46th Scottish Regional Meeting of the RSC Organic Division

9th January 2018

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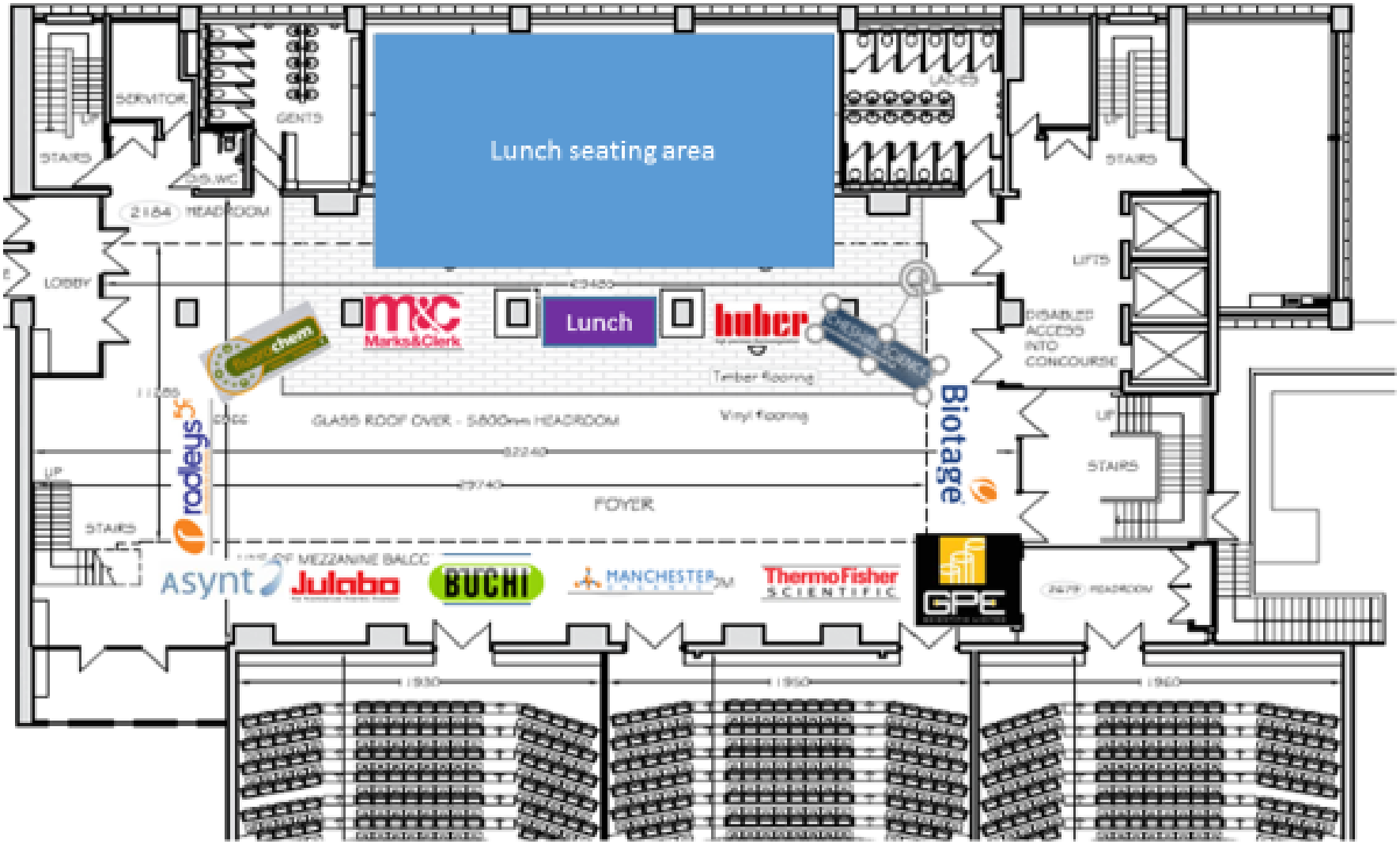
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Programme

46th Scottish Regional Meeting of the RSC Organic Division: Lecture Theatre 5, Appleton Tower, Edinburgh

Tuesday 9th January 2018

Programme

09.30–10:15	Assembly, Poster Preparation and Tea/Coffee
10.15-10.25	Opening Remarks: Professor Guy Lloyd-Jones
Session 1	Chair: Professor Neil McKeown
10.25-10.50	Dr Andrew Thomson (Glasgow University)
	Computational Design of Peptide Conformational Switches
10.50-11.15	Dr Filipe Vilela (Heriot-Watt University)
	Conjugated Materials as Heterogeneous Photocatalysts
11.15-11.40	Prof Matteo Zanda (Aberdeen University)
	Synthetic Tubulysins: Ultra-potent cytotoxic drug candidates for oncology
11.40-12.05	Prof Ian Gilbert (Dundee University)
	Drug Discovery for Neglected Diseases
12.05-12.30	Dr James E Taylor (St Andrews University)
	Catalytic Activation of Alcohols
12.30–14.00	Lunch, Poster Session and Sponsor Exhibition
Lunch generously sponsored by the RSC; Advion; Asynt; Biotage; Buchi; Cheshire Sciences; Fluorochem; GPE Scientific; Huber; Julabo; Manchester Organics; Marks & Clerk; Radleys; Thermofisher Scientific	
Session 2	Chair: Dr Paul Lusby
14.00-14.15	Dr Amit Mahindra (Glasgow University)
	Novel Amino Acids Incorporating Zinc-Binding Groups as inhibitors of HDAC co-repressor complexes
14.15-14.30	Dr Phill Lowe (St Andrews University)
	Last-step enzymatic [18F]fluorination for positron emission tomography
14.30-14.45	Dr Jamie Withers (Strathclyde University)
	Nucleic acid assembly mediated by the fluorous effect
14.45-15.10	Dr Fernanda Duarte (Edinburgh University)
	Chiral Ion-Pairs: Dissociation, Dynamics and Asymmetric Catalysis
15.10-15.35	Dr Marc Reid (Strathclyde University)
	Computer Vision in Chemistry
15.35-16.00	Tea/Coffee, Poster viewing + Vendors
Session 3	Chair: Professor Alison Hulme
16.00-17.00	PLENARY LECTURE: Prof Varinder Aggarwal FRS
	The RSC 2017 Synthetic Organic Chemistry Award Lecture
17:00-17:10	Closing remarks and Poster Prizes: Professor Guy Lloyd-Jones
17:10	Posters and Wine Reception
Wine Reception generously sponsored by the RSC; Advion; Asynt; Biotage; Buchi; Cheshire Sciences; Fluorochem; GPE Scientific; Huber; Julabo; Manchester Organics; Marks & Clerk; Radleys; Thermofisher Scientific	

Talk Abstracts

Talk

Computational Design of Peptide Conformational Switches

S. Crecente-García, A. Zimmermann, A. R. Thomson

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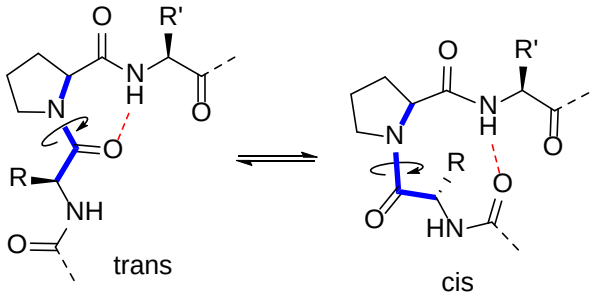
Many fundamental biological regulatory processes rely on conformational switching events, which are often difficult to recapitulate in simplified designed molecules. The cis-trans isomerisation of a proline amide bond has recently been shown to act as a regulatory mechanism in biological signalling pathways. This conformational switch, though embedded in a complex environment, is simple enough at a molecular level to be a tractable target for de novo design. Investigating these switching processes will not only shed light on their behaviour in their biological context, but will also allow the design of synthetic switches that operate along similar principles. These switching events are being explored using a combined experimental and computational approach. Information from the protein data bank is being used to probe the ability of the local sequence to influence the cis-trans ratio of the proline amide bond. Similarly, structural models[1] are being used to probe sequence-specific energy differences between the two states. These computational methods are being used to guide sequence selection for NMR studies with synthetic peptides. These studies will guide the design of more-complex devices for applications such as sensing.



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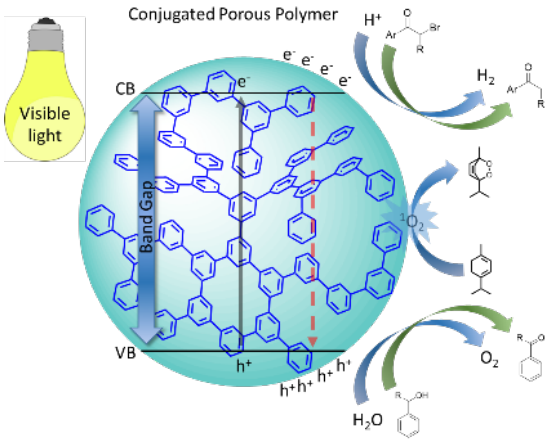
Talk

Conjugated Porous Polymers as Heterogeneous (Photo)Catalysts

Filipe Vilela. (FV) is a materials chemist whose research interests lie on the interface of polymer chemistry and photochemistry. FV was appointed as an Assistant Professor in 2013 at the Institute of Chemical Sciences at Heriot Watt University, where he currently works. FV completed his PhD in polymer chemistry in 2008 under the supervision of Prof David C. Sherrington FRS (University of Strathclyde) and then went on to a post-doctoral position under the supervision of Peter J. Skabara (University of Strathclyde) in the field of organic electronics. In 2010, FV was appointed as a research group leader for 3 years at the Max Planck Institute for Colloids and Interfaces, Potsdam, Germany working in the topical field of heterogeneous photocatalysis.

School of Engineering and Physical Sciences, Heriot-Watt University, Edinburgh, EH14 4A, UK. email: f.vilela@hw.ac.uk

In recent years, Conjugated Porous Polymers (CPPs) have been identified as a new class of materials that can excel in a wide-range of applications including gas storage and separation, organic solar cells, water purification and catalysis, just to name but a few. These insoluble organic semiconductors with tuneable band-gaps and high surface areas are particularly suited as heterogeneous (photo)catalysts, and as such, have been successfully employed in a variety of chemical transformations.[1] However, these polymers have several shortcomings that need to be addressed. Herein we present synthetic strategies that allow for CPPs to be produced in different shapes and formats;[2, 3] the development of metal-free synthetic strategies of CPPs and the introduction of specific metal-based nanoparticles into CPP pores for enhanced (photo)catalytic processes.[4] Furthermore, we will also discuss how photocatalysis can interface with materials science and stimulate new opportunities for the continuous development of light-harvesting technologies especially geared towards flow chemistry.[5]



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Talk

Synthetic tubulysins: ultra-potent cytotoxic drug candidates for oncology

Matteo Zanda.

Kosterlitz Centre for Therapeutics, Institute of Medical Sciences, School of Medicine, Medical Sciences and Nutrition, University of Aberdeen, Foresterhill, Aberdeen, AB25 2ZD, Scotland, UK
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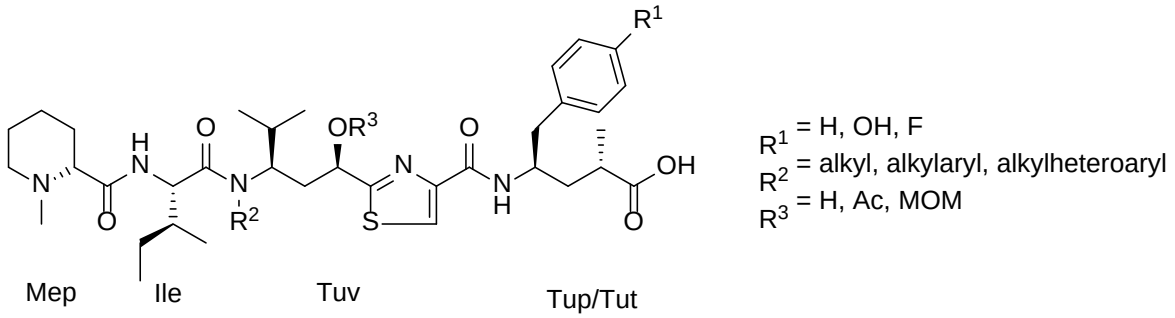
Natural tubulysins are tetrapeptides isolated from myxobacterial culture extracts. These compounds received a great deal of interest since their discovery, principally for their potent cytotoxicity (IC_{50}values in the pico-/nano-molar range) against various human tumor cell lines. Various synthetic approaches have been investigated for producing tubulysins and their analogues in amounts sufficient for performing preclinical or clinical studies. Although both natural and synthetic tubulysins showed strong anti-cancer potential, to our knowledge unconjugated tubulysin derivatives have never been successfully used *in vivo*, due to their reported extremely narrow therapeutic windows. Furthermore, the preparation and use of tubulysin-based antibody-drug-conjugates (ADCs) have met with considerable challenges.
This talk will describe the multi-step synthesis of tubulysins having non-hydrolysable *N*-substituents on tubuvaline (Tuv), which were obtained in high purity and good overall yields. A SAR study using a panel of human tumor cell lines showed strong anti-proliferative activity for all the synthetic tubulysins, with IC_{50} values in the sub-nanomolar range, which were distinctly lower than those of natural Tubulysin A, vinorelbine, and paclitaxel. The lead compound exhibited potent antitumor activity at well tolerated doses on *in vivo* models of diffuse malignant peritoneal mesothelioma. ADCs incorporating tubulysins and trastuzumab were also prepared and successfully used in vivo.
These results indicate that synthetic tubulysins could be used both as standalone chemotherapeutic agents as well as cytotoxic warheads for ADCs in difficult-to-treat cancers.



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Talk

Drug Discovery for Neglected Diseases

Ian Gilbert on behalf of the Drug Discovery Unit.

Drug Discovery Unit, Wellcome Centre for Anti-Infectives Research, Division of Biological Chemistry and Drug Discovery, University of Dundee, Dundee, DD1 5EH
i.h.gilbert@dundee.ac.uk

The Drug Discovery Unit (DDU) was set up at the University of Dundee in 2006. It is a fully integrated drug discovery unit, combining hit discovery, medicinal and computational chemistry, drug metabolism and pharmacokinetics. The key aims of the unit are to tackle unmet medical need. We have two main therapeutic focuses: neglected tropical diseases such as malaria, tuberculosis and kinetoplastid infections; and novel drug targets emerging from the academic sector. In this presentation, I will summarise some of the work that we have carried out on drug discovery for neglected diseases.

