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Heterocyclic Symposium

TUESDAY

ARENE C–S BOND FORMATION USING IRON TRIFLIMIDE CATALYSIS

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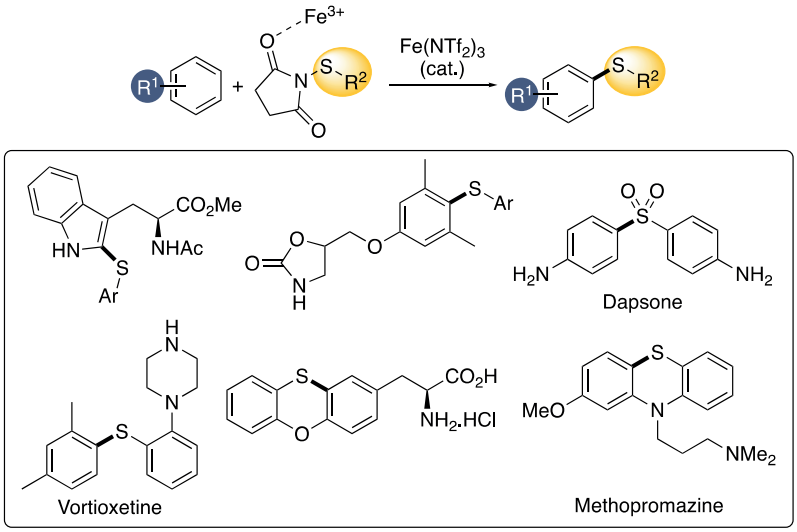
The prevalence of functionalized arenes in many areas of science has meant that the mild, selective synthesis of substituted aromatic compounds is still a key objective of organic chemistry. Our contribution has involved the development of super Lewis acids, such as iron(III) triflimide for the activation of *N*-halogenated succinimides and subsequent regioselective functionalization of arenes.[1] Combined with copper-catalyzed Ullmann-type reactions, this has allowed the one-pot synthesis of aryl C–N and C–O bonds.[2] More recently, we have shown iron(III) triflimide can be used for the direct thioarylation of arenes.[3] This procedure has been used for the late-stage sulfenylation of drug compounds and as the key step for the synthesis of pharmaceuticals such as dapsone and vortioxetine. This reaction has also been used in combination with copper-mediated cyclizations for the synthesis of phenoxathiins and phenothiazines.[4] In these processes, the iron-mediated thioarylation reactions have been accelerated using Lewis bases, resulting in a dual catalytic transformation. This presentation will discuss the development and application of these methods, including recent work involving iron-catalyzed arene thiocyanation.



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PHOSPHODIESTER FOLDAMERS

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The precise three-dimensional secondary structure of biopolymers (proteins, nucleic acids etc.) underpins many biological processes in all living organisms despite being composed of a small alphabet of monomers. Mirroring this conformational control with abiotic building blocks poses an attractive challenge for synthetic chemists. Non-natural oligomers which fold into discrete secondary structures, *foldamers*, have come to the forefront of synthetic research to invent novel architectures with the added challenge of designing inherent features which can cause the molecule to fold.[1-5] Herein, we report investigations into a novel foldamer architecture: aromatic phosphodiesters. Although the phosphodiester bond is present in nucleic acids, its participation in local conformational control is minimal. These foldamers exploit the phosphodiester's excellent hydrogen bond acceptor ability to stabilise the local conformation with a neighbouring aromatic amide group. A library of monomers has been generated and their propensity to form N-H---O=P intramolecular hydrogen bonds (IMHBs) is explored (**Figure 1-a**).

