Dublin Chemistry
Graduate Programme

Third Year PhD Talks 2024

Wednesday 29th May 2024

THE HAMILTON BUILDING

Trinity College Dublin

School of Chemistry, TCD
School of Chemistry, UCD

UCD DUBLIN

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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Dublin Chemistry Graduate Programme

Lilly Answers That Matter.

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Eli Lilly - Dublin Chemistry

Third Year PhD Talks Programme 2024

(each talk is strictly 20 minutes, including questions)

Hamilton Building, Trinity College Dublin, Wednesday May 29th 2024

8.50-9.00 Welcome: Professor Stephen Connon, Trinity College Dublin

Talks	Room LTEE1 Sessions A1 – A4	Room LTEE2 Sessions B2/B4	Room LTEE3 Sessions C1 – C4
9.00 - 10.30	**A1: Organic Synthesis 1** Ian Martin Niamh Lehane Zoe Beato Vanessa Becker		**C1: Transition Metals 1** Manting Mu Liam Jowett Munirah Ghariani Pei-Hsuan Wu
		Tea/Coffee	
11.00 - 12.30	**A2: Organic Synthesis 2** Adam Cruise Christine Coffey Fahad Alkhathami Matthew Kiernan	**B2: Sustainable Chemistry 1** Minu Masliha Jessica De Micco Zoe Byrne Lorenzo Pedrini	**C2: Nano-scale Fabrication** Amrutha Augustine Dominik Duleba Aoife Kananagh Luisa Lavelle
		Lunch (Campus Outlets)	
2.00 - 3.30	**A3: Organic Synthesis 3** Aoife Martin Amber Barry Niamh Disney Jonathan Devlin		**C3: Transition Metals 2** Aizuddin Sultan Francesca Adami Olivia Breen Viktorija Mikaite
		Tea/Coffee	
4.00 - 5.40	**A4: Organic Synthesis 4** Dandan Lin Parth Naik Owen Oseghale Louisa Sigurvinsson	**B4: Peptide Chemistry** Nikita Ostrovitsa Tomasz Pawlak Inés Rabadán-González Periklis Karamanis	**C4: Sustainable Chemistry 2** Karlijn Hertsig Gearóid Manning Filippo Pota Rachel Lynch

5.45 Reception

6.00: Awarding of Prizes: Dr. Michael Carroll (Eli Lilly)

Speaker		Supervisor	Abstract Title
SESSION A1: Organic Synthesis 1			Chairs: Declan Gilheany and Elaine O'Reilly
Martin, Ian	TCD	Stephen Connon	Dynamic Kinetic Resolution of Azlactones towards Amide Formation
Lehane, Niamh	UCD	Pat Guiry	Synthesis of Heterocycles Containing α-Aryl Stereocentres via Decarboxylative Asymmetric Transformations
Beato, Zoe	UCD	Xiangming Zhu	Exploring New Methodology in Thioglycoside Synthesis
Becker, Vanessa	UCD	Eoghan McGarrigle	Synthesis and Applications of Organosulfur Compounds
SESSION A2: Organic Synthesis 2			Chairs: Declan Gilheany and Elaine O'Reilly
Cruise, Adam	UCD	Marcus Baumann	Exploring the Utility of Radicofugal Groups in Photochemical Flow Processes to access Ynones
Coffey, Christine	UCD	Tom Hooper	Towards Phosphorus Cations as Main Group Catalysts
Alkhathami, Fahad	UCD	Marina Rubini / Paul Evans	Synthesis of the *cis*- and *trans*-3-Fluoro Analogues of Febrifugine and Halofuginone
Kiernan, Matthew	UCD	Paul Evans	Stereoselective Synthesis of Saturated Nitrogen Heterocycles
SESSION A3 Organic Synthesis 3			Chairs: Stephen Connon and Ramesh Babu Padamati
Martin, Aoife	UCD	Elaine O'Reilly	Expanding the Scope of Transaminase-Triggered Aza-Michael Chemistry for the Synthesis of High Value Targets
Barry, Amber	UCD	Elaine O'Reilly	Development of Convergent Biocatalytic Transformations for the Synthesis of Complex Alkaloids
Disney, Niamh	UCD	Marcus Baumann	A Cyanide-Free Continuous Synthesis of Nitriles and their Manipulation En Route to *N*- and *O*-Heterocycles
Devlin, Jonathan	UCD	Marcus Baumann	Harnessing the Untapped Potential of Multiple High-Energy Species via a Safe and Scalable Continuous Flow System
SESSION A4: Organic Synthesis 4			Chairs: Stephen Connon and Ramesh Babu Padamati
Lin, Dandan	UCD	Paul Evans	An Electrochemical Oxidation Prins-Type Cyclisation Sequence for 1,3- Oxazinan-2-Ones via N-Acyliminium Ions
Naik, Parth	UCD	Marcus Baumann	Flow Approaches for the Improved Synthesis of Pharmaceutical Building Blocks
Oseghale, Owen	TCD	Thorfinnur Gunnlaugsso	Approaches towards the Synthesis of MOF Ligands for Novel Battery Material Applications
Sigurvinsson, Louisa	TCD	Thorfinnur Gunnlaugsso	Naphthalimides Exhibiting Aggregation Induced Emission for Bioimaging Applications

SESSION B2: Sustainable Chemistry 1

Chairs: Eoghan McGarrigle and Xiangming Zhu

Masliha, Minu	TCD	Ramesh Babu	Valorisation of Wood Residues into Products
De Micco, Jessica	TCD	Ramesh Babu	Extraction, Depolymerization and Fractionation of Lignin from Irish Wood for Valorization into Products
Byrne, Zoe	UCD	Pat Guiry	Utilising Lignin Degradation Products as Starting Materials for the Synthesis of Natural Products
Pedrini, Lorenzo	TCD	Stephen Connon	Development of Novel Ionic Catalysts for Glycolytic Depolymerisation of Polyethylene Terephthalate

SESSION B4: Peptide Chemistry

Chairs: Declan Gilheany and Xiangming Zhu

Ostrovitsa, Nikita	TCD	Eoin Scanlan	On-Resin Hydrothiolation towards Peptide Ligation and Macrocyclisation
Pawlak, Tomasz	TCD	Joanna McGouran	Bioconjugation Strategies for Creating Structurally Distinct Protein Scaffolds: Use as Radical Probes of
Rabadán-González, Inés	TCD	Eoin Scanlan	Applications of Thiol-Ene/Yne Chemistry for Peptide Stapling and Bioconjugation
Karamanis, Periklis	UCD	Marina Rubini	Exploring Synthetic and Semi Synthetic Approaches for the Engineering of the Antifungal Cyclic Lipopeptide Iturin

SESSION C1: Transition Metals 1 — Chairs: Grace Morgan and Wolfgang Schmitt

Mu, Manting	TCD	Max García-Melchor	From Heterobimetallic to Monometallic Cobalt and Iron Systems: Ligand and Solvent-Driven Selective
Jowett, Liam	UCD	Dermot Brougham	Physical Chemical Properties of Iron Oxide Nanoparticles in various Media
Ghariani, Munirah	TCD	Yurii Gun'ko	Multimodal Metal Carbonate-Based Structures for Potential Biomedical Applications
Wu, Pei-Hsuan	TUD	Bernadette Creaven	Copper Complexes: Unravelling Their Dual Role in Cancer Therapy through Redox Chemistry and DNA Interactions

SESSION C2: Nano-scale Fabrication — Chairs: Grace Morgan and Wolfgang Schmitt

Augustine, Amrutha	TCD	Larisa Florea	Nanocomposite Photoresists for Direct Laser Writing
Duleba, Dominik	UCD	Robert Johnson	Understanding Ion Transport Processes in Nanopores
Kavanagh, Aoife	TCD	Yurii Gun'ko	I-III-VI Type Colloidal Semiconductor Nanocrystals
Lavelle, Luisa	TCD	Larisa Florea	Photopolymerisation and Photoreduction for the Realisation of Photo-Thermal Micro-Actuators

SESSION C3: Transition Metals 2 — Chairs: Larisa Florea and Dermot Brougham

Sultan, Aizuddin	UCD	Grace Morgan	Incorporation of Spin Crossover Compounds in Light Harvesting Devices
Adami, Francesca	UCD	Grace Morgan	Investigation of Novel Mn(III) and Fe(III) SCO Complexes and Hybrid Materials
Breen, Olivia	UCD	Tony Keene	This Isn’t Even My Final Form: A String of Polymorphs while Looking for Battery Precursors
Mikaite, Viktorija	UCD	Tony Keene	Radical MOFs Toward Magnetic, Optical, and Bioimaging Applications

SESSION C4: Sustainable Chemistry 2 — Chairs: Larisa Florea and Dermot Brougham

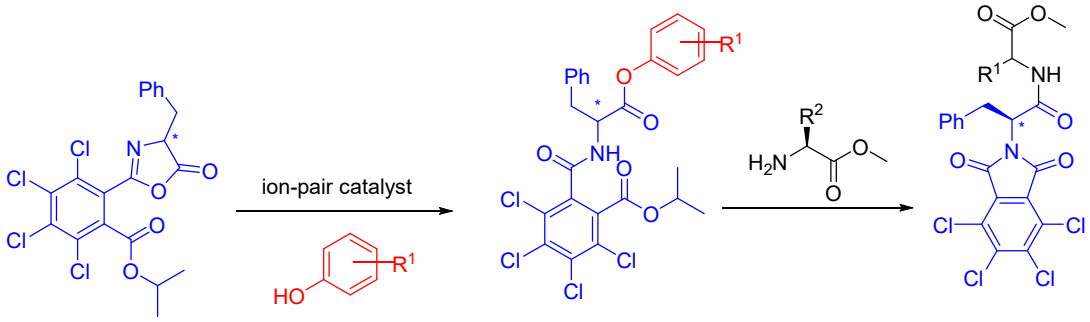
Hertsig, Karlijn	TCD	Peter Dunne	Towards Sustainable Nanomaterials: Greener Routes to Quantum and Carbon Dots
Manning, Gearóid	TCD	Wolfgang Schmitt	Metal-Organic Frameworks for Electrochemical and Photoelectrochemical Energy Conversion Systems
Pota, Filippo	TCD	Paula Colavita	Porous *N*-Doped Carbon-Encapsulated Metals: Novel Catalyst Architecture for the Electrocatalytic Hydrogenation
Lynch, Rachel	UCD	Peter Byrne	Carbon Dioxide Utilisation for Construction of High Value Carboxyl-Containing Organic Products

Dublin Chemistry Graduate Seminars 2023/24

Dynamic kinetic resolution of azlactones towards amide formation

Stephen Connon, Lee Anderson and Ian Martin
Trinity Biomedical Sciences Institute, School of Chemistry, Trinity College Dublin, Dublin 2, Ireland
email: connons@tcd.ie, iamartin@tcd.ie

Azlactones are cyclised amino acid derivatives that can undergo dynamic kinetic resolution in the presence of a chiral catalyst.[1] They have been of great interest to organic chemists for the past three decades due to their large number of possible transformations; including enantioselective ring-opening reactions. A key limitation associated with this process is the lack of non-alcohol derived nucleophiles; with enantioselective thiolysis[2] and aminolysis[3] being a desirable but currently limited in scope. This project aims to develop a reproducible and enantioselective peptide ligation *via* indirect aminolysis of racemic azlactones. This would serve as a useful resource to peptide chemists in the synthesis of enantioenriched unnatural amino acids. Towards this end, a phenolate ester intermediate is displaced using an amine nucleophile to circumvent the problem of direct non-selective addition and a class of novel, highly modifiable cinchona-derived ion-pair catalysts have been developed.



Scheme 1 : Generic reaction scheme for the dynamic kinetic resolution of racemic azlactones

References:

1. P. P. De Castro, A. G. Carpanez and G. W. Amarante, Chem. Eur. J., 2016, **22**, 10294-10318.
2. Z. Rodríguez-Docampo, C. Quigley, S. Tallon and S. J. Connon, J Org Chem, 2012, **77**, 2407-2414.
3. Y.-C. Zhang, Q. Yang, X. Yang, Q.-N. Zhu and F. Shi, Asian J. Org. Chem., 2016, **5**, 914-919.

Project: 16566

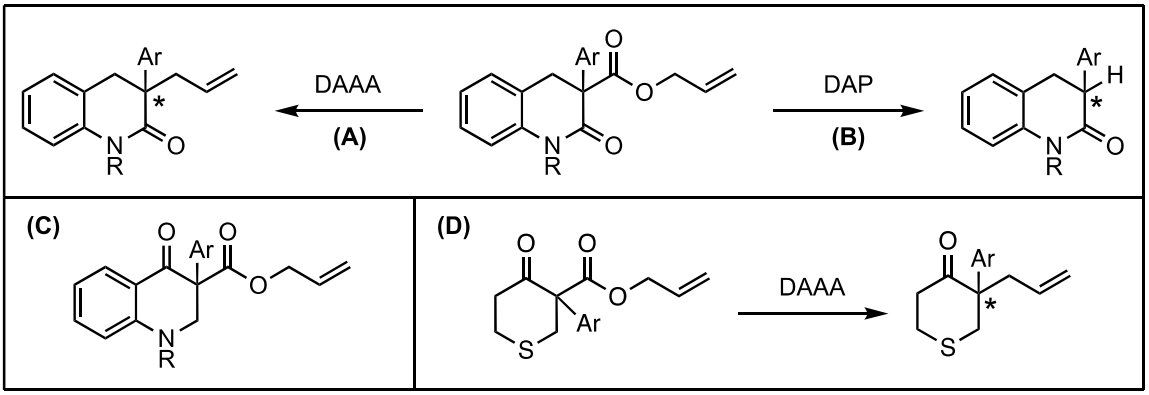
SYNTHESIS OF HETEROCYCLES CONTAINING α-ARYL STEREOCENTRES *VIA* DECARBOXYLATIVE ASYMMETRIC TRANSFORMATIONS

Niamh Lehane and Patrick J. Guiry
UCD Centre for Synthesis and Chemical Biology, School of Chemistry, University College Dublin, Belfield, Dublin 4, Ireland

email: niamh.lehane@ucdconnect.ie, p.guiry@ucd.ie

Heterocycles constitute a significant portion of therapeutic agents in medicinal chemistry and are a prevalent motif in natural products.[1] Many biologically important molecules contain α-aryl stereocentres. Pd-catalysed decarboxylative asymmetric transformations of α-aryl β-amido/keto allyl esters is an effective route to install these centres. The allylic group is a well-explored functional handle that has many applications in the synthesis of a wide range of structures. Our group has previously applied this decarboxylative catalysis to a range of substrates possessing α-aryl motifs.[2]

This project explores the synthesis of nitrogen- and sulfur-containing heterocycles *via* decarboxylative asymmetric transformations. The synthesis of α-allyl, α-aryl 3,4-dihydroquinolinones *via* decarboxylative asymmetric allylic alkylation (DAAA) will be described, with a range of substrates transformed to the desired product in high conversions and moderate enantioselectivities **(A)**. The synthesis of α-aryl 3,4-dihyroquinolinones *via* decarboxylative asymmetric protonation (DAP) will also be outlined, with good yields and excellent enantioselectivities **(B)**. The 2,3-dihydroquinolinone substrate has been synthesised and preliminary catalytic studies have commenced **(C)**. The α-aryl, β-keto allyl tetrahydrothiopyranones have been applied to DAAA catalysis, with varying success, to study the effects of substituent electronics **(D)**.



