

RSC Heterocyclic and Synthesis Group
35th Postgraduate Symposium: Virtual Format
Thursday 17th/Friday 18th September 2020

Thursday 17th September

- 13.30 – 13.40 Opening remarks (Dr Susannah Coote, Lancaster University, H&S Group Secretary/Treasurer)
- 13.40 **Session 1** Chair: Dr Lorna Duffy (Synature)
- 13.40 – 14.05 **Edward Briggs** (Imperial College)
Synthesis of Sulfonimidamides from Sulfenamides via an Unprecedented Alkoxy-amino- λ^6 -sulfanenitrile Intermediate
- 14.05 – 14.30 **Bethan Donnelly** (University of Bristol)
Sequential Photochemical and Prins Reactions for the Diastereoselective Synthesis of Tricyclic Scaffolds
- 14.30 – 14.55 **George Rodgers** (University of Sheffield)
New Functionality-Rich Boronic Acid Scaffolds
- 14.55 – 15.10 *Tea/Coffee break (bring your own!)*
- 15.10 **Session 2** Chair: Dr Marc Kimber (Loughborough University)
- 15.10 – 15.35 **François Richard** (Queen Mary)
Unprecedented γ -Selectivity in the Palladium-Catalysed Asymmetric Allylic Alkylation of Siloxyfurans
- 15.35 – 16.00 **Oskar Hoff** (University of Oxford)
Towards the Total Synthesis of (+)-Lophotoxin
- 16.00 – 16.25 **Jacqueline Bitai** (University of St. Andrews)
Enantioselective Palladium and Isothiourea Dual Catalysis
- 16.25 Closing Remarks. A prize for the best talk will be announced on Twitter shortly after the end of the webinar!

Friday 18th September

- 13.30 – 13.40 Opening remarks (Dr Susannah Coote, Lancaster University, H&S Group Secretary/Treasurer)
- 13.40 **Session 1** Chair: Dr Nadia Ahmad (Charles River)
- 13.40 – 14.05 **Antoine de Gombert** (University of Oxford)
Desulfonative Cross-Couplings: Mechanistic Insights for Reaction Optimisation
- 14.05 – 14.30 **Sheenagh Aiken** (University of Bristol)
An Iterative Approach to the Stereocontrolled Total Synthesis of Bahamaolide A
- 14.30 – 14.55 **Kleopas Palate** (University of York)
Expanding the Scope of Successive Ring Expansion
- 14.55 – 15.10 *Tea/Coffee break (bring your own!)*
- 15.10 **Session 2** Chair: Prof. Andrew Smith (University of St. Andrews, H&S Group Chair)
- 15.10 – 15.35 **Abigail Herbert** (University of Manchester)
Structure and Engineering Methyltransferases to Create Alternative Bioalkylation Pathways
- 15.35 – 16.00 **Vincent Duong** (University College Dublin)
Synthesis of Pyridylsulfonium Salts and their Application in Transition Metal-Free Formation of Functionalised Bipyridines
- 16.00 – 16.25 **Scott Rice** (University of Leeds)
Synthesis of Novel Polyfunctional 3D Scaffolds for Drug Discovery
- 16.25 Closing Remarks. A prize for the best talk will be announced on Twitter shortly after the end of the webinar!

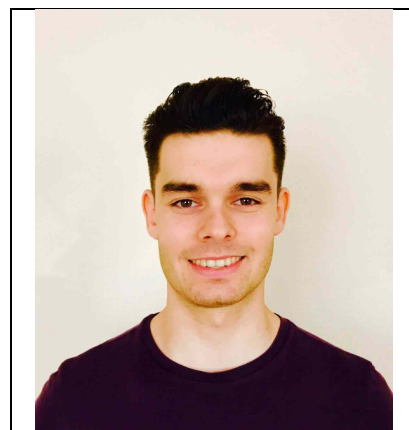
Synthesis of Sulfonimidamides from Sulfenamides via an Unprecedented Alkoxy-amino- λ^6 -sulfanenitrile Intermediate¹