Talk

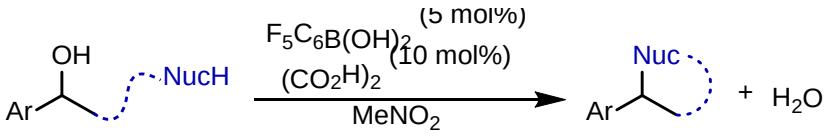
Catalytic Activation of Alcohols

Estopiñá-Durán S., Donnelley, L., Mclean, E.; Hockin, B.; Taylor J. E.

EaStCHEM, School of Chemistry, North Haugh, University of St Andrews, Fife, KY16 9ST, UK
email: jet20@st-andrews.ac.uk

The alkylation of heteroatoms is one of the most widely used synthetic reactions, constituting *ca.* 20% of all reactions performed within the pharmaceutical industry.[1] Alkylations are traditionally performed using substitution reactions of alkyl halides or stoichiometrically activated alcohols with suitable nucleophiles. These processes typically require the use of super-stoichiometric amounts of activating agents and/or produce potentially hazardous by-products. The development of catalytic substitution processes that use simple alcohols as electrophiles would be highly desirable given the wide availability of alcohol substrates and the fact that water would be the only by-product.

In this regard, we have investigated the use of simple aryl boronic acids as mild Lewis acid catalysts for the substitution of benzylic alcohols with various nucleophiles.[2] We have found that commercially available pentafluorophenylboronic acid (5 mol%) in combination with oxalic acid (10 mol%) is a mild and efficient catalytic system for both inter- and intramolecular dehydrative substitution reactions of benzylic alcohols.[3] This talk will discuss the development of such reactions using a second alcohol as the nucleophile to form ether products, as well as the use of enolisable 1,3-diketones as nucleophiles for carbon-carbon bond formation. Initial insights into the reaction mechanism will also be discussed.



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Talk

Chiral Ion-pairs: Dissociation, Dynamics and Asymmetric Catalysis

Fernanda Duarte

EaStCHEM School of Chemistry, University of Edinburgh, Joseph Black Building, David Brewster Road, Edinburgh EH9 3FJ, U.K.
(Fernanda.Duarte@ed.ac.uk)

Ion-pairing with a charged, chiral catalyst has emerged as a versatile strategy in asymmetric catalysis.[1] However, theoretical work on the stereoselectivities of these transformations remains a challenging task. This is due to the difficulties in identifying the most stable configurations in a given environment, where the predominantly electrostatic nature of these interactions make them less directional and more solvent dependent than *e.g.* hydrogen-bonding or dispersion interactions.

Here we investigate the structures, dynamics and stabilities of the chiral ion-pairs in the condensed phase for the landmark anionic asymmetric PTC ring-opening reaction of *meso*-aziridinium and episulfonium cations.[2] We find that the stability of chiral ion-pairs, a pre-requisite for asymmetric catalysis, is dominated by electrostatic interactions at long-range and by CH--O interactions at short-range. The decisive role of non-bonding interactions and solvent on enantioselectivity are quantified by complementary computational approaches. Our study rationalizes several experimental results and introduces a combined classical/quantum approach to perform realistic-modelling of chiral counterion catalysis in solution.[3]

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Talk

Computer Vision in Chemistry

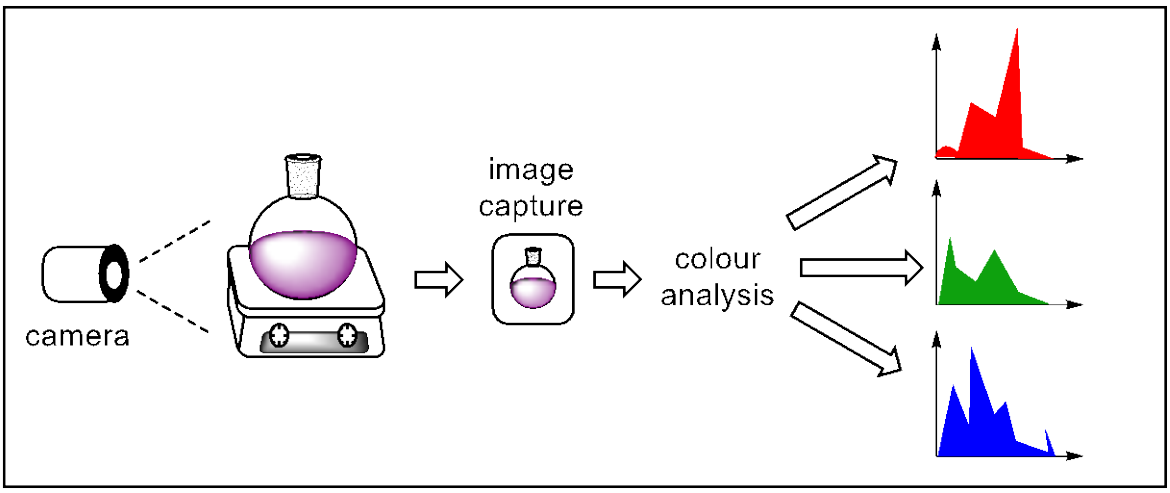
Ellis Cruickshank and Marc Reid.

University of Strathclyde, Dept. of Pure & Applied Chemistry, WestCHEM, Thomas Graham Building, 295 Cathedral Street, Glasgow G1 1XL, UK
email: marc.reid.100@strath.ac.uk

Colour changes are everywhere in Chemistry.

Until recently, however, chemical colour changes were rarely quantified,[1,2] especially not in real-time. Now, with the ubiquity of digital camera technologies, there are boundless opportunities to develop colour analysis tools based on computer vision. Additionally, digital imaging techniques are attractive to chemists and biologists due to the simplicity, portability, and low cost of such technologies *versus* traditional spectroscopic methods. Quantification of real-time colour changes also creates opportunities to apply machine learning and Big Data techniques to Chemistry problems in previously unexplored ways.

This talk focuses on our research towards colour analysis software for the quantification of real-time chemical colour changes.



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Early Career Researchers Talk Abstracts

Talk

Novel Amino Acids Incorporating Zinc-Binding Groups as inhibitors of HDAC co-repressor complexes

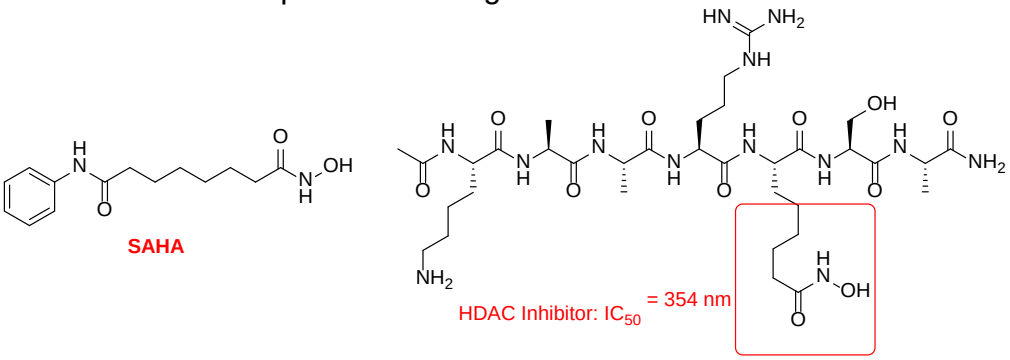
Dr. Amit Mahindra, Dr. Peter Watson, Dr. Chris Millard, Dr. John Schwabe and Dr. Andrew Jamieson*

University of Glasgow, School of Chemistry, WestCHEM, Joseph Black Building, University Avenue, Glasgow G12 8QQ, UK
email: amit.mahindra@glasgow.ac.uk

Epigenetic regulation of the human genome is vital for understanding both the etiology and fundamental mechanisms of diseases. Molecular regulation of gene expression is controlled in part by two distinct classes of lysine-modifying enzymes, the histone deacetylases (HDACs) and the histone acetyltransferases (HATs). HDACs have attracted considerable attention as therapeutic targets, especially due to their ability to modify the landscape of post-translational modifications (PTMs) on histone proteins in chromatin. Modifications in HDAC function have been linked to neurological disorders, muscular dystrophy, cardiac hypertrophy, cancer, HIV infection, and many other diseases.

Class I, II, and IV HDACs are zinc dependent enzymes. These isozymes are inhibited by molecules having zinc binding groups (ZBGs) such as SAHA (Figure).[1] Here, we describe the synthesis of novel amino acids containing ZBGs and their incorporation into H4K26 histone tail.[2] The foremost advantage of these amino acids (AAs) is they can be incorporated at any position in the peptide sequence without modification of standard Fmoc SPPS protocols.[3] This synthetic strategy is facilitating the rapid generation peptide inhibitors.

Initial data will be presented that demonstrates that these peptides are potent inhibitors of the HDAC I corepressor complex and provide critical structure information for the development of next generation of HDAC inhibitors.



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Talk

Last-step enzymatic [^{18}F]fluorination for positron emission tomography

Phillip Lowe, Qingzhi Zhang, Stephen Thompson, Sergio Dall'Angelo, Ian Fleming, Monica Piras, Matteo Zanda, David O'Hagan

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Abstract: The fluorinase enzyme (5'-fluoro-5'-deoxyadenosine synthase), originally isolated from the soil bacterium *Streptomyces cattleya,*[1] catalyses the C-F bond forming reaction of S-adenosyl-L-methionine (SAM) and fluoride ion to generate 5'-fluoro-5'-deoxyadenosine (5'-FDA) and L-methionine, the first step in the biosynthetic pathway of fluoroacetate and 4-fluorothreonine. This enzyme has since been shown to mediate a transhalogenation reaction from 5'-chloro-5'-deoxyadenosine (5'-ClDA) to 5'-FDA *via* SAM.[2] Our interest is in the exploitation of this function using the fluorine-18 isotope to permit the direct [^{18}F]radiolabelling of biologically relevant molecules through the generation of chemically stable C-^{18}F bonds, under aqueous ambient conditions and at near neutral pH. By capitalising on a critical localised specificity tolerance at the C2 position of the adenine base of 5'-ClDA we have been able to tether bioactive cargo *via* an alkyne-bearing tetraethylene glycol (TEG) linker and establish a protocol to allow for last step fluorinase mediated [^{18}F]fluorine-labelling of peptides and cancer targeting molecules for PET, as illustrated in figure 1.

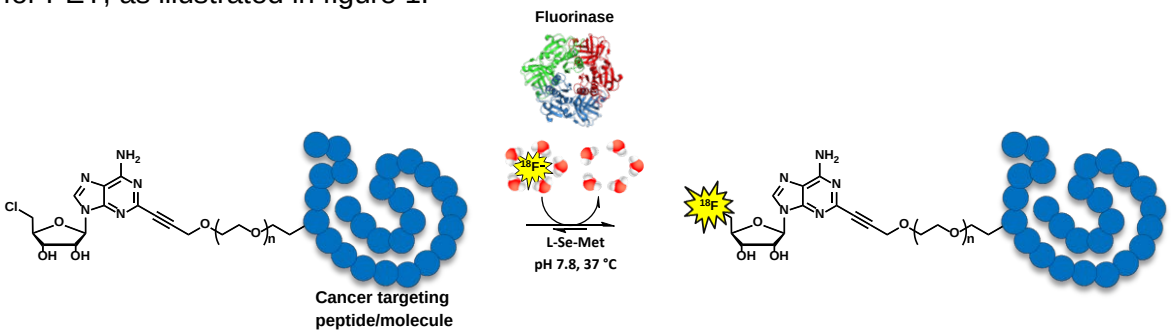

Figure 1. Fluorinase-catalysed last step ^{18}F-labelling of peptides for Positron Emission Tomography (PET).

To date we have validated this protocol through the [^{18}F]fluorine-labelling of RGD peptides using both 'click' (using mono or multimeric RGD conjugates)[3, 4] and Barbas bioconjugation strategies.[5] This methodology has also been extended to acid/amine peptide ligations involving PSMA targeting peptides and towards an [^{18}F]biotin based pre-targeting approach to PET imaging. Furthermore, we have recently employed this strategy to the direct [^{18}F]radiolabelling of a new class of 5'-FDA based A_{2A} adenosine receptor agonist in an effort to deliver novel tracers for exploration in PET studies.[6]

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Nucleic acid assembly mediated by the fluorous effect.

Jamie M. Withers,[a] Andrea Taladriz-Sender,[a] Gabriella E. Flynn,[b] Gerard Macias,[b] Sarah L. Henry,[b] Justin R. Sperling,[b] Alasdair W. Clark,[b] Glenn A. Burley.[a]

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E-mail: jamie.withers@strath.ac.uk, glenn.burley@strath.ac.uk.

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DNA nanostructures provide a level of programmability and nano-scale resolution that is unrivalled in molecular self-assembly; however, maintaining long-range ordering of functional nanostructures into the micron-range is still a formidable challenge. Conversely, lithographic methods of fabrication are scalable, but begin to reach the limits of technological miniaturization when nanoscale components are required. The integration of top-down and bottom-up synthesis is necessary to bridge the gap between these assembly techniques.

Our approach is to use lithographically patterned fluorous surfaces in combination with DNA self-assembly – incorporating short-range organisational elements (i.e., Watson-Crick base-pairing) with stronger, longer-range fluorous-fluorous recognition elements. This presentation will describe our recent efforts to explore how the fluorous effect[1-2] can be used as an effective tool to direct the immobilization of fluorous-tagged oligonucleotides (R_F-ODNs) and fluorous-tagged DNA nanostructures within fluorous-patterned surfaces (Figure).[3] The synthesis of fluorous phosphoramidites is compatible with conventional solid phase synthesizers, providing a simple, facile route to fluorous functionalisation of DNA. In contrast to conventional covalent immobilization, fluorous-directed immobilization is fully reversible; enabling directed surface patterning, regeneration, and re-patterning of surfaces without any associated degradation of immobilization efficiency or disruption of Watson-Crick base-pairing.

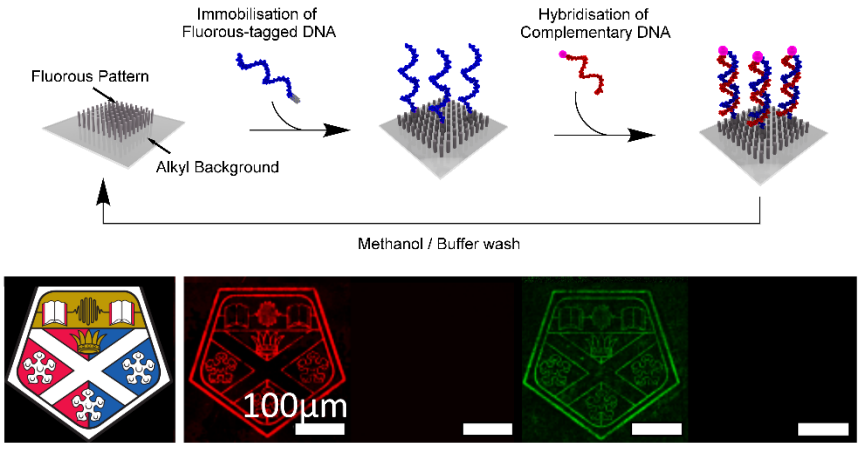

Figure. (**A**) Directed immobilisation of R_F-ODNs onto a fluorous-patterned surface, hybridisation of complementary DNA, and surface regeneration. (**B**) Fluorescence images showing two cycles of this process.

