Abstract

10th Catalysis and Sensing for Our Environment Symposium and Networking Event in Kitakyushu

5 April 2024

REAL-TIME NEAR INFRARED FLUORESCENCE IMAGING RESEARCH TOOLS WITH THE POTENTIAL FOR CLINICAL USE

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This presentation is concerned with our ongoing development of macrocyclization reactions of bisazido azadipyrromethene fluorophores 1 for bioorthogonal chemistry such that the structural constraints imposed by the macrocyclization imparts changes in fluorescence lifetimes which can be detected in live cells using fluorescence lifetime imaging microscopy (FLIM).[1] As macrocyclization reactions are often low yielding, suffering from unwanted oligomerizations, a unique strain promoted double azide cycloaddition using Sondheimer diyne 2 has been developed (Figure). Experimentally, the sequential azide / diyne cycloadditions of 1 with 2 proved highly effective for the macrocyclization of bis-azido azadipyrromethenes. Macrocyclic fluorophores 3 could be produced in minutes at rt in water with changes in fluorescence lifetimes measurable upon reaction. Fluorescence lifetime imaging showed that the bioorthogonal macrocyclization could be detected in live cellular compartments identified using stimulated emission depletion microscopy (STED) super-resolution imaging.[2] Our clinical trial progress on the use of a novel fluorescence guided surgery approach will also be presented. This combines biophysics-inspired modelling and artificial intelligence to intraoperatively analyse dynamic changes in NIR fluorescence intensities of the clinically approved fluorophore indocyanine green (ICG) 4, in colon cancer patients (Figure, inset). This dynamic imaging approach could provide clinically useful tissue classifications with high specificity within minutes of ICG administration.[3]

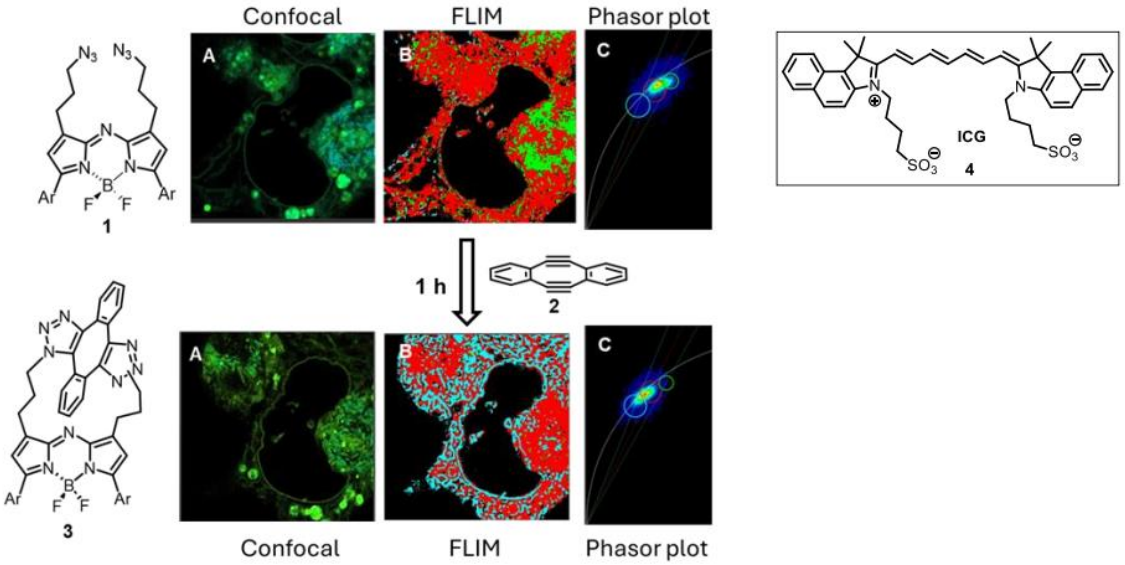

Figure. FLIM imaging of bioorthogonal macrocyclization reaction of 1 (R = BF2) with 2 in live MDA-MB 231 cells to produce macrocycle 3. (A) Confocal images of a single live cell before and after bioorthogonal reaction. (B) Phasor mapped FLIM images of a single live cell before and after

bioorthogonal reaction. (C) Phasor plots of a single live cell before and after bioorthogonal reaction. Structure of clinically used indocyanine green (ICG) 4.

