanographene's.[2] Herein, we report the synthesis of a [7]-helicene featuring naphthalimide functionalization and an extended π-conjugated backbone via a Diels–Alder-based strategy followed by a twofold Scholl cyclization. These structural modifications significantly enhance the photophysical properties, yielding a fluorescence quantum yield of 40%, representing a twofold increase compared to the unfused precursor. The racemic mixture was successfully resolved into its enantiomers via chiral high performance liquid chromatography (cHPLC) techniques. Chiroptical studies of the isolated enantiomers reveal strong dissymmetry factors, with gabs values on the order of $10^{-2}$. Complementary theoretical investigations were performed to elucidate the electronic structure, while optical spectroscopy and cyclic voltammetry measurements support the calculated bandgap and electronic transitions.

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# Photochemical Hydroarylation of Enamides using Aryl Sulfonium Salts: A Modular Synthesis of Arylethylamines

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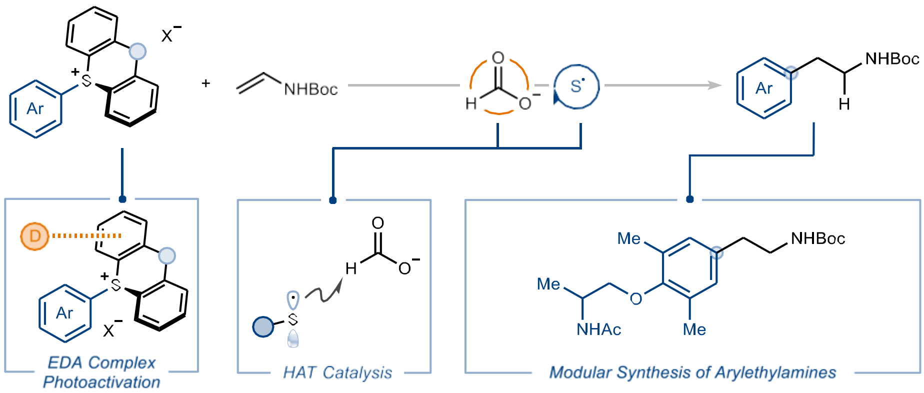


The biologically-active β-arylethylamine motif is exceptionally prevalent in compounds of pharmaceutical and agrochemical importance.[1] Since the advent of photoredox catalysis, classical routes towards this moiety – reliant on transition metal catalysis and heavily pre-functionalised substrates – have been largely surpassed by modular photochemical alkene difunctionalisation strategies.[2] Among these is the hydroarylation of enamides or ene-carbamates, enabled by the photochemical generation of highly reactive aryl radicals from stable precursors.[3–6] However, existing enamide hydroarylation approaches require hard-to-synthesise or pre-functionalised radical precursors, electronically biased coupling partners or strongly-reducing photocatalysts.

In this work, we exploit visible-light aryl sulfonium salt electron donor-acceptor (EDA) complex photoactivation, combined with a thiol-formate hydrogen atom transfer (HAT) system[3,5] to achieve enamide hydroarylation in a photocatalyst- and transition metal-free approach. The use of sulfonium salts generated from the parent arene allows for a broad substrate scope as well as *in-situ* sulfonium salt formation, and the mild and practically simple photochemical protocol can be translated to large-scale batch and flow conditions.

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# Photophysical investigation of a visible light 2+2 cyclase

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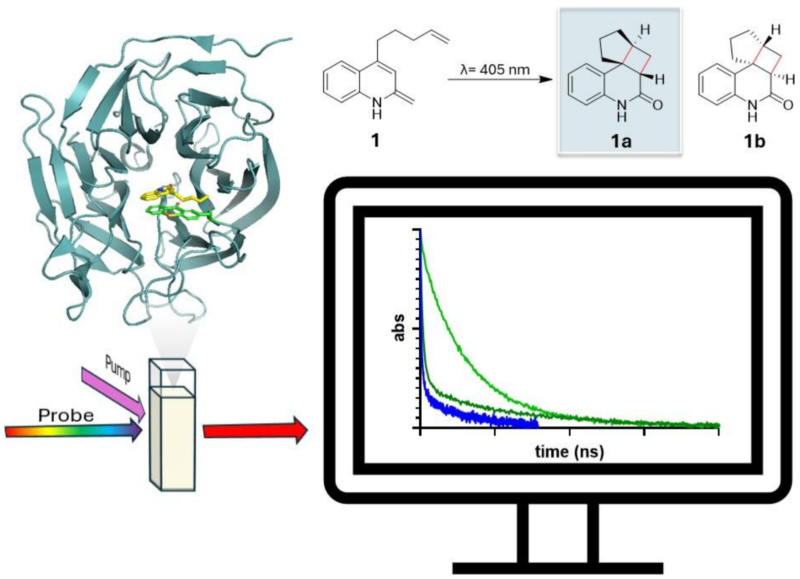
Photocatalysis enables access to a plethora of excited-state chemistry that is not possible in the absence of light. Organic photocatalysts such as benzophenone, xanthone and thioxanthone have exhibited broad application in both photoredox and energy transfer (EnT) photocatalysis. To enable enantioselective transformations, these sensitizers have been coupled to chiral H-bonding templates [1, 2]. More recently, these chromophores have been incorporated into enzyme scaffolds as noncanonical amino acid side chains, for the development of photoenzymes. The engineered photoenzymes exhibit high selectivity and oxygen tolerance, posing advantages over small-molecule catalytic strategies [3]. However, little is known about the precise mechanism of these photoenzymes, and the effects of active site interactions upon the photosensitizer excited state are yet unknown. This project aims to investigate the photophysical properties of the [2+2] photocyclase enzyme VEnT using laser flash photolysis experiments. We hope to uncover how directed evolution of photoenzymes affects EnT photophysics, with the goal of using these findings for more informed design and evolution of EnT photoenzymes in the future.

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# Chemoenzymatic Synthesis of Sialylated Polymer-tethered Nanoparticles

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*b.* Manchester Institute of Biotechnology, University of Manchester, 131 Princess Street, Manchester M1 7DN, UK

Sialyltransferases (STs) are key glycosylation enzymes that catalyse the transfer of sialic acid residues onto glycoconjugates, thereby regulating a wide range of biological recognition and signalling processes.[1,2] Harnessing their high substrate specificity and enzymatic efficiency in synthetic contexts offers an effective route for introducing structural diversity into glycopolymers, which can be challenging to achieve using fully synthetic methods alone. In this work, we present a chemoenzymatic strategy for generating sialylated plasmonic nanoparticles through the surface modification of gold nanoparticles with glycopolymer substrates amenable to enzymatic sialylation. This approach produces tailored nanoscale interfaces where reaction-induced changes in surface composition and glycan presentation can be systematically investigated. Optical spectroscopy, especially UV-vis monitoring of the localised surface plasmon resonance, provides a sensitive readout of changes in the particle's local dielectric environment as sialylation proceeds and as glycans reorganise at the interface, while complementary characterisation methods provide insights into glycan presentation and structural variation. Preliminary findings reveal that both glycan architecture and nanoparticle surface organisation strongly affect the extent and the efficiency of enzymatic sialylation. Overall, this methodology offers a versatile and tunable platform for producing structurally diverse glyconanoparticles, with potential utility in viral testing and broader nanobiotechnology applications.[3,4]

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# Upcycling waste to value-added with hetero-atomic MFI zeolites

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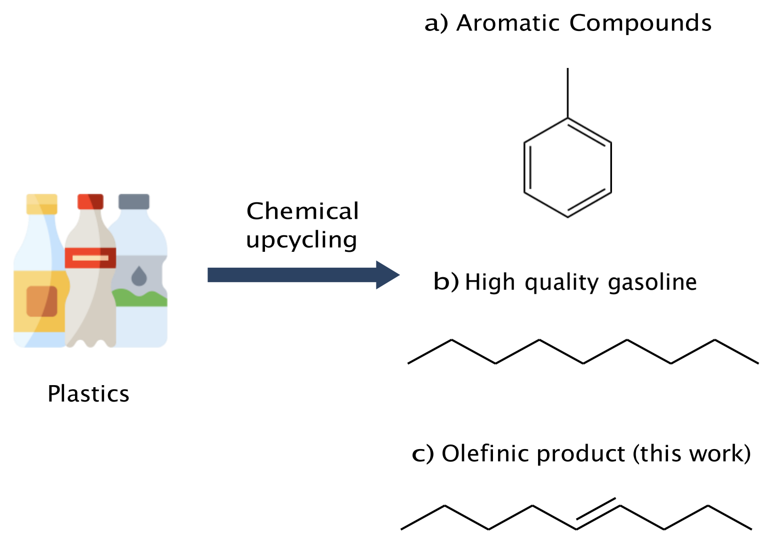
While synthetic plastics have revolutionized modern life, their large-scale production has resulted in extensive waste accumulation worldwide, highlighting the urgent need to transform plastic waste into value-added chemical products. Herein, we developed a hetero-atomic MFI-type zeolite (BAIS) that enables the conversion of low-density polyethylene (LDPE) into higher olefins ($C_{6+}$) with >99% selectivity in the liquid yield under an inert atmosphere at a mild reaction temperature of 270 °C. The incorporation of boron into the zeolite framework modulates the Brønsted acidity and introduces trigonally coordinated boron species, thereby steering the reaction pathway toward the preferential formation of higher olefins. This study offers a promising route for the sustainable production of higher olefins, reducing the heavy reliance on the petroleum industry for the manufacture of renewable materials.

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***Evaluating the mobility-size-shape relationship of nanosized ions across size-pressure scales in Ion Mobility Spectrometry (IMS)***

*Authors: Kacper Kulikowski[1,2], Anisha Haris[1], Perdita Barran[2], Jakub Ujma[1]*

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## Introduction

In ion mobility (IM) separators, ions travel through a gas under the influence of an electric field. Knudsen number (Kn) is the ratio of the mean free path (λ) to the efective radius of an ion–gas pair (r_ef) and it governs the system's flow regime. For Kn>10 (free molecular flow), ions primarily undergo binary collisions, and their drift velocity depends on the collision cross section ($\Omega \sim r\_ef^2$). At $Kn<10^{-3}$ (continuous flow), ions experience frequent collisions with multiple gas molecules, and their motion is inversely proportional to their efective radius (r_ef) and gas friction. Between these two extremes ($10>Kn>10^{-3}$) lie intermediate regime(s), which combine characteristics of both behaviours. While Ion Mobility Spectrometry (IMS) research typically assumes binary collisions, large ions such as viral capsids or nanoparticles may fall within the intermediate regimes. In this work we aim to investigate how particles with diferent shapes behave as they transition between regimes.

## Methods

We reviewed the existing theoretical models used to describe mobility of large particles in gases and proposed a non-binary correction factor which can be used with Mason-Schamp equation. These models will be evaluated experimentally using an open-source drift tube IMS (Reinecke and Clowers, HardwareX, 4, 2018). Commercial Charge Detection Mass Spectrometer (Xevo CDMS™, Waters Corporation) will be used to determine charge distribution of the analytes. The studied systems will feature spherical particles (e.g., adeno-associated viruses and other large proteins) as well as those with varying degrees of sphericity (e.g., keyhole limpet hemocyanin aggregates).

## Results

We present theoretical approaches for analysing macromolecules of diferent shapes across varying mobility regimes in ion mobility spectrometry systems. These predictions are supported by experimental data obtained from both Drift Tube IMS and CDMS systems.

# Allosteric Regulation of a Chemically Fuelled Rotary Molecular Motor through Bipyridine-Pt(II) Complexation

**Adam Lehchilli**,[a] Prodip Howlader,[a] Félix Hernández Culebras,[a] Alexander Betts,[a] David A. Leigh[a]*

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At a time when motor chemistry is developing, drawing heavily on **biological molecular machines** to study their mechanisms, it is becoming essential to study the potential factors that can modify their functionality. The conditions, the motor structure and the one of its fuel are all powerful and essential tools to **control dynamics** and molecular machines at the nanoscale.[1,2] Another important factor that proves to be pervasive in biological machines is **allosteric regulation**, where a localized perturbation occurring away from the active site affects the properties of the system. The **specific design** of new binding sites in biological rotary molecular motors can be efficiently used to regulate motor properties, such as V-ATPases where allosteric modulation through engineered pseudo-active sites can facilitate ADP release from catalytic sites, thereby accelerating its rotational dynamics.[3]

This concept has already been studied and applied to **synthetic systems**, to improve and regulate the performances of light- and chemically-driven molecular motors and pumps through local modulation of the structure or electronic properties of the molecular machine.[4] Inspired by these studies, we aim to incorporate an allosteric **bipyridine binding site** into our rotary molecular motor to observe how allosteric interactions can alter the motor's properties, with a chemomechanical cycle inspired by the **single-bond autonomous motor** published in 2022.[1] This would allow both a better understanding of the chemomechanical cycle associated with motor operation and access to a system with potentially enhanced or externally tunable dynamic behaviour.

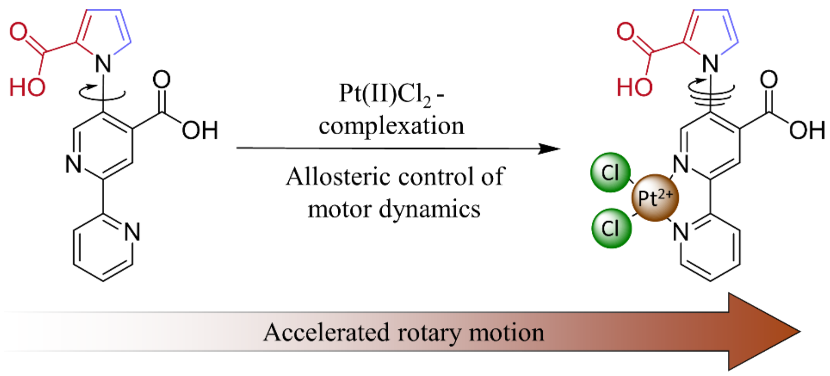


**Figure 1**: Pt(II) allosteric binding on a bipyridine chemically fuelled rotary molecular motor.

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# Investigating USP7 Dynamics and Binding Interfaces with Solution NMR to Guide Cancer Drug Discovery

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Structurally aided drug design scientists usually rely on static pictures to optimize the interactions between the ligand and the target. However, downstream effects can not be predicted with the same techniques. We postulated that different ligands can have various long-distance effects on the protein upon binding, caused by dynamic networks within the protein. In this study, we are analysing ubiquitin-specific protease 7 (USP7) and its dynamic changes with different drug candidates. Protein dynamics will be analysed with biomolecular solution NMR relaxation experiments, which can show us any major changes occurring in specific residues. One of the tested ligands has already shown millisecond dynamic changes in loop regions for residues that did not have any direct interactions with the ligand (residues 215, 274, 483, 484) (Figure 1). This suggests that inhibitor binding affects USP7 dynamics through long-range allosteric networks, even in regions not in direct contact with the ligand. Further, two inhibitors will be analysed and compared to test our hypothesis. These results will provide beneficial information for cancer drug development targeting USP7 and will help us understand the dynamics of this important therapeutic target, which should help us select candidate drugs with desired outcomes.

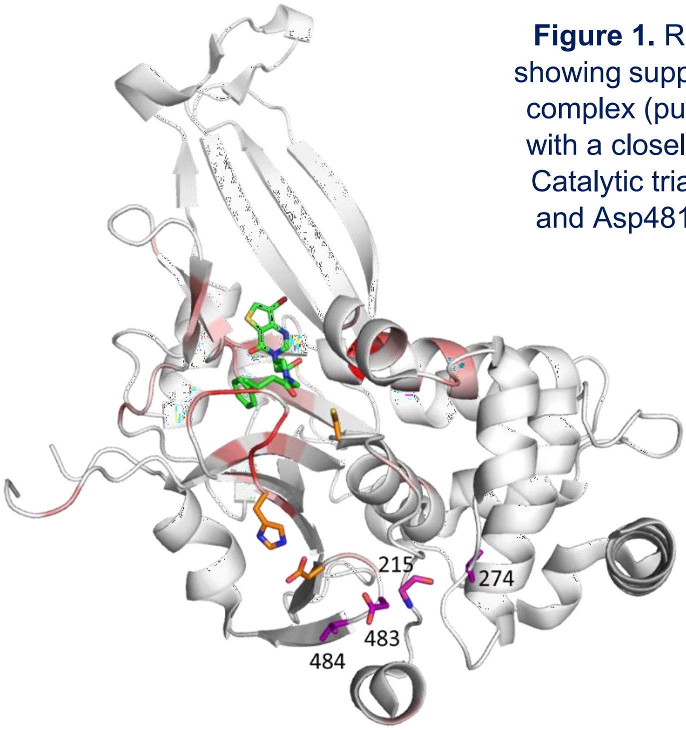


**Figure 1.** Residues (215, 274, 483, 484) showing suppressed motions in the inhibitor complex (purple) on a co-crystal structure with a closely analogous inhibitor (green). Catalytic triad residues (Cys223, His464, and Asp481) are represented in orange. PDB ID 5N9R [1].

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# Tandem Biocatalytic Oxidation-Cycloaddition Sequences for the Stereoselective Construction of Benzofused Scaffolds.

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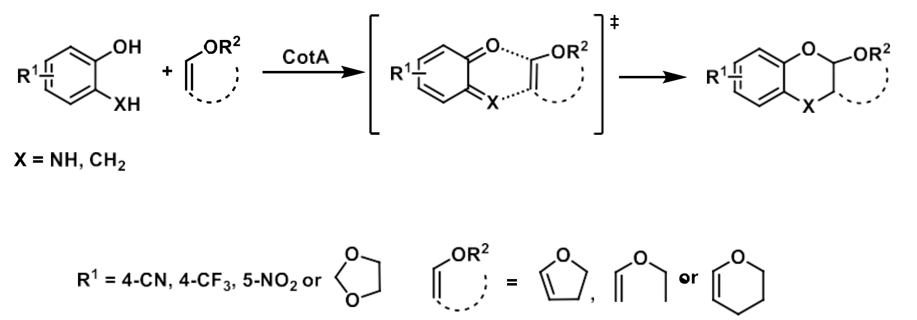
Tandem catalytic reactions offer an efficient and greener route to synthesis of complex molecular structures.[1] In this work, we investigate biocatalytic oxidation–cycloaddition sequences for the stereoselective synthesis of benzofused scaffolds via in situ generation of highly reactive o-quinoid intermediates.[2]

We demonstrate that the multicopper oxidase CotA can efficiently oxidise o-aminophenols to o-iminoquinone intermediates, which subsequently undergo inverse electron-demand Diels–Alder (IEDDA) cycloadditions with suitable dienophiles. Reaction optimisation using a design of experiments (DoE) approach enabled identification of key parameters to favour product formation. Comparative preparative-scale reactions were performed using CotA and molecular oxygen (as the terminal oxidant), horseradish peroxidase (HRP) with hydrogen peroxide, and the chemical oxidant diacetoxyiodobenzene. While full substrate consumption was observed, product yields were limited by competing side reactions.

Despite these challenges, CotA-mediated transformations showed comparable or improved yields relative to the other methods investigated, demonstrating its potential as a sustainable and selective catalyst. Additionally, preliminary results indicate that CotA can also access o-quinone methide intermediates from o-methyl phenol derivatives, expanding the accessible substrate scope. Here, o-quinone methides undergo an IEDDA reaction to form a new C-C bond, resulting in the formation of chromane products.

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# PolyRapid: Automated High-Throughput Screening of Polymers Using a Computational Workflow

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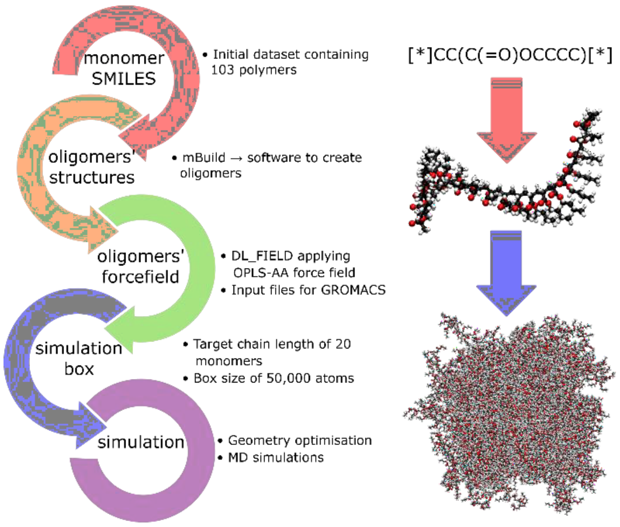
High-throughput computational screening of polymers offers a powerful way to address the imbalance between the vast number of polymers synthesised for diverse applications and the relatively small subset that can be studied using atomistic simulations. We present PolyRapid: an automatic workflow designed to enable the rapid and efficient screening of an extensive polymer library. The variety of systems in the dataset allows for adoption of machine learning approaches for a variety of tasks including accurate glass transition prediction.

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# A High-throughput screening of the Composition Effects on Thermodynamic and Structural Properties in styrene-butadiene Rubber Compounds

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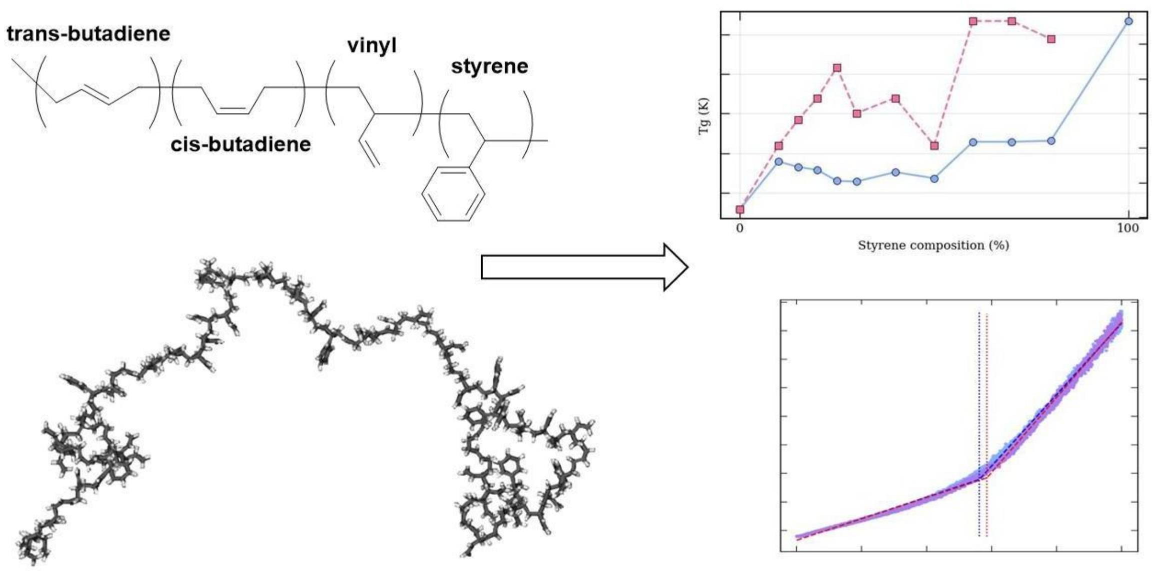
Styrene-butadiene rubber (SBR) is one of the most used synthetic elastomers in the automotive industry, with its microstructure playing a directive role in its industrial performance.[1,2] Adjusting the copolymer microstructure, such as variations in the styrene/butadiene ratio, shifts the glass transition temperature ($T_g$), changes segmental mobility, and affects local chain rigidity. However, a clear understanding of how specific changes in microstructure or copolymer architecture affect these properties is lacking, as current research is often limited by variations in monomer ratios or block architectures. This work aims to systematically assess how variations in microstructure and copolymer architecture affects the thermodynamic and structural properties of styrene-butadiene rubber compounds by presenting a comprehensive high-throughput screening designed to clarify these relationships, eventually leading to the prediction of this relationship from a given a microstructure using machine learning.

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# Oxadiazolones as precursors to N-aryl carbamimidate esters

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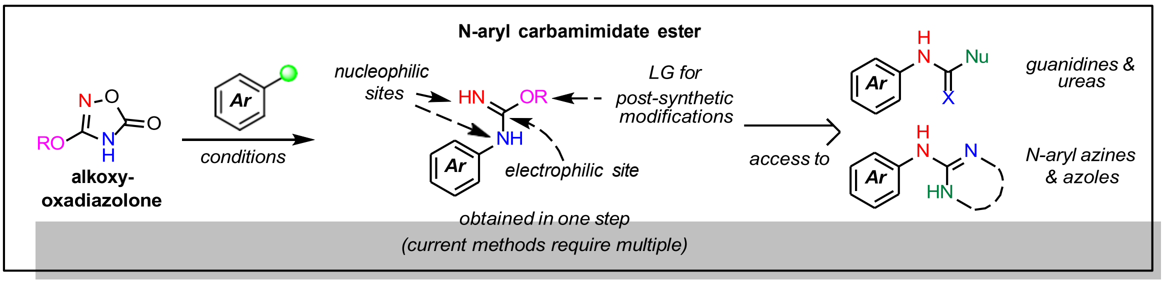
The use of acyl nitrenes to install amide functionality onto compounds has been well-documented and developed. The most common source of these nitrenes are dioxazolones which are easy to prepare, have wide reactivity amongst numerous chemistries and are safe to handle compared to their traditional azide counterparts. Imidyl nitrenes, whilst less-developed, have been shown to be accessible via oxadiazolones. An investigation towards installing carabamimidate esters via oxadiazolones has been undertaken and their potential highlighted.