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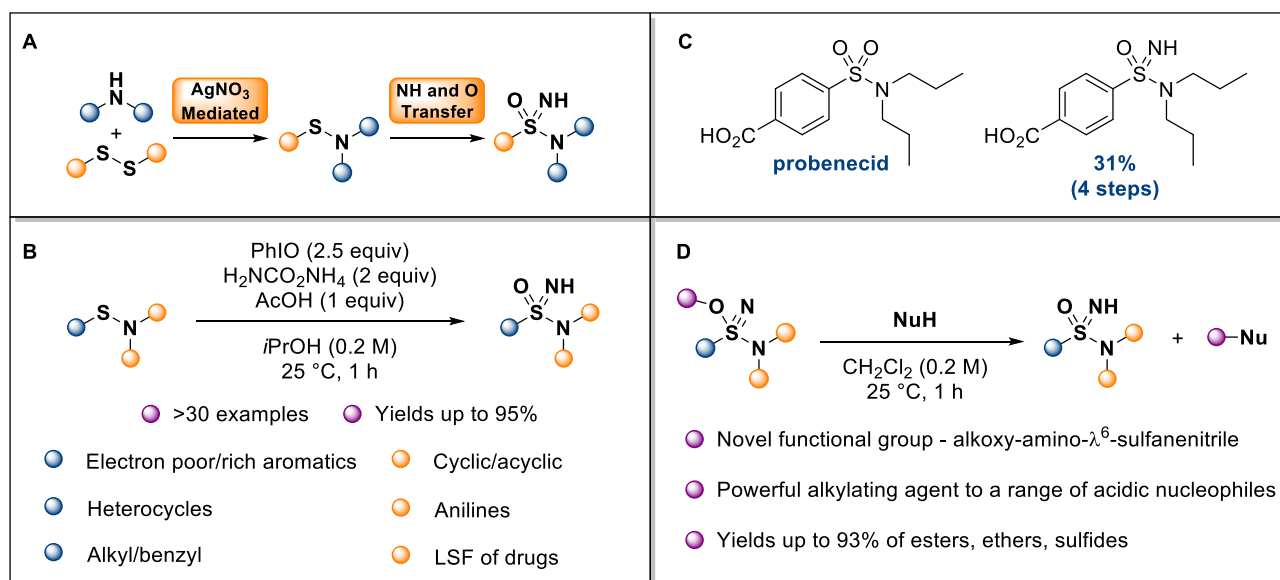
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The adoption of unusual functional groups into medicinal and agrochemical research programmes provides enhanced coverage of both chemical and intellectual property space.² In this regard, sulfoximines and sulfonimidamides, the mono-aza analogues of sulfones and sulfonamides respectively are receiving considerable attention as bioisosteres in drug design.³ Reports of biologically active examples of sulfonimidamides including the aza-analogues of sulfonamide drugs celecoxib⁴ and tasisulam⁵ have aroused interest in these emerging functional groups. However, restrictive synthetic methods have, in part, limited the utility of these motifs in the life sciences.⁶ Here, we report the development of a new strategy for the direct synthesis of NH-sulfonimidamides from sulfenamides as stable and previously unexplored substrates. This sequence enables access to sulfonimidamide scaffolds in just two straightforward steps from commercially available starting materials (**A**).¹

A highly selective one-pot NH and O transfer is achieved using a hypervalent iodine reagent, iodosobenzene, as an oxidant, along with ammonium carbamate as an easy-to-handle source of ammonia. These conditions are mild and selective and allow for a broad variety of sulfonimidamides to be synthesised, including late stage functionalisation reactions on amine containing drugs desipramine and fluoxetine (**B**). The method was used in the synthesis of an aza-analogue of the sulfonamide drug probenecid, as well as displaying possible useful N-functionalisation reactions on this scaffold, demonstrating the utility of the methodology for medicinal chemistry (**C**). Detailed mechanistic studies have been carried out and in the absence of added acid, an unprecedented alkoxy-amino- λ^6 -sulfanenitrile is isolated as a reaction intermediate. The isolation and characterisation of several examples of this novel species identifies the solvent as one source of the oxygen atom in the product. These newly formed alkoxy-amino- λ^6 -sulfanenitriles act as powerful alkylating agents to a range of acidic nucleophiles (**D**).



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Sequential Photochemical and Prins Reactions for the Diastereoselective Synthesis of Tricyclic Scaffolds

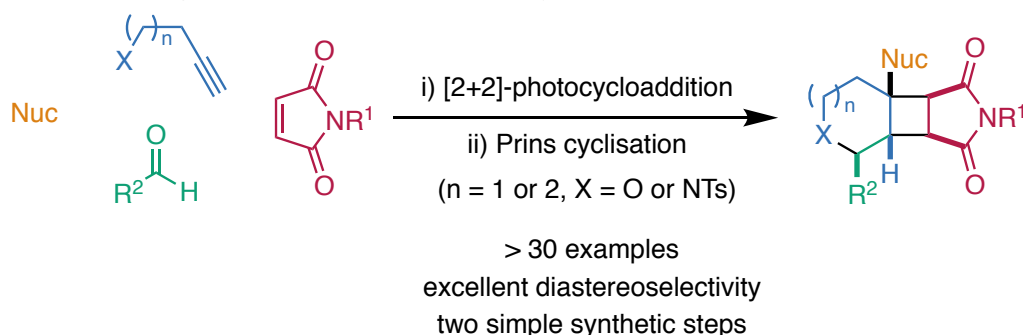
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Structures rich in sp^3 centres are underrepresented in drug discovery, despite the evidence that conformationally restricted small molecules can prove versatile scaffolds in medicinal chemistry.^{1,2} Among these, saturated heterocycles have been particularly successful although their use in industry has been limited partially due to the lack of methods for their synthesis. Reaction sequences that rapidly build up molecular complexity from simple starting materials with multiple sites for further derivatisation are therefore of great value to medicinal chemistry.



Scheme 1 – Synthesis of tricyclic scaffolds through photochemical and Prins cyclisations

Recently, our group developed an efficient two-step process to transform four simple, cheap and readily available starting materials into tricyclic structures with excellent diastereoselectivity. To the best of our knowledge, the reaction constitutes the first example of a cyclobutene undergoing Prins cyclisation to give a cyclobutane fused tetrahydropyran.³

[2+2]-Photocycloaddition of maleimide and homopropargyl alcohol gives a cyclobutene alcohol which can be reacted with an aldehyde under acidic conditions in the presence of a nucleophile to give the cyclised products. Optimisation using design of experiments allowed a 30% increase in the reaction yield and computational work has been carried out to rationalise the observed stereochemistry.

Through this reaction, formation of five new contiguous stereocentres and multiple sites for further diversification make these products attractive for use as drug-like scaffolds. Successful nucleophiles in the reaction include acetonitrile, which leads to the amide product upon hydrolysis, and tetrafluoroboric acid which gives the tertiary fluoride. Numerous aldehydes are tolerant to the reaction conditions as well as various maleimide protecting groups.