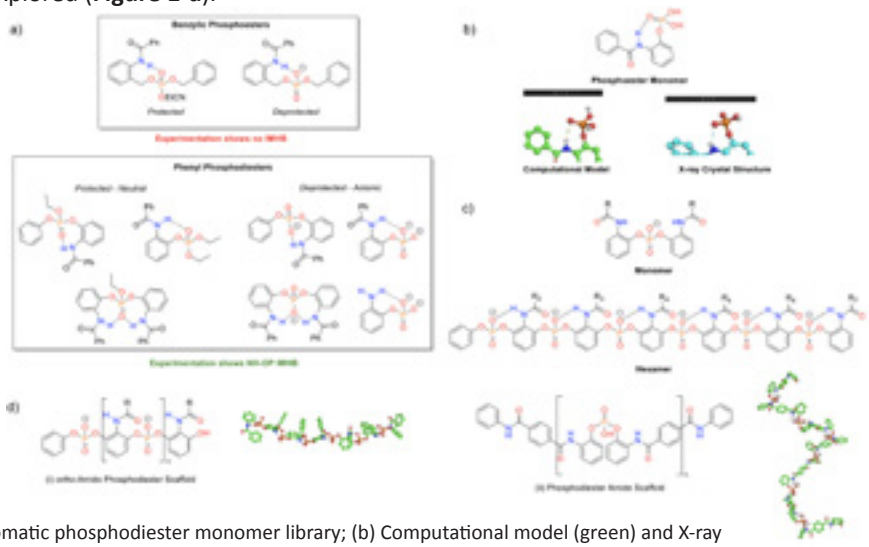

Figure 1 (a) Aromatic phosphodiester monomer library; (b) Computational model (green) and X-ray crystal (blue) of a phosphoester monomer revealing a 7-membered hydrogen bonded ring; (c) A phosphodiester foldamer scaffold; (d) Computational models (green) of extended foldamer architectures showing linear and helical secondary structures.

X-ray crystallography, studies in *silico*, and NMR experimentation (^{1}H-^{31}P HSQC, HOESY, H-D exchange, and hydrogen bond acidity calculations[6]) confirm the presence of an IMHB between the amide N-H and the phosphate P-O forming a stable 7-membered hydrogen bonded ring system (**Figure 1-b**). Diversifying the "R" groups on the aryl building blocks can code these foldamers in various ways, affecting their global conformations. Future potential applications for this class of foldamers include protein surface recognition or disruption of protein-protein interactions owing to the foldamers' ability to access many points across a large protein surface area.

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NMR IN ORGANO- AND PHOTOCATALYSIS – PUSHING THE LIMITS

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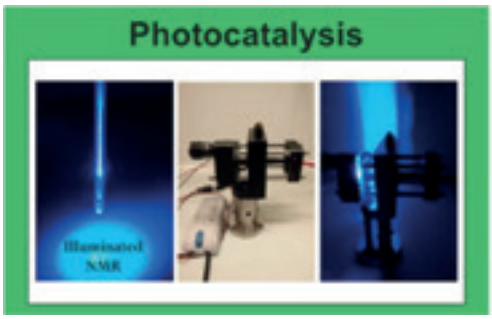
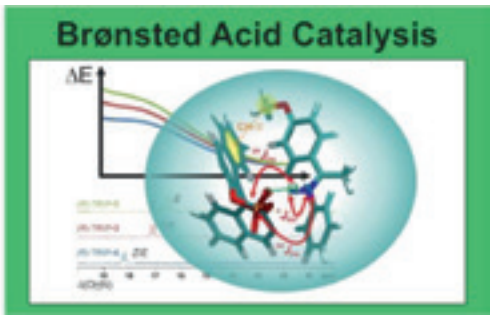
The detection and characterization of intermediates in catalytic reactions is crucial for the rational optimization of reaction conditions. However, in many rapidly expanding fields of asymmetric catalysis, mechanistic studies as well as structural investigations on intermediates or intermolecular interactions are scarce. In this talk I will present techniques and methods to extend the application of NMR in photocatalysis and ion pair catalysis and explain their impact on examples. First our LED based NMR illumi-nation device [1] will be introduced together with the new triple combination illumina-tion/NMR/UV [2] and an NMR access to intermediates below the detection limit [3]. These methods allow for new insights into one- versus two-electron processes usually inaccessible to UV/Vis [4], the inclusion of radical species into NMR reaction profiles [2], the structure elucidation of thermally labile photoswitches [2], the sequencing of tiny intermediates [5], and even insights into photosteps in photocatalysis [6]. Last, the structure elucidation, H-bond analysis, reactivity/selectivity understanding and experimental transition state combination analysis of chiral phosphoric acids in ion pair catalysis is demonstrated [7]. Here, the NMR time scale could be extended so far that even the switching of a single hydrogen bond can be detected experimentally [8].