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# Biocatalytic $S_NAr$ with Nitroalkanes Enables Access to Chiral α-Tertiary Amine Precursors

**Qiutong Lin**[a], Thomas M. Lister[a], Fei Zhao[a], George W. Roberts[a], Anthony P. Green[a*]

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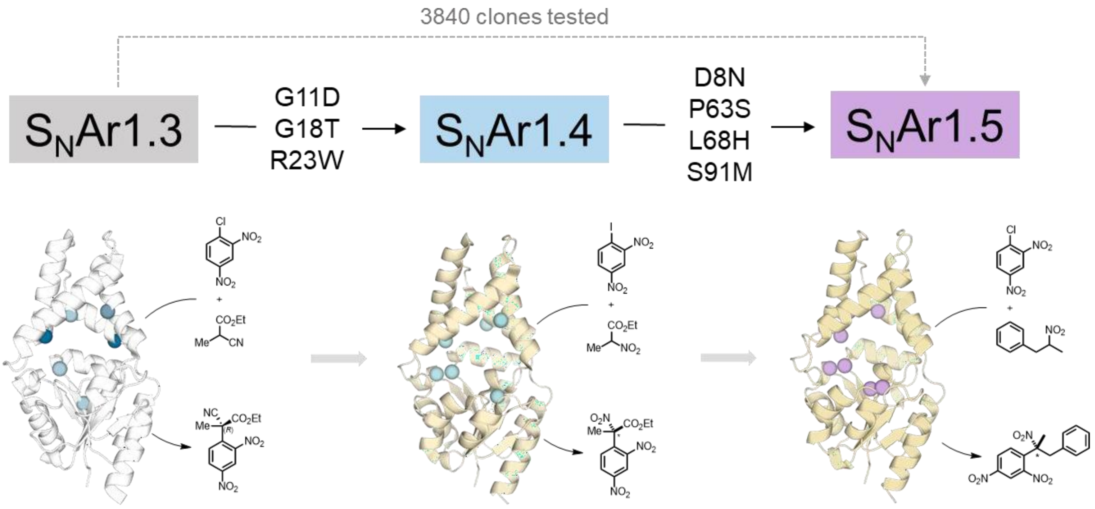
Nucleophilic aromatic substitution ($S_NAr$) reactions are widely used in pharmaceutical and agrochemical synthesis for constructing C–C and C–X (X = O, N, S) bonds. $S_NAr$ reactions typically require harsh conditions and catalytic $S_NAr$ strategies are underdeveloped, meaning stereo-, regio- and chemoselective reactions are rare.[1] Our group has recently engineered enzymes for regio- and enantioselective $S_NAr$ catalysis, variant $S_NAr1.3$ exhibited a 160-fold improvement in activity over its parent $S_NAr1.0$ and enabled coupling of electron-deficient (hetero)aryl halides with carbon nucleophiles in >99% *e.e.*.[2] Substrate profiling of $S_NAr1.3$ revealed the enzyme could promote couplings with α-nitro esters. The resulting nitroalkane $S_NAr$ adducts provide a versatile platform for functional group interconversion and serve as key precursors to chiral α-tertiary amines (ATAs) and α-quaternary amino acids.[3] ATAs feature a quaternary carbon centre bonded to a nitrogen atom and are prevalent in bioactive natural products and pharmaceuticals, yet efficient catalytic access to these motifs remains limited.[4,5] Two rounds of directed evolution from $S_NAr1.3$ yielded $S_NAr1.5$, which enables formation of α-nitro ester units and α-tertiary amine precursors with moderate yields and high enantioselectivities (96% *e.e.*). This expands biocatalytic $S_NAr$ chemistry and provides a sustainable route to chiral building blocks, including α-amino acids and α-tertiary amines.

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# Control of the Local Environment Enables Sustainable Methanol Production from $CO_2$

**Isabelle Nebel**, [a] Samuel Cobb [a]

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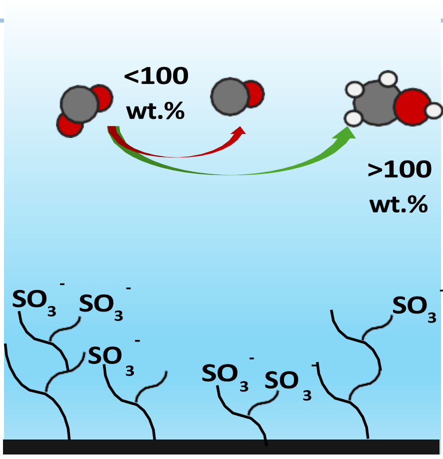
Electrochemical reduction of $CO_2$ to produce sustainable fuels is an efficient carbon utilisation strategy that closes the carbon cycle. CoPc is a well-established molecular electrocatalyst that selectively reduces $CO_2$ into CO with high efficiencies, while methanol formation has been reported less selectively.[1,2] As a six-electron reduction product and an important industrial feedstock, methanol is an attractive target for $CO_2$ electroreduction.[3] However, the pathway for methanol formation on CoPc remains poorly understood. Although CO has been identified as a key intermediate, further mechanistic understanding is required to design selective and scalable electrolyser systems for methanol production.[4] Previous studies have highlighted the importance of proton transport and high local CO concentrations, yet the underlying structure-activity relationship remains unclear.[5] Here, we demonstrate that counterintuitively high mass loadings of PFSA can facilitate methanol production across a range of $CO_2$ concentrations, including under dilute 1% $CO_2$ feed. These findings provide critical insight into the catalyst role and the structure of the microenvironment enabling different routes for tuneable product formation, while also providing a route towards the direct utilisation of point source $CO_2$ sources such as flue gas to produce methanol.

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# Aerosol Jet-printing of Water-based and Biocompatible Graphene Inks

**Yulia Sorokina**,[a] Florine Jude Rajan Francis,[a] Khaled Parvez,[a] Alessandro Grillo,[a] Xuzhao Liu,[b] and Cinzia Casiraghi[a]

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Inkjet printing (IJP) is widely adopted for the fabrication of electronic devices based on graphene and other two-dimensional (2D) material inks due to low-cost production, low material waste, and scalability.[1, 2, 3] However, IJP requires specific ink rheology, and it is also too slow for large-scale production. Aerosol jet printing (AJP) has emerged as a promising alternative to IJP, because it enables high-resolution printing via aerosolised ink droplets transported by a carrier gas and focused by a sheath gas, allowing the deposition of inks over a significantly broader viscosity range.[4] Additionally, AJP allows for continuous tuning of film morphology and thickness, making it suitable for the fabrication of combinatorial printed films and 3D structures.[5, 6]

In this study, we directly compare IJP and AJP using water-based, biocompatible graphene inks.[7] Graphene films were printed onto silicon and paper substrates using IJP under previously optimised conditions, varying the number of printing passes (PPs).[7] For AJP, in addition to PPs, key process parameters, including printing speed, infill density, platen temperature, and standoff distance, were investigated with the aim to achieve the smallest sheet resistance for the fewest number of PPs on both substrates. The printed films were characterised using optical microscopy, electrical measurements, and cross-sectional scanning electron microscopy to gain insight into the nanosheets packing. Under optimized conditions on silicon, a sheet resistance of 11 kΩ/□ is found with just one PP. This is comparable to the sheet resistance of the film printed by IJP with 20 PPs, hence making AJP much faster than IJP. On paper substrates, we observed under optimised conditions a sheet resistance of 4 kΩ/□ with just one PP, which cannot be achieved with IJP under the same conditions. Annealing further reduces the sheet resistance for at least one order of magnitude. Finally, we present preliminary results on printed graphene-based strain sensors with gauge factor up to 419.

Overall, this work highlights AJP as a powerful printing technique for graphene-based printed electronics, enabling the fabrication of conductive graphene films with a single PP, which significantly reduces processing time and production cost.

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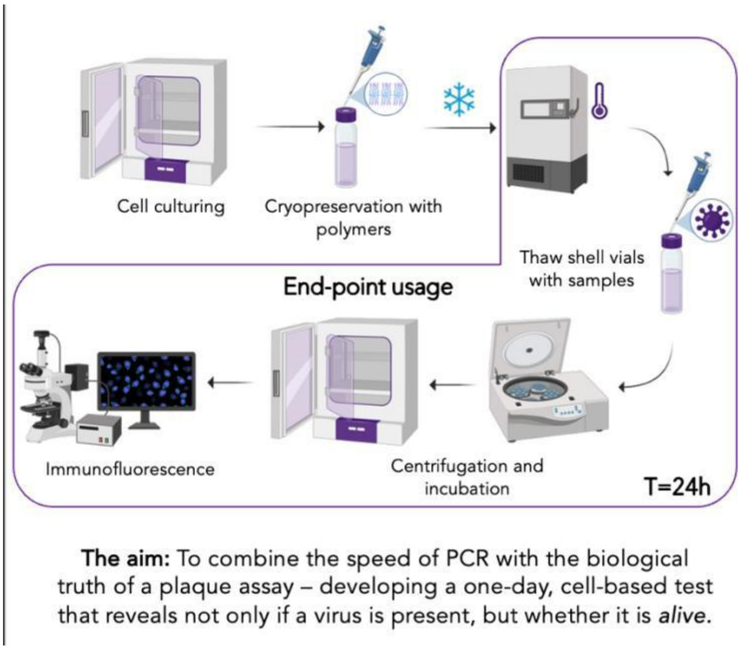
## Poster Title

***Ashish Choudhary, Matthew Gibson***

Viral diagnostics play a critical role in managing infectious disease outbreaks by enabling timely treatment and containment. With nearly 10 viral epidemics in the last decade alone, the demand for faster, more scalable diagnostic tools has never been greater. The focus of this research is on the development of ready-to-use viral rapid diagnostics through cryopreservation of Vero cell monolayers in shell vial format. We are investigating novel polyampholytes (polymers with both positive and negative charges) as cryoprotectants, alongside DMSO and pollen water as an ice nucleator [1]. This combination has demonstrated over 150 % cell recovery post-thaw in 96-well assays, outperforming conventional cryopreservation techniques [2]. Current work aims to improve post-thaw cell adhesion by modifying coverslip surfaces with Poly-L-Lysine and Type I Collagen coatings. If successful, this platform will remove the need for on-site cell culture, replacing time-consuming assays such as plaque tests with a streamlined, pre-packaged diagnostic tool. This innovation has the potential to reduce diagnostic turnaround times by up to 72 hours, improving clinical outcomes and relieving pressure on healthcare systems. Presenting this research offers a valuable opportunity to engage with industrial stakeholders, gain critical feedback, and support the translation of this technology from bench to bedside.

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# Biomimetic *N*–Terminal homologation of amino acids

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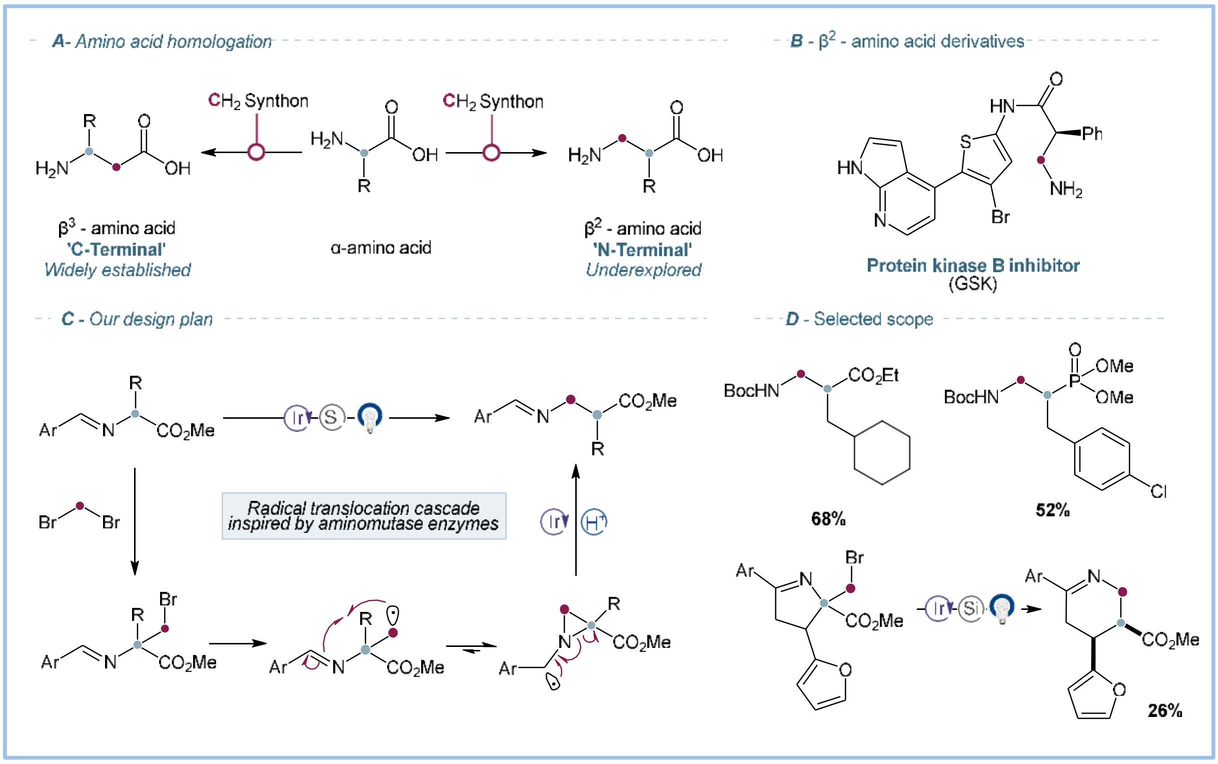
Homologation, or the insertion of a single carbon atom into a molecular chain, has represented one of the most powerful strategies for drug discovery. This approach enables rapid scanning of synthetic space for improved pharmacokinetic properties and biological activity. Amino acids are ideal candidates for this transformation due to their prevalence in organic and medicinal chemistry. Additionally, their β-amino acid analogues can exhibit improved dynamic and conformational properties that are advantageous in peptide and small-molecule lead compounds [1]. In this area, 'C-terminal' homologations towards $\beta^3$-amino acids are widely represented in literature [2], but direct 'N-terminal' homologations towards $\beta^2$ analogues remains underexplored (**A**), despite their demonstrated potential as therapeutic lead compounds (**B**).

Inspired by the action of aminomutase enzymes [3], our methodology leverages a biomimetic radical translocation cascade from a bromomethylated α-amino acid Schiff base, driven by electron transfer (C). This enables direct access to diverse cyclic and acyclic $\beta^2$-amino acids and phosphonates, unlocking new synthetic opportunities within drug discovery programs (**D**) [4].

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# MOLECULAR QUGATES: BUILDING TUNABLE LIGHT-SWITCHABLE MULTI-QUBIT ARCHITECTURES

**Mor Tsfania**, Selena J. Lockyer, George F. S. Whitehead, Grigore A. Timco, Eric J. L. McInnes, and Richard E. P. Winpenny

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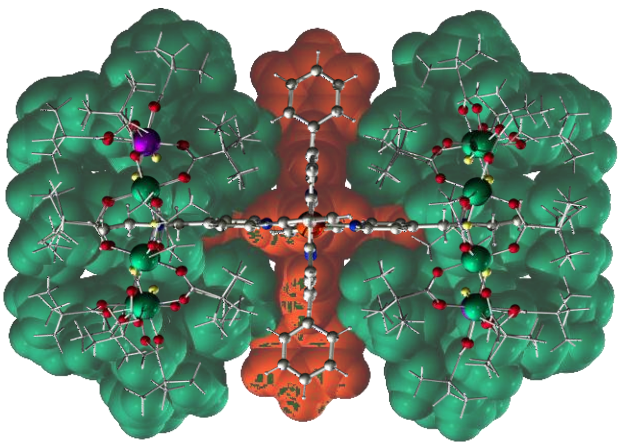
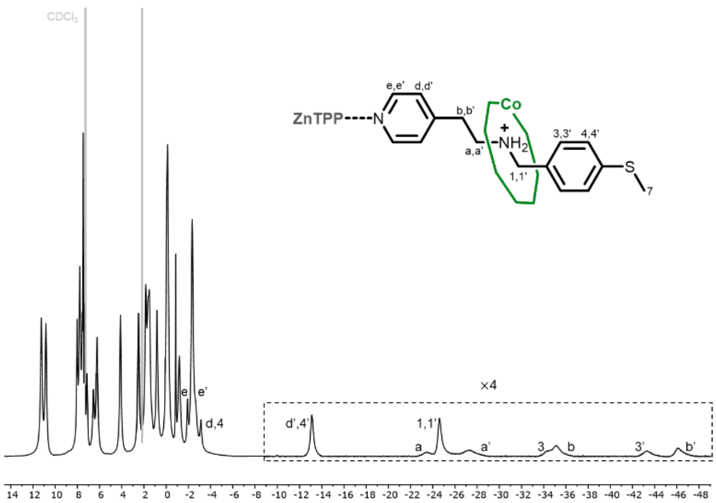
Building multi-qubit architectures requires molecular components that can be linked into complex structures while retaining their individual identities [1], placing this firmly in supramolecular chemistry, compared with more conventional covalent linkages.

Porphyrins are among the most studied candidates for quantum information processing, with free-base porphyrins acting as switches and metalloporphyrins as qubits or qudits [2], offering long coherence times and well-established photophysics. By linking porphyrins through their central metal site, our studies reveal shape recognition between metalloporphyrins and the heterometallic rings used as qubits [3], introducing variable rigidity across different supramolecular assemblies. To extend this work toward assemblies incorporating two heterometallic rings per porphyrin, we have investigated Ru(II) porphyrins, which can be substituted sequentially under orthogonal reaction conditions to build complex supramolecular arrays. Paramagnetic $^{1}$H NMR characterisation of such assemblies is typically prohibitive, however the electronic properties of these heterometallic rings allow spectral elucidation, providing a unique window into the solution-state structure.



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# Pure shift 1D TOCSY with high sensitivity

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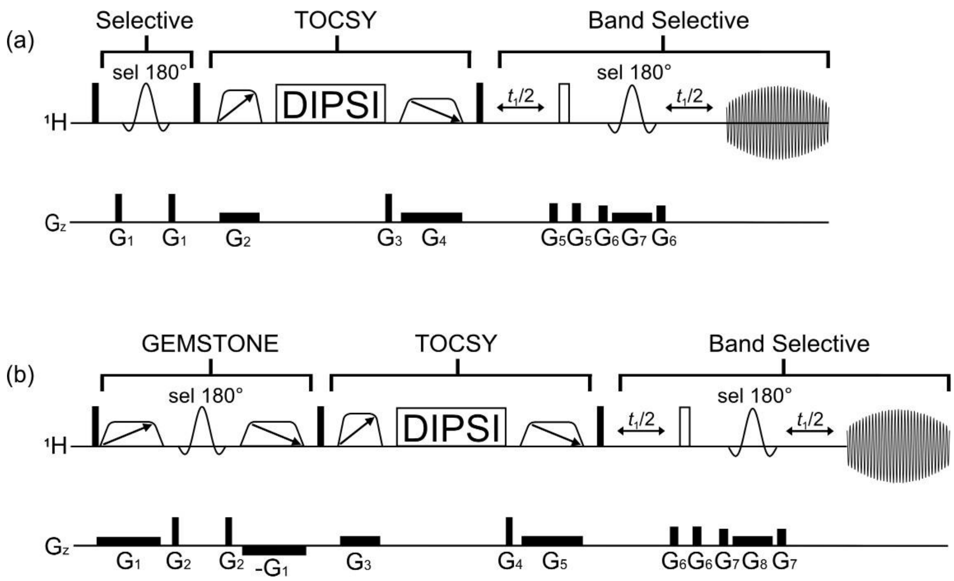
$^1$H NMR is an important analytical tool for obtaining molecular structure and conformational information. However, spectra are often negatively affected by overlap, hindering the acquisition of key information. Selective experiments, including 1D TOCSY, can be used to obtain the spectrum of a single spin system in a complex sample, significantly reducing the complexity and eliminating overlap with different spin systems. However, even the selected spin system can show significant overlap that complicates interpretation. Here pure shift methods such as PSYCHE[1] can be used to improve the resolution by suppressing multiplet structure. This has been shown to work well for 1D selective methods[2], but at a very significant cost in sensitivity. One example is the TREASURE[3] experiment, which combines GEMSTONE[4] – for ultra-high selectivity – with PSYCHE; it can give excellent results, but still at a very high cost in sensitivity.

Here we introduce a band-selective pure shift selective TOCSY method that can greatly improve sensitivity while retaining the selectivity and resolution of 1D selective TOCSY pure shift. The new experiment is compatible with GEMSTONE as well as with conventional selective pulses and enables rapid and accurate acquisition of pure shift spectra from complex spectra.

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# Optimising Rapid Scan EPR for the kinetic study of light-induced processes

**Saverio B. Canu[a], Adam Brookfield[a], Murali Shanmugam[a], Alexander Golovanov[a], David Collision[a], Alice M. Bowen[a].**

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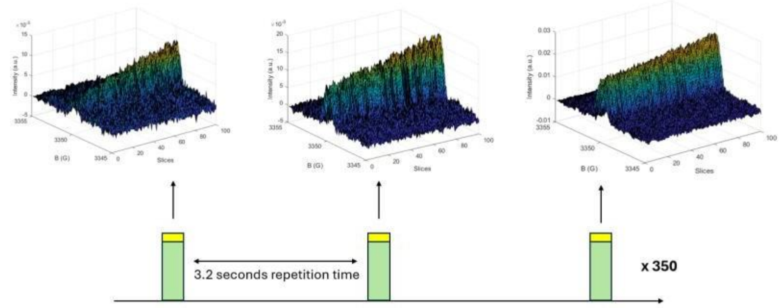
Rapid Scan Electron Paramagnetic Resonance (RS-EPR) is an emerging continuous-wave (CW) technique that offers a significantly enhanced signal-to-noise ratio (SNR) and superior temporal resolution compared to conventional field-modulated CW-EPR [1]. A primary advantage of RS-EPR is its high acquisition speed making it exceptionally well-suited for the kinetic study of light-induced processes. Here we present our work towards the development of novel methodologies for time-resolved RS-EPR with in-situ illumination, utilizing the recently released commercial Bruker Rapid Scan (RS) accessory [2]. We have successfully developed a time-resolved setup with a resolution of 35 ms and validated this by observing the spin-trapping of photo-generated hydroxyl radicals from $H_2O_2$ using DMPO; in-situ illumination was achieved via the EPR-torch method [3]. Subsequently we have exploited the full temporal resolution of the RS instrument (up to 10 μs) for optically initiated experiments, by integrating Xepr API scripting with an external pulse generator. This overcomes the hardware constraints that limit the number of acquirable RS slices. Additionally, a known limitation of RS-EPR is its restricted scan width, which complicates the characterization of broad spectral features. To circumvent this, we have implemented a "stitching" protocol to combine multiple RS traces. Using 100G wide RS slices, a 4000G wide spectrum was successfully reconstructed, with background artifacts efficiently removed via Fourier filtering.

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# Making cells into factories: New metalloenzyme radical catalysts for in vivo synthesis monitored by whole cell EPR

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Methods for cyclopropane biocatalysis have primarily focused on concerted metal carbene reactions. Despite this, cyclopropanation has also been shown to be catalysed by a different radical mechanism when the metal centre is substituted with cobalt (II) or Iron (III)1,2. We have optimised the production, assay, and analysis of Co(II)-hemeprotein catalysts for radical olefin cyclopropanation, to meet the longer term goal of developing a biocatalytic E. coli platform capable of tracking this reaction in vivo by electron paramagnetic resonance (EPR). Our current data suggests these radicals may not be trackable in aqueous solvent. In order to track the formation of a Co(III) alkyl radical, as has been achieved in dichloromethane (DCM) with free porphyrin, we may have to use a more stable radical trapping agent.

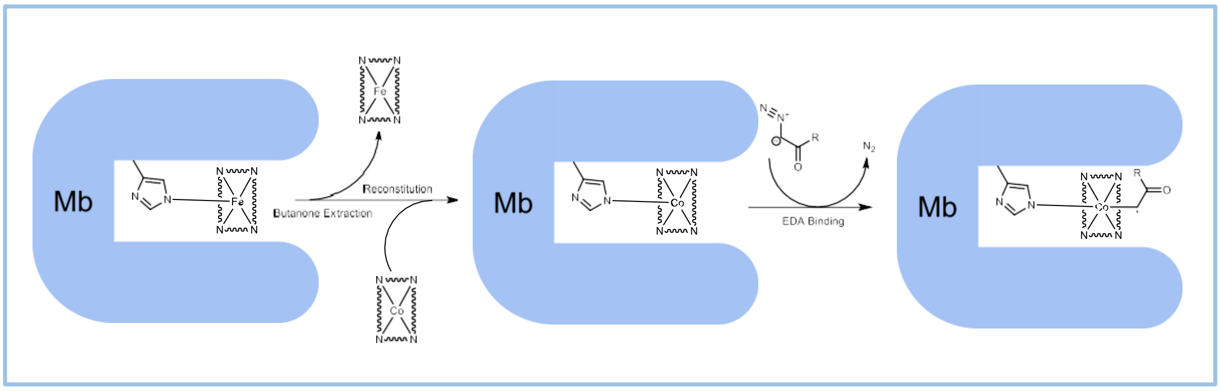


**Figure 1:** Graphical Abstract showing the extraction and replacement of iron protoporphyrin IX with cobalt protoporphyrin IX to create a cobalt myoglobin, followed by the reaction with ethyl diazoacetate (EDA) to form a carbon-centred radical to be studied by EPR.

