Dublin Chemistry Graduate Programme

Lilly Answers That Matter.

Third Year PhD Talks 2023

31st May 2023

O'BRIEN CENTRE FOR SCIENCE HUB

University College Dublin

School of Chemistry, TCD
School of Chemistry, UCD

About the Dublin Chemistry Graduate Programme

Dublin Chemistry is a joint initiative between the Schools of Chemistry in UCD and TCD. It aims to develop new dimensions in graduate education in Chemistry that will act to support and enhance the postgraduate research experience. All students entering either of the two Schools will be members of Dublin Chemistry.

Dublin Chemistry staff members are active in both applied and basic research, attracting an annual research income in excess of €10 Million with over 100 publications per year in international journals. There is strong activity in the traditional areas of Inorganic, Organic and Physical Chemistry which act to underpin multidisciplinary initiatives that are increasingly characteristic of our cutting edge research. We have a special focus on:

- **Synthesis and Chemical Biology**
- **Functional Materials and Nanotechnology**
- **Computational Modelling**

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Eli Lilly - Dublin Chemistry

Third Year PhD Talks Programme 2023

(each talk is strictly 20 minutes, including questions)

UCD O'Brien Centre for Science Hub, Wednesday May 31st 2023

8.50-9.00 Welcome: Professor Declan Gilheany / Professor James Sullivan

Talks	**Icon Theatre**	**Intel Theatre**	**Lynch Theatre**
	Room H1.13 (Theatre D)	**Room H1.26 (Theatre E)**	**Room H1.37 (Theatre F)**
	Sessions A1 – A3	**Sessions B1 – B3**	**Sessions C1 – C3**
9.05 - 10.30	**Sustainable Chemistry 1**	**New Analytical Chemistry**	**Stereoselective Synthesis**
	Eva Naughton	Ioanna Bampouri	Fionn McNeill
	Annie Regan	Zhan Ban	Rachel O'Sullivan
	Kavin Arunasalam	Emer Farrell	Aoibheann O'Connor
	Cansu Ilhan	Pallavi Dutta	Kate Donaghy
		Tea/Coffee	
11.00 - 12.45	**Sustainable Chemistry 2**	**New Physical Chemistry**	**Peptide Chemistry**
	Christian Schröder	Wanting Zhang	Valerio Cataldi
	Anna Ciotti	Fiona Moclair	Mark Nolan
	Peter McDermott	Justynne Joy Fabian	Glenna Swinand
	Rosa Fernández-Pisón	Annaël Sort-Montenegro	Alby Benny
		Tigran Simonian	
		Lunch (Campus Outlets)	
1.45 - 3.15	**DNA Sensing**	**New Heterocyclic Synthesis**	**Medical Applications**
	Shekemi Denuga	Adam O'Connell	Connor O'Leary
	Donal Whelan	Kathryn Yeow	Laura Ramirez Lázaro
	Maria Byrne	Arlene Bonner	Mairéad Gallagher
	Clare Zehe	Robert Redmond	Iñigo Iribarren
		Intermission	

4.00 **Awarding of Prizes: Dr. Michael Carroll (Eli Lilly), Icon Theatre (Room H1.13, Theatre D)**

4.15 **Wheeler Lecture: Professor Paul Anastas (Yale University), Icon Theatre (Room H1.13, Theatre D)**

Followed by Reception on First Floor Concourse, O'Brien Centre for Science East

Speaker		Supervisor	Abstract Title
SESSION A1: Sustainable Chemistry 1			Chairs: Leila Negahdar and Joseph Byrne
Naughton, Eva	UCD	James Sullivan	Development of Materials for Sustainable Artificial Photosynthesis
Regan, Annie	TCD	Peter Dunne	Sustainability *and* Quality: Hydrothermal Synthesis of Magnetic Nanomaterials for Medicine
Arunasalam, Kavin	TCD	Valeria Nicolosi	Low Dimensional Composite Materials as Binder-Free Anode for Energy Storage Applications
Ilhan, Cansu	TCD	Mick Morris	Novel Transition Metal Dichalcogenides for Photochemical Hydrogen Fuel
SESSION A2: Sustainable Chemistry 2			Chairs: Vitaly Buckin and Tom Hooper
Schröder, Christian	TCD	Paula Colavita	Carbon Electrode Materials for Electrocatalytic Hydrogenation of Biomass Derived Chemicals
Ciotti, Anna	TCD	Max García Melchor	Accelerating Electrochemical Organic Reductions by Tuning the Cathode H Surface Coverage
McDermott, Peter	UCD	Eoghan McGarrigle	Organocatalysed Conjugate Additions to α,β-Unsaturated Phosphonates
Fernández-Pisón, Rosa	UCD	Andrew Phillips	Highly Stable α,α-Diimine Silver(I) Catalysts that Incorporate CO_2 into Alkyne Frameworks
SESSION A3: DNA Sensing			Chairs: Kenneth Dawson and Michael Morris
Denuga, Shekemi	UCD	Robert Johnson	A Nanopore Sensor for the Detection of SARS-CoV-2
Whelan, Donal	UCD	Robert Johnson	Development of a DNA Based Biosensor for the Detection of Foodborne Illness
Byrne, Maria	UCD	Susan Quinn	Multi-Emissive Silica Nanomaterials for DNA Sensing
Zehe, Clara	UCD	Susan Quinn / Gareth Redmond	Advanced Spectroscopy of Carbon Based Nanoparticles

Speaker		Supervisor	Abstract Title
SESSION B1: New Analytical Chemistry			Chairs: Declan Gilheany and Max Garcia Melchor
Bampouri, Ioanna	UCD	Vitaly Buckin	Application of Ultrasonic Shear Wave Spectroscopy for the Assessment of Surface Hydrophobicity and Drying Dynamics of Aqueous Droplets
Ban, Zhan	UCD	Kenneth Dawson	Identification and Characterization of RNA Granule Proteome with Machine Learning
Farrell, Emer	UCD	Robert Johnson	Ion-Current Rectifying Nanopores in Aprotic Solvent: from Fundamentals to Applications
Dutta, Pallavi	UCD	Robert Johnson	Development of a Solid-State Sensor towards Pesticide Detection Utilizing Ion Current Rectification in Functionalized Conical Nanopipettes
SESSION B2: New Physical Chemistry			Chairs: Declan Gilheany and Kirill Nikitin
Zhang, Wanting	UCD	Kenneth Dawson	Capturing the Protein Release and Further Trafficking of Nanoparticle-Protein Complex in Cellular System
Moclair, Fiona	UCD	Kenneth Dawson	The Detection & EHS Risk Determination of Nanomaterials in the Semiconductor Industry
Fabian, Justynne Joy	TUD	Brendan Duffy / Susan Warren	Surface Modifications of Titanium Alloys for Biomedical Applications
Sort--Montenegro, Annaël	TCD	Larisa Florea	Movement Generation under the Application of an Electric Field: Electrotaxis and Electro-Actuation
Simonian, Tigran	TCD	Valeria Nicolosi	Structural Characterization of $BaZrS_{(3-y)}Se_y$ Perovskite Thin Films via Scanning Transmission Electron Microscopy
SESSION B3: New Heterocyclic Synthesis			Chairs: Patrick Guiry and Vivek Sundaravel
O'Connell, Adam	UCD	Elaine O'Reilly	Development of Transaminase-Triggered Cascades for the Synthesis of Nitrogen-Containing Natural Products and Analogues
Yeow, Kathryn	UCD	Elaine O'Reilly	Biocatalytic Cascade Synthesis of Iminosugars from Monosaccharides
Bonner, Arlene	UCD	Marcus Baumann	Transferring the Baldwin Rearrangement Process to Continuous Flow
Redmond, Robert	UCD	Paul Evans	Double-Reduction of Cyclic Sulfonamides: a Novel Approach towards the Total Synthesis of (+)-Aphanorphine

Speaker		Supervisor	Abstract Title
SESSION C1: Stereoselective Synthesis			Chairs: Stephen Connon and Marcus Baumann
Mc Neill, Fionn	UCD	Pat Guiry	Enantioselective Synthesis of Sterically Hindered α-Allyl-α-Aryl O-Heterocycles via Decarboxylative Asymmetric Allylic Alkylation
O'Sullivan, Rachel	UCD	Pat Guiry	The Development of Novel Ferrocenyl Ligands via Acid-Mediated Transformations
O'Connor, Aoibheann	UCD	Pat Guiry	A New Paradigm for the Asymmetric Diels-Alder Reaction
Donaghy, Kate	UCD	Eoghan McGarrigle	Stereoselective Synthesis of α-Galactosides
SESSION C2: Peptide Chemistry			Chairs: Stephen Connon and Fintan Kelleher
Cataldi, Valerio	TCD	Joanna McGouran	Activity Based Probes to Unravel New Insights into P53 Deubiquitination
Nolan, Mark	TCD	Eoin Scanlan	Clicking to Sulfur: a Radical Approach for Peptide and Protein Modification
Swinand, Glenna	TCD	Eoin Scanlan	Synthesis of Fluorescent Lipopeptides as Activity Probes for Bacterial Lipoprotein Processing Enzymes
Benny, Alby	TCD	Eoin Scanlan	Thioaspartic Acid Mediated Methods for Peptide Ligation and Macrocyclisation
SESSION C3: Medical Applications			Chairs: Declan Gilheany and Aniello Palma
O'Leary, Connor	TCD	Joanna McGouran	Tumour Responsive Systems for Targeted Drug Delivery
Ramirez Lázaro, Laura	TCD	Eoin Scanlan / Thorfiunnur Gunnlaugsson	Naphthalimide Conjugates for Improved, Targeted Cancer Cell
Gallagher, Mairéad	TUD	Fintan Kelleher / Gordon Cooke	Synthesis of the Human Metabolites of Common Antibiotics and Assessment of their Role in Antimicrobial Resistance Development
Iribarren, Iñigo	TCD	Stephen Connon / Cristina Trujillo	Theoretical development of new class of phase transfer catalysts: applications in the pharmaceutical industry

DEVELOPMENT OF MATERIALS FOR SUSTAINABLE ARTIFICIAL PHOTOSYNTHESIS

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Since the industrial revolution atmospheric CO_2 levels have been increasing leading to global warming. One method to tackle this is the artificial photosynthesis (AP) reaction. Reacting CO_2 with H_2O to form CO or hydrocarbons using a sustainable energy source has become hugely desirable. This method harnesses abundant, cheap, and pollution-free solar energy to drive CO_2 conversion processes.

This project focuses on developing materials to promote the AP reaction. Work so far has focused on two areas of photocatalysis: z-scheme systems and plasmonic systems. "Z-scheme" is the term used to explain the observed efficient electron/hole separation mechanism obtained using two co-located semiconductors[1]. These systems consist of a CO_2 reduction photocatalyst coupled with a H_2O oxidation photocatalyst (SC II and SC I in Fig. 1, respectively). This system leads to retention of strong redox abilities in both semiconductors and spatial separation of charge carriers[2]. Z-scheme systems studied are $BiVO_4/Cu_2O$ and Ag_3PO_4/Cu_2O.

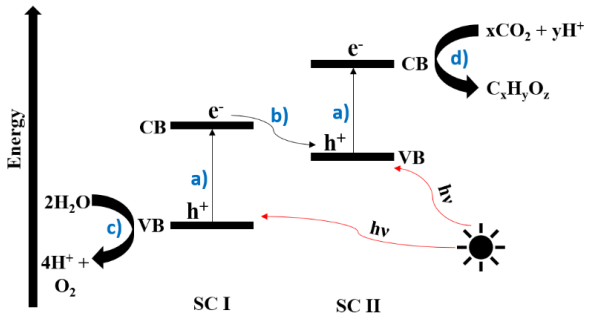

Fig. 1: schematic representation of the AP reaction mechanism using z-scheme photocatalysis where a) is photon absorption, b) is neutralisation and charge carrier separation, c) is H_2O oxidation, d) is CO_2 reduction.