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[2] a) R. Akula, P. J. Guiry, *Org. Lett.* **2016**, *18*, 5472-5475; b) J. James, P. J. Guiry, *ACS Catal.* **2017**, *7*, 1397-1402; c) M. Jackson, C. Q. O'Broin, H. Müller-Bunz, P. J. Guiry, *Org. Biomol. Chem.* **2017**, *15*, 8166-8178; d) J. James, R. Akula, P. J. Guiry, *Adv. Synth. Catal.* **2018**, *360*, 3138-3149; e) J. James, R. Akula, P. J. Guiry, *Eur. J. Org. Chem.* **2019**, *2019*, 2421-2427.

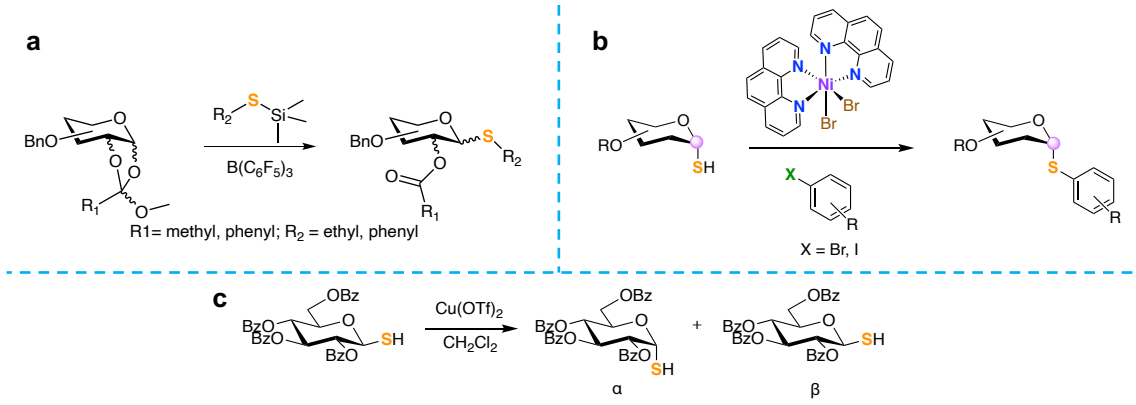
Grant code: 18/EPSRC-CDT/3582

EXPLORING NEW METHODOLOGY IN THIOGLYCOSIDE SYNTHESIS

Zoe Beato and Dr Xiangming Zhu
School of Chemistry, University College Dublin, Belfield, Dublin 4, Ireland

email: zoe.beato@ucdconnect.ie, xiangming.zhu@ucd.ie

Carbohydrates are a diverse class of molecules with a range of roles in biological processes such as cell signalling, infection, and immunity.[1] Their synthesis is crucial in understanding diseases and developing new therapies. Thiosugars, especially 1-thioglycosides, have become ubiquitous in carbohydrate chemistry. As glycosyl donors, their popularity arises from their stability, mild activation, and tuneable reactivity, making them essential to one-pot glycosylation strategies.[2] They are also employed as glycomimetics due to the enzymatic stability of the thioglycosidic linkage.[3] Stereochemistry at the anomeric centre plays an important role in both applications of thioglycosides, affecting reactivity and biological function of sugars.[1,4] However, control of this configuration is not trivial, with access to 1,2-*cis* thioglycosides remaining a major challenge in thioglycoside chemistry. This project aims to explore new methodology for the synthesis of stereochemically defined thioglycosides. Firstly, we have devised a synthesis of 'superarmed' thioglycosides via ring opening of 1,2-orthoesters which utilises trimethylsilyl thioethers and *tris*(pentafluorophenyl)borane to form the desired thioglycosides in exclusively 1,2-*cis* conformation (**a**).[5] We have also explored glycosyl thiols as nucleophilic agents for the formation of thioglycosides, facilitating retention of anomeric stereochemistry during alkylation and arylation reactions. We employ a nickel (II) catalyst for C-S cross coupling which, based on the work of Lipschutz,[6] can be carried out in aqueous surfactant solution (**b**). Crucial to this work is access to the glycosyl thiols in α conformation for which we aim to devise a mild, copper-catalysed epimerisation procedure (**c**).



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Dublin Chemistry Graduate Seminars 2023/24

Synthesis and Applications of Organosulfur Compounds

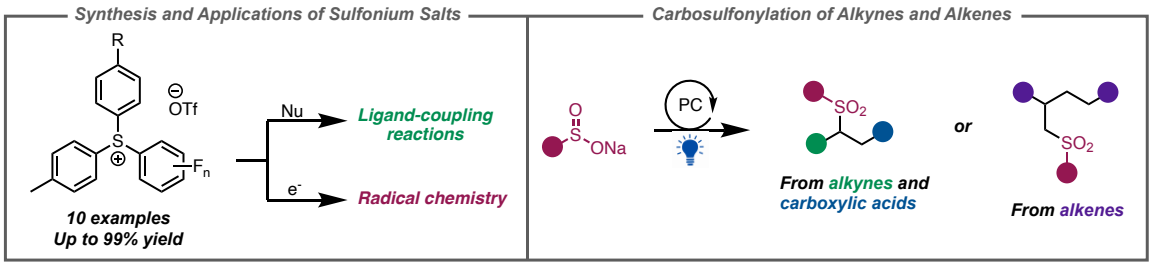
Eoghan M. McGarrigle, M. B. Reddy and Vanessa E. Becker
Centre for Synthesis and Chemical Biology, School of Chemistry, University College Dublin, Belfield, Dublin 4, Ireland

email: eoghan.mcgarrigle@ucd.ie, vanessa.becker@ucdconnect.ie

Organosulfur compounds have found widespread applications as both reagents and/or target compounds in organic chemistry. As a result, means in which these compounds can be synthesised or employed in reactions are of use to synthetic chemists. This work is focused on developing novel routes to organosulfur compounds, with a particular focus on sulfonium salts and sulfones.

Triarylsulfonium salts are a class of sulfonium salt finding increased attention in C-C bond forming reactions in recent years, however salts containing a polyfluorinated ring represent an underexplored class of these compounds.[1,2] This project focuses on the synthesis of sulfonium salts containing a polyfluorinated aryl ring *via* the arylation of sulfides by an iodonium salt. 10 examples have been synthesised in up to 99% yield. The applications of these salts in both ligand-coupling reactions and photochemical Giese additions has been explored.

Organosulfone compounds are highly versatile due to their prevalence in materials science, synthetic chemistry and pharmaceuticals.[1] Furthermore, sulfinates have recently emerged as good radical acceptors in photochemical reactions.[3] The second part of this talk will focus on the synthesis of sulfones *via* the metal-free photochemical carbosulfonylation of alkynes or alkenes with arylsulfinates. These strategies allow access to heavily functionalised sulfone products. Additionally, the functionalisation of these product molecules is discussed, with the synthesis of two *Sedum* alkaloids shown.[4]



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[2] S. I. Kozhuskov, M. Alcarazo, *Eur. J. Inorg. Chem.* **2020**, *26*, 2486-2500.
[3] J. M. Smith, J. A. Dixon, J. N. deGruyter, P. S. Baran, *J. Med. Chem.* **2019,** *62*, 2256-2264.
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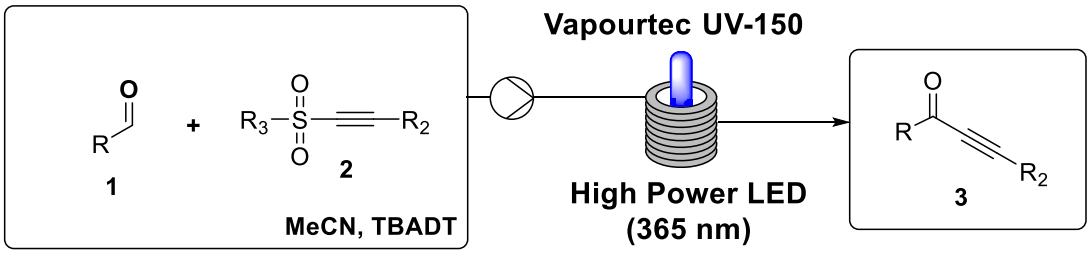
Exploring the Utility of Radicofugal Groups in Photochemical Flow Processes to Access Ynones

Marcus Baumann and Adam Cruise
UCD Centre for Synthesis and Chemical Biology, School of Chemistry, University College Dublin, Belfield, Dublin 4, Ireland

email: marcus.baumann@ucd.ie, adam.cruise@ucdconnect.ie

Recent advancements in photoredox catalysis, photosensitisers and photoflow processes have together created a versatile toolkit for all chemists, enabling efficient and viable routes to access a large range of carbon and heteroatom-based radicals.[1] A very common application of these generated radical species is their addition to electron deficient π-systems, resulting in the loss of a π-bond[2]. This work investigates the viability of radicofugal groups to restore π-bonds in Giese-type additions. This is achieved by the radicofugal groups stability as a free radical, its activation of the π-bond, and its ability to undergo β-scission to restore the previously broken π-bond.

This work is focused on the use of acyl radicals generated from aldehydes to access ynones (**3**). Through a known method of generating acyl radicals using tetrabutyl ammonium decatungstate[3] subsequent radical addition to the alkynes with an installed sulfone based radicofugal group (**2**) affords ynone (**3**). Typically, accessing ynones requires the use of Pd and Cu in the Sonagashira reaction in a moisture sensitive process or the use of strong bases and oxidative conditions. Instead, this route offers air and moisture tolerance, modest to excellent yields, superior functional group tolerance and proceeds in a short time frame. This work also demonstrates the advantages of flow chemistry for photochemical processes. Exploiting spatiotemporal processing and photosensitisers, unwanted side reactions are inhibited, resulting in a more sustainable route to the target ynones (**3**).



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[1] (a) L. Capaldo, D. Ravelli, *Org. Lett.* **2021**, *23*, 2243-2247; (b) D. Ravelli, M. Fagnoni, T. Fukuyama, T. Nishikawa, I. Ryu, *ACS Catal.* **2018**, *8*, 701-713; (c) J. Wang, Y.-B. Pang, N. Tao, R.-S. Zeng, Y. Zhao, *J. Org. Chem.* **2019**, *84*, 15315-15322; (d) X. Q. Hu, J. R. Chen, Q. Wei, F. L. Liu, Q. H. Deng, A. M. Beauchemin, W. J. Xiao, *Angew. Chem. Int. Ed.* **2014**, *53*, 12163-12167.

[2] B. Giese, *Angew. Chem. Int. Ed. Engl* **1983**, *22*, 753-764.

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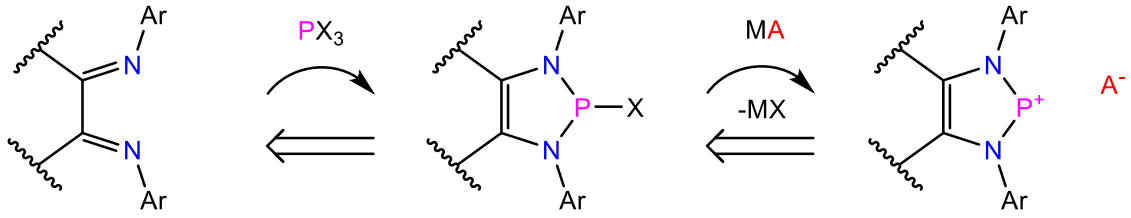
TOWARDS PHOSPHORUS CATIONS AS MAIN GROUP CATALYSTS

Tom N. Hooper and Christine M. Coffey
School of Chemistry, University College Dublin, Belfield, Dublin 4, Ireland

email: tom.hooper@ucd.ie, christine.coffey@ucdconnect.ie

Dependence on an ever-dwindling supply of transition metals (TMs) for their catalytic ability necessitates research into the development of candidates based on more-abundant elements.[1] Phosphenium cations (**3**), divalent phosphorus centres with a positive charge, have been shown to be effective main group catalysts in reactions such as imine reductions and hydroborations and are of interest for their potential in Frustrated Lewis Pair (FLP) chemistry.[2] The aim of this work is to determine the catalytic viability and potential scope of a number of phosphenium cations through the synthesis and subsequent analysis of catalytic candidates, with the view to provide viable alternatives to their well-established and widely employed TM counterparts.



Diimine Ligand (**1**) Phosphine Halide (**2**) Phosphenium Cation (**3**)

The phosphenium cations presented here are elements of a particular subset referred to as N-heterocyclic phosphenium cations (NHPs), characterised by the formation of a 5-member aromatic ring. Isolation of phosphenium cations involved synthesis of α-diimine ligand backbones (**1**), insertion of phosphorus centres through reaction with phosphorus trihalides and subsequent salt metathesis reactions to exchange the strongly coordinating halides with a weakly coordinating anions (A^-).[3] A number of novel diimine ligands, phosphine halides (**2**) and phosphenium cations were synthesised. It is hoped that this work will add to the library of existing phosphenium cations, as well as provide the reactivity studies required for the determination of their catalytic viability.