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Water-soluble urea cryptands

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The design of synthetic hosts that selectively recognize a specific guest species in water is challenging. Whilst the majority of water-based host-guest systems exploit ionic interactions and/or hydrophobic effects[1], we here present a class of charge-neutral urea cryptands that bind anionic guests[2] in water solely by hydrogen bonds[3]. We discuss the templated strategy that leads to effective one-pot formation of those cryptands and their anion binding capability that mimics the sulfate binding proteins in bacteria.

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Fluorescent chemosensors: the past, present and future

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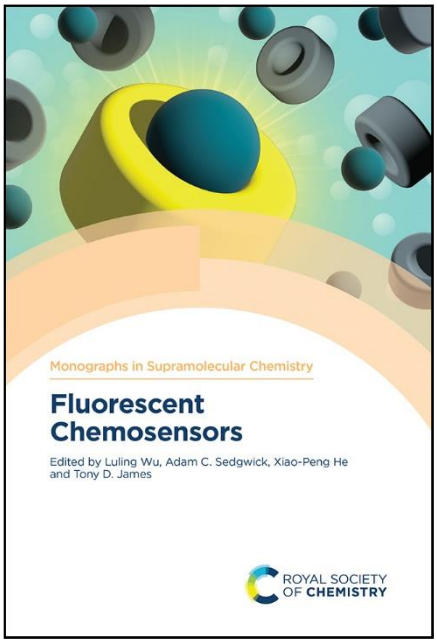

Sensors and imaging agents can be used to monitor analytes within physiological, environmental, and industrial scenarios. The interactions between the "chemosensor" and an analyte of choice occurs on a molecular level and as such gathering and processing the information is challenging. Therefore, I will outline the trials and challenges encountered in the development of several robust chemical molecular sensors "chemosensors" able to detect such analytes selectively and signal or map their concentration in a biological or environmental scenario. During the talk you will be introduced to a variety of fluorescent probes designed for diols (D-glucose), anions, and redox imbalance. With the goal being the development of chemosensors capable of determining the concentration (and location) of a target species in any medium. Particular attention will be paid to the underlying chemistry associated with the construction of practical chemosensors for both sensing and imaging applications.

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Design of Permeable Polymersomes and Hybrid Liposomes with Block Copolymer Channels

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We have developed intrinsically permeable vesicles based on maltopentaose-*block*-poly(propylene oxide). These vesicles are permeable to low molecular weight compounds but retain proteins. Their permeability arises from the partition of solute molecules into the membrane, and the fact that hydrophobic polymers exhibiting LCST-like behavior are suitable components for constructing permeable vesicles. By leveraging the molecular weight-dependent permeability, we explored their applicability as enzymatic nanoreactors both *in vitro* and *in vivo*. Additionally, we discovered that incorporating the carbohydrate-conjugated block polymer into liposomes enables it to function as artificial molecular channels. Moreover, we have recently succeeded in developing artificial cation channels that permit the passage of cations, such as potassium ions.

Chiral Metallosupramolecular Polymerization Accompanying Helical Inversion and Morphology Transformation