Plasmonic nanostructures can act as co-catalysts with semiconductors, speeding up the transfer of excited electrons to acceptor molecules (either directly transferring "hot electrons" from decayed plasmon resonances to an acceptor, or first injecting the electron into the CB of the SC) and suppressing charge recombination, thereby increasing catalytic efficiency[3]. The plasmonic systems studied in this work are RuO_2 combined with GaP or Fe_2O_3.

References:

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Dublin Chemistry Graduate Seminars 2022/23

SUSTAINABILITY *AND* QUALITY: HYDROTHERMAL SYNTHESIS OF MAGNETIC NANOMATERIALS FOR MEDICINE

Annie Regan,[1,2] Nguyen T. K. Thanh[3] and Peter W. Dunne[1]

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Magnetic nanomaterials such as the spinel-type oxides, MFe_2O_4 (M = Fe^{2+}, Co^{2+}, Ni^{2+}, Zn^{2+}) have emerged as key materials in nanomedicine, with highly tuneable properties, accessed by varying composition or surface modification with functional ligands.[1] Their biomedical applications, such as magnetic hyperthermia; an adjuvant to cancer therapies, require the nanoparticles to be water-dispersible, biocompatible, and possess sufficiently high magnetic saturation.[2] As such, control of these properties is essential in the synthesis of these materials. While there are many examples in the literature of ways to obtain iron oxide nanoparticles, there is a happy medium between synthetic control and sustainability that has not yet been realised by any one technique in particular. The present work aims to provide a comprehensive comparison of some of the most commonly employed synthetic techniques for producing nanoparticles for this application; assessing each method in terms of both synthetic control of material properties as well as compliancy to green chemistry principles. In doing so, this talk will introduce the promising capabilities of a new technique – a novel, custom-built hydrothermal injection reactor – designed to combine the green sensibilities of traditional hydrothermal synthesis with the synthetic control of the popular hot injection and thermolysis methods. A variety of spinel ferrites have been targeted by each of these synthetic techniques, each characterised by powder X-ray diffraction, electron microscopy, and magnetometry, before narrowing in on cobalt ferrite ($CoFe_2O_4$) – a hard ferromagnet which offers high chemical stability and good saturation magnetisation. It has been found that hydrothermal injection synthesis allows the formation of $CoFe_2O_4$ nanoparticles with size, monodispersity, surface capping, and magnetic properties comparable to those obtained by conventional thermolysis, but with the added green credentials of hydrothermal processing. Overall, this talk aims to showcase a new sustainable route to magnetic nanoparticles with suitable properties for use in medicine; bringing green chemistry to a rapidly expanding field.

References:

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SFI Centre for Doctoral Training in Advanced Characterisation of Materials

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Dublin Chemistry Graduate Seminars 2022/23

Low Dimensional composite materials as binder-free anode for energy storage applications

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The prolonged use of non-renewable energy such as fossil fuel and coal is having a deteriorating impact on our environment leading to severe climate changes. Hence, there is a dire need to explore new methods for energy generation and storage which are environmentally friendly, cost effective and sustainable. Sodium-ion batteries have been attracting great interest as an alternative to lithium-ion batteries due to their material abundancy, lower cost, and sustainability. However, a high-performance viable anode for the sodium-ion battery has yet to be discovered because of the difference in its molecular size and intercalation mechanism to the comparatively smaller lithium ions.

This problem has attracted the attention of researchers around the globe and developing suitable anodes has become a viable field in different areas of material science, including in 2D materials research. 2D materials are known for their unique structure and electronic properties such as hardness, tuneable band gap by variation of the number of layers and their high surface area. These properties make them intriguing candidates for applications in batteries and electrocatalysis. Black phosphorus, a well-studied material of the 2D class materials, has previously been reported to show very high theoretical capacity for both sodium and lithium-ion battery systems, but suffers from low cycling stability due to chemical and structural instability.[1] To overcome this problem, we decided to explore the prospect of a new 2D composite material made from nanosheets of black phosphorus (phosphorene) and $Ti_3C_2T_x$ MXene to be potentially used as an anode in a sodium-ion battery. The $Ti_3C_2T_x$ MXene layers with terminating fluorine and oxygen functionals are expected to promote the growth of stable solid-electrolyte interfaces (SEI) which in turn is expected to further improve the overall coulombic efficiency of the battery.[2][3]

Both nanomaterials were synthesized via liquid-phase exfoliation (LPE). Phosphorene is notorious for being oxidized easily. Hence, to protect the phosphorene, a novel layer-by-layer (LBL) vacuum filtration technique was implemented to obtain the electrode as shown in Figure 1. The resulting electrodes were then assembled in a coin cell to study their cycling stability and rate capacity. It was found that the electrode material showed a high discharge capacity of 700 mAh/g at 0.2 C with 98% coulombic efficiency for 100 cycles. XPS, SEM, EDX, UV-Vis, XRD and AFM characterization were performed on the composite nanomaterial to study its morphology, as well as compositional and structural changes upon processing.

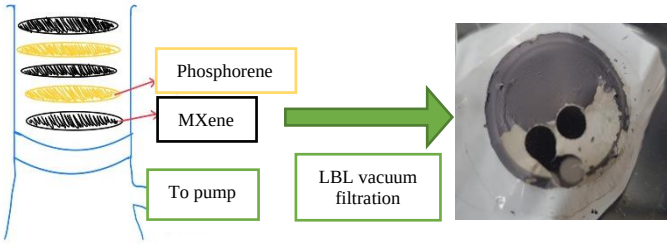

Figure 1: Illustration of the novel layer-by-layer (LBL) vacuum filtration. This was done to protect the phosphorene from oxidation and to produce a heterostructure in the electrode material for enhanced performance.

References

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Carbon Electrode Materials for Electrocatalytic Hydrogenation of biomass derived chemicals

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Biooil, derived from biomass, has the potential to become a renewable carbon feedstock of chemicals and fuels.[1] As biooil contains many oxygenated compounds, there is a need to upgrade those compounds to improve its energy density. One of the reactions that can enable this is hydrogenation, which is often done through thermal catalytic conversion, requiring pure hydrogen and high pressure and temperature. An alternative to hydrothermal processes is electrocatalytic hydrogenation (ECH), which works under mild conditions and can be powered by renewable energy. The required hydrogen in ECH is produced in-situ at the electrode.[2] For this reason, catalyst materials, which are good for hydrogen evolution reaction, could be candidates for the ECH. Platinum and Pt group metals show good activity in the ECH,[3] but due to their high cost, their scarcity and their susceptibility to poisoning are not viable for a scale-up of the ECH. For this reason, the development of new, low cost electrocatalyst materials is in the focus of research.

This presentation focuses on the design of advanced carbon based heterostructured materials for the ECH. Carbon based materials offer a variety of benefits for electrocatalytic applications: carbon is widely available, environmentally benign and can be chemically modified for different electrocatalytic reactions. This has been reported for the electrocatalytic oxygen reduction reaction[4] and the hydrogen evolution reaction.[5] In this work we investigate the activity of nitrogenated carbon based materials towards the ECH of organic compounds.

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Accelerating electrochemical organic reductions by tuning the cathode H surface coverage

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In the context of the current climate crisis, power-to-X technologies are emerging as a greener alternative to organocatalytic reductions for the synthesis of platform chemicals.[1] In fact, they replace organometallic catalysts and organic solvents with electricity and water, or mixtures of water and alcohols, and circumvent substrate functionalization by tuning the reaction potential.[2] Although the usage of aqueous electrolytes is hampered by the competition with the hydrogen evolution reaction (HER), this can be hindered under alkaline conditions.[3]

In this talk, I will present the electrochemical hydrogenation (ECH) of acetophenone (AC) to 1-phenylethanol (*Fig. a*), carried out at alkaline pH to inhibit HER. Under these conditions, AC does not efficiently source H from H_2O,[4] and therefore, we hypothesized that the ideal ECH catalyst should hydrolyse H_2O itself, while adsorbing the generated protons neither too weakly nor too strongly, so that they can be sourced for the ECH of AC. To verify our hypothesis, we modelled transition metals characterized by different ΔG_{*H} and H coverages (*i.e.* Ag, Au, Cu, Ni, Pt, and In). We found that both experimentally and computationally the highest product yields were observed for Ag, Au and Cu, which are capable of hydrolysing H_2O without retaining H too strongly (*Fig. b*). Conversely, poor yields were obtained for highly endo- or exergonic values of ΔG_{*H} (*Fig. c*), thus confirming our predictions. Further theoretical investigations highlighted the important role of explicit H_2O molecules in shuttling the H atoms from the surface coverage to AC.

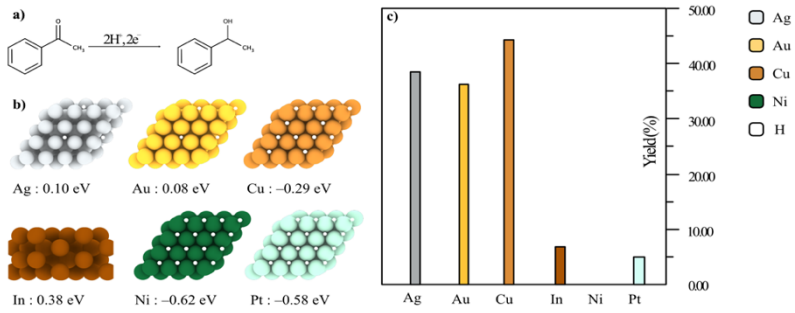

Figure. a) ECH of AC to 1-phenylethanol. b) Top views of the H surface coverages predicted under ECH conditions. c) Experimental ECH yields

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ORGANOCATALYSED CONJUGATE ADDITIONS TO α,β-UNSATURATED PHOSPHONATES

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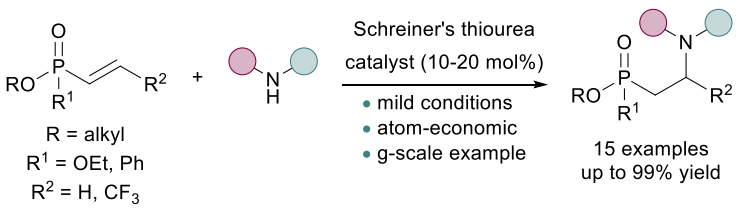
Conjugate additions are an atom-economical strategy for the synthesis of carbon-carbon and carbon-heteroatom bonds. Thiourea catalysts have been successfully used to catalyse the addition of a wide range of nucleophiles to α,β-unsaturated carbonyl,[1,2] nitro,[3] and sulfonyl[4] compounds *via* hydrogen bonding catalysis. Phosphonates are stronger hydrogen bond acceptors than similar carbonyl compounds.[5] Despite this, thiourea-catalysed conjugate additions to unactivated α,β-unsaturated phosphonates have not been reported until now.

Here, we report a thiourea-catalysed conjugate addition of amines to α,β-unsaturated phosphonates and phosphinates.[6] The organocatalytic methodology was used to synthesise 15 β-aminophosphonates and -phosphinates in yields up to 99%. A gram-scale example gave the corresponding β-aminophosphonate in an isolated yield of 99% with 97% catalyst recovery. Additions to pro-chiral substrates and kinetic resolutions of racemic vinylphosphinates were also attempted. However, only low levels of selectivity were achieved. Based on mechanistic experiments, hydrogen bonding between the phosphoryl oxygen and thiourea is proposed to play a crucial role in substrate activation.