References:

[1] C. Wilkins, R. L. Melen, *Coord. Chem. Rev.* 2016, *324*, 123-139.
[2] D.W. Stephan, *Acc. Chem. Res*. 2015, *48*, 306−316.
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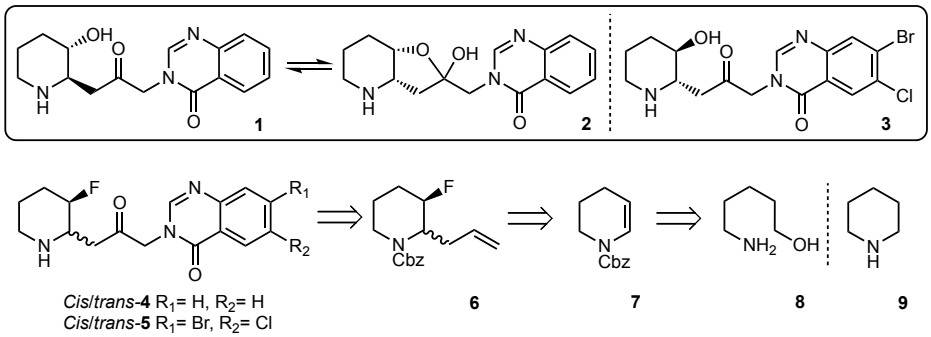
Dublin Chemistry Graduate Seminars 2023/24

Synthesis of the *cis*- and *trans*-3-Fluoro Analogues of Febrifugine and Halofuginone

Fahad Alkhathami, Marina Rubini and Paul Evans
UCD Centre for Synthesis and Chemical Biology, School of Chemistry, University College Dublin, Belfield, Dublin 4, Ireland

email: fahad.alkhathami@ucdconnect.ie

The quinazolinone alkaloid Febrifugine **1** and its hemiketal isomer **2** have been isolated from leaves and roots of *Dichroa febrifuga* and have been subject of research due to their anti-malarial properties. A non-natural analogue termed Halofuginone **3** has been explored as a potential pharmaceutical.[1] The main goal of this project is the synthesis and bioactivity characterization of the novel fluorinated analogue of **1**. Thus, the synthesis of racemic *cis*- and *trans*-3-fluorofebrifugine **4**/3-fluorohalofuginone **5** is described. This seven-step process relies on an electrophilic fluorination-allylation sequence[2] that generates a mixture of *N*-Cbz protected, diastereomeric 2-allyl-3-fluoropiperidines **6**. On separation, the allyl group of each diastereomer underwent a Wacker oxidation-methyl functionalisation sequence that enabled introduction of the required quinazolinone/haloquinazolinone portion. Finally, removal of the *N*-Cbz protecting group lead to isolation of **4** and **5** as their dihydrobromide salts. Finally, the interconversion between the *cis*- and *trans*-diastereomers of **4** was studied.



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Grant code: 1071769390

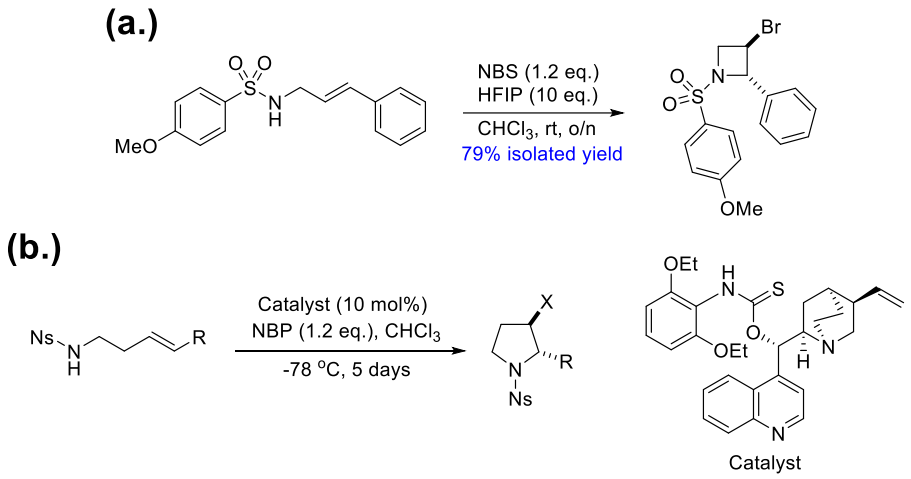
Stereoselective Synthesis of Saturated Nitrogen Heterocycles

Matthew Kiernan, Paul Evans

paul.evans@ucd.ie, matthew.kiernan@ucdconnect.ie

Centre for Synthesis and Chemical Biology, School of Chemistry, University College Dublin, Belfield, Dublin 4.

Cyclic nitrogen-containing compounds are commonly encountered in natural products and active pharmaceutical ingredients, with a recent article identifying that 59% of small molecule-based drugs contain a nitrogen heterocycle.[1] As a result, methods to construct this valuable type of compound are of vital importance to both the synthetic and medicinal chemistry communities. Furthermore, as the vast majority of medicinally-relevant saturated nitrogen heterocycles contain chiral centres around their rings, particular emphasis has recently been placed on the ability to produce these structures stereoselectively.



Our work in this area is specifically focused on harnessing bromonium ion induced cyclizations to provide access to these heterocycles. Recent efforts have resulted in the discovery of a highly diastereoselective, hexafluoroisopropanol (HFIP) induced bromoaminocyclization of allylic sulfonamides to the corresponding brominated azetidines (Figure 1a.) This represents the first reaction to furnish azetidines from allylic amine derivatives that employs only commercially available reagents. Furthermore, we are also investigating the viability of applying a recently reported asymmetric pyrrolidine-forming bromoaminocyclization (Figure 1b.)[2] to the synthesis of complex, heterocyclic scaffolds, such as that found in natural products like crinane.

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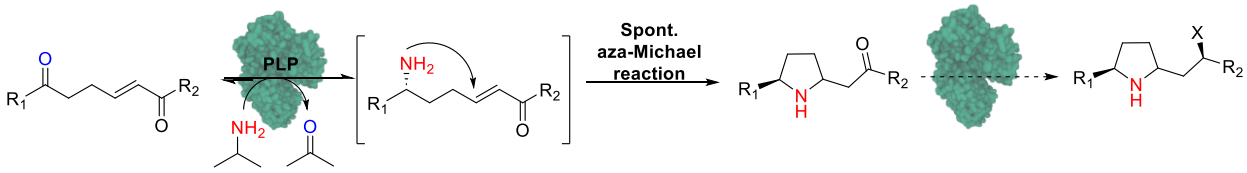
EXPANDING THE SCOPE OF TRANSAMINASE-TRIGGERED AZA-MICHAEL CHEMISTRY FOR THE SYNTHESIS OF HIGH VALUE TARGETS

Elaine O'Reilly and Aoife Martin
School of Chemistry, University College Dublin, Belfield, Dublin 4, Ireland

email: elaine.oreilly@ucd.ie, aoife.martin1@ucdconnect.ie

In recent times, biocatalysis has become one of the well-established pillars of asymmetric catalysis. Most of the focus on the application of enzymes has involved enzyme mediated single functional group interconversion to give a final product, but this work aims to develop enzyme-triggered reactions. An enzyme-triggered reaction is considered a biocatalytic conversion of a substrate to an intermediate that spontaneously undergoes a subsequent inter- or intramolecular chemical reaction.[1]

We propose a transaminase (ATA)-triggered intramolecular aza-Michael reaction (IMAMR), where a simple prochiral ketoenone undergoes regio- and stereo-selective amination to form a chiral amine that spontaneously cyclises, affording disubstituted pyrrolidines. The pyrrolidine scaffold is ubiquitous in natural products, synthetic drugs and organocatalysis.[2,3] This work expands the scope of the ATA-triggered aza-Michael chemistry that has been previously reported by our group to synthesise 2,6-disubstituted piperidines and cyclic β-enaminones.[4,5] The ketoenone panel was converted to their corresponding chiral pyrrolidine products using commercially available ATAs. While the transamination reactions are highly selective, the spontaneous IMAMR results in the formation of diastereoisomers that were isolated as inseparable mixtures. Further enzymatic steps are being investigated to further derivatise the ketone functional handle following the ATA-triggered aza-Michael reaction.



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DEVELOPMENT OF CONVERGENT BIOCATALYTIC TRANSFORMATIONS FOR THE SYNTHESIS OF COMPLEX ALKALOIDS

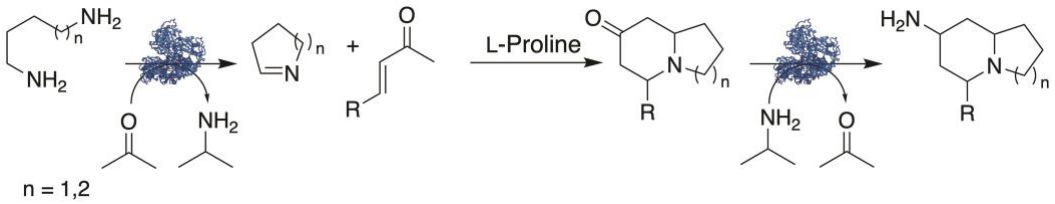
Elaine O'Reilly and Amber L. Barry
UCD School of Chemistry, O'Brien Centre for Science, University College Dublin, Belfield, Dublin 4, Ireland, D04 V1W.

email: elaine.oreilly@ucd.ie, amber.barry@ucdconnect.ie

Biocatalysis involves the use of catalytic proteins (enzymes) to perform chemical transformations of simple, achiral materials into high value, chiral products. Biocatalysis enables sustainable synthetic routes to access synthetically challenging compounds, operating in mild reaction conditions.[1] The impressive selectivity and control of enzymes offers an attractive alternative to traditional catalysis,[2] finding a diverse range of applications in industry.[3]

Alkaloids are a class of naturally occurring nitrogen-containing organic compounds that exhibit many physiological effects.[4] Synthetic methodologies accessing *N*-heterocycles and their derivatives is of interest to chemists, but previous synthetic routes developed often require precious metal catalysts and energy-demanding reaction conditions.

The design of a novel cascade methodology involving biocatalysis and organocatalysis to synthesise complex natural product alkaloids and their derivatives was envisaged. This biomimetic approach is initiated by a transaminase-catalysed transformation of a diamine into a reactive cyclic imine,[5] which can subsequently undergo an L-proline facilitated intramolecular Mannich-*aza*-Mannich reaction (IMAMR), with an aryl enone.[6] The use of additional enzymes can further functionalise products, thereby creating a novel multi-enzyme cascade.



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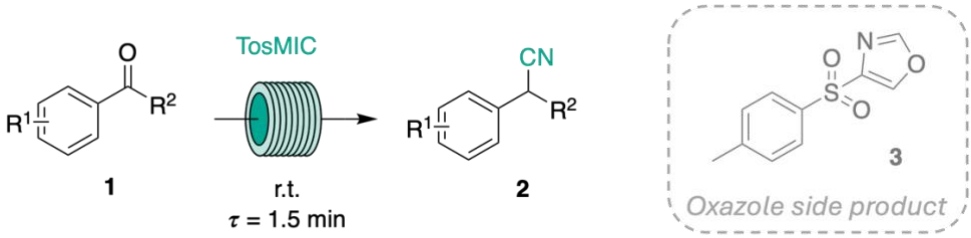
A Cyanide-Free Continuous Synthesis of Nitriles and Their Manipulation En Route to N- and O-Heterocycles

Assoc. Prof. Marcus Baumann and Niamh Disney
UCD Centre for Synthesis and Chemical Biology, School of Chemistry, University College Dublin, Belfield, Dublin 4, Ireland

email: marcus.baumann@ucd.ie, niamh.disney@ucdconnect.ie

Modern chemical synthesis typically relies on the use of traditional batch reactors. Although straightforward, this approach can become problematic when performing hazardous or difficult to control reactions on a larger scale. Recently however, continuous flow synthesis has been gaining momentum as an exciting alternative which offers improved reaction control and scalability. The platform uses narrow tubing to allow for the synthesis of compounds 'on tap' in a fast, safe, and efficient manner.[1]

Herein, we describe an efficient cyanide-free synthesis of nitriles (**2**) in continuous flow mode, using a masked nitrile transfer reagent known as TosMIC. The reaction was initially explored in the 1970s using traditional batch synthesis but was highly inefficient.[2] Upon transferring this reaction to a flow setup high yields were achieved in just 1.5 min and the characterisation of an oxazole side product (**3**) gave additional insight into the reaction mechanism.[3] This novel process rendered multigram quantities of product in short periods of time (8.8 g/h) demonstrating the scalability and usefulness of this process in large scale manufacturing.



Advantages over batch:

✓ Short residence time ✓ Scalable ✓ High throughput

Selective DIBAL-H reduction of the resulting nitriles has been achieved at ambient temperature in a continuous flow setup en route to access medicinally relevant N- and O-heterocycles.

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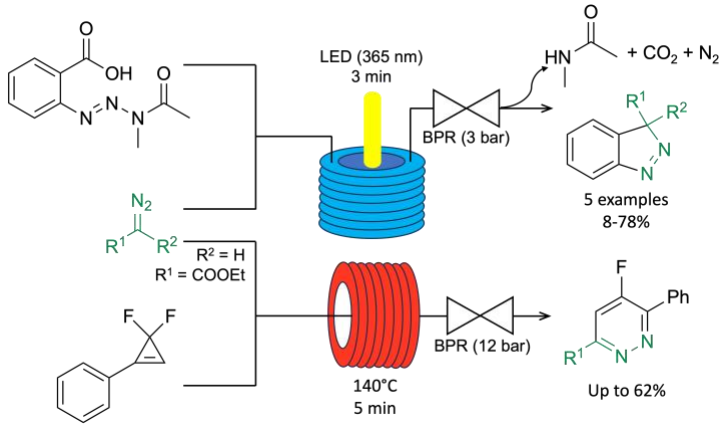
Harnessing the Untapped Potential of Multiple High-Energy Species *via* a Safe and Scalable Continuous Flow System

Prof. Marcus Baumann and Jonathan Devlin
School of Chemistry, University College Dublin, Belfield, Dublin 4, Ireland

email: marcus.baumann@ucd.ie, jonathan.devlin@ucdconnect.ie

Flow chemistry provides a safer and more controlled environment for handling hazardous materials. It can achieve this primarily through reducing the quantities involved and facilitating more precise control over the reaction conditions. This leads to superior mixing and temperature control, allowing for enhanced reproducibility. Continuous flow systems aid in scaling up hazardous reactions, as the throughput is a factor of operational run time as opposed to volume.