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Helical motifs, such as DNA and proteins, are prevalent in many biomolecular systems. They often undergo helicity inversion in various physiological processes, which is paired with specific bio-functional transformations. Inspired by these biological helices and the associated helical chirality inversion phenomena, numerous chemists have sought to design smart systems with tunable helical chirality for practical applications. In this context, stimuli-responsive supramolecular assemblies offer a novel platform where helical preference can be modulated by external stimuli, including changes in solvent or temperature, light irradiation, redox reactions, the addition of chemical species, or rotary stirring. Recently, we explored a unique dynamic helix inversion mechanism in self-assembled terpyridine-based ligands comprising varying numbers of peptide moieties with metal ions. This mechanism amplifies chirality from an achiral terpyridine moiety.[1-5] The helical chirality of the metal centers, coordinated by the terpyridine ligands, is governed by chirality in conjunction with complex ligand-to-metal ion ratios. Furthermore, we discovered that this distinct helical inversion mechanism is profoundly influenced by the number of peptides attached to the ligands. In this conference, I will share our latest findings on the synthesis of metal-coordinated supramolecular polymers and their morphological transformations accompanied by chirality inversion.

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Sequencing Sequence Defined Polymers

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There is little argument that many of the grand achievements of biotechnology, biochemistry, and chemical biology stem from advances in synthetic organic chemistry, embodied in the development of solid-phase synthetic approaches for proteins and nucleic acids. Of equal importance to the synthesis of the biopolymers, however, are methods for their sequencing. Revolutions in nucleic acid sequencing have led to single molecule and Next-Gen parallel methods. Similar advances in protein sequencing have lagged. In collaboration with the Marcotte group at UT Austin, we created a single-molecule peptide sequencing routine referred to as fluorosequencing. Therein, peptides are N-terminal captured, the amino acids selectively labelled with fluorophores, C-terminal differentiated, and then placed on TIRF microscope for rounds of Edman degradation. The development and implementation of the organic chemistry necessary in the method will be discussed. Further, the sequencing of sequence-defined polymers other than nucleic acids and proteins shows promise as a new paradigm for data storage. We have devised the first use of self-immolative oligourethanes for storing and reading encoded information. As a proof of principle, the approach will be described by using a text passage from Jane Austen's *Mansfield Park*. It was encoded in oligourethanes and reconstructed via self-immolative sequencing. We developed Mol.E-coder, a software tool that utilizes a Huffman encoding scheme to convert the character table to hexadecimal. The oligourethanes are then generated by a high throughput parallel synthesis. Sequencing of the oligourethanes by self-immolation was done concurrently in a parallel fashion, and the LC/MS information decoded by our Mol.E-decoder software. The passage was capable of being reproduced wholly intact by a third-party, without any purifications or the use of MS/MS, despite multiple rounds of compression, encoding, and synthesis. Overall, this presentation will highlight the interplay and utility of synthesis and sequencing in sequence-defined polymers.

Peptidomimetic Large Macrocycles: Synthesis, Assembly and Functions

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Macrocycles are important host molecules in supramolecular chemistry, the syntheses of them, however, are not feasible. Many efforts have been paid to easy the synthesis, one useful strategy is to employ a template that binds to the chain-like precursor to make the two reactive termini into close proximity, that the intramolecular cyclization is promoted. We report here to use our discovery of the folded β-turn structure in *N*-acylaminoacid based amidothiourea motif, as the *in situ* generated templates to promote the macrocyclization reactions (Figure 1). Using dihydraazines made from an amino acid residue, such as alanine and phenylalanine, we succeeded in synthesizing in a one-pot reaction the 46-membered or even larger peptidomimetic macrocycles in good yields, with no need of ultra-dilution reaction condition and tedious separation procedures. The macrocyclic compounds were found easy to crystallizer, that nanopores are formed via inter-cycle hydrogen bonding, capable of transmembrane transportation. Interesting anion binding and chiral characters were respectively observed with the macrocycles and during their cyclization.

