RSC Heterocyclic and Synthesis Group 1st Postdoc Symposium (Virtual Format)
Thursday 8th/Friday 9th July 2021

Thursday 8th July

13.00 – 13.05	Opening remarks (Dr Susannah Coote, Lancaster University, H&S Group Secretary/Treasurer)
13.05	**Session 1** Chair: Dr Marc Kimber (Loughborough University)
13.05 – 13.40	**Dr Joshua Tibbetts** (University of Bath) *Photocatalytic α-C–H functionalisation of unprotected primary amines*
13.40 – 14.15	**Dr Sundaravel Vivek Kumar** (University College Dublin) *Development of a Novel Family of para-Cyclophane-based Chiral N,O-Ligands for Asymmetric Catalysis*
14.15 – 14.50	**Dr Rebecca Clarke** (University of Glasgow) *Synthesis of Carbazole-Derived Amino Acids as New Fluorescent Probes*
14.50 – 15.00	*Tea/Coffee break (bring your own!)*
15.00	**Session 2** Chair: Dr Nadia Ahmad (Charles River)
15.00 – 15.35	**Dr James Donald** (University of York) *Bifunctional Vector-Specific 3-D Building Blocks for Fragment-Based Drug Discovery*
15.35 – 16.10	**Dr Matthew Leech** (University of Greenwich) *Achieving the Impossible with Electrosynthesis*
16.10 – 16.55	**Prof. Mark Levin** (University of Chicago) *Advancing Single Atom Logic for Skeletal Editing*
16.55	Closing Remarks (Prof. Andrew Smith (University of St. Andrews, H&S Group Chair)

Friday 9th July

13.00 – 13.05	Opening remarks (Dr Susannah Coote, Lancaster University, H&S Group Secretary/Treasurer)
13.05	**Session 3** Chair: Prof. Rob Stockman (University of Nottingham)
13.05 – 13.40	**Dr Stefan Roesner** (University of Warwick) *Synthesis of sp^3-rich cyclic hydrazine frameworks for drug discovery*
13.40 – 14.15	**Dr Wei Sun** (University of Southampton) *Sequential Thermal and Photochemical Ring Expansions for the Synthesis of 8-Membered Nitrogen Heterocycles from Cyclobutenones*
14.15 – 14.50	**Dr Antonio Romero Arenas** (University of Sheffield) *Atroposelective Strategies for the Synthesis of Axially Chiral Heterobiaryls and Chan-Lam Amination of Alkyl Boronic Esters*
14.50 – 15.00	*Tea/Coffee break (bring your own!)*
15.00	**Session 4** Chair: Nessa Carson (Syngenta)
15.00 – 15.35	**Dr Adam Green** (University of Pennsylvania) *Photochemical Synthesis of an Epigenetic Focused Tetrahydroquinoline Library*
15.35 – 16.20	**Prof. Sophie Rousseaux** (University of Toronto) *New Strategies for the Synthesis and Functionalization of Cyclopropanols and Nitriles*
16.20	Closing Remarks (Prof. Andrew Smith (University of St. Andrews, H&S Group Chair)