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New Functionality-Rich Boronic Acid Scaffolds

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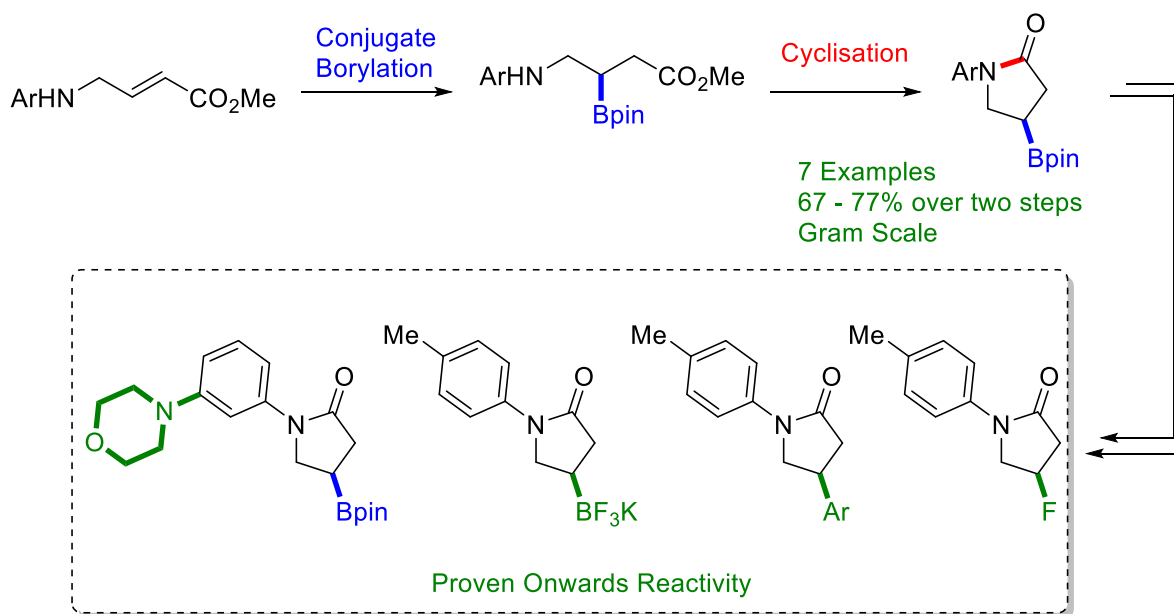
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C-sp³-rich building blocks are of much interest to medicinal chemistry due to the drive for drug candidates to have more “three-dimensional” characteristic.¹ Access to saturated heterocyclic boronic acid derivatives is lacking in comparisons to their heteroaromatic counterparts. Given this access to libraries of C-sp³-rich heterocyclic scaffolds for pharmaceutical research and development are seen as highly desirable.

We have developed a protocol to access 4-pinacol boronic ester δ -lactams, through a process of conjugate borylation and lactamisation. Furthermore, we have shown that these scaffolds are useful chemical building blocks through exploring their further reactivity. Compatible transformations include oxidation, Suzuki-Miyaura cross coupling, homologation and fluorination chemistry.²⁻⁴



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Unprecedented γ -Selectivity in the Palladium-Catalysed Asymmetric Allylic Alkylation of Siloxyfurans

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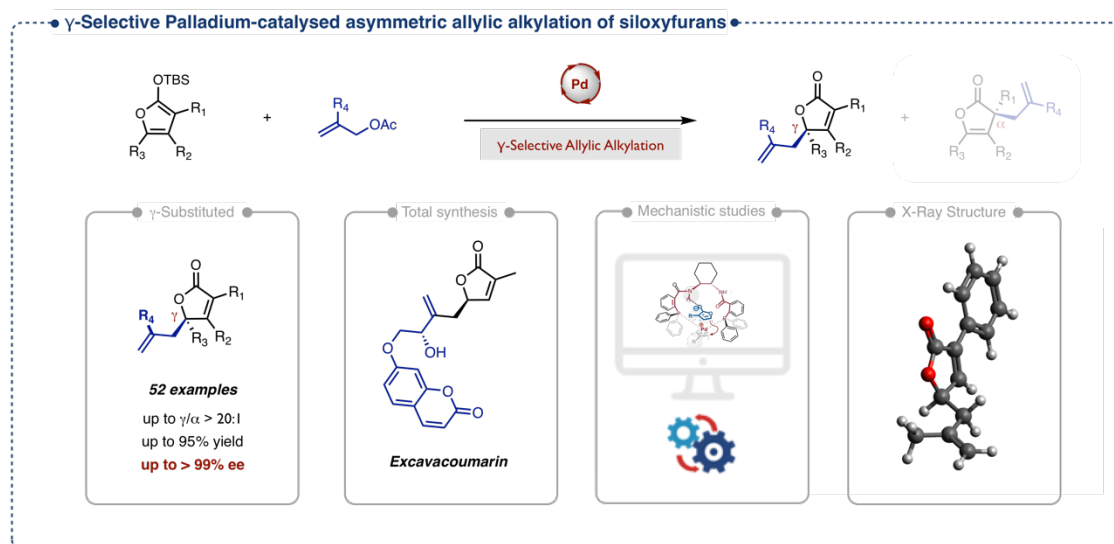
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The asymmetric allylic alkylation reaction is now recognised as a particularly attractive tool for the construction of C-C bonds and to set the configuration of quaternary and tertiary carbon stereogenic centres. When applied to butenolide precursors, this reaction has always shown to exhibit an α -selectivity independently of how the reactive dienolate intermediate is generated.^[1] Interestingly, when using *tert*-butyldimethylsiloxyfurans in conjunction with 2-substituted allyl acetates, we were able to trigger a complete regioselectivity shift favouring the formation of the γ -allylated product (γ/α up to >20:1) with concomitant increase of the enantioselectivity (up to >99% ee). The method was successfully applied to more than 50 butenolide precursors and is currently being used as a key step in the synthesis of a series of *O*-terpenoidal coumarin natural products known as excavacoumarins. Mechanistic studies reinforced by DFT calculations enabled to rationalise the shift in the regioselectivity and the enhanced enantiodiscrimination obtained on the γ -regioisomer.