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Dublin Chemistry Graduate Seminars 2022/23

HIGHLY STABLE α,α-DIIMINE SILVER(I) CATALYSTS THAT INCORPORATE CO_2 INTO ALKYNES FRAMEWORKS

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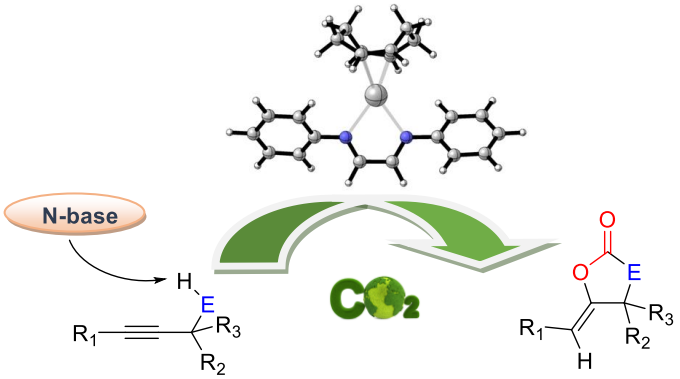
Carbon dioxide is a potentially valuable and highly accessible C1 feedstock. However, the application of this ubiquitous gas in industrial processes is comparably limited due to thermodynamic restraints and general inertness towards C-activation. This work addresses the development of novel room temperature stable cationic silver(I) complexes supported by N,N'-chelating α,α-diimines, that demonstrate high alkynophilicity. These complexes are highly efficient in incorporating CO_2 into organic alkynes frameworks,[1,2] affording cyclic carbonates and carbamates under mild conditions. The unusual high stability of these silver(I) pre-catalysts was accomplished by employing a η^2:η^2-chelating cis-cyclo-octadiene which was predicted through DFT calculations. The ability of these novel α,α-diimines silver(I) complexes to catalyse the incorporation of CO_2 into a propargylic alcohols/amines and the subsequent cyclisation was evaluated using a variety of terminal and internal alkynes substrates was evaluated in the presence of different non-nucleophilic nitrogen bases. All reactions were performed at 25 ºC under 1 to 6 bars of CO_2 pressure affording the corresponding α-alkylidene cyclic products, which are employed as precursors for drugs and polymers. This family of catalysts shows high conversion at atmospheric CO_2 pressure, using 1-5 mol% catalyst loading. The reaction pathway proved was fully modelled with DFT/solvent corrections, showing the deprotonation of the propargyl alcohols or amines as the rate limiting step.



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A NANOPORE SENSOR FOR THE DETECTION OF SARS-COV 2 BASED ON ION CURRENT RECTIFICATION.

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Covid-19 is an infectious disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] SARS-CoV-2 has four major structural proteins, with its spike protein known to bind to the surface of host cells via the S1 subunit.[2] Electrochemical biosensors have emerged as an attractive platform for the rapid, sensitive, and cost-effective detection of infectious diseases with low-complexity instrumentation.[3] [4] [5] Herein, a novel biosensor based on ion current rectification (ICR), capable of detecting the spike protein expressed on the surface of SARS-CoV-2 is presented. ICR, a phenomenon observed in geometrically asymmetric nanopores, has been used as the basis of the developed sensor technology.[6]

110 nm conical nanopipettes were fabricated, and the surface of these nanopipettes functionalised with a DNA aptamer sequence capable of selectively binding the S1 subunit of the SARS-CoV-2 spike protein. As quartz nanopores exhibit a sensitive response to the surface charge variation, each step of the surface modification process and the detection of SARS-CoV-2 could be monitored using cyclic voltammetry. The presented results provide the foundations for the development of a universal biosensor sensing strategy, where ion-current rectification holds great potential as a sensitive, selective, cost-effective, and versatile biosensor for detecting infectious diseases in their initial stages.

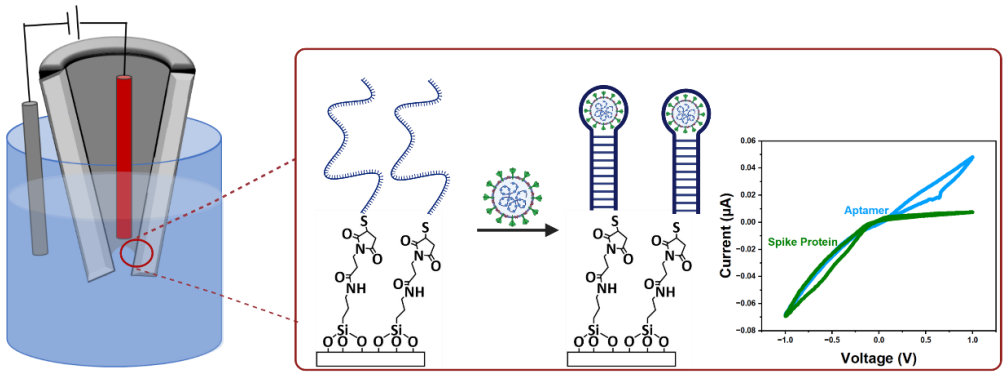

Figure 1: Schematic of an aptamer functionalised nanopipette surface, and a representative voltammogram of the successful detection exploiting an aptamer conformational change and the surface charge dependence of ICR.

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Development of a DNA Based Biosensor for the Detection of Foodborne Illness

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This report addresses the development of a novel electrochemical biosensor for food-borne pathogen detection through the development of a surface modification strategy for a boron-doped diamond electrode. A thiolated ssDNA probe strand, designed to capture the target of interest, was covalently attached to a diamond electrode surface through a 4-[(N-Boc)aminobenzene] diazonium linker before it was hybridized with a complementary target ssDNA strand. Using a redox active target strand, this attachment can be detected using cyclic voltammetry. The stability of the surface bound DNA was explored to demonstrate the commercial viability of the developed sensor. The operational stability was examined using chronoamperometry and DNA bound to boron-doped diamond electrodes were found to resist reductive desorption, compared to typically used thiol-modified gold electrodes where the same DNA probe strand reductively desorbs. Peak currents were also recorded in complex biological media. In BSA solution, diamond biosensors saw reduced but present peaks, while typical gold systems of the type reported in the literature had little to no operability. Other carbon materials such as glassy carbon and graphene foam were also explored to determine their viability as a sensor substrate.

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Multi-Emissive Silica Nanomaterials for DNA Sensing

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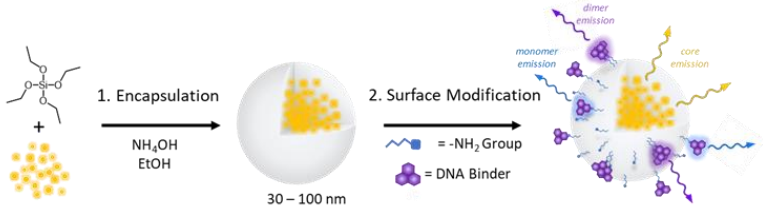
Nanomaterial properties including variable size, shape, surface functionality and solubility make them attractive for biological applications, with functions from drug delivery to biosensing to cellular imaging and more. Silica (SiO_2) nanoparticles present an ideal candidate for such applications due to their facile, size-controlled synthesis, ease of surface functionality, dispersibility in aqueous solution and their bioavailability[1,2]. DNA is a highly important diagnostic and therapeutic target, to which silica nanomaterials can be specifically tailored, due to their known affinity for DNA[3]. Silica nanomaterials smaller than 100 nm are optimally scaled for controlling parameters such as cellular interactions and biocompatibility[4].

In this work, the encapsulation of luminescent materials into Stöber type[5] SiO_2 NPs of 30 – 100 nm diameter, conveys emissive properties to the nanoparticles, establishing trackable nanomaterials with potential sensing applications. Functionalisation of the SiO_2 NPs surface chemistry allows control of their cellular uptake and toxicity and creates anchor groups for further reactions. The addition of luminescent DNA probes to the surface of emissive SiO_2 NPs produces multi emitting, DNA binding systems with the capacity for multiple sensing events and trackability in cells. Alternating the luminescent core dye used and controlling the extent of surface coverage with emissive groups also creates variable sources of emission within the SiO_2 NPs. These SiO_2 NPs can also act as delivery systems through selective uptake and release of internalised materials. The dissolution of these luminescent SiO_2 NPs has been studied under simulated biological conditions. This nanoparticle system could greatly enhance the pharmaceutical efficacy of drugs, the sensitivity of biosensors and the success of biomedical therapies.



Scheme 1. Synthesis and modification to produce dual emissive, DNA binding silica nanomaterials

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Advanced spectroscopy of carbon based nanoparticles

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Carbon nanoparticles (NPs) have emerged as an exciting group of materials with many applications in chemical sensing, biomedicine and bioimaging due to their bright luminescence, tuneable properties, biocompatibility and cost-efficient formation.[1] This work highlights the application of advanced spectroscopic methods to study the properties and interactions of carbon nanoparticles.

Firstly, the internal nanoenvironment, diffusion dynamics and energy transfer (ET) in CP NPs doped with varying concentrations of two squaraine (SQ) dyes were resolved using steady-state, time-resolved and polarised spectroscopy. The particles were prepared via a reprecipitation method. Sensitivity of the SQs to local polarity through sovatochromic shifts and their response in time resolved anisotropy made them promising candidates as molecular microenvironment probes. Secondly, the physical and photophysical properties of green and red luminescent CDs with sizes around 3 nm were studied. CDs were prepared solvothermally from organic precursors.[3,4] As the luminescence mechanism of many CDs is still subject to debate,[2] ultrafast spectroscopy was conducted to resolve the energetics processes underlying their optical response. Interaction with DNA yielded luminescent quenching and spectroscopic shifts with selectivity towards guanine content and topology of the DNA system. Studying interactions of CDs with DNA is an emerging field with only few reports to date. The findings from these studies will be useful to enable applications in drug delivery, targeted therapy, chemical sensing and bioimaging.

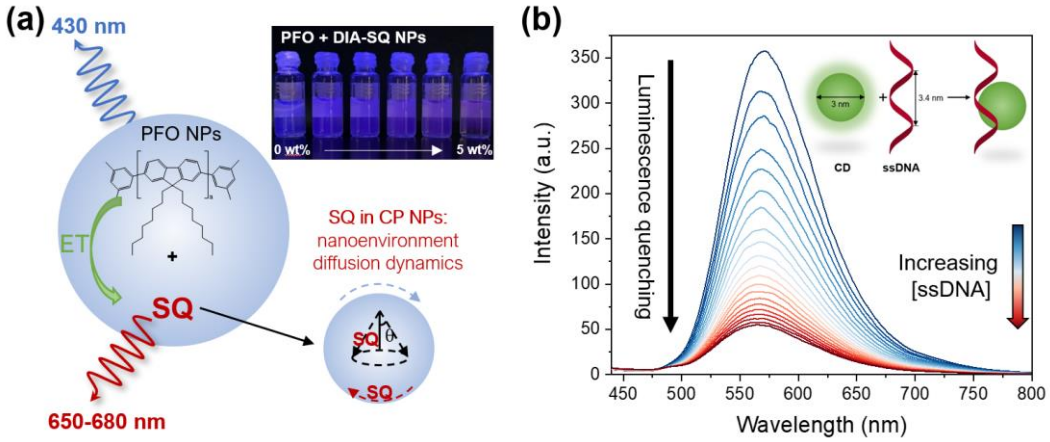

Figure 1 (a) *Schematic representation of the composite particle system and studied dynamics and image of NP suspensions with 0-5 wt% SQ dopant under UV irradiation showing gradual colour change due to ET.* ***(b)*** *increasing luminescence quenching with addition of ssDNA showing schematic interaction between DNA and oPD CDs.*

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APPLICATION OF ULTRASONIC SHEAR WAVE SPECTROSCOPY FOR THE ASSESSMENT OF SURFACE HYDROPHOBICITY AND DRYING DYNAMICS OF AQUEOUS DROPLETS

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Wettability and droplet evaporation play an important role in nature, daily life, and many technological applications, manufacturing engineering, chemical and medical products. Understanding the interaction and wetting dynamic of droplets with various surfaces, and the complex mechanisms of drying processes is essential [1, 2]. Moreover, the formation of drying defects and watermarks (WM), after the wet cleaning procedures in the semiconductor industry, has been identified as a serious problem [3]. Quantifying these phenomena and correlating surface properties (i.e., roughness) and drying defects will provide in-depth information on the quality of the materials and cleaning liquids.

