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POSTER ABSTRACTS

LIGHT INITIATED ENANTIOSELECTIVE α–FUNCTIONALISATION OF β–KETOESTERS

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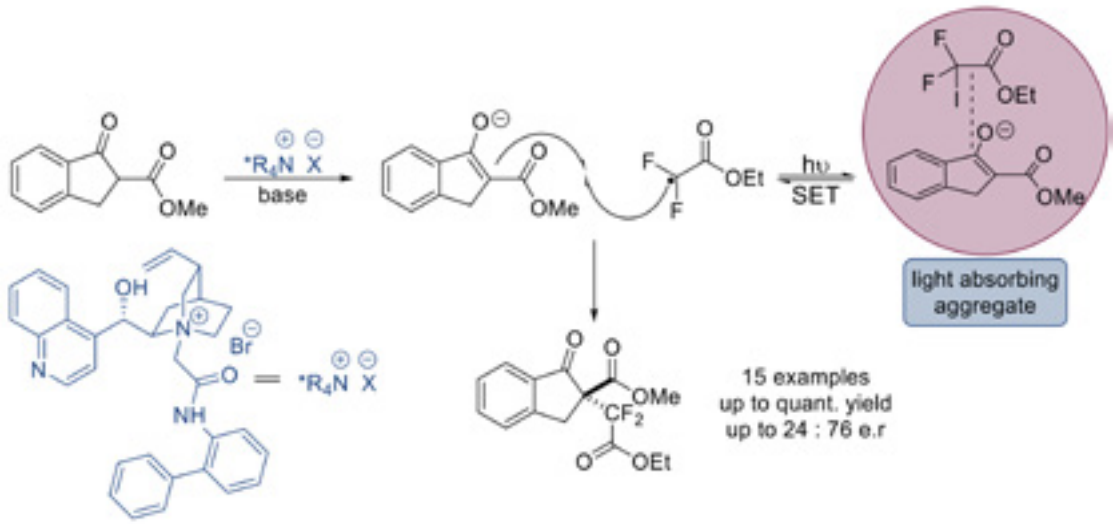
Harnessing light poses as a sustainable alternative to the traditional methods frequently employed within organic chemistry.[1] As a cost-effective and renewable source of energy, it has been utilised to produce highly sought-after transformations. Since the renaissance of photoredox, typically requiring precious metal catalysts, a concerted effort has been made within the field to develop alternative methods to access typically difficult reactive intermediates.[2]

One such method that removes the requirement of such additives, investigates reactants that alone are unable to be directly excited by light. However, an *in-situ* aggregation of specific reactants that is capable of absorbing light, allows access to target reactive species.[3] Whist this method has been thoroughly investigated, little has been achieved to utilise these mild conditions for enantioselective bond formation.

To further develop light initiated processes, we realised a visible light absorbing species between an electron rich intermediate and an electron deficient fluorinated ester, could be utilised to form a previously difficult carbon – carbon bond. Through the separation of solid and liquid phases of the reaction, the electron rich species could be trapped with an organocatalyst to invoke bond formation in an asymmetric fashion.



TOWARDS THE SYNTHESIS OF A NATURAL COMPOUND AS A POTENTIAL ANTI-MESOTHELIOMA AGENT JBIR-101

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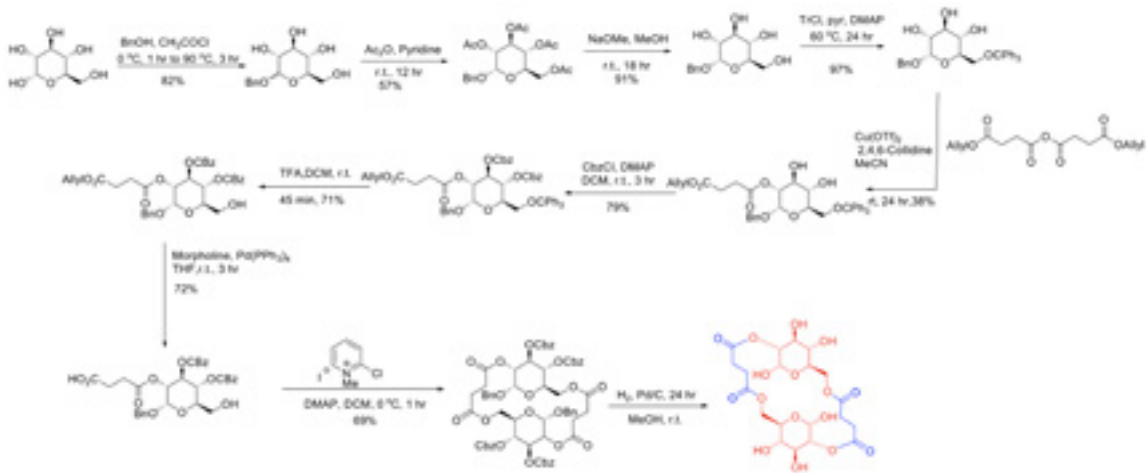
Malignant pleural mesothelioma (MPM) is an aggressive neoplasm that has been developed from the pleura and is extremely invasive to surrounding tissues. It is linked to asbestos fibre exposure.[1,2] MPM has been shown to be resistant to all conventional therapies, including chemotherapy, radiotherapy and surgery and patients' prognoses are still quite dismal. As a result, it is a tumour that continues to pose a clinical challenge.[3,4] Consequently, innovative therapeutic drugs against MPM are urgently needed.[5] From Streptomyces sp. AK-AB27, Kazuo Shin-ya et al. have isolated novel anti-MPM agents called JBIR-23 (1) and -24 (2).[5] Then they have isolated a novel macrocyclic dilactone (JBIR-101) from Promicromonospora sp. RL26.[6] No synthetic routs have been reported to make JBIR-101, 23 and 24. This work obtains an innovative synthetic methodology to prepare JBIR-101.



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FRAGMENT ELABORATION IN 3-D: SYNTHESIS AND SUZUKI-MIYAURA CROSS-COUPLING OF HETEROCYCLIC CYCLOPROPYL BORONATES

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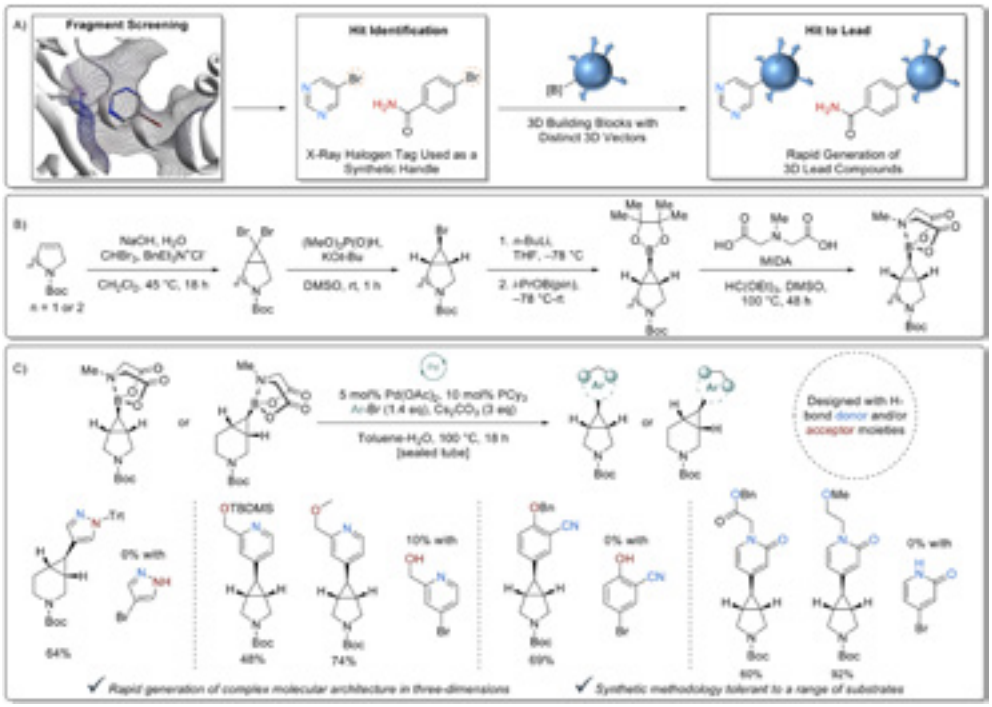
Fragment -based drug discovery (FBDD) is a powerful strategy for identifying lead compounds in drug discovery by using small molecules, known as fragments, to identify potential binding sites on target proteins.[1] The efficiency of the FBDD process is dependent on, and limited by, the available synthetic methodologies for fragment elaboration and development.[2] To address this issue, the O'Brien group have developed a synthetic platform to efficiently transform small, simple fragments into more complex, 3D molecular frameworks (A). The versatility of this methodology has been demonstrated by successfully cross-c oupling over 70 examples of aryl halides with the York 3-D building blocks, showcasing the methodology in synthesising lead-like compounds in FBDD.

This project focuses on the application of the methodology to medicinally relevant fragments known as FragLites, which are a collection of 31 fragments designed to map protein binding sites using hydrogen-bond donors and/or acceptors.[3] The four-step route to the 3-D building blocks is shown below (B). Cross-coupling reactions of a range of FragLites yielded excellent results, but reduced yields were observed for aryl halides with exposed amino or hydroxyl groups. To overcome this issue, cross-coupling of protected FragLites showed significant improvement compared to the unprotected versions (C). Application of this methodology to the entire set of FragLites will be presented.



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C–N ATROPISOMERIC HALOAMIDES: SYNTHESIS, STABILITY AND STEREODYNAMICS

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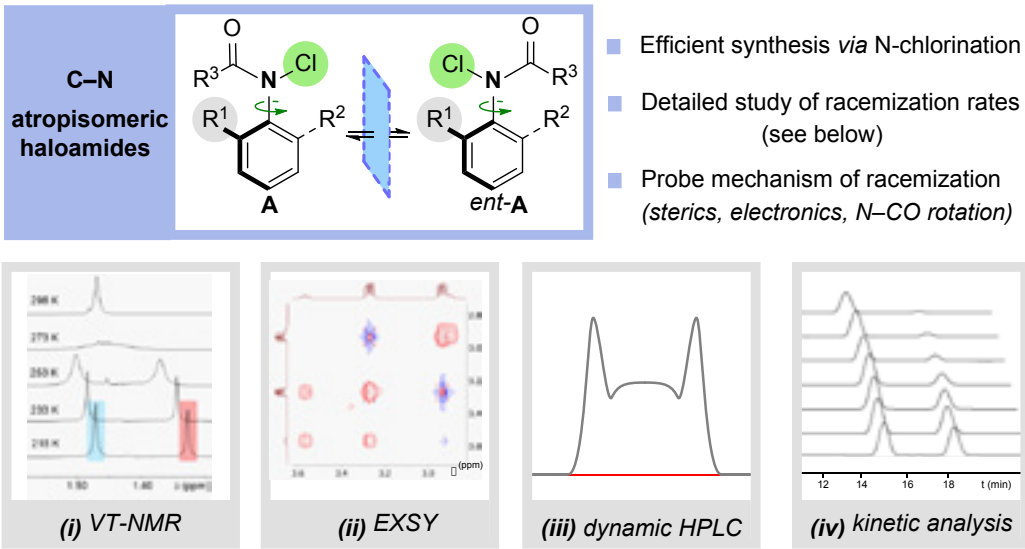
The study of C–N atropisomeric materials is a rapidly developing area, with important applications in healthcare, agrochemistry and materials science.[1-4] The archetypal examples are *ortho*-substituted axially chiral anilides bearing N-aliphatic or aromatic substituents, which can be targeted using a variety of different synthetic approaches and exhibit atropisomeric behaviour. Building upon this, we wish to report the preparation of the first examples of atropisomeric N-haloamides *via* a high-yielding electrophilic chlorination reaction of secondary anilides. These products can be isolated on gram-scale and display remarkably high levels of chemical stability allowing purification by routine workup and column chromatography. Detailed experimental studies have been performed to probe the rates of bond rotation about both the Ar–N and N–CO bonds, employing a variety of analytical techniques, including variable temperature NMR, exchange spectroscopy (EXSY), dynamic HPLC, and studying the rate at which the optical purity of an enantioenriched sample decays over time.[5] This reveals that N-haloamide atropisomers display robust configurational stability, with racemization half-lives of up to 18 days at room temperature. The theory and methodology associated with these conformational stability studies is summarized, and the correlation between structural variation of the amide scaffold and bond rotation rates are discussed. Moreover, comparing these results with solid state structural parameters obtained from X-ray crystallographic analysis sheds light on the fundamental mechanism of racemization in atropisomeric amides, in which rotation about the Ar–N bond is heavily influenced by the conformation and degree of delocalization in the adjacent amide bond.[6] Preliminary data suggests that these effects may apply generally across other atropisomeric amide scaffolds.



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STAPLED β-SHEETS

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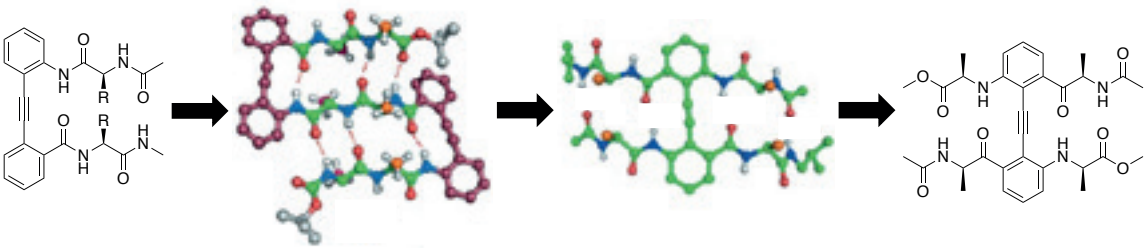
Protein-protein interactions (PPIs) are defined as the physical contacts between two structured protein domains or peptides that allow one to selectively recognise the other.[1] These types of interaction are essential for nearly every aspect of cellular function and have been implicated in protein misfolding diseases.[2] PPIs between β-structures account for 16% of all PPIs,[3] therefore utilization of these interactions by tertiary structure mimicry provides a promising route to PPI inhibition.

β-Sheets are tertiary structures adopted by peptides with defined angles that orientate amide bonds co-planar to the compound face and amino acid side chains alternatively above and below the plane.[4] To mimic this, rigidifying structures are required to promote folding in short sections of peptide. In this work a diphenylacetylene staple is used to rigidify and promote a hydrogen bonding of the functionalised amino acids strands.

The diphenylacetylene staple, first used in work by Kemp et.al [5] as a β-turn mimic, has been validated and further developed to include; a range of amino acids, multiple strands, [6] and progression to a central staple to promote bi-directional β-sheet formation. [7]

Here, the synthesis of a small library of in register diphenylacetylene-stapled β-sheet mimetics is underway, with the intention of producing mimics with validated structures in both organic and aqueous medias, possessing a variety of natural and unnatural amino acid side chains of varying lengths, that are capable of inhibiting PPIs, with the intention of adapting this synthesis to the solid phase.



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SYNTHESIS AND BIOLOGY OF ANTIPARASITIC NATURAL PRODUCTS

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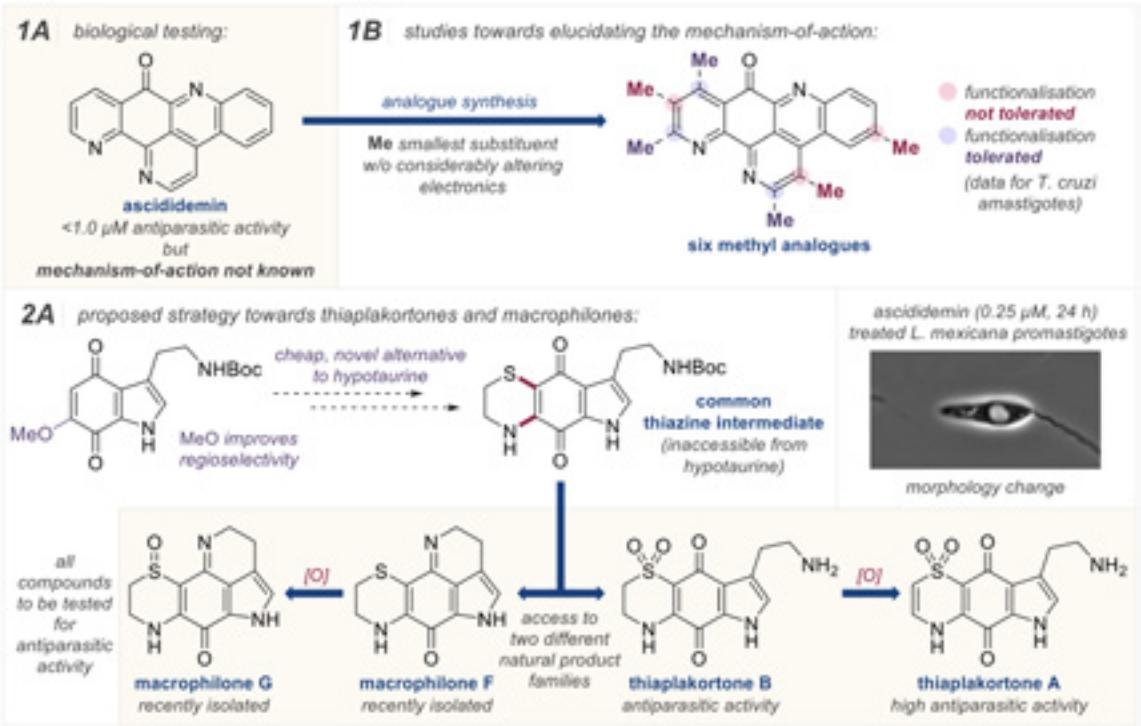
Ascididemin is a pentacyclic marine alkaloid natural product with promising antiparasitic activity. Some structure–activity relationship (SAR) studies have been conducted; however, the mechanism-of-action (MOA) has not yet been elucidated.[1,2] In collaboration with the Wheeler and Tempone groups, two novel *Leishmania* species have been tested against this natural product (Figure 1A). The synthesis and testing of six methyl-ascididemin analogues has identified functionalisation-sites around the core which could be used to install a probe for further MOA studies (Figure 1B). In parallel, a separate natural product with promising antiparasitic properties, thiaplakortone A, is also being investigated. Thiaplakortone A is yet to be tested against *Leishmania*;[3] however, our hypothesis is that activity could translate between parasite species, as is the case with some other families.[4] A novel strategy for the synthesis of thiaplakortone A is ongoing (Figure 2A), which aims to overcome previous issues with the only published route to this natural product.[5] A cheap and novel alternative to hypotaurine could be used to generate a common thiazine intermediate to divergently access structurally different, potentially antiparasitic, natural products.[6]