Photocatalytic α-C–H Functionalisation of Unprotected Primary Amines

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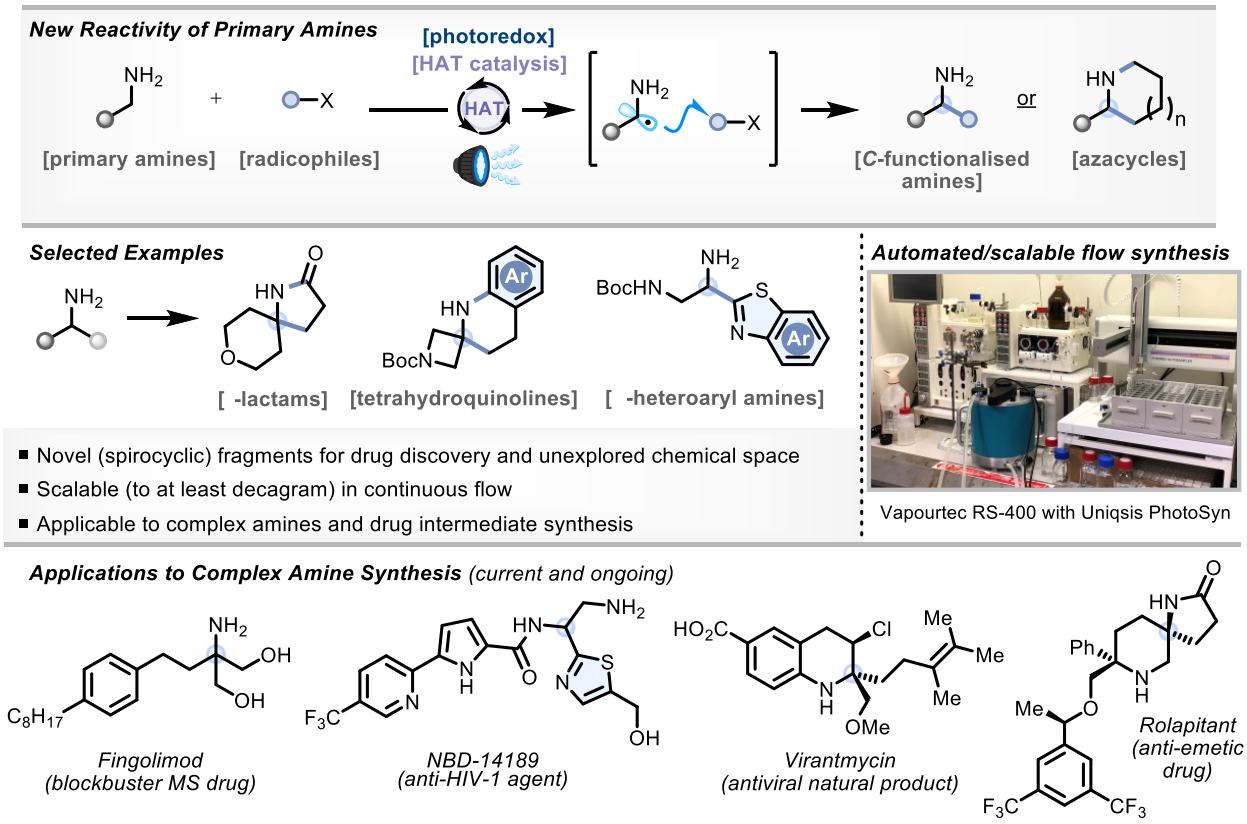
We have recently found that primary aliphatic amines without *N*-protection can be employed directly in photoredox catalysis to form new C–C bonds α- to nitrogen, using a variety of radicophiles as coupling partners.[1–3] This is a key advance for amine synthesis, providing a highly simplifying disconnection for α-tertiary amines and saturated azacycles, including spirocycles.

Our strategy uses an organic photocatalyst in combination with a hydrogen atom transfer (HAT) catalyst, and we have so far applied this methodology to the direct synthesis of *C*-alkylated primary amines,[1,2] as well as heterocycles including γ-lactams,[1] tetrahydroquinolines,[3] azetidines[4] and α-(benzo)thiazolyl amines.[4]

These compounds are of significant interest in drug design but can be cumbersome to access using current state-of-the-art. The scalability of our chemistry has also been demonstrated in continuous flow (up to decagram scale), and we have recently applied this methodology to a single-step synthesis of the blockbuster drug Fingolimod.[3]



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Development of a Novel Family of *para*-Cyclophane-Based Chiral *N*,*O*-Ligands for Asymmetric Catalysis