The current project suggests the application of shear wave ultrasonic spectroscopy for studies of aqueous droplet shape and dynamics of drying on surfaces with different hydrophobicity. We probe the 'bottom' part of the droplet, which is in contact with the surface studied. A generated shear wave propagates through the material into the liquid and attenuates in a very thin layer of liquid that resides on top of the surface, thus providing information on the surface area and the properties of the system (surface and thin layer of liquid attached). The effective thickness of the probed liquid layer can be changed from the micron to nanometer range by changing the frequency of the wave. This allows for quantitative assessment of surface hydrophobicity and real-time characterization of different amounts of liquid positioned on the surface during the drying process, distinguishing the pinned and unpinned modes of evaporation (see Fig. 1). Further analysis provided knowledge on the contact angle, during different times of evaporation, showing interesting results at the last moments of drying.

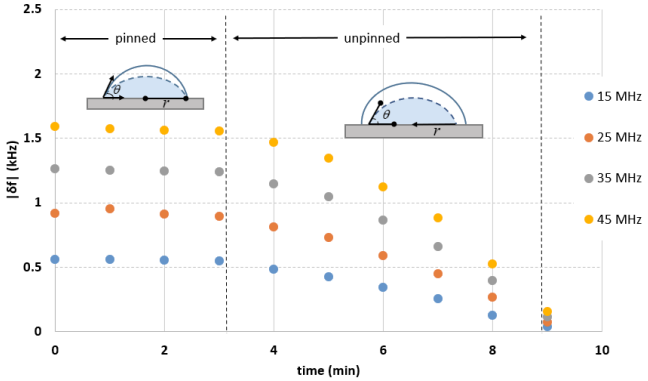

Fig. 1 Experimental results of the frequency shift (δf) of ultrasonic sensor, covered by Ti film, during evaporation of a 2 μL water droplet, measured in various frequencies as a function of time at room temperature. Two modes of evaporation (pinned and unpinned) can be well distinguished.

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Identification and Characterization of RNA Granule Proteome with Machine Learning

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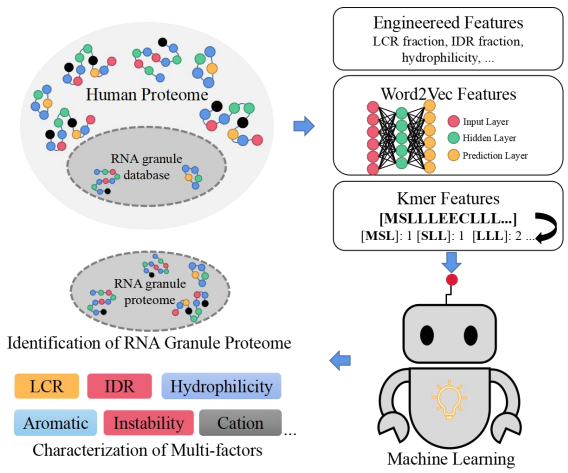
RNA granules are functional compartments within cells that play a crucial role in regulating gene expression at the posttranscriptional level [1]. Despite significant progress made in the past few decades, there remain many unanswered questions regarding RNA granules, including the identification of the granule proteome [2] and the exploration of the biomolecular patterns involved in their formation, particularly with regard to rare negative samples. To address these issues, we constructed robust machine learning models with embedded protein features determining their phase behavior by integrating weak parallel models with limited local datasets. The models accurately and robustly predicted potential RNA granule proteins (stress granule and P-body) with AUCs up to 0.8 (95% CI: 0.77, 0.83) within human proteome. Furthermore, in the highly challenging scenario of completely lacking negative samples, our analysis offers more specific and reliable identification of the RNA granule proteome, utilizing limited high-confidence tier 1 samples, compared to previous models that solely concentrated on phase behaviors [3]. We found that RNA granule proteins exhibit higher disorder, lower hydrophobicity, and greater aromatic fractions compared to non-RNA granule proteins identified through reliable classifiers.
In summary, our study provides a foundation rooted in molecular principles to enhance our understanding of RNA granule formation behavior. The identified characteristics and molecular grammars of RNA granule proteins can serve as a platform for future studies and the development of therapeutic interventions targeting RNA granule-related diseases.



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ION-CURRENT RECTIFYING NANOPORES IN APROTIC SOLVENT: FROM FUNDAMENTALS TO APPLICATIONS

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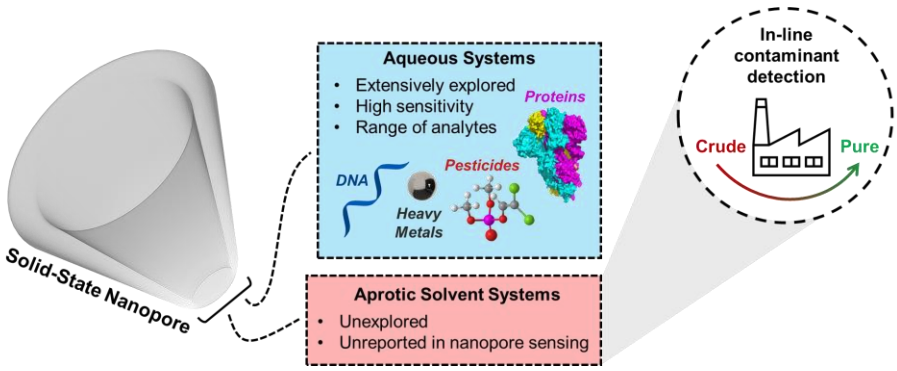
Electrochemical phenomena in asymmetric glass nanopores, including ion current rectification (ICR), are highly reported in aqueous nano-electrochemical systems and sensors,[1, 2] but lack exploration in organic solvent systems, due to the additional complexity introduced through the use of aprotic solvents. ICR in aprotic electrolyte reportedly arises due to the formation of an effective positive surface charge, through solvent dipole alignment on the nanopore surface.[3, 4] Inspired by prior reports, we present a detailed experimental and theoretical study on rectification ratio (RR) as a function of electrolyte concentration in highly polar and mildly polar organic electrolyte.[5] To explain our surprising experimental results, we present a novel phenomenon: the formation of a double-junction diode inside the nanopore due to solvent enrichment/depletion effects.[5] Understanding the complex processes that arise in aprotic nanopore systems is essential in the development of nanopore sensors which can operate in organic solvents, facilitating a wider range of industrial applications than those for which such aqueous sensors are currently developed.[2] These include the detection of both gaseous and solution phase analytes, with benefits including the development of in-line contaminant detectors for the chemical industry.



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Development of a Solid-State Sensor towards Pesticide Detection Utilizing Ion Current Rectification in Functionalized Conical Nanopipettes

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Synthetic, conical nanopore systems like nanopipettes exhibit Ion Current Rectification (ICR), a phenomenon which is highly dependent to interfacial charge and the asymmetric geometry. Nanopipettes are thus highly appealing for use as sensors. ICR is characterized by an asymmetric diode-like current-voltage response, where the current recorded at one voltage polarity is higher than the current recorded at the same voltage of opposite polarity.[1] Functionalizing nanopipettes with biorecognition agents on the pore surfaces such as antibodies and nucleic acids can be used to detect various analytes with high sensitivity.[2] A thorough understanding of the ion transport behaviours within the nanopore systems further aids in the development and optimisation of sensors utilising ICR.

The work presented herein shows the effect of electrolyte concentration on ICR, followed by the development of a universal sensing strategy for a DNA-functionalized nanopipette capable of detecting sequence complementary to a 16 base-pair region of the mecA gene of MRSA exposed to it. This provides proof of concept that ICR can be utilised for the development of sensitive and specific biosensors for pathogenic DNA. Building up from this knowledge, preliminary studies for the development of aptamer functionalised nanopipettes that can detect pesticides are investigated.

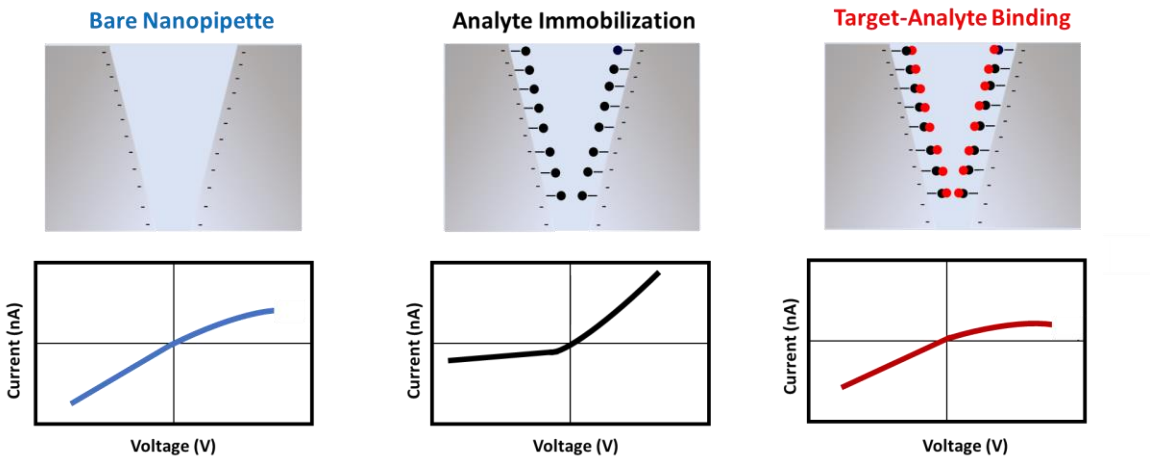

Figure 1. *A representation of the sensing approach based on exploiting the surface charge dependence of ICR.*

Capturing the protein release and further trafficking of nanoparticle-protein complex in cellular system

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Nanoparticles (NPs) are promising tools for drug delivery. It is now widely accepted that when NPs exposure to the biological fluids, they are surrounded by a layer of biomolecules, mainly protein adsorbing to the surfaces, known as the protein corona (PC)[1]. The biological identity to NPs is provided by PC, their composition and orientation can lead to different endocytosis and exocytosis patterns of nanoparticles. NPs typically exit the cell via lysosome secretion and the PC degrade in the lysosome[2].

Our group assembled a type of particle protein complex and reintroduce it to cell cultures in order to investigate the interaction of the particle-protein complexes with organelles such as mitochondria. Based on the results of single live cell imaging and proteomics analysis, we hypothesized that when this particle-protein complex is transported in vesicle, some of the protein layer over the particles surface tend to detach from the particles and release to the cytoplasm[3], however the relative location of protein layer and vesicle is still unclear due to the limited subcellular structure information in fluorescence imaging. A novel technique called correlative light and electron microscopy (CLEM) is introduced by combining fluorescence microscopy (FM) with high-resolution electron microscopy (EM), so we can have cellular function (from FM) and ultrastructure (from EM) at the exact same area of interest.

Herein, my project focuses on capturing the particle-protein complex cellular activities by CLEM and EM technique. Since clathrin-mediated endocytosis (CME) is the major endocytic pathway in mammalian cells[4], my particular interest includes the protein layer detachment and release events in cellular system and their subsequent interaction with organelles and clathrin proteins, aims to determine specific interactions between nanoparticles-protein complex and their environment. Presented here is the CLEM result of my work to date, with the scale bar of 500 nm. The Cy5-dye conjugated NPs with Alexa Fluor 405 labelled protein layer over the surface was introduced into cell with MitoTracker™ Orange CMTMRos stained mitochondria.