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# Smiles-Truce Rearrangements via Carbon Dioxide Radical Anion ($CO_2^{\bullet-}$)

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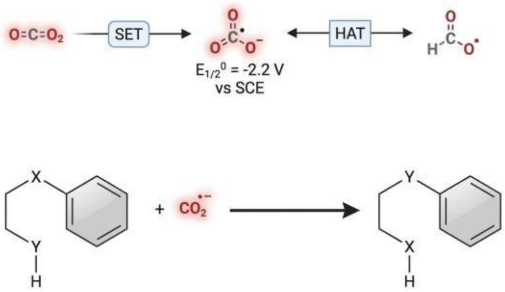
*The Smiles rearrangement is valuable synthetic tool for constructing complex molecular architectures, has been extensively employed in organic synthesis.[1] $CO_2$ has attracted wide attention as an abundant, inexpensive, and C1 building block in the chemical synthesis from the viewpoint of environmental protection and resource utilization.[2] Recent advances in organometallic chemistry and catalysis provide effective means for the chemical transformation of $CO_2$ as a versatile single-electron species that can directly carboxylate alkenes, alkynes, imines, and halides to give carboxylic acids, α-amino acids, and related products under mild conditions.[3] Herein, we report a strategy for integrating $CO_2$ radical into the Truce–Smiles rearrangement of allyl phenylsulfonyl acetamides through multiple pathways, proceeding via a 1,4-aryl migration to afford aryl carboxylic acids and related derivatives. This approach merges the synthetic versatility of the Smiles rearrangement with the sustainable promise of $CO_2$ fixation, providing a streamlined route to value-added carboxylic acid scaffolds.*




*Initial efforts were directed toward the synthesis of Smiles rearrangement products employing $CO_2$ as a radical anion source. Further investigation of the reaction parameters and mechanism is needed to make this approach practical for synthesis.*

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# Coherent Manipulation of Organometallic Ti (III) and Hf (III) Molecular Spin Qubits

**Liangmeng Hao**,[a] Yuxiang Zhu,[a] Maggie E. Mahaney,[b] Daniel N. Huh,[b*] Floriana Tuna[a*]

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**Abstract**: The advancement of quantum information science relies on the realization of robust qubits with long coherence times [1]. Since spin–orbit coupling (SOC) usually accelerates the decoherence, mitigating the influence of SOC has become an effective strategy for extending the coherence times. Herein, two S = ½ group 4 molecular systems have been researched by cw-EPR and pulsed-EPR, considering that pseudo-$C_3$ symmetry could enable the unpaired electron in the $d_{z^2}$ orbital [2], which also permit the orbital mixing with s orbital [3]. Pulsed EPR shows the bigger $T_m$ value of Hf$^t$Bu than Ti$^t$Bu which is attributed to the greater degree of *s*-orbital mixing, despite the shorter $T_1$ of Hf$^t$Bu arising from the heavy-atom effect of Hf. The observation of Rabi oscillations reflects the creation and measurement of arbitrary superposition states, thereby establishing this Hf$^{III}$ complex as a strong candidate for molecular qubits.

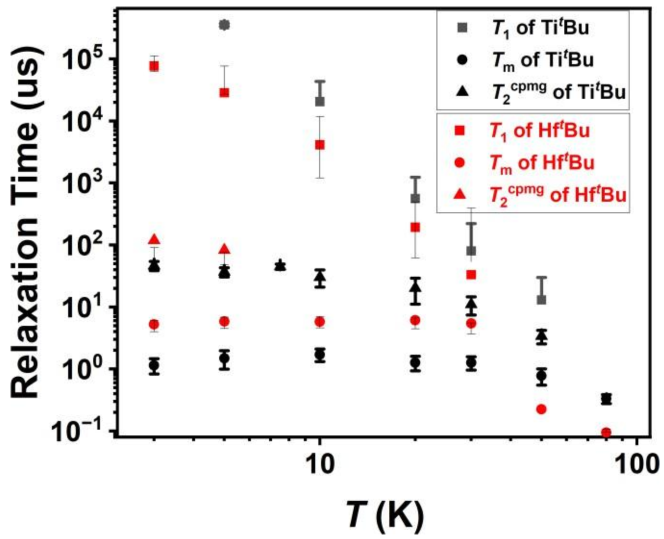


***Figure.*** *Temperature dependence of $T_1$, $T_m$, $T_2^{cpmg}$ for Ti$^t$Bu and Hf$^t$Bu at OP2 ($B_0 \perp C_3$).*

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# Electrochemical Electrolyte Characterisation for Membrane Free Flow Batteries

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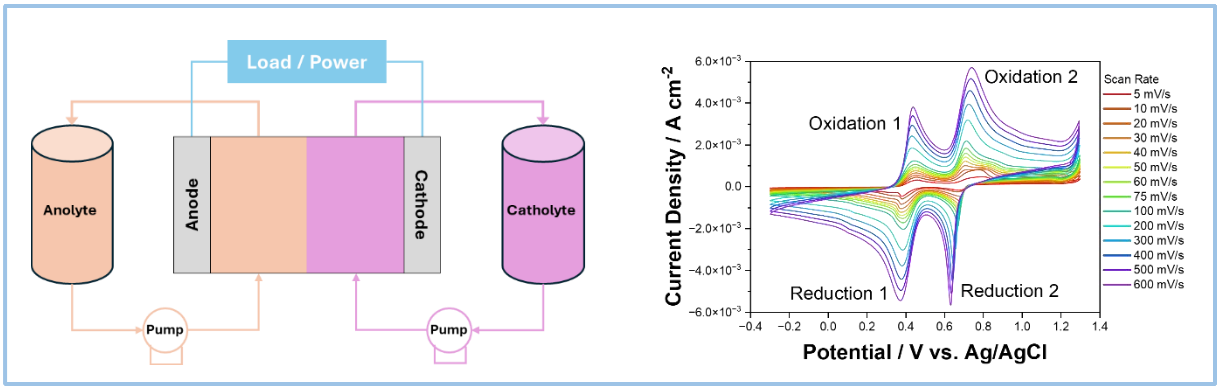
With the transition to renewable energy sources, the supply of electricity will become more intermittent in nature requiring long duration energy storage (LDES) such as Redox Flow Batteries to manage surges in consumer demand relative to energy generation at any given time. [1] Flow Batteries consist of two separate electrolyte solutions, known as the catholyte and anolyte, that are stored in two reservoir tanks external to the cell stack. [2] [3]. The cell stack, where each electrolyte is pumped into, consists of current collectors, bipolar plates, electrodes, gaskets and a membrane. [2] [3] The flow battery can be charged/discharged when the external circuit is complete allowing for storage/dissipation of electricity. [2] [3]

All Vanadium RFBs are the most commercialised but high material cost of membranes and Vanadium limit their use over Lithium-Ion Batteries. [4] Membrane-free Redox Flow Batteries have the potential to achieve further cost reductions through the removal of the Nafion membrane and vanadium species by using an aqueous biphasic system. LiCl and LiTFSI form a liquid-liquid interface at high concentrations based on their immiscibility. [5] At these high concentrations, the electrolytes change from being salt-in-water to water-in-salt which expands their electrochemical stability window from 1.2 V to 3.0 V by limiting Hydrogen and Oxygen evolution from free water molecules. [6] [7] In this project, we are adding redox active species such as LiBr, LiI, $ZnCl_2$, ZnTFO and ZnTFSI to these electrolytes and exploring their electrochemistry.

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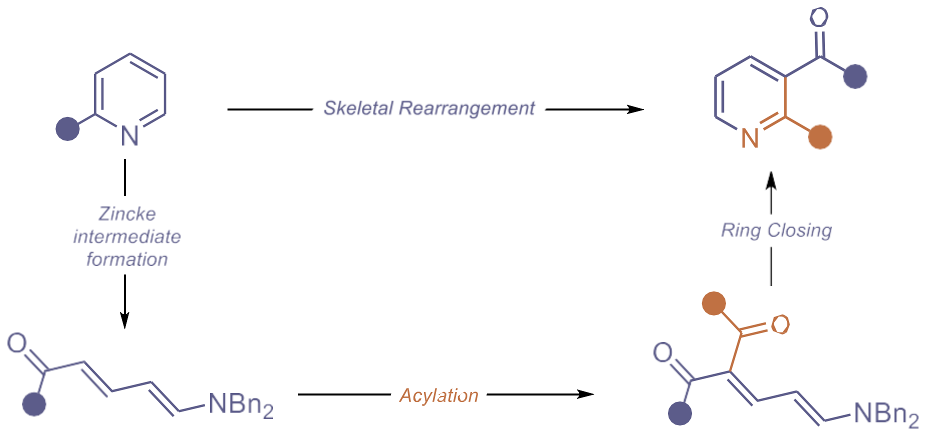
# Trifluoromethylation of Pyridines through Skeletal Rearrangement

**Nilanjan Bhaduri**[a†], Haiwen Wang[a†], Michael F. Greaney[a]
*a.* Department of Chemistry, The University of Manchester, Manchester, M13 9PL

A novel pyridine skeletal rearrangement has been developed that enables selective functionalization at the challenging C2 position through Zincke intermediates, along with the installation of valuable 3-(*het*)aroyl and 3-formyl substituents. Pyridines are first converted into ring-opened Zincke intermediates,[1,2] which undergo regioselective fluoroacylation with inexpensive and readily available fluorinated acylating agents. Subsequent ammonia-mediated ring closure proceeds through an alternative cyclization pathway to furnish rearranged pyridines bearing the valuable electron-poor substituents including $CF_3$, $CF_2H$, and $CO_2Et$ at C2 position. The method provides a practical and highly selective route to C2-trifluoromethylated pyridines, overcoming the poor C2/C4 selectivity commonly encountered in conventional Minisci-type radical functionalization. A broad substrate scope was demonstrated, including aryl-, heteroaryl-, fused heterocyclic pyridines, as well as medicinally relevant scaffolds.




- Zincke chemistry - C2 fluoroalkylation - C3 aroylation/formylation - Rearranged trifunctional pyridines -

Importantly, the rearrangement simultaneously converts the original C2 substituent into synthetically versatile 3-aroyl functionality, while C4-substituted pyridines generate corresponding 3-formyl derivatives - a valuable synthetic handle for further derivatization. The nucleophilic nature of the Zincke intermediates further enabled sequential electrophilic functionalization, allowing efficient synthesis of densely substituted 2,3,5- and 2,3,4-trisubstituted pyridines through halogenation[2] and Heck arylation[3] strategies. This work established ring-opening/ring-closing skeletal editing as a versatile platform for selective pyridine diversification and fluorinated heterocycle synthesis.[4]

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# Engineering an essential gene neochromosome in *Saccharomyces cerevisiae*

**Warren Ho[1], Leandro V. dos Santos[1], Conrad A. Nieduszynski[2], Yizhi Cai[1]**
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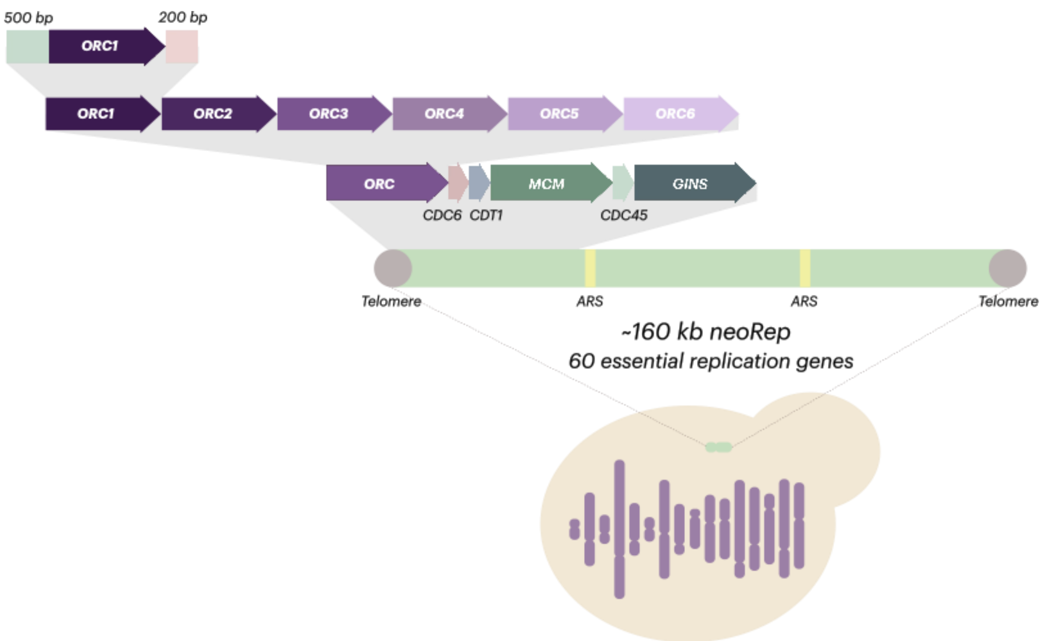
[2]Earlham Institute, Norwich Research Park, Norwich, NR4 7UZ, UK

Sc2.0 represents the first foray into the design, engineering, and characterisation of a synthetic designer eukaryote—the baker's yeast *Saccharomyces cerevisiae*[1]. Two key features are a) SCRaMbLE, an evolution mechanism leveraging symmetrical *loxP* sequences downstream of non-essential genes to reshape the entire genome[1], and b) the relocation of all 275 tRNA genes onto a *de novo* neochromosome[2]. Together, they enable the exploration of gene organisation, context, and evolution and the development of a minimal eukaryotic genome.

However, Cre recombinase indiscriminately deletes essential genes, thereby precluding robust genome minimisation. As such, the next stage of the project—Sc3.0—aims to restructure all essential genes onto a modular, *de novo*-designed neochromosome free of *loxP* sites, insulating essential genes from SCRaMbLE's deleterious effects[3].

Here, we present the neoRep, a ~160-kb neochromosome housing 60 essential genes for DNA replication, organised hierarchically by function. To maximise stability and enable targeted CRISPR/Cas manipulation of the genomic background, all coding sequences have been synonymously recoded according to a codon reassignment scheme, and orthogonal replication origins from non-*S. cerevisiae* yeast species are used. The neoRep will be a versatile testbed for interrogating fundamental replication biology and achieving a minimal and modular genome.

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# Thermoelectric properties of clathrates $Si_{46}Ge_{46}$and $Sn_{46}$

**Zhiwu Wang**,[a] Dr Joeseph Flitcroft,[a] Dr Jonathan Skelton [a]

The inorganic tetra clathrates are the basis of an archetypal family of `phonon-glass electron-crystal' materials with promising thermoelectric properties. Most real materials incorporate framework substitutions and filler ions, and understanding the effects of these modifications is critical to optimising the performance.

In this work, we use a fully ab initio modelling workflow to obtain high-quality predictions for the thermoelectric figure of merit *zT* and constituent physical properties of the pristine clathrates. All three frameworks show relatively large absolute Seebeck coefficients, and the power factors are dominated by the increase in electrical conductivity with doping level. We predict that pristine n-type $Ge_{46}$could achieve a large *zT* = 1.8 at T = 1000 K with optimal doping, while $Sn_{46}$ could achieve the industry-standard *zT* = 1.23 at T = 500 K.

These results establish the strong baseline performance of the tetrel clathrates and highlight control of the thermal transport and stabilisation of Sn-based systems at higher temperatures as promising avenues for future improvement.

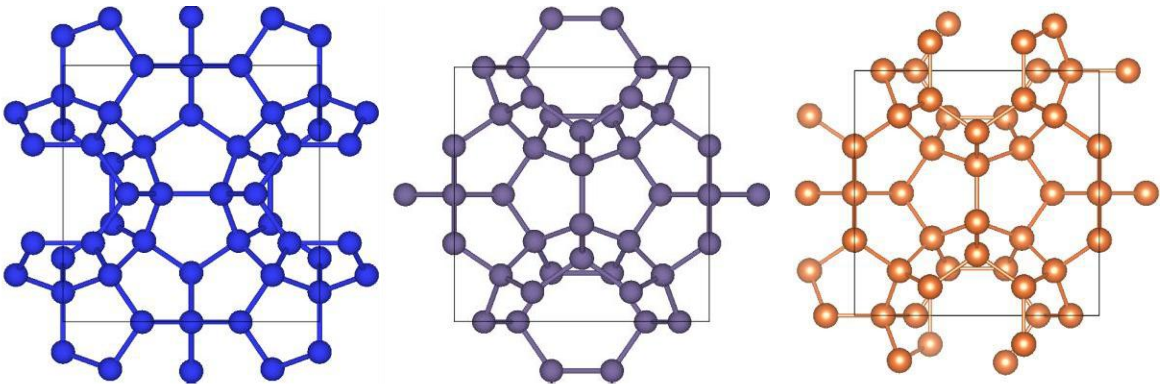

*Figure 1 Optimised structure of $Si_{46}$, $Ge_{46}$, and $Sn_{46}$*

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## Expanding the Scope of Carbohydrate Active P450s for Selective Saccharide Demethylation

**Iulia Cisu**,[a] Samarth Pratap Singh,[a] Matthew Treadell,[a] Claire Morley,[a] Jane Whittaker,[b] Robert Field[c] and Jack Rowbotham[a]

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The development of carbohydrate-based pharmaceuticals (therapeutics, antibiotics, vaccines) remains limited due to challenges in synthesising and purifying complex molecules at scale and low cost. Traditional chemical synthesis relies heavily on protecting group strategies to differentiate similar hydroxyl groups, which are resource-intensive and must be tailored for each target. In contrast, Nature achieves selectivity through enzyme catalysis, offering inspiration for cleaner, programmable synthetic routes. This project seeks to harness enzymatic tools to enable selective activation of carbohydrate sites, advancing high-throughput synthesis on demand. A central focus is the use of methyl ethers as protecting groups, which are easily introduced but difficult to remove. Conventional demethylation requires harsh chemical conditions, whereas cytochrome P450 enzymes naturally catalyse O-demethylation via oxygen-driven C-H activation. P450s are notable for their evolvability, allowing engineered selectivity through directed evolution. However, their application to carbohydrate chemistry remains underexplored,[1,2] particularly given the hydrophilic nature of sugars versus the hydrophobic character of most P450 active sites. This project aims to (i) investigate P450-mediated O-demethylation of carbohydrates, (ii) engineer enzyme selectivity for site-specific activation, and (iii) establish a framework for programmable, enzyme-driven carbohydrate synthesis, enabling scalable production of valuable carbohydrate-based compounds.


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# Investigating the Effects of Non-Steroidal Anti-Inflammatory Drugs on Lipid Metabolism in Prostate Cancer using Multimodal Imaging

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Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) have proposed anti-tumour properties, with evidence showing that they can modulate lipid metabolic pathways[1]. Prostate cancer progression is strongly associated with lipid metabolism dysregulation, and there has been an increasing interest in the COX-2 enzyme and its potential role in tumour metastasis[2]. There is evidence to support that aspirin can block this pathway[3], however, the exact effects and localization of NSAIDs in prostate cancer lipidomics are still poorly characterized.

In this work, we have combined Time-of-Flight Secondary Ion Mass Spectrometry (ToF-SIMS) and vibrational spectroscopy techniques, Fourier-Transform Infrared (FT-IR) and Optical-Photothermal Infrared (O-PTIR), to chemically image the spatial lipid profile of prostate cancer cells after treatment with aspirin, specifically monitoring the in-vitro uptake and metabolism of arachidonic acid, which initiates the COX-2 metabolomic pathway. ToF-SIMS enabled label free imaging of cultured PC-3 cells, with high biological sensitivity and specificity at a single cell resolution. FT-IR facilitated high-throughput analysis of the same cell populations, supported with complementary data from the sub-micron imaging with O-PTIR. As part of this work, we addressed the challenges associated with multimodal imaging, such as sample preparation and reproducible workflows. We discuss the integration of different imaging modalities and their effective utilization in single-cell analysis, contributing to a better understanding of cellular lipidomics and their role in disease progression.

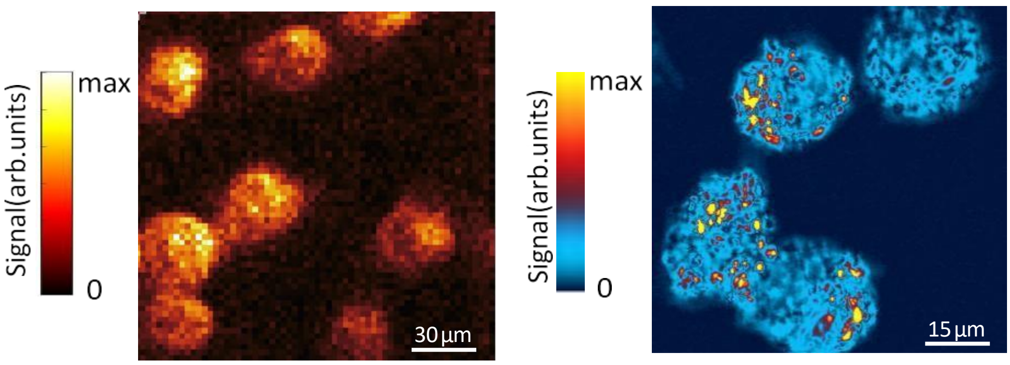


*Figure 1:* Example of PC-3 cell lipid localisation imaging using a) ToF-SIMS (*m/z* 91.05) b) O-PTIR (1744 $cm^{-1}$)

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# Structure and Mechanism of PhdC, a Prenylated-Flavin Maturase

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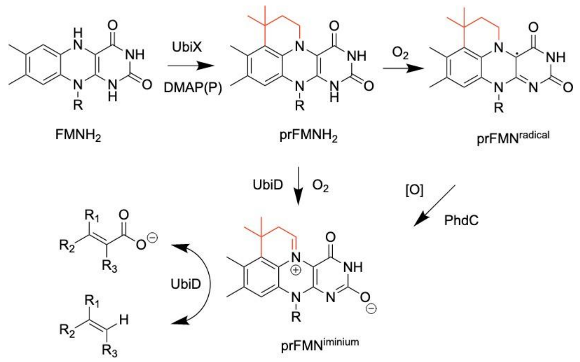
Prenylated flavin mononucleotide (prFMN) is a modified flavin cofactor required by the UbiD family of (de)carboxylase enzymes. While the reduced $prFMNH_2$ form is produced by the flavin prenyltransferase UbiX, the corresponding two-electron oxidized $prFMN^{iminium}$ form is required to support UbiD catalysis. Thus, oxidative maturation of $prFMNH_2$ is required, which can be catalyzed by UbiD. However, heterologous (over)expression of UbiDs frequently leads to the accumulation of the stable but non-active one-electron oxidized purple $prFMN^{radical}$ species. A dedicated prFMN maturase enzyme (PhdC) from *Mycolicibacterium fortuitum* was recently identified as capable of catalyzing the oxidative maturation of $prFMN^{radical}$ to $prFMN^{iminium}$, thereby enabling an effective supply of active cofactor to the associated phenazine-1-carboxylate (de)carboxylase PhdA. We report the crystal structure of PhdC in complex with flavin, revealing it is a distant member of the class I HpaC-like family of short-chain dimeric flavin reductases and demonstrate catalytic conversion of the $prFMN^{radical}$ species to $prFMN^{iminium}$ in the presence of oxygen or ferricyanide. Co-expression of PhdC or a distant homologue from *Priestia megaterium* (YclD) with the canonical UbiD from *Escherichia coli* leads to activation of the latter, similar in effect to co-expression with the $prFMNH_2$-binding chaperone LpdD. Conserved Glu residues in the PhdC active site suggest catalysis occurs through C1′ proton-abstraction coupled oxidation. This study thus provides both structural and mechanistic insight into the function of PhdC, adding to the expanding repertoire of prFMN-binding proteins associated with the widespread UbiDX system.