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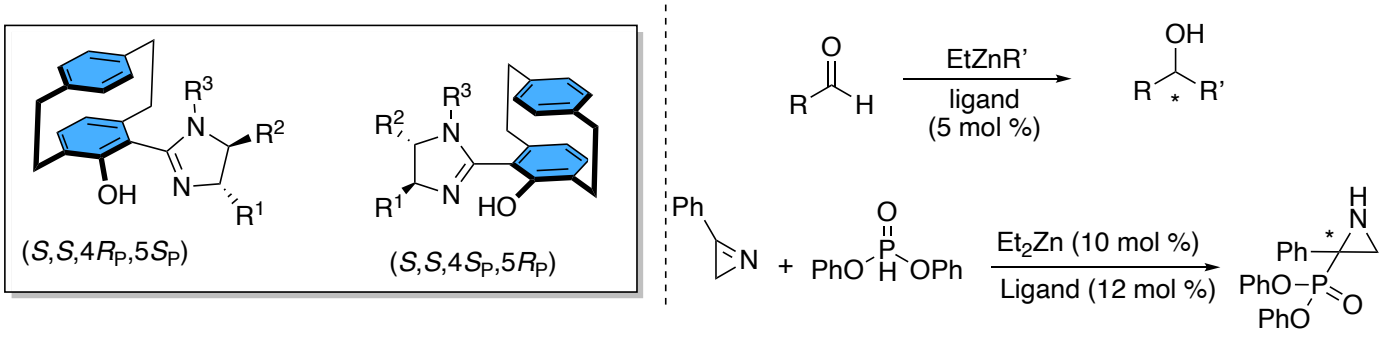
Planar chiral compounds are fascinating types of frameworks, utilised in various fields in chemistry including asymmetric catalysis. Our group has developed several ferrocene-based planar chiral ligands which have demonstrated their potential as ligands in various asymmetric transformations.[1] [2.2]Paracyclophane, another class of planar compounds which possesses unique electronic and steric properties, has advantages over ferrocene-based systems that have also been employed as promising ligands in asymmetric catalysis.[2]

In general, based on a disubstitution pattern only three types of the systems, namely *ortho*, *pseudo-ortho* and *pseudo-geminal* have been investigated extensively. In particular, *ortho*-substituted [2.2]paracyclophanes offer a high steric crowding which could be more useful in asymmetric catalysis. However, studies are rather limited compared to *pseudo-ortho* and *pseudo-geminal* patterns.[3]

We present the synthesis and resolution of a novel family of planar chiral [2.2]paracyclophane-based imidazolines and preliminary results on their use as efficient ligands for asymmetric ethyl- and phenylzinc additions to aldehydes and the enantioselective reaction of 2*H*-azirines with phosphonate.



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Synthesis of Carbazole-Derived Amino Acids as New Fluorescent Probes

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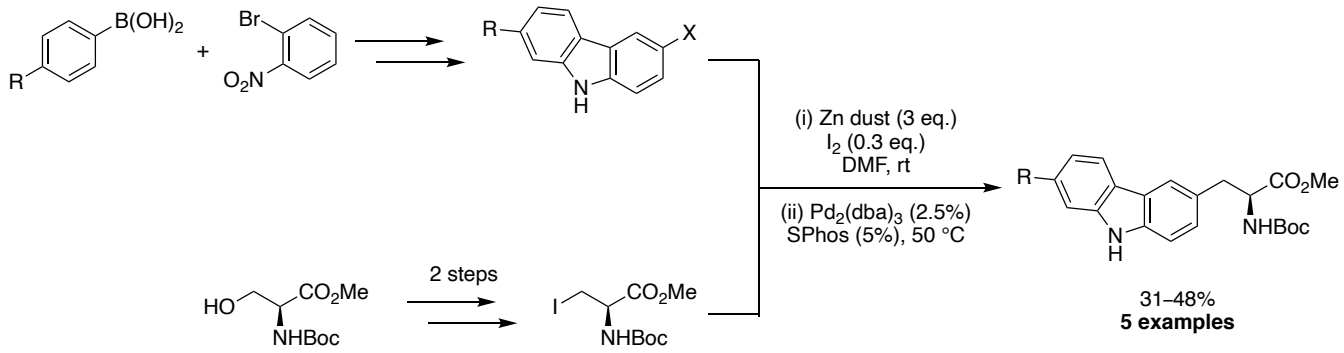
The advent of fluorescence spectroscopy has allowed for the study of biological processes and structures at a level of detail which was previously unattainable. Common targets for imaging studies are naturally occurring proteins and peptides, due to their essential roles in cellular function. However, their limited emission results in poor visualisation. This limitation can be overcome by the incorporation of unnatural, fluorescent amino acids into proteins and peptides, resulting in minimal structural perturbation of the target macromolecule. The main challenge in this research area is striking a balance between the size of the fluorescent side chain and the generation of desirable fluorescent properties.[1–3]