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Poster Abstracts

Generating superoxide using biologically-relevant compounds – an insight into pathological diseases?

Jude N. Arokianathar, John A. Murphy*

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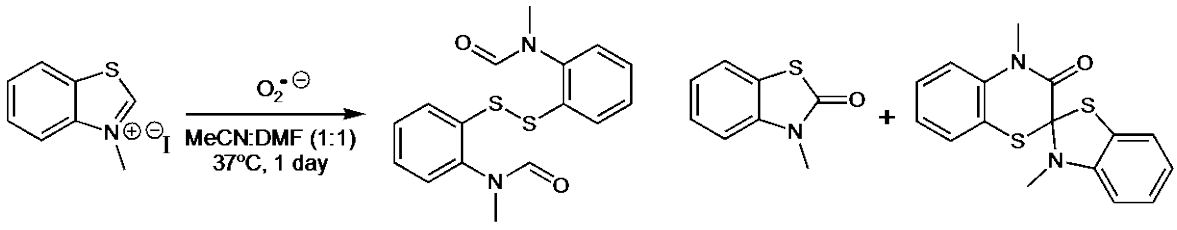
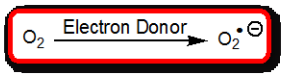
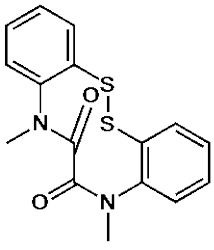
Superoxide, typically made by the single-electron reduction of molecular oxygen, is a Reactive Oxygen Species (ROS). Whilst it is essential for life, an elevated amount in the body can lead to protein denaturation, lipid peroxidation and DNA damage. The imbalance in such species i.e. oxidative stress, has been linked to various diseases e.g. diabetes, atherosclerosis, Parkinson's disease and cancer.[1]

In this poster, we explore the possibility of generating superoxide *via* the reduction of molecular oxygen using several biologically-relevant compounds (electron donors). In order to do so, we tested various superoxide detectors from which **1** was both selective and sensitive for our studies. **1** in the presence of a superoxide source such as KO_2 forms products **2**-**4**.[2] Would it be possible to replicate this result using O_2 and electron donors?



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





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Poster

Investigation of Benzyne Initiation in Transition-Metal free Coupling Reactions

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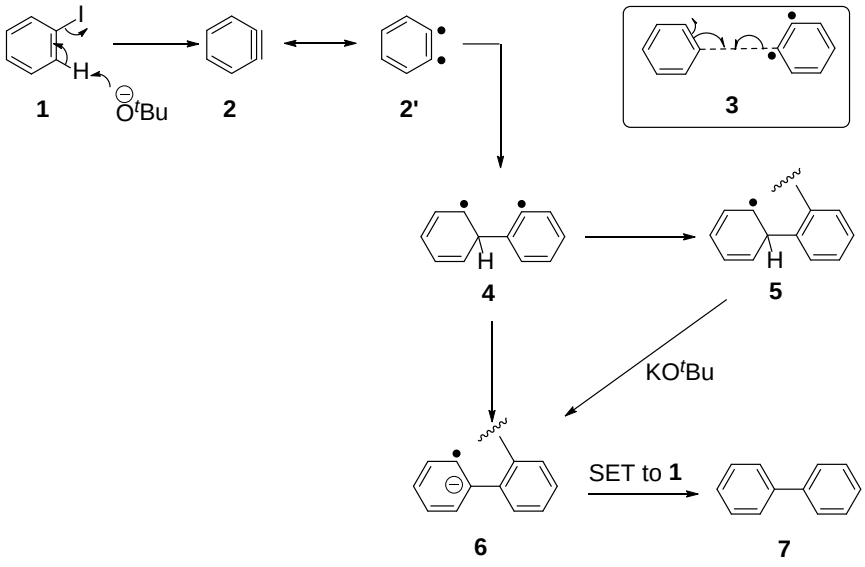
In recent years it has been demonstrated that a large number of organic electron donors are capable of donating electrons to aryl halides to promote transition metal-free coupling reactions of aryl iodides and benzene. These reactions are believed to proceed *via* a base-promoted hemolytic aromatic substitution (BHAS) mechanism.[1]

However, it is also known that at higher temperatures reactions are able to proceed without any electron donor present. In 2014 Murphy *et al*. proposed that the source of initiation for the BHAS cycle in these cases is benzyne formed from aryl iodide.[2]

To date evidence for this source of initiation has been limited to blocking the formation of benzyne to shut down blank reactions. This current work looks at methods of generating benzyne *in situ* through an additive with a view to using these as a source of initiation for transition-metal free coupling reactions.



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Poster

Counterion Activated Earth-Abundant Metal Catalysis

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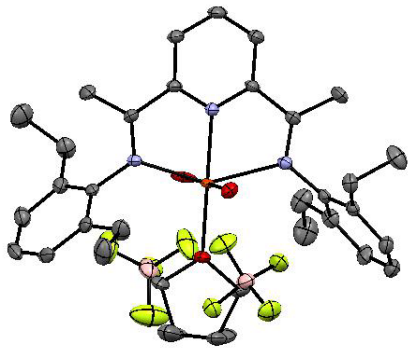
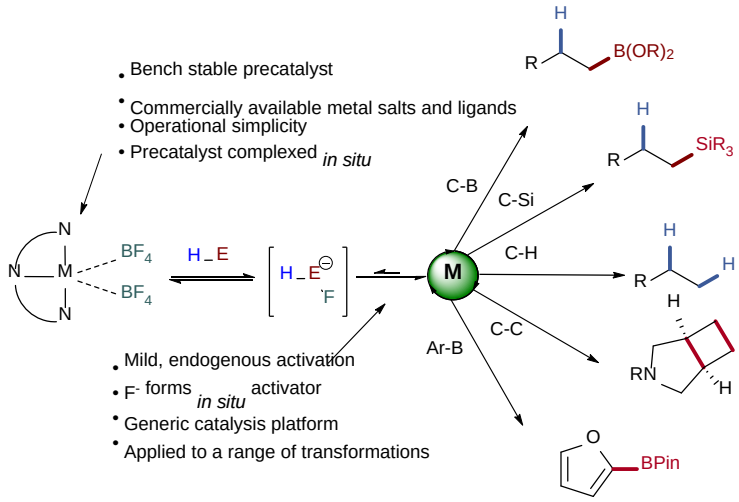
The application of iron and cobalt catalysis industrial and academic syntheses has been hampered by the limited air stability of the pre-catalysts used, and the need for pyrophoric reducing agents to generate a catalytically competent, low oxidation-state, species.[1,2,3] To circumvent these challenges, we have developed a mild, operationally simple method of activating bench-stable, commercially available metal salts for a variety of transformations. This mode of activation is facilitated by both the non-coordinating nature of the tetrafluoroborate counterion, as well as its ability to dissociate fluoride in solution. This system has been shown to be broadly applicable to hydrometalloidation reactions, and beyond this as a general mode of activation for hydrogenation, [2+2]-cycloaddition and C–H borylation reactions.





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Poster

Exploiting the synthetic chemistry of enone derived α-amino acids- The synthesis of highly fluorescent pyrazoloquinazoline functionalised amino acids for biological imaging

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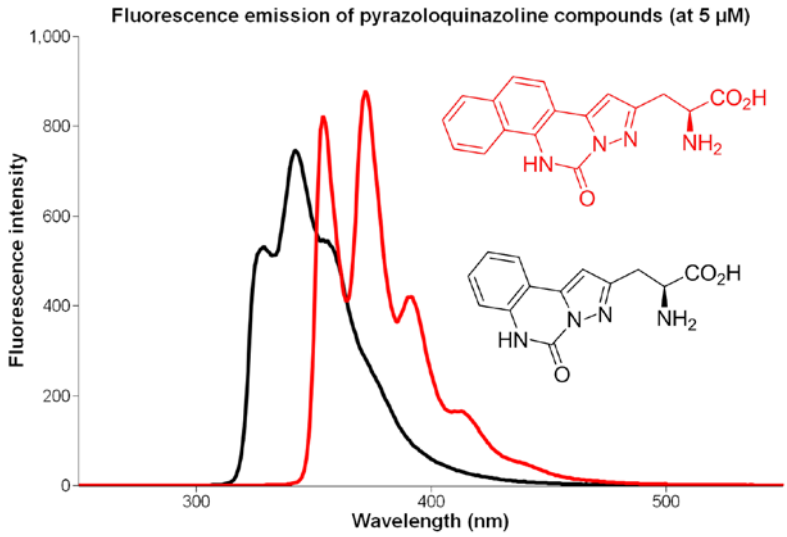
Abstract: Fluorescence spectroscopy has become a powerful technique for probing complex biological processes, including enzyme mechanisms and protein-protein interactions.[1] Small non-natural fluorescent amino acids provide a convenient approach to introduce fluorescence into either a peptide chain or a protein, without significantly modifying the original structure.[2] Whereas the use of large fluorescent proteins such as the green fluorescent protein (comprising of 238 amino acids) may drastically alter the structure of the protein being investigated.

Recent developments in the Sutherland group have established an effective and flexible 10-step synthesis from L-aspartic acid to a class of non-natural highly fluorescent α-amino acids, known as pyrazoloquinazolines. Key synthetic steps involved a heterocyclisation of the enone with hydrazine, followed by reaction of an aniline substituted pyrazole with triphosgene to give the rigid tricyclic chromophore. These pyrazoloquinazoline compounds were found to exhibit exciting fluorescent characteristics.[3] Fluorescent quantification of these compounds have shown very high quantum yield values, and hence this class of compounds have the potential to act as excellent fluorescence probes for biological investigations.



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Poster

Development of a Divergent Synthetic Strategy for the Asbestinins

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The 2,11-cyclised cembranoids comprise a broad family of natural products which includes the asbestinins. In recent years, over thirty members of the asbestinin family of natural products, such as 11-acetoxy-4-deoxyasbestinin D, have been isolated from the gorgonian octocoral species *Briareum asbestinum* (Figure 1A).[1] Structurally, the asbestinins consist of a tetracyclic core containing 5−9 membered rings with 9−10 contiguous stereocentres and a fully substituted tetrahydrofuran.

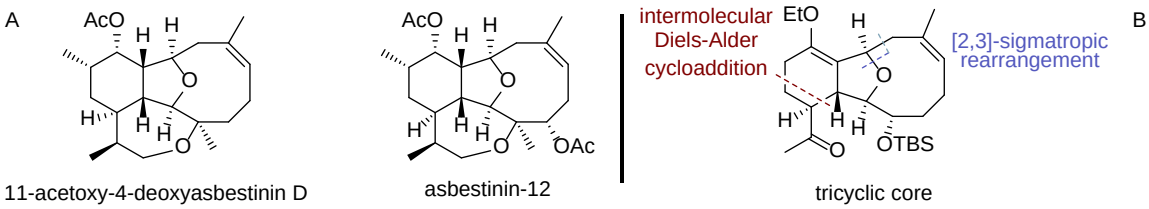
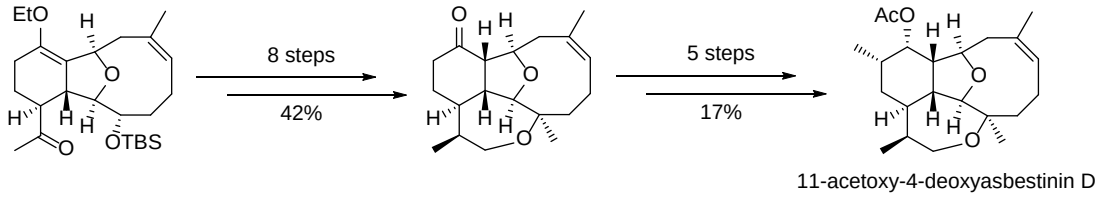


Figure 1

Previous work within the Clark group developed methodology for the formation of the tricyclic core present in this family of cembranoids (Figure 1B).[2] The desired tetracyclic core could be synthesised from the tricyclic ketone in eight steps (Scheme 1).[3]



Scheme 1

The tetracycle was converted to the natural product, 11-acetoxy-4-deoxyasbestinin D in five steps giving the natural product in 25 overall steps with this being only the second total synthesis. The methodology developed will then be applied to the synthesis of multiple members of the asbestinin family allowing structural elucidation of these compounds.

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Poster

Towards a Unified Biomimetic Approach to the Brevianamide Alkaloids.

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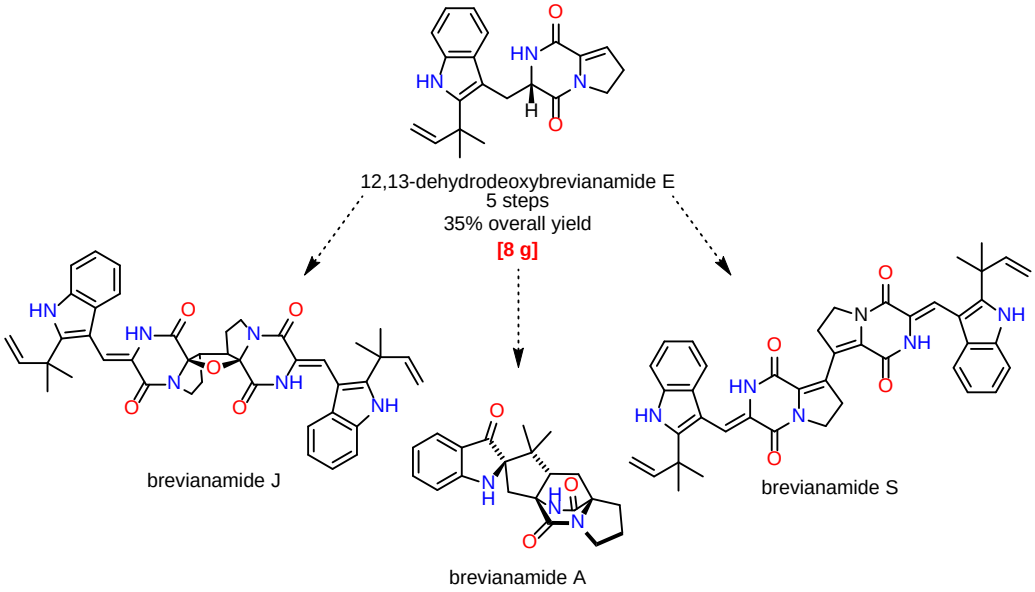
The brevianamides are a family of fungal-derived non-ribosomal peptide indole alkaloids.[1-3] We are developing a new biomimetic synthetic strategy to allow access to various members of this well known family of highly complex structures. The lynchpin intermediate in our synthetic strategy is the natural product 12,13-dehydrodeoxybrevianamide E. We have developed the shortest reported total synthesis of this natural product, requiring just 5 steps and proceeding in 35% overall yield, which compares favourably to Williams' 12-step, 8% overall yield, synthesis.[1,5,6] The archetypal family member, brevianamide A, has a complex pentacyclic structure and has been the subject of intense synthetic attention.[1,7] Previous biomimetic syntheses have only been able to provide access to racemic material and have exhibited opposite diastereoselectivity to that required for the natural configuration.[1] Brevianamides J and S are the only reported dimeric members of this family and they have not yet been synthesised.[2,3] Recent results from our efforts to achieve the shortest total syntheses of brevianamides A, J and S from 12,13-dehydrodeoxybrevianamide E will be presented.