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# Effect of Mesaconate Linker Modification on MOF-801 $C_2H_6/C_2H_4$ Separation

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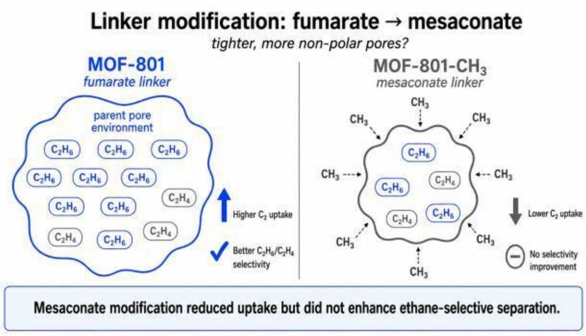
Ethylene purification remains an energy-intensive industrial process because steam cracking produces ethylene streams contaminated with chemically similar ethane. Adsorptive separation using metal–organic frameworks offers a potential lower-energy route to industrial energy-intensive cryogenic distillation, particularly through inverse $C_2$ separation, where ethane is preferentially adsorbed and ethylene is recovered as the less-retained product. In this work, the $C_2H_6/C_2H_4$ separation performance of parent MOF-801 and a linker-modified analogue, MOF-801-$CH_3$, was examined. Parent MOF-801 is constructed from Zr(IV) oxo clusters and fumarate linkers with ethane-selectivity, while the modified material replaces fumarate with mesaconate to introduce a methyl group intended to narrow the pore environment and increase pore-wall non-polarity. The working hypothesis was that tighter, more hydrophobic pores would enhance favourable interactions with ethane over ethylene.

The materials were assessed using PXRD, TGA, and single-component $C_2H_6$ and $C_2H_4$ adsorption isotherms measured by IGA at 283.15, 298.15, and 313.15 K. The results show that methyl modification reduced overall $C_2$ uptake, consistent with decreased accessible porosity or restricted pore transport. However, this reduction did not translate into improved $C_2H_6/C_2H_4$ selectivity. Instead, parent MOF-801 retained stronger ethane-preferential separation behaviour than the mesaconate-modified analogue. These findings indicate that simple pore tightening and increased non-polar character are insufficient to improve inverse $C_2$ selectivity in this system. The reduced performance of MOF-801-$CH_3$ may arise from non-uniform pore modification, partial pore blocking, or disrupted optimal host–guest geometry.

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## Biosensor-Guided Directed Evolution of Silyl Hydrolases for Sustainable Organosilicon Recycling

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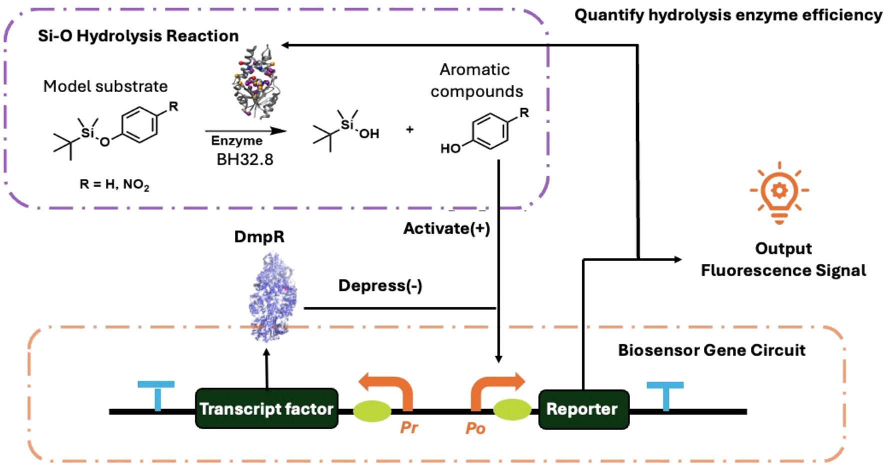
Organosilicon materials are widely used, but their production and recycling remain challenging due to the high chemical stability of Si–O bonds and the reliance on energy-intensive or chlorosilane-based chemistry. Enzymatic Si–O bond hydrolysis could provide a milder and more selective route towards organosilicon recycling, but efficient biocatalysts for this transformation remain underdeveloped. This project aims to develop a high-throughput platform for evolving the artificial silyl hydrolase BH32.8-SRSH3 towards improved Si–O bond hydrolysis activity. Phenol release from *tert*-butyldimethylsilyl phenyl ether (TBDMS-OPh) was used as the screening output to identify more active silyl hydrolase variants and support greener organosilicon recycling.

To enable high-throughput screening, a chromosomally integrated DmpR/GESS biosensor was developed to convert phenol release from the hydrolysis of the substrate into a fluorescence signal. The biosensor showed a concentration-dependent response to phenol and was sensitive enough to detect simal amount phenol after TBDMS-OPh hydrolysis. The expression level for BH32.8-SRSH3 was optimized by comparing TRC and pBAD-based expression, together with induction time and temperature. These results showed that the biosensor is compatible with flow cytometry and can support FACS-based screening when a single-cell fluorescence separation is observed. A biosensor-coupled FACs workflow was then applied to BH32.8-SRSH3 mutant libraries. Initial screening showed modest fluorescence separation between library with substrate group and BH32.8-SRSH3 with substrates group, indicating a narrow enrichment window. Ongoing work focuses on multiple rounds of low mutation rates library screening, single-clone analytical validation, and focused library redesign to identify improved BH32.8-SRSH3 variants for enzymatic Si–O bond hydrolysis.

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# Towards Optimization of Coarse-Grained Forcefields for Polymers Using Gaussian Processes

**Miltiades Angelides**,[a,b] Paola Carbone,[a]

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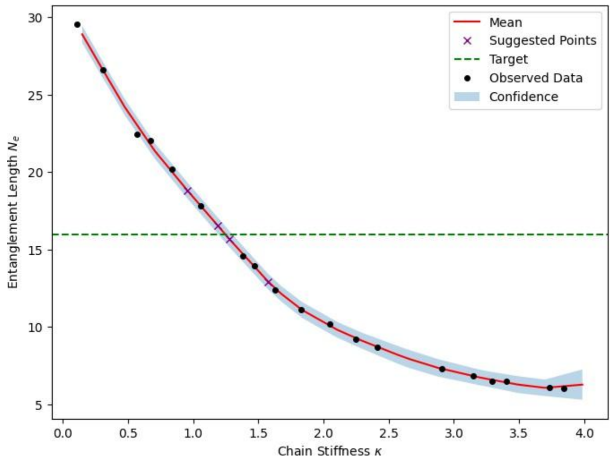
Polymer simulation properties can be highly sensitive to long-range interatomic interactions and are thus of critical importance to capture correctly when parameterizing forcefields. In this work, Gaussian Process guided Molecular Dynamics simulations are used to parameterize coarse-grained forcefields of polymers targeting emergent bulk behaviours. A Gaussian Process is trained as a surrogate model predicting entanglement length from selected forcefield parameters which are then used to initiate simulations expected to reproduce target behaviours. An automated workflow enables the iterative improvement of the model through repeated training using goal-oriented simulation parameters. This approach allows for the efficient parameterization of coarse-grained forcefields for polymer molecular dynamics.

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# Producing Triacylglycerides for Biofuel from Lignocellulosic Hydrolysate via *Yarrowia lipolytica*

**William Chipperfield**,[1] Neil Dixon[1]

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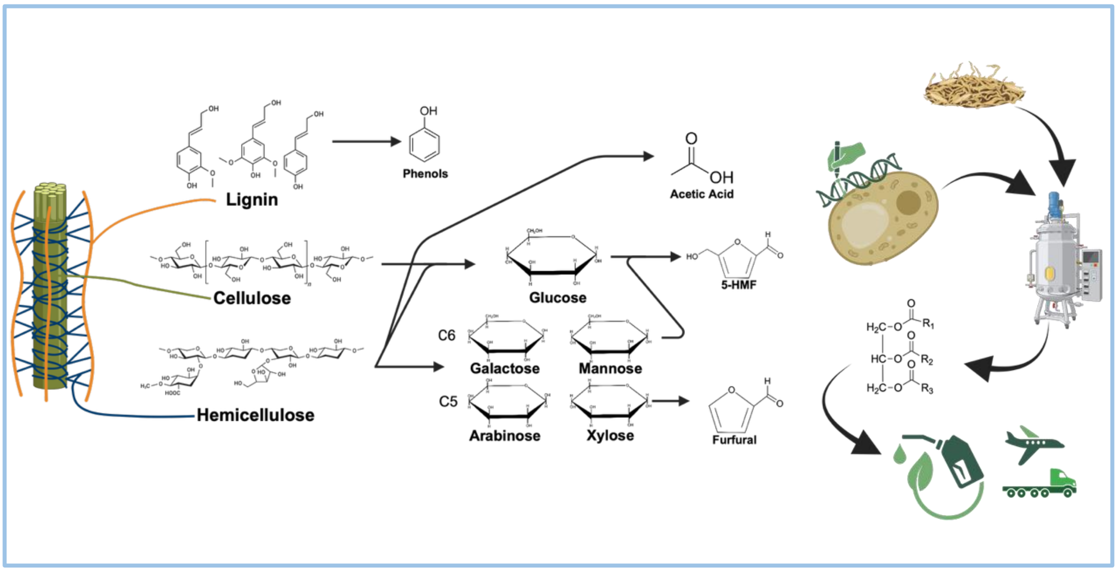
Burning non-renewable petrochemical-derived fuels contributes greatly to Earth's climate degradation. Improvement of public transport and electrification of terrestrial vehicles offers an alternative. However, some sectors, such as long-haul aviation or long-haul transport, rely on fuel for efficiency and quick re-fueling, making the transition to electric problematic. Microbial-based oil from oleaginous organisms aims to produce specialised or drop-in fuels from waste, such as lignocellulosic biomass, an abundant material from crop farming. Once processed into a hydrolysate it is rich in monosaccharides, as well as potentially inhibitory compounds. This project aims to produce strains of *Yarrowia lipolytica* which can produce high amounts of lipids, as a precursor to biofuels, from lignocellulosic biomass hydrolysate. To achieve this aim, we engineer strains to utilise all available carbon, as well as growing in the presence of inhibitors through rational genetic engineering and adaptive laboratory evolution.



# Photoinduced dynamically controlled ice binding materials

**Aparna Augustine**,[a] Matthew I. Gibson [a,b]

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Ice recrystallisation represents a major challenge in the field of cryopreservation as it constitutes as the primary cause of cellular and acellular damage. During the process of freezing and subsequent thawing, there can be a growth of large ice crystals at the expense of smaller crystals. This selective growth is governed by the thermodynamically driven phenomenon known as Ostwald ripening, and the progression of this process can compromise and lead to irreversible structural deterioration of the surrounding matrix or potentially cell death.[1]

The suppression of ice crystal growth therefore is a critical and active area of research where ice binding proteins (IBP) and their mimics have been extensively studied for this purpose. However, IBPs are not scalable, practical and have not found widespread application. In polar fish, IBPs are produced not in response to cold but via a light-sensitive feedback mechanism. Abiotic IBP mimics are 'static' and cannot be controlled by external stimuli, but spatio-temporal control over IRI function is desirable.

Work done by the Gibson group have been focused on polymer and small molecule antifreeze protein mimics, and in this project, we will be focusing on the small molecule L-phenylalanine[2] and polymer PVA[3] which have known 'static' IRI activity.

Drawing inspiration from already known synthetic ice binding materials, the production of synthetic mimics caged with photocleavable units that can be used to stimulate antifreeze activity is the goal for this project. Using the family of o- nitrobenzyl photocleavable protecting groups as caging units we create ice binding materials that are responsive and controllable using light.

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# Optimising FDCA bioproduction using a genetically encoded biosensor

**Lani Peel**[a], Bhumishree Bhumisuta Dehury[a], Thomas Butterfield[a], Karl Payne[a], David Leys[a], Neil Dixon[a]

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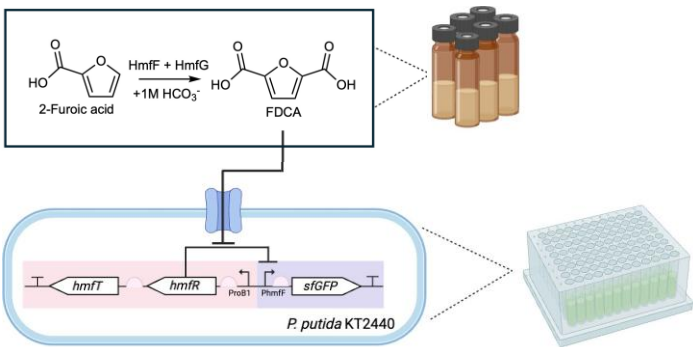
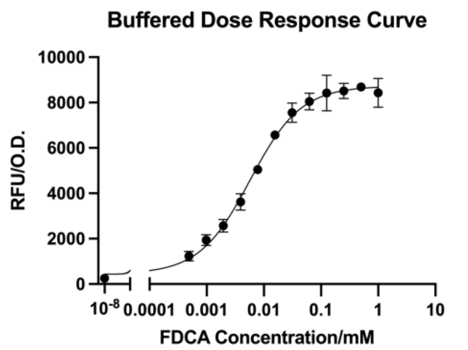
The aromatic diacid 2,5-furan dicarboxylic acid (FDCA) is a key renewable alternative to terephthalic acid for the production of polyester plastics. FDCA can be derived from the dehydration products of hexose and pentose sugars. Pentose sugars derived from hemicellulose are underutilised biogenic carbon sources. Bioproduction of FDCA from pentose sugars occurs via direct carboxylation of 2-furoic acid (2FA). However, enzymatic carboxylation of 2FA to FDCA has previously resulted in low titres. Here we show how a genetically encoded biosensor can be used as a high throughput screening tool for optimising FDCA bioproduction from 2FA. Through a multidisciplinary approach combining bioinformatic identification of candidate genomic loci with biochemical and structural characterisation, we identified HmfR as an FDCA-responsive allosteric transcription factor and used this knowledge to develop an FDCA-responsive biosensor. We showed that fluorescent output from the biosensor can be used to monitor FDCA production and is directly comparable to more laborious analytical techniques, such as HPLC. Furthermore, we demonstrated that the bioproduction and biosensing of FDCA can occur within a single cell, allowing for direct phenotype-genotype screening using FACS. Our results demonstrate that genetically encoded biosensors can be powerful tools for monitoring and optimising the biosynthesis of industrially relevant monomers. This work focusing on FDCA can be used as a starting point for the development of further biosensing systems. Furthermore, the one cell system established in this work lays the groundwork for more sophisticated high throughput screens, for example of pooled genetic variant libraries.

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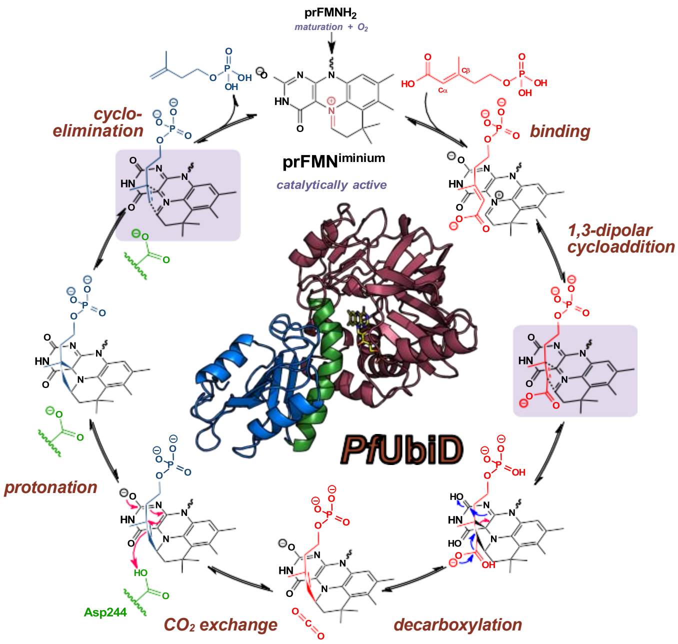
## From Structure to Catalysis:
# Engineering Flavin-Dependent UbiD Biocatalysts from Extremophiles for Sustainable Chemical Transformations

**K. M. Leung,** K. Payne, M. Yuen, D. Whittall, G. Roberts, S. Hay, D. Leys.

Manchester Institute of Biotechnology, The University of Manchester

The flavin-dependent UbiD enzyme superfamily has attracted significant interest due to its ability to catalyse industrially relevant reversible (de)carboxylation reactions, offering considerable potential for sustainable chemical synthesis and biofuel production[1]. However, reliably achieving efficient and specific enzymatic activities under industrial conditions remains challenging. This study characterises a highly thermostable UbiD enzyme from *Pyrococcus furiosus* (*Pf*UbiD) with an unusual preference for binding native cofactor flavin mononucleotide (FMN) over prenylated flavin mononucleotide[2] (prFMN) *in vivo*. Static light scattering analysis revealed exceptional stability of *Pf*UbiD up to temperatures approaching 95°C, surpassing previously explored ranges. We identified *trans*-anhydromevalonate 5-phosphate (*t*AHMP) as its probable native substrate and hereby report the first crystal structure of this enzyme bound to FMN at 2.3 Å resolution, revealing an open conformation with a notably polar active site. We demonstrated successful *in vitro* prFMN reconstitution with direct evidence of enzymatic activity in prFMN-bound *Pf*UbiD. Molecular docking and dynamic simulation of its ‘closed’ substrate-bound structure is modelled for targeted active-site mutagenesis. Collectively, this work establishes *Pf*UbiD as a robust, thermostable platform candidate suitable for targeted evolution aimed at a versatile scaffold capable of sustainable industrially relevant catalysis.




Scheme 1 | Proposed catalytic reaction mechanism of the prFMN-*Pf*UbiD specific substrate binding decarboxylation with *t*HAMP (red). *Pf*UbiD likely catalyses the decarboxylation through covalent catalysis mediated by the prFMN$^{iminium}$ cofactor (black). Neighbouring carboxyl-terminal residue (D244) was identified in potential contribution to $CO_2$ exchange and protonation steps during catalysis. Figure 1 (center) | Unpublished crystal structure of FMN-*Pf*UbiD monomer in an open-domain conformation.

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# Imine- and Imidazole-Based Covalent Organic Polymers as a Platform for Stable, High-Performance Supercapacitors

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**Abstract:** Nitrogen-rich covalent organic polymers and frameworks (COPs and COFs) have recently emerged as a highly promising class of functional materials in the field of materials science. The incorporation of nitrogen atoms within the framework introduces abundant lone pairs, which enhance electronic polarization and makes N-rich COPs particularly attractive for applications in Pseudo-capacitors[1] and batteries.[2] Among the diverse nitrogen-containing linkages, imidazole-based COFs[3] remain comparatively under-explored despite their significant potential. In this work, a series of imine and imidazole-based N-rich COPs were successfully synthesized via a facile synthetic approach, avoiding the harsh conditions typically associated with conventional COF synthesis. Our synthesized materials are analysed using various characterization techniques including Fourier-transform infrared (FTIR) spectroscopy, powder X-ray diffraction, solid state NMR, thermogravimetric analysis and Brunauer Emmett-Teller isotherm. The as-prepared frameworks and polymers were systematically evaluated for electrochemical energy storage applications, particularly in pseudo-capacitors. Electrochemical characterization using cyclic voltammetry and galvanostatic charge-discharge measurements revealed that our synthesized COFs/COPs exhibits a promising areal capacitance in the range of 90 mF $cm^{-2}$. To further enhance the electrochemical properties, ongoing efforts are focused on tuning the ionic conductivity in these covalent organic polymers through guest molecule incorporation, specifically via iodine adsorption[4].

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# Integration of Synthetic Biology and Chemoenzymatic Approaches towards Diversified Tetrahydroisoquinoline Alkaloids

**Chloe Lipinski**,[a,b] Ryo Tanifuji,[b] Hiroki Oguri,[b] David Leys,[a] Rainer Breitling,[a] Eriko Takano[a]

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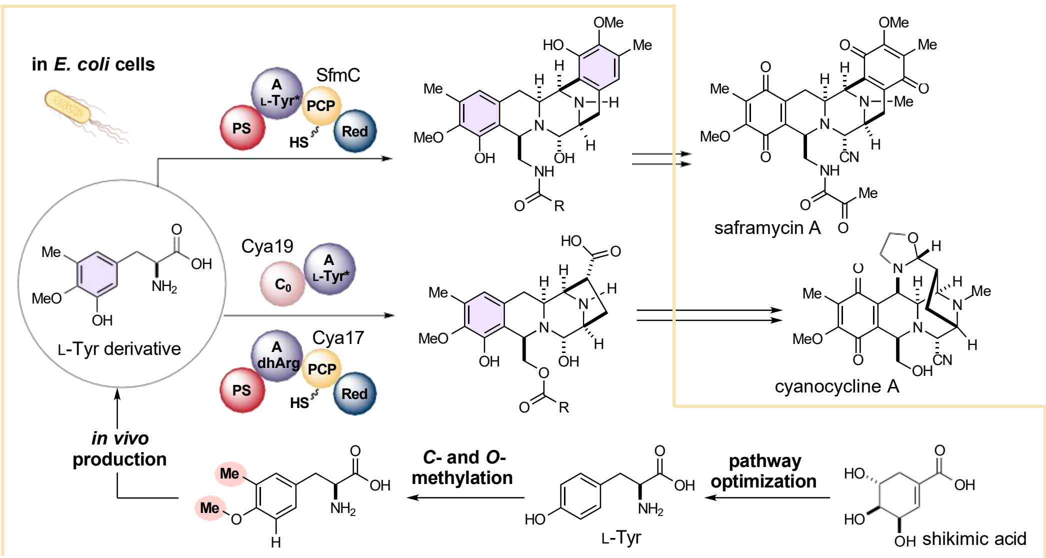
Ecteinascidin 743 (ET-743) is approved for the treatment of soft tissue sarcomas; its synthetic derivative, lurbinectedin, was approved in 2020 for the treatment of metastatic small cell lung cancer. Consequently, this family of natural products—the tetrahydroisoquinoline (THIQ) alkaloids—is anticipated to have further applications as pharmaceutical lead compounds. Although ET-743 is biosynthesized from amino acids in native microorganisms, only trace amounts can be extracted from biological samples. Hence, chemical synthesis has been essential for supply. But due to its structural complexity, ET-743 requires over 20 steps of chemical transformations and purification. Establishing a more straightforward and environmentally friendly synthetic platform for the rapid supply of such natural products could accelerate the application of complex molecules. This research aims to establish a process for the short-step and comprehensive synthetic platform and production of ET-743 and its analogues by actively integrating synthetic biology, *in vitro* enzymatic transformations, and chemical synthesis. Design-Build-Test-Learn cycles will be applied to establish a new *in vivo* production system for the tyrosine-derived THIQ precursor, with around 1 g/L of culture broth produced. Then, nonribosomal peptide synthetase genes will be introduced into the microorganism to achieve *in vivo* production of complex THIQ scaffold intermediates at a yield of over 50 mg per liter of culture broth. And finally, employing both chemical synthesis and enzymatic transformations, the goal is to achieve the synthesis of ET-743 and analogues in a short pathway (<10 steps) with a milligram scale yield.

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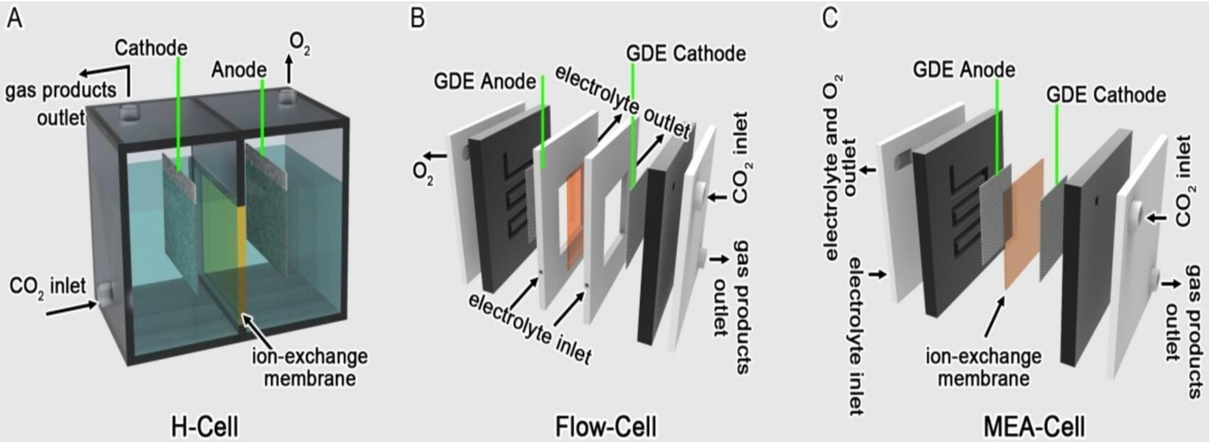
# Reactor geometry regulates local reaction environment in CO2RR

**Shijie Liu**,[a] Samuel Cobb,[a]

The electrochemical carbon dioxide reduction reaction ($CO_2$RR) offers a promising route for converting carbon dioxide into high-value-added chemicals and fuels[1]. While extensive research has been devoted to catalyst development, understanding of other factors—such as electrolyser design and microenvironment regulation—remains limited. In particular, the influence of electrolyser geometry on the local reaction environment and $CO_2$RR selectivity has not yet been fully understood[2]. In this study, using the same copper-based catalyst and controlled operating conditions, we systematically compared representative $CO_2$RR electrolyser configurations, including H-type, flow and membrane electrode assembly (MEA) electrolyser cells. The results indicate that reactor geometry significantly influences proton transport and local $CO_2$ concentration, thereby modulating the local pH and CO coverage at the catalyst interface. Compared with the H-type cell, the flow cell exhibits enhanced $CO_2$ transport capacity and suppressed hydrogen evolution reaction (HER), thereby improving CO selectivity. Furthermore, under current-controlled operation, the MEA cell exhibited enhanced proton transport capability and higher interfacial *CO coverage, facilitating the formation of $C_2^+$ products. These findings highlight the critical role of reactor geometry in regulating the local reaction microenvironment and provide important insights for the rational design of high-performance $CO_2$RR electrolysers.