THE DETECTION & EHS RISK DETERMINATION OF NANOMATERIALS IN THE SEMICONDUCTOR INDUSTRY

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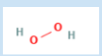
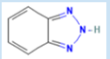
The semiconductor industry is a significant user of nanomaterials in its manufacturing process as a means to enhance the quality of the finished semiconductor device (chip). Silica nanoparticles are utilised in one part of the manufacturing process called the Chemical Mechanical Planarisation (CMP) process. There is very little knowledge regarding the environmental risk and fate of these nanomaterials utilised in such processes. On the other hand, it is acknowledged that the environmental behaviour and fate of nanoparticles is highly dependent upon particle characteristics e.g., size, shape etc. as well as the conditions of the environmental medium e.g., pH, ionic strength etc.[1] This implies that once in the aquatic environment, nanoparticles are highly affected by their surroundings and consequently undergo transformations.[2]

The current project utilises a lab-scale wastewater treatment system that simulates the copper CMP wastewater stream. Such an experimental platform has enabled the investigation into silica nanoparticles' characteristics within the wastewater treatment system. While comprehending the wastewater effluent components noted below, aspects such as concentration, hydrodynamic size, influence of pH, ability to aggregate etc. were integral in ascertaining the nanoparticles' environmental risk and fate.

Wastewater Effluent Components

Name	Cupric Chloride	Acetic Acid	Hydrogen Peroxide	Total Dissolved Solids	PFBS	Ethylene Glycol	nMP	SiO_2 FITC Nanoparticles	Benzotriazole
Structure				n/a					
Molecular Formula	$CuCl_2$	$C_2H_4O_2$	H_2O_2	n/a	$C_4HF_9O_3S$	$C_2H_6O_2$	C_5H_9NO	SiO_2	$C_6H_5N_3$

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SURFACE MODIFICATIONS OF TITANIUM ALLOYS FOR BIOMEDICAL APPLICATIONS

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Titanium dioxide nanotubes (TiO_2 NTs) **(a)** have been extensively studied over the last few decades. From the early generations of TiO_2 NTs featuring short NT lengths and ribbed structures, to the modern generations displaying longer and highly self-ordered NTs, these structural improvements have resulted in the pursuit for additional modifications. To better suit many different fields, including energy storage, aerospace, and biomedical applications, a range of wet-chemical methods and electrochemical methods were developed.

This project employs anodisation of titanium alloys to form ordered NTs using a neutral, aqueous-based electrolyte with moderate experimental conditions. Incorporation of antimicrobial agents into TiO_2 NTs was achieved by successful electrodeposition of silver **(b)** and copper **(c)** nanoparticles with various morphology and distribution. Based on the fact that modification of the TiO_2 NT structure and electrodeposited nanoparticles is easily obtainable by the variation of electrochemical parameters, the current work attempts to address two highly clinically-relevant issues related to implant failure: poor osseointegration of the implant with the surrounding bone,[1] and implant associated infections (IAIs).[2]

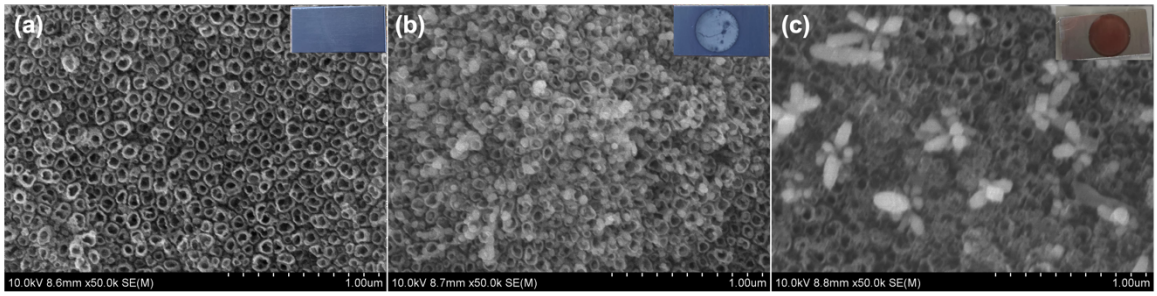

Figure 1: (a) TiO_2 NTs with electrodeposited silver (b) and copper (c) nanoparticles.

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MOVEMENT GENERATION UNDER THE APPLICATION OF AN ELECTRIC FIELD: ELECTROTAXIS AND ELECTRO-ACTUATION

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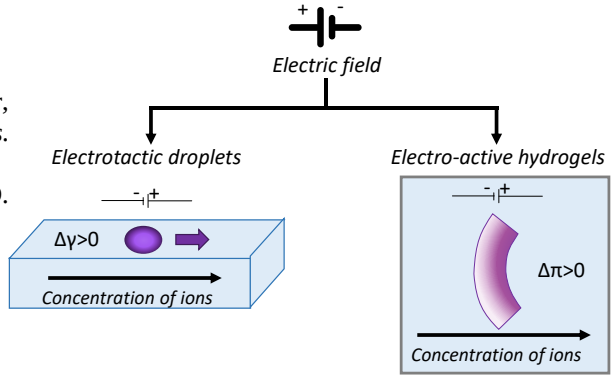
The use of an electric field to stimulate actuation in soft materials holds great appeal as a means for generating movement in a non-contact and facile manner.

This work describes the development of two types of materials capable of performing sustained motion upon the application of an electric field: 1) electrotactic ionic liquid (IL) droplets, and 2) electro-active polyelectrolyte hydrogels (EAH). In both systems, actuation is driven by a redistribution of mobile ions upon the application of an electric field.

In the case of electrotactic droplets, the asymmetric distribution of ions translates into a surface tension gradient ($\Delta\gamma$) responsible for the generation of Marangoni flows to achieve electro-activated propulsion (*aka* electrotaxis) of droplets at the air/electrolyte interface.[1] Droplet taxis was characterised as a function of the ionic strength and surface tension of the surrounding electrolyte solution, and the strength and direction of the applied electric field. Upon system optimisation, reversible droplet electrotaxis with speeds up to 0.71 ± 0.13 body length$\cdot s^{-1}$ was achieved. Furthermore, we demonstrate that such electrotactic droplets can be employed as micro-vessels for cargo transport and release, and for sensing and reporting on their local chemical environment.

In the case of electro-active hydrogels, the asymmetric distribution of ions can be used to generate an osmotic pressure difference ($\Delta\pi$) that allows for controlled, unidirectional actuation (*e.g.*, bending) of polyelectrolyte-based hydrogels.[2] A range of hydrogel structures consisting of polycationic networks based on quaternised ammonium monomers are demonstrated. Furthermore, additive manufacturing of such EAH allows for the realisation of 3D actuator structures such as grippers and swimmers, capable of performing directional motion in response to electro-stimulation.

This work demonstrates the use of an electric field as an efficient way to achieve reversible, unidirectional and controllable actuation of soft matter, in the form of micro-droplets and hydrogel structures. This study paves the way for the development of programmable and autonomous materials, capable of on-demand actuation while providing feedback to adapt their response.



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Dublin Chemistry Graduate Seminars 2022/23

Structural Characterization of $BaZrS_{(3-y)}Se_y$ Perovskite Thin Films via Scanning Transmission Electron Microscopy

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Chalcogenide perovskites show great potential for becoming solar cell materials due to their tuneable, direct bandgaps in the visible range, physics-rich combination of ionic and covalent bonding, and use of nontoxic/abundant elements [1]. While high quality thin film growth of these materials was previously difficult, recent advances in chalcogenide molecular beam epitaxy enabled a new route to study their fundamental properties. For example, in this work, by alloying $BaZrS_3$ and $BaZrSe_3$, the bandgap of the resulting material can be tuned from ~1.8 to ~1.3 eV with high polarizability for polaron formation and slow defect-assisted recombination rates. Complete control of properties, however, necessitates understanding the formation of other extended defects, such as antiphase boundaries and rotation variants, in the alloy films.

In this talk, we expand on previous work [2] by characterizing thin films of the $BaZrS_{(3-y)}Se_y$ (BZSSe) perovskite alloy system grown on a $BaZrS_3$ (BZS) template on a $LaAlO_3$ (LAO) substrate by molecular beam epitaxy. Specifically, we will discuss the structure of BZSSe films (y = 1 – 3) and their defects determined using atomic-resolution scanning transmission electron microscopy (STEM), energy dispersive X-ray spectroscopy (EDX) and electron energy loss spectroscopy (EELS). We will show that the crystal structure of both the template and the alloy layers is perovskite, and exhibits two competing epitaxial relationships, as previously seen in pure BZS films. While the film is relaxed overall, there is a high concentration of antiphase boundaries (APBs) in both layers. Those in the template region are predominately oriented perpendicular to the grown plane, while those near the surface in the alloy predominately lie in-plane. Moreover, EDX and EELS indicate a gradient of Se concentration that reaches down to the substrate interface and correlates with the rotation of the of the APBs. Finally, we will also show that structural distortions introduced by the APBs explain features in the X-ray diffraction profiles.

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SFI-18/EPSRC-CDT/3581

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Development of Transaminase-Triggered Cascades for the Synthesis of Nitrogen-Containing Natural Products and Analogues

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Piperidine-, quinolizidine- and indolizidine-containing alkaloids are naturally occurring secondary metabolites, with numerous medicinal applications, including acting as antibiotics, antivirals and anticancer agents.[1] Due to their low natural abundance, development of chemical routes for the total synthesis of these compounds has gained much interest,[2] yet often requires the use of expensive metal catalysts and environmentally un-friendly solvents. Development of a (chemo)enzymatic route, starting from simple building blocks, to access these alkaloids and their derivatives was envisaged, exploiting a Mannich or an intramolecular aza-Michael reaction (IMAMR). Specifically, a hybrid bio-organocatalysed approach for the synthesis of (±)-pelletierine was developed, involving a transaminase-induced, L-proline catalysed Mannich reaction starting from cadaverine and acetone (Figure 1). [3]

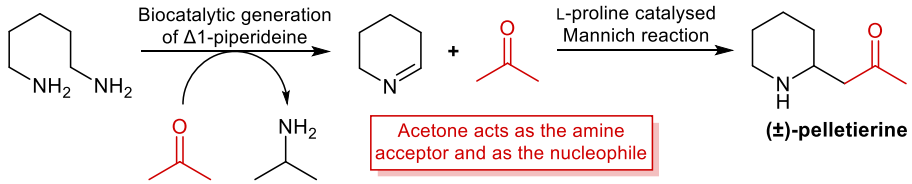

***Figure 1**: Proposed bio-organocatalytic route for the synthesis of (±)-pelletierine.*

A second transaminase-triggered cascade is currently being developed, utilising a double intramolecular aza-Michael reaction to generate quinolizidine- and indolizidine-containing structures starting from bis-α-β-unsaturated carbonyl compounds (Figure 2). Eight ketoenone substrates were synthesised and subjected to a commercially available transaminase under optimised biotransformation conditions.