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Towards the Total Synthesis of (+)-Lophotoxin

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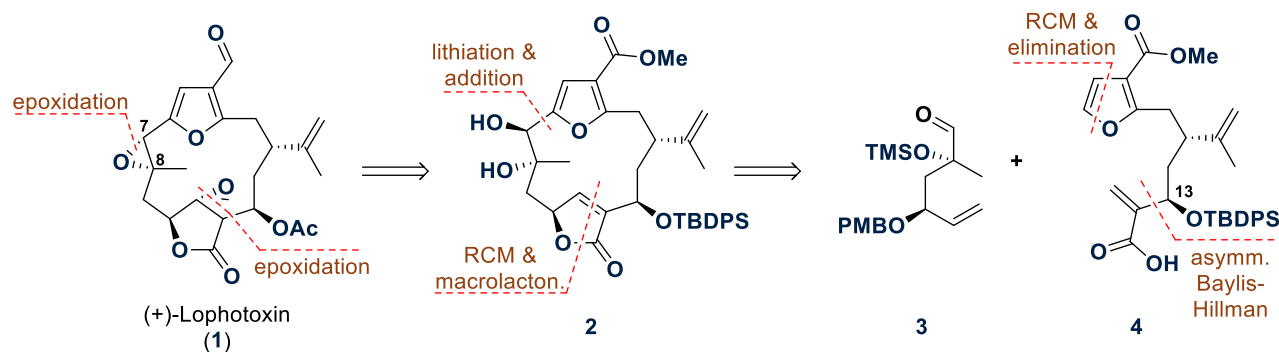
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(+)-Lophotoxin (**1**) was first isolated in 1981 from pacific sea whips (Lophogorgia) by Fenical and co-workers [1]. It is highly toxic and acts as irreversible antagonist of nicotinic acetylcholine receptors [1,2]. Syntheses of other furanocembranoids and fragments (+)-Lophotoxin (**1**) have been reported. However, a method to install epoxide C-7/8 in the correct configuration within the 14-membered macrocycle, and therefore a synthesis of (+)-Lophotoxin (**1**), remains elusive.

Our approach is based on two late-stage epoxidation reactions of intermediate **2**. Ring-closing metathesis (RCM), macrolactonisation and fragment coupling via aldehyde addition reaction are the key disconnections leading back to coupling partners **3** and **4**. Applying an RCM based furan methodology developed by our group,[5] we synthesised fragments **3** and **4** on gram-scale. The stereocentre C-13 was successfully installed by means of an organocatalytic, asymmetric Baylis–Hillman reaction. Following the described strategy, the carbon skeleton of (+)-Lophotoxin was successfully assembled.



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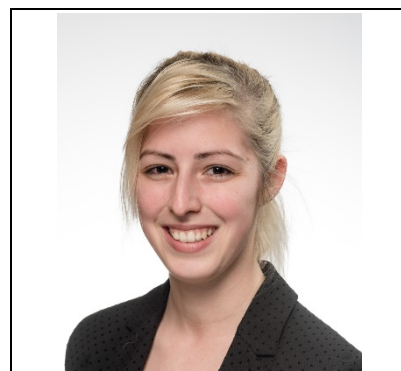
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Enantioselective Palladium and Isothiourea Dual Catalysis

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Dual catalytic processes that employ two catalysts in a one pot setup are attractive reactions that allow for efficient and complexity inducing transformations.¹ Combining transition metal catalysis and organocatalysis is of particular interest, as it allows for the combination of their unique modes of activation and new opportunities for stereocontrol, yet requires catalyst compatibility to ensure inhibition is not observed.² This has been successfully showcased in recent examples using palladium catalysis and isothiourea Lewis base catalysis.^{3,4} Commonly, an electrophilic palladium π -allyl species and a nucleophilic isothiourea bound ammonium enolate are employed as reactive intermediates. Even though the compatibility of palladium and isothiourea catalysis has been demonstrated, the combination of α,β -unsaturated acyl ammonium catalysis and palladium catalysis has not been reported and is the subject of this investigation.