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# Activation of $CO_2$ by lanthanum tris(cyclopentadienyls)

***Samilli Vasconcelos,***[a] *and David P. Mills*[a*]

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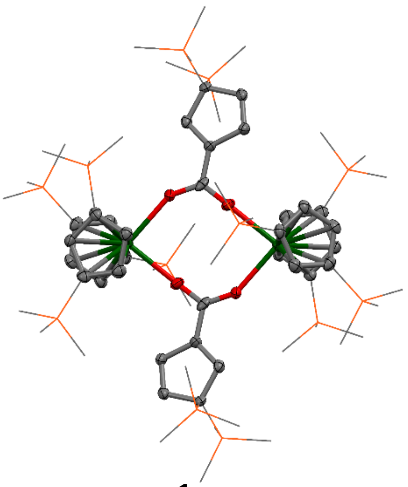
Rare earth (RE) small molecule activation chemistry has recently provided landmark results including carbon monoxide and dinitrogen fixation, and the reductive disproportionation of carbon dioxide.[1] As an O-donor ligand, $CO_2$ represents a more favourable HSAB match for RE ions than most other small molecules.[1] Previously, $CO_2$ activation by RE complexes has resulted in the formation of carbonates, carboxylates and oxalates.[1] Although this reactivity has been recognised for decades[2] it continues to attract growing interest.[3,4] We aim to elucidate the mechanisms of these reactions through the treatment of homoleptic RE substituted cyclopentadienyl ($Cp^R$) complexes with $CO_2$.

In this work we will present the reactivity of lanthanum *tris*-$Cp^R$ complexes with $CO_2$. This has resulted in the formation of carboxylate products that show a range of coordination modes of the carboxylated $Cp^R$ ligands to the lanthanum metal centres (Figure). We also present how different substituents on the $Cp^R$ ligand can affect the observed reactivity profiles.

We thank the University of Manchester for funding the project.



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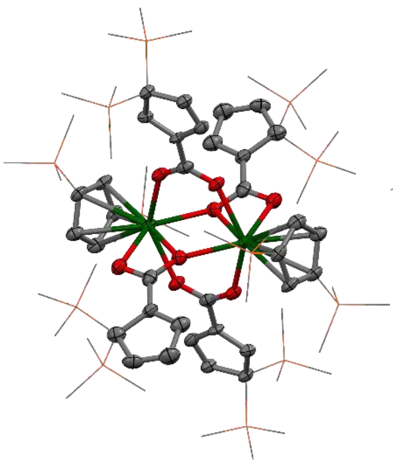

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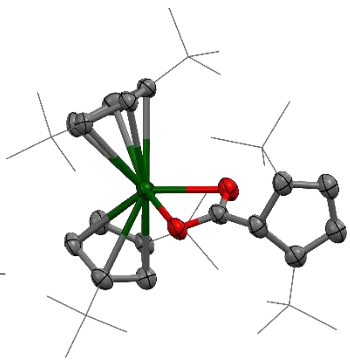

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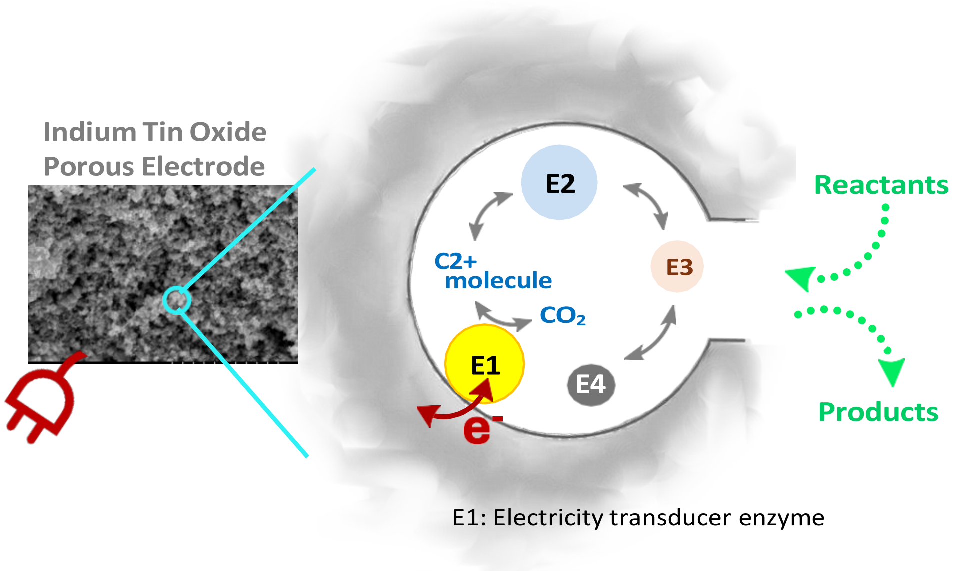
# Electro-enzymatic platforms for $CO_2$ fixation into complex high value chemicals

Sophie Kelly[a], Dr Clare Megarity[a]
[a]University of Manchester

Electrochemical $CO_2$ reduction is a key strategy for sustainable fixation of carbon into valuable organic molecules. Major challenges revolve around the design of catalysts that can afford fast, energy efficient and selective $CO_2$ conversion, especially into multi-carbon products. Carboxylating enzymes perform C-C bond formation reactions with astonishing speed, selectivity and energy efficiency.

Here, the (de)carboxylation enzymes, isocitrate dehydrogenase (IDH) and phosphogluconate dehydrogenase (PGD) are electrochemically driven in an emergent electro-enzymatic platform, the electrochemical leaf. This platform drives reduction and oxidation of biology's key reducing agent, NADP(H), through direct electron exchange between a porous indium tin oxide electrode and the photosynthetic enzyme, ferredoxin NADP$^+$ reductase (FNR). The electricity-derived reducing power was used by IDH, co-entrapped in the porous electrode along with FNR, to reduce $CO_2$. PGD has thus far been driven electrochemically in its oxidation direction. Work is ongoing to co-entrap an extended cascade that will not only allow conversion to valuable, complex products, but also drive the carboxylation reactions forward by rapid product removal.

In a parallel project, a next-generation electrochemical platform is under development exploiting an alternative electron-transfer central enzyme capable of unusual decarboxylation. The goal is to engineer this enzyme to enable it to catalyse its reverse reaction to fix $CO_2$, and to extend the cascade to produce C2+ molecules. So far, this enzyme has been expressed recombinantly for the first time and purified anaerobically to yield active enzyme; its catalysis has been successfully driven electrochemically through direct electron tunnelling between the enzyme's active site and an electrode.



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# From 4D to 2D: Efficient Computation of the Electron Correlation Energies of Atoms in Molecules

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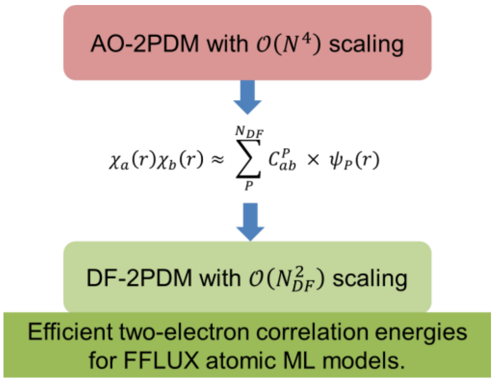
Abstract:

The accurate modelling of biomolecular systems remains a major challenge in computational chemistry. Thus, machine learning potentials (MLPs) have emerged as a promising approach, combining the efficiency of classical force fields with near quantum-mechanical accuracy.[1] Among these, the physics-informed MLP FFLUX employs the Interacting Quantum Atoms (IQA) energy partitioning scheme to decompose molecular energies into atomic contributions derived from quantum mechanics for machine learning (ML).[2] However, incorporating two-electron correlation energies into IQA, and consequently into FFLUX, is currently impractical, due to the steep computational scaling associated with the necessary storage and evaluation of the two-particle density matrix (2PDM).[3]

In this work, we introduce a proof-of-concept workflow that employs a density fitting (DF) approximation[4] of the 2PDM to enable the IQA partitioning of two-electron correlation energies. By expressing traditionally four-centre electron repulsion integrals in terms of auxiliary DF basis functions, the DF approximation reduces the computational scaling of the 2PDM from $O(N^4)$ to $O(N_{DF}^2)$, where $N$ is the number of basis functions and $N_{DF}$ is the size of the auxiliary basis set. The method is demonstrated using coupled cluster singles and doubles (CCSD) densities. The resulting reduction in computational cost and memory requirements enables correlated IQA analyses for significantly larger systems than previously accessible. Thus, this development provides an important step towards incorporating explicit electron correlation and dispersion directly into FFLUX atomic ML models, thereby improving both their physical robustness and transferability.

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# Ruthenium-Based Metalloenzymes for Enantioselective C–H Functionalisation

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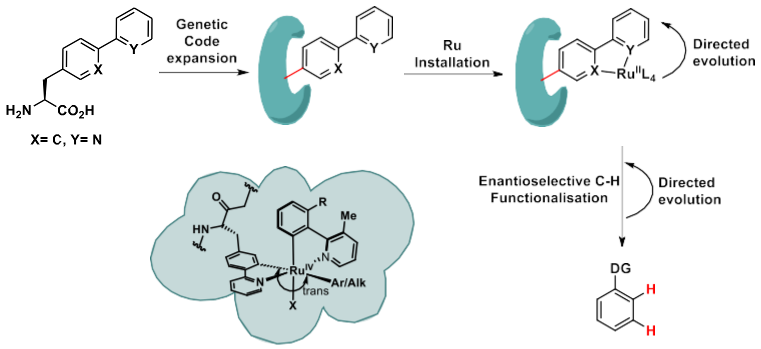
Over the past five decades, transition-metal catalysis has enabled significant advances in organic synthesis, but challenges remain in achieving high stereo- and regioselectivity. For example, ruthenium catalysts show potential in C-H activation and coupling reactions,[1] but often with little or no selectivity, especially with substrates containing multiple reactive sites. Conversely, enzyme catalysis commonly displays excellent selectivity but is limited by the functionality present in canonical amino acids and cofactors. Artificial metalloenzymes (ArMs) incorporate abiotic metal cofactors into proteins, thereby offering a promising hybrid solution.[2] However, limitations in genetically encoded ligands and cofactor positioning reduce their activity compared to free catalysts.

We aim to design an artificial metalloenzyme (ArM) incorporating a Ru catalyst positioned in the active site for asymmetric C-H functionalization of aromatic compounds with diverse coupling partners. By integrating a genetically encoded non-natural amino acid with a Ru-compatible ligand, we target precise control over Ru placement and ligand environment. Subsequently, the ArM will undergo optimization through directed evolution to enhance catalytic performance. Ultimately, these ArMs will enable regio- and enantioselective C-H arylation, alkylation, and other metal catalysed transformations, ranging from small synthetic building blocks to bioactive molecules, including drug scaffolds.

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# Ultra-Thin MOF-5 Crystals Enabled by Gas Blow Coating

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Metal-organic frameworks (MOFs) are attractive candidates for a wide range of applications in catalysis and sensing due to their exceptional surface areas.[1] A lot of research is currently focusing on new MOF synthesis methods because traditional solvothermal routes are often slow, solvent-intensive, costly, hard to scale and often produce large, irregular crystals that are difficult to process into pellets, films, or composites, hence hindering their integration into devices. Alternative techniques are currently being investigated with the aim of producing ultra-thin crystals and nanosheets, as they offer distinct advantages, including reduced diffusion lengths, increased surface area, and a higher number of active sites, as compared to bulk MOF crystals. These features collectively enhance mass transport, functional performance, and processability.

Here we use a novel, rapid and low-cost crystallisation method, the gas blow coating,[2] to produce ultra-thin MOF crystals at room temperature, directly on a substrate, without using any additive. MOF-5 (IRMOF-1) is selected as a prototypical system to demonstrate the effectiveness of this approach in producing ultra-thin MOF-5 crystals directly onto a surface. The rapid gas-assisted spreading and solvent evaporation enable controlled nucleation and spatially confined crystal growth, yielding MOF-5 nanosheets with a thickness below 10 nm and an aspect ratio between 4 and 6, depending on the deposition conditions. Raman spectroscopy and X-Ray diffraction confirm the crystalline nature of the material, although the structure is somehow distorted as compared to perfect MOF-5 crystals, possibly due to structural distortions, such as interpretation and/or changes in pore occupancy, in agreement with their lack of cubic morphology.

Our results show that the gas-blow coating method offers enhanced scalability, reduced processing complexity, and improved control over film thickness without the need for auxiliary agents, highlighting the potential of this approach for the scalable production of ultra-thin MOF crystals suitable for integrated into 2-dimensional based devices.

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# Dinuclear Copper Macrocycle for Selective Electrocatalytic $CO_2$-to-Methane Conversion

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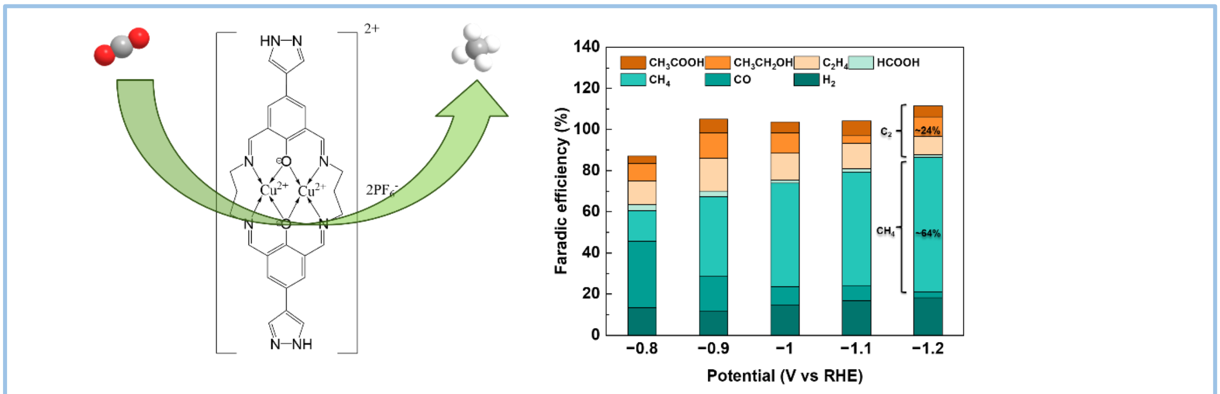
The electrocatalytic conversion of $CO_2$ into value-added products offers a promising route to mitigate excessive $CO_2$ emissions, yet achieving high selectivity toward deeply reduced products such as methane remains a significant challenge due to the similar redox potentials of competing pathways. Inspired by the tunable coordination environments of metal–organic frameworks (MOFs), we designed a pyrazole-functionalized macrocyclic ligand in which the macrocyclic core provides well-defined dinuclear copper active sites for catalysis, while the pyrazole groups are incorporated to enable future MOF construction. The resulting dinuclear copper macrocyclic complex was evaluated as an electrocatalyst for $CO_2$ reduction, exhibiting selective conversion to methane with Faradaic efficiency of 64% towards methane at -1.2 V vs. RHE, demonstrating the potential of macrocyclic copper complexes as a platform for selective $CO_2$-to-methane electrocatalysis.

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# Spin-System Selective 2DJ Spectroscopy

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Analysis of $^1$H NMR spectra is commonly hindered by extensive signal overlap due to the narrow chemical shift range and broad multiplet structures. Selective 1D experiments can be used to target key information and produce spectra that are simpler than the conventional 1D or 2D parent experiment. These are especially useful in cases of mixture analysis, where signals from multiple spin systems routinely overlap, but often lack the resolving power to provide unambiguous separation of signals. Pure shift experiments, including the 1D selective TOCSY-PSYCHE[1] and the recently published TREASURE,[2] have been developed in an attempt to provide the much-needed additional resolution, simplifying wide multiplets to singlet peaks. Although very successful, pure shift approaches remove essential spin-spin coupling information, making confirmation and elucidation of molecular structure and conformation more difficult. An ideal experiment would target one specific spin system, suppressing other signals; provide pure chemical shift information to identify, and determine the number of, chemical environments; and provide coupling information without compromising resolution. A logical approach to this ideal is to incorporate J-resolved spectroscopy[3] into a selective experiment, facilitating signal resolution and aiding mixture analysis.

Here, we introduce a new type of selective 2D NMR method, spin-system selective 2DJ spectroscopy, which generates a 2DJ spectrum containing only the signals of a chosen spin system. This approach is compatible both with conventional selective excitation, and with the ultra-selective GEMSTONE[4] element that uses spatial multiplexing to allow the selection of a single frequency even in significantly overlapped spectral regions.

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# Biomimetic cobalt porphyrins towards enzymatic C-H fluorination

**C. Doan,[a]** J. He, [a] H. Chen,[a] J. Sharratt,[a] C. Haigh,[a] I. Cisu,[a] O. Conboy,[a] B. Jones,[a] S. de Visser,[a] & J. S. Rowbotham[a,*]

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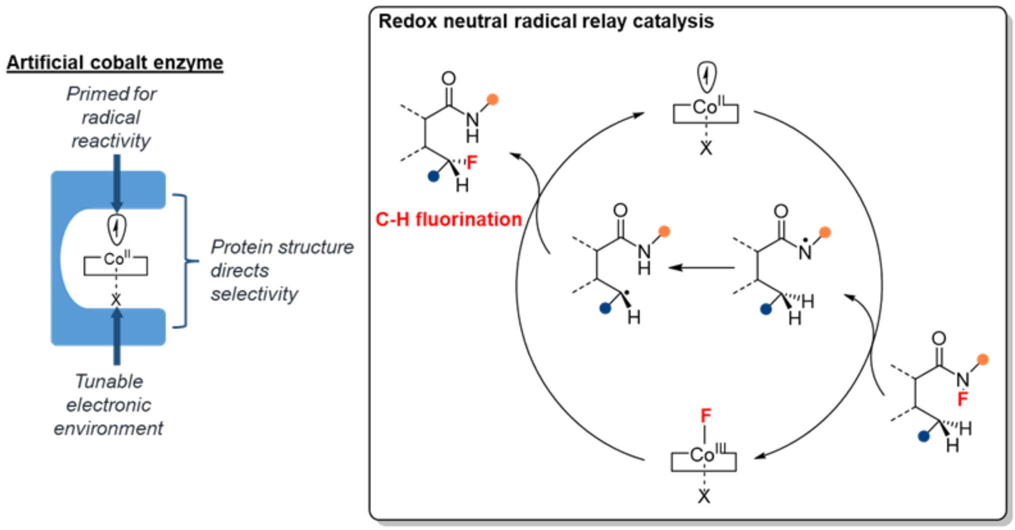
Complexes of first row transition metals (Fe, Co, Mn) are well-known for their ability to catalyse challenging chemical transformations *via* redox-neutral radical relay mechanisms. Whilst radical relay-type mechanisms are known in nature (e.g. vitamin $B_{12}$ and FeS clusters) the scope and applicability is vastly limited compared to reactions achievable by homogeneous catalysts. Recently, Fe-centred hemoproteins have been adapted to catalyse new radical relay reactions, with close control over the stereoselectivity.(1-3) In addition to this, the Rowbotham Group has developed routes to hemoprotein scaffolds containing metalloporphyrin cofactors where the native Fe is replaced by metals such as Co, Mn, Ni and Cu. The cobalt(II)-centred proteins are of particular interest, because the unpaired electron in the $dz^2$ orbital is well-situated for performing controlled radical chemistry.(4) Mutation of the axially bound amino acid also enables variation of the metal electronic environment for further tuning of the reactivity. This poster describes preliminary work to develop enzymatic Co-centred radical relay catalysis. In particular, by using *N*-fluoroamides as a route to amidyl radicals, selective C-H fluorination can be achieved. Translation of this chemistry into a protein scaffold will allow control over stereochemistry through mutagenesis of the active site.

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# *Force-controlled release of monomers with a rotaxane actuator*

**Oswald Philipsen**,[a] Guillaume de Bo,

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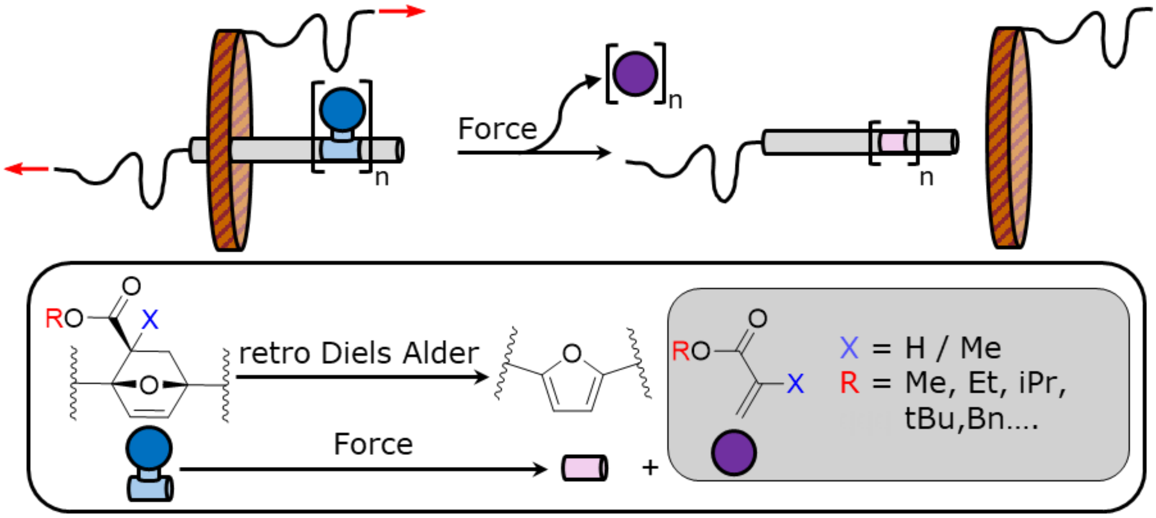
As properties and stability of polymer materials are closely intertwined with their chemical or macroscopic structure, a loss in structural integrity may result in critical loss of functionality and even catastrophic structural collapse. Increased material life span and continued performance can be achieved through site specific self-healing system, autonomously repairing any damage suffered. However, current systems suffer from structural integrity and expensive design, minimal damage threshold or presence of specific reactive groups[1,2].

In this study we have designed a system that is able to harness destructive forces and convert these into energy for the release of reactive monomers for the repair of polymers at the molecular level, employing the shuttling nature of rotaxane macrocycles and the reversibility of Diels Alder chemistry. We investigated the release of acrylate monomers with differently sized substituents using the benzo-21-crown 7 and pillar[5]arene[3] macrocycles.

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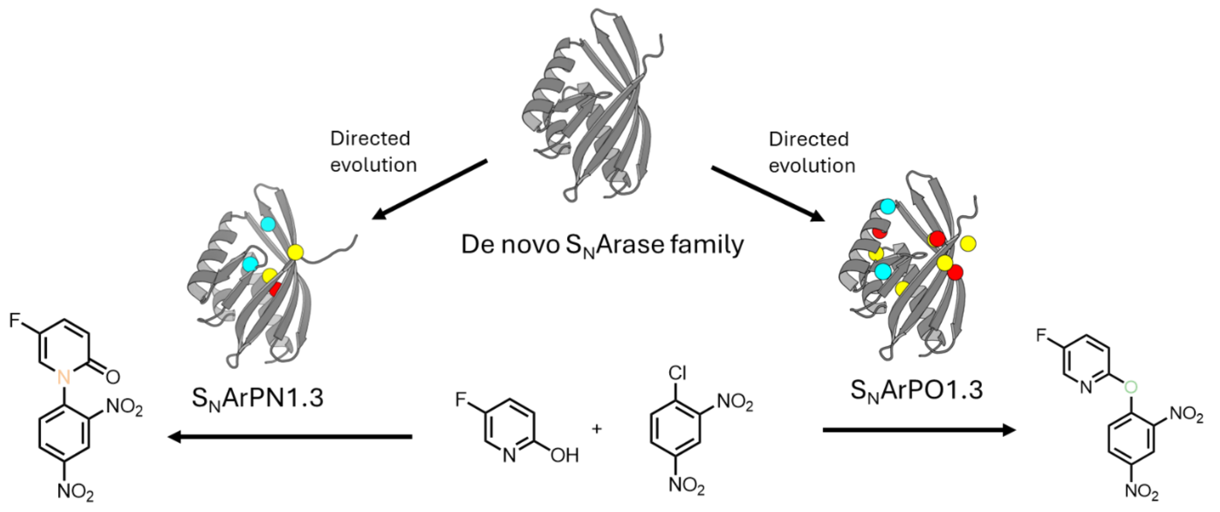
# Engineering a De novo enzyme for regioselective pyridone SNAr reactions

**Yilin an**,[a] Dr George W. Roberts, [a] Dr Fei Zhao, [a] Dr Thomas M. Lister

Supervisor: Prof. Anthony Green [a]

*a.* Manchester Institute of Biotechnology (MIB)

Nucleophilic aromatic substitutions ($S_NAr$) typically involve the coupling between an electron-deficient (hetero)aromatic ring and a nucleophilic partner. [1] The $S_NAr$ reactions are widely used in synthetic pathways in pharmaceuticals and agrochemicals, due to their robustness and simplicity in forming new C-C, C-O, C-S, or C-N bonds.[2] However, these reactions are typically performed under forcing conditions. There are limited catalytic strategies reported for $S_NAr$ reactions, with fewer enantio- and regio- control examples. The few reported natural $S_NAr$ases are restricted to hydroxide nucleophiles.[3-6] In previous works of our group, a highly efficient and enantioselective enzyme was engineered to mediate a coupling between an electron deficient aryl halide and a carbon nucleophile. [7] Another family of $S_NAr$ases ($S_NAr$2.0 - $S_NAr$2.5) was evolved from computationally designed NTF-2 scaffold, that were orders of magnitude more active. [8] The aim of my PhD project is to further engineer this NTF-2 like SNArase towards new substrate categories of industrial interest.