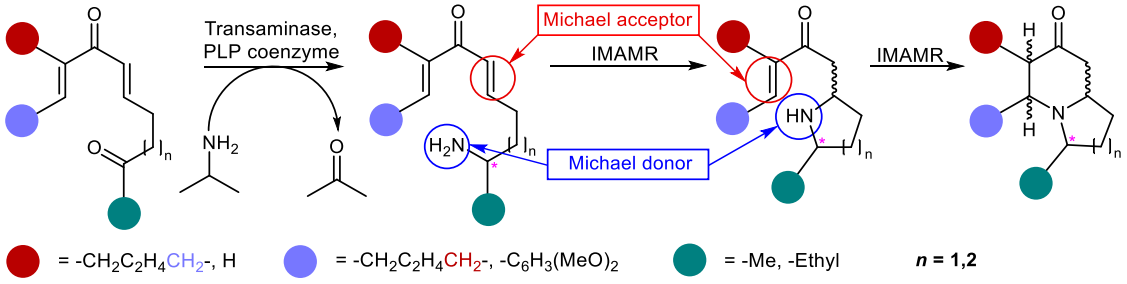

***Figure 2**: Proposed biocatalytic route towards quinolizidine and indolizidine containing structures.*

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Fondúireacht Eolaíochta Éireann Sfi Dá bhfuil romhainn
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BIOCATALYTIC CASCADE SYNTHESIS OF IMINOSUGARS FROM MONOSACCHARIDES

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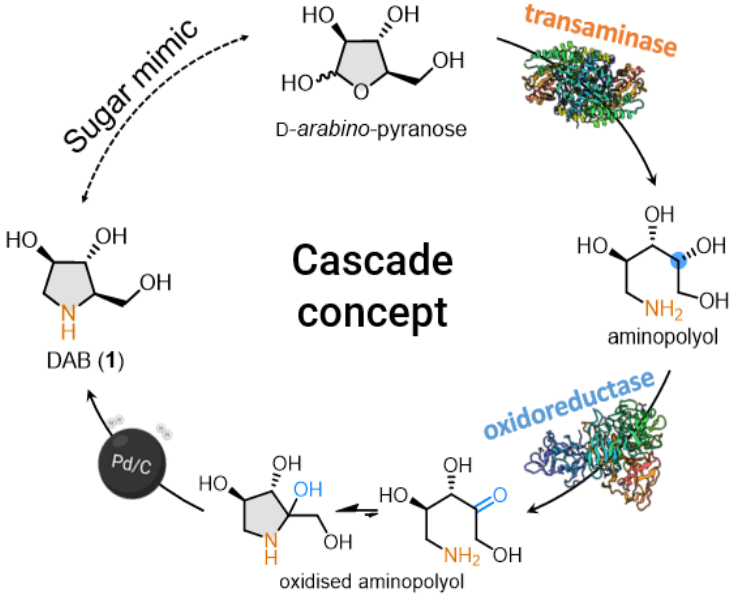
Iminosugars, such as DAB (**1**), are polyhydroxylated alkaloids and sugar mimics, with an endocyclic nitrogen in place of an oxygen atom. These naturally occurring compounds are of pharmaceutical relevance because they interact with and inhibit carbohydrate processing enzymes and possess beneficial drug-like properties.[1] The absence of efficient syntheses for preparing structurally diverse derivatives has been highlighted as a barrier to the advancement of second-generation iminosugars as therapeutics.[2]

Here, we develop the three-step cascade for the preparation of iminosugars from readily available monosaccharides, *via* transamination, regioselective biocatalytic oxidation and non-selective imine reduction. [3-5] This methodology can be extended to a range of commercial sugars to access valuable pyrrolidine, piperidine, and azepane iminosugar compounds.



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TRANSFERRING THE BADLWIN REARRANGEMENT PROCESS TO CONTINUOUS FLOW

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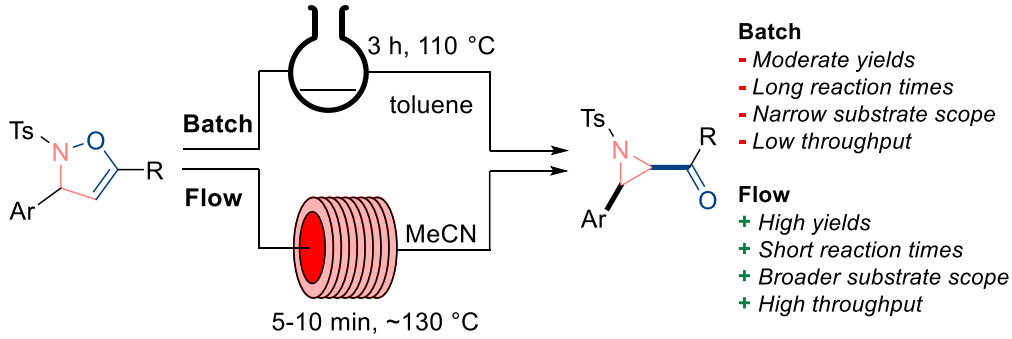
Modern chemical synthesis relies on traditional batch synthesis or technology. As technology has developed, chemists have started to incorporate new enabling technologies to improve synthetic methodologies. One such enabling technology is continuous flow chemistry. Several works in the literature have demonstrated that performing chemical reactions in continuous mode, using tubing as vessels, lead to a number of advantages; for example, improved heat and mass transfer, safety, and scalability, are exploited to improve chemical processes and often, to perform chemical reactions that have been forgotten or are forbidden in batch.[1]



This talk focuses on how the Baldwin rearrangement process was transferred from batch to continuous flow. The Baldwin rearrangement is the thermal ring contraction of isoxazolines into valuable drug-fragment aziridine molecules.[2,3] This reaction – which was first reported in the 1960s – was initially explored using traditional batch synthesis but suffered from moderate yields, long reaction times, and a narrow substrate scope. The process was greatly improved upon its transfer to continuous flow, which involved high yields of up to 16 substrates – compared to moderate yields of up to 10 substrates in batch – and short reaction times. Furthermore, the highly efficient, novel process rendered multigram quantities of product in short periods of time, enabled by the facile scalability associated with continuous flow.

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DOUBLE-REDUCTION OF CYCLIC SULFONAMIDES: A NOVEL APPROACH TOWARDS THE TOTAL SYNTHESIS OF (+)-APHANORPHINE

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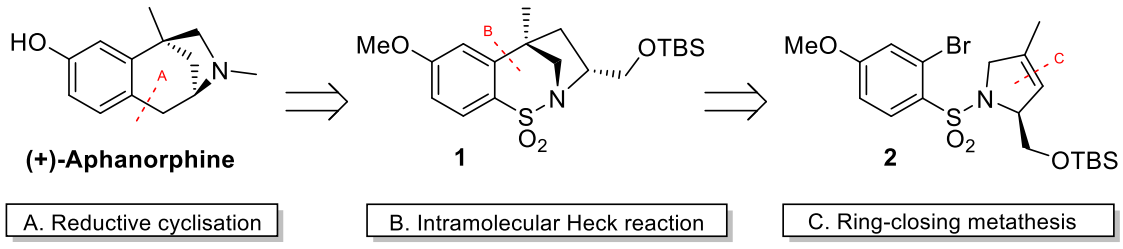
N-Heterocycles are an important class of chemical compounds, particularly in the pharmaceutical and agrochemical industries. They are included in about 60% of the top selling 200 synthetic drugs on the market and are found in a vast number of naturally occurring compounds.[1] The Evans group use a novel traceless tether approach to synthesise N-heterocycles through cyclic sulfonamides. Utilising the double-reduction (C-S and N-S bond cleavage) of the sulfonamide unit, we can easily install aryl substituents onto cyclic amines.[2,3] The sulfonamide motif is involved in three main steps of the process. Initially, it acts as a nitrogen protecting group, effectively removing nitrogen's basicity, nucleophilicity and its ability to coordinate to metal atoms. It then allows the two "tethered" molecular fragments to come into close proximity, facilitating their intramolecular coupling. Lastly, the reductive cleavage of the sulfonyl group produces functionalised N-heterocycles.[4] Based on previous findings, this project focuses on applying this methodology to the total synthesis of a tricyclic alkaloid (+)-aphanorphine.[5] To date, compound **2** has been prepared as a single enantiomer from L-methionine in a sequence featuring a ring-closing metathesis reaction. Compound **2** undergoes a regio- and stereoselective Pd-mediated Heck reaction, which following alkene reduction gives cyclic sulfonamide **1**. We envisage a tandem cyclisation will directly follow the double-reductive process described above, forming (+)-aphanorphine's intricate molecular scaffold.



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Enantioselective Synthesis of Sterically Hindered α-Allyl-α-Aryl O-Heterocycles *via* Decarboxylative Asymmetric Allylic Alkylation

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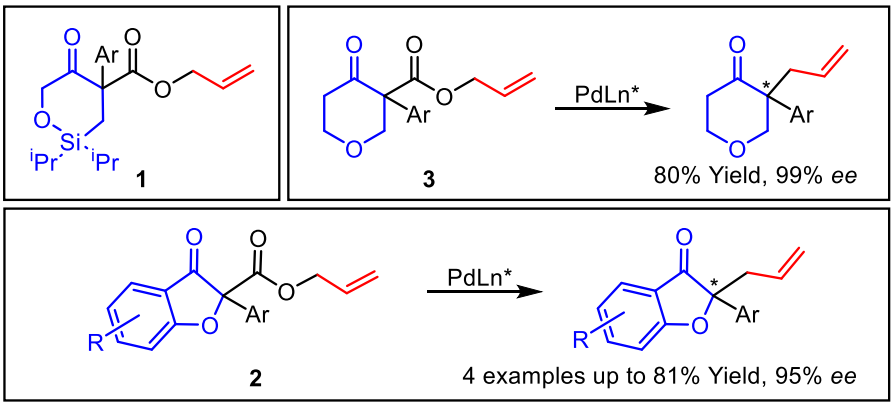
Oxygen-containing heterocycles are a common motif found in natural products and biologically active compounds. Additionally, quaternary α-aryl stereocenters are found in nature and have been shown to have interesting properties. Recent efforts with certain O-heterocycles have focused on the installation of aryl groups at the α-position to generate sterically hindered all-carbon quaternary stereocenters.[1] These products can be accessed from the Pd-catalysed decarboxylative asymmetric allylic alkylation (DAAA) of α-aryl β-keto allyl esters. Although this methodology has been previously limited to small alkyl chains or functionalities distant from the reactive centre, the Guiry group has already extended the scope to other α-aryl containing substrates *via* the use of aryllead reagents to install the bulky groups on the reactive center before applying to catalysis.[2]

This project has focused on the utilisation of DAAA with three different O-heterocycles: cyclic siloxyketones (**1**),[3] benzofuranones (**2**)[4] and tetrahydropyranones (**3**). The steps towards the synthesis of the model substrate in each case is described along with the optimisation of the DAAA reaction for both **2** and **3**, each demonstrating high yields and high enantioselectivities.



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The Development of Novel Ferrocenyl Ligands *via* Acid-Mediated Transformations

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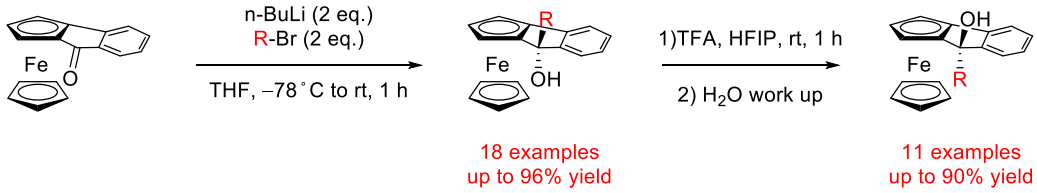
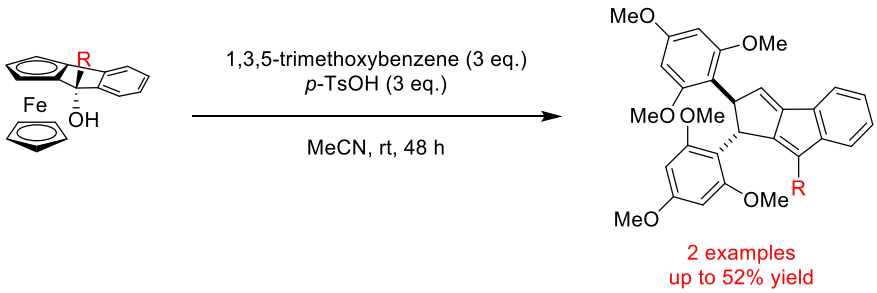
Ferrocene was discovered in 1951 by Kealy and Pauson and has since found uses in asymmetric catalysis, organometallic chemistry, and medicinal chemistry.[1] The Guiry group have previously reported the optimised synthesis of chiral ferrocenyl scaffolds and applied these as ligands in asymmetric organocatalysis.[2]

This project investigates acid-mediated transformations of chiral ferrocenyl alcohols. The reactivity and selectivity of the ferrocenyl monoketone has been exploited in this project for the synthesis of 18 chiral α-ferrocenyl alcohols in high yields of up to 96%. The acid-mediated inversion of the chiral centre at the α-ferrocenyl position was reported in 2020.[3] The scope of this reaction has been further investigated in this project to access 11 inverted chiral alcohols in high yields of up to 90%.