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Poster

Towards the Total Synthesis of Agariblazeispirol C

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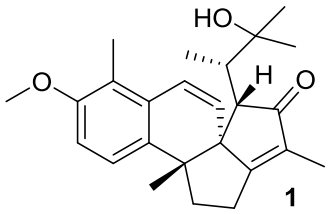
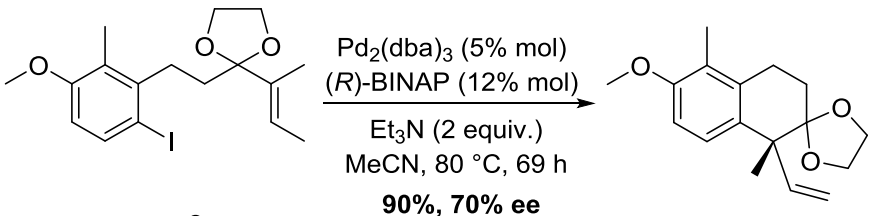
Agariblazeispirol C **1** is a natural product which has been extracted and isolated from *Agaricus blazei,* a rich source of bioactive compounds. Within our research team, studies are underway towards the total synthesis of Agariblazeispirol C. Thus far, we have established the key core skeleton of the natural product through two effective metal-mediated cyclisation processes; intramolecular Heck and Pauson-Khand reactions.



1

Agariblazeispirol C

Focusing on the intramolecular Heck transformation, we envisaged the use of an asymmetric variant to construct the key 6,6-bicyclic system **3**. This poster will describe the synthesis of the targeted Heck precursor **2** and the initial optimisation of the key asymmetric intramolecular Heck reaction.



2 **3**

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Poster

Asymmetric Tsuji-Trost Allylation Reaction: Application Towards the Functionalisation of Cyclic Ether Systems

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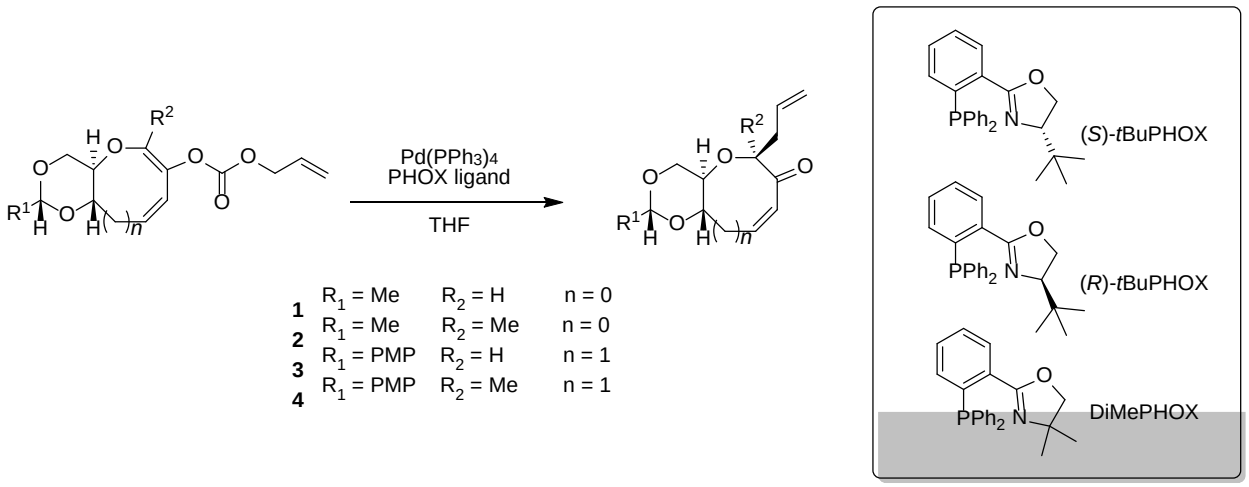
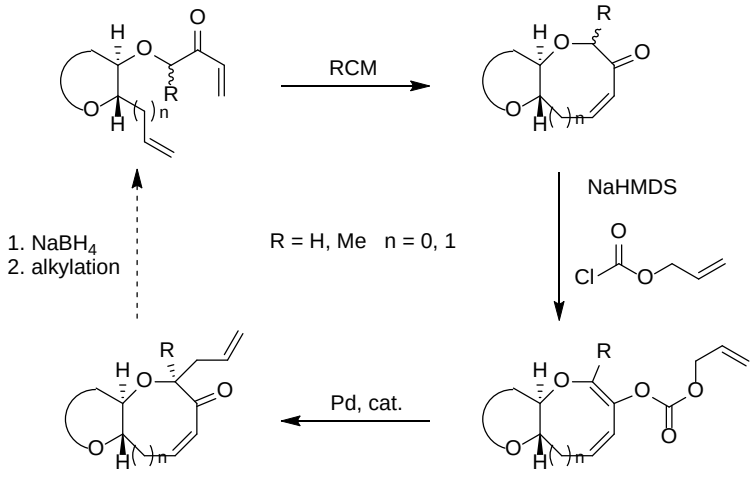
The stereoselective Tsuji-Trost allylation reaction[1] is a potentially powerful reaction for the functionalisation of cyclic and polycyclic ether systems. A series of seven- and eight-membered substrates were designed in order to investigate the versatility of the Tsuji-Trost allylation and to determine the effect of different chiral phosphinooxazoline (PHOX) ligands[2] upon the diastereoselectivity of the reaction.



This methodology could enable the rapid and efficient construction of polycyclic ether cores, such as those found in a number of marine natural products, by sequential ring-closing metathesis, Tsuji-Trost allylation, reduction and alkylation.



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One-pot Multi-Bond Forming Reactions for the Asymmetric Synthesis of Optically Active Indanols and Aminoindanes

Poster

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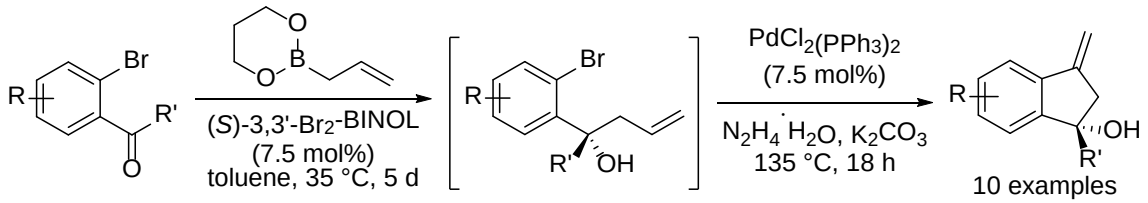
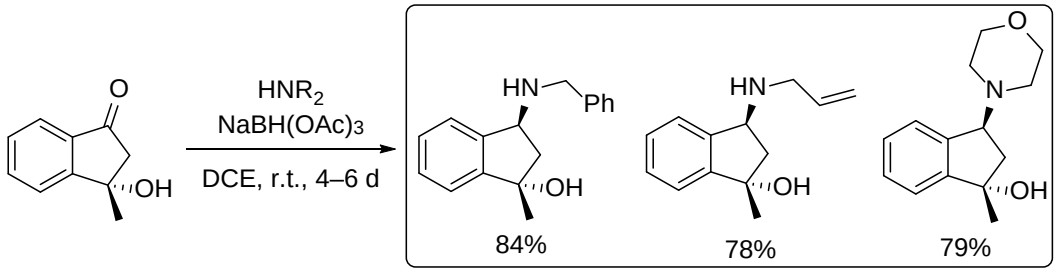
Indanols and aminoindenes are fused bicyclic motifs found in a range of natural products and pharmaceutical compounds. Despite their synthetic utility, only a few methods have been published to build such scaffolds, which mainly focus on their racemic preparation.[1] Therefore, novel methods are required for the rapid and easy access to these compounds. Within our group we have demonstrated that a two-step, one-pot allylboration/intramolecular Heck reaction could be used to generate these carbocycles.[2] The aim of the current project was to develop a highly efficient one-pot process for the asymmetric synthesis of *exo*-methylene containing indanols with a fully substituted C1 carbon atom from 1-(2'-bromophenyl)ethan-1-ones. The synthetic route of these 1-(2'-bromophenyl)ethan-1-ones consisted of the 1,2-addition of 2-bromobenzaldehydes and subsequent oxidation.

The asymmetric allylation of ketones was optimised and successfully coupled with the intramolecular Heck reaction.[3] This one-pot process efficiently delivered a number of novel *exo*-methylene containing indanol compounds. For the investigation of the stereoselectivity, the *exo*-cyclic indanols were synthesised in their racemic form to serve as standards for chiral HPLC.



The synthetic utility of these compounds was explored and several possible transformations were investigated in order to access compounds with structural diversity. The 1,1-disubstituted double bond underwent ozonolysis, and from this indanone species a general diastereoselective one-pot reductive amination for the preparation of amino-substituted indanols was developed.



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Poster

Novel fluorinated motifs for drug discovery

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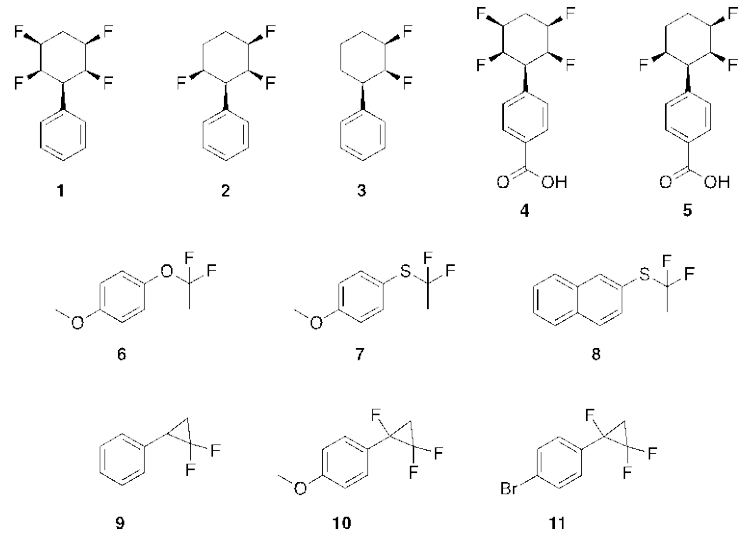
We are interested in partially fluorinated hydrocarbon motifs as potential substituents in drug discovery. Such motifs become polarized where fluorination results in a decrease in Log P (less lipophilic). Our motifs include all-*cis* fluorocyclohexanes **1** to **5**,[1] α,α-difluoro thio- and oxo- ether eg. **6** to **8**[2] and partially fluorinated cyclopropanes **9** to **11**[3]. Lipophilicities were measured (reverse phase HPLC) and their metabolism was explored in incubations with the model organism (fungus) *Cunninghamella elegans*.[4]



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Poster

Catalytic Diastereoselective Reductive Aminations

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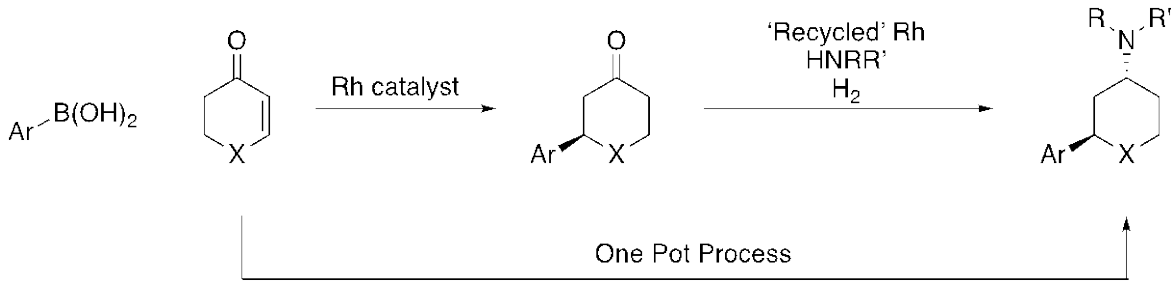
The enantioselective synthesis of tertiary amines is a highly desirable goal, but few efficient synthetic methods exist.[1]. A possible atom efficient route to form tertiary amines is through catalytic hydrogenation.[2]. While enantioselective hydrogenation of unfunctionalised enamines to give tertiary amines has been achieved, none of these reports reach the efficiency required to make it commercially viable.[3]. Additionally, no enantioselective reductive amination routes that give tertiary amines have been achieved.

This project looks at developing a direct reductive amination of amines with 3-substituted cyclohexanones to give high diastereoselectivity. The reaction was explored and optimised by studying effects such as pressure, temperature and ligands on the reaction efficiency. The scope of this reductive amination was also explored using different aryl substituents and amines.

Following this the reductive amination was incorporated into a one pot multi-step process. A single rhodium source was used for an enantioselective conjugate addition to generate a 3-aryl cyclohexanone followed by the diastereoselective reductive amination to give a tertiary amine with multiple chiral centres.



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Poster

New Tools for Visualising Nanoparticle Drug Delivery

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Biodegradable polymeric nanoparticles (NPs) are becoming increasingly popular for targeted drug delivery and controlled release. Recent work in the Williams group (Scottish Centre for Regenerative Medicine),[1] has shown that poly lactide-*co*-glycolide (PLGA) NPs can be used for drug delivery to the central nervous system to promote remyelination in multiple sclerosis disease models. However, as yet no direct link between the observed biological effect and nanoparticle delivery has been established.

Stimulated Raman scattering (SRS) microscopy can be used to give quantitative real-time, bond-specific imaging in live cells, [2, 3] introducing a bio-orthogonal label into the PLGA will allow the NPs to be visualised using SRS microscopy. We have developed a synthetic route to deuterated PLGA, which is Raman active in the cellular silent region.[2] We have also optimised the fabrication of PLGA nanoparticles by both the emulsion-evaporation and nanoprecipitation methods, as confirmed by dynamic light scattering and electron microscopy.