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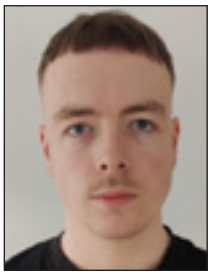
METAL-FREE SYNTHESIS OF FUNCTIONALISED PYRROLIDONE SCAFFOLDS *VIA* A TRUCE-SMILES CASCADE



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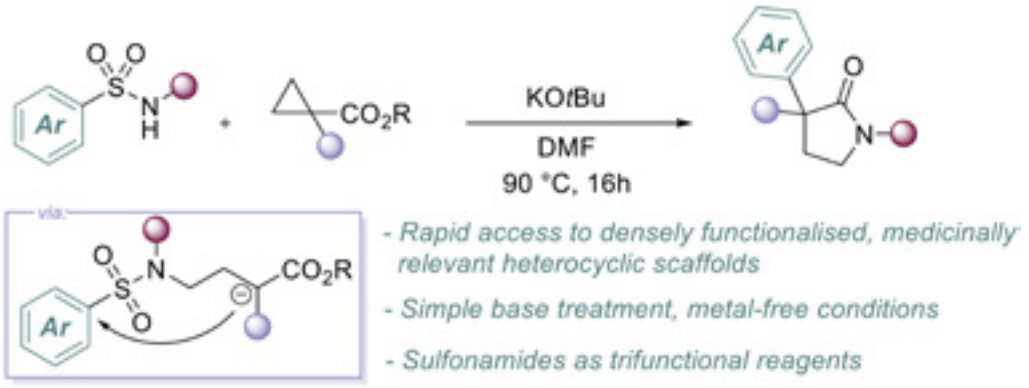
Pyrrolidones are heterocyclic scaffolds ubiquitous throughout chemistry, present as key pharmacophores in numerous biologically active compounds. As such, there exists a plethora of methods for their synthesis and functionalisation, often requiring multiple steps to arrive at highly functionalised compounds. Less common however are single-step procedures which afford pyrrolidone scaffolds with multiple functional handles pre-installed. Inspired by previous work in the group which exemplifies sulfonamides as aminoarylation agents, we proposed to develop such a transformation.

We have thus developed a cascade method for the synthesis of highly functionalised pyrrolidone scaffolds, starting from widely commercially available starting materials and utilising operationally simple reaction conditions. The substrate scope of the transformation is broad, encompassing various electron-deficient arenes alongside substitution of both the sulfonamide and cyclopropane starting materials. The reaction sequence begins with deprotonation of the sulfonamide, which adds as a nucleophile to the electron-deficient cyclopropane. The enolate formed then undergoes a 6-membered, desulfonylative Truce-Smiles rearrangement, unmasking a reactive amine which cyclises to form the product. This chemistry thus uniquely showcases sulfonamides as trifunctional reagents, building on their rich amphiphilic history. Further exploration of the substrate scope and mechanism of this transformation is currently underway in our laboratory.