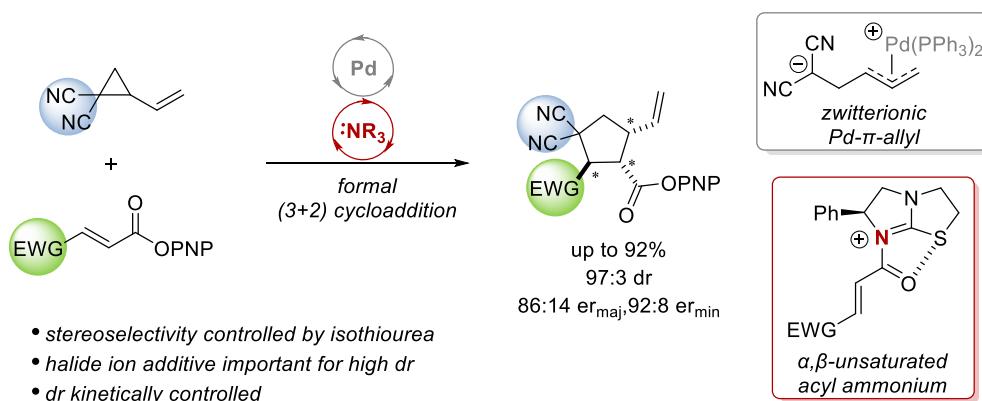


Figure 1 Enantioselective palladium and isothiourea dual catalysis

This project showcases the symbiosis between palladium catalysis and isothiourea Lewis base catalysis using zwitterionic palladium π -allyl species and α,β -unsaturated acyl ammonium species as the reactive intermediates (Figure 1). The enantioselective formal (3+2) cycloaddition between activated vinyl cyclopropanes and α,β -unsaturated esters leads to highly functionalised cyclopentane products with multiple contiguous stereocentres. Initial results show promising reactivity and selectivity, giving products in up to 92% yield, 97:3 dr, and 86:14 er_{maj}. Control experiments highlight the importance of both catalysts for the transformation and reveal interesting aspects of the reaction mechanism. The scope and limitations of this dual catalytic transformation will be reported.

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Desulfinate Cross-Couplings: Mechanistic Insights for Reaction Optimisation

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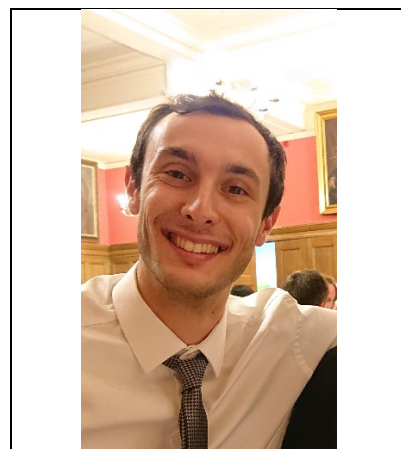
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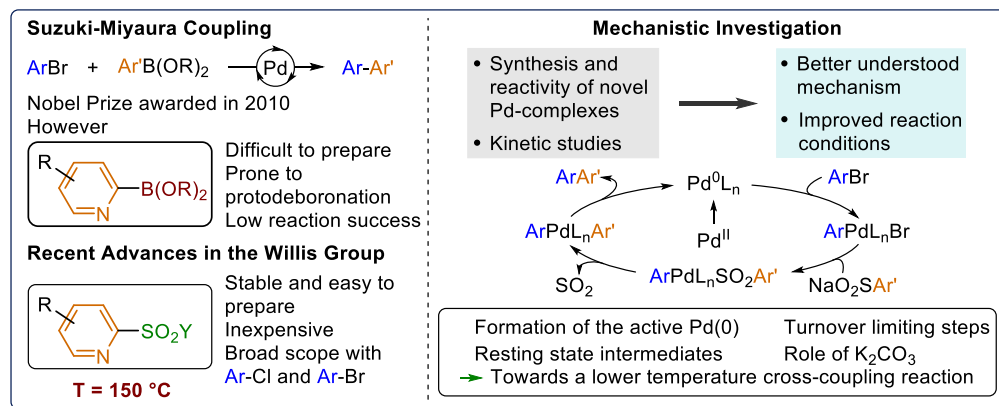
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The Suzuki-Miyaura reaction has undeniably revolutionised the art of synthesis, particularly in the pharmaceutical industry. However, the coupling of 2-pyridine boronic acids has long remained a challenge.[1] Indeed, these heterocyclic nucleophiles are hard to prepare, unstable, and prone to decomposition under typical cross-coupling conditions. In this context, the Willis group has recently reported the use of sulfinate salts as efficient alternatives to boron-based reagents.[2]

Despite the robustness and broad scope of this newly developed reaction, the necessity of high temperatures is a problem that needs to be tackled for this method to be more appealing. To address this issue, we have recently investigated the mechanism of such desulfinate coupling reactions and shed light on the challenges that must be overcome to deliver improved, lower temperature versions of these synthetically important transformations.[3]



The synthesis and characterisation by X-ray crystallography of novel aryl palladium sulfinate complexes have allowed us to deconvolute the elementary steps of the cross-coupling reaction. In combination with kinetic studies, we were able to identify the catalyst resting states and turnover limiting steps of the reaction, and discovered that their nature depend on the nature of the sulfinate salt employed. The role of the potassium carbonate base was also investigated, the use of which is crucial for high yield reactions.

We are currently working on using this extensive experimental dataset in combination with DFT calculations to design novel ligands for lower temperature reactions.