Carbazoles are fluorescent heterocyclic scaffolds which possess desirable photophysical properties and can be easily modified. Carbazole-based chromophores are used in several applications, such as in dye sensitised solar cells[4] and in bioimaging.[5] We present a short and convergent approach to carbazole derived amino acids. A series of 3-halo-carbazoles were prepared using a reaction sequence comprising a Suzuki-Miyaura coupling followed by a Cadogan cyclisation.[6,7] A Negishi coupling of the halogenated carbazoles with 3-iodoalanine allowed access to a library of novel amino acids in good overall yields.[8,9] These carbazole amino acids display interesting optical properties, such as high emission wavelengths (>350 nm) and high fluorescence quantum yields. Further work has led to a synthesis of an Fmoc protected derivative for application in solid phase peptide synthesis. These findings make this class of unnatural fluorescent amino acids promising candidates for fluorescent imaging.



Scheme 1: Synthetic route to novel, carbazole derived amino acids.

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Bifunctional Vector-Specific 3-D Building Blocks for Fragment-Based Drug Discovery

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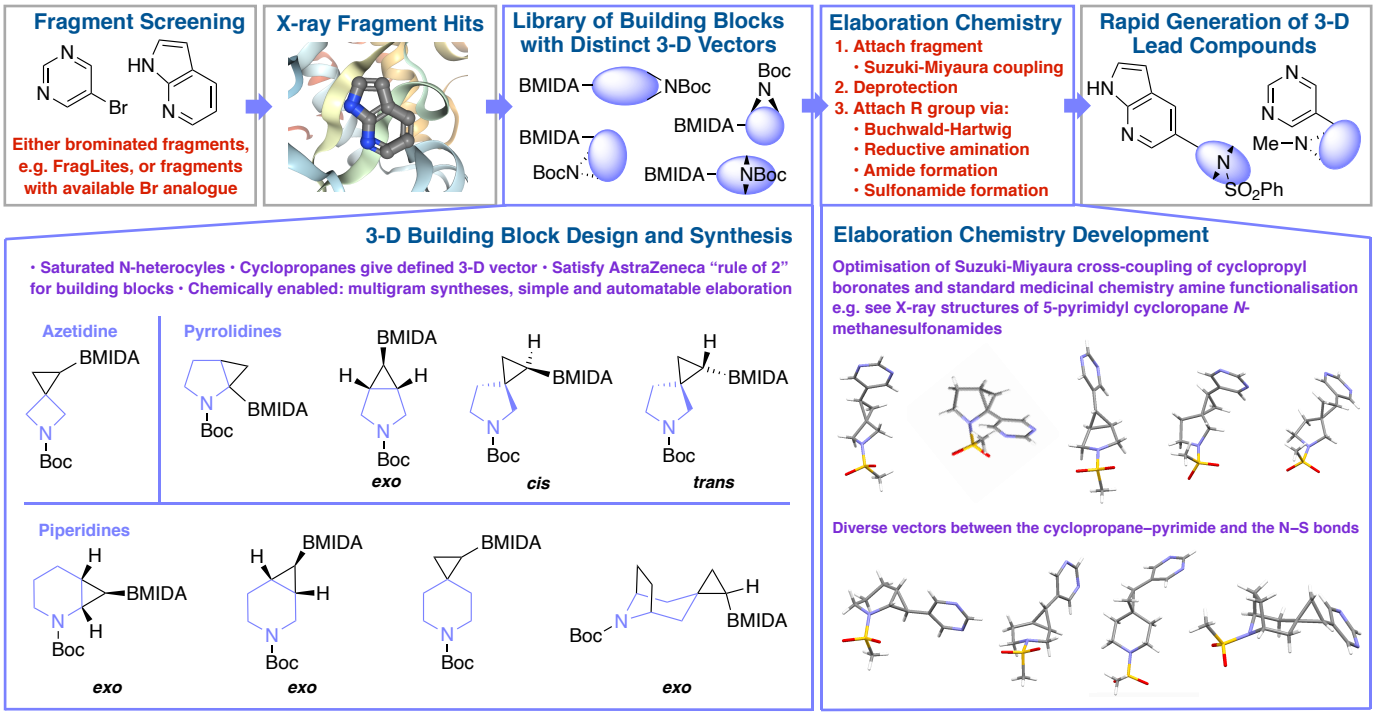
In their 2016 essay on fragment-based drug discovery, Murray and Rees stated that "synthetic organic chemistry is often the rate limiting step in the elaboration of drug fragments" and "ideally it should be possible to synthetically elaborate fragments in 3-D from many different growth points/vectors using methodology that is experimentally worked out prior to fragment screening. This will increase the chance of success during the fragment-to-lead optimisation stage."