OXIDATIVE TRANSFORMATIONS WITH PHOTOACTIVATED PHENANTHRENEQUINONE AND ITS ELECTRON-DEFICIENT DERIVATIVE

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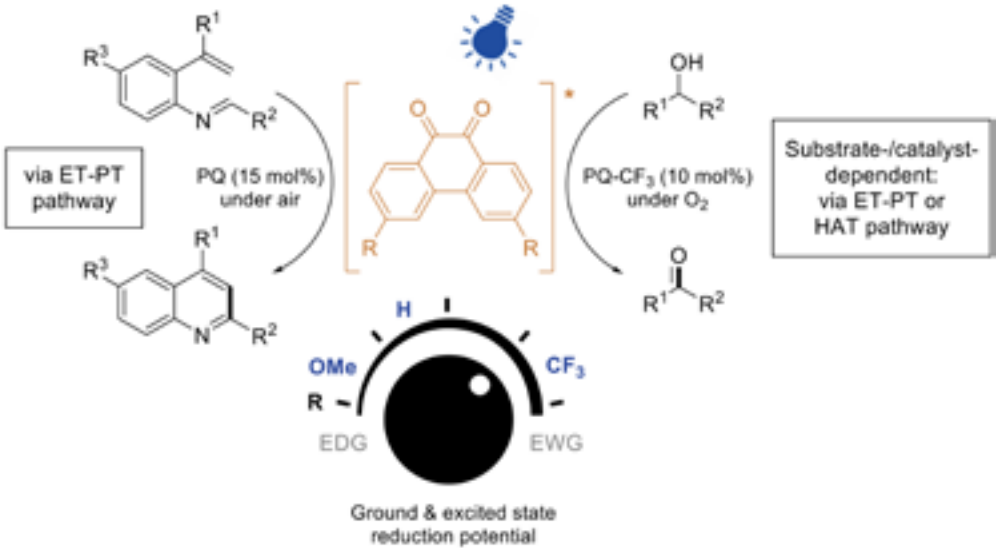
During recent years, photoredox chemistry has emerged as a milder strategy to perform oxidative reactions. Especially organophotocatalysts provide an interesting and greener alternative to more traditional methods, which generally require high temperatures or pressures, expensive metal catalysts, or strong Lewis acid reactants. 9,10-Phenanthrenequinone (PQ) is known to act as a photoactivated oxidant[1] but to this date, PQ is used as a visible-light-excited photocatalyst only in a few procedures. We developed a method where PQ catalyses electrocyclisation of 2-vinylarylimines to polysubstituted quinolines, producing up to quantitative yields already after 1 h of excitation with blue LEDs at room temperature.[2] On the basis of experimental and DFT studies, we propose that excited-state PQ induces one-electron oxidation of the imine substrate, which triggers the electrocyclisation mechanism.

Most secondary alcohols exhibit higher oxidation potentials than vinylarylimines, limiting efficient PQ-catalysed oxidation of alcohols to electron-rich benzylic alcohols. We observed that the redox properties of PQ could be tuned by structural modification.[3] The ground and excited state reduction potential of 3,6-bis(trifluoromethyl)-substituted PQ (PQ-CF3) was significantly higher comparing to PQ. With PQ-CF3 as an organophotocatalyst, oxidation of secondary alcohols occurred efficiently in mild conditions, even when electron-deficient aryl alcohols or aliphatic alcohols were used as substrates. Mechanistic investigations revealed that contrary to electrocyclisation of imines, the reaction mechanism of alcohol oxidation was both substrate- and catalyst-dependent. By adjusting the electron-deficiency of the substrate, the oxidation occurred either via electron transfer proton transfer (ET-PT) or hydrogen atom transfer (HAT) pathway.



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THE USE OF BIORENEWABLE FEEDSTOCKS IN AGROCHEMICAL RESEARCH: OPPORTUNITIES AND CHALLENGES

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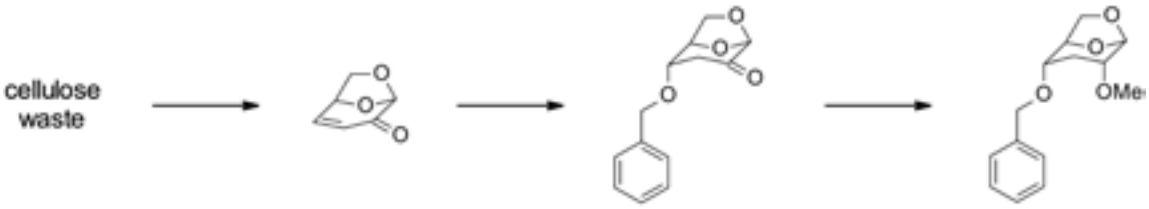
The expected reduction in fossil fuel production over the next decade means that alternative sources of chemical feedstocks need to be found. Several different approaches to this problem are being investigated.