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AUTOMATED SYNTHESIS OF MONOSACCHARIDE BUILDING BLOCKS AND APPLICATIONS IN OLIGOSACCHARIDE SYNTHESIS

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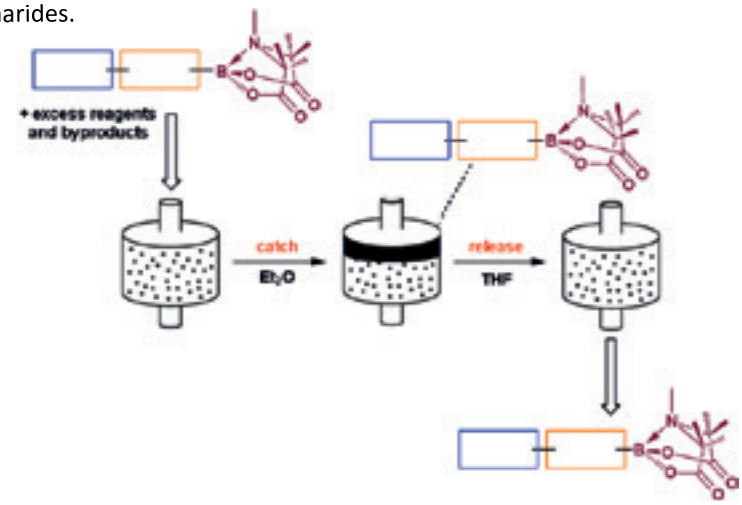
The development of effective techniques for the synthesis of carbohydrates with complex structural organization is crucial to the discipline of glycosciences. Despite significant progress in the synthesis of oligosaccharides, the synthesis of targets featuring complex glycosidic linkages of monosaccharide building blocks remains a challenge. These compounds are present in a wide range of biologically relevant compounds.

While much of the emphasis in the development of automated platforms for carbohydrate synthesis has been on the construction of oligosaccharides, manual syntheses of monosaccharide building blocks can represent up to 90% of the synthetic effort and thus constrain throughput[1]. This is often laborious and time-consuming. Furthermore, excess amounts of glycosyl donor building blocks are frequently used in glycosylations, presenting a pressing need to develop methods for streamlining the acquisition of monosaccharides.

The aim of this work is to improve the purification of monosaccharides, which is often a bottleneck in the preparation of important carbohydrates. By using a purification tag, TIDA,[2] it is hoped that the process of purifying monosaccharides can be made simpler and more efficient. One of the key findings of this research is that the silica binary affinity properties of the TIDA tag can be extended to monosaccharides bearing a variety of protecting groups. This characteristic proved beneficial during the synthesis of the tagged molecules, as it simplified purification and eliminated the need for arduous column chromatography. As a result, this process is potentially amenable to automation. Additionally, the tagged building blocks can be used to synthesize a trisaccharide in high yield, indicating that the TIDA tag is appropriate for the syn simple oligosaccharides.



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RARE-EARTH HOSTS: NEW PLATFORMS FOR QUANTUM TECHNOLOGY

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A fluorinated cage structure has been designed, inspired by similar molecules by Takemura[1] and Flood[2] that could be used to bind lanthanide ions. One of the target compounds is shown in figure 1 and features fluorotriazole motifs with the fluorine lone pair binding to the central rare-earth. A multi-step synthesis towards this target has been designed, starting from commercially available organic building blocks using a 'click' chemistry approach to build the desired structure. Progress has been made in synthesising target cage structures such as the pyridine-based cage in figure 1 and phenol-based compounds have also been investigated.

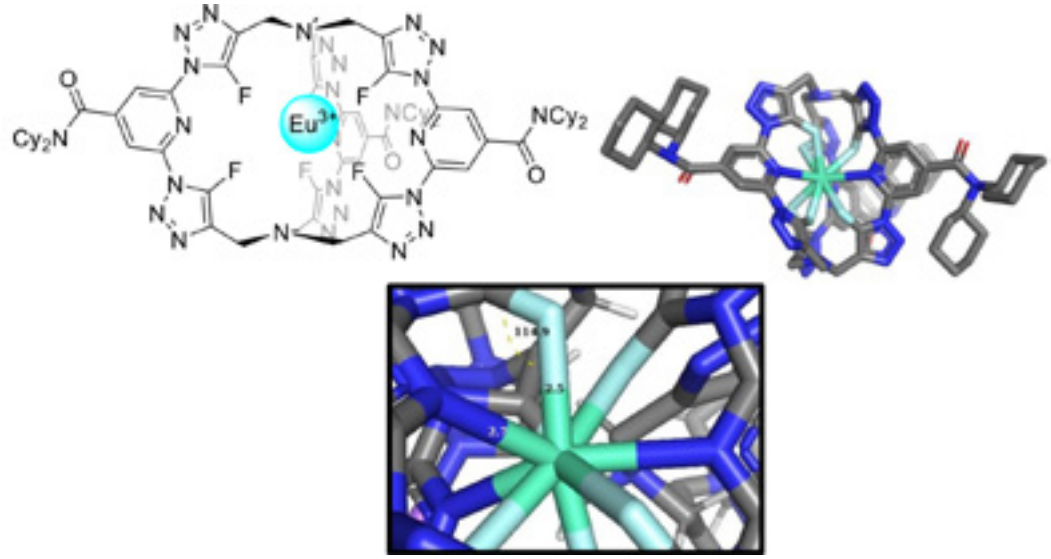

Figure 1: Target triazolo cage binding to a europium ion with both fluorine and nitrogen donor atoms.

One potential application for these compounds is as a single photon source for quantum technology. A novel solution in the search of a low loss single-photon source could be the use of lanthanide ions isolated as a host-guest complex. The defined environment that the organic host provides could reduce the problem of quantum decoherence. Lanthanide ions have been previously investigated for use in quantum technology due to their unique electronic properties[3,4] however, the use of a lanthanide complex as a source of single photons has yet to be explored.

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PREPARATION OF SELENATED 1,2,3-TRIAZOLES FOR CHALCOGEN BONDING CATALYSIS

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Two synthetic routes have been investigated to access novel chalcogen bonding catalysts (*Figure 1*). Of particular importance, *N*-aryl substituents are required that bear electron-withdrawing groups to increase the chalcogen bonding ability of the catalysts.

First, the lithiation-selenation of triazoles bearing electron-withdrawn *N*-aryl groups was studied (*Figure 1, **Route A***). This revealed the potential for decomposition of the lithiated-intermediates such as **4** (*Figure 1, **Challenges A**)* and substrate-dependant regioselective lithiation, both of which were promoted by the presence of the electron-withdrawing groups on the *N*-aryl substituent. The lithiation conditions were optimised through lithiation-deuteration experiments leading to the use of the more sterically hindered LiTMP as base when Ar = perfluorophenyl (PFP), due to competitive S_NAr when using LDA as base (*Figure 2**A***). The choice of selenating agent was also substrate-specific, with S_NAr by phenylselenide occurring with PFP-triazole **6** when Ph_2Se_2 was used as the selenating agent. This could be circumvented by using PhSeBr (*Figure 2**B***). When applying the optimised lithiation-selenation conditions to the bis-triazole structure of interest however, the yields achieved were lower than desired.

This led to the exploration of an alternative synthetic route using a ruthenium-catalysed alkyne-azide cycloaddition (*Figure 1, **Route B***). This route also presented challenges when using electron-withdrawn aryl azides, as a catalytically inactive Ru-tetraazadiene complex **5** can form via a Ru-nitrene complex following nitrogen extrusion (*Figure 1, **Challenges B***). However, following an optimisation study, the isolation of the desired bis-seleno-triazole compounds can be obtained in excellent yields. Currently, a small range of novel chalcogen bonding catalysts are being prepared through this route, which will then be used in benchmark reactions to showcase their catalytic activity.

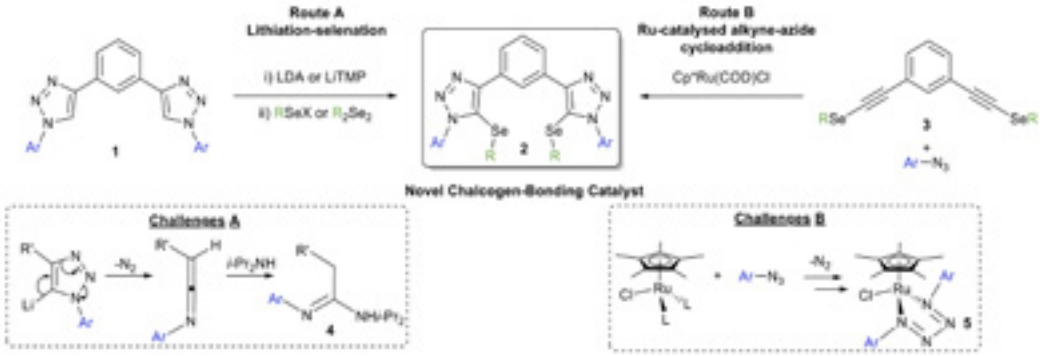

Figure 1: Synthetic Routes to Novel Chalcogen Bonding Catalysts

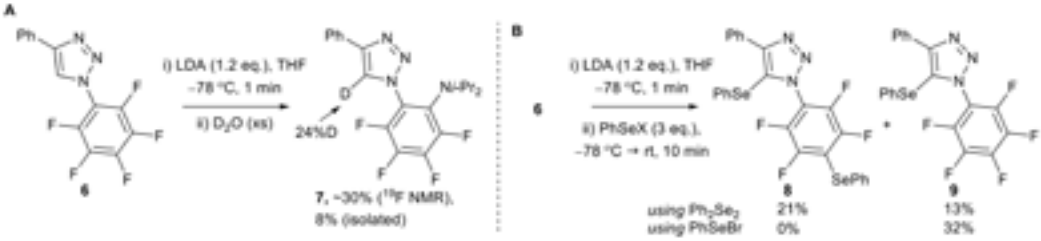

Figure 2: Competitive S_NAr using LDA, **A:** Lithiation-Deuteration, **B:** Lithiation-Selenation

SYNTHESIS OF VINYL ARENES AS A MODEL GRIGNARD REACTION IN FLOW

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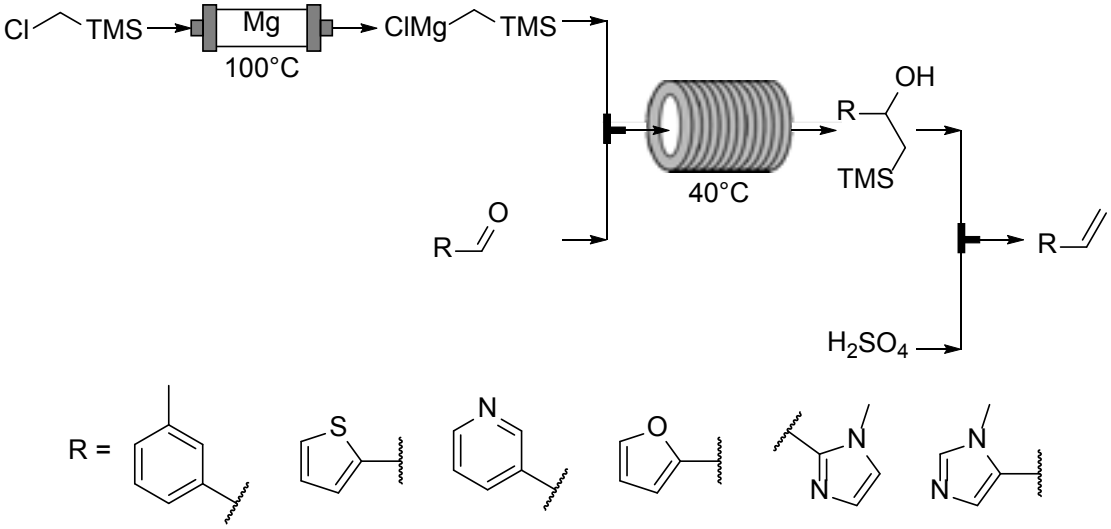
Anionic exchange membrane (AEM) fuel cells and electrolysers are a promising technology for the interconversion of excess green energy and green hydrogen, and reduction of CO2 into useful chemicals (SELECTCO2). Following on from proton exchange membrane fuel cells and liquid electrolyte anionic fuel cells, they aim to make use of the inherently faster kinetics of the alkaline environment at the cathode to reduce the use of precious metal catalysts at the cathode. Development of new AEMs is necessary to improve their stability, conductivity and permselectivity. In the group, we create AEMs by electron beam radiation grafting of styrene-like chloro-substituted polymer chains into commercial films followed by displacement of chlorides with tertiary amines to provide ammonium head groups to permit mobilisation of anions. Co-grafting with selected unsubstitutable vinylarenes may further improve AEM properties so, to this end, using flow synthesis, multiple small vinylarenes have been synthesised. Flow synthesis is employed due to its safety advantages alongside the simplified scale up and transfer to industry compared to batch synthesis. The one-step synthesis involved in-flow formation of a silylmethyl Grignard reagent and Peterson olefination with arylaldehydes to give the vinyl group. Multiple issues required addressing for flow synthesis including: inline quenching of the Grignard reagent to prevent blockages upon exit, the possibility of decreasing yields due to decreasing residence time as magnesium is consumed, the solubility of oxymagnesiumchloride intermediates during flow synthesis, and the purification and isolation of volatile products post-flow reaction.



INTERDISCIPLINARY APPROACHES TOWARDS A SYNTHETICALLY USEFUL DIELS-ALDERASE

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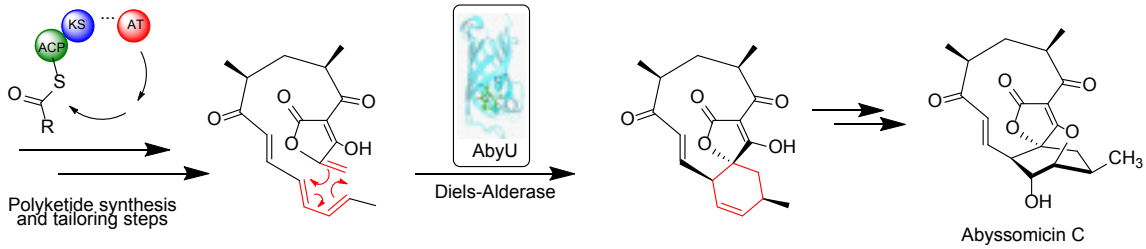
The Diels-Alder reaction is a cornerstone of synthetic chemistry for the synthesis of substituted cyclohexenes. Only a small number of enzymes that catalyse Diels-Alder reactions have been identified and characterised. As such their utility in synthesis remains underexploited. One such enzyme, AbyU, catalyses the intramolecular Diels-Alder cyclisation of a linear precursor to a complex polycyclic scaffold, which is further elaborated to the polyketide natural product abyssomicin C.[1, 2] Belonging to the spirotetronate subfamily, abyssomicin C itself is an attractive target due to its antibiotic activity, notably against both methicillin-resistant and vancomycin-resistant *Staphylococcus aureus*.[3]



To enable the widespread use of AbyU as a biocatalyst, its substrate scope, tolerance, selectivity, and catalytic efficiency is being investigated using an interdisciplinary approach. Computational studies including DFT calculations and use of molecular dynamics has enabled the prediction of substrate scope which is being experimentally validated through substrate synthesis and assays with AbyU.

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USE OF 1,3-DIIODOBICYCLOPENTANE AS A PRECURSOR TO NOVEL ODOUR ADDITIVES FOR HYDROGEN TECHNOLOGY

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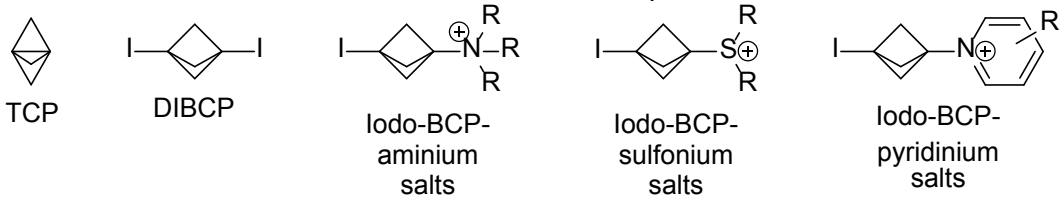
The need for a hydrogen odorant that is non-toxic, distinct in its scent, relatively economical and has no impact on the catalyst in a fuel cell is important for a future where the public can confidently use hydrogen-based technology. Bicyclo[1.1.1]pentanes (BCP's) have been of increasing interest to synthetic chemists in recent years due to their unique structure and potential pharmaceutical use. This has led to a diverse range of functionalisation, owed to by the highly strained molecule known as, tricyclo[1.1.1.$0^{1,3}$]pentane (TCP) or [1.1.1]propellane, which shows remarkable reactivity due to its strained central bond between the two bridgehead carbons. Due to the structure of these compounds, the use of specifically functionalised BCP's have the potential to also be employed as odorants. The iodine adduct of TCP, 1,3-diiodobicyclo[1.1.1] pentane (DIBCP), shows remarkedly improved storability while still providing access to functionalised BCP's through nucleophilic attack and cross-coupling reactions. In spite of this, chemistry involving DIBCP remains extremely niche. So far, work has centered around the formation of aminium, sulfonium and pyridinium salts; the succession to this will most likely involve the cross-coupling of both moieties to yield the potential odorants.