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(b) **de Gombert, A.**; Willis, M. C. *Trends Chem.* **2020**, 10.1016/j.trechm.2020.04.004

An Iterative Approach to the Stereocontrolled Total Synthesis of Bahamaolide A

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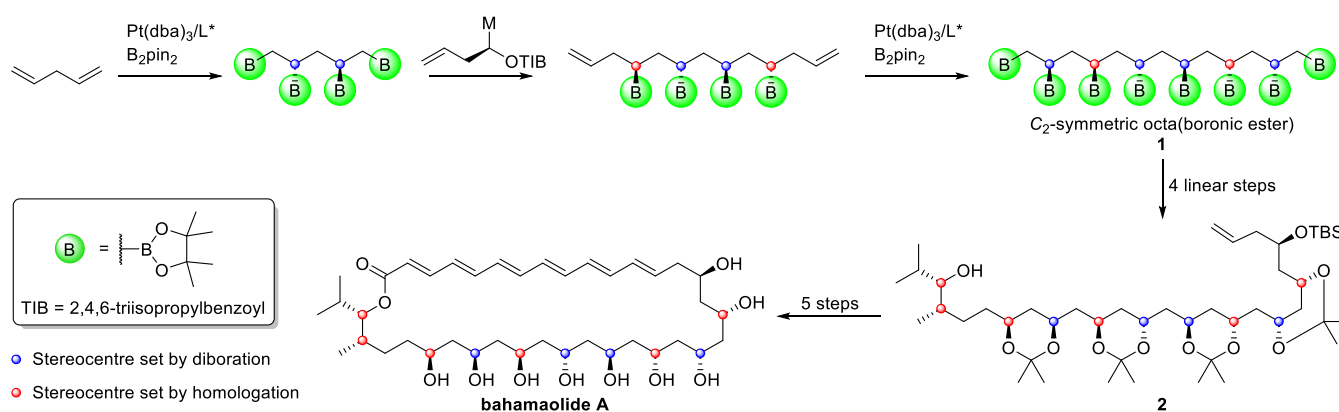


Polyketide-derived natural products are of particular interest due to their highly specific and potent biological activity and structural diversity. A common structural motif among polyketide synthase metabolites is the (*syn*- or *anti*-) 1,3-diol unit, or higher order 1,3-polyol arrays.

Bahamaolide A is an oxopolyene macrolide with potent antifungal activity, isolated from a *Streptomyces* species, cultured from a sediment sample from North Cat Cay, Bahamas.¹ There are no reported syntheses of bahamaolide A in the literature to date.

The key synthetic challenge is the extended 1,3-polyol unit, comprising 9 stereodefined contiguous but skipped hydroxyl groups. Previous work in the Aggarwal group demonstrated the stereocontrolled synthesis of secondary-secondary and secondary-tertiary 1,3-diols by performing lithiation–borylation reactions with 1,2-bis(boronic esters),² which can be obtained through asymmetric diboration of terminal alkenes.³ Iterative enantioselective alkene diboration and reagent-controlled homologation with a homoallylic benzoate would enable the construction of a stereodefined 1,3-polyol. No repetitive oxidation level changes or functional group interconversions are necessary between iterations, since the boronic esters both mask the hydroxyl functionality, which can be revealed in a later stereospecific oxidation, and enable the homologation through lithiation–borylation reactions.

Our synthetic approach to bahamaolide A focused on the rapid construction of the key *C*₂-symmetric octa(boronic ester) building block **1**. The merging of catalyst-controlled diboration and reagent-controlled homologation in a bidirectional manner enabled its preparation in just 3 steps from 1,4-pentadiene, setting 6 stereocentres. Sequential homologation at the terminal primary boronic esters followed by oxidation of all 8 boronic esters and acetonide protection afforded advanced intermediate **2** which contains the entire stereodefined 1,3-polyol motif of bahamaolide A. **2** can then be transformed to the natural product in a further 5 steps to complete the first total synthesis of bahamaolide A. Currently we have a sample of crude synthetic bahamaolide A awaiting purification.



Expanding the Scope of Successive Ring Expansion

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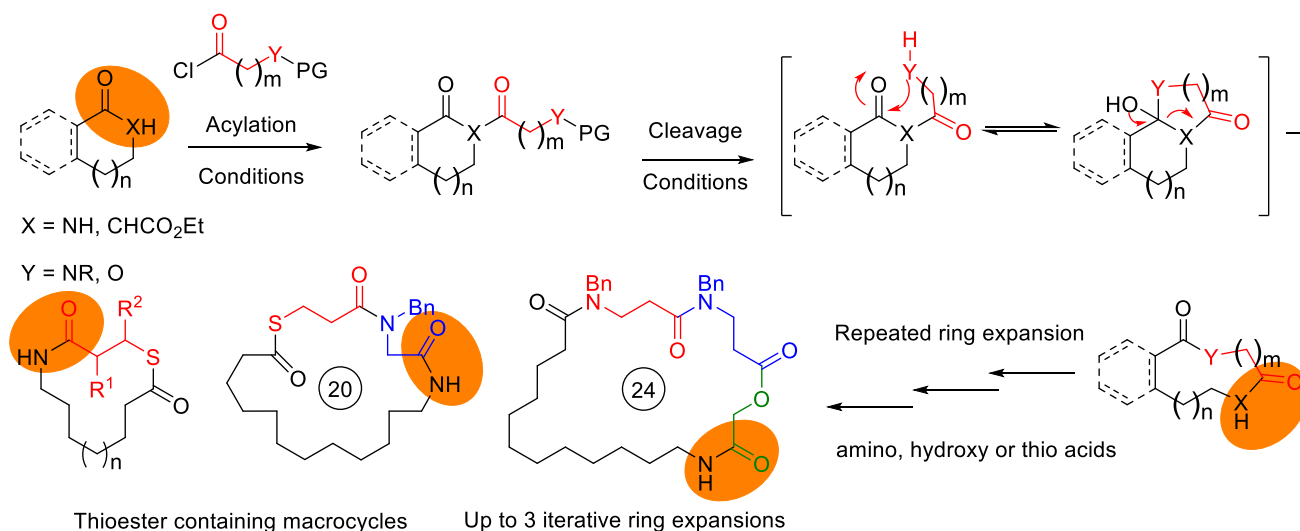