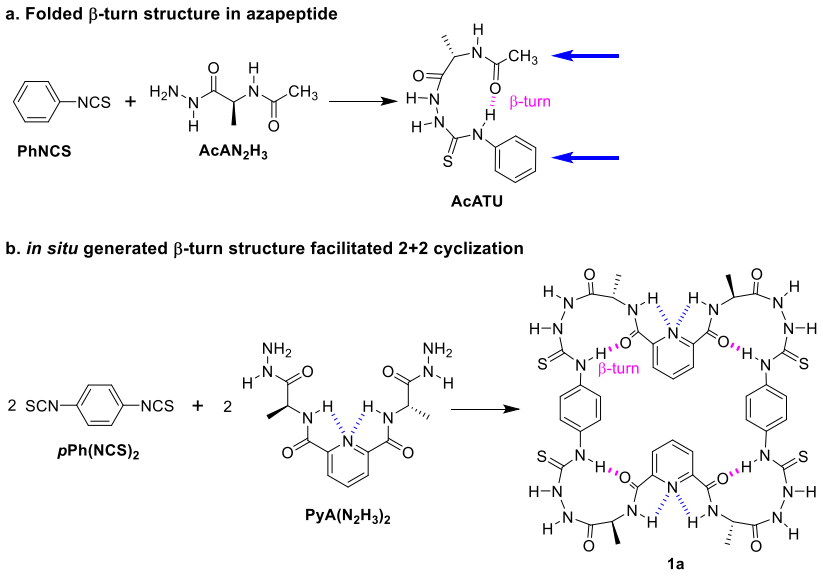

Figure 1. (a) Folded β-turn structure and (b) *in situ* generated β-turn templated macrocyclization involving alanine residue (Y.-B. Jiang, *et al.*, *J. Am. Chem. Soc.*, **2023**, *145*, 9530-9539).

I thank the financial supports of the NSF of China and the MOE of China. Contributions from my colleagues and students are also thanked.

Modulation of Protein-Protein Interactions Employing Intrinsically Disordered Motifs: A Supramolecular Chemical Biology Approach

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Protein-protein interactions (PPIs) regulate virtually all cellular signalling processes thus developing methods to modulate PPIs represents a significant challenge of immense biochemical and medical importance. However, methods to target intracellular (PPIs) using synthetic molecules are not well established. A significant proportion of PPIs involve short motifs that undergo a disorder-order transition on interaction with target proteins, providing ideal templates for modulator design. This presentation will discuss the development of enabling methods to characterize PPIs and design peptide and peptidomimetic based inhibitors. A suite of approaches will be described that rely on the use of experimentally validated computational predication of hot-spot residues; these are used to inform design of inhibitors by introduction of constrains, through backbone modification and through dynamic ligation screening to replace segments of interfacial peptides, piece by piece.

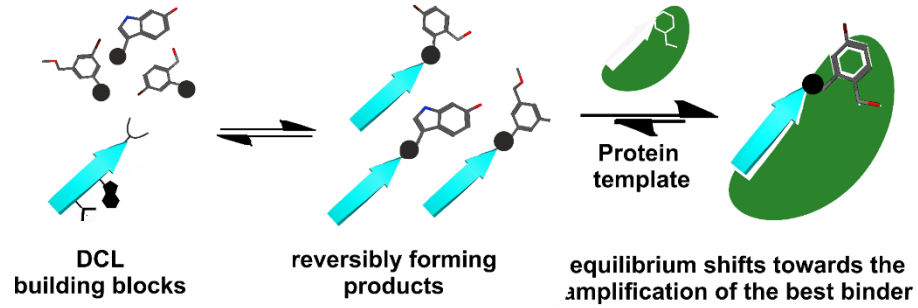

Figure 1: Schematic illustrating one strategy for accelerated preparation and screening of candidate protein-protein interaction inhibitors.

Near-infrared luminescent sp^3 defect formation in carbon nanotubes through molecular functionalisation

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Single-walled carbon nanotubes (SWCNTs) show photoluminescence (PL) in the near infrared (NIR) region. NIR PL is applicable to advanced optical applications such as deep-tissue bioimaging and sensing. Local chemical functionalization (slight amount of chemical modification) of SWCNTs has been developed to introduce sp^3 carbon defects in the sp^2 carbon network of the tube walls, by which luminescent defect sites with a narrower bandgap and exciton trapping feature are produced (**Fig. 1**).[1-3] Consequently, the resultant locally functionalized SWCNTs (lf-SWCNTs) show defect PL (E_{11}* PL) with red-shifted wavelengths (*e.g.* >1000 nm) and increased quantum yields compared to original PL of pristine SWCNTs based on the lowest energy transition (E_{11} PL). For lf-SWCNTs, the modifier molecules allow us to not only produce sp^3 carbon defects but also integrate molecular functions on the defect site for the defect PL wavelength modulation[4,5] and the sensing function creation[6-9]. Namely, molecular design of the modifier molecules can be a key approach for further functionalization of lf-SWCNTs.