In Syngenta we are exploring how to use bio-derived and sustainable chemical building blocks in our early stage research projects. Our aim is to access novel areas of chemical space, whilst ensuring that the future manufacturing of products arising from this work could be achieved from sustainable feedstocks.

This approach brings both challenges and opportunities, which will be illustrated by a collaborative research project based on a chiral feedstock that can be produced from biomass waste.



BEYOND THE CONVENTIONAL: UNIQUE SYNTHETIC TRANSFORMATIONS ENABLED BY LIGHT

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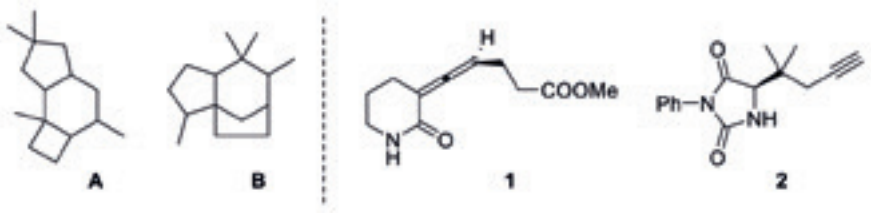
Photochemistry enables an access to reaction pathways that are thermally not viable. In this context, the talk will focus on two unique transformations which our group has studied in recent years and which show the power of light-induced transformations. In the first section, a short route to the skeleton of protoilludane- **(A)** and prezizane-type **(B)** sesquiterpenes will be discussed.[1] Starting from an achiral 1-indanone, the complete carbon backbone of the natural products is constructed in a two- or three-photon cascade reaction.



The second part of the talk will deal with the conversion of a racemic mixture to a single enantiomer in a catalytic photochemical deracemization.[2] The entropically disfavored and thermally impossible process is driven by light energy and allows to prepare enantiomerically pure (>90% ee) heterocycles such as piperidinone **1** and hydantoin **2** in a single operation.