One underutilised hazardous species of note is benzyne. Although it was discovered almost a hundred years ago, it remains underexploited due to safety concerns and scalability issues. [1] A photochemical benzyne forming process was chosen due to the beneficial synergy between photochemistry and flow chemistry. [2-4] The resulting benzyne was reacted in situ with diazo species in [3+2]-cycloadditions, resulting in indazole products. Similar reactions have been carried out in batch, with Kobayashi's reagent as the benzyne source, but these tend to have long reaction times of up to 24 hours. [5] The flow reactions were rapid with a residence time of only 3 minutes, while still allowing the reaction to be scaled up. Diazo species were also paired with difluorocyclopropenes, yielding 5-fluoropyridazine products. Batch reactions could take over 48 hours. Flow allowed this to be cut down to 5 minutes through superheating the solvent, allowing the throughput to be far superior. [6] The flow system also benefitted by switching from DMF to a more benign solvent (i.e. MeCN) and removing the requirement for an argon atmosphere.



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AN ELECTROCHEMICAL OXIDATION PRINS-TYPE CYCLISATION SEQUENCE FOR THE CONSTRUCTION OF 1,3-OXAZINAN-2-ONES *VIA N*-ACYLIMINIUM IONS

Dandan Lin, Paul Evans, Elaine O'Reilly
UCD Centre for Synthesis and Chemical Biology, School of Chemistry, University College Dublin, Belfield, Dublin 4, Ireland

email: dandan.lin@ucdconnect.ie

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

In this project (**Figure 1**), we perform the electrochemical oxidation using an ElectraSyn device, and then use a Prins-type cyclisation[4] to construct the 1,3-oxazinan-2-one skeleton **(4)** from a variety of cyclic and acyclic *N*-Boc compounds **(1)**. The scope of the sequence to date and its stereochemical outcome will be described, which includes the substituents (R), ring size and acyclic examples. Also included will be the optimisation of the Prins-type cyclisation to form **(4)**.

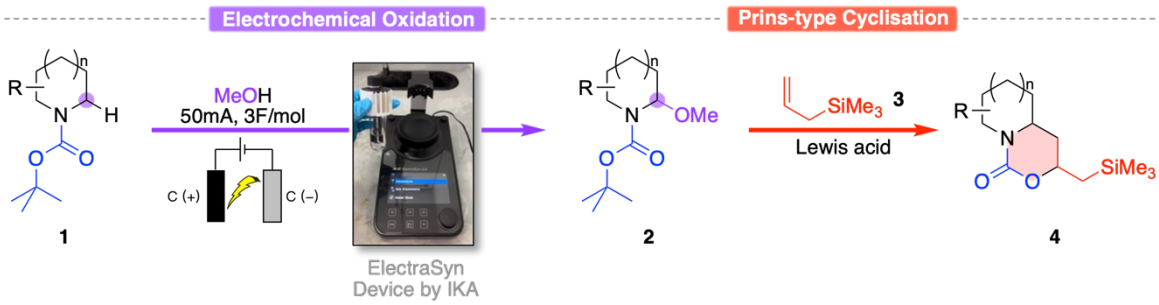

Figure 1. An Electrochemical Oxidation Prins-type Cyclisation Sequence

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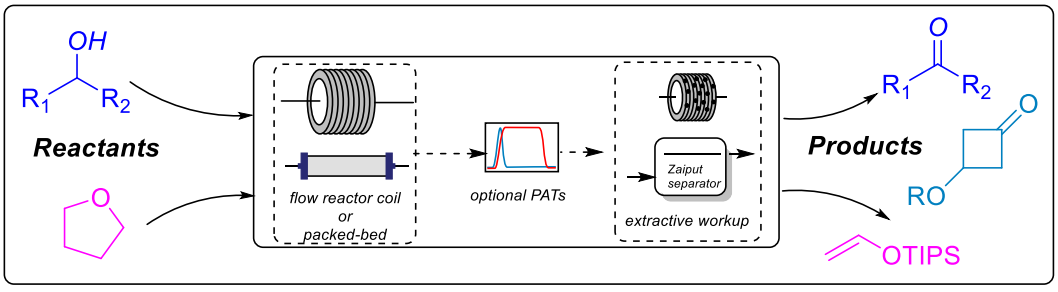
FLOW APPROACHES FOR THE IMPROVED SYNTHESIS OF PHARMACEUTICAL BUILDING BLOCKS

Parth Naik[a], Patrick O'Neill[#] and Marcus Baumann[a*]
UCD Centre for Synthesis and Chemical Biology, School of Chemistry, University College Dublin, Belfield, Dublin 4, Ireland
[#] Pfizer Ireland, Ringaskiddy, Cork, Ireland

email: parth.naik@ucdconnect.ie, pat.o'neill@pfizer.com, marcus.baumann@ucd.ie

Flow Chemistry is an enabling technology for the development of robust processes and the safe scale-up of hazardous and highly reactive chemistry, it offers precise control over temperature and mixing to develop safer and robust processes specifically involving high energy intermediates.[1] In recent years, this technology has gained traction in the fine chemical industry and academia to perform and discover new chemical reactions.[2-3]

In our studies to develop robust scalable flow processes, we initially focused on the selective oxidation of alcohols to demonstrate easy scalability. The developed methodology was well tolerated by commercial substrates as well as drug like molecules.[4] A subsequent study addressed the challenge of handling hazardous pyrophoric materials such as organolithium reagents which can limit the scale of batch reactions. This issue can be addressed by minimising the reaction volume when performed in a coil reactor which provides excellent heat transfer rates. Flow chemistry can be a useful tool to tune reaction parameters to maximise the degradation of THF and utilize the degradants in potential uses such as cycloaddition reactions. A useful coupling partner for cycloaddition reactions from a chemist's repertoires are ketenes as they allow expanding the chemical intermediates inventory. One of the applications of ketene chemistry can be targeted to generate 3-hydoxycyclobutanone as a valuable building block for the fine chemical industry.



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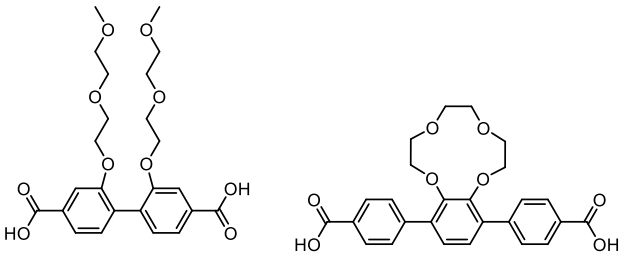
Approaches Towards the Synthesis of MOF Ligands for Novel Battery Material Applications.

Thorfinnur Gunnlaugsson and Owen Oseghale
Trinity Biomedical Sciences Institute, School of Chemistry, Trinity College Dublin, Pearse Street, Dublin 2, Ireland

Email: *GUNNLAUT@tcd.ie, oseghalo@tcd.ie*

In the current age of technology, machines and devices have upgraded and evolved at extraordinary rates and continue to do so. To keep up with the demand of rapidly advancing technology, the optimisation of how we produce, use, and store energy must be incentivised. Limitations in the natural energy resources are also more evident day by day.[1] Out of the many ideas that have been explored in order to face the current energy crisis, one novel approach is the utilisation of reticular chemistry. Reticular chemistry has steadily been researched and improved, leading to porous, versatile, and tuneable crystalline frameworks.[2],[3] Over the past three decades, metal-organic frameworks (MOFs) and covalent organic frameworks (COFs) have quickly demonstrated their advantages in many areas, including ionic and electronic conduction.[4] MOFs have been designed as materials for electrodes in lithium-ion batteries. Most of these, however, do not perform very well due to their poor redox activity and instability in the aqueous environment of the electrolyte.[5] A battery suitable MOF which could harbour Li^+ ions and exhibit adequate redox activity then becomes the main focus in this area.

This project is aimed towards synthesising MOF compatible ligands focused on Li^+ capturing properties by exploiting the functionalities of crown ethers. Further modification of these ligands will allow for the exploration of alternative ion capturing properties. Following this, the secondary aim is to synthesise various MOFs with prospects of implementation into Li^+, Na^+, or Sulphur batteries.



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Grant Code: 15821

NAPHTHALIMIDES EXHIBITING AGGREGATION INDUCED EMISSION FOR BIOIMAGING APPLICATIONS

[a]L. Constance Sigurvinsson, [a]Adam F. Henwood, [b]Massimiliano Garre, [b]Donal F. O'Shea, [a]Thorfinnur Gunnlaugsson,

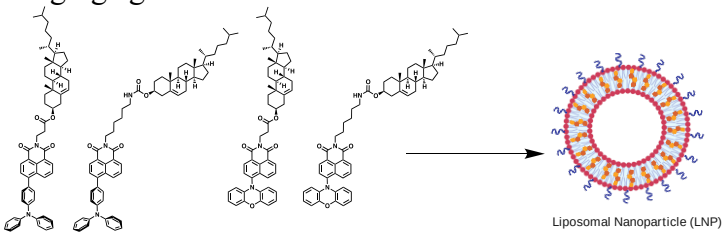
[a] *School of Chemistry and Trinity Biomedical Sciences Institute, Trinity College, Dublin, Ireland*

[b] *Department of Pharmaceutical and Medicinal Chemistry, Royal College of Surgeons in Ireland, 123 St Stephen's Green, Dublin, Ireland*

email: sigurvil@tcd.ie, gunnlaut@tcd.ie,

1,8-Naphthalimides (Naps) are highly versatile organic moieties that have been used in many different applications ranging from therapeutics, luminescent bioimaging agents, sensors, soft materials, and organic light-emitting devices.[1] A growing class of Naps are those exhibiting aggregation-induced emission (AIE)[2,3] which has rendered them useful, for example, as nitroaromatic sensors[4] or very recently as real-time lipid droplet imaging agents.[5] The latter example was built on Naps combining an electron donor-acceptor structure with multiple singly-bonded aromatic rotor groups, conferring AIE that could be visualised using fluorescence lifetime imaging (FLIM) as the dyes are delivered into cells and localise within the lipid droplets.

This project builds on this work by addressing three key areas: 1) photophysics; 2) biological properties; 3) dye delivery. Incorporation of stronger electron donors redshifts the emission and induces delayed fluorescent lifetime signatures that are identifiable with FLIM. Addition of cholesterol moieties generates dyes with specific targeting units for organelles such as the cell membranes, as well as facilitating the self-assembly process with polymer lipids to generate lipid nanoparticles (LNPs) capable of delivering the imaging agents to the cells.



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Dublin Chemistry Graduate Seminars 2023/24

VALORISATION OF WOOD RESIDUES INTO PRODUCTS

Ramesh Babu and Minu Masliha
School of Chemistry, Polymeric Materials & Nano Composites Group, Trinity College Dublin, The University of Dublin, College Green, Dublin 2, Ireland

email: BABUP@tcd.ie, pallikkm@tcd.ie

The relentless pursuit of sustainable practices within various industries has fuelled exploration into innovative methods for extracting valuable compounds from renewable resources and byproducts. The forestry industry, for instance, generates a significant amount of bark residue during log debarking, typically used for heat generation through combustion. However, the bark, constituting 9-15% of the volume and 13-21% of the dry weight of a log, is a complex material comprising pectic compounds, phenolic polymers, polysaccharides, and cross-linked polyesters[1]. Tannin polyphenols, known for their eco-friendliness and diverse applications, have gained interest due to their abundance; however, extraction remains a major challenge due to their heterogeneous nature[2]. This project focuses on the valorisation of bark residues to create value-added materials, particularly emphasizing the production of next-generation wood materials. The focus lies on extracting tannins using various efficient methods, including pressurized hot water extraction, ultrasonication-assisted extraction, and hydrodynamic cavitation-assisted extraction. Tannin being an abundantly available bio-based polyphenol exhibits good intumescence and char-forming characteristics upon exposure to heat[3]. The extracted tannins were then incorporated into wood fibre to improve the thermal properties of medium-density fibreboard [MDF] products. Furthermore, the bark extracts are evaluated as a carbon source to produce biodegradable polymer polyhydroxyalkanoates [PHAs]. PHA holds immense promise as an eco-friendly alternative to conventional plastics derived from fossil fuels[4]. Another aspect involved utilizing lignin, a residual by-product from the forest industry, which offers various functional groups, enabling its chemical modification for water purification applications[5]. Lignin has been repurposed as a flocculant to eliminate aqueous phosphates from dairy wastewater. Presented here is a brief overview of the work done thus far that contributes to the sustainable utilization of forest residues as a functional material and holds promise for developing environmentally friendly and economically viable materials.

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NXTGENWOOD
An Roinn Talmhaíochta, Bia agus Mara
Department of Agriculture, Food and the Marine
#2019PROG704

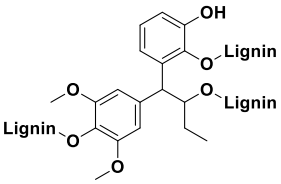
Extraction, depolymerization and fractionation of lignin from Irish wood for valorization into products

Jessica De Micco [1,2], Mauricio Troncoso Castellanos [3], Colm Faulkner [2], Kevin O' Connor [3], Ramesh Babu Padamati [1,2]
[1] Polymeric Materials & Nano Composites Group [PMNC], [2] Trinity College Dublin, Dublin 2, Ireland [3] University College Dublin, Belfield, Dublin 4, Ireland

email: jdemicco@tcd.ie, babup@tcd.ie

Fossil-fuel based sources are responsible not only for 25% of greenhouse gas emissions but also for environmental pollution due to lack of biodegradability [3]. Therefore, a transition towards a circular and bio-based economy is necessary, preferring bioresources to current petroleum-derived materials [2]. Particularly, lignin biomass has great potential as feedstock for the chemical industry due to its high abundance, renewability, aromaticity, and biodegradability [4]. However, lignin application is strongly influenced by its source and its extraction techniques. One of the major challenges of converting lignin into high-value products is its depolymerization and fractionation due to its complex structure [1,5]. Lignin pre-treatment is a crucial step in the depolymerization process as it greatly impacts lignin fragmentation efficiency and final value [2].