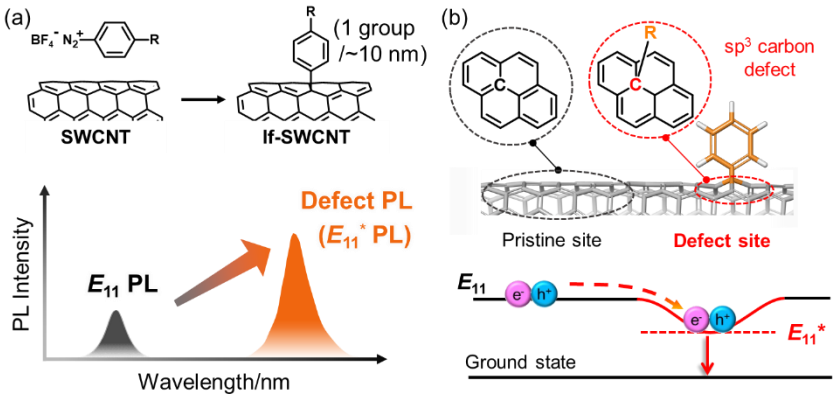

Fig. 1. Schematic images of (a) PL features of lf-SWCNTs and (b) the generation of defect (E_{11}*) PL level with the narrower bandgap and exciton trapping function.

For sensor applications, firstly, we have introduced molecular recognition groups such as phenylboronic acid and azacrown ether at the defect sites of lf-SWCNTs to produce NIR PL sensors based on sugar recognition[6] and metal ion inclusion[7], respectively. Therein, E_{11}* PL spectral shifts for sensing are induced by electronic withdrawing/donating property changes of the molecular recognition moieties modified at the lf-SWCNT defect sites based on the selective binding of target substances.

As a basis for macromolecular (*e.g.* proteins) sensing applications, we have recently found the unique microenvironment responsiveness of E_{11}* PL of lf-SWCNTs; namely, greater wavelength shifts of E_{11}* PL than E_{11} PL are observed by dielectric atmosphere changes[10] and the E_{11}* PL shifting response can be modulated based on the chemical structure differences of the defect sites[11]. From

these findings, we have used the microenvironment responsiveness of the E_{11}* PL to detect macromolecule adsorption at the defect sites of lf-SWCNTs for NIR sensor fabrications.[8,9] As the first example of the protein detection/recognition using lf-SWCNTs, we have employed an avidin-biotin interaction for a selective and strong binding of various types of avidin derivatives at the defect site of lf-SWCNTs.[8] The lf-SWCNTs tethering biotin groups (lf-SWCNTs-b) were synthesized through diazonium chemistry, followed by its subsequent-modification. When neutravidin was mixed with a lf-SWCNTs-b solution, E_{11}* PL peak was red-shifted, indicating the higher polarity environment formation by the neutravidin adsorption on lf-SWCNTs-b. When avidin or streptavidin was used, wavelength shifting behaviours of E_{11}* PL were clearly changed depending on the used avidin derivatives. The results indicate the different polarity environment formation deriving from structural differences of each avidin derivative. Moreover, the detection signal enhancement was observed in a film device using lf-SWCNTs-b.