SYNTHETIC AND BIOSYNTHETIC STUDIES ON THE ANTIBIOTIC MUPIROCIN

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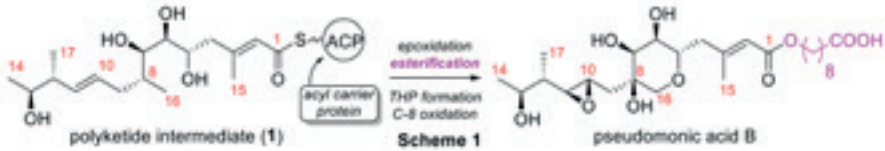
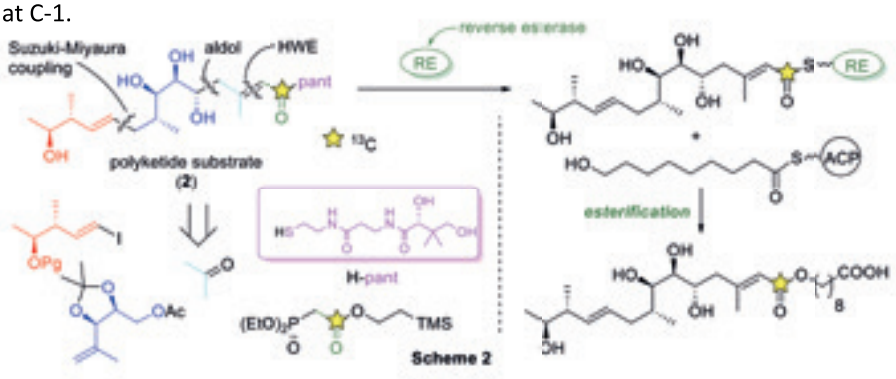
The antibiotic mupirocin, produced by soil-dwelling bacterium *Pseudomonas fluorescens*, consists of a mixture of pseudomonic acids which show specific activity against MRSA.[1]

Detailed investigations using isotopic feedings studies, *in vitro* reconstitution of enzymes, and *in vivo* gene knockout experiments with *P. fluorescens* have revealed that mupirocin is assembled via a complex and fascinating biosynthetic pathway. Following construction of the linear polyketide intermediate (**1**), several modifications occur, including tetrahydropyran ring formation, epoxidation, C-8 processing, and esterification with a 9-hydroxynonanoic acid unit.[1-4]



Scheme 1

One crucial step in the biosynthesis of mupirocin is formation of the ester bond which unites the polyketide and fatty acid fragments, the timing and mechanism of which remains elusive. To explore the esterification reaction with purified enzyme components, the chemical synthesis of a putative polyketide intermediate (**2**) was undertaken, utilising Suzuki-Miyaura, aldol, and Horner-Wadsworth-Emmons (HWE) reactions (Scheme 2). The synthesis will furnish the desired pantetheine-derived substrate (**2**) with incorporation of a ^{13}C label at C-1.



Scheme 2

Once synthesised, substrate **2** will be used to prime a native enzyme with proposed reverse esterase function and *in vitro* bioassays will be conducted to esterify hydroxy acid units to this polyketide fragment.

The incorporation of a single ^{13}C-label at C-1 will allow the esterification to be followed by both high-resolution protein mass spectrometry and NMR spectroscopy, illuminating the mechanism of this esterification step and the timing of this process with respect to the other late-stage modifications.

This work will solve one of the key unknown steps in the biosynthesis of this important antibiotic and shed light on the promiscuity and potential biocatalytic utility of this proposed esterase.

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STEREOSELECTIVE SYNTHESIS OF α-GALACTOSIDES

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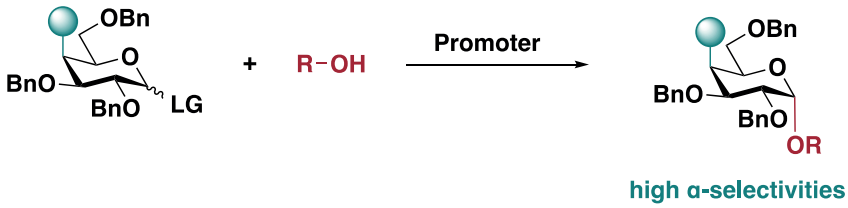
Nature employs carbohydrates as an integral source of structural biodiversity across all organisms. It is understood that the biological properties of these natural products can be fine-tuned *via* alteration of glycosidic patterns, particularly with respect to stereochemistry. Consequently, stereochemical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

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

As part of our ongoing research into glycosylation methodologies,[5,6] we investigated the effect of different protecting groups at position 4 of galactosyl donors on the stereochemical outcome of glycosylation reactions. A range of galactosyl donors were accessed *via* regioselective ring-opening of 4,6-*O*-benzylidene-protected galactosides and, for example, subsequent esterification using Mukaiyama's salt. It was found that some galactosyl donors gave excellent α-selectivity (**Scheme 1**).[7] In this poster, we will report on our findings of the scope, particularly with respect to acceptor nucleophilicity.



Scheme 1. Galactosidation reactions using donors bearing a range of protecting groups at the 4-position.

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RATE AND EQUILIBRIUM CONSTANTS FOR THE ADDITION OF TRIAZOLIUM SALT DERIVED N-HETEROCYCLIC CARBENES TO HETEROAROMATIC ALDEHYDES

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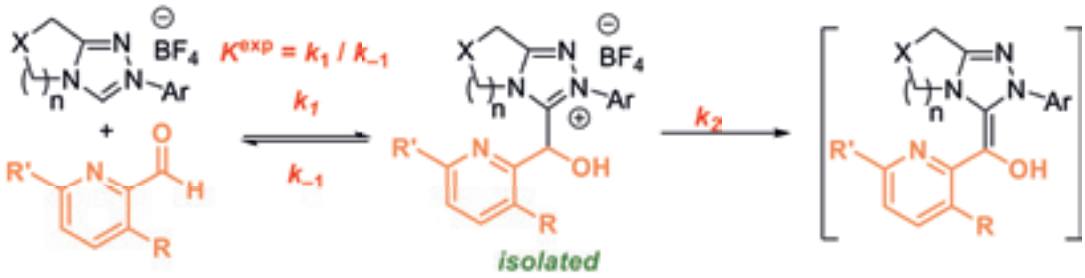
Heteroaromatic aldehydes are often used preferentially or exclusively in a range of NHC-catalysed process that proceed through the generation of a reactive diaminoenol or Breslow Intermediate (BI), with the reason for their unique reactivity currently unexplored.[1] This project reports measurement of rate and equilibrium constants for the reaction between N-aryl triazolium NHCs and heteroaromatic aldehydes, providing insight into the effect of the NHC and heteroaromatic aldehyde structure up to formation of the BI.[2] Variation in NHC catalyst and heteroaromatic aldehyde structure markedly affect the observed kinetic parameters of adduct formation, decay to starting materials and onward reaction to BI. In particular, large effects are observed with both 3-halogen (Br, F) and 3-methyl substituted pyridine-2-carboxaldehyde derivatives. Key observations indicate that increased steric hindrance leads to a reduction in both k_2 and k_{-1} for large (2,6-disubstituted)-N-Ar groups within the triazolium scaffold, and sterically demanding aldehyde substituents in the 3-position, but not in the 6-position of the pyridine-2-carboxaldehyde derivatives. As part of this study, the isolation and characterisation of twenty tetrahedral adducts formed upon addition of N-aryl triazolium derived NHCs into heteroaromatic aldehydes are described. These adducts are key intermediates in NHC-catalysed umpolung addition of heteroaromatic aldehydes and are BI precursors.



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SYNTHESIS AND EVALUATION OF NEW DIHYDROTETRATHIAFULVALENE SYSTEMS FOR METAL SURFACE ADSORPTION AND HYDROGEN BONDING

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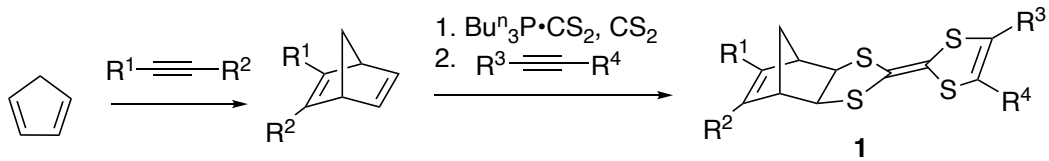
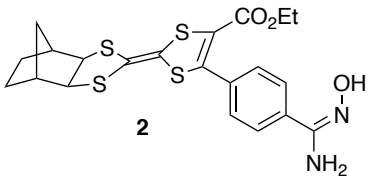
Some years ago we described a new direct method to prepare norbornane-fused dihydro-TTF compounds **1**.[1,2] Although yields are only moderate, the method allows modular construction of a wide range of substituted examples and structural and electronic properties of a range of these will be presented.



1

$R^{1–4}$ = H, Ph, CO_2Me, CO_2Et

We have already shown that a tetrakis(thiol-functionalised) analogue is efficiently adsorbed on a gold surface,[3] and current work towards new functionalised dihydro-TTFs capable of metal binding and self-association through hydrogen bonding will be described. In particular the amidoxime-compound **2** is designed to bind strongly to copper, the NHC **3** should show metal binding, the target tetrazine donor acceptor compound **4** is of interest.



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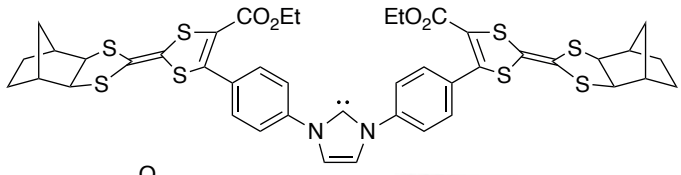

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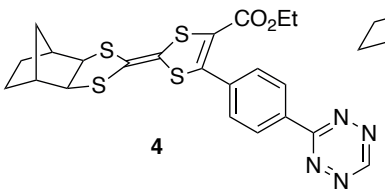

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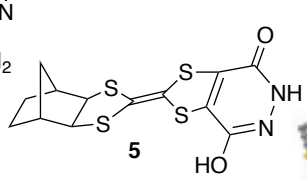

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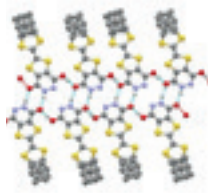

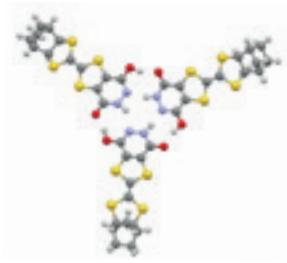

The pyridazinedione compound **5** forms several different hydrogen bonded crystal forms including a cyclic trimer and a linear ribbon structure depending on the conditions of crystal formation.

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USING BIOTRANSFORMATIONS TO GENERATE TETRAHYDROPYRANS

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Tetrahydropyran (THP) rings are structural motifs which are abundant in medicinally relevant compounds, making their synthesis the subject of continuous innovation.[1–4] In natural products, these motifs are constructed by enzymes which exhibit exquisite control over stereo- and regiochemistry. Typically, THP rings can be biosynthesised in one of two ways: through oxa-Michael addition, catalysed by pyran synthases, or by selective epoxide ring opening, catalysed by epoxide hydrolases.[5]

Mupirocin is a polyketide antibiotic produced by *Pseudomonas fluorescens* which contains a core THP ring, essential for its antibiotic activity.[6] We have previously shown that this heterocycle is biosynthesised by the dual action of two enzymes, MupW and MupZ.[7] MupW is a Rieske oxygenase which catalyses the oxidation of the unactivated 8,16-methyl group in mupirocin W4 to an epoxide (Figure 1A). MupZ is an epoxide hydrolase existing as an + barrel fold (Figure 1B) which catalyses the less favoured 6-*endo* cyclisation to give desepoxy pseudomonic acid B (PA-B). In its absence, the favoured 5-*exo* cyclisation to the THF ring occurs spontaneously.

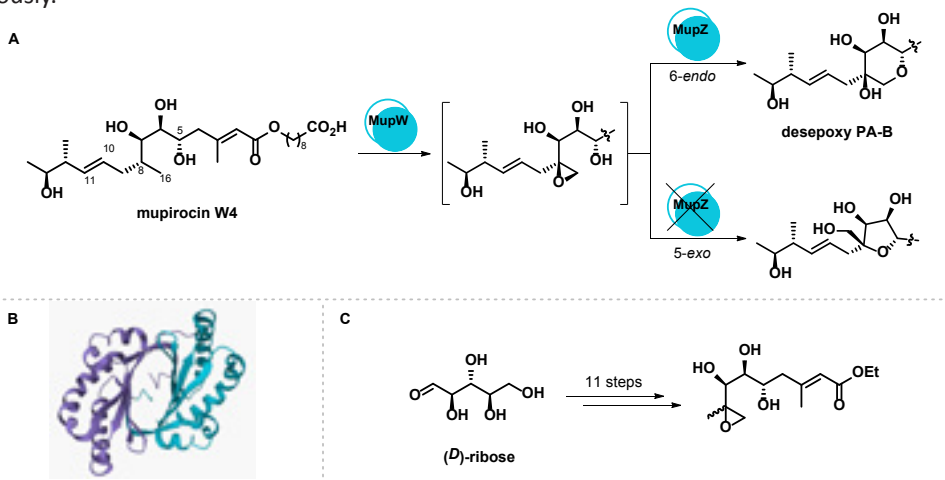

Figure 1: A: Biosynthesis of the mupirocin THP ring by MupW and MupZ; B: X-ray structure of MupZ (PDB ID: 6FXD); C: Synthesis of a model substrate.

Despite their potential synthetic utility, epoxide hydrolases have been scarcely studied. The aim of this project is to investigate the substrate scope of MupZ with a view to examining its effectiveness as a biocatalyst. The natural substrate for MupZ has never been synthesised. Chemoselective epoxidation of an alkene at the 8,16-position in the presence of the 10,11-alkene, and potential cyclisation of the 5-OH, make its synthesis highly challenging. As such, a synthesis towards a model substrate (Figure 1C) has been developed, facilitating investigations into its stability and biotransformation with MupZ.

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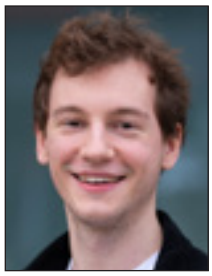
SUBSTITUTED DIHYDROPYRIDINE SYNTHESIS BY DEAROMATIZATION OF PYRIDINES



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Dearomatization is an effective method to transform readily available N-heterocycles into partially saturated motifs. Manipulation of dihydro-derivatives holds great potential and provides access to a variety of semi-saturated N-heterocyclic building blocks.[1] However, current strategies are limited in scope and the use of sensitive reagents restricts the applicability in synthetic laboratories. Herein, we report the synthesis of a broad variety of N-substituted 1,4- and 1,2-dihydropyridines by very mild and selective reduction with amine borane for the first time.[2]

References:

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A BRØNSTED ACID-CATALYSED ROUTE TO A-HETEROCYCLIC *CIS*-AZIRIDINES

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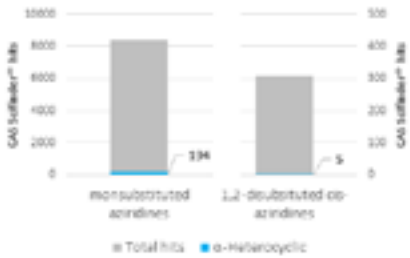
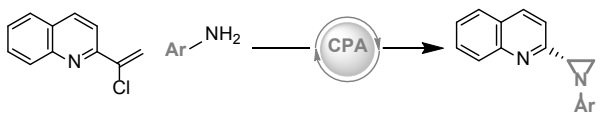
As the nitrogen analogue of epoxides, aziridines are less common yet attractive scaffolds in organic synthesis, with an increasing interest in the pharmaceutical industry.[1] Certain aziridine motifs have shown promising activity as anticancer drugs, often acting as DNA alkylators owing to the reactivity of a strained 3-membered ring.[2] Similarly, many bioactive molecules contain aromatic heterocycles;[3] yet the inclusion of both an aziridine and heterocycle motifs within single compounds remains challenging, thus leading to an underexplored field in synthesis (Figure 1, a).[4] Previous work within our group has generated monosubstituted chiral α-heterocyclic aziridines through the use of a chiral phosphoric acid catalyst using terminal vinyl chloroamines as substrates (Figure 1, b).[5]

We now report the synthesis of α-heterocyclic 1,2-disubstituted aryl aziridines under general Brønsted acid catalysis. The reaction can proceed with diastereomeric control in polar protic solvents *via* a proposed destructive pathway towards the *trans*diastereomer, giving the corresponding *cis*-diastereomer (up to 99:1 *d.r.*).