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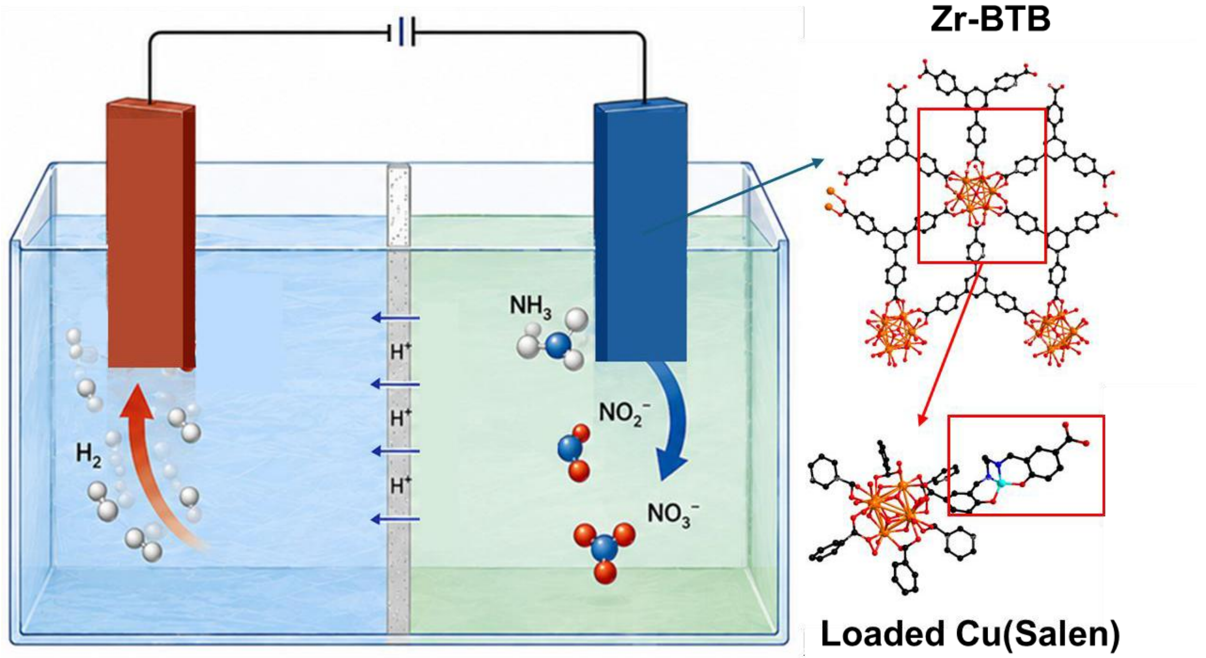
# Cu(Salen) loaded Zr-BTB MOF for electrical ammonia oxidation to nitrite and nitrate

**Tianrui Ma**,[a] Yujie Ma*, [a] Sihai Yang*, [a] Martin Schröder* [a]

*a.* University of Manchester

Nitrite ($NO_2^-$) and nitrate ($NO_3^-$) play important roles in many fields, including industry, agriculture, and food engineering. Currently, most nitrite and nitrate are produced via the Ostwald process, an established industrial method, which is associated with high energy consumption and the generation of harmful byproducts[1]. In recent years, researchers have increasingly focused on the electro-oxidation of ammonia to produce nitrite and nitrate. Although various materials have been developed, their catalytic performance and stability still require improvement[2-3]. Hence, we loaded a Cu-Salen complex onto a 2D MOF (Zr-BTB) to obtain a Cu-Salen loaded Zr-BTB catalyst. This material can produce 0.19 mg $h^{-1}$ $cm^{-2}$ of nitrite at 2.0 V vs. RHE with a Faradaic efficiency of 68%, demonstrating good performance among reported catalysts. Moreover, the material shows good stability during electrochemical synthesis of nitrite.

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# Poster Title

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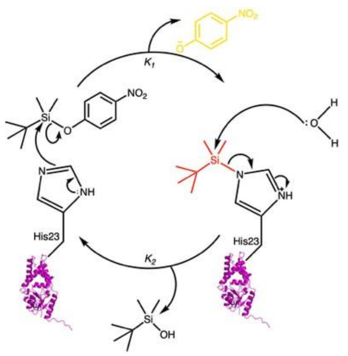
Silicon is one of the most versa8le elements on the planet, and in the form of siloxanes (Si-O), is used in a myriad of applica8ons that include the medical and food industries[1-3]. However, current silicon extrac8on methods from high grade quartz are very energy intensive and environmentally detrimental as they require use of chlorinated byproducts associated with their own environmental hazards[4-10]. Therefore, greener approaches to produce and/or recycle siloxane monomers are highly desirable.

While natural enzymes that can hydrolyse and condense Si-O bonds exist, most notably the family silicatein origina8ng from the *Demospongiae* class of marine sponges, the silicatein sila-$\alpha$ demonstrates ac8vity only 11.6-fold higher than background levels[4]. *De novo* protein design has been explored to allow for biocatalysis of previously biologically unreachable industrial chemistry, but usually produce designs that are very inac8ve and require mul8ple rounds of mutagenesis before they approach kine8c viability[5]. One such designed and improved enzyme, BH32.8, was discovered to have much higher hydroly8c ac8vity for silyl ethers compared to sila-$\alpha$ from the silicatein family despite being designed for a different reac8on, that of the MoriQa-Baylis- Hillman reac8on[6]. Therefore, BH32.8 was selected as a star8ng point for engineering an improved silyl hydrolase.

Engineering efforts of BH32.8 saw a mul8-disciplinary approach using computa8onal simula8on of the protein-ligand complex combined with molecular biological engineering methods for a semi-ra8onal design methodology and mechanis8c inves8ga8on into a possible enzyme-silicon covalent intermediate.

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# The Effect of Dynamic Correlation in Simulation of X-ray Absorption Spectra of Uranyl

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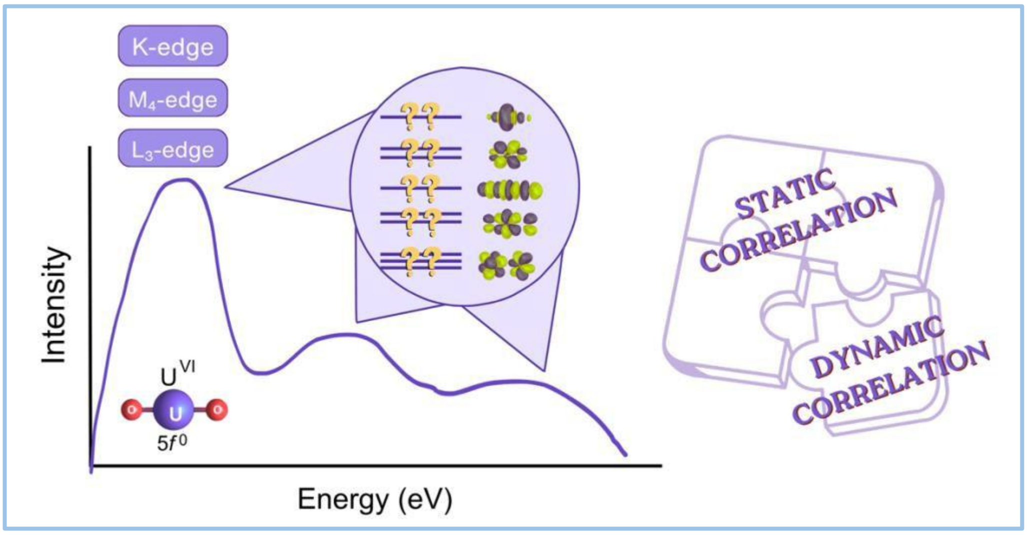
Accurate modelling of X-ray absorption spectroscopy (XAS) is essential for spectral interpretation of systems with complex electronic structures. Actinide systems have inherent multiconfigurational character and strong relativistic effects, which require appropriate theory to predict actinide properties. Here, we investigate the performance of the restricted active space self-consistent field method with spin-orbit coupling (RASSCF-SO)[1-3], and subsequent approaches for capturing dynamic correlation energy (multiconfigurational pair-density functional theory [RASPDFT-SO][4] and second-order perturbation theory [RASPT2-SO][5]). We model the oxygen K-edge, $L_3$-edge and the $M_4$-edge XAS of $[UO_2]^{2+}$. We find that inclusion of dynamic correlation is important for reproducing excitation energies, peak splittings, and peak assignments with closer agreement with experiment. However, the magnitude of these effects depends on both the electronic structure method and on the absorption edge under investigation. We conclude that despite large variability between method performance, the more computationally economic RASPDFT-SO offers a competitive alternative RASPT2-SO dynamic correlation methods.

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# A Novel Vertex for Metal-Organic Cages

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Over the past 30 years, metal-organic cages (MOCs) have been established as an effective tool in the field of stereoselective,[1] enantioselective[2] and regioselective[3] catalysis. However much of the literature within this field emphasizes cavity-directed catalysis, wherein the metal ions function as a structural component of the cage, rather than a direct participant in redox catalysis. Application of these metal vertices as conventional transition metal catalytic components has in contrast remained underexplored.[4]

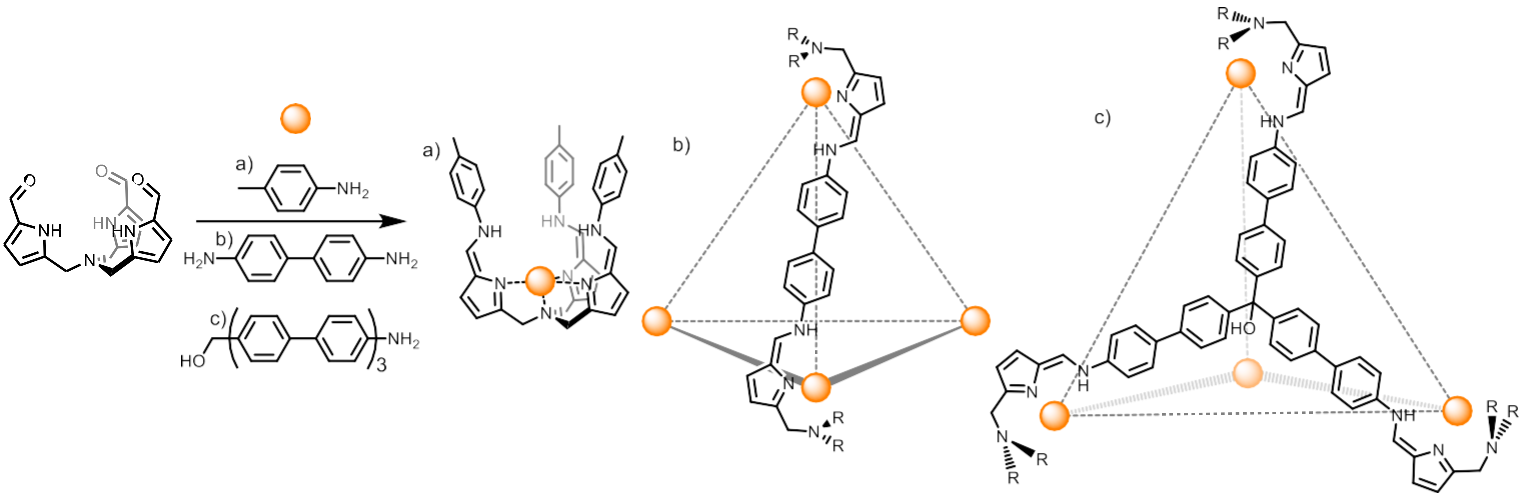


***Figure 1:*** *General synthesis scheme for a) the complexation of Zn(II) to $H_3tpa^{CO}$ & toluidine, b) the self-assembly of an edge-bridged MOC, c) the self-assembly of a face-capped MOC.*

Elsewhere, work from Fout and coworkers[5] has detailed a tripodal ligand scaffold, capable of forming dynamic imine bonds and binding metal ions. This complex has been shown to catalyse nitrite and perchlorate reduction reactions via the formation of an iron-oxo species.[6,7] Here we discuss our efforts towards the incorporation of this mononuclear binding motif into a larger supramolecular structure. Once expanded into a multinuclear species we envision fine-tuning of the ligand will allow for size-selectivity within the cavity, combining the advantages of catalytic MOCs with conventional redox catalysis.

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# Tuning Ion Transport with Gate Voltage

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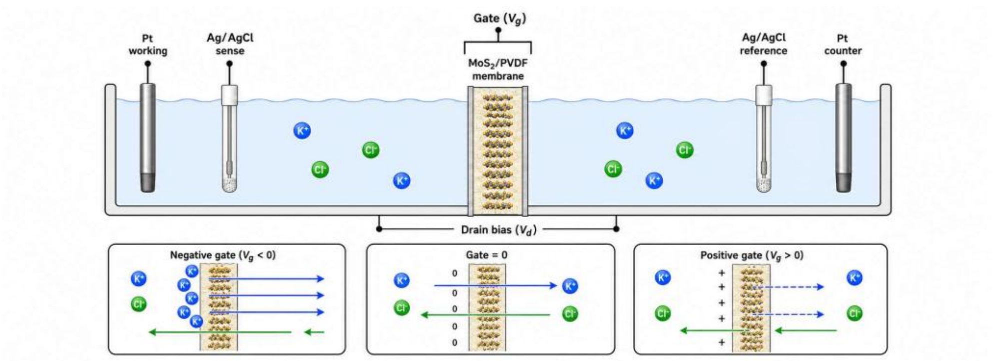
Ion transport through membranes depends on salt concentration, ion type and surface charge. Here, a $MoS_2$/PVDF membrane was tested in a five-electrode cell. A small voltage was swept across the membrane, while the $MoS_2$ surface was held at selected potentials. KCl was used to study salt concentration, TEACl was used to compare a larger cation, and bare PVDF was used as a control. The $MoS_2$/PVDF membrane showed linear ion transport and a clear change in conductance when the surface potential was changed. Bare PVDF showed only a weak response. The effect became smaller at higher KCl concentration, which is expected when salt screens the electric field. TEACl gave lower conductance and stronger rectification than KCl, showing that ion size also affects transport. These results show that $MoS_2$/PVDF can be used to control ion transport by changing surface potential, salt concentration and ion type.

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# Tandem Biocatalytic Oxidation-Cycloaddition Sequences for the Stereoselective Construction of Benzofused Scaffolds.

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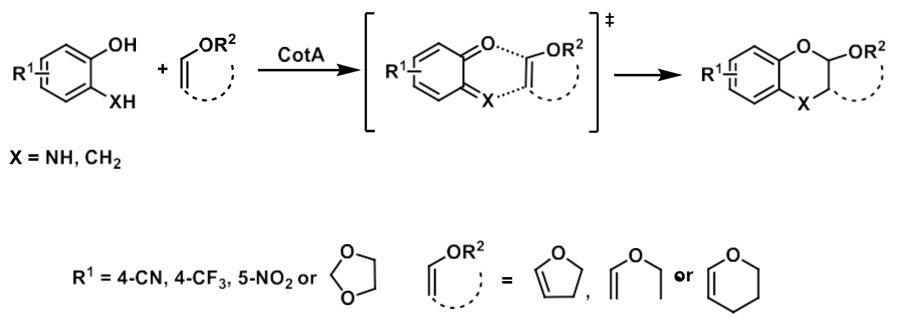
b. Department of Chemistry, University of Manchester, Oxford Road, Manchester M13 9PL

Tandem catalytic reactions offer an efficient and greener route to synthesis of complex molecular structures.[1] In this work, we investigate biocatalytic oxidation–cycloaddition sequences for the stereoselective synthesis of benzofused scaffolds via in situ generation of highly reactive o-quinoid intermediates.[2]

We demonstrate that the multicopper oxidase CotA can efficiently oxidise o-aminophenols to o-iminoquinone intermediates, which subsequently undergo inverse electron-demand Diels–Alder (IEDDA) cycloadditions with suitable dienophiles. Reaction optimisation using a design of experiments (DoE) approach enabled identification of key parameters to favour product formation. Comparative preparative-scale reactions were performed using CotA and molecular oxygen (as the terminal oxidant), horseradish peroxidase (HRP) with hydrogen peroxide, and the chemical oxidant diacetoxyiodobenzene. While full substrate consumption was observed, product yields were limited by competing side reactions.

Despite these challenges, CotA-mediated transformations showed comparable or improved yields relative to the other methods investigated, demonstrating its potential as a sustainable and selective catalyst. Additionally, preliminary results indicate that CotA can also access o-quinone methide intermediates from o-methyl phenol derivatives, expanding the accessible substrate scope. Here, o-quinone methides undergo an IEDDA reaction to form a new C-C bond, resulting in the formation of chromane products.

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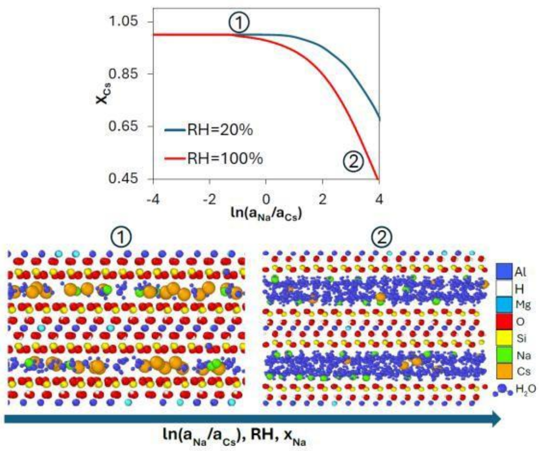
# Competitive Retention of Na/Cs in Montmorillonite Interlayers: A Hybrid Molecular Dynamics and Grand Canonical Monte Carlo Study

**Adel Najafimarghmaleki**, Paola Carbone

University of Manchester, Department of Chemistry, Oxford Road, M13 9PL, Manchester, United Kingdom

Adsorption and retention of toxic cations in soils and subsurface environments strongly influence their long-term environmental impact. In particular, $Cs^+$ can be retained in montmorillonite (MMT) through cation exchange with $Na^+$, a common interlayer ion in natural clays. However, the molecular-scale mechanisms governing the preferential uptake and hydration of $Cs^+$ versus $Na^+$ under varying humidity and solution conditions remain insufficiently understood. In this work, we employ hybrid molecular dynamics and grand canonical Monte Carlo (MD/GCMC) simulations of MMT across a range of $Na^+/Cs^+$ interlayer compositions, interlayer spacings, relative humidity (RH), and aqueous ion activities. The Gibbs free energy of ion exchange is computed by integrating the normal pressure across the clay layers as a function of interlayer spacing, enabling determination of equilibrium $Cs^+$ loading from the global minimum of the free energy landscape. Our results show that in homoionic systems, Na-MMT exhibits a humidity-dependent transition from monolayer hydration at low RH to bilayer hydration at high RH. In contrast, Cs-MMT remains in a stable monolayer state across all humidity conditions. This indicates that the swelling behavior of Na-MMT is closely linked to hydration state transitions, which are suppressed upon $Cs^+$ exchange. Furthermore, decreasing RH and increasing aqueous $Cs^+/Na^+$ ratios significantly enhance $Cs^+$ uptake in the interlayer region, highlighting a strong thermodynamic preference for $Cs^+$ retention under partially hydrated conditions. Overall, this study provides molecular-level insight into competitive $Na^+/Cs^+$ exchange in MMT and establishes a thermodynamic framework for predicting $Cs^+$ mobility in environmental and geological systems.



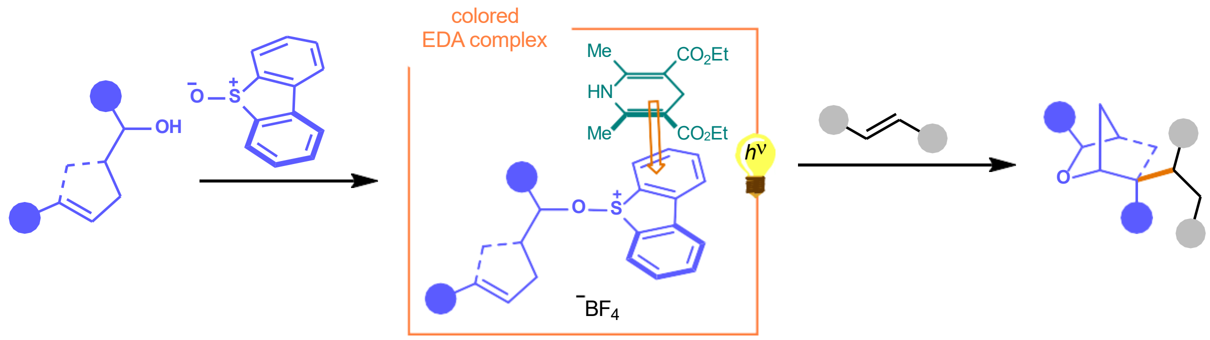
# Cyclization of alkoxy radicals with olefins by electron donor-acceptor complex photoactivation

**Shiquan Gao**, Jordan Berreur*, David Procter*

Given that tetrahydrofuran (THF) motifs are ubiquitous in natural products and pharmaceutical agents and are often incorporated into oxygen-bridged bicyclic frameworks, the development of efficient and versatile methods to access both simple THF rings and more complex bridged architectures remains highly desirable.

Recently, a new photocatalytic method-- electron donor-acceptor (EDA) complex-- has been extensively studied by chemists. Today, many EDA systems have been exploited to generate corresponding radicals under visible light activation, which allows sensitive functional group existing in the system. Among them, sulfonium salts are bench-stable, typically solids that can be prepared on a scale, which are studied widely to form radicals in mild conditions. Not only applied in EDA system, sulfonium salts also can generate different radicals by photocatalysts.

Specially, our group synthesized alkoxy sulfonium salts and realized the difunctionalization of alkenes by photoreaction. Following by this work, we utilized alloxysulfonium salts with Hantzsch ester to form EDA complex, which can be activated by visible light to generate alkoxy radicals to undergo 1,5-exo addition quickly and then be trapped by different radical traps, forming a series of tetrahydrofuran motifs products and [2.2.1] oxygen-bridged bicyclic products.

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# Ultrahigh throughput directed evolution of RNA polymerases for *in vitro* transcription

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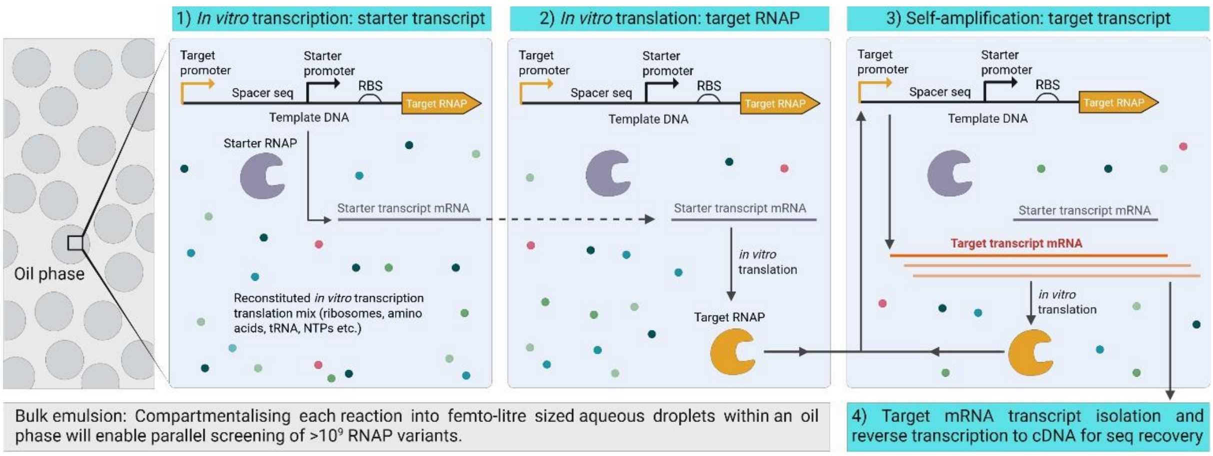
Large scale mRNA vaccine production relies on T7 RNA polymerase (RNAP) enzyme for *in vitro* transcription (IVT) of DNA templates encoding an immunostimulatory target protein[1]. However, IVT often generates immunogenic by-products including truncated and double-stranded RNAs[2]. In addition, IVT becomes progressively challenging as the template length increases, with phage-derived RNAPs exhibiting relatively low fidelity. Unlike DNA polymerases, for which a variety of commercial toolkits are available, RNAPs have been far less explored. To date RNAP engineering has primarily focused on T7 RNAP and has been limited to semi-rational, low throughput screening approaches.