As another example, we have developed a serum albumin (SA) detection sensor (**Fig. 2**).[9] Here, a palmitic acid group that binds to SA strongly and selectively, was functionalized at the defect site of lf-SWCNTs (lf-SWCNTs-p). lf-SWCNTs-p showed E_{11}* PL red-shifts according to the addition of SA in phosphate-buffered saline. The E_{11}* PL red-shifts occurred by formation of a high dielectric environment based on the specific binding between SA and the palmitic acid groups on the defect sites. Different SA from human, bovine, and mouse could be detected using the E_{11}* PL responsiveness. Furthermore, the lf-SWCNTs-p detected SA-spiked serum and albuminuria of diabetic mouse in body fluids.

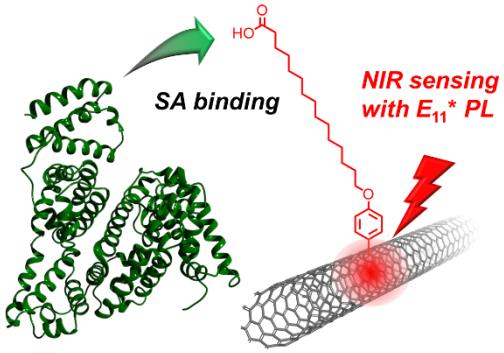

Fig. 2. SA detection sensor using E_{11}* PL shifts induced by the selective SA binding on the defect site of lf-SWCNTs-p.

Therefore, lf-SWCNTs have a high potential for development of biomolecule and protein detection/recognition systems using NIR PL, which would be applicable to a disease diagnosis and other bioapplications based on their molecular design-based defect site engineering of lf-SWCNTs.

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Anion transport by macrocyclic systems

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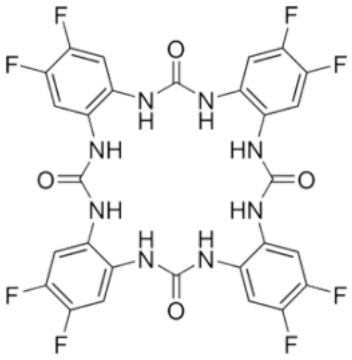
Abstract: The development of synthetic anionophores continues to be the focus of several groups worldwide due to the potential application of these compounds in the treatment of diseases caused by faulty anion transport (e.g., cystic fibrosis)[1] and in disrupting anion concentration gradients and pH gradients leading to apoptosis and disruption of autophagy.[2]



This presentation will give an overview of work in the Gale group over the last few years and in particular focus on the development of new assays to measure membrane transport and the development of selective transporters.[3] PAG pays respect to the Gadigal people of the Eora Nation, the traditional owners of the land on which we teach, research, and collaborate at the University of Technology Sydney. This work was supported by the Australian Research Council (DP180100612, DP200100453, DP210100039) and the University of Sydney.

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Functional Materials using Photoactive Macrocycles

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This presentation will outline current research towards the use of chromophores as photosensitizers for singlet oxygen production in an aqueous environment by synthetic modification and subsequent formation of nanoparticles and macromaterials. Due to the encryption of the chromophore within a compact scaffold the photosensitizer is protected from the usual deactivation pathways caused by aggregation and in some cases shows aggregation enhanced singlet oxygen generation properties due to the hindered environment within the local environment. The application of the chromophore encryption concept towards a range of structurally diverse chromophores and the formation of aggregated bulk materials capable of singlet oxygen photosensitization will also be discussed.

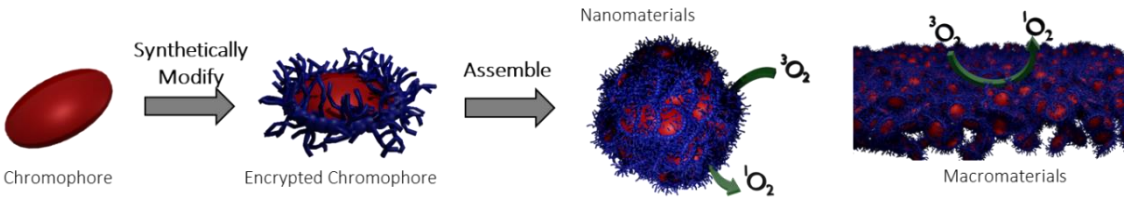

Figure 1. Macrocycles as scaffolds to produce nano-assemblies for biological applications.