The present work evaluates different pre-treatments techniques to enhance lignin depolymerisation using low energy consumption methods to develop efficient and sustainable fractionation processes. Lignin-derived products were used to generate i) biodegradable polymer polyhydroxyalkanoate (PHA) by fermentation and ii) lignin-based composites by melt mixing. Cavitation resulted in an efficient pre-treatment method to increase lignin dispersibility in water. Depolymerization – via thermal hydrolysis – was carried out using mild conditions and a higher yield was obtained when water/ethanol was used as solvent compared to water. The isolated liquid fraction was used as a carbon source for *P. Putida KT2440* bacteria's growth. The recovered solid fraction was combined with commercial bio-polybutylene succinate (Bio-PBS) in different percentages. Preliminary results showed that *P. Putida KT2440* bacteria strain grows on degraded lignin-based compounds. Furthermore, composites prepared with depolymerised lignin present improved thermal properties compared to virgin lignin composites with Bio-PBS polymer.



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Dublin Chemistry Graduate Seminars 2023/24

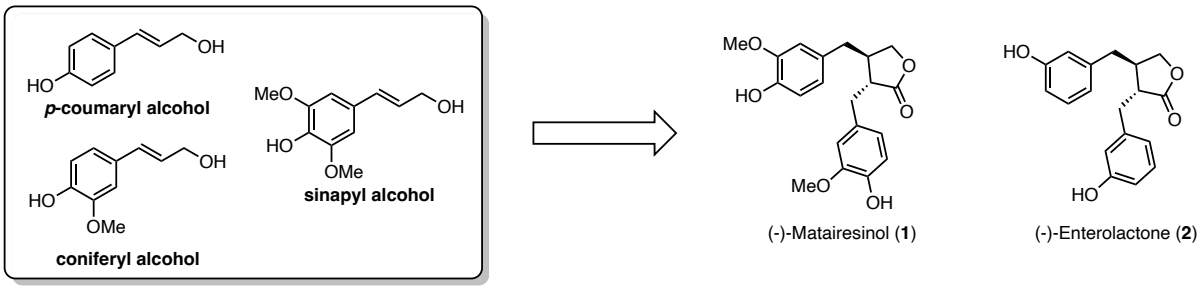
UTILISING LIGNIN DEGRADATION PRODUCTS AS STARTING MATERIALS FOR THE SYNTHESIS OF NATURAL PRODUCTS

Zoë Byrne and Patrick J. Guiry
UCD Centre for Synthesis and Chemical Biology, School of Chemistry, University College Dublin, Belfield, Dublin 4, Ireland

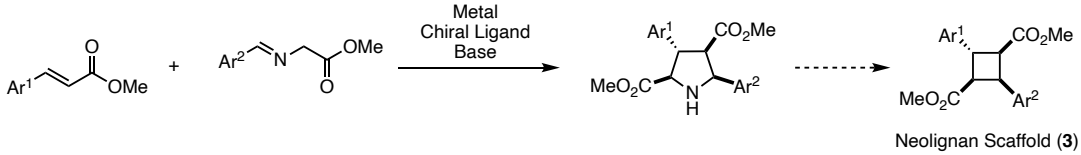
email: zoe.byrne2@ucdconnect.ie, p.guiry@ucd.ie

Lignin is a complex, three-dimensional phenolic biopolymer, which constitutes one of the three primary components of lignocellulose, along with cellulose and hemicellulose. It is formed from the polymerisation of three phenylpropanoid units; *p*-coumaryl alcohol, sinapyl alcohol, and coniferyl alcohol, collectively termed monolignols.[1] The nature of these monomers makes lignin a potential sustainable feedstock for the production of platform chemicals. In addition, by virtue of their phenolic nature, the monolignols display a range of bioactivities which can be exploited. To date however, this feedstock has been vastly underutilised, with lignin routinely being combusted for energy production by the pulp and paper industry. [2]

This project focuses on utilising these monolignols as starting materials for the synthesis of lignans, a large class of natural products present in plants. Lignan natural products possess a great variety of different structures, most commonly featuring two aryl groups linked by a C-4 unit, all of which display distinct pharmacological properties.[3] Presented here is work carried out to date on the development of a general strategy to access a range of dibenzylbutyrolactone lignans, namely (-)-matairesinol (**1**) and (-)-enterolactone (**2**).



More recent work looks at utilising monolignols in the [3+2] asymmetric cycloaddition reaction to access chiral pyrrolidines. Subsequent ring contraction of these pyrrolidines *via* skeletal editing is proposed to give rise to chiral cyclobutane scaffolds which will act as precursors to a series of neolignan natural products (**3**).[4]



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An Roinn Talmhaíochta, Bia agus Mara
Department of Agriculture, Food and the Marine

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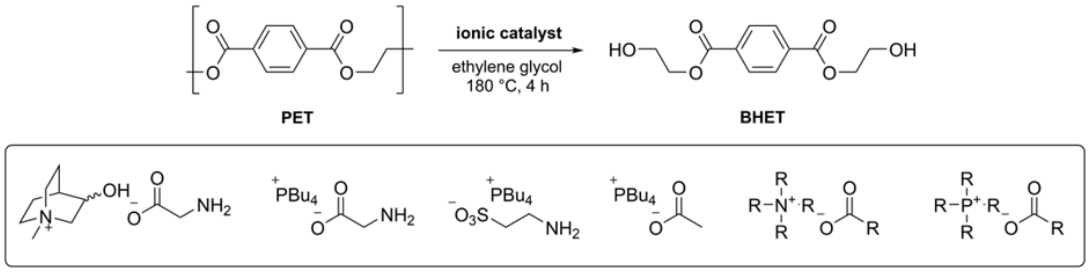
Development of novel ionic catalysts for glycolytic depolymerisation of polyethylene terephthalate.

Stephen J. Connon, Cristina Trujillo, Diana Bura and Lorenzo Pedrini
TCD Trinity Biomedical Science Institute, School of Chemistry, Trinity College Dublin, Dublin, Dublin 2, Ireland

email: connons@tcd.ie, cristina.trujillodelvalle@manchester.ac.uk, burad@tcd.ie, pedrinil@tcd.ie

Polyethylene terephthalate (PET) is a petroleum derived plastic, constituent of beverage, bottles, fibres and food packaging, and one of the most common plastics present in of our everyday life.[1] The development of efficient, green, and inexpensive ways of recycling this polymer to virgin-like quality material is the goal for a long-term polymer life cycle, leading towards a circular economy around the use of PET. In this sits the potential of chemical catalytic recycling which can deliver pure monomer while utilising green solvents for the process.[2] Our work focuses on the development of ionic catalysts for the glycolytic-depolymerisation of PET to generate monomeric units of bis(2-hydroxyethyl) terephthalate (BHET). Experimental studies led to the understanding of the importance of the carboxylate anion in the catalysis. In addition, systematic studies revealed that cation substitution of the benchmark cholinium cation for a tetrabutylphosphonium unit substantially enhanced activity. Mechanistic studies highlighted the often overlooked role of ethylene glycol as the source of hydrogen bonding stabilisation in the transition state, demonstrating both experimentally and computationally the lack of advantage associated with the use of cholinium cation for the catalysis.[3] Recent efforts focus on the screening of different carboxylate anions and phosphonium/ammonium cations toward structure activity relationships in the search for even more efficient catalyst systems.



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Science Foundation Ireland sfi For what's next
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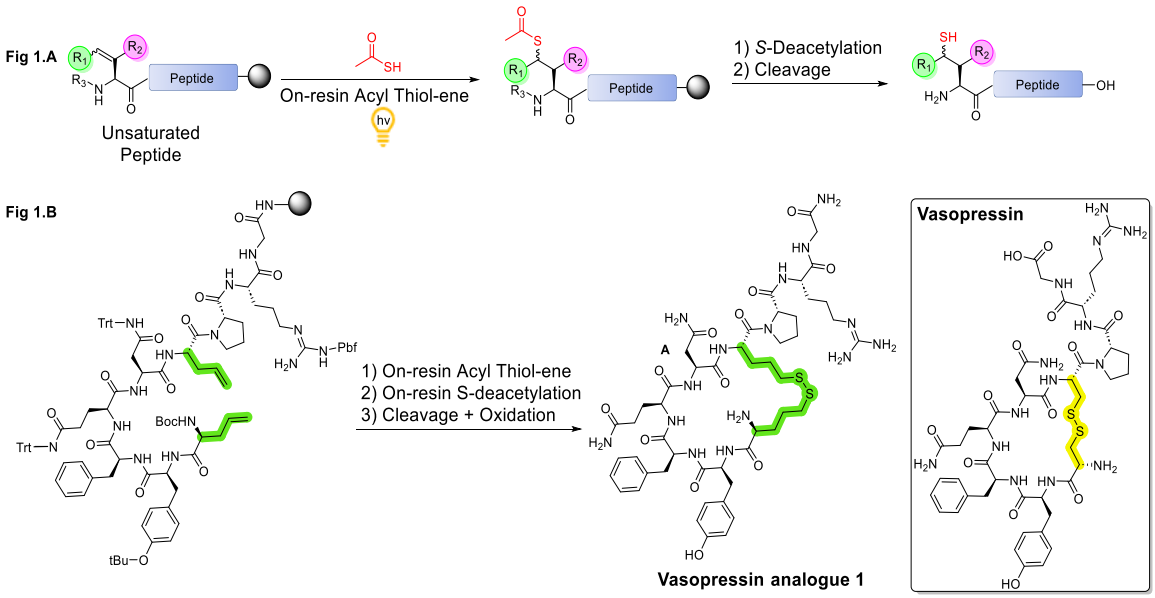
Dublin Chemistry Graduate Seminars 2023/24

ON-RESIN HYDROTHIOLATION TOWARDS PEPTIDE LIGATION AND MACROCYCLISATION

Eoin M. Scanlan, Joshua McLean and Nikita Ostrovitsa
School of Chemistry and Trinity Biomedical Sciences Institute, Trinity College Dublin, 152-160 Pearse Street, Dublin 2, Ireland

email: scanlae@tcd.ie, jmclean@tcd.ie, ostrovin@tcd.ie

The thiol moiety is a ubiquitous synthetic handle employed for chemical modification of peptides and chemical proteins synthesis via native chemical ligation (NCL).[1] The radical mediated thiol-ene reaction has been widely utilized in peptide chemisty for macrocyclization and for chemical modifications including lipidation and glycosylation, but applications for the direct thiolation of peptide substrates remain underutilized.[2,3] This work describes the application of sequential acyl thiol-ene and *S*-deacetylation chemistries on-resin to furnish structurally diverse thiolated peptidic targets. Incorporation of unsaturated amino acids during peptide assembly permits the installation of thiol group under mild conditions, prior to global deprotection and peptide cleavage (**Fig 1.A**). The utility of this on-resin methodology is demonstrated through the synthesis of a range of thiolated peptides suitable for NCL, avoiding the laborious synthesis of thiolated natural amino acids. Finally, the methodology was applied to the generation of a small library of disulfide-based cyclic neuropeptides of vasopressin and somatostatin (**Fig 1.B).** Systematic replacement of cysteine with longer alkenyl amino acids followed by on-resin thiolation, provided access to diverse vasopressin and somatostatin derivatives with altered ring sizes.



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Grant code 210287

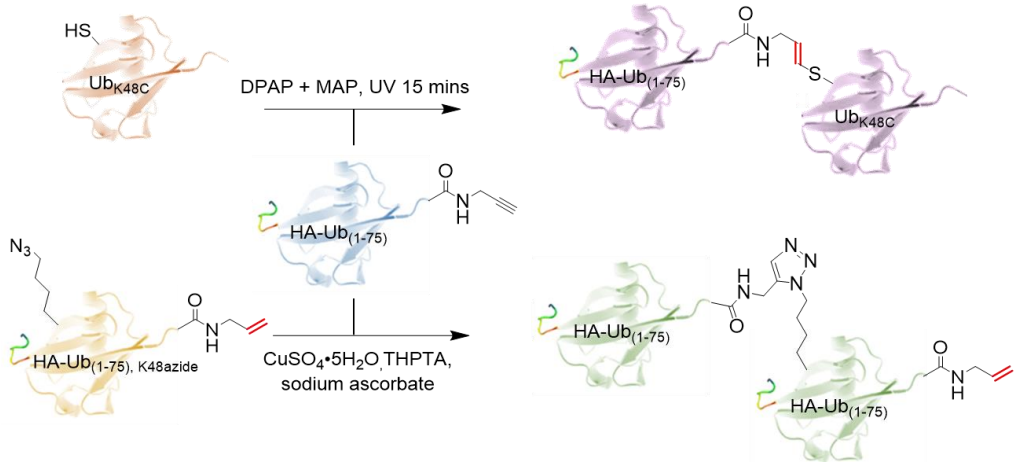
BIOCONJUGATION STRATEGIES FOR CREATING STRUCTURALLY DISTINCT PROTEIN SCAFFOLDS AND THEIR USE AS RADICAL PROBES OF DEUBIQUITINASES

Tomasz Pawlak, Suzannah Calvert, and Joanna McGouran
Trinity College Dublin School of Chemistry, Trinity Biomedical Sciences Institute, Pearse St, Dublin 2, Ireland

email: pawlakt@tcd.ie, calverts@tcd.ie, mcgouranj@tcd.ie

Deubiquitinases (DUBs) are enzymes that hydrolyse isopeptide bonds within polyubiquitin chains, or trim ubiquitin from target proteins.[1] Editing of protein ubiquitination regulates fundamental processes within cells. DUBs are therefore crucial for maintaining cellular homeostasis, and are often dysregulated in inflammation, cancer, and neurodegeneration.[2] Determining specificity, context-sensitive activation and time-resolved localization of DUBs *in vitro* and *in vivo* requires novel latent probes that imitate distinct substrates of DUBs.[3]

To address this challenge, we've constructed biocompatible di-ubiquitin Activity Based Probes (ABPs), specific for active DUBs targeting K48-linked polyubiquitin chains. Created ABPs contain latent alkenes with thiol-ene labeling capability,[4] either at the C-terminus, or as a linker between monomers. In this talk, we will present first examples of light-activated, radical thiol-yne protein-protein conjugation, resulting in a latent alkene linker. We will also present a K48-linked di-ubiquitin construct containing a terminal alkene, which was inspired by prior research on azido-substitution of lysines.[5]



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Project 211666, Award 16958

APPLICATIONS OF THIOL-ENE/YNE CHEMISTRY FOR PEPTIDE STAPLING AND BIOCONJUGATION

Eoin M. Scanlan, Lorenzo Guazzelli, Donal F. O'Shea, Andrea Mezzetta, Nikita Ostrovista, Sheila Fitzgerald, Joshua T. McLean, Inés Rabadán González.