[1] The O'Brien group are addressing this challenge with a library of bifunctional, vector-specific 3-D building blocks bearing orthogonal cyclopropyl boronate and Boc-protected secondary amine functionalities. Suzuki-Miyaura cross-coupling[2] of an X-ray fragment hit (or brominated analogue) to the cyclopropyl boronate of a 3-D building block from the library will facilitate growth along a specific vector; with subsequent deprotection and elaboration of the amine producing functionality at a known distance and angle to the cyclopropane–fragment bond. This talk will describe the development of multigram synthetic routes to nine cyclopropane-fused small heterocyclic building blocks [now available for purchase through Redbrick Molecular], and the optimisation of reaction conditions to effect Suzuki-Miyaura cross-couplings and *N*-derivatisation at the two orthogonal functional groups. Throughout the design phase care was given to establish a library of building blocks containing members with a diverse set of vectors between the two functional handles in 3-dimensions, hence providing maximal exploration of medicinal chemistry space (see X-ray structures below).



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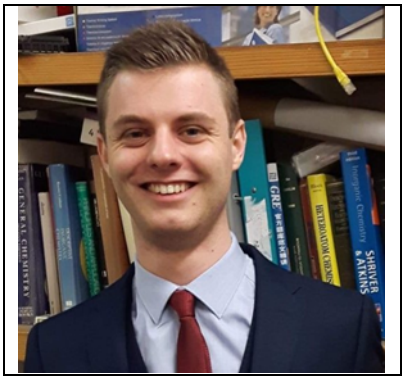
Achieving the Impossible with Electrosynthesis



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Electrosynthesis, the direct use of electrons to achieve chemical transformations, is a powerful and versatile tool for the modern synthetic chemist.[1] Previous obstacles, such as a lack of standardisation, limited reproducibility, and the need for specialist equipment and knowledge have been overcome through the advent of simpler and more user-friendly electrosynthesis setups.[2,3] As a result, the field has been revitalised, with numerous examples of chemical syntheses achieved using electrosynthesis at both laboratory- and industrial-scale.[4,5]

Electrosynthesis represents a greener, more cost-effective, and safer alternative to traditional synthetic methodologies, while avoiding some of the pitfalls of complimentary methods such as photochemistry (e.g. use of expensive photocatalysts, toxic solvents, etc).[6] With the ever-increasing awareness of the environmental impact of chemical synthesis, the field of electrosynthetic chemistry will continue to develop, expand, and flourish.