Using the emulsification-evaporation method has allowed the encapsulation of BSA as a model protein, and rhodamine which has allowed for fluorescence imaging of the NPs in cells. Preliminary studies have shown the release rate of rhodamine from NPs *in vitro*, and we are currently investigating surface functionalisation of NPs to target them to specific cells.

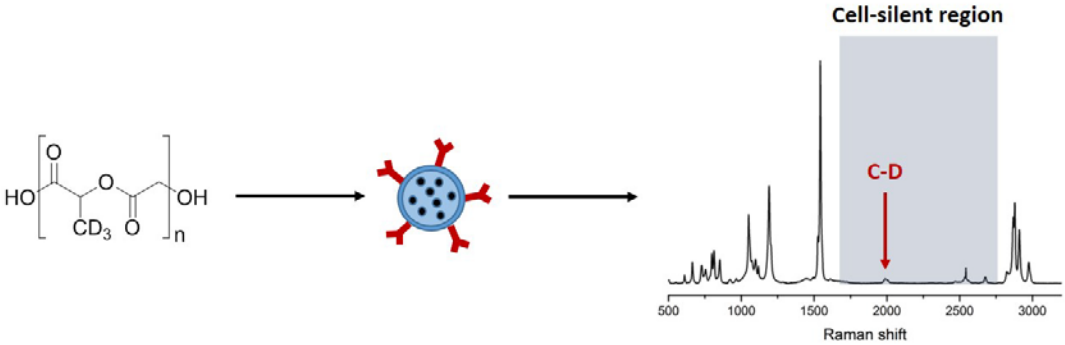

Figure 1: Deuterated PLGA used to form targeted NPs, which can be imaged using Raman spectroscopy.

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Poster

Development of an Auto-Tandem Catalytic Dehydrogenation/Oxidative Heck Reactions on 2,2-Disubstituted Cyclopentanediones[1]

Claire J. C. Lamb, Bryan G. Nderitu, Gemma McMurdo, John M. Tobin, Dr Filipe Vilela, Dr Ai-Lan Lee

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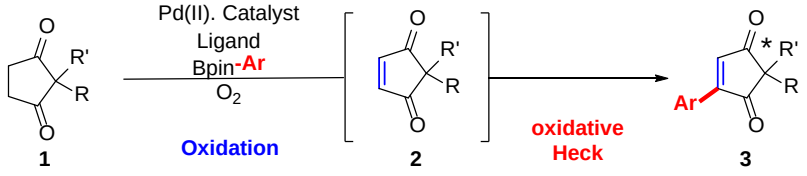
The synthesis of cyclopentenediones is of great synthetic interest as the motif is present in a wide variety of biologically active natural products such as madindolines A and B, similian A and preussidone. In 2015, the Lee group published the first Pd(II)-catalysed oxidative Heck desymmetrisation coupling reaction with 2,2-disubstituted cyclopentene-1,3-diones **2** with aryl boroxines, in up to quantitative yields and 94:6 er of the coupled product **3**.[2]

However, the dehydrogenation reaction of **1** to **2** is usually carried out using stoichiometric amounts of $CuBr_2$. This is an environmentally unfriendly process as it generates stoichiometric amounts of halogenated waste. In 2011, Stahl and co-workers developed a Pd(II)-catalysed aerobic dehydrogenation of cyclic ketones to enones.[3] This work raises an intriguing possibility of employing the same Pd(II)-catalyst for two mechanistically different steps within a one-pot process: a dehydrogenation and an oxidative Heck coupling reaction, in an efficient approach to the coupled cyclopentene-1,3-dione product **3** (Scheme 1).

In this poster, we will discuss the successful development of a one-pot dehydrogenation/oxidative Heck reaction **1**→**3**. This auto-tandem reaction was also applied to a continuous flow process and investigated for enantioselective desymmetrisation of the all-carbon quaternary centre.



- Auto-tandem catalysis: batch and continuous flow
- Pd catalyses two different reactions
- Telescoped synthesis for enantioselective desymmetrisation

Scheme 1: Auto-tandem catalytic dehydrogenation/oxidative Heck reaction to compound **3**

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Poster

Gas-Phase Reaction of Heterocycles over Solid-Supported Molybdenum Trioxide

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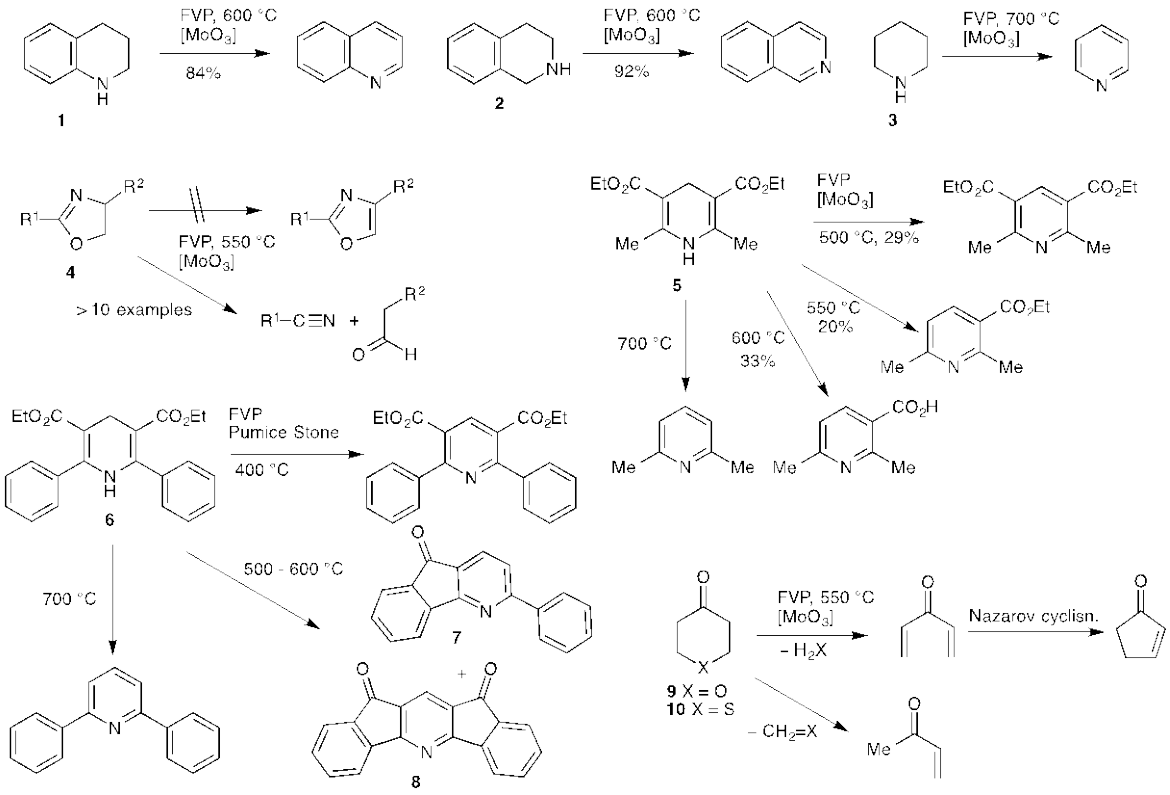
Based on some unpublished preliminary studies[1] we have explored the use of MoO_3 supported on pumice stone chips as a solid reagent / catalyst in flash vacuum pyrolysis of heterocyclic compounds. Aromatisation of tetrahydroquinoline and -isoquinoline **1** and **2** as well as piperidine **3** is easily achieved. Attempted extension to oxazolines **4** gave no oxazoles, but instead resulted in clean thermal cleavage into nitrile and aldehyde fragments, in what appears to be a previously unreported reaction.



The Hantzsch dihydropyridines **5** and **6** are readily aromatised at lower temperatures but as the temperature is raised more interesting products are formed including **7** and **8**. The pyranone and thiopyranone **9** and **10** undergo loss of (thio)formaldehyde to give methyl vinyl ketone and also loss of water or H_2S to form divinyl ketone which undergoes Nazarov cyclisation to cyclopentenone.

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Poster

Tracking intracellular uptake and localisation of alkyne tagged fatty acids

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The uptake, distribution and metabolism of lipid species is vital for normal cell function. Dysregulation of these processes has been linked to numerous disease states including neurodegenerative diseases[1] and cancer.[2] In order to develop new and effective treatments for such diseases, it is important to gain a detailed understanding of lipid biochemistry.

Raman spectroscopy is a promising technique for the analysis of intracellular lipid species as they give rise to strong signals. This approach also allows biological samples to be analysed in their native state.[3] Alkyne tags have become important in Raman spectroscopy as their unique signal (~2110 cm^{-1}) can be observed in the biologically 'silent' region of the spectrum (~1800–2800 cm^{-1}).[4] The use of alkyne tagged lipids could therefore allow us to gain an insight into the uptake and localisation of lipids within cells.

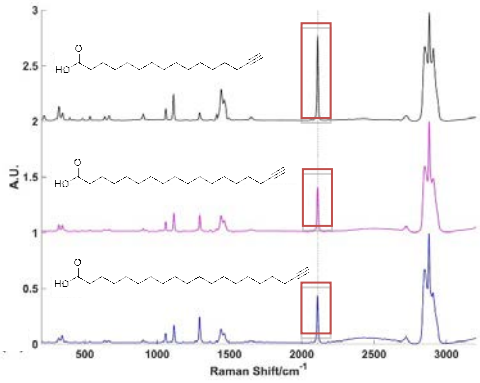

Figure 1: Raman spectra of C14, C16 and C18 alkyne tagged fatty acids highlighting key signal.

Within this poster we describe the synthesis of a series of alkyne tagged fatty acids[5] and use these to study the uptake and distribution of fatty acids in single cells using Raman spectroscopy. This facilitates our understanding of the biology associated with these lipid species.

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Immobilization by surface conjugation of cyclic peptides for effective mimicry of the HCV-envelope E2 protein as a strategy towards synthetic vaccines

Poster

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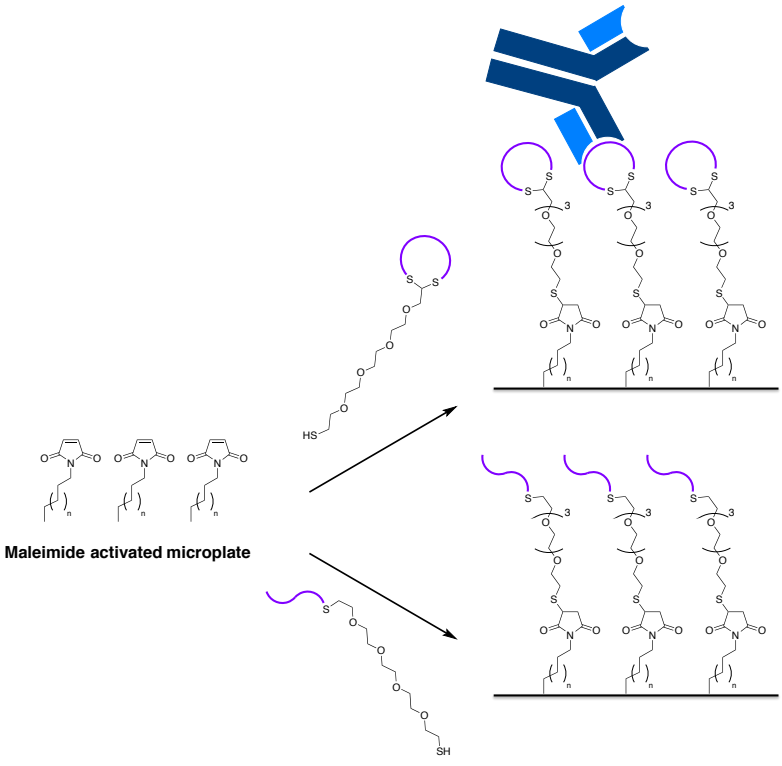
ABSTRACT: Mimicry of the binding interface of antibody-antigen interactions using peptide-based modulators (*i.e.* epitope mimics) has promising applications for vaccine design. These epitope mimics can be synthesized in a streamlined and straightforward fashion, thereby allowing for high-throughput analysis. The design of epitope mimics is highly influenced by their spatial configuration and structural conformation. It is widely assumed that for proper mimicry sufficient conformational constraints have to be implemented. This paper describes the synthesis of bromide derivatives functionalized with a flexible TEG linker equipped with a thiol-moiety that could be used to support cyclic or linear peptides. The cyclic and linear epitope mimics were covalently conjugated via the free thiol-moiety on maleimide-activated plate surfaces. The resulting covalent, uniform, and oriented coated surface of cyclic or linear epitope mimics were subjected to an ELISA to investigate the effect of peptide cyclization with respect to mimicry of an antigen-antibody interaction of the HCV E2 glycoprotein. To our knowledge, the benefit of cyclized peptides over linear peptides has been clearly demonstrated here for the first time. Cyclic epitope mimics, and not the linear epitope mimics, demonstrated specificity towards their monoclonal antibodies HC84.1 and V3.2, respectively. The described strategy for the construction of epitope mimics shows potential for high-throughput screening of key-binding residues by simply changing the amino-acid sequences within synthetic peptides. In this way, leucine-438 has been identified as a key-binding residue for binding monoclonal antibody V3.2.



Poster

New Selective PET Imaging Agents for $S1P_5$ Receptors

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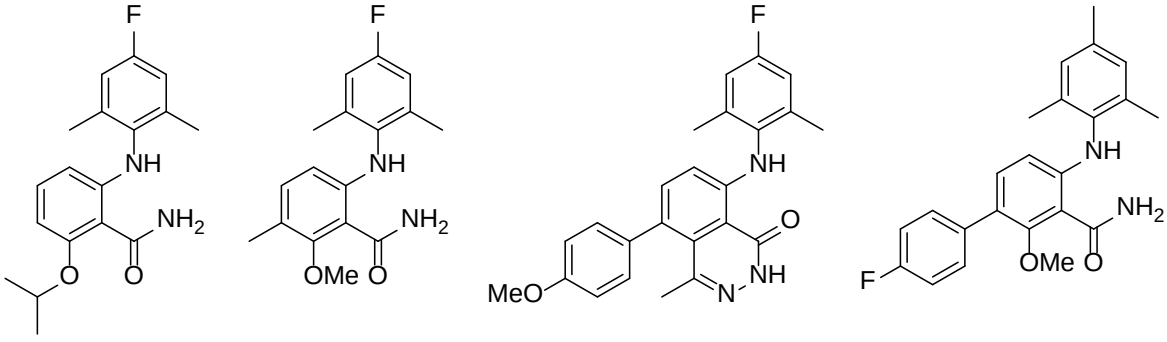
Multiple sclerosis is a demyelinating disease that affects approximately 100,000 people in the UK, with 5,000 people newly diagnosed with the condition each year. Within the central nervous system, sphingosine-1-phosphate (S1P) receptors are predominantly expressed in oligodendrocytes, brain cells that are involved in the process of myelin production. As demyelination processes are typical in multiple sclerosis, understanding the role of $S1P_5$, a sub-type S1P receptor in mediating this process may lead to new treatments.[1]

Recent work by Novartis has identified amino aryl substituted benzamide compounds which are selective agonists of $S1P_5$.[2] The focus of this project is to develop tools that will allow an understanding of the interdependence of $S1P_5$ in demyelination. We have designed novel PET imaging agents, which are structural analogues of these benzamide compounds and that will act as $S1P_5$ agonists in the human brain. To explore the SAR of the benzamide agonists, three libraries of cold fluoride analogues have been synthesised and have undergone pharmacokinetic testing, prior to biological testing *in vitro*. Methods for labelling any lead compounds with ^{18}F will then be assessed. This poster will describe the design and synthesis of various approaches towards these potential PET imaging agents of $S1P_5$.