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EXPLORING OXONIUM ION CHEMISTRY IN NATURAL PRODUCT SYNTHESIS

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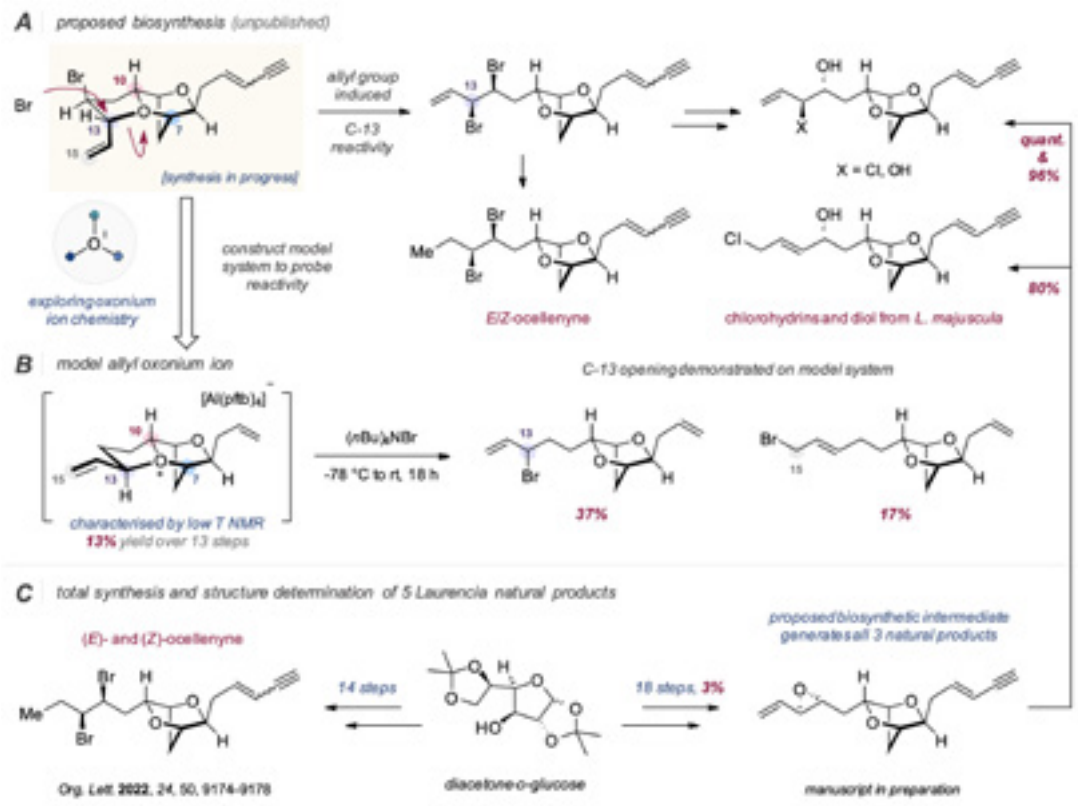
Oxonium ions frequently find themselves proposed as reactive intermediates in the biosynthesis of numerous Laurencia natural products.[1-9] Our group has a keen interest in synthesising *L*. natural products, with a particular focus on studying and characterising the proposed biomimetic oxonium ions.[3,5,10-12] The current project centres on a novel biosynthesis proposal, which utilises a complex *trialkyl allyl oxonium ion* to control site reactivity at C-13 to yield 5 natural products (scheme 1A). To support our initial hypothesis, a model allyl oxonium ion was synthesised and characterised by low temperature NMR (Scheme 1B).[13] Crucially, this allyl oxonium ion was shown to react at C-13, in direct contrast to structurally similar non-allyl oxonium ions.[3] To further support the hypothesis, the configuration of 5 novel *L*. natural products was determined by total synthesis, with the configurations found to be in keeping with the proposed biosynthesis (Scheme 1C).[12,13] Work is currently underway to synthesise the proposed biomimetic allyl oxonium ion (Scheme 1A) and study its reactivity.



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eFLUORINATION USING CHEAP AND READILY AVAILABLE TETRAFLUROBORATE SALTS

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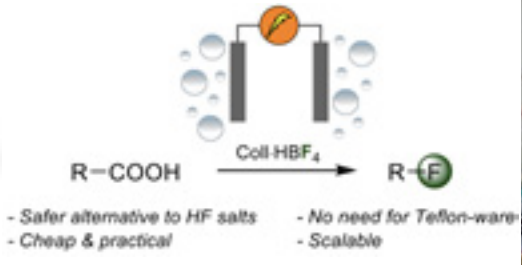
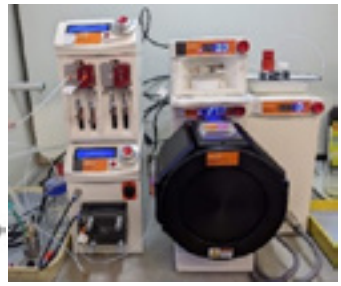
Electrosynthesis, the direct use of electrons to achieve chemical transformations, is a powerful and versatile tool for the modern synthetic chemist.[1] Previous obstacles, such as a lack of standardisation, limited reproducibility, and the need for specialist equipment and knowledge have been overcome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

Aside from representing a greener and more cost-effective alternative to traditional synthetic methodologies, electrosynthesis often offers improvements in safety, while avoiding some of the pitfalls of complementary methods such as photochemistry (e.g. expensive photocatalysts, toxic solvents, etc).[6]

Using oxidative decarboxylation in the presence of 2,4,6-collidinium tetrafluoroborate (Coll·HBF_4), cheap, bench-stable, and easily synthesised fluorinated supporting electrolyte, we have been able to develop a practical electrochemical method for the rapid, safer, and mild synthesis of tertiary hindered alkyl fluorides.[7] In contrast to established methods, there is no requirement for expensive and potentially explosive reagents, or HF salts which necessitate Teflon cells. Moreover, a significant substrate scope has been screened, with a wide range of alkyl fluorides reported. Lastly, the scalability of this new method has been demonstrated using both traditional batch-chemistry and more modern flow-electrosynthesis. The development and implementation of this methodology will be presented.