Trinity Biomedical Sciences Institute, Trinity College Dublin, 152-160 Pearse street, Dublin 2, Ireland

Email: SCANLANE@tcd.ie, rabadngi@tcd.ie.

In recent years, peptide modification is gaining significance across a range of biomedical applications. Synthetic modifications, which are often analogous to post-translational modifications (PTMs), can be achieved using several methods, depending on the biomedical objective. Modified peptides have been used as drug candidates in the treatment of cancer, enzyme deficiency or metabolic disorders and infectious.[1] Free-radical mediated reactions are powerful tools for the modification of peptides and proteins. The thiol-ene coupling (TEC) reaction has emerged as a mild and efficient method for peptide stapling, macrocyclization and disulfide rebridging.[2] The radical mediated TEC reaction exhibits high atom economy, excellent yields and good regiocontrol. It is also robust in its tolerability to aqueous conditions and to a myriad of functional groups. Most crucially in the case of biomedical applications, it can be performed without the addition of toxic reagents.[1] More recently, the related thiol–yne coupling (TYC) reaction has been exploited to synthesise highly functionalised peptides.[3]

This work describes the development of peptide modification methodologies using both the TEC and TYC reactions in two distinct but complimentary approaches. For peptide bioconjugation, TEC mediated reactions under continuous-flow were reported in both aqueous conditions and 'green' solvents, furnishing biologically active glycopeptides in high yield (**Fig 1a**). For peptide rebridging, a highly efficient TYC mediated approach was reported that can be applied to disulfide containing peptides (**Fig 1b**). Following disulfide reduction, the radical mediated crosslinking of the free thiol moieties via sequential TYC and TEC ligation furnishes the covalently bound peptide macrocycle.

Fig 1a: Continuous flow TEC bioconjugation

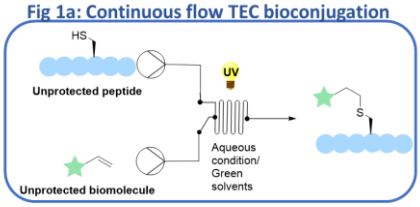
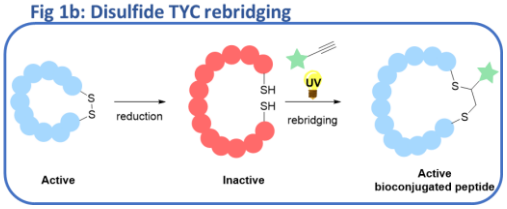


Fig 1b: Disulfide TYC rebridging



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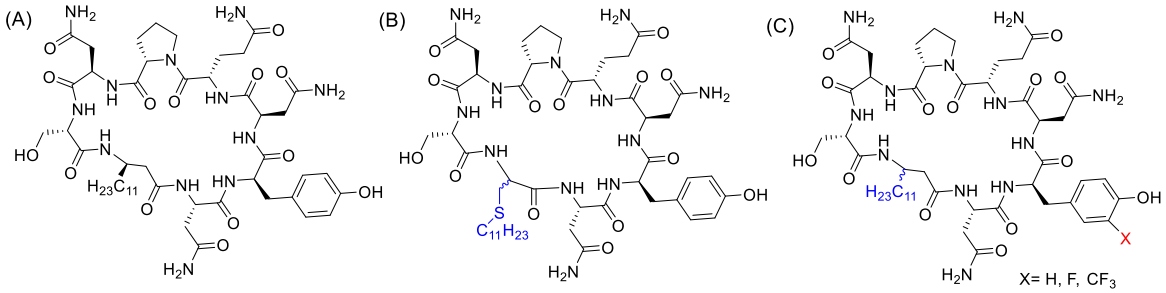
Dublin Chemistry Graduate Seminars 2023/24

EXPLORING SYNTHETIC AND SEMI-SYNTHETIC APPROACHES FOR THE ENGINEERING OF THE ANTIFUNGAL CYCLIC LIPOPEPTIDE ITURIN A

Periklis Karamanis[1,2], Cormac D. Murphy[2,3] and Marina Rubini[1,2]
1. School of Chemistry, University College Dublin, Belfield, Dublin 4, Ireland,
2. BiOrbic Bioeconomy SFI Research Centre, University College Dublin, Belfield, Dublin 4, Ireland,
3. School of Biomolecular and Biomedical Science, University College Dublin, Belfield, Dublin 4, Ireland

email: periklis.karamanis@ucdconnect.ie, marina.rubini@ucd.ie

Iturin A is a cyclic lipopeptide, produced by *Bacillus* sp., that exhibits pronounced antifungal activity against different fungal pathogens. Its structure consists of seven α-amino acids and one β-amino fatty acid (**Fig. A**) and its mechanism of action involves hydrogen bonding between the D-Tyr$_3$ residue and the fungal membrane sterols, followed by penetration of the cell membrane by the alkyl chain.[1] The addition of fluorine or of a trifluoromethyl group at the ortho position of the hydroxy group of D-Tyr$_3$ should provide the lipopeptide with increased metabolic stability and enhanced hydrogen bond formation capacity.[2] Further, it can unlock new characterisation techniques (such as ^{19}F NMR).[3] This work aims to obtain monofluorinated and trifluoromethylated iturin A analogues and to assess the effect of the addition of fluorine on the bioactivity of the lipopeptide. Firstly, a total synthesis approach will be presented. This includes the synthesis of simplified analogues containing an alkylated cysteine residue, in place of the β-amino acid **(Fig. B)**, and the synthesis of fluorinated analogues of the natural lipopeptide (**Fig. C**).[4] Lastly, semi-synthetic approaches, such as the late-stage trifluoromethylation of iturin A and the precursor directed biosynthesis of the fluorinated analogues will be also shown.



Natural iturin A | Alkyl-cysteine iturin A analogues | Fluorinated iturin A analogues

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Dublin Chemistry Graduate Seminars 2023/24

From Heterobimetallic to Monometallic Cobalt and Iron Systems: Ligand and Solvent-Driven Selective Deprotonation

Manting Mu,[a] Marconi N. Peñas-Defrutos,[a] Lewis Maddock, [b] Alessandra Logallo, [b] Na Jin,[b] Eva Hevia[b] and Max García-Melchor[a]

[a]*School of Chemistry, Trinity College Dublin, College Green, Dublin 2, IE*
[b]*Department für Chemie und Biochemie Universität Bern Freiestrasse 3, 3012 Bern, CH*
email: muma@tcd.ie

Heterobimetallic systems utilising the cooperativity of a highly polar alkali-metal amide and a less polar metal amide (e.g., Al, Zn, Fe) have become a prominent class of reagents for the selective deprotonation of arenes.[1] Recently, we reported the bimetallic partnership between [Na(HMDS)] and [M(HMDS)$_2$] (M = Fe^{II} or Co^{II}, HMDS = hexamethyldisilazide), highlighting their incapability to activate pentafluorobenzene alone.[2] Expanding on these studies, I will present in this talk our latest findings on C–H metalation using enhanced monometallic Co and Fe systems with the more basic amide ligand, 2,2,6,6-tetramethylpiperidine (TMP). An unexpected, solvent-regulated reaction pathway leading to different bisaryl products will be conveyed, emphasising the key roles of the Co and Fe centres in the observed reactivity (Fig. 1).[3] Furthermore, I will present the unique effect of the solvent-metal interaction through activation strain analysis and microkinetic modelling. These novel monometallic systems offer direct, controlled C–H metalations at room temperature, delivering the desired metalation product in quantitative yields.

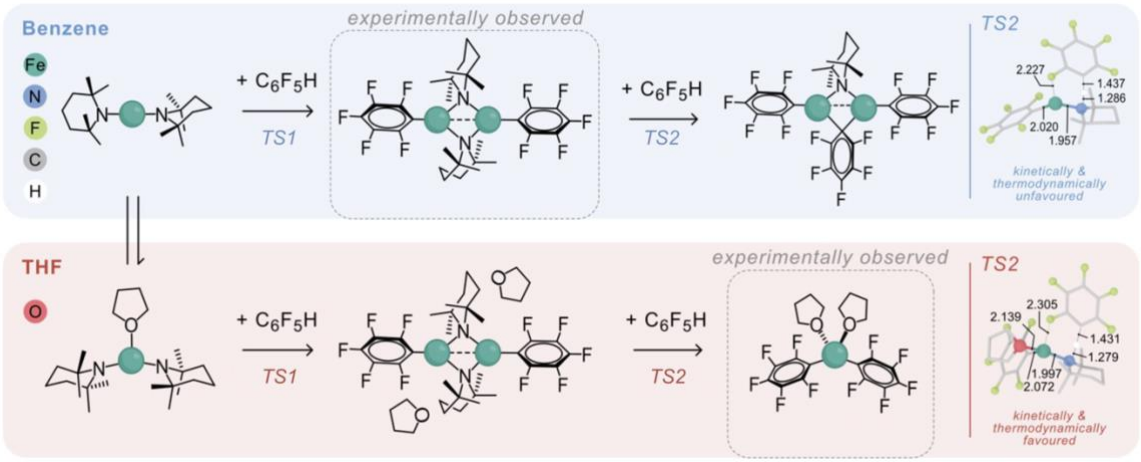

Figure 1. C–H metalation of C_6F_5H with [Fe(TMP)$_2$] complex in different solvents.

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Physical Chemical Properties of Iron Oxide Nanoparticles in Various Media

Liam Jowett, Dr. Karina Nigoghossian, Professor Dermot Brougham
UCD Centre for Synthesis and Chemical Biology, School of Chemistry, University College Dublin, Belfield, Dublin 4, Ireland

email: liam.jowett@ucdconnect.ie

Magnetic iron oxide nanoparticles are attractive candidates for next-generation MRI contrast agents as they generate strong image responses and they can heat strongly under AC magnetic field stimulation. Multicore iron oxide nanoparticles, or nanoflowers (NFs), are particularly attractive as they have stronger magnetic properties when compared with nanospheres of the same size due to their strong magnetisation and rapid moment dynamics. Challenges remain in understanding these responses and in optimising the surface chemistry for biological applications.

A NF synthesis is described that provides reproducible magnetic properties with SAR (AC-field heating efficacy) of 300 W g^{-1} and relaxivities (MRI contrast efficacy) of 310 s^{-1} mM^{-1} [1]. Coating NFs with silica would be useful as silica layers are biocompatible, can be porous and have tuneable thickness. Silica layers on spherical MNPs are known [2], however there are no reports for silica-coated NFs. The conditions (pH, ethanol concentration, mixing conditions, dilution factor and surface stabilisation route) investigated for silica layer growth on NFs will be described. Silica layers were formed but, so far, not in a reproducible fashion.

Hydrogels have been shown to be excellent mimics for the extracellular matrix and are hence useful in cell culture studies. Furthermore, when 3D printed, hydrogels can be used to provide textured supports for tissue engineering. By combining NFs with hydrogels, localised heating can be achieved on AC-field stimulation, allowing temperature/drug release gradients to be achieved across printed magnetic gels [3]. Infra-red video-thermography has been used in the group to measure the spatially resolved heating of NFs patterned into gelatin hydrogels. A new ratiometric fluorescence method will be described designed to provide heat-maps with better spatial resolution using two dyes, one with temperature-dependent emission and one without. In parallel, the internal dynamics of water in NF gels are being studied by fast field cycling NMR relaxometry to provide a complementary view of the response at the microscale in magnetic gels.

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Dublin Chemistry Graduate Seminars 2023/24

Multimodal metal carbonate-based structures for potential biomedical applications

Munirah Ghariani, Caroline O'Sullivan and Yurii K. Gun'ko
Sami Nasr Institute of Advanced Materials, School of Chemistry, Trinity College Dublin, College Green, Dublin 2, Ireland

email: gharianm@tcd.ie , igounko@tcd.ie

Multimodal composite materials are an important class of materials in the rapidly developing field of nanoscience. They have been immensely used due to their wide variety of applications including targeted cell drug delivery, biomedical imaging and cell labelling. [1] The main aim of this project is to develop new magnetic metal carbonate-based composites for potential biomedical applications. Calcium carbonate ($CaCO_3$) and magnetite (Fe_3O_4) were chosen as the main functional materials for this research, thus combining the modalities of biocompatibility and magnetisation. [2,3,4]

Magnetic nanoparticles have been prepared using a precipitation approach both in the absence and presence of a negatively charged polyelectrolyte which was used as a stabiliser.

For the very first time, the magnetic nanoparticles were encapsulated within the $CaCO_3$ shell using different synthetic techniques which lead to the development of a variety of distinctive morphological structures. Additionally, the novel composites were loaded with specific dyes and drugs as models to investigate their potential use for drug delivery including drug uptake and release processes.

This research opens up a route to new multimodal composite materials with unique properties and a range of potential applications.

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COPPER COMPLEXES: UNRAVELLING THEIR DUAL ROLE IN CANCER THERAPY THROUGH REDOX CHEMISTRY AND DNA INTERACTIONS

Pei-Hsuan Wu, John Colleran and Bernadette Creaven
School of Chemical & BioPharmaceutical Sciences, Central Quad, Grangegorman,TU Dublin, Dublin 7, D07 H6K8, Ireland

email: d20128746@mytudublin.ie

Copper complexes have emerged as promising candidates in the realm of cancer therapeutics, capturing considerable attention owing to their demonstrated efficacy. The prevailing literature underscores their anticancer properties, which are believed to emanate from their capability to engage in Fenton-like reactions, culminating in the generation of hydroxyl radicals—a potent source of cytotoxicity. This mechanistic insight has propelled the exploration of copper complex metallo-drugs as potential agents for targeted cancer treatments.[1]

A pivotal aspect in comprehending the therapeutic potential of copper complexes lies in unravelling their redox chemistry within the intricate milieu of biological systems. Through investigation into the *in-situ* formation of copper complexes, evidence suggests the propensity of these metallo-drugs to undergo ligand exchange with anionic species prevalent within cellular environments. This revelation not only sheds light on the dynamic behaviours of copper complexes but also unveils novel avenues for probing their intricate interactions within the cellular landscape.