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Towards the synthesis of Novel β-turn and α-helix mimics, and their incorporation into Peptides.

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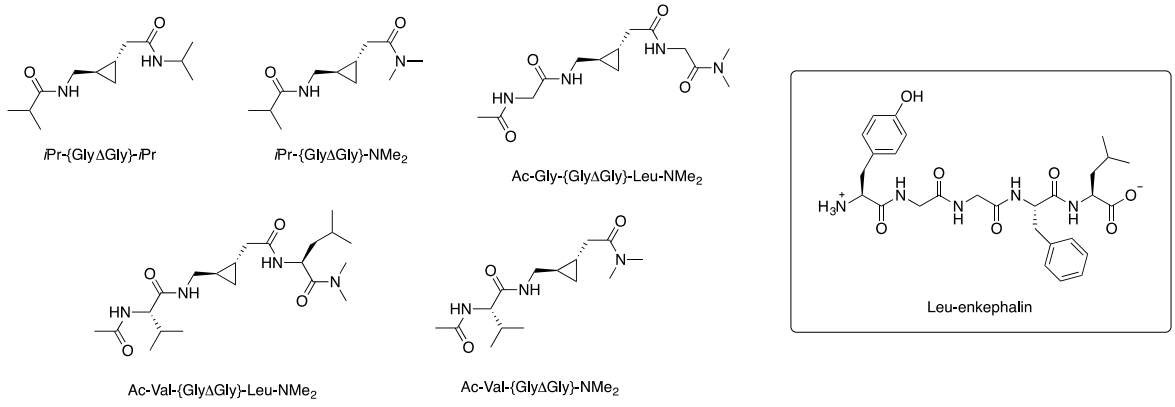
Natural peptides and proteins are crucial in biological processes; depending on their structure and location in the body they play different important roles in structural,[1] dynamic[2] and chemical transformations.[3] *In vivo*, peptides and proteins can be cleaved under mild conditions by proteases,[4] which degrade and reduce the activity of certain peptides. Studies have shown that peptide bonds can be mimicked in order to prevent cleavage *in vivo* while retaining bioactivity and having the ability to control the folding and shape of the peptide.[5-7] To this end, the synthesis of peptidomimetics containing cyclopropane as amide bond isostere has been explored. Furthermore, the incorporation of a cyclopropane moiety allows the molecule to be constrained conformationally, bringing hydrogen bond donor and acceptor groups closer together and thus facilitating β-turn formation through hydrogen bonding. To demonstrate this concept with respect to β-turn formation, the {GlyΔGly} dipeptide replacement unit containing a cyclopropane was synthesised and then incorporated into a peptide chain.
IR and concentration-dependant NMR analyses have been conducted on each peptide in order to detect hydrogen bond formation.[7] In the event that these model systems adopt the desired conformation, novel cyclopropane-based bioisosteres will be incorporated into Leu-enkephalin peptide at various positions.



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Poster

Prodrugs Activated by Implantable Microsystems

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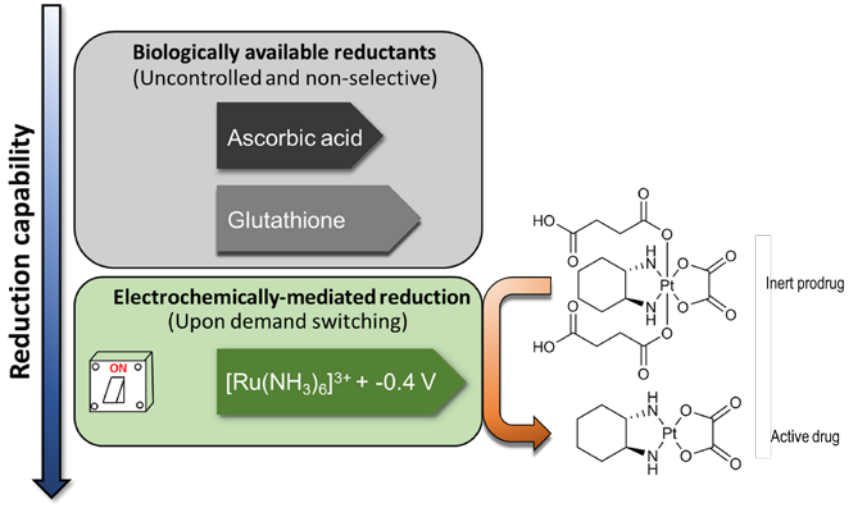
Conventionally, prodrugs are activated to their biologically active parent drugs by enzymatic processes. However, due to these enzymes having population-dependent variances or presence in both cancerous and healthy tissues, selectivity and efficacy can be attenuated[1]. In order to overcome this, here, a novel method of prodrug activation has been developed that uses an electrochemical stimulus to activate a Pt(IV) prodrug. A redox mediator was immobilised on an electrode surface that can reduce, and thus activate, a Pt(IV) prodrug. The oxidised mediator is regenerated by constant application of a low reductive potential providing an electro-catalytic prodrug activation system. Discrete mediator–electrode devices were created using polymeric encapsulation of the mediator at the electrode surface. This system was optimised to afford efficient and simple application and its ability to function in complex 2D and 3D cellular environments was characterised. Electrochemical prodrug activation was shown to be effective in inducing cell death in a colon cancer cell line. Longer-term aspiration is an implantable device capable of activating cancer prodrugs with external control, affording unprecedented selectivity and control where, when and how much active drug is generated.



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Poster

Investigating the Role of KO*t*-Bu and DMF in Electron Transfer Reactions

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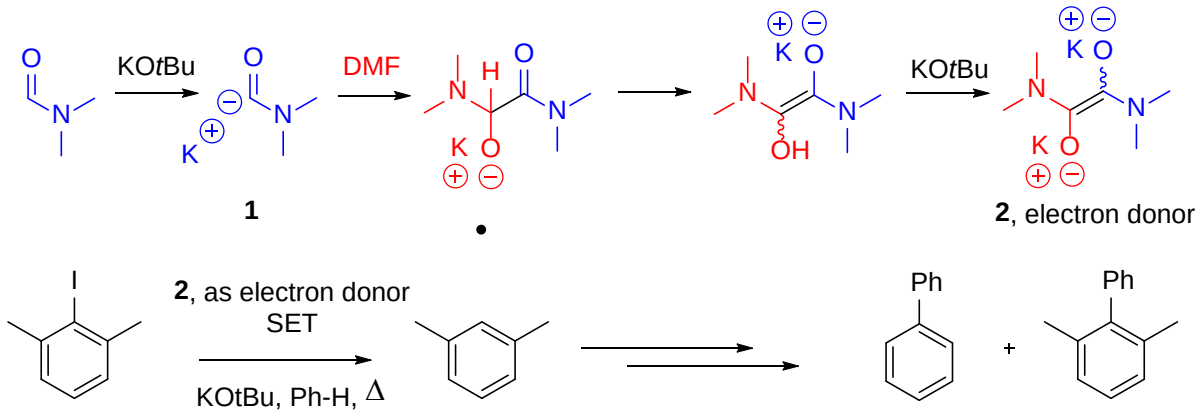
In the literature, many recent studies have reported that KO*t*Bu in DMF as solvent is involved in single electron transfer reactions.[1,2] Many authors proposed single electron transfer from the salt **1**.[3,4] We now reveal the *in situ* formation of the novel organic electron donor **2** *via* DMF dimerisation promoted by KO*t*Bu,[5] and illustrate the scope of its reactions.



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Poster

Acylative Kinetic Resolution of Alcohols Using a Recyclable Polymer-Supported Isothiourea Catalyst in Batch and Flow

Neyyappadath R. M.,[‡] Chisholm R.,[†] Greenhalgh M. D.,[†] Rodríguez-Escrich C.,[‡] Pericàs M. A.,[*,‡,§] Hähner G.[†] and Smith A.D.[*,†]

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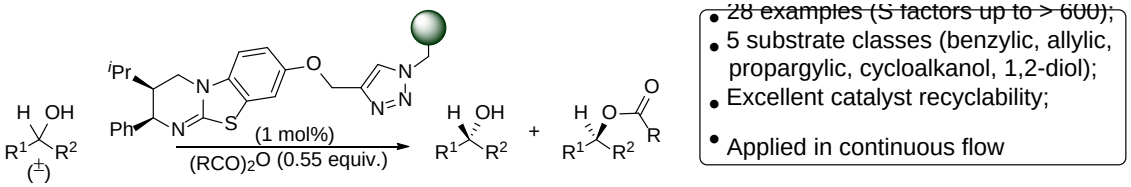
Catalytic kinetic resolution (KR) processes allow the separation of a racemate into its two enantiomeric forms through the selective reaction of one enantiomer promoted by a chiral catalyst.[1] The catalytic acylative KR of alcohols is a powerful method to prepare highly enantioenriched alcohols.[2] Chiral Lewis base catalysis is most commonly applied for this transformation, with a range of excellent catalysts reported for the KR of many classes of secondary alcohols. A current limitation of this method is that the Lewis base catalyst is rarely recovered from the reaction. A common strategy to facilitate catalyst recovery is catalyst immobilization on an insoluble solid support.[3]



A polystyrene-supported isothiourea catalyst, based on the homogeneous catalyst HyperBTM, has been prepared and used for the acylative kinetic resolution of secondary alcohols. A wide range of alcohols, including benzylic, allylic and propargylic alcohols, cycloalkanol derivatives and a 1,2-diol, has been resolved using either propionic or isobutyric anhydride with good to excellent selectivity factors obtained (28 examples, S up to 645). The catalyst can be recovered and reused by a simple filtration and washing sequence, with no special precautions needed. The recyclability of the catalyst was demonstrated (15 cycles) with no significant loss in either activity or selectivity. The recyclable catalyst was also used for the sequential resolution of 10 different alcohols using different anhydrides with no cross-contamination between cycles. Finally, successful application in a continuous flow process demonstrated the first example of an immobilised Lewis base catalyst used for the kinetic resolution of alcohols in flow.

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Poster

Applying Unconventional Ligands to Transfer-Hydrogenation and Hydrogen-Borrowing Catalysis

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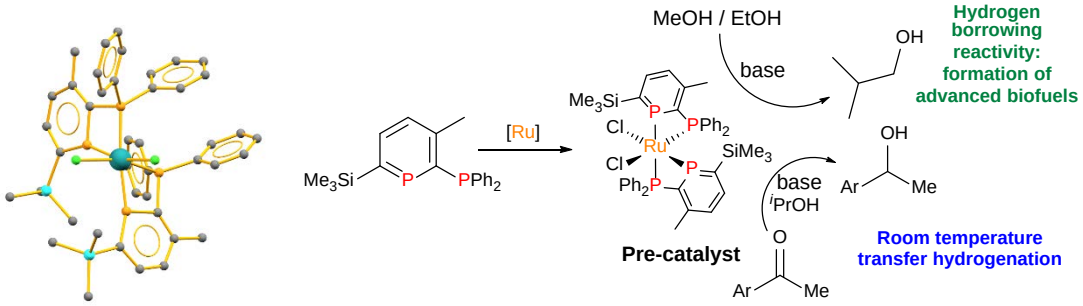
Transfer hydrogenation holds great potential in chemical synthesis because it replaces hazardous reducing agents, such as hydrogen gas or metal hydrides, with more convenient chemical sources of hydrogen, commonly isopropanol or formic acid/formate.[1] Related to this are hydrogen-borrowing processes that involve the oxidation of a saturated substrate by transfer of an equivalent of dihydrogen to a metal centre, thereby facilitating new reactivity, before the borrowed hydrogen is then returned. Developing catalysts that incorporate unconventional ligands can offer different pathways for catalysis, including metal-ligand cooperation or bifunctional reactivity. Phosphinophosphinines, which are bidentate ligands containing the phosphorus analogue of pyridine,[2] offer many unusual reactivity pathways. A Ru complex using this ligand has been shown to be a very active catalyst for the room temperature transfer hydrogenation of acetophenone, as well as a catalyst for isobutanol formation (a so called 'advanced biofuel') from ethanol / methanol mixtures in a hydrogen borrowing process at elevated temperatures.[3]



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Poster

Synthesis of Biaryls via Gold-Catalysed Direct Arylation

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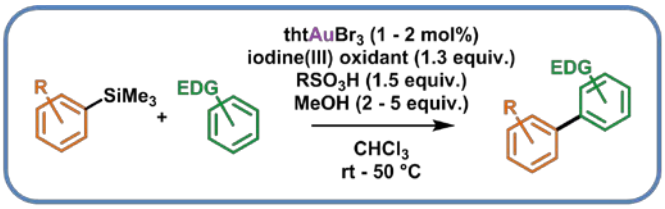
Chiral biaryls are found in many biologically active natural compounds.[1] Variants on the classical cross-coupling reactions, such as the Nobel Prize winning[2] Suzuki-Miyaura coupling involving an aryl organometallic (Ar1-M) and an aryl halide (Ar2-X), are common methods for the synthesis of chiral biaryls. However, a more concise direct arylation reaction, whereby an organometallic (Ar1-M) couples with an arene (Ar2-H) to give the biaryl (Ar1-Ar2) product would be a very appealing replacement.

Recently, the Lloyd-Jones group reported the gold-catalysed coupling of aryl silanes with arenes under oxidative conditions.[3] These reactions are performed using comparatively mild conditions, under air, with the vast majority working at room temperature and being complete in under 3 h with 1 - 2 mol% of a homogeneous gold catalyst.



- Mild conditions
- Versatile scope
- Easy-to-handle reagents
- Predictable regioselectivity
- Orthogonal to Pd^0 chemistry
- Tolerant of air and moisture

As an extension of this work, we have investigated the production of enantioenriched chiral biaryls, it would simultaneously add another method to synthesise these complex structures and inform us of the environment of the gold catalyst throughout the reaction.