A novel tricyclic indene has been synthesised *via* an acid-mediated arylation of ferrocenyl alcohols. A di-C-H-functionalisation of the unactivated cyclopentadienyl ring of the ferrocenyl alcohol results in deprotection of the fulvene and a loss of iron. This is a diastereoselective reaction as only the *trans*-tricyclic indene is observed, and *cis*-addition does not occur. Work is ongoing to further explore the enantioselectivity and the scope of this unprecedented transformation.



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A NEW PARADIGM FOR THE ASYMMETRIC DIELS-ALDER REACTION

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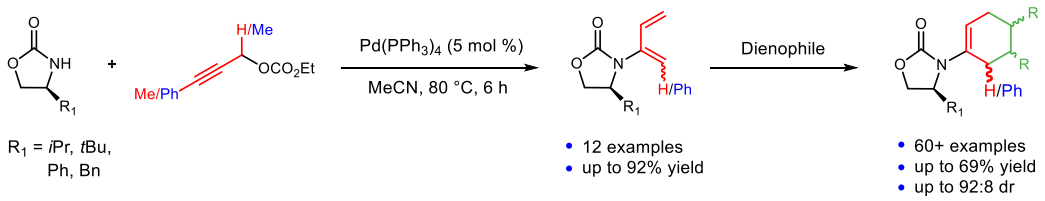
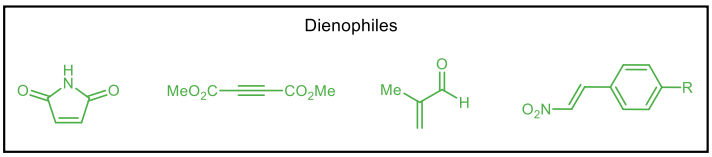
The Diels–Alder (DA) reaction has been intensively developed and refined to become one of the most powerful carbon–carbon bond forming methods in organic chemistry.[1][2][3] The asymmetric variation of the DA reaction was first investigated more than 50 years ago, and continues to see further development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

A catalytic method to prepare a library of chiral 2-amido-1,3- and 2-amido-1-phenyl-1,3-dienes from a range of oxazolidinones is reported. This palladium-catalysed carbon-nitrogen bond-forming reaction provides the corresponding chiral amido-dienes in moderate to excellent yields (12 examples, up to 92%). The resulting chiral amido-dienes are employed as novel dienes in DA reactions with over 60 examples. These novel chiral amido-dienes are a significant addition to the existing class of chiral dienes in the strategies towards the asymmetric DA reaction.





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STEREOSELECTIVE SYNTHESIS OF α-GALACTOSIDES

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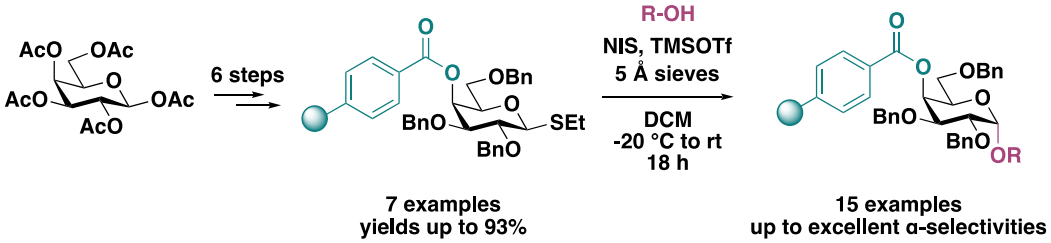
Nature employs carbohydrates as an integral source of structural biodiversity across all organisms. It is understood that the biological properties of these natural products can be fine-tuned *via* alteration of glycosidic patterns, particularly with respect to stereochemistry. Consequently, stereochemical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

This work is concerned with stereoselective control in α-galactosidation reactions. α-Galactoside units are found in many biologically important compounds, for example in the human blood group antigens.[2] However, existing methods for the α-selective synthesis of galactosides that are broadly applicable to a range of galactosyl substrates are limited. Thus, further understanding around the stereochemistry of α-galactosidation is required.[3,4]

In this work, a range of galactosyl donors bearing *para*-substituted benzoate protecting groups at position 4 were accessed *via* 6 steps in yields up to 93%. The electronic effect of this *para*-substituent and the nucleophilicity of the acceptor substrate were observed to have a significant effect on the stereochemical outcome of galactosidation. It was found that some galactosyl donors gave excellent α-selectivity.[5] The efficacy of this methodology was demonstrated in the synthesis of a trisaccharide.



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ACTIVITY BASED PROBES TO UNRAVEL NEW INSIGHTS INTO P53 DEUBIQUITINATION

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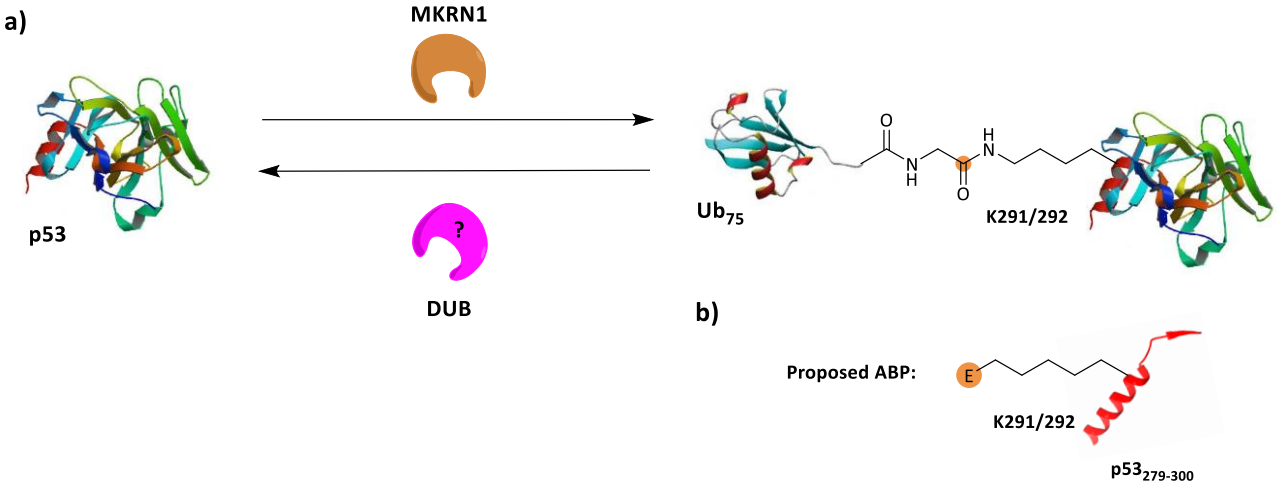
p53 is a highly versatile transcription factor. Its activity is modulated by different Post Translational Modifications (PTMs).[1] In healthy cells, ubiquitination and subsequent degradation by the 26S Proteasome keep p53 basal levels low. However, following stress or DNA damage p53 is saved from proteasomal degradation and activated with a vast array of PTMs, triggering a stress-specific response. In humans, the enzymes responsible for rescuing proteins from proteasomal degradation by removing or editing the ubiquitin tag are a family of proteases called deubiquitinating enzymes (DUBs). With respect to p53, nearly 15 DUBs have been reported to interact with p53, either as positive or negative regulators.[2] However, the DUB (or set of DUBs) responsible for deubiquitylation at recently discovered K291/K292 sites has not yet been characterized (**Fig.1a**).

To capture this elusive enzyme/s this project aims to synthesize Activity Based Probes (ABPs) that mimic the structure of p53 and feature a reactive handle that is able to covalently modify the set of DUBs interacting with p53. ABPs are useful chemical tools used to characterize new enzymes by capturing their active form in complex cellular environments.[3,4] In this study, ABPs were generated using a portion of the p53 sequence as a recognition scaffold, in which the key lysines K291/K292 were synthetically modified to incorporate different electrophilic moieties (**Fig.1b**).

Efforts have been directed to synthesize a series of Fmoc-protected modified amino acids that were implemented into the recognition scaffold via Solid Phase Peptide Synthesis (SPPS). The short sequence acting as a recognition scaffold consists of a 22mer covering residues 279-300 of p53. The last coupling allows an effective on-resin biotinylation to allow tag installation on the growing peptide before its cleavage from the resin.

Following preliminary labelling assays on HEK293T cell lysates, the biotin tag allowed for visualization of labelled proteins via Western Blot and their isolation and characterization by proteomic assays. Being designed to target p53 deubiquitylation only, this approach aims to discover new functions of DUB enzymes and increase our knowledge on p53 PTMs.



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CLICKING TO SULFUR: A RADICAL APPROACH FOR PEPTIDE AND PROTEIN MODIFICATION

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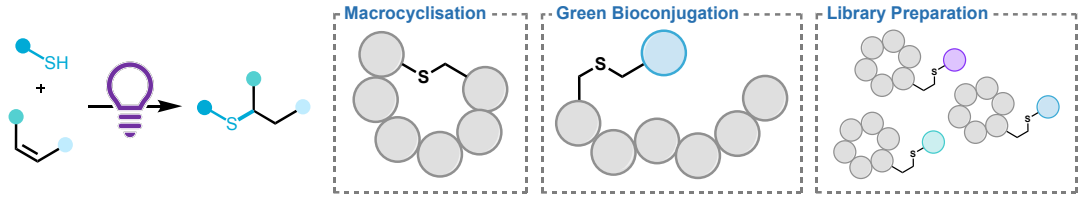
Covalent modification of peptides and proteins is a topic of growing importance owing to advancements in the application of such compounds as therapeutics.[1] This area of research relies heavily on a myriad of chemical approaches, of which new methods are of considerable interest. Radical thiol-ene chemistry offers a powerful approach for chemoselective modification of peptides and proteins *via* reaction of a thiol and alkene.[2] The "Click" characteristics of this reaction provide an efficient bioconjugation platform, with orthogonality over many two-electron reactive groups present in biomolecules.

This work covers three applications of thiol-ene chemistry on peptides; (i) peptide macrocyclisation, (ii) green bioconjugation and (iii) high-throughput diversification. We have demonstrated the intramolecular reaction of a cysteine residue with an allylglycine to form robust thiother linkages *via* thiol-ene reaction, replacing natural disulfide bonds.[3] Secondly, we have developed a Green bioconjugation platform, utilising deep eutectic solvents as a favourable alternative to harmful solvents such as DMF.[4] Finally, we present an approach for diversification of alkene-containing peptide macrocycles in high-throughput, affording libraries of high purity crude mixtures amenable to so-called "direct-to-biology" applications.[5]



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Synthesis of Fluorescent Lipopeptides as Activity Probes for Bacterial Lipoprotein Processing Enzymes

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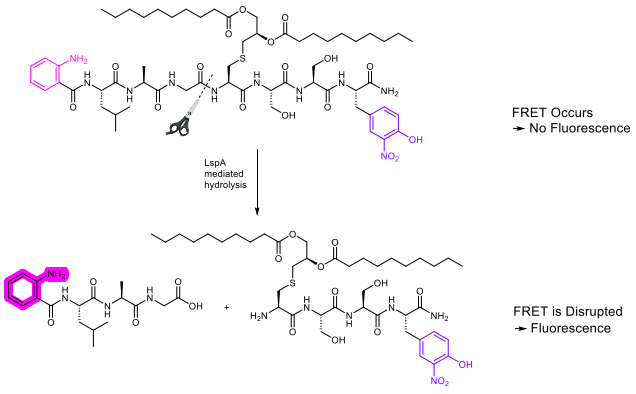
Lipoproteins are essential for survival and virulence in many species of bacteria. These bacterial lipoproteins feature a characteristic N-terminal diacylglyceryl modification which is post-translationally installed by the bacterial lipoprotein processing pathway. This pathway consists of a unique series of enzymes which are not present in eukaryotes and thus inhibition of these enzymes offers opportunities for novel antibiotic discovery.[1] To facilitate high-throughput screening for potential inhibitors, suitably specific and sensitive molecular probes for these enzymes are required.[2]

This work focuses on the synthesis of a range of fluorescent lipopeptide probes containing a diacylglyceryl modification at cysteine that mimics the native lipoprotein structure. We have developed a convergent method for the synthesis of these lipopeptides as well as a linear route using solid phase peptide synthesis (SPPS). The flexibility afforded by these synthetic strategies enables the facile introduction of both native and non-native lipid structures. This has provided access to a library of lipopeptide-based probes that have been used to develop a high-throughput fluorescence resonance energy transfer (FRET) assay for lipoprotein signal peptidase II (LspA)[3] and investigations towards development of a fluorescent peptide probe for lipoprotein diacylglyceryl transferase (Lgt) are ongoing.