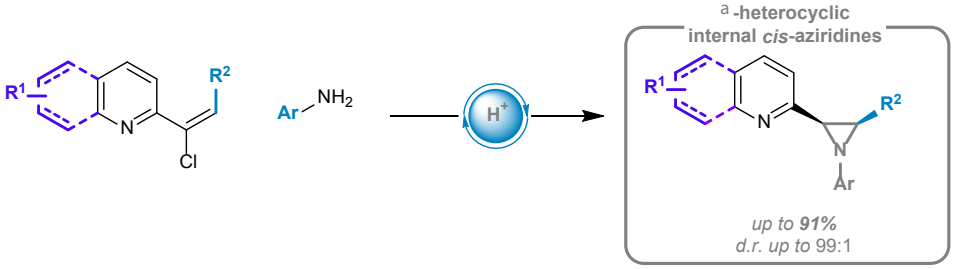
a) Reports of [a] -heterocyclic aziridines



b) Previous work



c) This work



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A COBALT-CATALYZED WAGNEER-MEERWEIN REARRANGEMENT WITH CONCOMITANT HYDROFLUORINATION

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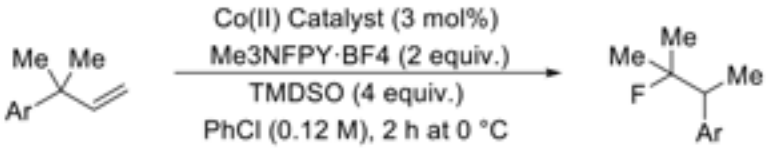
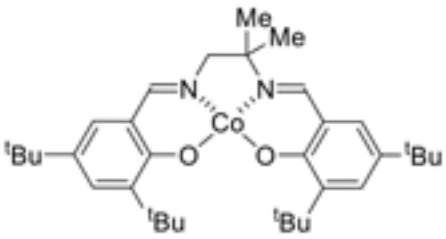
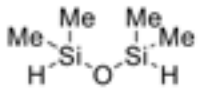
Carbocations are highly reactive intermediates which are difficult to control due to the low energetic barriers associated with skeletal rearrangements and bond migrations. This gives arise to complex reaction pathways with a multitude of possible products. Being able to tame a carbocations reactivity would allow for improved reaction design and selective formation of skeletally edited products. Generating carbocation intermediates from unactivated alkenes is generally challenging and requires the use of harsh reagents with the added difficulty of avoiding HF reagents for hydrofluorinations.[1] The few reported procedures for hydrofluorinations of alkenes, which employ mild metal-based conditions, are radical in nature.[2,3] We report a cobalt-catalysed procedure that allows for selective formation of a 1,2-aryl shift fluoroalkane products from *geminal*-substituted alkenes. Preliminary evidence suggests the reaction proceeds through a radical-polar-crossover pathway in which a pseudo-carbocation intermediate is generated via a Co(IV) alkyl species.





Co(II) Catalyst

$Me_3NFPY·BF_4$



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ENANTIOSELECTIVE COBALT-CATALYSED SEMIPINACOL REARRANGEMENTS OF α-ARYL ALLYLIC ALCOHOLS

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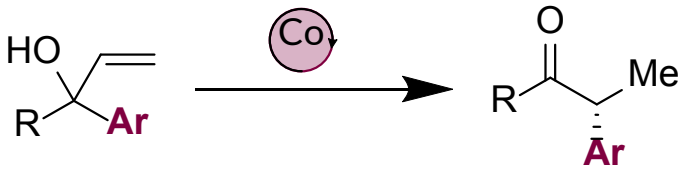
Enantioenriched α-aryl carbonyl compounds are synthetically useful targets in organic chemistry as they appear in a number of bioactive natural products and marketed pharmaceuticals. The enantioselective synthesis of this motif, through transition metal catalysed enolate arylation, poses challenges as products are prone to racemisation under basic conditions[1]. Our methodology provides enantioselective access to α-aryl carbonyls through a semipinacol rearrangement pathway. The 1,2-aryl migration occurs after hydrogen atom transfer and a radical polar crossover event[2] with high yield (up to 95%) and enantioselectivity (up to 99 : 1 er) using catalytic amounts of an appropriate chiral cobalt salen complex.



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EXPLORING CUBANES AS BIOISOSTERES FOR BENZENE RINGS: TOWARDS THE SYNTHESIS OF 1,3-DISUBSTITUTED CUBANES

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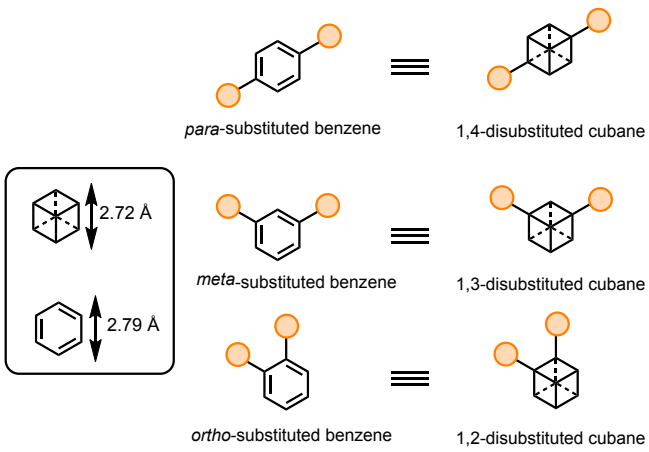
Cubanes are caged, polycyclic carbocycles comprising eight carbon atoms arranged at the vertices of a cube. These remarkably stable molecules are strained, providing them with a unique set of characteristics that have facilitated their exploitation as polymers and explosives. Having achieved the landmark synthesis of cubane in the 1960s,[1] Eaton postulated that cubane may behave as a bioisostere for benzene rings due to similarities in the distances across connecting atoms. The highly saturated nature of cubane also gives rise to out-of-plane substituents, potentially allowing drug candidates to be engineered such that substituents are positioned with precise three-dimensional orientation. However, applications of cubanes as benzene bioisosteres are limited to the use of mono- and 1,4-disubstituted cubanes behaving as bioisosteres of terminal and para-substituted benzene rings respectively (Figure **1**).[2,3] Whilst 1,3-disubstituted cubanes are theorised to behave as bioisosteres for meta-substituted benzene rings, the lack of scalable routes towards these molecules means that applications of these scaffolds in medicinal chemistry are scarce.

To address this challenge, our work focuses on developing routes to cubanes bearing substitution patterns that are currently inaccessible. We present a new approach to 1,3-disubstituted cubanes, focusing our route on redirecting a key intermediate in Eaton's original synthesis of 1,4-disubstituted cubanes. Ongoing work towards the synthesis of cubane analogues of benzene-containing pharmaceuticals is underway to examine the potential of 1,3-disubstituted cubanes as meta-substituted benzene bioisosteres.



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eFLUORINATION OF ACTIVATED TERTIARY ALCOHOLS USING COLLIDINIUM TETRAFLUOROBORATE

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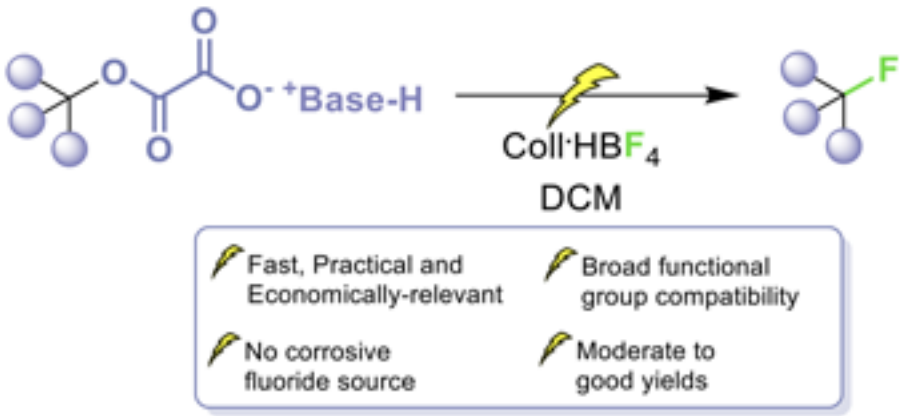
Tertiary C-F bonds are structural designs of great importance;[1] in fact, by taking advantage of fluorine's high electronegativity and small size it is possible to use it as a hydrogen bioisostere and modify drugs' physicochemical properties and pharmacokinetics.[2]

However, assembling hindered C-F centres has long been challenging for synthetic chemists. Although several methods have been developed, they often rely on using corrosive amine-HF salts ($Et_3N{\cdot}HF$ or pyridine·9HF), as well as expensive or hazardous reagents (explosive DAST or XeF_2).[3]

Electrochemistry allows new chemical bonds to be forged using electricity,[4] one of the cheapest and greenest reagents. In this poster, we introduce collidinium tetrafluoroborate as an efficient fluorinating agent for anodic decarboxyfluorination and deoxyfluorination reactions.[5]



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5. « eFluorination using cheap and readily available tetrafluoroborate salts | Organic Chemistry | ChemRxiv | Cambridge Open Engage ».

TRANSITION METAL-FREE CONTINUOUS FLOW CONVERSION OF 1,3-DIENES INTO VALUABLE 2,5-DIARYL FURANS

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Jai-Ram Mistry,[a] Mark R. J. Elsegood,[a]
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The furan ring is a highly important class of heterocycle, frequently found in natural products, several on-market pharmaceuticals, as well as being used in materials chemistry.[1–3] The orthodox preparation of 2,5-diarylfurans is by the Paal-Knorr synthesis and requires access to the requisite 1,4-dicarbonyl precursor, preparation of which can be lengthy, particularly if unsymmetrical 2,5-diaryl furans are the target. Accordingly, several approaches to 2,5-diarylfurans using transition metals have been developed. Yet, despite the success of these approaches to 2,5-diaryl furans, there has been a growing necessity to reduce our reliance on transition metal catalysed reactions.[4]

A direct transformation 1,3-dienes into valuable 2,5-diarylfurans using transition metal-free conditions is presented. By employing a simple oxidation – dehydration[5] sequence on readily available 1,3-dienes, important 2,5-diarylfuran building blocks frequently used in medicinal and materials chemistry are prepared. The oxidation step is realised using singlet oxygen, and the intermediate endoperoxide is dehydrated under metal-free conditions and at ambient temperature using Appel reagent. Notably, this sequence can be streamlined into continuous flow,[6] thereby eliminating the isolation of the intermediate, often unstable endoperoxide. This leads to a significant improvement in isolated yields (*ca.* 27% average increase) of the 2,5-diarylfurans, while also increasing safety and reducing waste.

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INTERMOLECULAR [2π+2σ]-PHOTOCYCLOADDITION ENABLED BY TRIPLET ENERGY TRANSFER

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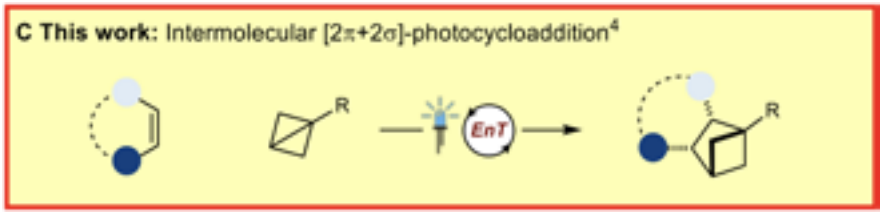
An energy transfer-enabled [2π+2σ]-photocycloaddition by introducing bicyclo[1.1.0]butanes as 2σ-reactants is disclosed. This strain-release approach allowed us to escape the restrictions of conventional [2+2]-photocycloadditions, while providing a straightforward and modular synthetic access towards bicyclo[2.1.1]hexanes (BCHs) – a dense and rigid C(sp^3)-framework, which is becoming increasingly sought-after in bioisosterism, thus highlighting the relevance of our methodology for its application in medicinal chemistry.



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A NOVEL APPROACH TO SYNTHESIS OF AXIALLY CHIRAL, BIARYL TETRAHYDRO-ISOQUINOLINE ALKALOIDS FROM THE ANCISTROCONGOLINE AND KORUPENSAMINE CLASS OF NAPHTHYLISOQUINOLINE ALKALOIDS

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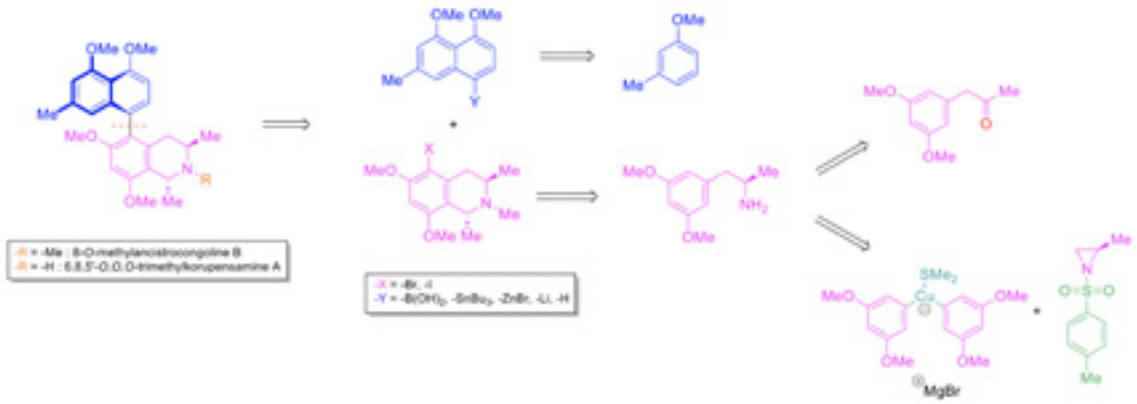
Korupensamine A and Ancistrocongoline B are biaryl compounds from the naphthylisoquinoline class of alkaloids and are the promising lead-like molecules to combat against a life-threatening neglected tropical disease; visceral leishmaniasis (also known as ***Kala Azar***),[1] outperforming the standard (Pentostam) used in the biological tests against the leishmanial pathogen *L. donovani* [IC_{50} (Pentostam) = 47.2 µg/mL, IC_{50} (Ancistrocongoline B) = 18.8 µg/mL] also revealing that higher degrees of *O*-methylation result in better inhibitory response towards the pathogen.[2] Hence, a novel approach to the total synthesis of 8-*O*-methylancistrocongoline B has been proposed by our research group, commencing with a convergent synthesis of both the Naphthalene (starting from 3-methylanisole [3]) and the chiral tetrahydroisoquinoline fragments (involving reductive amination of arylacetone/bis-arylcuprate mediated aziridine ring-opening, Bischler-Napieralski cyclisation, asymmetric reduction and regioselective halogenation as key steps).[4] Since the target alkaloid is axially chiral (atropisomerism), various kinds of Pd-catalysed biaryl couplings using chiral ligands [5] as well as a novel C-H activation of the naphthalene fragment for biaryl coupling will be attempted to achieve a single atropdiastereomer with high de%.



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ISOTHIOUREA-CATALYZED ENANTIOSELECTIVE REACTIONS OF IMINES TO α,β-UNSATURATED ESTERS EMPLOYING A,B-UNSATURATED ACYL AMMONIUM INTERMEDIATES

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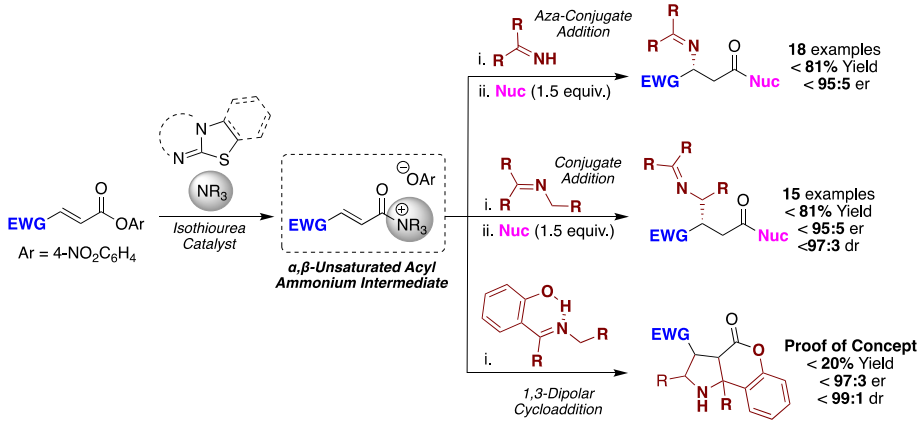
The development of enantioselective conjugate addition and cycloaddition reactions is of widespread importance due to their ability to access important structural motifs in natural products and medicinally relevant compounds (i.e. β-amino acids, γ-amino acids, pyrrolidine compounds).[1] Among the synthetic methods, arguably the most simple involves the use of α,β-unsaturated carbonyl electrophiles for various conjugate and cycloaddition reactions. To date, these successful approaches typically rely upon the use of enals,[2a-c] enones,[3a-c] N-acyl pyrazoles,[4a-b] and nitro-olefins[5a-c] as Michael acceptors, with the use of thiourea[2a,3c,5b,5c] or squaramide[4b] based bifunctional organocatalysts, or Lewis basic pyrrolidines[2a-c,3a,5a] commonplace. However, organocatalytic enantioselective reactions using α,β-unsaturated ester substrates are difficult to achieve due to their recalcitrant nature. In previous work, the generation of α,β-unsaturated acyl ammonium intermediates from α,β-unsaturated esters using isothiourea catalysts has been demonstrated,[6] and this work expands these protocols to enantioselective conjugate addition and cycloadditions of imines to α,β-unsaturated esters. Investigations of the scope and limitations of this procedure showed that β-electron-withdrawing substituents within the α,β-unsaturated ester component was necessary for good product yield, giving rise to a range of β- and γ-imino ester and amide derivatives (up to 81% yield, 95:5 er, and 97:3 dr), and a proof on the organocatalytic 1,3-dipolar cycloaddition reaction showing high enantio- and diastereoselectivity (<20% yield, 97:3 er, 99:1 dr).