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Poster

Advancements in Selective Gold Catalysis

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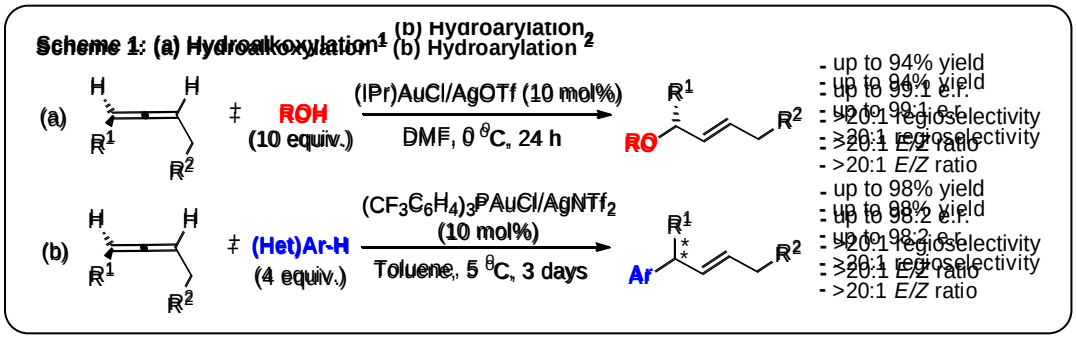
Introduction

The development of two gold-catalysed reactions will be presented. The first showcases the selectivity of gold-catalysis by demonstrating excellent chirality transfer with allenes and the second combines gold with visible light photoredox catalysis to achieve regioselective C-H activation cross-couplings.

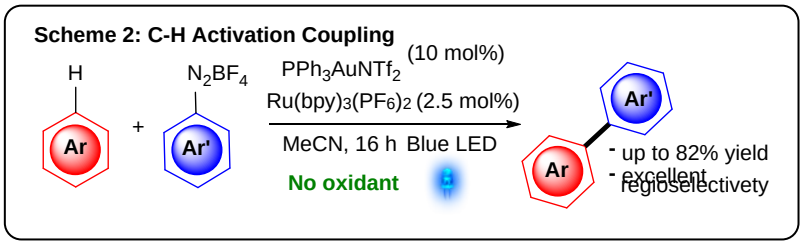
Chirality Transfer in Gold(I) Catalysed Reactions of Allenes[1,2]

Gold-catalysed hydroalkoxylation of allenes with efficient chirality transfer has traditionally been extremely challenging due to competing gold-catalysed allene racemisation: previous reported attempts resulted in poor chirality transfer. We have successfully developed the first gold-catalysed hydroalkoxylation (Scheme 1a) and hydroarylation (Scheme 1b) that occurs with excellent chirality transfer as well as regioselectivity, by developing conditions that suppress allene racemisation.



Dual Gold and Photoredox Catalysed C-H Activation Couplings[2]

This constitutes the first gold-catalysed C(sp^2)-H activation reaction (Scheme 2) which does not require stoichiometric oxidants. The procedure confers regioselectivity, via the crucial gold-catalysed C–H activation step, which is not present in the unselective photocatalysis-only counterpart and due to there being no stoichiometric oxidant, functional group tolerance is improved and no stoichiometric organic waste from the oxidant is produced.



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46th Scottish Regional Meeting of the RSC Organic Division, University of Edinburgh, 9th January 2018

FBI Investigates Ivermectin Resistance in Nematodes **Poster**

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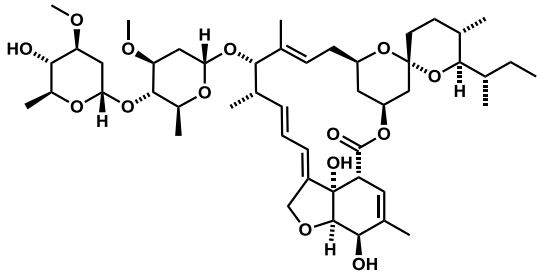
Parasitic nematodes (roundworms) are responsible for many diseases around the world. The World Health Organisation (WHO) estimates 1.5 billion people suffer from helminth (parasitic worm) infections.[1] Nematode infection in cattle and sheep causes losses of an estimated $1 billion per annum (Australia) and infection in crops approximately $80 billion per annum (worldwide).[2]

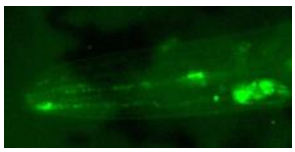
Numerous anthelmintics are available to treat nematode infections, the most successful being the 16-membered macrocyclic lactone ivermectin (IVM). Its importance is exemplified by its inclusion in the WHO List of Essential Medicines and its discovery earned the 2015 Nobel Prize for Medicine.



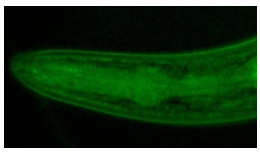
IVM

Resistance to IVM is a global burden and pockets of IVM resistant nematodes are becoming increasingly numerous.[3] Both the primary route of uptake and the mechanisms of IVM resistance are unknown. It was hypothesised that uptake of IVM is through the amphids (sensory structures), and that an operative mechanism of resistance is mutation of the amphids, resulting in impaired uptake of IVM.

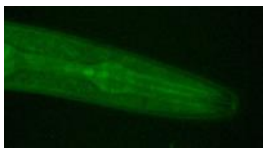
To investigate these hypotheses, a fluorescent probe (FBI) based on IVM was synthesised and administered to *C. elegans*. Administration of FBI to IVM sensitive *C. elegans* successfully confirmed the route of uptake of IVM as amphidal. Administation of FBI to IVM resistant strains established that loss of function of the amphids is an operative mechanism of IVM resistance in nematodes.



IVM Sensitive



IVM Resistant (Dyf-7)



IVM Resistant (Tp-238)

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Poster

Electron-Transfer and Hydride-Transfer Pathways in the Stoltz-Grubbs Reducing System (KO^tBu/Et_3SiH)[1]

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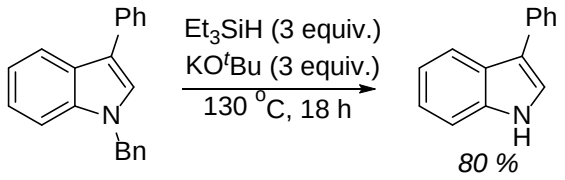
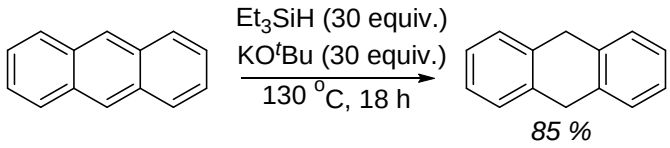
Recent studies by Stoltz, Grubbs et al. have shown that triethylsilane and potassium *tert*-butoxide react to form a highly attractive and versatile system that shows (reversible) silylation of arenes and heteroarenes[2] as well as reductive cleavage of C-O bonds in aryl ethers[3] and C-S bonds in aryl thioethers.[4] Their extensive mechanistic studies[5,6] indicate a complex network of reactions with a number of possible intermediates and mechanisms, but their reactions likely feature silyl radicals undergoing addition reactions and S_H2 reactions.

This poster focuses on the same system, but through computational and experimental studies, reports complementary facets of its chemistry based on a) single-electron transfer (SET) (Scheme 1), and b) hydride delivery reactions to arenes (Scheme 2).



Scheme 1: SET to *N*-Benzylindoles



Scheme 2: Hydride-Transfer to Arenes

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Poster

A biocatalytic approach for the synthesis of enantiopure amines

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Enantiopure D-amino acids are a group of fundamental building blocks for manufacturing pharmaceuticals and other bioactive compounds[1]. For instance, D-Phenylglycine (D-Phg) and D-4 Hydroxyphenylglycine (D-Hpg) is consumed at several thousand tons per year for the synthesis of β-lactam antibiotics[1].
The conventional process to manufacture D-Phg is via the Strecker reaction of benzaldehyde with highly toxic cyanide followed by diastereomeric crystallization with D-camphorsulfonic acid to give 68% yield[2].
Aminotransferase (AT) enzymes have been identified as a more efficient and sustainable alternative for the preparation of optically pure amines from the corresponding ketones substituting, in many cases, the existing chemical[3,4].
The stereo-inverting D-phenylglycine aminotransferase (D-PhgAT) from *Pesudomonas stutzeri* ST-201 catalyses the reversible transamination of L-glutamic acid (L-glu) with benzoylformate (BZF), or 4-hydoxybenzolyformate (HBF), as amino acceptor, yielding D- Phg, D-Hpg and α-ketoglutarate (AKG)[5].

L-glutamic acid | R = H (BZF), R = OH (4-OHBZF) | R = H (D-Phg), R = OH (D-4OHPhg) | 2-oxoglutarate

D-PhgAT represents a strong target enzyme for the synthesis of enantiomerically pure D-Phg and D-HPhg in a single step, using a cheap amino donor such as L-glutamic acid, providing a more concise and sustainable route to their biosynthesis than has previously been available[2]. We describe an optimised biocatalytic approach to a large scale synthesis of D-Phg and various derivatives in high % e.e. Substrate scope has been explored with several amino acceptors showing the enzyme is capable of yielding D- phenylalanine, D- tyrosine and D- tryptophan. The D-PhgAT is an ideal industrial biocatalyst for production of many high value aromatic D-amino acids and further work will be done on the optimization of this bioconversion to develop its industrial potential.

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Poster

Studies Toward the Structural Elucidation and Total Synthesis of Leiodolide A

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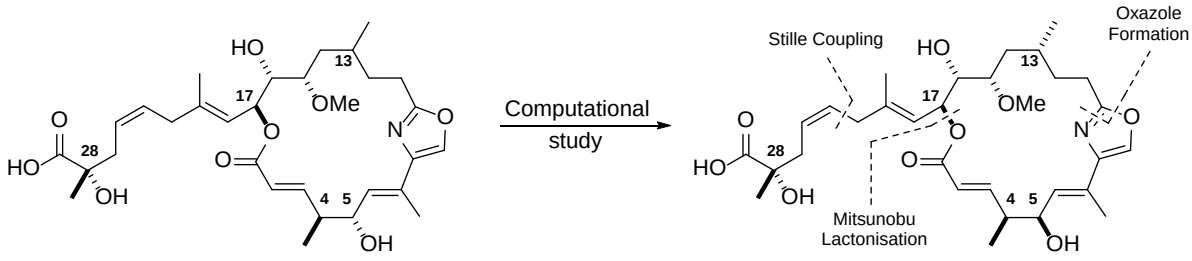
Leiodolide A is a secondary metabolite isolated from a marine sponge of *Leiodermatium sp.*[1] By employing coupling constant and NOE analysis in conjunction with chemical derivatisation, the stereochemistry of the C_{15}, C_{16}, C_{17} and C_{28} positions were confidently determined. Similar analysis of the C_4 and C_5 stereocentres yielded "tenuous" assignments and the remote nature of the C_{13} stereocentre prevented its assignment. Leiodolide A was tested against the National Cancer Institute's 60-cell line assay and showed micromolar activity against three unrelated cell lines.

This poster details a flexible approach that was developed to allow access to all possible diastereomers alongside a completed computational study which has determined the likely correct diastereomer of Leiodolide A as 4*S*5*S*13*R*, the principal target of synthetic work. The construction of the two major fragments are also detailed, including the formation of the key C_4 and C_5 stereocentres *via* the Evans anti-Aldol methodology,[2] and the current progress towards the coupling of the major fragments.



(4*R*5*S*13*X*) (4*S*5*S*13*R*)

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Poster

Synthesis of Oxygenated Cyclopentenones *via* the Pauson-Khand Reaction

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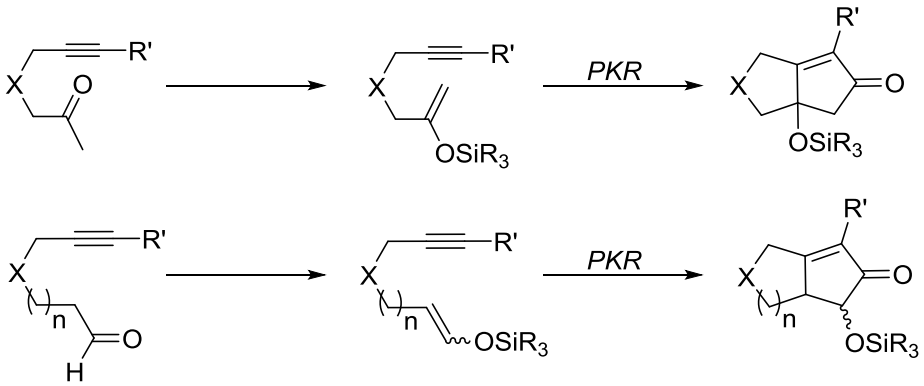
The use of three-dimensional scaffolds to generate highly potent, selective bioactive molecules with desirable pharmacokinetic properties has received a great deal of interest in the field of medicinal chemistry. The synthesis of such sp^3-rich, functionalised scaffolds often requires several synthetic steps. The development of a range of many metal-mediated organic transformations has vastly increased the number of molecules which are accessible *via* organic synthesis, often allowing the simplification of synthetic routes by lowering the number of steps. One such metal-mediated transformation is the Pauson-Khand reaction (PKR) which delivers cyclopentenones from an alkene, an alkyne (as its hexacarbonyldicobalt complex) and carbon monoxide.

There are, however, few examples of the PKR which utilise more functionalized coupling partners to generate diversified products. Here we report the use of silyl enol ethers as alkene partners in the Pauson-Khand reaction (**Figure 1**), to deliver oxygenated cyclopentenones with potential pharmaceutical utility. Whilst some examples of the use of standard enol ethers or vinyl acetates as alkene equivalents in the PKR are known,[1,2] such examples result in cleavage of the additional functionality. The process reported here is complementary to these examples where the heteroatom functionality is retained to give oxygenated cyclopentenones.



X = $C(CO_2Me)_2$, O, NTs
R' = H, Me
n = 1, 2

Figure 1

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Poster

Metallosupramolecular capsule-bound quinones for use in catalysis

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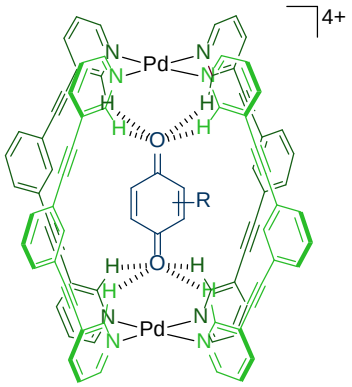
Self-assembled metallosupramolecular capsules offer an alternative route to building complex catalysts.[1] Almost all current approaches utilise substrate encapsulation, wherein the microenvironment influences various factors such as enantio-[2] and regioselectivity.[3] The drawbacks of this approach include narrow substrate scope and the frequent occurrence of product inhibition, which limits genuine catalysis to quite specific reaction types.