Most cyclic compounds are synthesized *via* the cyclization of a linear precursor, typically carried out towards or at the end of a synthesis. However, this approach often requires high dilution conditions to avoid undesired intermolecular reactions leading to dimer or oligomer formation. Successive Ring Expansion (SuRE) chemistry developed in the Unsworth group can be utilized to 'grow' macrocyclic lactams or β -keto esters *via* sequential ring enlargement reactions. There are two variations of SuRE, depending on whether a β -keto ester or a lactam is used as a starting material.

Ring expansion reactions occur over two sequential steps. A cyclic molecule is first acylated with an amino, hydroxy, or thio acid derivative. Following this, a spontaneous ring expansion reaction proceeds *via* a transient bicyclic intermediate. Crucially, this process yields a product with the same functionality as the starting material, allowing the product of the reaction to undergo iterative ring expansions.

This works seeks to expand the scope of successive ring expansion chemistry by employing more diverse cyclic lactams and amino acid derivatives. The key aim is to introduce new functionality into medium sized rings and macrocycles in order to be explored as novel scaffolds in medicinal chemistry.

To date, conformationally restricted benzannulated lactams and a variety of amino acid derivatives have been synthesized and implemented in ring expansions to access functionalized medium sized rings and macrocycles. The viability of ring expansions can be predicted using computational tools, as covered in a recent publication.⁵ Finally, SuRE has recently been demonstrated to be compatible with thioacids, with novel thioester containing macrocycles accessible for the first time.



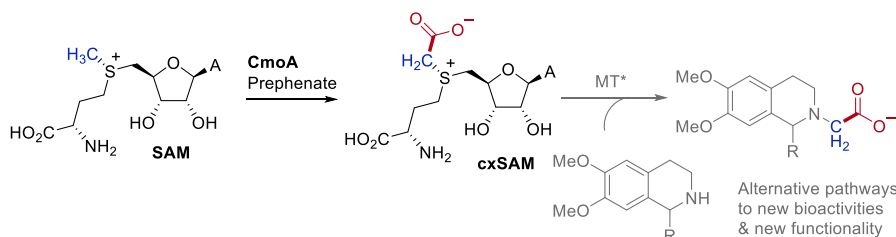
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Structure and Engineering Methyltransferases to Create Alternative Bioalkylation Pathways

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Methylation is one of the most fundamental and common reactions in nature, controlling important cellular functions such as gene expression and modulate the bioactivity of therapeutically important natural products, including antibiotics. It is well recognised that the addition of a single methyl group can have a significant effect on a molecule's physical properties, with the 'magic methyl effect' utilised to tune the bioavailability and pharmacokinetics of drugs. S-adenosyl-L-methionine (SAM)-dependent methyltransferases (MTs) catalyse the majority of methylation reactions in cells, utilising the ubiquitous cofactor SAM as an electrophilic source of CH_3 for transfer to a vast array of small metabolites, including bioactive natural products, proteins, DNA and other biomacromolecules with exquisite chemo- and regio-selectivity.

The innate promiscuity and versatility of many known MTs has been exploited to reprogram nature's major methylation pathway to perform highly selective non-native alkylation reactions of both synthetic and biological molecules. The majority of artificial SAM-analogues active with WT and engineered MTs are short chain unsaturated moieties that overcome increased active site steric strain through conjugative stabilisation of the transition state. However, the discovery of the only known naturally occurring SAM analogue, carboxymethyl-SAM (cxSAM), provides an exciting opportunity for the development of orthogonal alkylation pathways both *in vitro* and *in vivo*, overcoming many of the pitfalls associated with synthetic and exogenous SAM analogues (not limited to; high cost, low stability, arduous purification, competitive SAM activity and inactive diastereoisomers).

Recently, we determined the first crystal structure and established the substrate scope of a key MT enzyme, coclaurine-N-MT (CNMT), involved in the production of plant secondary metabolite N-methyl tetrathydroisoquinolines (THIQs), a privileged scaffold intermediate in the formation of a variety of bioactive benzoisoquinoline alkaloids.¹ In one of our most recent manuscripts, we rationally engineer MTs (inc. CNMT) with improved selectivity for cxSAM, and demonstrate how these 'orthogonal' MTs can be combined with CmoA to create new tandem enzymatic carboxymethylation pathways; generating novel carboxymethylated natural products possessing the THIQ pharmacophore.² In addition, we provide an enzymatic route to a new co-factor, carboxyethyl-S-adenosylethionine (cxSAE), and demonstrate how WT and engineered MTs can transfer the chiral carboxyethyl substituent from cxSAE to acceptor substrates with complete stereoselectivity (100 % e.e.). This research describes the first example of how CmoA and cxSAM can be combined with MTs to create new carboxymethylation pathways; also demonstrating the ability of MT to catalyse the stereoselective transfer of a chiral functional group from a SAM-like co-factor. The addition of a negatively charged carboxyl group can dramatically change the properties of target compounds which can lead to new functions and bioactivity, also provide a chemical handle for further derivatisation and conjugation. This work was also recently featured in a *Nature Chemistry*.³