To delve deeper into the mechanistic underpinnings of copper complex anticancer activity, DNA-modified electrodes were prepared.[2] By leveraging DNA-facilitated long-range electron transfer mechanisms,[3] these specialized electrodes serve as invaluable tools for elucidating the intricate interplay between copper metallo-drugs and DNA.[4, 5] This avenue of research shows potential for elucidating the therapeutic mechanisms and redox chemistry of copper metallo-drugs, aiming to enhance cancer treatment efficacy.

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NANOCOMPOSITE PHOTORESISTS FOR DIRECT LASER WRITING

Amrutha Augustine,[1] Jing Qian,[2] Teodora Faraone,[1] Srikanth Kolagatla,[1] A. Louise Bradley,[2] Colm Delaney,[1] Larisa Florea[1]*

[1]*School of Chemistry & AMBER, The SFI Research Centre for Advanced Materials and Bioengineering Research, Trinity College Dublin, College Green, Dublin 2, Ireland*

[2]*School of Physics, Trinity College Dublin, College Green, Dublin 2, Ireland*

Email: augustia@tcd.ie

Direct laser writing by two-photon polymerisation (DLW-2PP) is a maskless optical lithographic technique that enables fabrication of complex 3D microstructures with sub 300 nm resolution and minimal topological constraints.[1] Micro and nanostructures fabricated via DLW-2PP are utilised for applications in a wide range of fields such as microelectromechanical systems (MEMS)[2], tissue engineering[3] and micro-robotics.[4] The addition of nanofillers results in added functionality to polymer microstructures, such as enhanced conductive and magnetic properties, among others.[5] Herein, we demonstrate the development of two novel nanocomposite photoresists suitable for DLW-2PP for the fabrication of multifunctional microstructures.

In the first example, silica particles (SiO_2 NPs) were incorporated into compatible acrylate-based photoresists at varying concentrations, to form highly stable dispersions. Photopolymerisation of these nanocomposite photoresists via DLW-2PP allowed for the realisation of photonic microstructures responsive to changes in immersion solvent, yielding a wide gamut of tuneable colours covering the entire red–green–blue (RGB) colour space. Furthermore, the presence of SiO_2 NPs endows significant mechanical reinforcement properties to the microstructures, which was confirmed via AFM and scanning electron microscopy (SEM).[6] The second nanofiller investigated was cellulose nanocrystals (CNCs). At relevant concentrations, CNCs have the ability to self-assemble into a left-handed chiral nematic (cholesteric) phase. This was demonstrated in selected photoresists allowing for tunability of the reflected colour depending on the pitch of the cholesteric phase. Vibrant colours over a wide range of the visible spectrum were yielded and these colours were dynamically changed in response to the local chemical environment. Such photonic microstructures find application in colour displays and encryption micro-devices.

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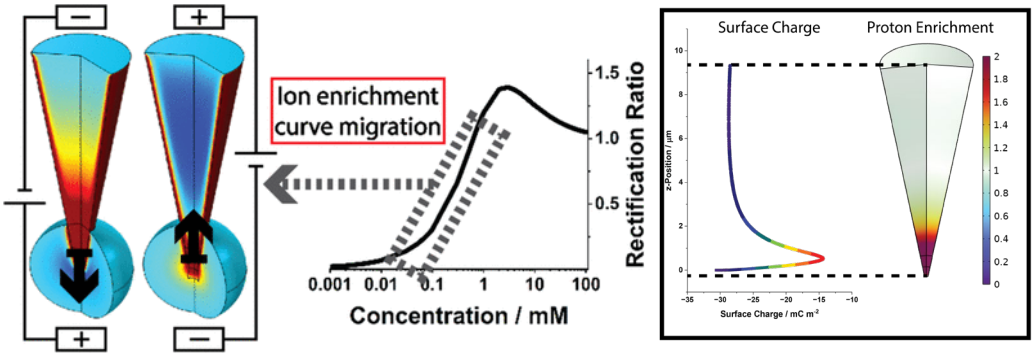
Understanding Ion Transport Processes in Nanopores

Dominik Duleba, Emer Farrell, Shekemi Denuga, Pallavi Dutta, Robert P. Johnson
UCD Centre for Synthesis and Chemical Biology, School of Chemistry, University College Dublin, Belfield, Dublin 4, Ireland

email: dominik.duleba@ucdconnect.ie, robert.johnson@ucd.ie

Nanopore sensors are an emerging electroanalytical technique with potential for the portable high sensitivity detection of a range of analytes. A more recent arrival among nanopore sensors are nanopores that exhibit ion current rectification (ICR), where the immobilization of an analyte onto the nanopore surface modulates the ion transport, allowing analyte quantification. [1-3] A thorough understanding of the ion transport behaviours in these systems is needed for both optimization and development. The concentration-dependent electric double layers (EDLs) play a vital role in the ion transport. We have experimentally investigated the behaviour of the rectification ratio at very low electrolyte concentrations and found an inversion of rectification at sufficiently low concentrations. [4] Finite Element Simulations allowed us to correlate this behaviour to a migration of the ion enrichment distributions within the pore as the EDL thickness is varied by changing the electrolyte concentration and to the emergence of ion enrichment at the pore tip which overpowers concentration polarization further inside. Furthermore, other fundamental behaviours have also been investigated, such as the behaviour of the nanopore surface charge. The acid-disassociation of surface groups on the walls of a glass nanopipette generate the surface charges that drives the ion transport. The disassociation of surface groups is in fact influenced by the local H^+ and OH^- concentrations, which themselves deplete or accumulate within the conical nanopore when the voltage across it is changed. Despite this, most models of ion transport in conical nanopore systems assume a fixed surface charge and ignore localized pH changes. Ion transport, however, involves a complex feedback loop-based dependance on the intra-pore proton enrichment and depletion that gives rise to highly non-linear surface charge distributions whose shape and magnitude are influenced by the potential, the concentration, the surface group acidity constant, surface coverage, pH, the pore size and the cone angle. Such extended fundamental understanding may be exploited to develop novel approaches for using asymmetric nanopores for sensing.



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I-III-VI type colloidal semiconductor nanocrystals

Aoife Kavanagh, Lorenzo Branzi & Yurii Gun'ko
Centre for Doctoral Training in the Advanced Characterisation of Materials, School of Chemistry, Trinity College Dublin, Dublin 2, Ireland

email: kavana13@tcd.ie

Colloidal semiconductor nanomaterials, also known as quantum dots (QDs), have become a topic of extensive scientific research in the last several decades, due to their unique optical and electronic properties, with applications ranging from energy devices to biomedical imaging.[1] Currently, QD research is dominated by binary II-VI type systems. While these materials display excellent photoelectronic properties, the toxic nature of the heavy metal constituents presents a major drawback.[2] In recent years, ternary I-III-VI based systems have emerged as a new, heavy-metal-free type QD system. Such systems, (e.g., silver indium sulfide and copper indium selenide) also possess a number of distinct advantages compared to II-VI based systems, such as greater tunability, large Stokes shifts and enhanced stability.[3,4] These I-III-VI based nanocrystals (NCs) therefore offer a promising alternative to the current toxic heavy-metal containing systems, though as of yet, their synthesis, properties and potential applications have been investigated significantly less than those of their II-VI type counterparts.

This project focuses on the synthesis of these I-III-VI type NCs, their properties, and potential applications. Herein we present the synthesis of various ternary and quaternary I-III-VI based NCs, of varying composition, synthesised via both organic and aqueous approaches. The photodetector capabilities of copper indium sulfide/selenide based NCs were tested via electrophoretic deposition and dip coating methods. The potential of silver indium sulfide/selenide QDs for use in luminescent solar cell concentrators and red-light emitting diodes was demonstrated. Additionally, the cellular uptake capability and cytotoxicity of the QDs was tested *in vitro* using various cell lines, including healthy (HEK293) and cancerous (Caco-2) human and animal (L929) cells, demonstrating their promise for use in various biomedical applications.

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PHOTOPOLYMERISATION AND PHOTOREDUCTION FOR THE REALISATION OF PHOTO-THERMAL MICRO-ACTUATORS

Luisa Lavelle, Srikanth Kolagatla, Colm Delaney, Larisa Florea*

School of Chemistry & AMBER, the SFI Research Centre for Advanced Materials and BioEngineering Research, Trinity College Dublin, Dublin 2, Ireland

Email: llavelle@tcd.ie

Direct laser writing (DLW) by multi-photon polymerisation is a three-dimensional fabrication technology, based on nonlinear photon absorption, which allows for the construction of readily assembled structures with sub-300 nm resolution.[1,2] Recently, this technique has been applied to the fabrication of stimuli-responsive hydrogel microstructures.[3] Due to their size, such hydrogel structures showed improved response times compared to their macro-scale counterparts, where the inherently slow diffusion-controlled hydrogel expansion was countervailed. However, to date, most hydrogel 3D micro-structures are composed of a single polymeric material.

In this work, we showcase multi-material fabrication on the nano- and microscale, for the realisation of photothermal micro-actuators. Firstly, microstructures were photopolymerised *via* DLW in the thermo-responsive polymer poly(*N*-isopropylacrylamide) (pNIPAAM). pNIPAAM was the polymer of choice owed to its thermo-responsive properties associated with a phase transition at the lower critical solution temperature (32 ˚C).[4] Secondly, Ag nanoparticle (NP) patterns were fabricated *in situ* inside the thermo-responsive polymer structures via two-photon reduction from Ag^+. This allowed fine control over the Ag patterns and Ag NP concentration. Subsequent laser irradiation of the embedded Ag NP patterns enabled photo-thermal actuation of the microstructures in a fast, programable, and reversible manner.

Ongoing work consists in investigating the structural colour through the photonic properties of the Ag nanoparticles, as well as the ability to use the embedded Ag nanoparticles as seeds for the growth of subsequent Ag to form an electrically conductive 3D network.

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INCORPORATION OF SPIN CROSSOVER COMPOUNDS IN LIGHT HARVESTING DEVICES

Grace G. Morgan, Aizuddin Sultan
School of Chemistry, University College Dublin, Belfield, Dublin 4

email: aizuddin.sultan@ucdconnect.ie , grace.morgan@ucd.ie

Light induced spin-crossover (SCO) is possible in Fe^{3+} complexes and may also be active in SCO Mn^{3+} systems. Incorporating this with semiconductors with overlapping energy gaps with the high spin/low spin energy gap in a SCO complex may offer a route to a new form of dye-sensitised solar cell DSSC.[1] Anchorage of complexes on semiconductors is required and we report here the results of our bottom-up studies on attachment of SCO complexes to semiconductors through use of ligand-appended carboxylate tails.[2] Photo-induced SCO of the hybrids will be investigated to try and elucidate the mechanism for incorporation with the conduction band of the semiconductor. Surface preparations were also conducted *via* various routes e.g., spin coating or dip coating methods.

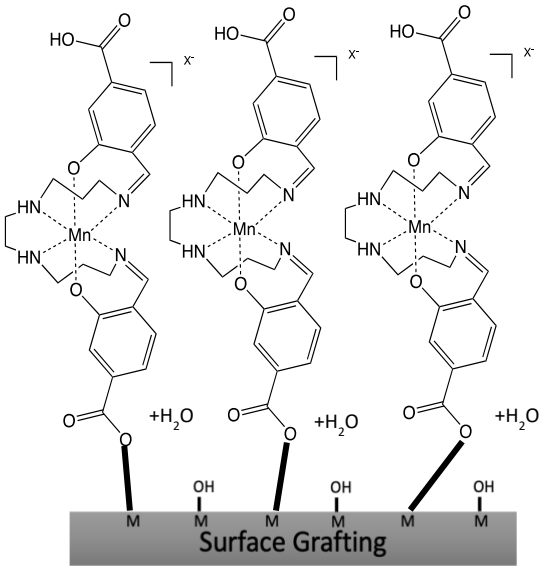

Figure 1. SCO compound anchored on semiconductor surface *via* carboxylate tails.

Complex precursors are anchored on surfaces through chemisorption means by hydrothermal synthesis *via* two methods: one-pot approach or pre-coated surface approach. Characterisatio methods included DLS, zetapotential, XPS, SEM and AFM techniques in addition to characterisation of the free complexes by single crystal X-ray diffraction, SQUID magnetometry, solution and solid-state UV-vis spectroscopy.

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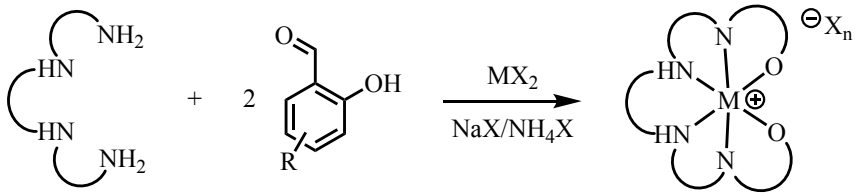
Investigation of Novel Mn(III) and Fe(III) SCO Complexes and Hybrid Materials

Francesca Adami,[1*] Komala Pandurangan,[1] Michael Griffin,[1] Jan Vlček,[2] Julia Bruno,[1] Grace G. Morgan[1]

[1]*UCD Centre for Synthesis and Chemical Biology, School of Chemistry, University College Dublin, Belfield, Dublin 4, Ireland*
[2] *Department of Functional Materials, Institute of Physics of the Czech Academy of Sciences, Na Slovance 1999/2, 182 00 Prague 8, Czeck Republic*

**email: francesca.adami1@ucdconnect.ie*

Manganese and iron have access to a manifold of different electronic states which have been employed over the years for a wide range of application, from catalysis to biological involvement and batteries.[1] Additionally, some of their complexes undergo spin crossover (SCO), increasing the number of electronic states they have access to.[2,3] We have synthesized a substantial library of compounds with a range of N_4O_2 ligands donor sets that promote a variety of SCO profiles with Mn(III) and Fe(III).[4] Recently, interest has developed towards exploring how these complexes interact with surfaces.[5]
We will present here new series of Mn(III) and Fe(III) complexes with N_4O_2 ligands of the type shown in the figure below (**1**), where the flexibility of the tetraamine, the substituents on the salicylaldehydes as well as the identity of the counterion influence both SCO profile and redox preferences. A range of spectroscopic and electrochemical techniques have been employed to analyse the properties of the resulting complexes. Subsequently, various methods, including spin coating and magnetron sputtering, have been used to prepare rough and pristine surfaces. On these surfaces, the complexes have been either physically or chemically bound, in order to investigate the properties of the hybrid materials.