Through the use of oxidative decarboxylation, we have been able to synthesise a plethora of compounds featuring carbon, oxygen, and nitrogen-centred radicals.[1,7] These can be engaged in a wide range of chemical transformations, including an unusual and rare sp^3-sp^3 cross coupling with electrogenerated alkyl-radicals, in the absence of a transition metal catalyst under ambient conditions.[6] The development of our methodology, alongside its potential applications in other fields, such medicinal and materials chemistry, will be presented.

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Synthesis of sp^3-Rich Cyclic Hydrazine Frameworks for Drug Discovery

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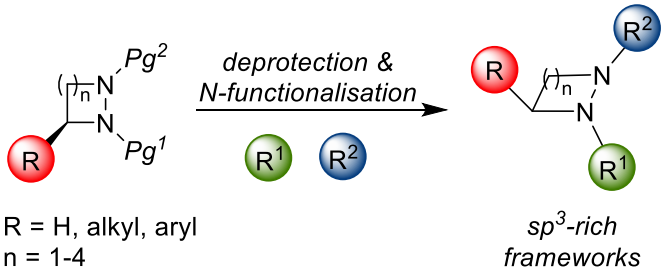
It has been demonstrated that increased molecular complexity correlates with improved chances of success in the drug discovery process.[1,2] Here, strategies for the synthesis of sp^3-rich, non-planar heterocyclic scaffolds suitable for drug discovery are described. Using a variety of chemistries, orthogonally protected, enantiomerically enriched cyclic hydrazines bearing varied C-3 substituents are synthesised. Iterative C–N functionalisation at the two nitrogen atoms using a range of chemistries and coupling partners produces structurally diverse chemical libraries. NMR and crystallographic studies confirm that these frameworks display significant sp^3-character with the nitrogen substituents adopting an *anti*-configuration under the control of a single stereogenic centre through exploitation of the fluxional behaviour of the two nitrogen atoms. This strategy is applied to the synthesis of 1,2-diazetidines[3] and larger cyclic hydrazine frameworks.[4]



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Sequential Thermal and Photochemical Ring Expansions for the Synthesis of 8-Membered Nitrogen Heterocycles from Cyclobutenones