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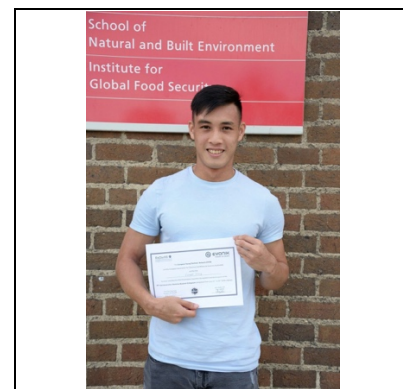
3. Work covered in *Nature Chemistry*, 2020; (<https://rdcu.be/b6kVm>)

Synthesis of Pyridylsulfonium Salts and their Application in Transition Metal-Free Formation of Functionalised Bipyridines

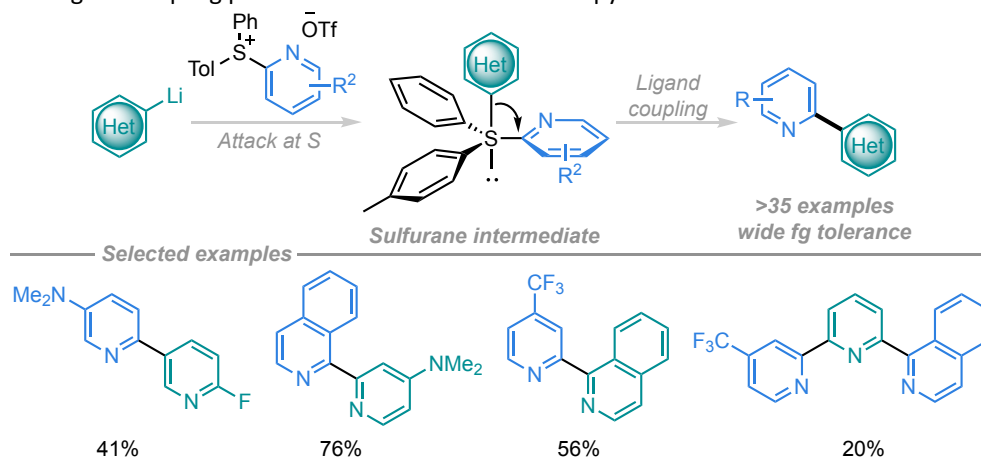
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Sulfonium salts have garnered considerable attention of late and their capability as a synthetic handle enables a multitude of reactions,¹ thus it is important to have a range of methods to access sulfonium salts. However, even with their synthetic potential to facilitate bond formation, heterocycle-heterocycle coupling mediated by sulfonium salts are under reported. Bis-heterocycles are very common motifs in organic synthesis, medicinal chemistry, and materials chemistry, especially the bipyridine core. Methods of accessing bipyridines are quite important and current methods have limitations and mainly involve the use of costly transition metals.² Recently, some metal-free protocols^{3,4} have been developed but none using sulfonium salts. Herein, we demonstrate a novel S-selective synthesis of an unexplored reagent class, pyridylsulfonium salts, and apply them in a highly modular synthesis of functionalised 2,2' and 2,3'-bipyridines.⁵ We developed a Cu-catalysed S-selective arylation of pyridylsulfides (9 examples). Electronically varied and sterically hindered pyridylsulfonium salts could be synthesised in good to excellent yields. We subsequently applied them in metal-free ligand coupling protocol with organolithiums to form a large scope of bipyridines (>35 examples). Electron-rich, electron-poor and dihalogenated systems were well tolerated in different substitution patterns. The ligand-coupling methodology also proceeded efficiently in the presence of trifluoromethyl and fluoro groups, two functionalities that are prevalent in medicinal chemistry. Our methodology is quite robust and tolerates a significant range of functionalities. In addition to this, the system is modular and enables access to a broad scope of ligands that were difficult to access previously using transition metal protocols. An iterative synthesis of a novel, unsymmetrical terpyridine, a privileged class of ligands, was also accomplished using our methodology. In conclusion, two new methods have been developed, firstly a versatile synthesis of pyridylsulfonium salts, followed by their use in a transition metal-free ligand coupling protocol to form functionalised bipyridines.



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Synthesis of Novel Polyfunctional 3D Scaffolds for Drug Discovery

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The control of molecular properties is essential in the design of new bioactive compounds, due to the inherent link between the molecular properties of lead compounds and their successful progression through the stages of clinical development. By preparing screening libraries that better target lead-like chemical space, any desirable compounds can then be grown through the optimisation stage of the drug discovery process, in terms of their molecular weight, lipophilicity and complexity to better target optimal drug-like chemical space. Therefore, a set of guidelines have been established in order to better aid the design of lead-like molecules.¹ In order to realise efficient lead-oriented synthesis, two separate “bottom-up” synthetic approaches have been employed. In both cases, simple commercially available starting materials have been functionalised to prepare cyclisation precursor molecules that contain various reaction handles in their core structure. A toolkit of cyclisation reactions has then been developed and utilised in order to cyclise between these reaction handles to prepare libraries of novel sp^3 -rich diverse scaffolds that are able to target lead-like chemical space. Each of the scaffolds prepared contains between 1-3 points of diversification that can be subsequently decorated to create a large number of lead-like screening compounds.