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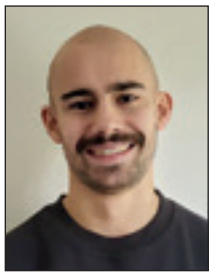
SYNTHESIS OF NOVEL BIFUNCTIONAL MOLECULES FOR THE POTENTIAL TREATMENT OF MESOTHELIOMA, FEATURING GUANIDINE MOIETIES



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Human malignant pleural mesothelioma (MPM) is an aggressive (fatal) lung cancer which is always associated with asbestos exposure. After diagnosis, life expectancy is around 12-18 months. Despite the fact that there are currently 3 FDA approved drugs for MPM[1], treatment for MPM still remains focused on palliative care.[2]. The amino acid arginine is essential in the development of various lung cancers. While most healthy cells are able to produce their own arginine, the majority of MPM tumours have lost the function of the gene ASS1, which is specifically responsible for the production of arginine.[3 4 5] Thus MPM cells have lost the ability to produce arginine themselves and instead have to obtain it from the blood. The concept behind this project is to use a part of the arginine structural motif as a targeting system to deliver a highly potent anti-cancer agent directly to the tumour. Specifically, focusing on the guanidine functionality connected to a platinum containing anti-cancer agent, by a triazole click linker.

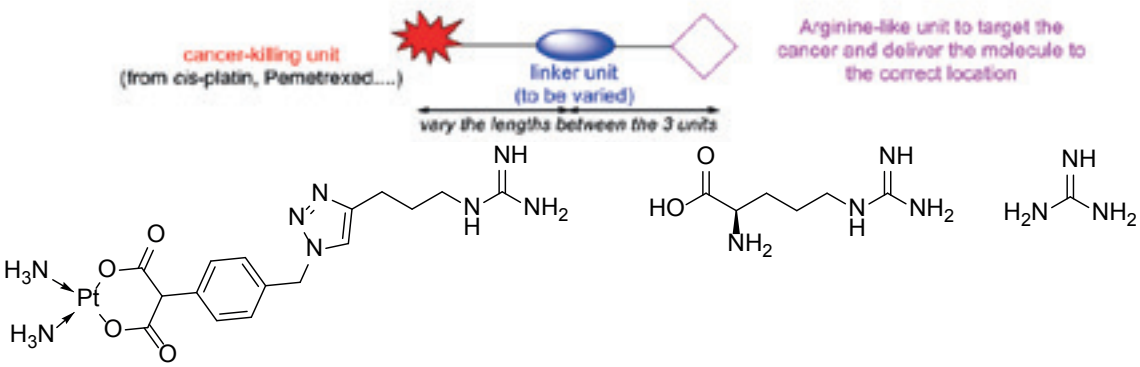

Figure 1:
Top: Generic design of bifunctional "arginine-toxic unit" coupled molecules.
Bottom: an example bifunctional target molecule, Arginine and Guanidine respectively.

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LIGHT-CONTROLLED REGIOSELECTIVITY IN AN EXEMPLARY PHOTODIMERIZATION REACTION OF VARIED AZAANTHRACENES

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Photochemical reactions are one of the essential processes in nature. Currently, photochemistry is experiencing an upswing, evidenced by the increasing number of scientific publications on this issue in previous years.[1] In this context, photoresponsive functional materials and catalysis are of much interest. Among photoreactions, photopolymerization is of central importance in the the fabrication of functional materials.[2] One of the most important groups of molecules which are utilized in the field of photopolymerization is anthracene derivatives.[3]

In recent years, photodimerization and photopolymerization of anthracene molecules have been extensively studied in our group. We focused primarily on the photoreactivity of an exemplary anthracenes mixture, where we showed that the photodimerization reaction between different models could be monitored in situ using NMR.[4] This is important because as the mixdimer is predominant in comparison to the two homodimers, the photofabrication of materials based on the mixdimers can be greatly facilitated. We also conducted research on the photopolymerization of the bisanthracene molecule, which forms n-mers under the influence of UV irradiation.[5] Here, as a tool for monitoring the progress and propagation of photodimerization, we presented the simultaneous utilization and synergy of two novel time-resolved NMR methods, i.e., time-resolved diffusion NMR and time-resolved nonuniform sampling.

The research into the photochemistry of anthracenes naturally aroused our interest in their heterocyclic analogues. Azaanthracenes can be considered anthracene analogues, in which the nitrogen atoms replace one or two carbon atoms. These nitrogen atoms provide a center for further derivatization and for the tuning of the physicochemical properties of azaanthracene systems. The essential biological, optical, and structural properties of azaanthracenes have already been determined; however, azaanthracenes are still an intriguing subject. Importantly, azaanthracenes have the ability to dimerize.

Here, photodimerization between various monomers of azaanthracenes molecules will be presented. The following azaaanthracenes were chosen for the purpose of our study: 2-azaanthracene (**A**) and *N*-Me-2-azaanthracene (**M**). During photodimerization process of one substrate (**A** or **M**), four regioisomers are possible (4 **AA** or 4 **MM**). In the case of irradiation of the mixture of two different azaanthracenes, as many as 12 different products may be formed (4 **AA**, 4 **MM** and 4 **AM**). In this context, controlling the selectivity of such a reaction is crucial. We carried out photodimerization experiments using two various light sources (365 and 420 nm) and two different solvents (MeOH and DCM). In methanol, we obtained a suitable mixture of *anti*-HT, *syn*-HT, *anti*-HH, *syn*-HH **AA** homodimers and a mixture of two *anti*-HT and *syn*-HT **MM** homodimers respectively. In the case of **A** and **M** mixture, the results were different for both irradiation wavelengths – for 365 nm we have got a mixture of **AA** homodimers and two **AM** isomers, whereas for 420 nm we obtained almost pure heterodimer **AM** in two isomeric forms. Thus, the appropriate selection of the light source and solvent can control the selectivity of this photoreaction. The presented results revealed that azaanthracenes offer a dynamic photoreactive system, which can be utilized in materials chemistry and supramolecular chemistry for the construction of more advanced functional systems.

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CIS-PLATIN ARGININE CONJUGATES FOR THE TARGETED TREATMENT OF MESOTHELIOMA

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Malignant pleural mesothelioma (MPM) is a rare and aggressive neoplasm which arises from exposure to asbestos[1,2]. MPM typically has a long latency period, which is sometimes over 30 years after exposure to asbestos[3]. There are currently no efficient or specific treatments for MPM, and as a result, the typical survival rate is 12-24 months post-diagnosis[4]. Evidence suggests that the majority of MPMs are deficient in arginosuccinate synthetase (ASS1); the rate limiting enzyme in the synthesis of arginine[5]. Research has shown arginine deprivation therapy improves progression-free survival in patients with ASS1 deficient MPMs[6]. This work aims to synthesise a library of cis-platin arginine conjugates, which could be used as a stand-alone treatment or in conjunction with arginine deprivation therapy to specifically target MPM. Once synthesised, our conjugates will be subjected to biological testing, and their activity compared to that of cis-platin.

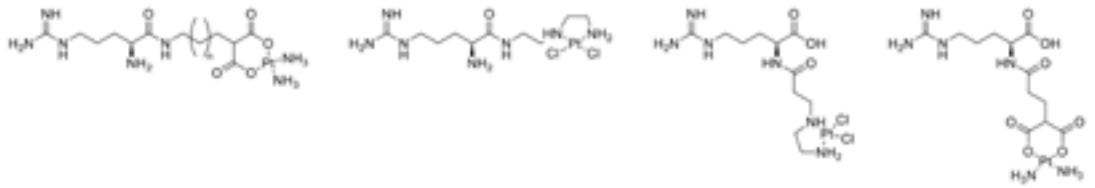
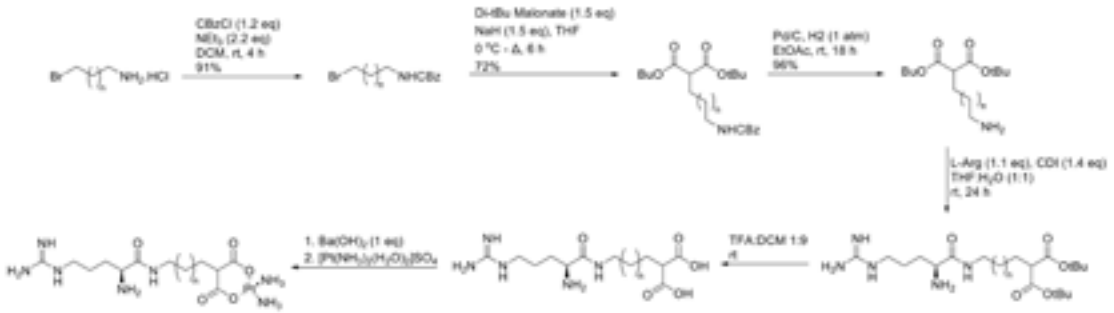


Figure 1: Target cis-platin arginine conjugates



Scheme 1: Example synthetic route to a cis-platin arginine conjugate

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STEREOSPECIFIC sp^3-sp^2 SUZUKI-MIYAURA CROSS-COUPLINGS OF SATURATED HETEROCYCLIC BORONATES

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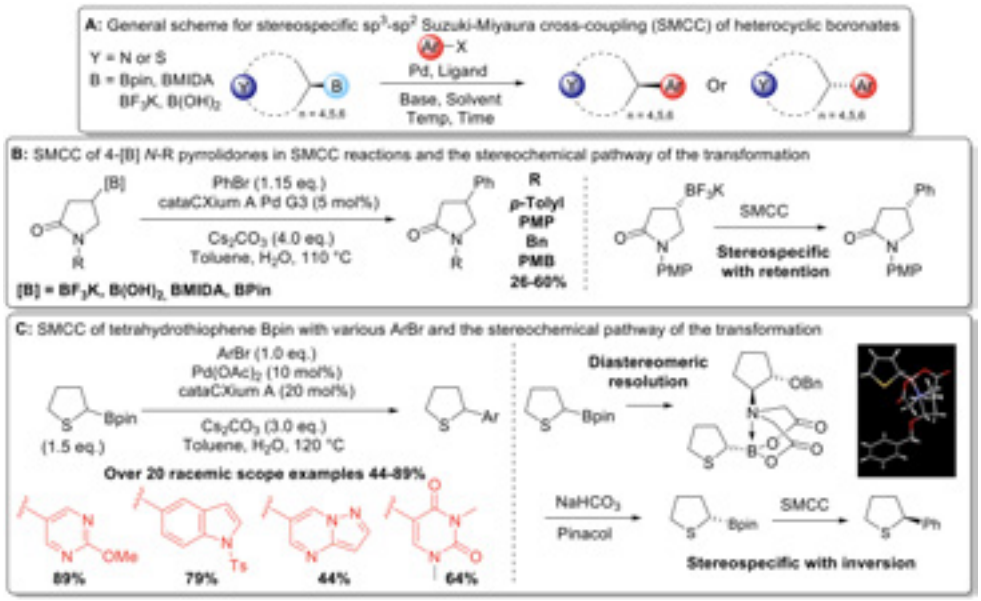
The Suzuki-Miyaura cross-coupling (SMCC) reaction is an incredibly useful reaction in medicinal chemistry, but its intensive use has led to an over-planarization of drug compounds, limiting the 3D chemical space of hit molecules.[1] As an increase in saturated architectural elements has been correlated to increased success in clinical trials,[1,2] demand from the pharmaceutical industry for a general method to cross-couple saturated heterocyclic boronates to deliver enantioenriched products has grown significantly.[3] Our groups have focused on the development of suitable conditions for stereospecific sp^3-sp^2 SMCC reactions, exploring whether the reactions proceed with stereo-retention or inversion (A).

A series of *N*-R 4-BF_3K pyrrolidones were synthesised and deployed in sp^3-sp^2 SMCC reactions (B) using conditions adapted from Partridge *et al*.[4] Optimisation was carried out using the readily removed PMP system and conversions up to 63% were obtained. Using *N*-PMP pyrrolidone of high er, the stereochemical pathway of the transformation was demonstrated to proceed stereospecifically **with retention** (B).

A novel sp^3-sp^2 SMCC reaction with tetrahydrothiophene Bpin has been developed. This system has provided one of the most robust SMCC reactions explored to date in our groups. Over 20 diverse and high yielding examples have been carried out (C). Of note, differing from the pyrrolidone system (B), the stereochemical pathway of the tetrahydrothiophene Bpin SMCC proceeded stereospecifically **with inversion** (C). These divergent stereochemical pathways are currently being explored using DFT calculations.



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ARYLOXIDE BASICITY MODERATES THE ISOTHIOUREA-CATALYSED REVERSIBLE MICHAEL ADDITION OF ARYL ESTERS TO 2-BENZYLIDENE MALONONITRILES

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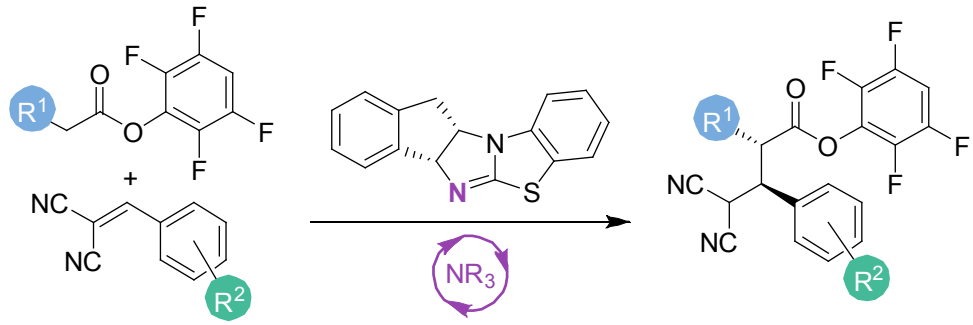
C(1)-ammonium enolate catalysis has become an efficient method for the α-functionalisation of carboxylic acids and their derivatives through C-C and C-X bond formation.[1] Chiral tertiary amines, for example chiral isothioureas, can be used to generate chiral C(1)-ammonium enolates.[2] Subsequent stereoselective reaction with an electrophile then allows access to highly enantioenriched complex products. Catalytic enantioselective transformations usually rely upon optimal enantioselectivity being observed in kinetically controlled reaction processes, with energy differences between diastereoisomeric transition state energies translating to stereoisomeric product ratios. Herein, stereoselectivity that occurs in a reaction process involving the unusual *reversible* addition of a C(1)-ammonium enolate derived from an aryl ester to 2-benzylidene malononitrile electrophiles is demonstrated. Notably the basicity of the aryloxide (derived from the aryl ester) and reactivity of the isothiourea Lewis base both affect product selectivity, and when coupled with a crystallisation-induced diastereomer transformation (CIDT)[3] allows isolation of products in high yield and stereocontrol.



- *Reversible* addition of C(1)-ammonium enolates to 2-benzylidene malononitriles
- ?? Novel crystallisation-induced diastereomer transformation
- 14 examples, up to 92%, 95:5 dr and 99:1 er

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BRØNSTED BASE CATALYSED ENANTIOSELECTIVE [2,3]- AND [1,2]-WITTIG REARRANGEMENTS OF OXINDOLES

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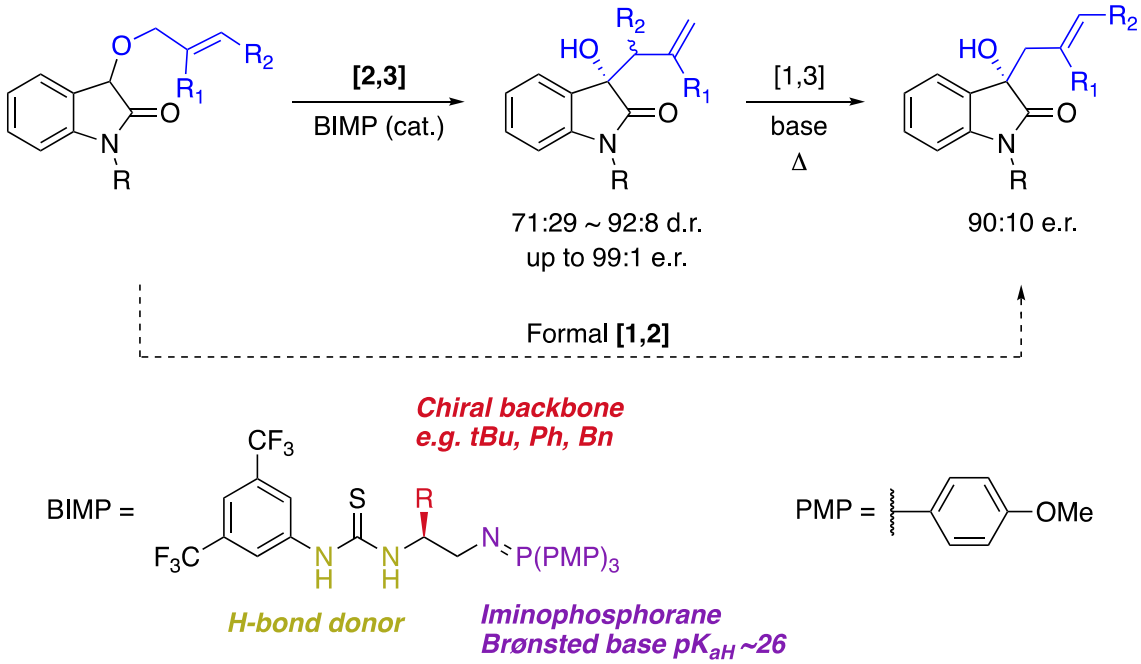
The [2,3]-Wittig rearrangement has been extensively studied and widely applied in organic synthesis over the last few decades.[1] This [2,3]-sigmatropic rearrangement transforms an allylic ether into a homoallylic alcohol, while simultaneously generating up to two contiguous stereocentres. This process is often competitive with the related [1,2]-Wittig rearrangement, with selectivity and stereocontrol of [2,3]- and [1,2]-Wittig rearrangements a recognised challenge to the scientific community.[2] While enantioselective [2,3]-Wittig rearrangements have been explored extensively in the past decade,[3-5] the corresponding [1,2]-Wittig rearrangements are much less developed. Herein we report the development of highly enantioselective and diastereoselective [2,3]- and formal [1,2]-Wittig rearrangements of oxindole systems by application of a chiral Brønsted superbase catalyst: bifunctional iminophosphoranes (BIMP).[6] Generally excellent enantioselectivity (up to 99:1 e.r.) with substrate-dependent diastereoselectivity (71:29 ~ 92:8 d.r.) has been obtained for the [2,3]-Wittig rearrangement, which act as precursors to a process that generates formally the [1,2]-Wittig rearrangement products in good enantioselectivity (90:10 e.r.).