General reaction scheme of the complexes (**1**)

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This isn't even my final form: a string of polymorphs while looking for battery precursors

Olivia D. Breen and Tony D. Keene
School of Chemistry, University College Dublin, Belfield, Dublin 4, Ireland

email: olivia.breen1@ucdconnect.ie, tony.keene@ucd.ie

Coordination polymers are used for a variety of purposes with the choice of ligand and metal allowing for tailored applications. However, unexpected products can form. This has resulted in this work which examines transition metal oxalates for their use as battery precursors and an interesting series of polymorphs. Climate change is an increasing problem and lithium-ion batteries are seen as a potential strategy to lower CO_2 emissions. Layered lithium transition metal oxides, such as lithium cobalt oxide, are the most popular commercially used cathodes due to their high energy density and good performance.[1] However, they use rare metals such as cobalt, so it is of importance to explore cathodes using abundant metals such as iron. Lithium iron oxide forms over ten polymorphs with most being electrochemically inactive. This work examines the viability of using lithium iron oxalate precursors to template the formation of electrochemically active polymorphs of lithium iron oxide upon calcination.[2]

Transition metal oxalate compounds are also known to form polymorphs. While exploring different synthetic methods to synthesise cathode precursor materials, an iron oxalate compound with ammonia ligands was synthesised. Copper ammonia oxalate compounds were first reported to show polymorphism in 1908 but other transition metals have been scarcely investigated.[3] This work expands this class of compounds to report 26 compounds with the formula $[M(NH_3)_x(C_2O_4)(H_2O)_y]$, where M is manganese, iron, cobalt, nickel, copper, or zinc, where x can take values between 0 and 6, and y can take values between 0 and 4. 22 of the compounds form coordination polymers and fit into three different classes of polymorphs that can be controlled based on reaction conditions.

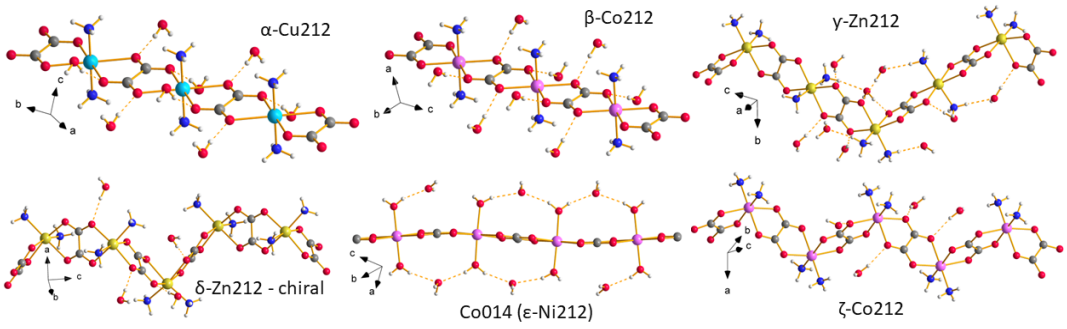

Fig 1. Polymorphs of $[M(NH_3)_2(C_2O_4)(H_2O)_2]$, also referred to as M212. ε-Ni212 forms a microcrystalline powder but is isostructural to $[Co(C_2O_4)(H_2O)_4]$, known as Co014.

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RADICAL MOFS TOWARD MAGNETIC, OPTICAL, AND BIOIMAGING APPLICATIONS

Viktorija Mikaite and Tony D. Keene
UCD School of Chemistry, University College Dublin, Belfield, Dublin 4, Ireland

email: viktorija.mikaite@ucdconnect.ie, tony.keene@ucd.ie

Metal-organic frameworks (MOFs) are a recent addition to the family of porous materials and have grown over the past three decades to become an exciting area of research activity. New applications for MOFs are continuously emerging due to their tuneable pore size, selectivity, and metal activity.[1] However, comparatively little study has been done on the potential applications of magnetic MOFs. Naphthalenediimides (NDIs) are chemically robust and electron deficient ligands[2,3]. NDI derivatives are of high interest not only because they can be used to form MOFs with varied structures and topologies, but they also possess interesting features like easy reduction into radical anions, redox-activity, and photochromism. The NDI radical form can be accessed by photo-irradiation as well as via situ electrochemistry[3]. Radical MOFs would be of particular interest for the synthesis of multifunctional materials with potential applications in biomedical imaging, gas separation, erasable printing, and many more.

This project is focused on the synthesis and development of MOFs using radical precursor ligands toward magnetic, optical, and biomedical imaging applications. Presented here will be a summary of our work to date, namely the structural and optical characterisation of several novel two- and three-dimensional MOFs based on radical precursor NDI ligands.

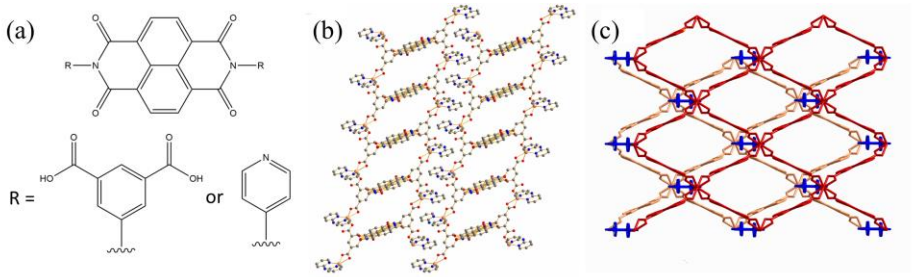

Figure 1. *(a) General structure of a naphthalenediimide (NDI) derived ligand, where R = BIPA-NDI or BP-NDI, (b) 2D sheets of a zinc MOF viewed along the b-axis, and (c) a simplified view of the 3D superstructure of a bismuth MOF.*

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TOWARDS SUSTAINABLE NANOMATERIALS: GREENER ROUTES TO QUANTUM AND CARBON DOTS

Peter Dunne and Karlijn Hertsig
School of Chemistry,
Trinity College Dublin,
Dublin 2,
Ireland

email: P.W.Dunne@tcd.ie, hertsigk@tcd.ie

Quantum dots are nanomaterials so small that their size determines their properties.[1] Last year the Nobel Prize in Chemistry was awarded to Moungi G. Bawendi, Louis E. Brus and Aleksey Yekimov for the discovery and synthesis of quantum dots.[2-4] Now they spread their light from televisions and LED lamps and guide surgeons when they remove tumour tissue, among many other things. As their technological and industrial importance grows, so too does their demand and prevalence; however conventional quantum dots are based on toxic heavy metals with potentially significant health impacts, and which carry a high environmental burden in both extraction and disposal.

In recent years carbon dots, nanoparticles of graphitic or polymeric carbon, have emerged as a cleaner, greener, non-toxic alternative, with proven potential in many of the same applications, with the added benefit of biocompatibility for biomedical uses.[5] Importantly carbon dots may be prepared by environmentally benign hydrothermal treatment of almost any carbon source including biomass.[6] This offers a route to in-demand, eco-friendly, functional nanomaterials by the treatment of waste streams or upgrading of biomass, creating opportunities for significant added value across multiple sectors.

Here, we report on our recent efforts towards developing greener routes to conventional quantum dots, minimising the environmental and societal impacts of this important class of materials. We further discuss the production of carbon dots from locally sourced seaweed feedstocks, bypassing many of the concerns associated with conventional quantum dots.

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Provost's PhD Project Awards

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Metal-Organic Frameworks for Electrochemical and Photoelectrochemical Energy Conversion Systems

Gearóid Manning, Éadaoin Whelan, Muhamed Mulahmetović, Wolfgang Schmitt.
School of Chemistry, Trinity College Dublin, Dublin 2, Ireland
email: gemannin@tcd.ie, schmittw@tcd.ie

For the global community to transition to a carbon-neutral economy, it is vital that clean alternative sources of fuels and chemical feedstocks be developed. This requires sustainable strategies for the interconversion of chemical and electrical energy. These strategies include the electrolysis H_2O to produce hydrogen, to be used as a clean energy carrier and a feedstock in industrial processes. Also, the electrochemical reduction of CO_2 (captured from the atmosphere or an industrial process), converting it into useful chemicals such as CO and hydrocarbons.

Metal-organic frameworks (MOFs) are an emerging class of materials in which individual metal ions or coordination clusters are linked through organic ligands, forming 2- or 3-dimensional networks with long range order. Owing to their modularity, reticular design principles and their amenability to chemical functionalisation, MOFs provide promising platforms for the development of advanced energy materials. [1,2]

This project focuses on the synthesis and physicochemical characterisation of novel MOFs, as well as evaluation of their catalytic performance towards either the electrochemical (or photoelectrochemical) oxygen evolution reaction (OER) or CO_2 reduction reaction (CO_2RR). The MOFs studied in this work are lanthanide (cerium and europium) and transition metal (nickel and cobalt) based, and were synthesised using heterocyclic-based ligands, as well a novel Ru^{II}-pyridyl metallo-ligand. The MOFs with heterocyclic-based ligands are accessed for their electrocatalytic activity, and the MOFs with the Ru^{II}-pyridyl metallo-ligand are accessed for their photoelectrocatalytic activity.

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Dublin Chemistry Graduate Seminars 2023/24

Porous N-doped carbon-encapsulated metals as a novel catalyst architecture for the electrocatalytic hydrogenation of organics

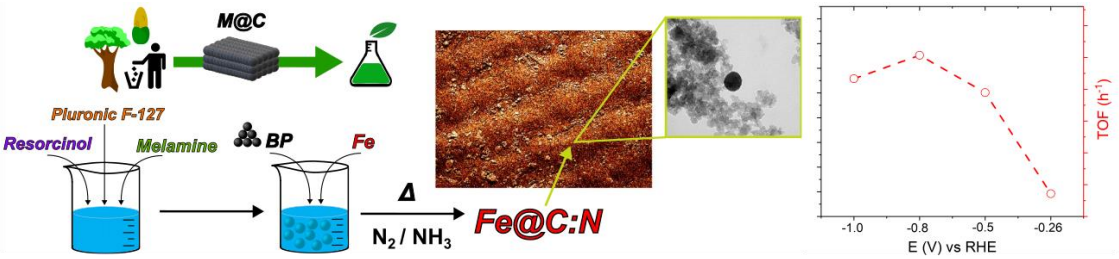
Filippo Pota[1], Maida Aysla Costa de Oliveira[1], Christian Schröder[1], Marc Brunet Cabré[1], Hugo Nolan[1], James A. Behan[2], Frédéric Barrière[2], Paula E. Colavita[1]

1-School of Chemistry, Trinity College Dublin, College Green, Dublin 2, Ireland
2-Univ Rennes, CNRS, Institut des Sciences Chimiques de Rennes – UMR 6226, F-35000 Rennes, France.

email: potaf@tcd.ie, colavitp@tcd.ie

Nowadays from biomass it is possible to obtain valuable chemicals and fuels using methods that involve precious metal catalysts, high temperatures and pressure.[1] This is seen as a significant approach in mitigating carbon emissions, even if the extreme conditions and the use of catalysts based on expensive metals raises concerns about the sustainability of the strategy. Electrocatalytic hydrogenation (ECH) offers an eco-friendly alternative by utilizing in situ generated hydrogen to catalyze the conversion of organic molecules from biomass, and at the same time eliminate the necessity for high-purity hydrogen and high pressures. Notably, literature underscores the potential of precious metals and carbon-supported precious metal (M/C) as promising electrocatalysts for ECH.[2]

In this work we focused on the design, synthesis and characterization of heteroatom doped carbon-based materials with base/abundant metal incorporation and explored their potential as electrocatalysts, particularly in ECH. A versatile hydrothermal method was employed to introduce different metallic nanoparticles and heteroatom functionalities into a nanocarbon scaffold with high conductivity and porosity. Electrochemical characterization involved voltammetry and chronoamperometry on different conductive carbon supports using benzaldehyde as a diagnostic substrate. Chromatographic product detection coupled to electrolysis experiments facilitated the determination of efficiency and selectivity in organic hydrogenations. The results provide insights into reactivity trends based on the choice of metal core, metal loading, and the potential for achieving selectivity in organic transformations relevant to sustainability. Moreover, measurements of turnover frequencies (TOF) enabled a comparison of the performance of prepared materials against that of precious metals supported on carbon, with encouraging results.[3]



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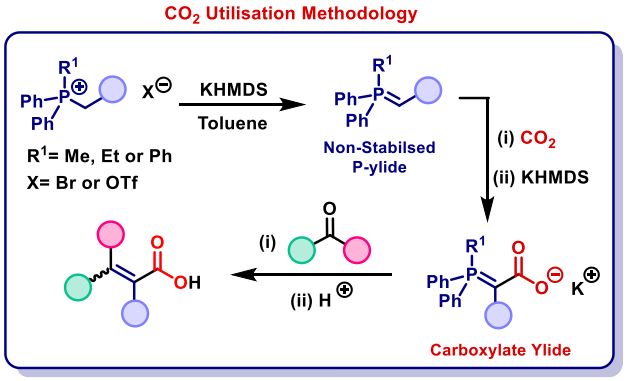
Carbon Dioxide Utilisation for Construction of High Value Carboxyl-Containing Organic Products

Rachel Lynch, Amy Lowry, Gerard P. McGlacken, Peter A. Byrne
University College Dublin, School of Chemistry, CSCB Building Belfield Dublin 4
email: rachel.lynch3@ucdconnect.ie, peter.byrne@ucd.ie

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

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



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