We have recently shown that a simple Pd_2L_4 system can bind p-quinone guests via favourable polar interactions.[4] We now demonstrate that this encapsulation mode modulates the inherent reactivity of quinones, converting what are usually stoichiometric oxidants into catalytic redox mediators. Here, the optimisation and scope of various catalytic reactions will be discussed.



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Living GenoChemetics: Synchronous biosynthesis, bio-halogenation and catalytic cross-coupling in bacterial cultures

Sunil V. Sharma, Cristina Pubill-Ulldemolins, Xiaoxue Tong, Christopher Cartmell, Emma Bogosyan, Emma J. Rackham, Enrico Marelli, Refaat Hamed & Rebecca J. M. Goss*

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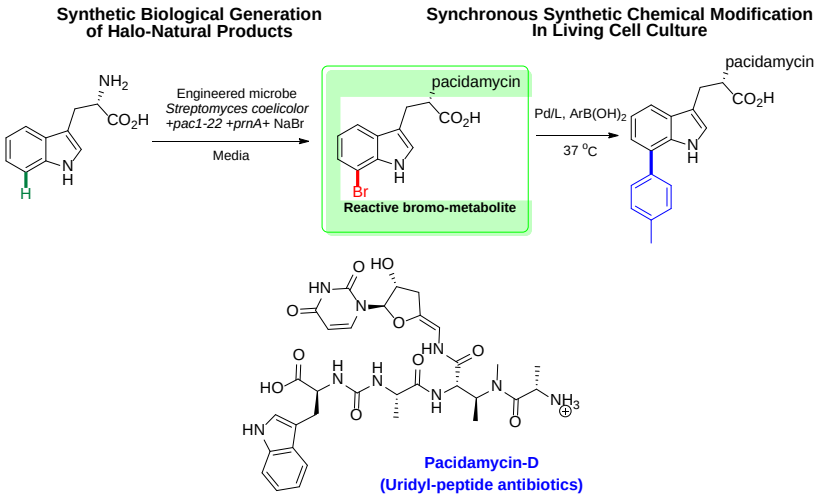
Abstract:

Bacterial natural products (NP) represent an unparalleled starting point for drug discovery, and NP analogues are desired to study modes of action, determine SAR and improve bioavailability/ bioactivity. However, the generation of NP analogues is often very challenging. Combining synthetic biology with synthetic chemistry provides a powerful approach toward NP diversification, utilizing the expediency and synthetic capability of biosynthetic pathways and chemical diversity enabled by organic synthesis. **GenoChemetics** is new approach pioneered by Goss group to facilitate NP analogue generation, where genetic modification is used to install an orthogonal handle into a complex NP scaffold that enables site-selective synthetic diversification, without employing protecting group chemistry. We envisaged that by installing a sufficiently reactive handle (e.g. a C-Br bond) and developing compatible mild aqueous chemistries, synchronous biosynthesis of the tagged metabolite and its subsequent chemical modification in living culture can be achieved. We report synthetic biological access to new-to-nature bromo-metabolites and the concomitant biorthogonal cross-coupling of halo-metabolites in living cultures.[1]



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46th Scottish Regional Meeting of the RSC Organic Division, University of Edinburgh, 9th January 2018

Towards the total synthesis of Dolabelide C

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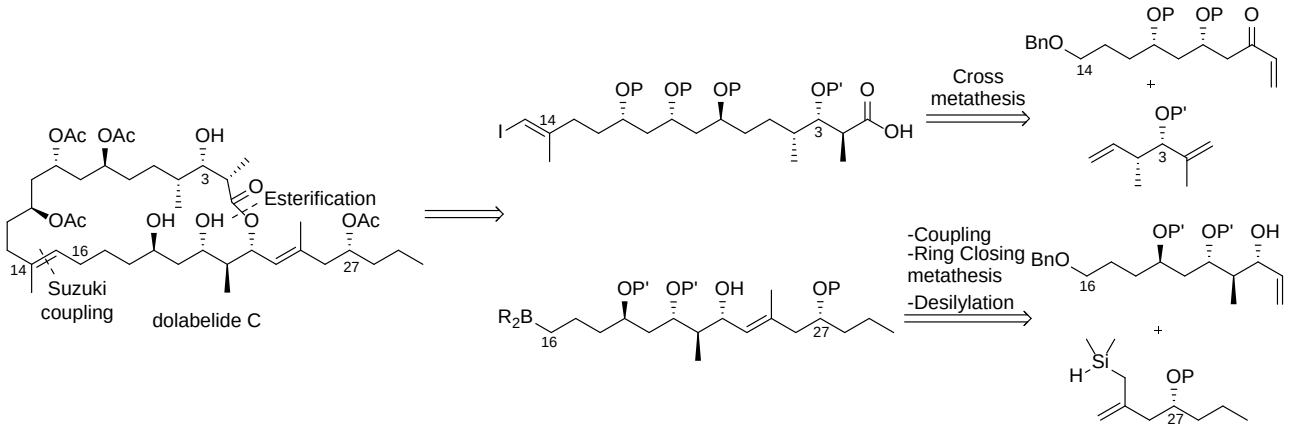
Abstract

Dolabelides exhibit cytotoxicity against cervical cancer HeLa-S_3 cells with IC_{50} values of 6.3, 1.3, 1.9 and 1.5 μg/mL for dolabelides A, B, C and D respectively. However, 138 kg (wet weight) of *Dolabella auricularia* was required to isolate just 99 mg of dolabelide C.[1] Thus the total synthesis of these complex macrolides has been of great interest and pursued by several groups in the last 20 years and the synthesis of two dolabelides have been reported.[2,3]

Our retrosynthetic synthesis of dolabelide C involves the coupling of the two fragments by a Suzuki coupling and an esterification.



The synthesis of Dolabelide C in the Prunet group has been envisaged by breaking down the molecule into two fragments the C1-C15 and the C16-C30. This work so far focuses mostly on the asymmetric synthesis of the C16-C30 fragment and a new methodology to construct trisubstituted olefins, such as the one present in dolebelide C, using a silicon-tethered ring-closing metathesis reaction.

Key references:

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Poster

Base Controlled Divergence in Gold-Catalysed Hydroaminations: Single vs Dual Activation Catalysis

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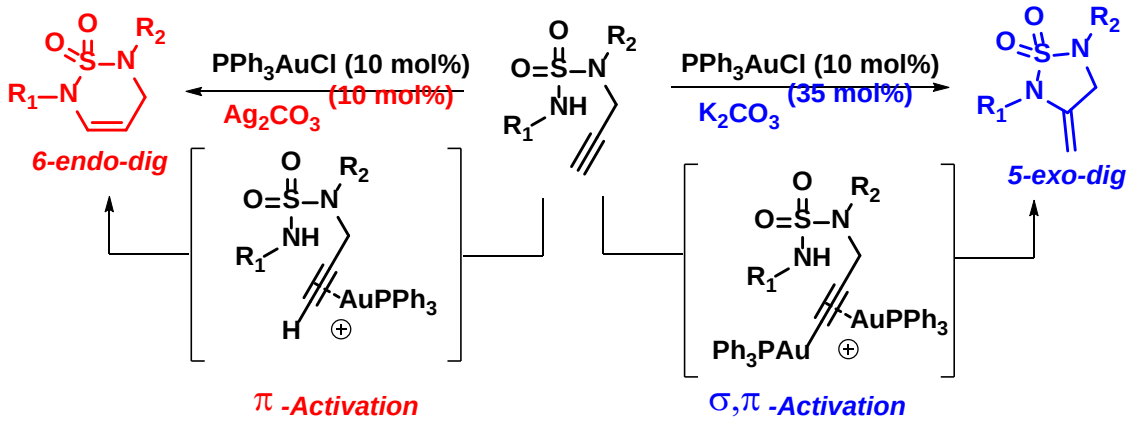
The mild and chemoselective activation of multiple bonds by means of gold complexes is currently a well stablished method, however, the mechanism of activation remains unclear. In the last years, the binding mode of gold in the activation of alkynyl derivatives have emerged as a new area of research.[1]

In this work, the different binding mode of the gold controlled by the use of different bases enables total regiocontrol of the hydroamination proccess, opening a straight access to either 5-exo-dig or 6-endo-dig cyclization products of the alkynyl sulfamides.



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Poster

Development of Thiosulfonates as novel cysteine protease inhibitors

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Cysteine proteases are ubiquitous throughout nature as part of the proteolytic machinery responsible for key physiological processes. Unregulated, uncontrolled or undesired proteolysis is often an important feature of many diseases.[1] Therefore, specific inhibitors of cysteine proteases offer a unique target for chemotherapeutic intervention. This is particularly true in many neglected tropical diseases (NTD's) caused by parasitic infections, as the parasitic species is often highly dependent upon the role of specific cysteine proteases not required by the host.[2] The majority of attempts at conferring specificity in the past have been derived from classical structure activity relationship (SAR) studies. In this work we aim to generate a new class of electrophilic traps, the thiosulfonates, as cysteine protease specific inhibitors. When combined with classical SAR, enabled by modeling studies, this two-pronged approach should greatly reduce off target effects, yielding a new warhead moiety of interest to the wider community.

We have drawn inspiration from simple organic compounds such as methyl methane thiosulfonate (MMTS), which are known to react selectively with sulfur centred nucleophiles, to be modified to suit our needs as cysteine protease inhibitors:

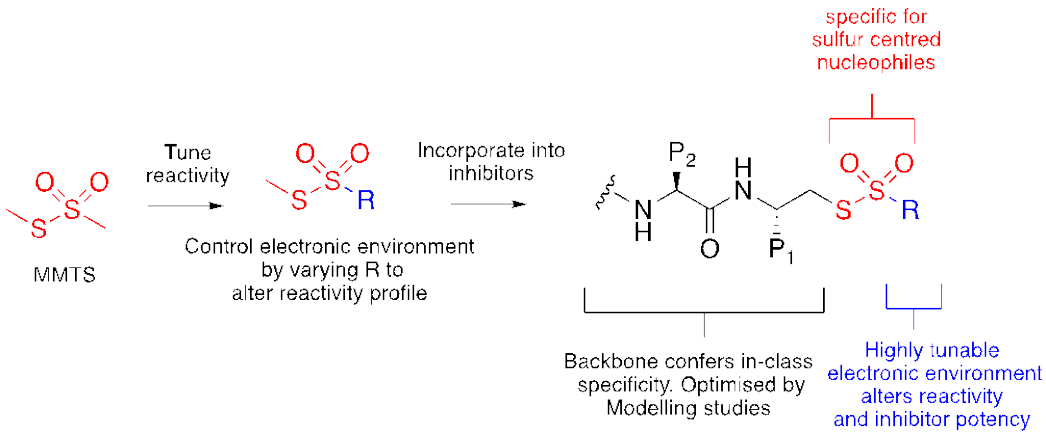

Figure 1: Overview of project concept

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Poster

Manganese catalysed hydrogenation of chiral esters

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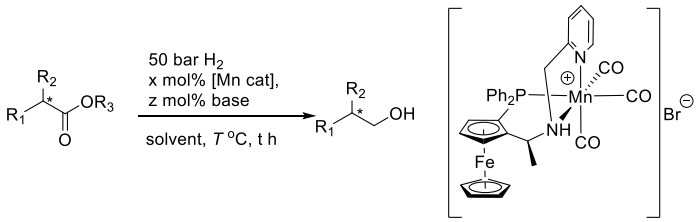
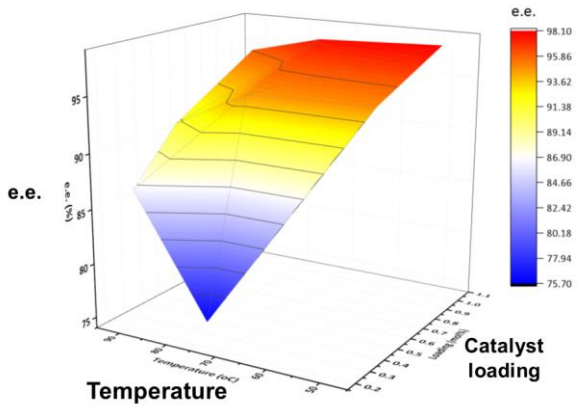
Manganese catalysed hydrogenations have recently seen an upswing in publications. In 2017 we published the first known report of asymmetric hydrogenation of ketones using a chiral manganese catalyst[1]. Here we present our continuing work on manganese catalysed hydrogenation of ketones and esters. We have developed conditions for the hydrogenation of enantiomerically pure esters with retention of configuration. For example, we can readily reduce bis-alkylated amino acid esters to their corresponding amino alcohols with no loss of enantiomeric purity.





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Poster

Understanding Metallophilic interactions

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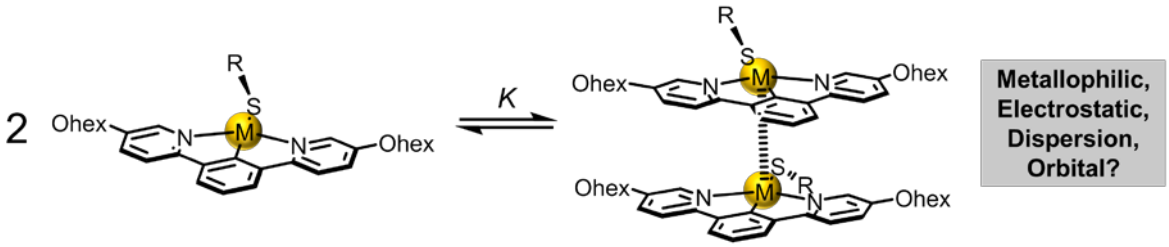
Metallophilic interactions are weak interactions between closed-shell (d^{10}, s^2) or pseudo-closed-shell (d^8) metal cations.[1] This type of interaction, alongside H-bonding, aromatic stacking and solvent effects, is generally believed to be responsible for various intriguing assembly behaviours, photoluminescence and catalysis properties.[2,3] However, the nature and strength of metallophilic interactions are still disputed. Here, we have quantified the strength of metallophilic interactions in Pt- and Pd-containing complexes, combining experimental measurement with theoretical calculations. Single-crystal x-ray diffraction demonstrates the presence of metallophilic interactions in the solid state, whereas ^{1}H NMR dilution studies allow access to solution binding constants between the complexes. These data show that Pt(II)–Pt(II) interactions are stronger than Pd(II)–Pd(II) interactions. By varying ligand-substituents, the dimerisation constants of the Pt-containing complexes were shown to increase in line with increasing electron withdrawing ability. DFT calculations to correlate electrostatic potential with the strength of Pt–Pt interactions are ongoing. Preliminary energy decomposition analysis using ETS-NOCV suggests that dispersion and electrostatic interactions are the major contributors to the dimerisation in this organometallic system.



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