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DEVELOPMENT OF MULTICOMPONENT REACTION CASCADES FOR THE SYNTHESIS OF INDOLES AND SPIROPYRANS

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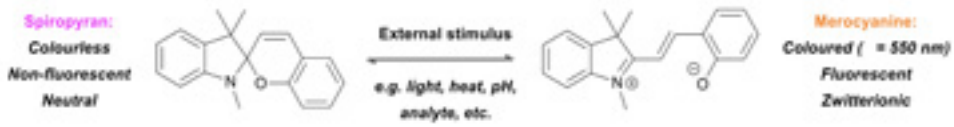
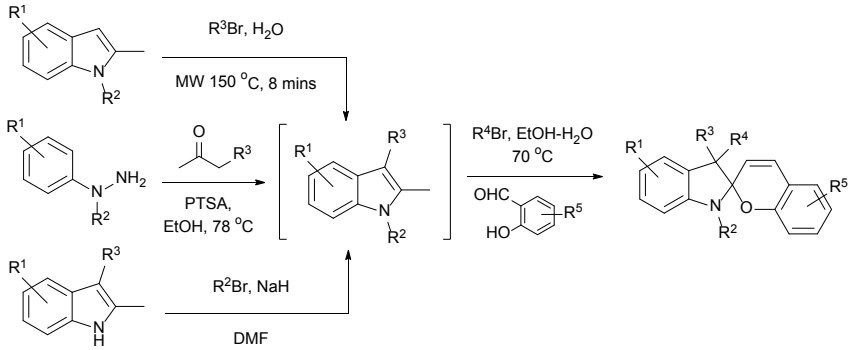
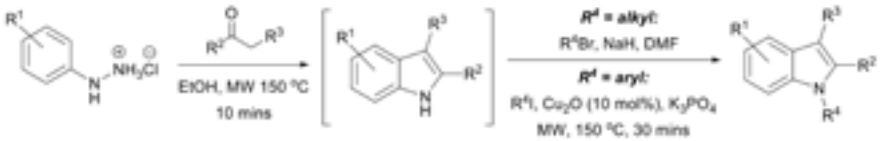
Spiropyrans are a class of photo-activated molecular switch which exist in controllable equilibrium with their isomeric merocyanine forms. They command widespread use in switching and sensing, with diverse applications ranging from cyanide sensors to light-controllable enzymes to photodynamic therapy drug candidates. Unfortunately, classical spiropyran synthesis – *via* indolenine *N*-alkylation – tends to be low yielding, laborious, and is inefficient for the exploration of diverse, novel spiropyrans, hence opportunities to advance the spiropyran field are presently constrained.



To address this synthetic bottleneck, we explored an alternative pathway, employing indole *C*-alkylation to generate intermediate indolium salts as substrates for condensation with salicylaldehydes. We have developed this sequence as a 3-component tandem cascade which enables rapid and high-yielding access to a diverse range of spiropyran structures.[1] We have extended this methodology to encompass *in-situ* generation of 1,2,3-trisubstituted indole precursors *via* Fischer indolisation, indole *N*-alkylation and indole *C*-alkylation, giving rise to 3 complementary 1-pot, 4-component reaction cascades for direct and straightforward access to a raft of structurally diverse spiropyrans.[2] To demonstrate their utility, we have employed these methodologies in combinatorial spiropyran synthesis, and for targeted synthesis of sterol-spiropyran conjugates (as tools for membrane research) and ratiometric metal cation sensors.



Development of the above methodology required synthesis of many indole substrates; hence we became interested in methods to streamline indole synthesis. Correspondingly, we have developed complementary one-pot Fischer indolisation–*N*-alkylation and –*N*-arylation sequences which facilitate simple, rapid and high yielding synthesis of substituted indoles bearing a range of useful functionality.[3]



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SYNTHESIS AND EVALUATION OF E3 UBIQUITIN LIGASE INHIBITORS AS ANTICANCER LEADS

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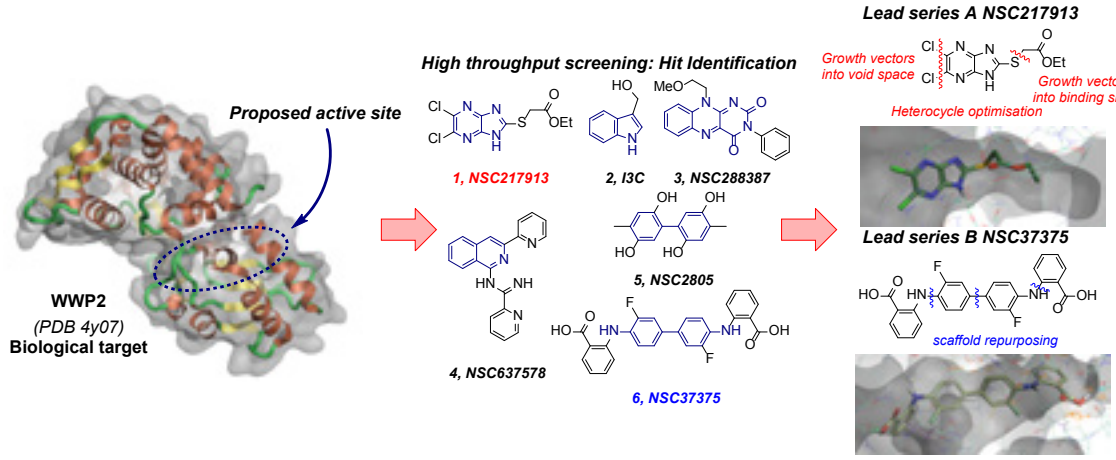
The ubiquitin proteasome system (UPS) is essential for the regulation of cellular protein quality and quantity within cells.[1] Within the UPS, E3 ligases are selective for certain proteins, tagging them with ubiquitin for eventual protein degradation. WWP2 (Figure) is a HECT E3 ligase overexpressed in several forms of cancers, such as oral and prostate cancers, suggesting WWP2 and its isoforms could be promising disease targets.[2,3,4] Within the research group, several molecules have been investigated for inhibitory activity against WWP2 by utilising STD and DEEP-STD NMR.[5] Currently we are exploring the synthesis and functionalisation of a number of hits with heterocyclic cores, including imidazo[4,5-*b*]pyrazine (***1***), indole (***2***), alloxazine (***3***), isoquinoline (***4***) as well as biaryl (***5***) and benzidine cores (***6***). Molecular docking is being utilised to aid in the design of analogues for structure-activity studies.



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eASSEMBLING OF HINDERED CENTRES: APPLICATION TO EFLUORINATION

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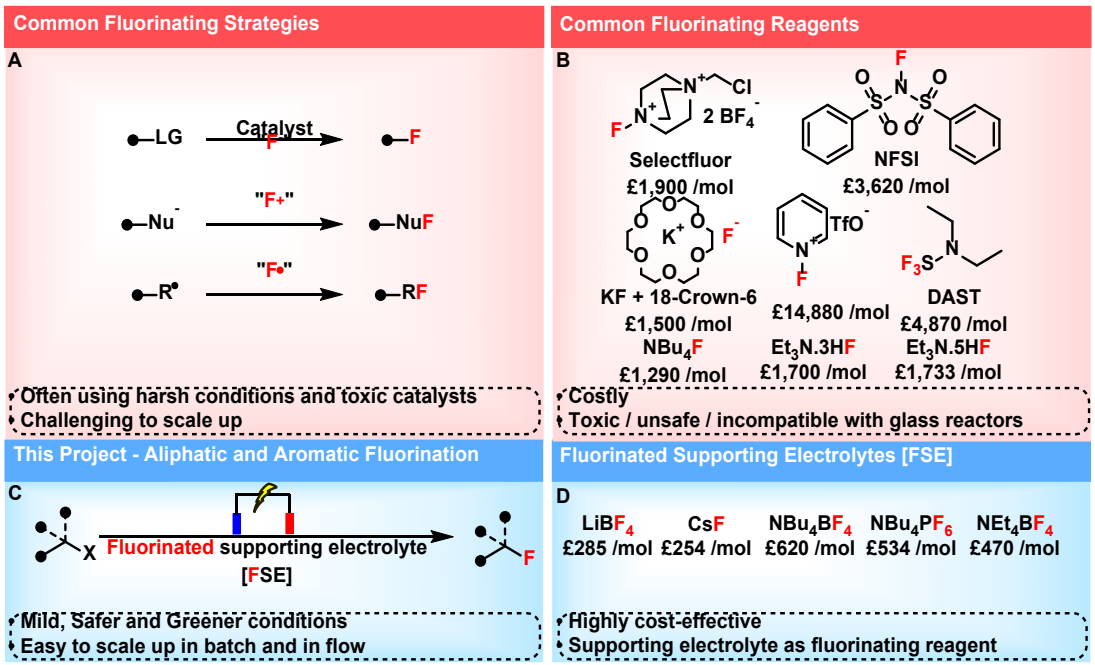
Organofluorine compounds display unique physical, chemical and biological properties in comparison to their hydrogenated analogues. Therefore, it is not surprising to find numerous fluorinated molecules among the top best-selling drugs.[1] However, the installation of a fluorine atom remains far from being trivial.

In this poster, we will disclose a mild electrochemical deoxyfluorination method that uses cheap, safe and readily available fluorinated supporting electrolytes.



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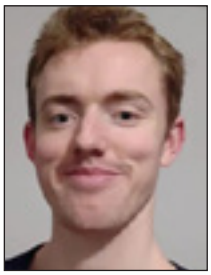
NOVEL ELECTROCHEMICAL C-H ACTIVATION METHODS FOR HETEROCYCLE SYNTHESIS AND APPLICATIONS IN TOTAL SYNTHESIS



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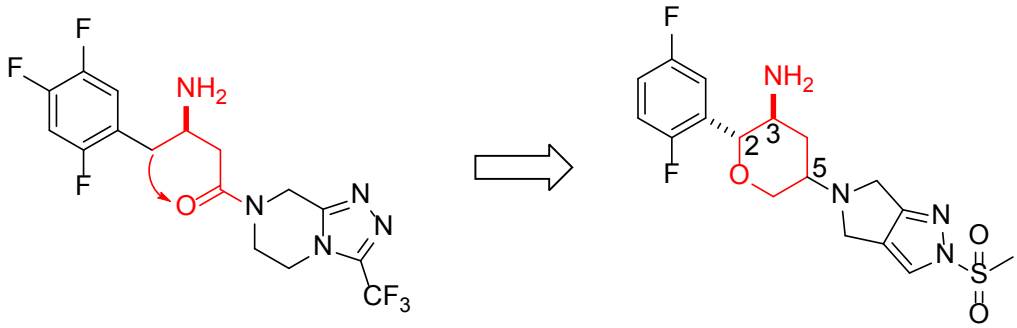
Electrochemical synthesis, in recent years, has rapidly evolved and has arguably become a central tool for the bottom-up assembly and late-stage diversification of molecular compounds. Organic electrochemistry embodies growing impetus for utilising evermore facile, environmentally benign, and ultimately efficacious methodologies. In addition, electrochemistry removes an overreliance on toxic and unnecessary harsh reducing and oxidising agents, by providing novel reaction pathways that are complimentary to traditional synthetic chemistry procedures.[1] In summary, electro-organic synthesis offers opportunities for tuneable, safe, scalable and sustainable chemistry. Nonetheless, preparative organic electrochemistry remains largely underestimated for heterocyclic synthesis.



Tetrahydropyrans (THP) are versatile building blocks and have frequently been used to improve a drug's pharmacokinetic properties (Fig. 1).[2] Moreover, these structural motifs are frequently used as synthons and a key intermediate for natural products.[3] Considering the important value of THP motifs, their synthesis methods have attracted a great deal of interest in the synthetic community.[3] Interestingly, the Prins cyclisation remains one of the most employed strategies for the construction of the THP ring.[3–6] Alternatively, our general strategy is to develop a novel Prins *esque* electrochemical procedure, with a mechanistic rational, for the attainment of THP scaffolds. In substitution for the harsh catalytic conditions, idiosyncratic of Prins cyclisation, we aim to establish the generation of six-membered heterocycles *via* facile electrogenerated carbocations.[7] Herein, we present our preliminary research that demonstrates the general feasibility of electrochemistry for hindered ether synthesis and C-H activated cyclisation.

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NEW NHC-BASED PHOTOSWITCHES FOR THE INTEGRATION IN ADAPTIVE NANOSYSTEMS

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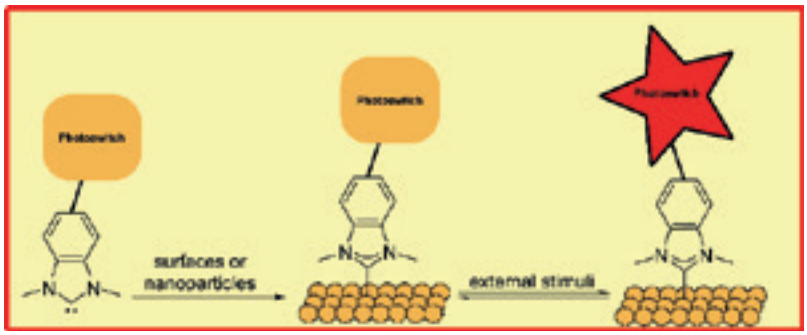
Molecular photoswitches are versatile sensors and actuators for the development of intelligent matter. We design NHCs based photoswitches as building blocks for the assembly of adaptive nanosystems. These photoswitches will be immobilized on nanoparticles and patterned on surfaces using soft lithography. Furthermore, the photoswitches developed will be integrated in a range of adaptive molecular systems, soft materials and solid-state nanosystems.

All diagrams should be drawn using ChemDraw ACS settings and centred.



TOTAL SYNTHESIS OF NEMAMIDES, EUGLENATIDES AND RELATED ANALOGUES

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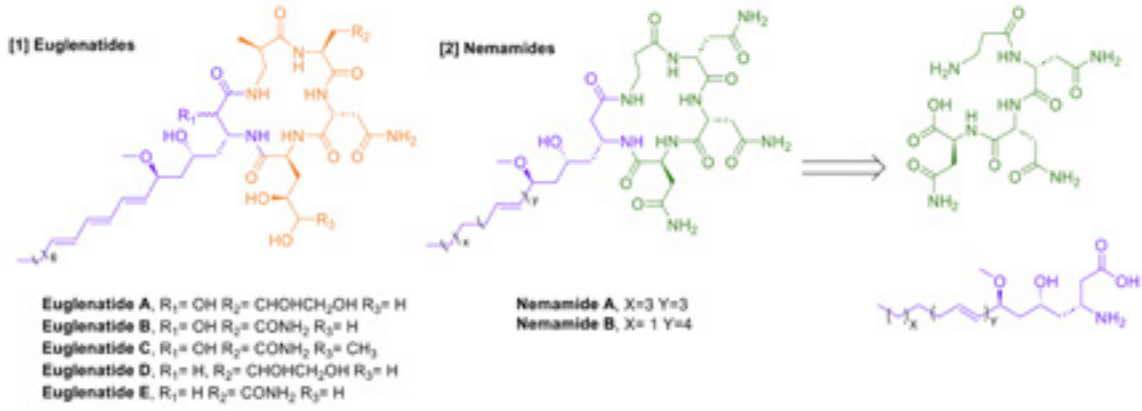
Cyclic peptide containing natural products are an increasing area of interest due to their natural targeting ability, reduced toxicity profiles and their enhanced cell penetrating powers.[1,2] Euglenatides **[1]** and Nemamides **[2]** were isolated from *Euglena gracilis* and *Caenorhabditis elegans*, two very different species, however, both families contain similar 5-mer cyclic peptide structures, comprising of non-proteogenic amino acids, bound to an aliphatic chain containing multiple stereocenters.[3,4] Euglenatides A-D were shown to have anti-fungal effects, alongside tumour supressing output against varying cancer cell lines.[4] Total synthesis of both families of cyclic peptides will be carried out, utilising chiral catalysts and auxiliaries for stereoinduction, amide coupling reactions, macrocyclization techniques and transition-metal catalysed couplings. Initial research focuses on the targeted synthesis of Nemamides A and B for structure confirmation and biological testing.