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THIOASPARTIC ACID MEDIATED METHODS FOR PEPTIDE LIGATION AND MACROCYCLISATION

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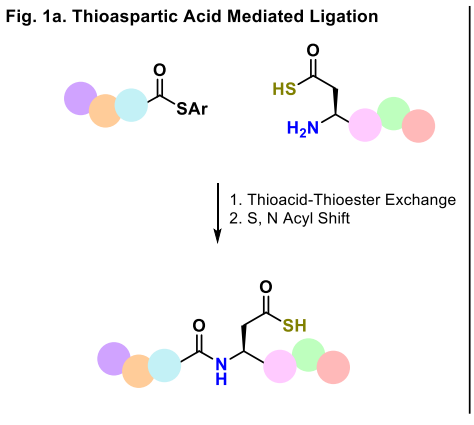
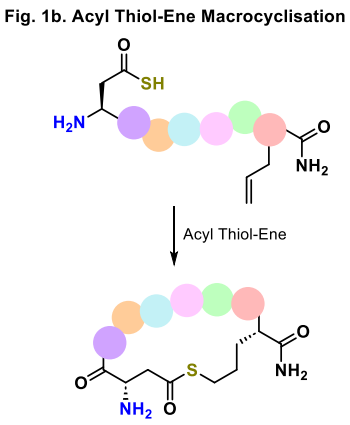
The development of Native Chemical Ligation (NCL) by Kent and co-workers revolutionised the field of chemical protein synthesis, however, limitations such as the requirement for a C-terminal cysteine residue continue to limit its general application.[1] A range of methods have been developed which use auxiliary groups or unnatural amino acids to expand the scope of NCL.[2] The thioacid analogue of the canonical amino acid aspartic acid, thioaspartic acid (**Fig. 1**), possess orthogonal reactivity due to its increased acidity, nucleophilicity and ability to form thiyl radicals. This project focuses on exploiting the unique reactivity of thioaspartic acid to develop novel ligation and macrocyclisation methods to enable the synthesis of peptides displaying novel and versatile functionalities.

Presented here is a summary of the progress to date, including the development of a thioaspartic acid mediated peptide ligation method that proceeds via a thioanhydride intermediate to furnish a native peptide bond (**Fig. 1a**). Secondly, an acyl thiol-ene, radical-mediated macrocylisation method has been developed to synthesise analogues of Auto Inducing Peptides (AIPs) from *Staphylococcus aureus* which possess a unique thioester linkage (**Fig. 1b**). In each case, the thioacid moiety functions as a critical residue for enabling ligation.





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TUMOUR RESPONSIVE SYSTEMS FOR TARGETED DRUG DELIVERY

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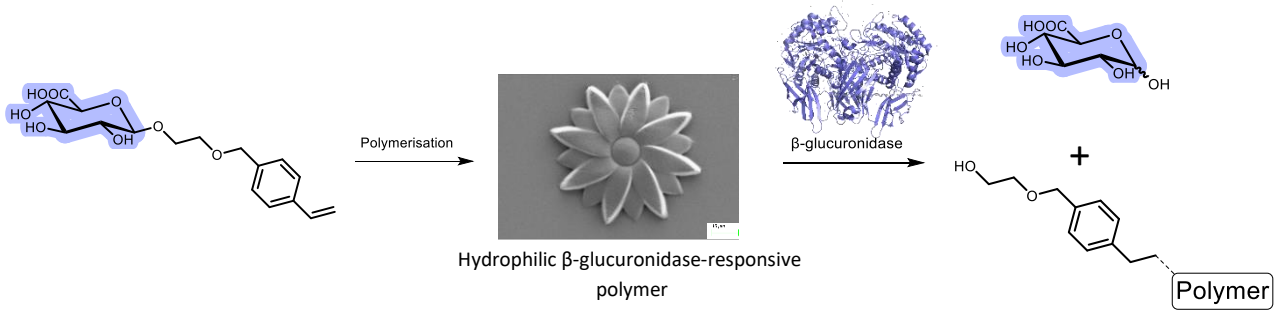
Current treatments used in cancer chemotherapy are limited due to their narrow therapeutic window and poor selectivity, making the development of targeted drug delivery platforms an urgent research challenge.[1] β-glucuronidase is overexpressed in the necrotic region of a range of tumour types, compared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

Polymer-based drug delivery systems represent a growing class of targeted therapeutics, with stimuli-responsive materials demonstrating applications across the field of materials science in a range of biomedical applications.[4] Here, we describe the synthesis of polymerisable groups bearing glucuronide moieties and their subsequent polymerisation via two-photon polymerisation (2PP) and UV polymerisation, suitable for incorporation into enzyme-activated bioresponsive systems.



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Naphthalimide Conjugates for Improved, Targeted Cancer Cell

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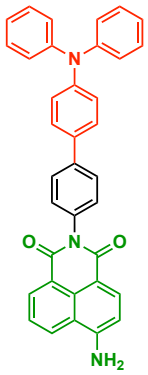
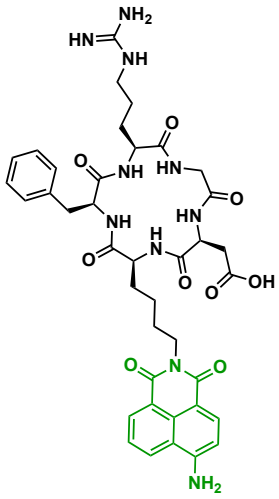
1,8-Naphthalimides are widely utilised fluorophores and dyes due to their excellent photophysical properties. They have high quantum yields, good photostability and large Stokes shifts. The rich photophysical properties of the napthalimides make them ideal candidates as probes, making them useful species for monitoring their uptake into cells and their binding to biomolecules. A key structural feature of 1,8-naphthalimides is that they are planar, which makes them well-suited candidates for intercalating DNA, offering potential as anticancer therapeutics.[1]

Arginine-Glycine-Aspartic acid (RGD) peptides are well known for targeting the $\alpha_v\beta_3$ integrin, which is highly expressed in tumours. Therefore, drug delivery and diagnosis through cyclic RGD peptides that bind $\alpha_v\beta_3$ integrin in tumours represents a promising strategy. However, these sequences lack chemical groups that enable their facile detection. The incorporation of organic fluorophores into the peptide sequence offers considerable potential as an approach to target cancer cells. Fluorescent cyclic peptides have been used in biological applications from live-cell imaging to *in vivo* detection of cancer.[4]

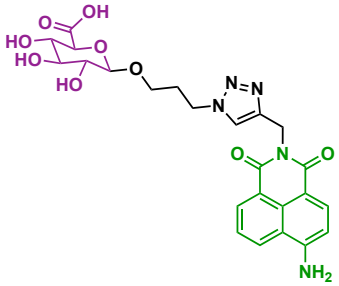
Herein we report the chemical synthesis of 1,8-naphthalimide conjugates as imaging agents and theragnostic for cancer.



ACQ-Nap



RGD-Nap



Sugar-Nap

SYNTHESIS OF THE HUMAN METABOLITES OF COMMON ANTIBIOTICS AND ASSESSMENT OF THEIR ROLE IN ANTIMICROBIAL RESISTANCE DEVELOPMENT

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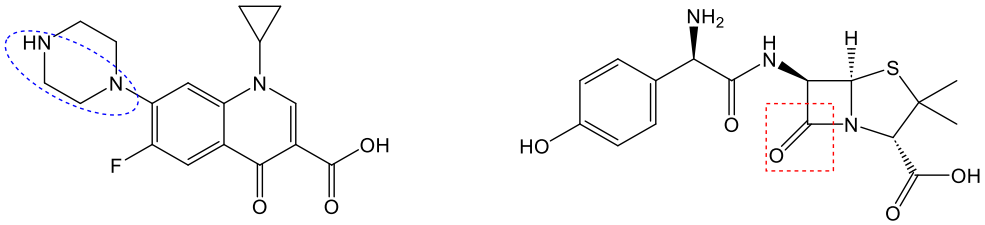
Bacterial antimicrobial resistance (AMR), also known as antibiotic resistance, was attributed to an estimated 1.27 million fatalities globally in 2019.[1] The entry of antibiotics, and their metabolites, into the environment is a crucial One Health issue and while the levels of antibiotics are monitored, metabolite levels are not. Bacteria exposed to sub-inhibitory concentrations of antibiotics can develop resistance, however, it is unclear what role the metabolites of antibiotics might have in resistance development to the parent antibiotic compounds.[2] Ciprofloxacin (**1**) and amoxicillin (**2**) are antibiotics from the fluoroquinolone (FQ) and β-lactam classes first brought to market in the last century. Previous research on their human metabolites has largely focused on their chromatographic separation and characterization from matrices such as blood and urine. We have successfully synthesized and characterized a number of the human metabolites of **1** and **2**, in sufficient quantities for biological assessment. Microbiological studies have been undertaken with the ESKAPE pathogen *Pseudomonas aeruginosa*; the results of these studies will be presented.



Ciprofloxacin (**1**) Amoxicillin (**2**)

Figure 1: Structures of 1 and 2 with main areas of metabolism highlighted

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Theoretical development of new class of phase transfer catalysts: applications in the pharmaceutical industry

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In recent decades, a diverse range of valuable organic compounds have been synthesized using chiral catalysts in various asymmetric transformations.[1,2] Among the asymmetric catalysis techniques, phase transfer catalysis[3] has been established as a robust approach to develop useful procedures for organic synthesis. In this work, the quinine-derived phase transfer catalyst (Figure 1 a) has been extensively studied in various chemical reactions; including the conformational analysis of the catalysts,[4] the non-covalent interactions (NCIs) governing the process,[5] and the different binding modes accessible from those NCIs have been the focus of these studies.

Furthermore, to address the tremendous flexibility and complexity of these catalysts and systems (Figure 1 b), a new workflow has been developed. This new pipeline has little to no human input, which has enhanced the accuracy of the results obtained. Overall, this study aims to, in collaboration with experimental groups, provide insight into the catalytic mechanisms of the quinine-derived phase transfer catalysts establishing a change of paradigm in which computational chemistry leads the catalysts design process, later validated experimentally.

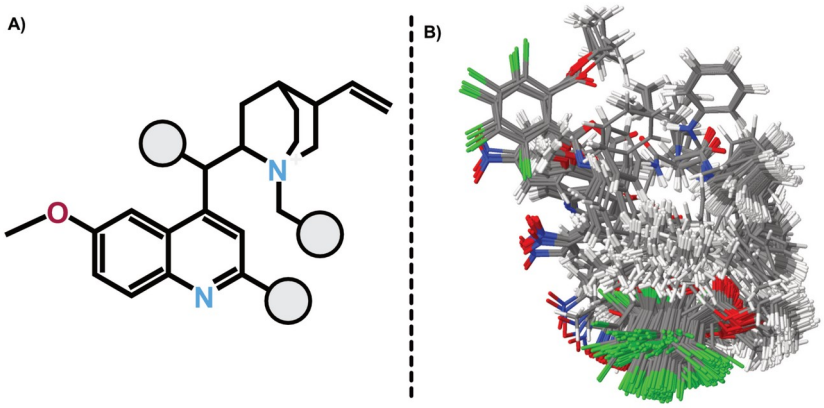

Figure 1.A) Catalyst scaffold under study. **B)** Transition state ensemble.

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