This project aims to develop a new platform for ultrahigh throughput directed evolution of RNAPs towards improved IVT performance. A self-amplification feedback loop is established by two promoters upstream of the target RNAP gene such that more proficient mutants of the target RNAP make more copies of the transcript encoding their own gene. Increasing the length of the spacer sequence between the promoters enables tuning of the selection pressure. Compartmentalisation of each IVT reaction into femtolitre sized aqueous droplets within an oil phase will allow the screening of large numbers of RNAP mutants ($>10^9$) in parallel.

This system will deliver RNAPs with enhanced processivity and selectivity, resulting in RNAPs with improved IVT performance for biotechnological applications.

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# Synthesis and Study of a Class II-III Uranium Mixed-Valence System

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Although cyanide (CN) and isocyanide (CNR) groups are very common ligands in organometallic chemistry, their chemistry with the ac<nide elements is rela<vely sparse and hence poorly developed.[1] We report the homoly<c cleavage of various alkyl isocyanide R-N bonds, which consistently produces a novel uranium(IV) isocyanide complex **2**, and when R is 1-adamantyl, benzene func<onalisa<on is reported.

A single-electron reduc<on can be carried out on the uranium(IV) isocyanide complex, readily forming its U(III) analogue, confirming the ligand's ability to stabilise various oxida<on states. This is further evidenced by the synthesis and characterisa<on of a novel mixed-valence diuranium cyanide bridged complex **4**, which, addi<onally, exhibits intervalence charge transfer (IVCT). Although well-documented and well-studied for decades in transi<on metal chemistry, this is a rarity for a homo-bimetallic ac<nide complex.[2-5]

Lastly, various experimental and computa<onal techniques were subsequently used to inves<gate the magne<c, electronic, and op<cal proper<es of these novel complexes, which showed that chemistry which is ubiquitous across *d*-block elements can be applied to *f*-block elements.

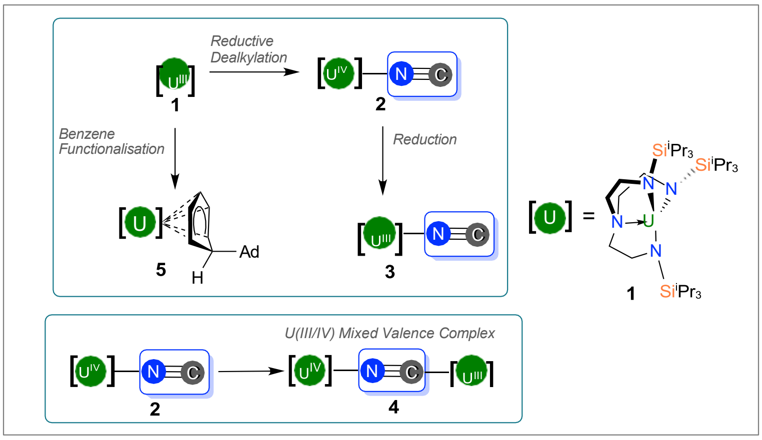


**Figure 1.** General uranium complex reac<vity schemes. (Top box) (right) reduc<ve dealkyla<on of alkyl isocyanides, followed by a single electron reduc<on (down). (LeO) Func<onalisa<on of benzene resul<ng from solvent par<cipa<on. (BoRom box) forma<on of mixed valence U(III)/(IV) complex.

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# Interplatform comparison of Ion Mobility Mass Spectrometry Lipid Characterisation

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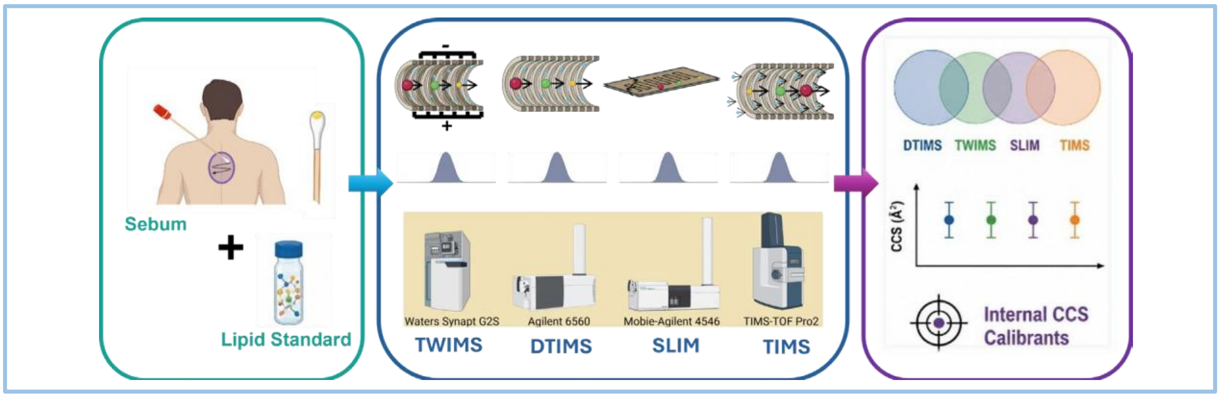
Lipid characterisation is complex due to the vast array of structural diversity resulting from chemical composition and presence of structural and stereoisomers. Ion mobility mass spectrometry (IM-MS) for lipid characterisation has received increasing interest due to the additional separation dimension provided by IM. When combined with MS, IM enables improved resolution of key lipidomics challenges, including double-bond identification and discrimination of isobaric and isomeric species.

Previous studies into Parkinson's disease using skin swabs of sebum, a lipid-rich biofluid, have demonstrated clear lipidomic differences between individuals with Parkinson's disease and healthy controls. The additional dimension provided by IM frequently reveals multiple species within *m/z* extracted lipid features, highlighting the potential of IM-MS for biomarker discovery. However, existing lipid collision cross section (CCS) databases have limited coverage, hindering annotation and emphasising the need to expand these libraries with measurements of lipid standards and ensure interplatform reproducibility.

Multi class lipid standards from Avanti Polar Lipids were analysed under three sample introduction conditions, direct infusion Electrospray ionisation (ESI), direct infusion nano-ESI and liquid chromatography-ESI across four IM-MS platforms: linear drift tube IMS (Agilent 6560), traveling wave IMS (Waters Synapt G2-S), Structures for Lossless Ion Manipulations (MOBILion Mobie/Agilent 6546) and Trapped IMS (TIMS-TOF Pro2). Lipid identification capabilities were further demonstrated using complex biological samples derived from sebum.

Here we present a workflow for obtaining and validating lipid CCS values, using optimised conditions for ion transmission, mobility resolution and accurate CCS calibration. Intraplatform comparisons demonstrated good agreement of lipid CCS values across all IM-MS platforms and infusion methods under optimised conditions, supporting their reproducibility and transferability. The consistent CCS measurements obtained for multi class lipid standards enable their use as transferable reference compounds that can be spiked into biological samples as internal CCS calibrants, improving annotation confidence and cross platform harmonisation in IM-MS lipidomics.



# PFAS Removal Using Metal-Organic Frameworks

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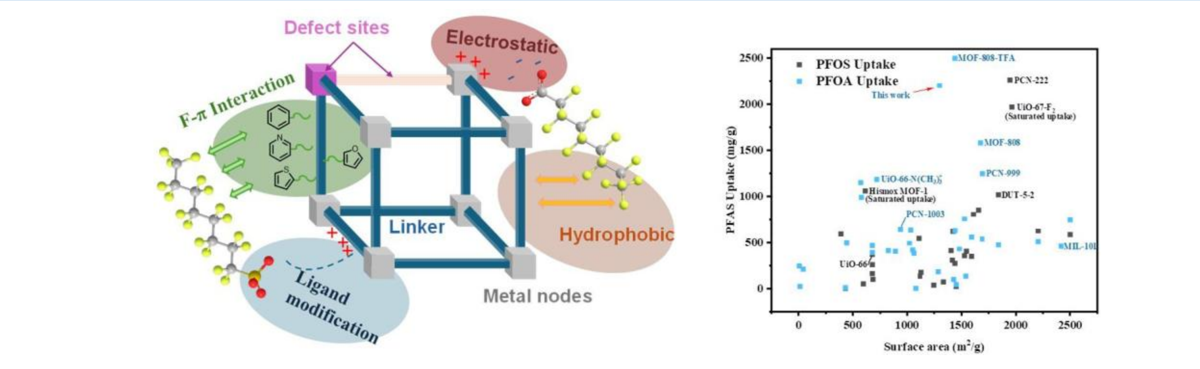
Per- and polyfluoroalkyl substances (PFASs) are a class of fluorinated compounds characterized by containing at least one fully fluorinated methyl or methylene carbon atom [1]. While perfluorocarboxylic acids (PFCAs) and perfluoroalkyl sulfonic acids (PFSAs) have been extensively studied. Current research has identified over 4,700 distinct PFAS compounds [2]. PFASs exhibit exceptional chemical stability due to their high C−F bond energies (~110 kcal·mol$^{-1}$) [3], leading to widespread industrial applications including metal electroplating, semiconductor manufacturing, and consumer products, leading to widespread pollution of aquatic systems, including surface water and groundwater resources.

This work employs metal-organic frameworks (MOFs) for PFAS adsorption. By utilizing the advantages of tunable pore size distribution, high surface area, and customizable surface chemistry of MOFs, aiming to achieve outstanding PFAS adsorption performance. Emphasis is placed on enhancing electrostatic interactions and Lewis acid-base interactions to further improve PFAS capture efficiency. The material has been proven to have 2200 mg/g PFOA capture capacity, fast kinetics that reached equilibrium within 20 minutes, ability of removing 95-99% PFOA at 100 ppm solution and can be reused 7 times.

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# Retuning Nature's Potential by Active Site Engineering and Electrochemical Control

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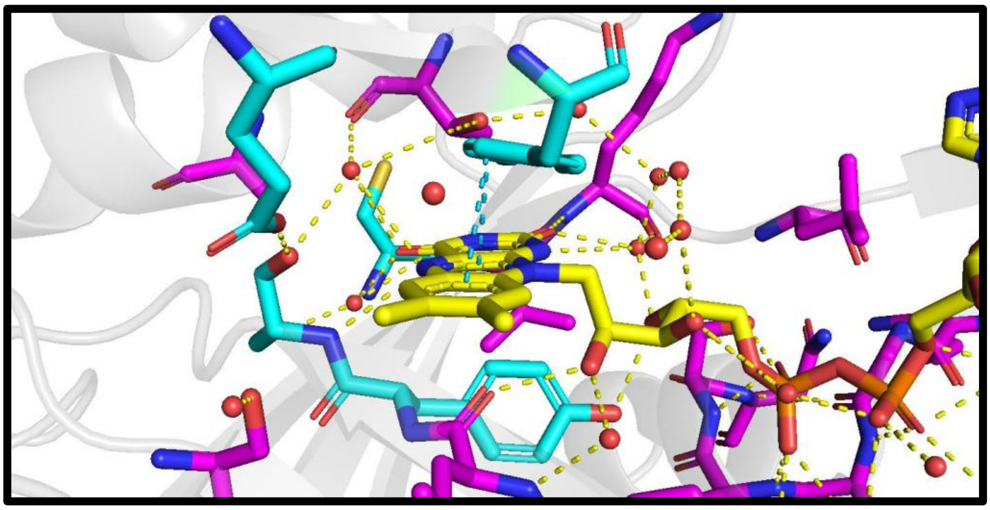
This project combines electrochemistry, enzyme engineering, and computational methods to investigate how biology fine-tunes the reduction potential of redox cofactors in enzymes, with an overall aim to establish rules for bespoke *de novo* enzyme design.

Ferredoxin NADP+ reductase (FNR), a pivotal enzyme in photosynthesis, catalyses the transfer of light-excited electrons to NADP+, providing reducing equivalents (NADPH) to the Calvin-Benson Cycle. FNR contains a non-covalently bound flavin adenine dinucleotide (FAD) cofactor, which is crucial as a two-electron sink and donor during the catalytic cycle. The binding of FAD in the enzyme significantly alters its potential, tuning it to be more negative (reducing) than when it is free in solution, thereby enabling FNR to catalyse NADP+ reduction.

The Electrochemical Leaf (e-Leaf) is a cascade operating platform that exploits FNR as a central enzyme. Here, direct control of FNR in the porous e-Leaf electrode has enabled an in-depth analysis of its flavin cofactor. When FNR's conserved C-terminal tyrosine is substituted for serine, the FAD's redox potential is altered, and its substrate specificity is switched to NAD(H). An investigation into this variant's greater overpotential requirement for NADP+ reduction, as well as increased substrate scope, will be discussed.

To probe the role of specific residues in the tuning of the FAD's redox potential, the active site of spinach FNR has been rationally engineered, and molecular dynamics simulations have been carried out. The analysis of 10 variants shows that each change in structure shifts the redox potential to a more oxidising potential.



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# Reactive CMC-Based Materials for Multifunctional Antimicrobial Wound Dressings

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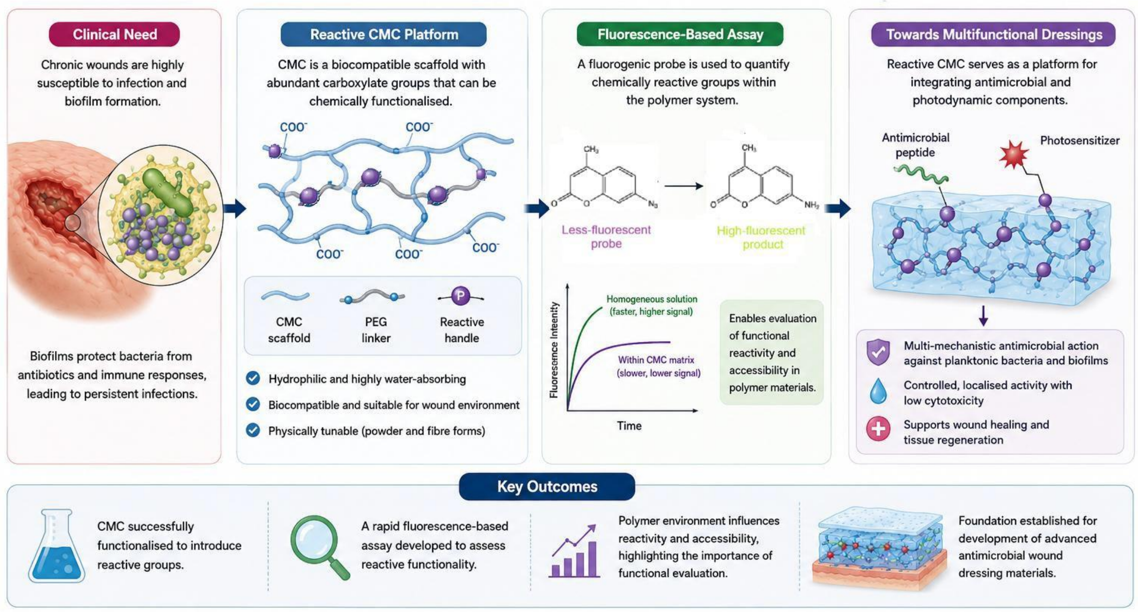
Chronic wounds are a major clinical challenge due to persistent infection, biofilm formation, and the limited effectiveness of conventional antimicrobial dressings. This work will develop chemically reactive carboxymethylcellulose (CMC)-based materials as multifunctional platforms for advanced wound care. CMC is a biocompatible, hydrogel-forming polymer with high uptake of wound exudate, properties that make it a popular choice for commercial wound dressings. CMC has abundant carboxylate groups available for modification, which allows functional groups to be introduced that may enhance its wound-healing properties.

Two morphological forms of CMC (powder and fibrous) were modified using flexible polyethylene glycol (PEG) linkers, introducing reactive functional groups while preserving aqueous compatibility and structural integrity. This strategy enabled the incorporation of molecular functionalities intended to support antimicrobial activity. In parallel, analytical methods were developed to evaluate not only reactive functional group presence but also the effective chemical reactivity within the CMC matrix.

A key recent outcome has been a fluorogenic assay based on selective reactivity between a small-molecule probe and phosphine-containing functionalities. This assay enables rapid quantification of the number of accessible reactive phosphine sites, overcoming the limitations of previous techniques, such as elemental analysis and solid-state NMR, that measure composition rather than accessibility. The assay highlighted the role of polymer microenvironment in governing reactivity. Studies of functionalized CMC derivatives against bacterial strains commonly found in hospital-acquired infections are currently ongoing.

Overall, this study has enhanced the applicability of the reactive CMC platform, supporting future development of antimicrobial and photodynamic wound dressings targeting biofilm-associated infections.

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# Expanding Lanthanide Redox Chemistry Using Redox-Active Pyridine Diimine Ligands

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The strong preference of lanthanides (Ln) to exhibit the +3 oxidation state lead to many chemists neglecting their redox chemistry for decades.[1] This previous oversight was unfortunate, as Ln compounds show a unique combination of properties, such as predominantly ionic bonding,[2] and a smooth trend of decreasing ionic radii with atomic number.[2] This provides a potential strategy to fine-tune the reactivity of Ln complexes through variation of metal ion, an approach that would be complicated by covalency and crystal field effects for d-transition metal complexes.

We are currently expanding Ln redox chemistry by using redox-active Pyridine Di-Imine (PDI) ligands, which can act as electron reservoirs by storing electrons within their π-systems.[3] We aim for Ln complexes that are capable of multi-electron transfer reactions using electrons stored within their PDI ligands.[4]

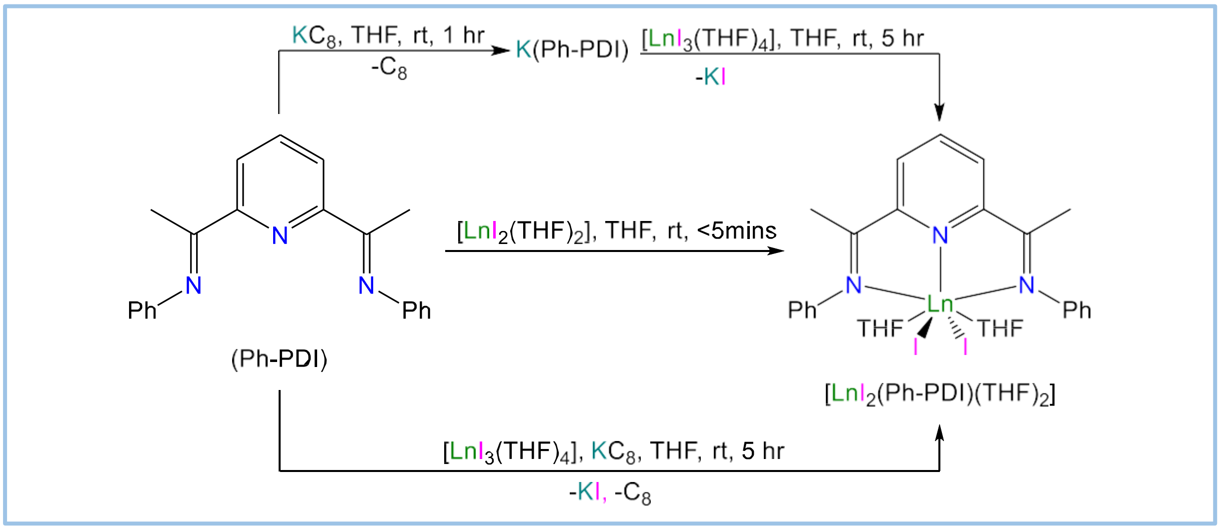


**Fig. 1.** Synthetic routes to $[LnI_2(Ph\text{-}PDI)(THF)_2]$.[4]

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# Multiphoton Dipolar Spectroscopy

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Double Electron Electron Resonance (DEER) is a technique used for measuring dipolar interactions between two radicals in Electron Paramagnetic Resonance (EPR) spectroscopy, which allows the distance between them to be determined. Now, it is possible for transitions between spin states can be realised using multiple photons, passing through virtual states and described by Floquet theory[1]. With both microwave (mw) and radiofrequency (rf) sources, resonances can be observed at frequencies of $\omega_{mw}$, $\omega_{mw} \pm \omega_{rf}$, $\omega_{mw} \pm 2\omega_{rf}$ etc. The transition probabilities for the various resonances can be manipulated with the choice of rf power and rf frequency used, and the $\omega_{mw}$ resonance can be made to disappear entirely, in a '$\pi$-photon-induced-transparency' condition [2],[3]. This project demonstrates the use of the '$\pi$-photon-induced-transparency' condition in a multiphoton version of the Double Electron Electron Resonance (DEER) experiment. Here, the pulse with simultaneous mw and rf (Figure 1) excites only resonances at frequencies which are distinct from those excited by the other pulses. This satisfies the frequency-difference requirement of DEER using just one mw frequency, which has the potential to bypass the limitations of pulse power and bandwidth that come from over-coupling the EPR resonator.

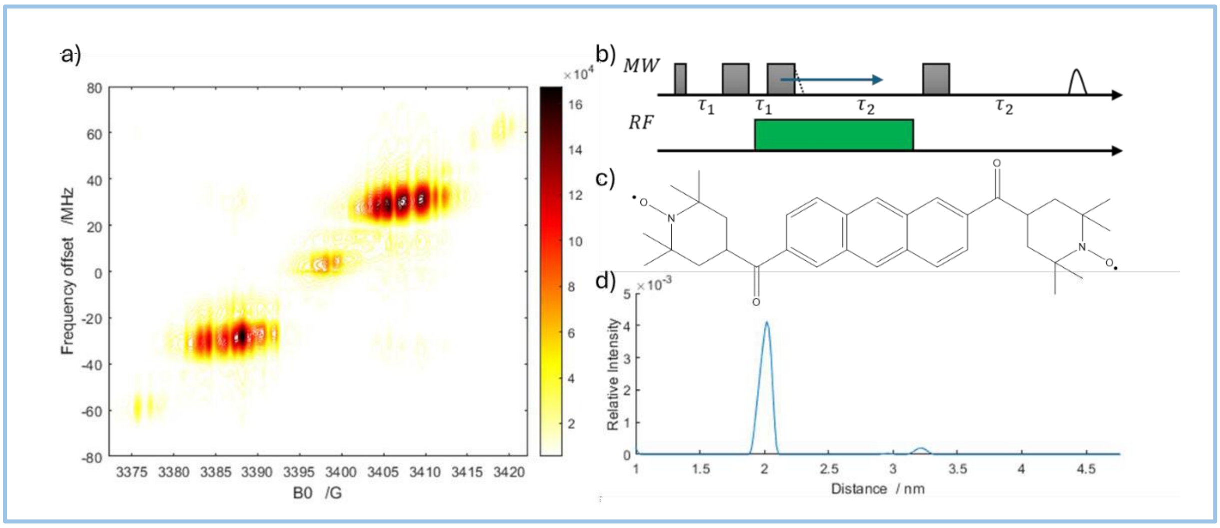


Figure 1: a) Multiphoton transitions observed for a Hahn echo with simultaneous mw and rf pulses on coal. b) Multiphoton DEER pulse sequence. c) A nitroxide biradical, for which d) shows the distance distribution obtained following a multiphoton DEER experiment.