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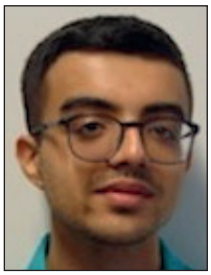
GAS-PHASE GENERATION AND REACTIVITY OF THE ISOMERIC PARENT OXAZINES AND THIAZINES



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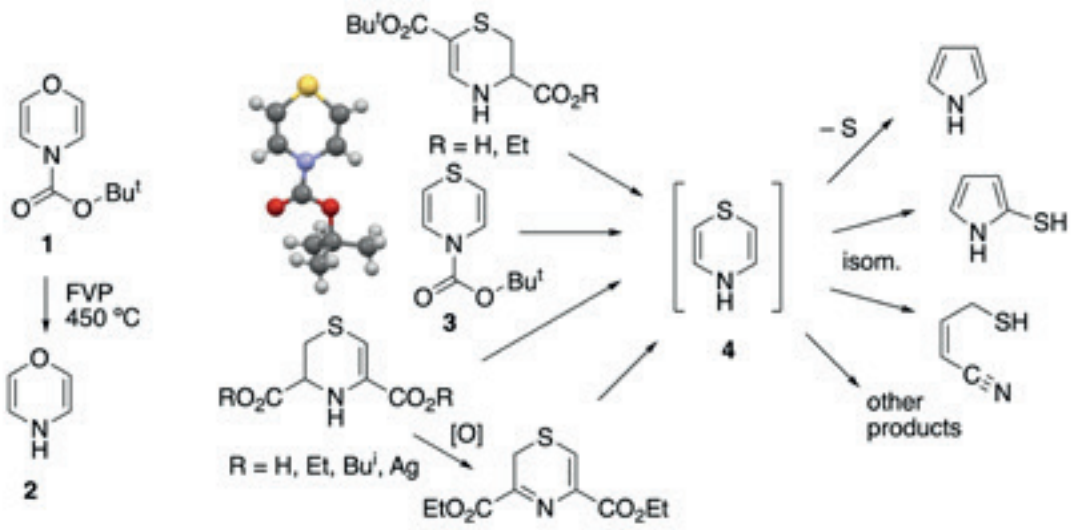
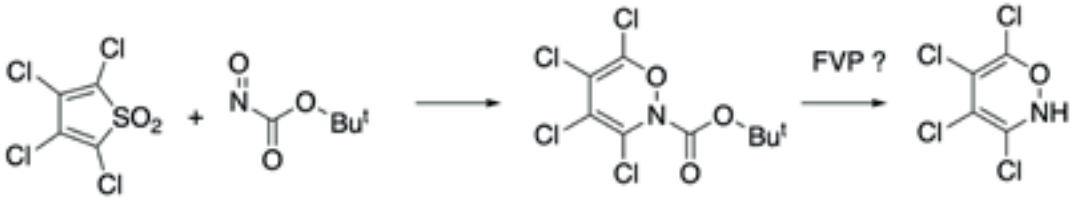
Some years ago we described the generation and spectroscopic characterisation of 1,4-oxazine **2** by flash vacuum pyrolysis (FVP) of the *N*-Boc precursor **1**.[1] This was the first among all the possible isomeric parent oxazines and thiazines to be so characterised, although there is an isolated early report, never subsequently reproduced, that claims the preparation of 1,4-thiazine **4** as a stable liquid.[2] We have now examined a range of precursors for the gas-phase generation of 1,4-thiazine including the obvious *N*-Boc derivative **3** characterised by X-ray diffraction. Whilst there is tantalising evidence for the formation of various interesting and reactive species, definitive evidence for 1,4-thiazine **4** is thus far lacking. It appears that it may undergo a range of thermal rearrangements under the conditions for its generation to give more stable isomeric products. The latest results will be presented.



Work towards a simple monocyclic 1,2-oxazine is also in progress and one approach to this is shown below.



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TOTAL SYNTHESIS OF JBIR-23 AND JBIR-24 AS A POTENTIAL ANTI MESOTHELIOMA COMPOUND

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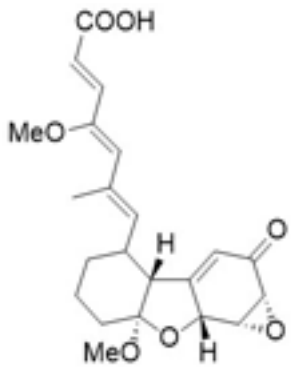
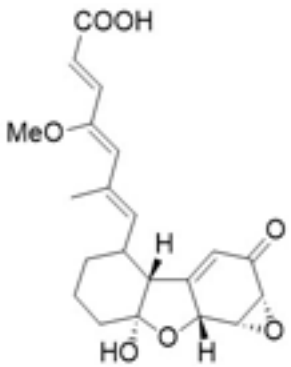
Malignant plural mesothelioma (MPM) is a rare form of lung cancer caused by oxidative stress in the plural cavity of the lungs. It has been linked to long term exposure to asbestos fibres.[1] MPM has been shown to be resistant to many palliative care methods including surgery and chemotherapy.[2] Due to the large number of people who have been exposed to asbestos in the last century there is an urgent need for possible treatments to this cancer. In 2008 Kazuo Shin-ya et al. were able to extract a potential treatment from *Streptomyces* sp which showed promising results when exposed to MPM cell line cultures.[3] These compounds were called JBIR-23 and JBIR-24. In 2021 Yi Man et al developed a total synthesis method for JBIR-23 and JBIR - 24.[4] The aim of the project is to improve the synthetic method developed by Yi Man et al and to further explore the biological activity presented by the target compounds.



JBIR-23



JBIR-24

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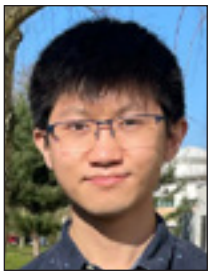
EXPANDING THE SCOPE OF NUCLEOPHILE INDUCED CASCADE RING EXPANSION



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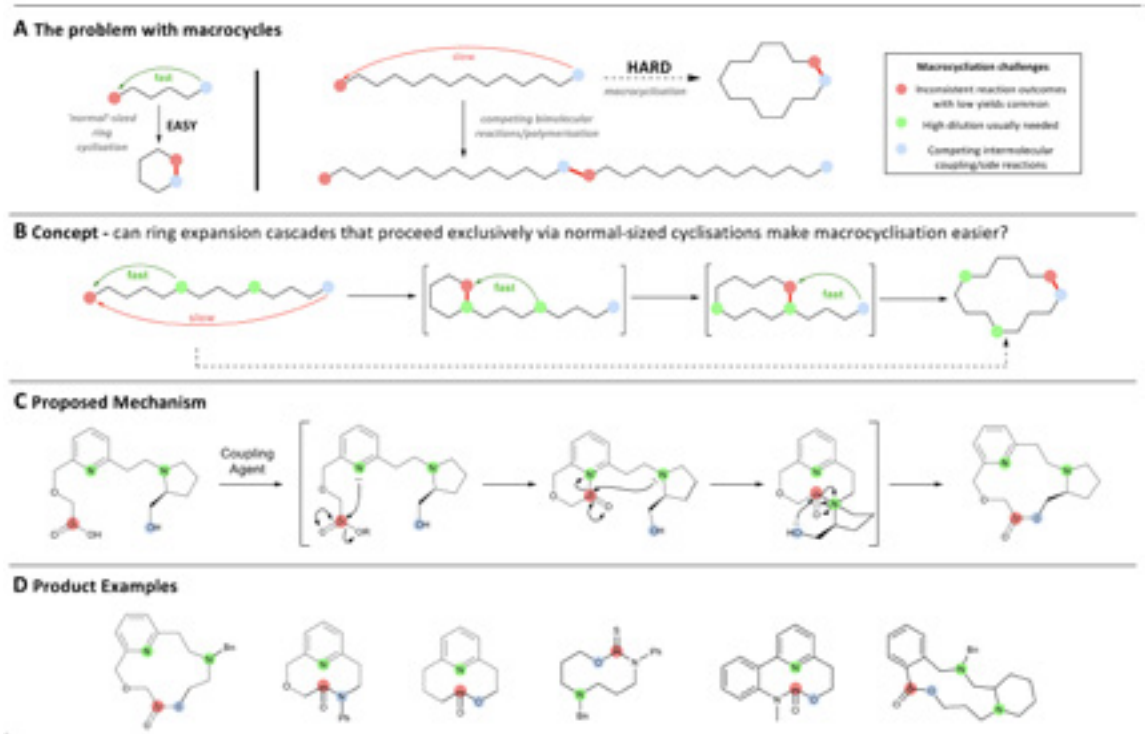
This poster is focused on my PhD research on the development of novel ring expansion reactions to synthesise biologically active medium-sized rings and macrocycles. Most macrocyclic compounds are synthesised via end-to-end coupling of a linear precursor under high dilution conditions, making them impractical and/or unsuitable for industrial applications.

Nucleophile Induced Cascade Ring Expansion (NICE) is a novel synthetic methodology developed in the Unsworth group which can be utilised to synthesise macrocyclic molecules *without the need for high dilution conditions*. NICE chemistry utilises internal nucleophiles as internal cyclisation catalysts, to dramatically increase the ease of end-to-end cyclisation by breaking it down into smaller ring cyclisation reactions and in situ ring expansion via cascade processes. This means that the intermolecular side reactions that plague traditional end-to-end macrocyclization reactions can be completely avoided. Medium-sized rings and macrocycles of various sizes and functionalities have been synthesised using this approach, and will be presented in this poster.



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PHOTOCHEMICAL TRANSFORMATIONS FOR THE EXPEDIENT SYNTHESIS OF SP^3-RICH MOLECULES IN THE FIELD OF MEDICINAL CHEMISTRY

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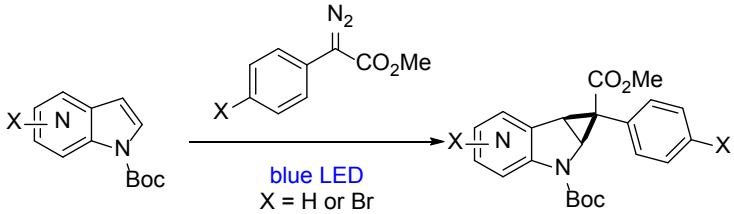
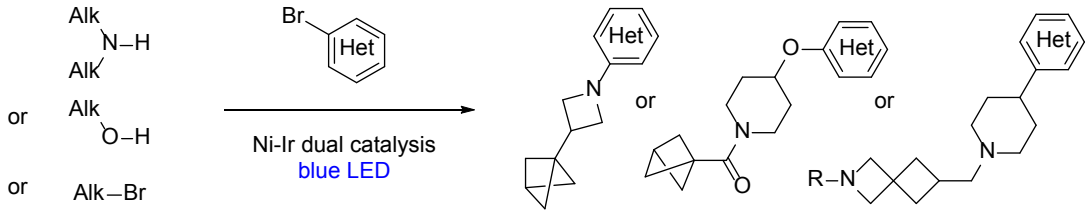
Compounds and intermediates in medicinal chemistry often present a bias toward the presence of multiple aromatic rings, as palladium-cross-coupling reactions have emerged as robust and versatile methodologies. Although synthetically tractable, such sp^2-rich compounds exhibit lower metabolic stability and less desirable physical-organic properties compared to their sp^3-rich counterparts. Following the mantra *escape from flatland*[1,2], SpiroChem identified *visible light photochemistry and photoredox catalysis* as an enabling technology to generate complexity from simple building blocks and give access to sp^3-rich fragments and building blocks.

Photoinduced dearomatization[3] and cycloadditions reactions were leveraged as atom-economical strategies to obtain sp^3-rich scaffolds from readily available "flat" starting materials. These scaffolds could later be used for the generation on DNA-encoded libraries.



Recent methodologies for C-N, C-O and C-C cross-couplings by nickel-photoredox dual catalysis were benchmarked on complex molecules and shown to be amenable to the synthesis of focused libraries in the fields of fragment-based-drug design[4] and molecular glues for protein degradation



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DESIGN AND SYNTHESIS OF SELECTIVE INHIBITORS OF THE CALCIUM-BINDING PROTEIN S100P AS ANTI-METASTATIC AGENTS

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S100P is a protein expressed in many cancers and is associated with significant changes in cellular behaviour resulting in cancer development. Extracellular S100P can bind with the receptor for advanced glycation end products (RAGE). When S100P is bound to RAGE, an array of events is activated including cell proliferation, drug resistance and metastasis. Based on the properties and effects of S100P, it is considered a potentially valuable therapeutic target to treat cancer, either alone or in combination with other chemotherapeutic agents.

The previous research conducted by our group identified a number of novel molecules that block the S100P-RAGE interaction (estimated IC50 ranges from 0.5 nM to >100 nM) and inhibit invasiveness of S100P-expressing cells.[1] This study aims to design a new set of small molecule inhibitors with increased potency based on knowledge of the proposed binding pocket which hosts the S100P - RAGE interaction. Computational modelling techniques utilised for the study include scaffold replacement, R-group screening and pharmacophore modelling.

A novel set of molecules has been proposed through the development of a new pharmacophore used in combination with *de novo* design and software modelling. An increase in computational binding affinities has been observed compared to previous inhibitors, as well as an increase in ligand efficiency (LE) and the number of interactions with the binding pocket. Two examples of structures with a predicted higher binding affinity include compounds **1** and **2** (Figure 1). Two out of the twelve proposed molecules are derived from compounds previously synthesised by this research group, though a majority of the proposed compounds are novel. Heterocyclic systems, especially indoles, have been shown to have a particularly advantageous scaffold for the binding pocket of interest. However, the required substitutions on the indole based compounds identified in computational studies are difficult to synthesise. Compounds based around **2** will be synthesised and biologically analysed to understand more about the binding pocket.

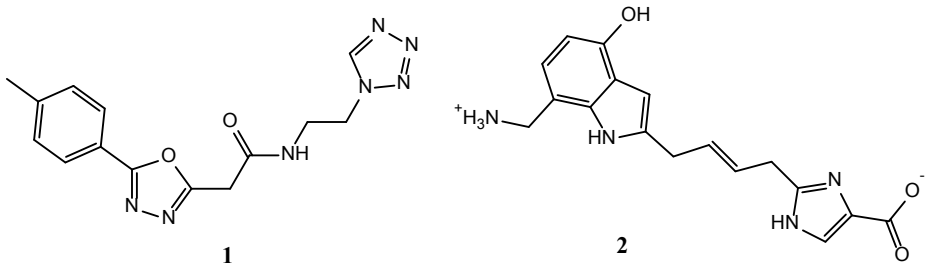

Figure 1: Proposed inhibitors, based upon the oxadiazole (1) and indole (2) scaffolds, identified in this study.

Compound **1** can be obtained from diethyl malonate, via acylation and cyclisation of an intermediate monohydrazide, followed by coupling to the 2-aminoethyltetrazole building block. Routes towards the synthesis of **1** and other newly designed molecules will be discussed.

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SYNTHESIS OF ANTI-INFLAMMATORY STILBENES AS POTENTIAL TOPICAL THERAPY FOR INFLAMMATORY LUNG DISEASES

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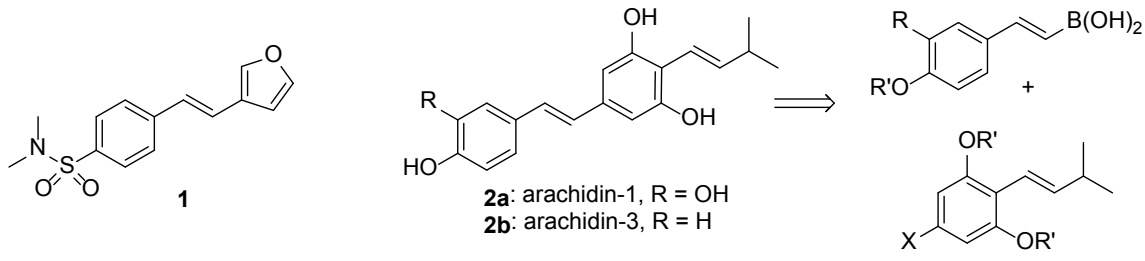
The anti-inflammatory activity of natural hydroxylated stilbene analogues, of which resveratrol is the most famous example, are of interest for their potential application as mediators of chronic inflammatory disease pathways. However, the low bioavailability and potency of these polyphenolic phytoalexins has limited research progress. Interest in other natural prenylated stilbenes, such as arachidin-1 and arachidin-3, **2a**, **2b**, stems from their superior anti-inflammatory activity and metabolic profile.[1]

We have previously demonstrated that synthetic stilbene sulfonamides and related heterocyclic analogues, such as **1**, inhibit a number of inflammatory pathways relevant to chronic lung disease.[2]

There is no published synthetic route to arachidin-1 and the published route to arachidin-3 has limited scope for further analogue development. Therefore, to explore these interesting molecules further, we have planned a convenient and flexible "building-blocks"-based synthesis of the arachidins and other prenylated stilbene analogues, deploying a stepwise coupling strategy (Figure 1). Progress in this synthetic approach will be presented.