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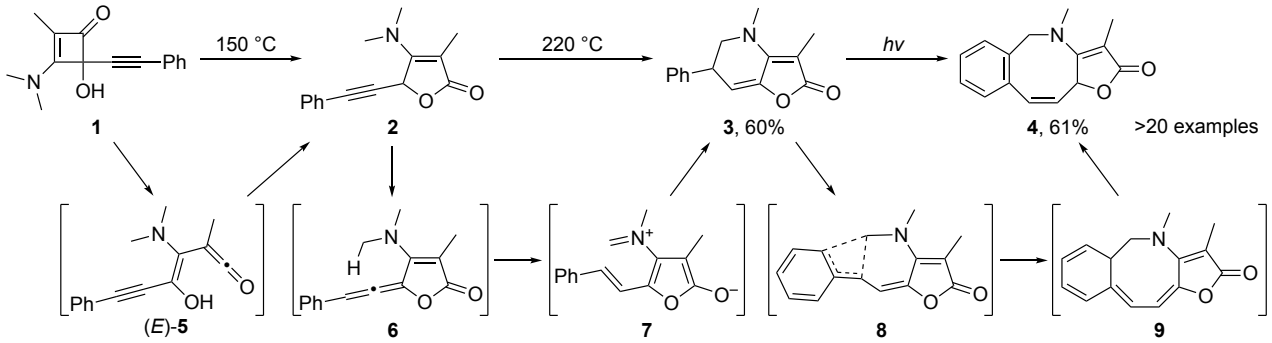
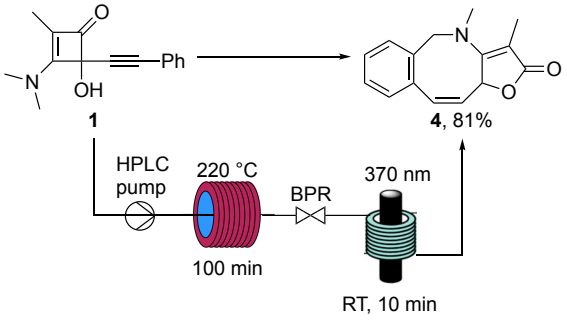
The presentation will describe our development of a series of thermal and photochemical rearrangements for the synthesis of 4-aminofuranones (*e.g.* **2**); furopyridinones (*e.g.* **3**) and benzoazocines (*e.g.* **4**) from alkynylcyclobutenones (*e.g.* **1**) through a sequence of newly discovered ring expansion reactions (Scheme 1). Each steps has an unusual feature. For example, the thermolysis of alkynylcyclobutenones **1** usually give rise to quinones via electrocyclic ring opening to a (*Z*)-vinylketene. However, in this case torquoselectivity in the electrocyclic ring-opening is switched by the amino-substituent such that it opens to vinylketene (*E*)-**5**, which closes to furanone **2**.[1] Further thermolysis of furanone **2** next induces a ring closure to furopyridinone **3**,[2] involving a metal-free C-H activation and annulation sequence. First, a 1,3-hydride shift in the alkynyl chain of **2** forms allene **6**. A 1,5-hydride shift then provides zwitterion **7** which readily undergoes electrocyclic ring closure to furopyridinone **3**.



Scheme 1: Sequential rearrangements for the synthesis of furanone **2,** furopyridinones **3** and benzoazocine **4** from cyclobutenone **1**

The presence of an extended chromophore in **3** prompted us to examine its photochemistry.[3] Pleasingly, when an acetonitrile solution of **3** was irradiated with UVA light (λ_{max} = 370 nm) under continuous flow, it gave benzoazocine **4** in 61% yield (Scheme 1). The mechanistic course of the reaction was examined by DFT, which indicated that the excited state [**3**]* could relax directly to benzoazocine **9** via a 1,3-sigmatropic rearrangement. A [1,5]-sigmatropic H-shift at ambient temperature then restored aromaticity, to give benzoazocine **4** in 61% yield.

Benzoazocine **4** can also be formed from alkynylcyclobutenone **1**, directly and in high yield, by sequencing the respective thermal and photochemical rearrangements under flow (Scheme 2). Thus, subjecting a dioxane solution of cyclobutenone **1** to thermolysis at 220 °C for a residence time of 100 min, then irradiating the resulting solution with 6 × 1.7 W UVA LEDs for 10 min gave benzoazocine **4** in 81% yield. Notably, the efficiency with which cyclobutanone **1** can be prepared from dimethyl squarate ensured that this and several related rearrangements, could be accomplished in just four steps with an overall yield of ~50%.



Scheme 2: A thermal and photochemical daisy-chain reaction

In conclusion, we have developed a new, atom-economic route for the synthesis of 8-ring nitrogen heterocycles from cyclobutenones. The ease with which these products can be prepared from dimethyl squarate in high yield makes this an attractive entry to a class of nitrogen heterocycles that is difficult to access using classical procedures. We are currently seeking to extend the method to other condensed heterocycles of medicinal relevance.