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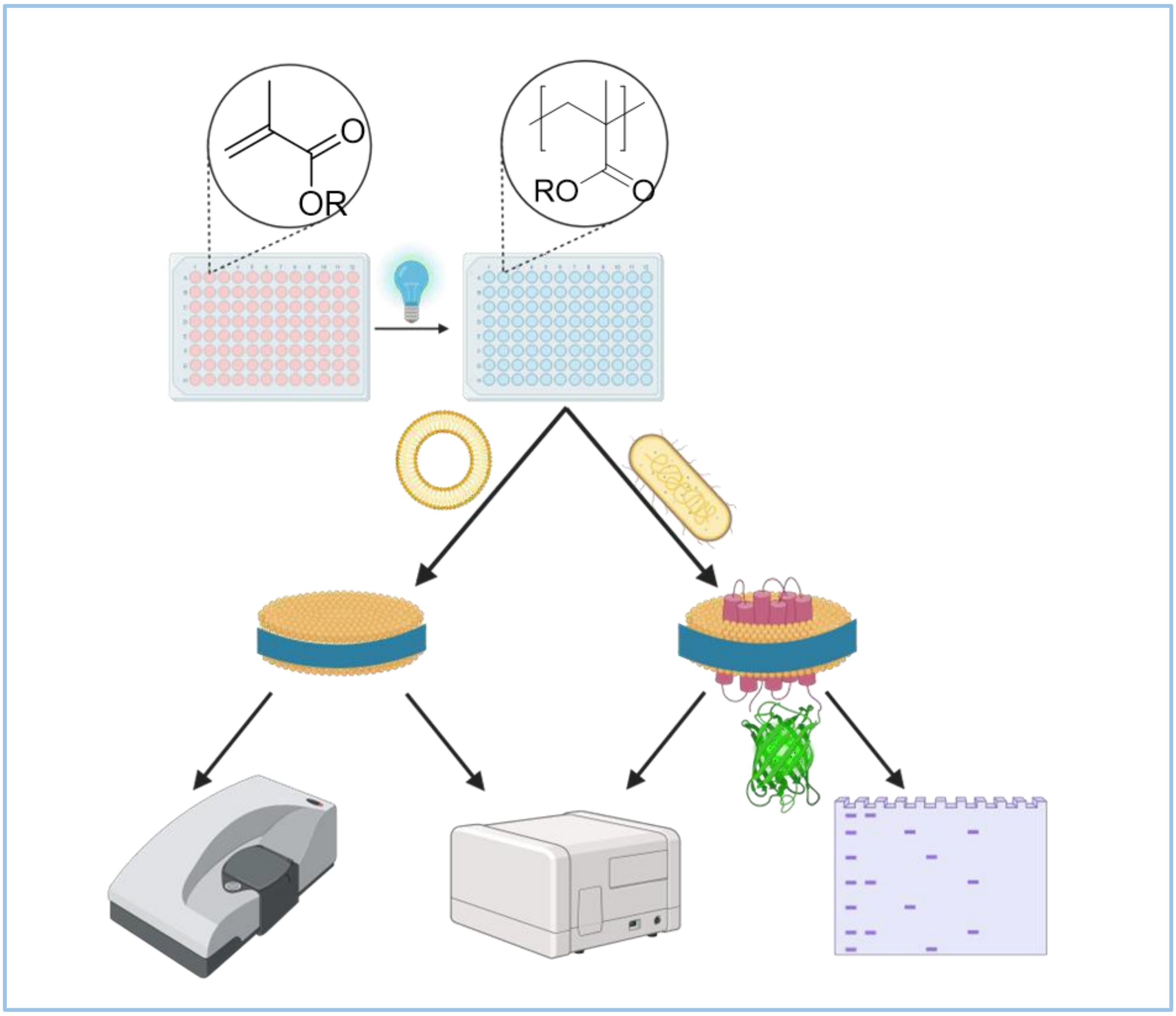


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# The Uncatalysed Reduction of Flavins by Nicotinamide Analogues

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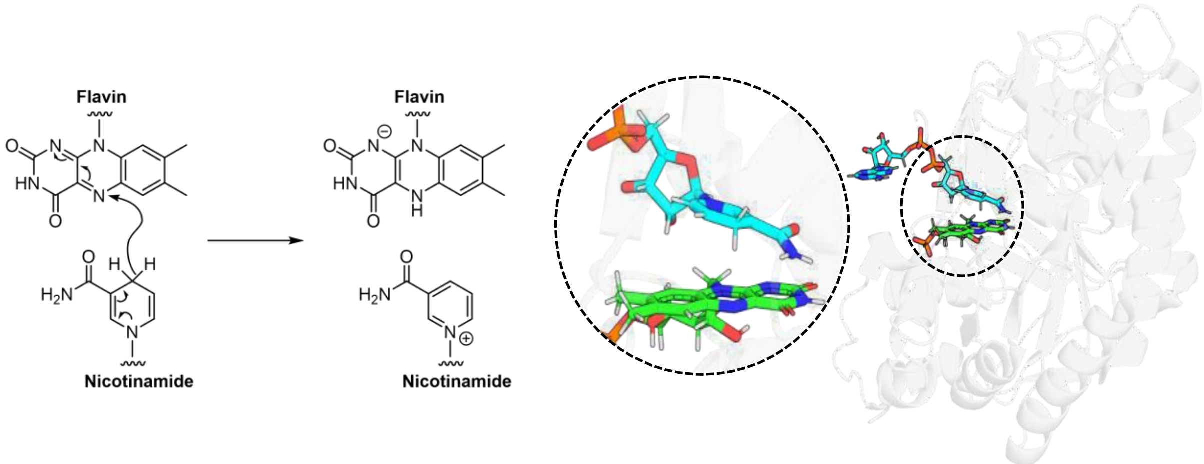
Flavin-dependent enzymes are present across all forms of life and nicotinamide coenzymes are common flavoenzyme substrates, performing 2-electron (hydride) oxidation or reduction of the flavin cofactor. Here, we have attempted to characterise the uncatalysed reduction of flavin by nicotinamide analogues which provides a reference reaction to investigate contributions to catalysis by coenzyme-dependent flavoenzymes. The reaction proceeds via an intermediate with weak charge transfer (CT) character. This enables a limiting rate of flavin reduction/hydride transfer to be estimated and allows a more meaningful comparison to enzyme data. We observe the rate of FMN reduction by NADH to be $1.6 \times 10^{-2}$ $s^{-1}$ at 298 K. This is significantly slower than MNAH with an observed rate of 7.4 $s^{-1}$. To help explain this, we have collected $k_{obs}$ data in the linear region for other NAD(P)H analogues such as β-NMNH and NRH. The predicted $V_{max}$ / $K_m$ for β-NMNH, NRH and MNAH is 0.2, 0.3 and 37.7 $M^{-1}s^{-1}$ respectively. It is possible that ribose alone is disrupting the CT complex to drastically slow the rate of hydride transfer and not conformational sampling of the NADH adenosine moiety.

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# Expanding the Genetic Code for Precision Antibody Engineering

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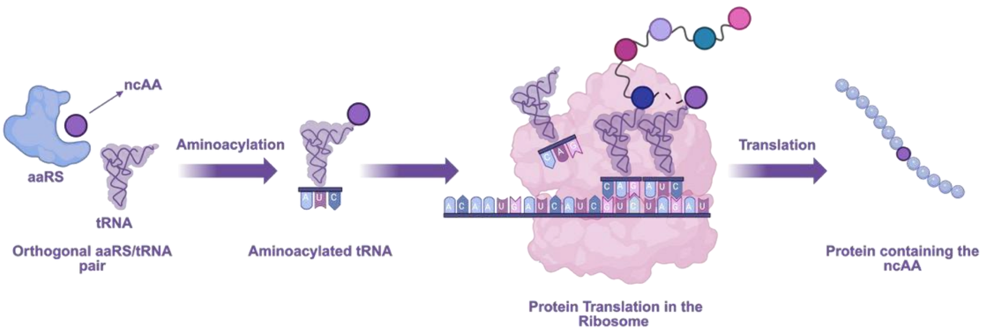
Genetic code expansion (GCE) has become a powerful approach for broadening the chemical and functional diversity of proteins beyond the constraints imposed by the 20 canonical amino acids. GCE relies on engineering of orthogonal aminoacyl-tRNA synthetase/tRNA pairs for the efficient incorporation of non-canonical amino acids (ncAAs) in proteins,[1-4] as recently demonstrated for a cyclopentadiene derivative of L-lysine (CpHK). Using GCE, CpHK can be site-selectively incorporated within antibodies, where it can covalently bind maleimide moieties, allowing the formation of antibody-drug-conjugates (ADCs), a promising tool for anti-cancer therapies. Despite the successful demonstration of ADC formation, low incorporation efficiencies demand a large excess of expensive CpHK, precluding widespread adoption.[5] This work aims to engineer translation components with improved incorporation of CpHK into proteins by directed evolution of pyrrolysyl-tRNA synthetases (PylRS) *via* ultra-high-throughput screening using fluorescence-activated cell sorting (FACS).[3,6,7] *Methanosarcina mazei* PylRS (*Mm*PylRS) was subjected to iterative rounds of directed evolution to achieve ~4.7-fold improvement, reaching a plateau of ~60% suppression efficiency at 2 mM CpHK. Subsequently, a second PylRS/$tRNA^{Pyl}$ pair (*1R26* PylRS) was chosen for engineering towards CpHK incorporation. A single round of directed evolution via error-prone PCR (epPCR) yielded a mutant capable of near-total stop-codon suppression at 2 mM CpHK, making it a promising candidate for further engineering.[8]

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# Redox Chemistry of *f*-block complexes with a Simple Diamide Ligand

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Oxidation state and electron transfer are fundamental chemical concepts, but lanthanides are limited to M(III) under most conditions. There are now molecular examples of all lanthanides (save Pm) as M(II) complexes in a range of different ligand frameworks. However, until recently, Ce(IV) was the only M(IV) lanthanide ion accessible in molecular complexes. La Pierre and Mazzanti have overturned this and delivered examples of Tb(IV),[1] Pr(IV),[2] and Pr(V)[3] using siloxide and imidophosphorane ligand systems (***Fig. 1A***). These works have also delivered actinide complexes across multiple oxidation states within conserved ligand frameworks.[4]

Zheng has shown that replacing monodentate Lewis basic groups on Tb(IV) and Pr(IV) complexes (***Fig. 1B***) with chelating groups increases the electrochemical accessibility of the M(IV) oxidation state.[5] Here we will discuss the use of a multidentate amide ligand towards stabilisation of M(IV) lanthanide complexes, and related actinide examples: their synthesis, structure, electrochemical properties, and electronic structure and bonding (***Fig. 1C***).

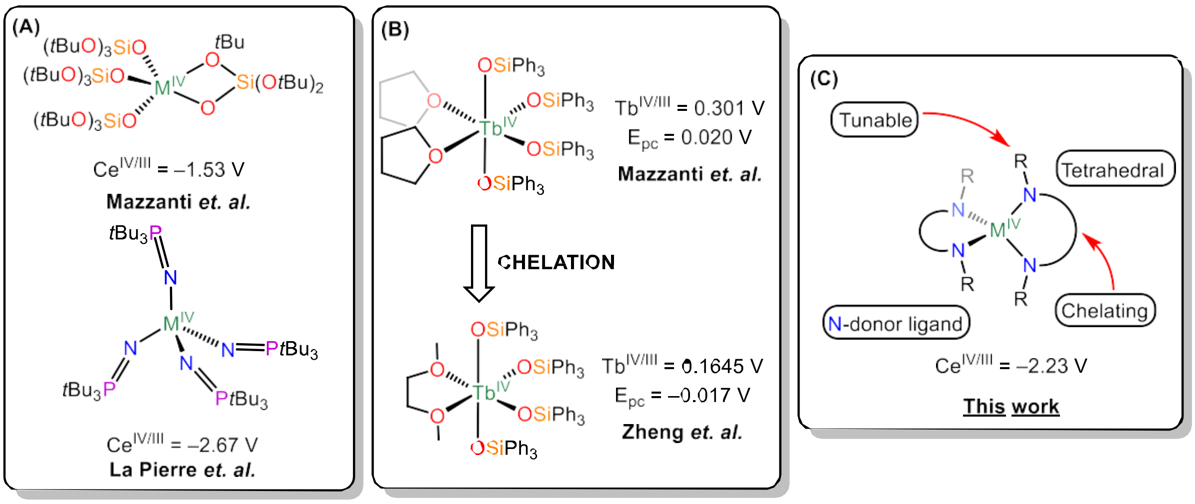


**Figure 1. (A)** Imidophosphorane and siloxide complexes of tetravalent lanthanides; **(B)** Improved stability of a Tb(IV) complex via chelation; **(C)** This work.

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# Biocatalytic Preparation of Sulfated Phenolic Compounds

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Sulfation is a key structural modification of biomolecules, such as polysaccharides, proteins and flavonoids, that enables changes to their bulk properties and potential functionality.[1,2] For example, the sulfation of biomolecules may increase their water solubility and biological activity, like immune adjuvant or anti-coagulant properties.[1,2] However, chemical sulfation presents challenges, including the need for an excess of harsh reagents, a lack of regioselectivity and challenging downstream purification.[2] Enzymatic sulfation can occur under milder, aqueous conditions and is selective, providing an attractive alternative.[3,4] Sulfotransferases catalyse the transfer of sulfate to amine and hydroxyl groups, and whilst eukaryotic sulfotransferases are more widely studied, bacterial aryl sulfotransferases are of interest due to their ability to use cheap, simple sulfate donors, such as para-nitrophenyl sulfate (*p*NPS) in place of 3'-phosphoadenosine 5'-phosphosulfate (PAPS).[5,6]

Herein aryl sulfotransferase A and B from *Desulfitobacterium hafniense* (*Dh*AST) were expressed and evaluated against a phenolic substrate library.[3,7] Promiscuity of the enzymes was demonstrated towards *para*-, *meta*- and *ortho*-substituted phenols, as well as polyhydroxylated substrates. Both *Dh*ASTs showed lower activity towards some non-phenolic substrates, including heterocyclic and aliphatic alcohols. Enzymatic sulfation on a 10 mg scale was successfully demonstrated on a phenolic model substrate.

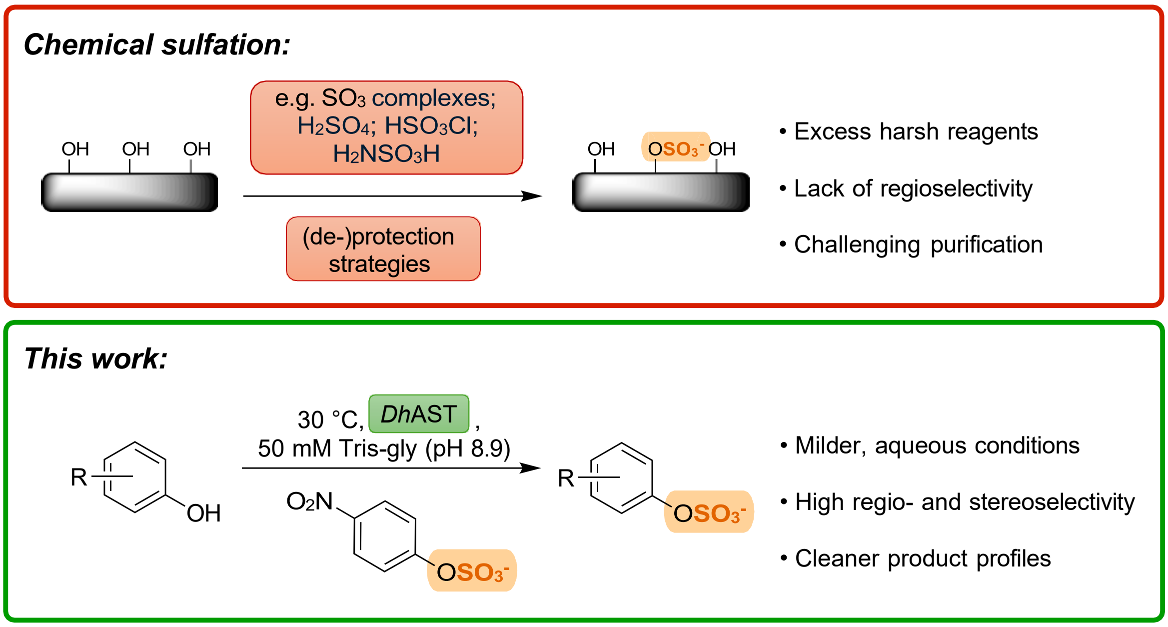


**Figure 1.** Enzymatic sulfation as an alternative to chemical sulfation.

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# Force-controlled capture and release of small molecules with covalent organic cages

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The mechanochemical release of small molecules holds significant potential for the advancement of many controlled release applications in medicine and materials science, e.g., drug delivery,[1] self-healing material,[2] etc. Various mechanophore (force-sensitive molecule) designs have been used for the release of small molecules.[3] Despite these advancements, the systems described are limited in the diversity and/or quantity of molecules they can release per stretching event because the cargo molecule must be covalently attached either to or as a part of the mechanophore. The ability to store and release cargo molecules not covalently bound to the polymer should enhance the diversity of cargo molecules and increase the efficiency of release. Here, we use mechanical force to actively deform the structure of a molecular cage to facilitate the capture and release of cargo molecule within its cavity.

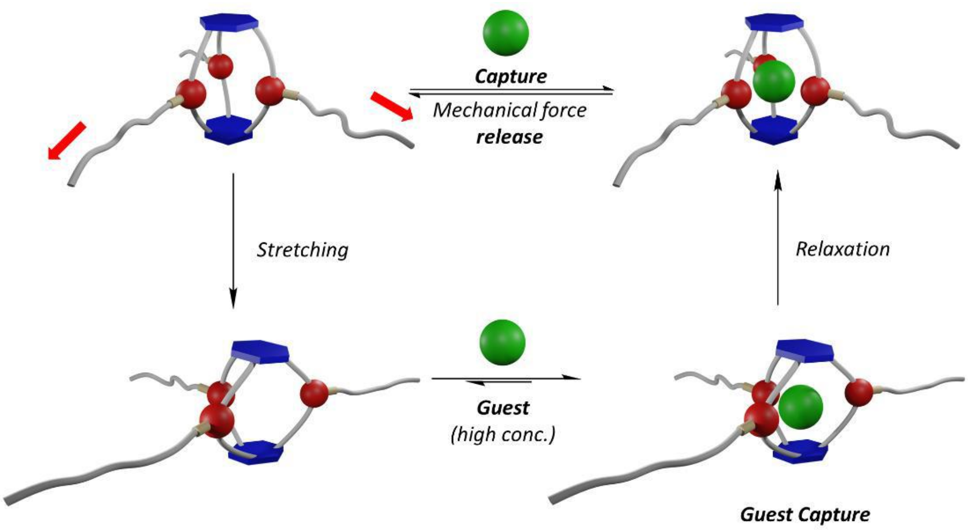


**Figure 1.** Capture and Release of cargo molecules using organic cage polymer

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# The influence of 5f/6d mixing on uranyl bonding and reactivity

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A detailed understanding of the electronic structure of uranyl is central to nuclear waste remediation.[1] In this work, we highlight the significance of U 5f/6d mixing in uranyl. A combined analysis U $L_3$-edge and $M_4$-edge resonant inelastic X-ray scattering (RIXS) is applied to spectroscopically identify the influence of 5f/6d mixing in a comparison of centrosymmetric $[PPh_4]_2[UO_2Cl_4]$ versus non-centrosymmetric $[PPh_4][UOCl_5]$, since 5f/6d mixing is parity-forbidden in the former yet permitted in the latter. U $L_3$-edge core-to-core-RIXS (C2C-RIXS) results provide evidence of dipolar enhancement to the 2p → 5f pre-edge. This enhancement arises in $[PPh_4][UOCl_5]$ due to mixing of U 6d into 5f, figures 1(a) and 1(b). U $M_4$-edge 3d4f RIXS measurements are applied to directly resolve the 5f ligand field splitting of both molecules, figures 1(c) and 1(d). The ligand field splitting reveals that the axially engaged π* and σ* orbitals of $[PPh_4]_2[UO_2Cl_4]$ sit at much higher energy than for $[PPh_4][UOCl_5]$. The influence of 5f/6d mixing on the relative energies of the antibonding orbitals is correlated with observed differences in the chemical reactivity of the two molecules.

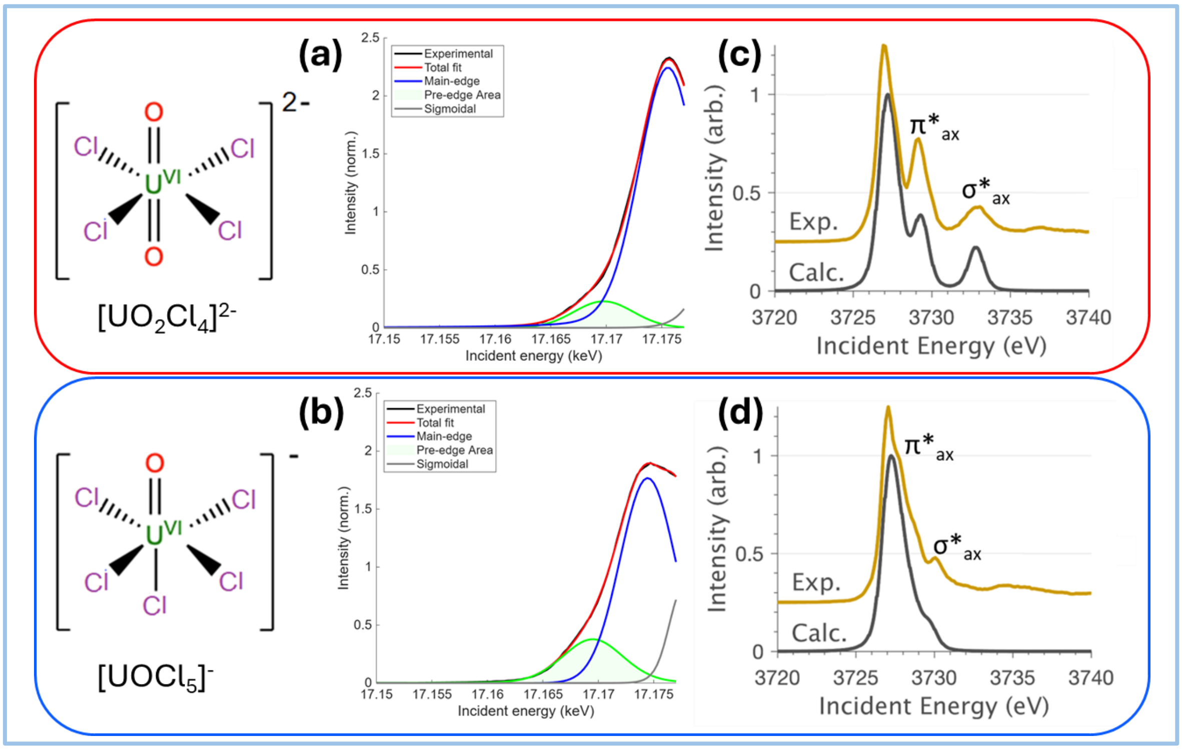


Fig. 1. (a) and (b) fits of the U L3-edge Core-to-Core Resonant Inelastic X-ray Scattering results for (a) [PPh4]2[UO2Cl4] and (b) [PPh4][UOCl5]. The enhanced area of the pre-edge region (green shaded region) of [PPh4][UOCl5] was computationally verified to result from dipole transition intensity into 5f states with mixed in 6d-character. (c) and (d) U M4-edge 3d4f RIXS results for (c) [PPh4]2[UO2Cl4] and (b) [PPh4][UOCl5]. The spectral feature that represents transition into the, respective, π* and σ* orbitals of [PPh4]2[UO2Cl4] and [PPh4][UOCl5] are highlighted in each spectrum.

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# High-throughput characterisation and engineering of nucleoside synthases for production of nucleoside analogues

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Nucleoside analogues represent a **powerful drug modality** for the treatment of a **wide range of diseases**, such as cancers and viral infections.[1] However, their chemical synthesis is often limited by poor stereoselectivity, extensive protecting-group chemistry, and lengthy synthetic routes which lead to low overall yields and poor step- and atom-economy.[2] **Enzymatic approaches** offer a solution[3], but these biocatalytic routes often require laborious optimisation such as time-consuming directed evolution campaigns.[4,5] This project aims to characterise and engineer nucleoside synthases, to produce nucleoside analogues, using a powerful emerging technique, High-Throughput Microfluidic Enzyme Kinetics (HT-MEK, **Fig.1.A**). HT-MEK uses state-of-the-art microfluidic “chips” to express, purify and quantitatively measure up to 1,500 enzyme variants per chip. HT-MEK provides the same high-fidelity turnover data as traditional enzyme engineering methodologies, key biochemical constants ($k_{cat}$ and $K_M$), with massively increased throughput.

Initial work focused on establishing HT-MEK at the University of Manchester, making it the only UK institution with this technology, and adapting it for nucleoside synthase engineering workflows. To that end, phosphate-sensing fluorescent assays were developed to quantify enzyme activity, which we are currently using to investigate reversible *N*-glycosidic bond formation by **nucleoside phosphorylases** (**Fig.1.B**). These advances provide the foundation for high-throughput mapping of nucleoside synthase specificity, sequence–function relationships, and variant performance. By integrating quantitative kinetics with enzyme engineering, this platform will support directed evolution of enzymes for efficient, scalable synthesis of non-natural nucleoside products with potential value in therapeutic discovery and sustainable chemistry.

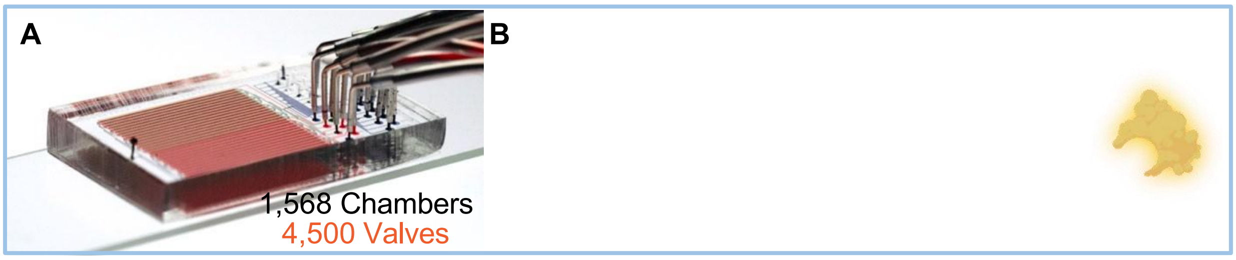


**Fig. 1. (B)** Image of HT-MEK microfluidic device **(B)** Enzymatic reaction of a purine nucleoside phosphorylase, and detection of orthophosphate by a fluorescent phosphate binding protein (PBP*) reporter.

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