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SP³-SP² SUZUKI-MIYAURA CROSS-COUPLING OF SATURATED NITROGEN HETEROCYCLES

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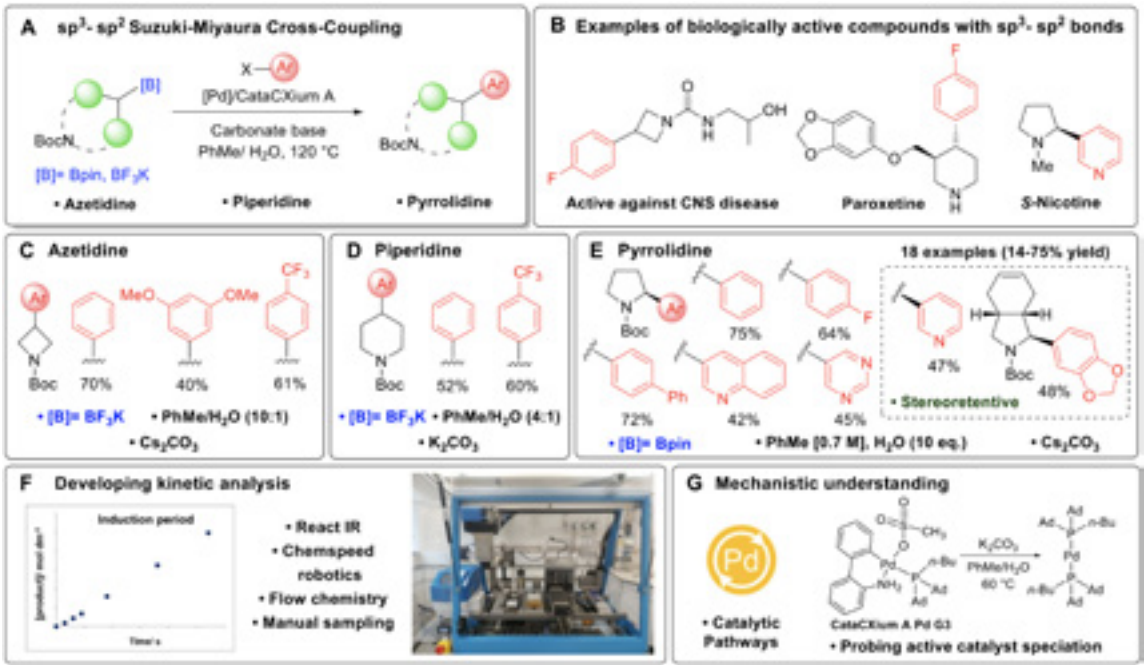
In view of the success of sp²-sp² Suzuki-Miyaura cross-coupling (SMCC) in medicinal chemistry,[1] the demand has grown for the development of a variant that would enable routine sp³-sp² couplings.[2] Methodology has been established for acyclic secondary alkyl boronate reagents[3-5] but cyclic systems have provided more challenges.[4,5] Our groups are currently interested in addressing this directly by developing Pd-catalysed stereospecific sp³-sp² Suzuki-Miyaura cross-coupling of saturated nitrogen heterocyclic boronates (A). Development of this methodology would enable a transformative, facile pathway to medicinally prevalent arylated nitrogen heterocycles (B), enabling the systematic exploration of 3-D pharmaceutical space.[6]

In this project, SMCC methodology has been optimised for three different *N*-Boc protected nitrogen saturated heterocyclic boronates: 3-BF_3K azetidine (C), 4-BF_3K piperidine (D) and α-Bpin pyrrolidine (E). Alongside this, scope using a range of aryl halides continues to be explored. Using enantioenriched α-Bpin pyrrolidine, the retentive stereospecificity of the SMCC has been established (E). In ongoing studies, we are collecting rich kinetic data (F) and have performed mechanistic studies (G) to probe catalyst speciation and the assumed problematic step of transmetallation.[4] Full details will be reported.



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MAKE IT 3D: ELECTROCHEMICAL SPIROCYCLISATION, A VERSATILE TOOL

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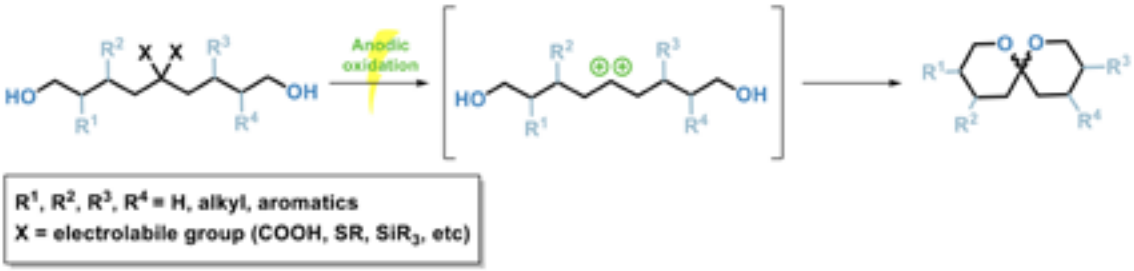
Spiroketals are three-dimensional structural motifs found in many biologically active natural products.[1] In the past decade, medicinal chemists have explored the diversity of spirocyclic systems, leading to several successful drug development.[2]

Electrosynthesis is a field in rapid expansion, and numerous novel elegant electrosynthetic methodologies have been reported over the last decades. Pioneering work by Marko *et al.* [3] showed that the anodic decarboxylation of malonate derivatives led to the formation of the corresponding ketones under unprecedented mild conditions.

Taking advantage of these precedents, our team is developing a variation of Marko's approach for the rapid and practical preparation of polysubstituted spiroketals. Our new methodology is rapid, practical, mild and versatile.



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DIAZO COMPOUNDS AND CARBENES WITHOUT THE BANG!

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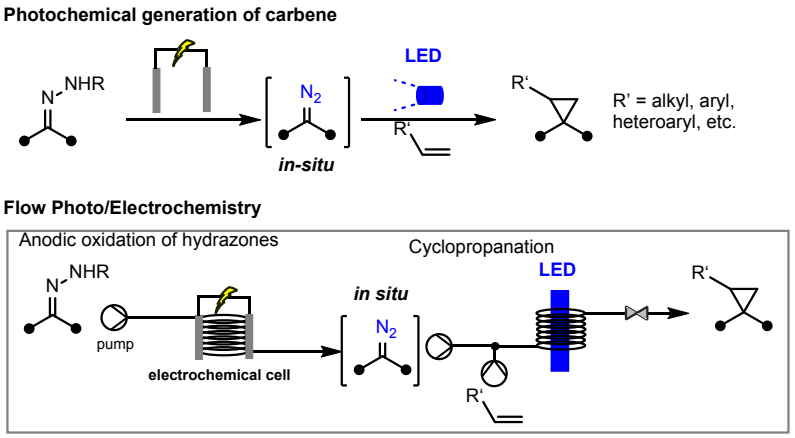
The versatility of diazo compounds has resulted in them being very attractive building blocks in academia and medicinal chemistry.[1] Diazo chemistry represents a significant research area and has been extensively explored by dedicated research teams since its discovery in the 1950s.[2] Carbenes, generated from diazo compounds, allow a unique disconnection approach in synthetic organic chemistry, such as C-H functionalisations.[3] However, due to their hazardous nature, diazo derivatives are scarcely used in industry. To circumvent this limitation, we combined the use of electrochemistry with photochemistry. In order to demonstrate the synthetic methodology's utility, we propose to electrochemically synthesise diazo compounds *in situ* and subsequently decompose them via photochemistry, minimising the risk by keeping the diazo compounds' concentration virtually close to zero during the whole process. The photo-generated carbene can then undergo cyclopropanation with a double bond, thus offering a facile synthetic method to form industrially-important cyclopropanes that are otherwise difficult to obtain.

The first results of this novel, green and practical methodology will be disclosed in this poster.[4]



Scheme 1: The overall concept for the safe and practical generation of carbenes.

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IMIDAZOLIUM-BASED LIPID ANALOGUES – A VERSATILE TOOLBOX FOR LIPID BIOLOGY AND BEYOND

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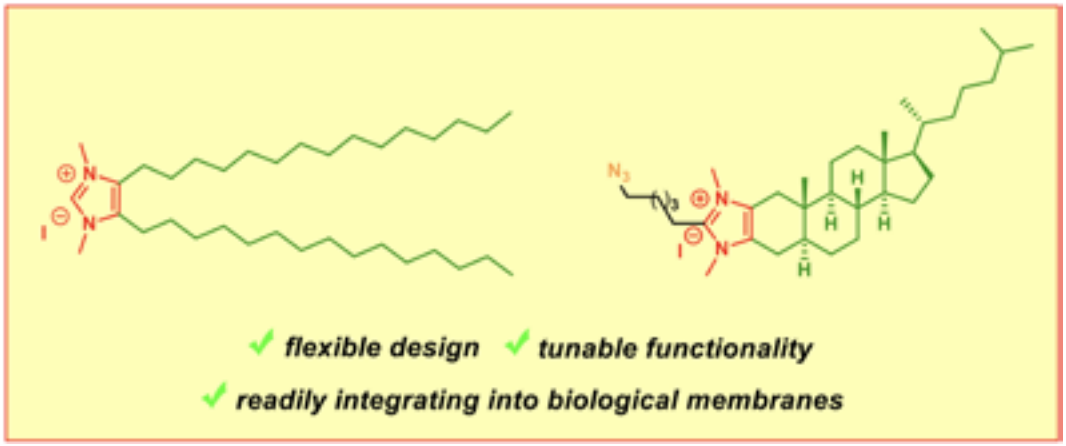
Lipids constitute the main component of biological membranes and therefore play an important role in mediating essential membrane properties such as lipid bilayer integrity, organisation and function. Despite their vast biological importance, the investigation and manipulation of lipids and cellular membranes is still limited by the availability of suitable tools to do so. Recently, we developed a new class of imidazolium-based lipid analogues that resemble natural lipids in their amphiphilic structure and therefore many of their biological properties, but can easily be tuned and derivatized for various purposes with regard to the investigation, modification and manipulation of biological membranes.[1–8] In particular, a series of imidazolium-based cholesterol analogues (CHIMs) was designed that could be shown to faithfully mimic biophysical and biological properties of native cholesterol, e.g. by readily integrating into cellular membranes.[4,5] These analogues could be utilized for various applications, including imaging of cholesterol distributions in live cells, protein decoration of biomembrane surfaces, implementation of artificial catalytic reactivity into cellular membranes, or as membrane-targeting antimicrobials.[4–8] We therefore envision imidazolium-based lipid analogues to serve as a valuable, broadly applicable toolbox for the investigation and manipulation of biological membranes and lipid-mediated cellular processes.



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ISOTHIOUREA-CATALYSED ACYLATIVE KINETIC RESOLUTION OF TERTIARY PYRAZOLONE ALCOHOLS

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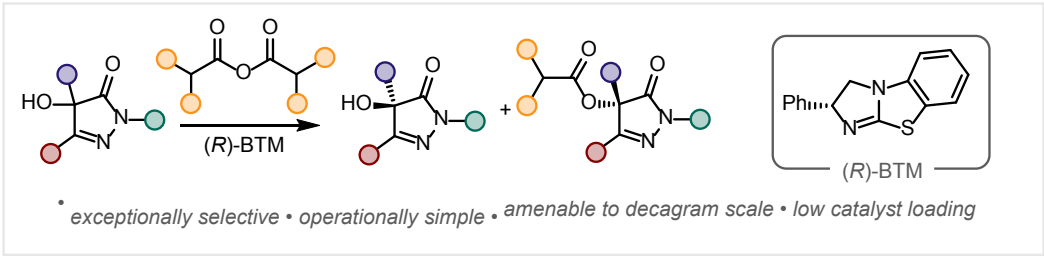
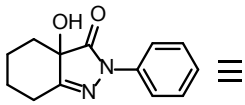
Pyrazolones are a widely prevalent heterocyclic motif in biologically relevant pharmaceutical and agrochemical compounds. However, routes to access enantioenriched pyrazolone derived tertiary alcohols remain scarce with the limited routes available possessing issues with both functional group tolerance and limited scope. The use of isothiourea organocatalysts has emerged as a powerful strategy in recent years, with their application for the acylative kinetic resolution of both secondary alcohols widely studied. A ***widely recognized remaining challenge*** is to develop the kinetic resolution of **tertiary alcohols** as (i) acylation is inherently difficult due to the sterically hindered nature of the alcohol; (ii) the acylation catalyst is required to discriminate between enantiomers bearing three non-hydrogen substituents at the carbinol centre.

In this work we report the application of isothiourea catalysts in the kinetic resolution of pyrazolone tertiary alcohol derivatives. The reaction exhibits extremely high selectivity across a broad range of substrates (>30 examples, selectivity factors typically >200), including pyrazolones derived directly from pharmaceutical compounds at low catalyst loadings. The reaction is also highly amenable to scale up, with decagram reactivity showing no drop in reaction efficiency.





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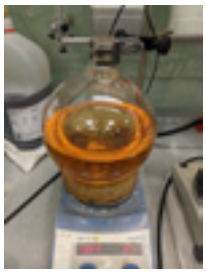
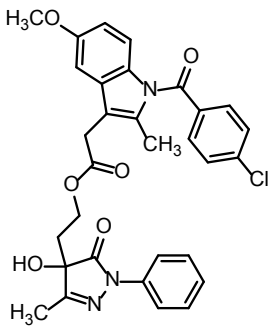


0.22 mol scale (50 g)



from indomethacin
alc: 52%, 97:3 er
est: 45%, 99:1 er
c = 49, *s* >200

INTERFACING PHOTOCATALYSIS AND WHOLE-CELL BIOCATALYSIS FOR GREENER ASYMMETRIC SYNTHESIS

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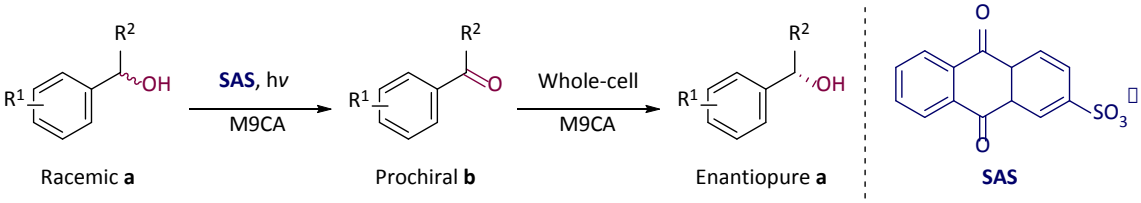
The chemical industry disproportionately consumes energy and produces environmentally harmful waste compared to other sectors. Recent developments in photocatalysis and biocatalysis have enabled the replacement of traditional methodologies with greener processes that exploit visible light energy and renewable feedstocks using mild reaction conditions.[1] Currently, most synthetic methodologies, especially in photocatalysis, remain incompatible with living organisms regarding solvent conditions, atmospheric composition, and phototoxicity. Applications are currently limited to expensive workflows using purified enzymes and stoichiometric co-factors.

This work focuses on incorporating living cells in photochemical synthetic routes as versatile, economical, and highly selective catalysts. We adapted a photocatalytic oxidation of racemic secondary alcohols to aerobic, aqueous, and biocompatible conditions.[2] This is interfaced with an enzymatic reduction to regenerate the enantiopure secondary alcohol. Protective strategies involving encapsulation and pigmentation are employed to preserve biocatalyst activity from phototoxicity.[3] The resulting one-pot model reaction, combining mild conditions and simple protection, demonstrates the ease and low cost of dual catalytic strategies merging photocatalysis and biocatalysis to generate stereocentres.



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CP*RH(III)-CATALYZED ENANTIOSELECTIVE C(SP^3)–H AMIDATION OF CYCLOBUTANES

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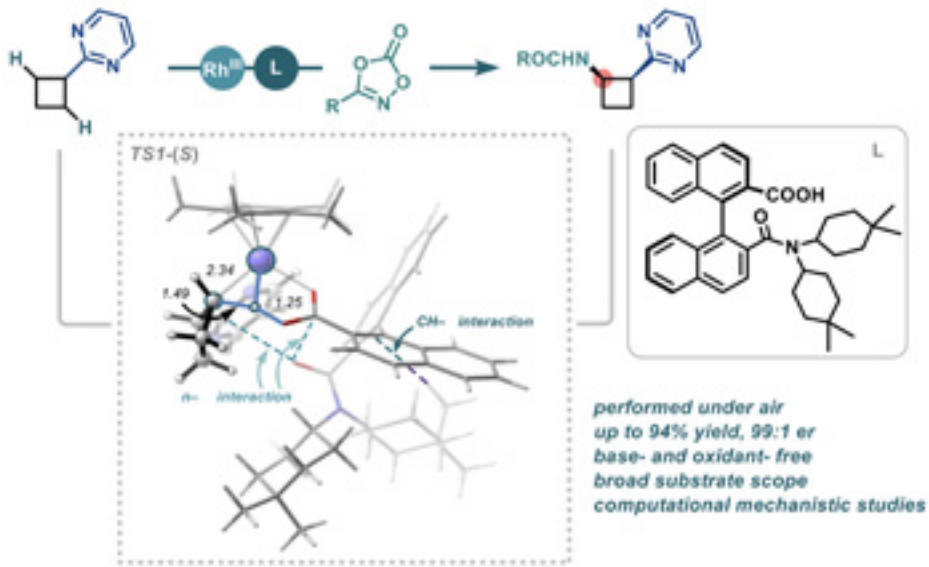
Cyclobutanes and N-containing heteroaromatics are core units found in many natural products and are important motifs embedded in a variety of biologically active molecules. However, the synthesis of cyclobutane scaffolds with precisely-controlled selectivity has proven difficult according to the previous methods. Most cyclobutane skeletons obtained through [2+2] photocycloaddition processes tend to be 1,3-disubstituted, or multi-substituted isomers, and suffer from poor stereoselectivity; meanwhile, the direct C(sp^3)-H functionalization of saturated cyclobutanes has received limited attention from the synthetic community.[1]

This work describes the first expedient access to affording the enantioenriched amidated cyclobutanes through the direct asymmetric C(sp^3)–H amidation of cyclobutanes with useful pyrimidine as a strong coordinating directing group in combination with an electron-deficient Cp*Rh(III) catalyst.[2] A newly designed axially chiral carboxylic acid (CCA) was found to be the key to obtaining high levels of enantiocontrol. We envision this methodology will broaden access towards enantioenriched cyclobutane building blocks and stimulate new developments in the merger of enantioselective desymmetrisation with Rh-catalyzed C-H activation.



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