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SMALL-MOLECULE *BIS*-DIAZIRINES AS UNIVERSAL POLYMER CROSSLINKERS

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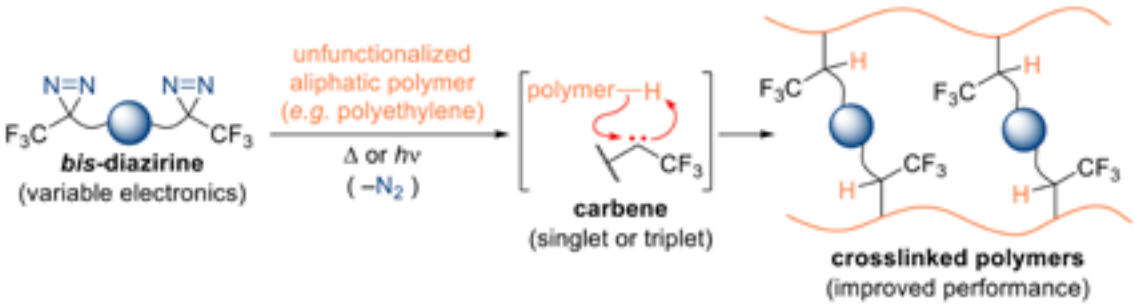
Adding chemical crosslinks between the chains of existing polymer materials provides increased mechanical strength, improved high-temperature performance, and enhanced solvent resistance. *Installing* these crosslinks, however, has historically required the use of distinct chemistry for each type of material: vulcanization for rubber, hydrosilylation for silicone, DMDHEU for cotton, etc.

We developed a family of rationally designed, diazirine-based crosslinker reagents that allow for the on-demand introduction of strong covalent bonds *to virtually any aliphatic polymer material*, through rapid C–H insertion reactions. This presentation will focus on the design, synthesis, and mechanism-driven optimization of this new class of polymer crosslinkers, and will briefly describe several applications, which arise through operationally simple, topical treatment of existing polymer materials. Selected applications may include: (1) adhesion of low surface energy materials, (2) upgrading the mechanical strength of ballistic protective fabric, (3) construction of novel fiber-reinforced UHMWPE–epoxy composites, (4) development of self-sterilizing fabrics, (5) enhancement of the mechanical robustness of omniphobic PDMS coatings, (6) upgrading of perovskite solar cell stability and performance, (7) photopatterning of electroluminescent quantum dot aggregates for next-generation displays, and (8) upcycling of mixed plastic waste into recyclable thermoset materials.



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TAKING INSPIRATION FROM NATURE

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Polyketide-derived natural products isolated from microorganisms exhibit a range of important biological activities making them attractive leads for the development of therapeutics and agrochemicals. They are assembled in the host organism *via* sophisticated multiple enzyme architectures – polyketide synthases. Using an interdisciplinary approach, our overall aim is to fully understand how polyketides are produced to (i) provide biocatalysts of potential value in organic synthesis, (ii) gain inspiration for strategies for the total synthesis of natural products and analogues and (iii) enable rational engineering of the complex biosynthetic machinery to deliver novel bioactive compounds cleanly and efficiently.

This lecture will focus on the combination of organic synthesis and synthetic biology to investigate polyketide biosynthesis enabling the generation of new bioactive targets and biocatalysts. Examples will be taken from our recent work and will showcase chemoenzymatic total synthesis and the value of a combined selective carbon-13 labelling/ NMR strategy to probe enzyme-catalysed transformations *in-situ*.

Abyssomicin antibiotic

Micromonospora maris

Biocatalysts for use in organic synthesis