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Atroposelective Strategies for the Synthesis of Axially Chiral Heterobiaryls and Chan-Lam Amination of Alkyl Boronic Esters

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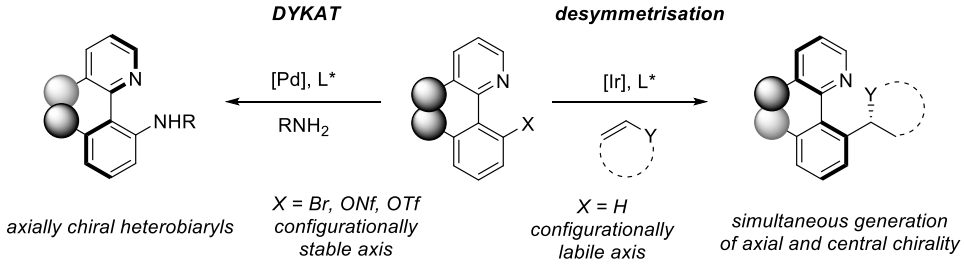
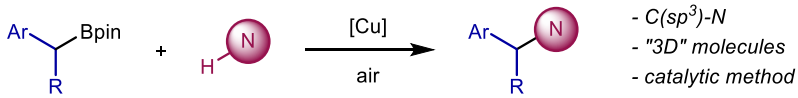
In the first part of this communication, two different approaches to synthesise axially chiral heterobiaryls will be discussed. These strategies rely on the configurational stability of the heterobiarylic starting materials.
The first employs different racemic electrophiles, based on naphthyl pyridines and analogues, which are transformed into the corresponding amines by combining the Buchwald-Hartwig reaction with a DYKAT (Dynamic Kinetic Asymmetric Transformation) strategy.[1] This method enables the formation of IAN-type (*I*soquinoline *A*mino *N*aphthalene) amines in high yield and excellent enantioselectivity.
Secondly, we also describe the deracemisation of configurationally unstable heterobiaryls through an Ir-catalysed hydroarylation of alkenes. This method generates heterobiaryls featuring both central and axial chirality with exquisite control of the regio-, enantio- and diastereoselectivity.[2]



The second section will address the challenging amination of alkyl boronic esters through a catalytic Chan-Lam coupling. Although this reaction has been previously reported in the Partridge group,[3] the coupling of secondary and tertiary benzylic boronic esters presented several limitations: the scope was somewhat limited to anilines, stoichiometric amounts of copper were required, and the reaction has to be conducted under inert atmosphere to avoid oxidation by-products.[4] In this communication, we address this limitation, describing a more general method for the coupling with aliphatic amines under catalytic and aerobic conditions.



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Photochemical Synthesis of an Epigenetic Focused Tetrahydroquinoline Library

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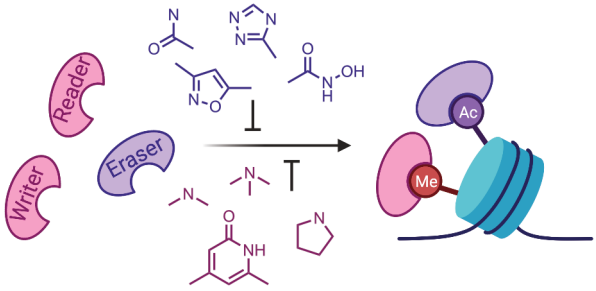
Discovery of epigenetic chemical probes is an important area of research with potential to deliver drugs for a multitude of diseases. However, commercially available screening libraries often used in drug discovery campaigns contain molecules that are focused on a narrow range of chemical space primarily driven by ease of synthesis and previously targeted enzyme classes (e.g., kinases) resulting in low hit rates for epigenetic targets. In an effort to overcome these limitations, we have proposed a new strategy for the design of epigenetic focused compound collections that will augment existing libraries[1] and present our early efforts towards their realization. To showcase this approach we have employed an α-alkylamino radical annulation of maleimides to give a focused compound collection based on the tetrahydroquinoline pharmacophore decorated with privileged isosteres. Cheminformatic analysis showed that our library contained unique chemical matter despite being enriched with known isosteres, demonstrating that new regions of epigenetically relevant chemical space can be accessed using our strategy and may enable the discovery of chemical probes against undrugged epigenetic targets.



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