Fuchsonarenes[1-4] are a class of macrocycles which we have been utilised for formation of nanoscale materials towards the formation of photodynamic therapy agents by developing the process of 'chromophore encryption. We have subsequently applied the same process to a range of chromophores for the formational of a variety of singlet oxygen generating functional materials.

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Screening Approaches for the Identification of Covalent Peptide Inhibitors

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Abstract: Stratified medicine is poised to fundamentally alter cancer therapy but is currently limited to just 10% of patients. This is due to a lack of inhibitors for most cancer proteins, which are often deemed undruggable as they lack binding pockets that can be targeted with small molecules. Undruggable proteins possess reactive nucleophilic residues that can be interrogated by targeted covalent inhibitors (TCIs). Most TCIs target cysteines, but many proteins lack cysteine residues. Electrophiles have been reported for nine other amino acids, but few unbiased screening methods exist to identify TCIs from diverse pools of candidate molecules. Consequently, the full potential of TCIs for targeting undruggable proteins is yet to be realised.

Our research aims to address this by using combinatorial chemistry and phage display to develop ultra-large libraries of covalent peptides for screening. Specifically, we develop libraries of targeted covalent macrocycles (TCMs) by cyclising billions of phage-displayed linear peptides with reactive linkers possessing latent electrophilic moieties. TCMs have the combined properties of a macrocyclic peptide (high affinity and specificity) and a covalent inhibitor (durable target engagement) and are particularly effective at engaging undruggable protein targets.

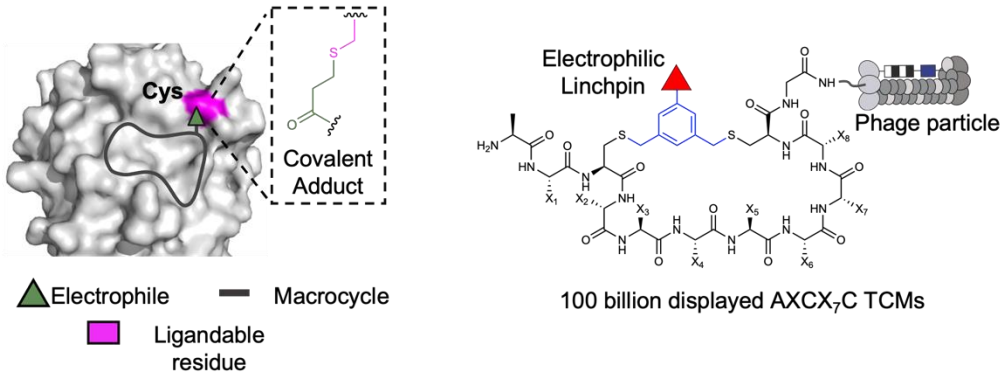

Figure 1: Protein inhibition with a TCM (left). Structure of a TCM phage library (right)

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Selective sp^2 to sp^3 functionalisation: From simple to complex molecules

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The asymmetric dearomatization of phenols offers a valuable method towards generating biologically relevant target molecules, owing to the high abundance of feedstock phenolic compounds. The hydroxylative dearomatization of *o*-alkylphenols leads to [4+2]-dimerization of the intermediate *o*-quinol, thus remarkably generating decorated bicyclo[2.2.2]octenones in a single synthetic step. Bicyclo[2.2.2]octenones derived from *o*-quinols are present in several natural products such as bis(monoterpenoid) (+)-biscarvacrol, and bacterial metabolite (–)-bis(2,6-xylenol). Therefore, methods to access such products bears significant importance.

Previous reports regarding enantioselective *ortho*-hydroxylative phenol dearomatization, such as those by Porco and Quideau feature an undesirable requirement for stoichiometric chiral reagents to successfully invoke the reaction, as well as limited scope.[1] Therefore, a general, catalytic method for enantioselective *o*-hydroxylative phenol dearomatization has ***remained elusive***.

In this study, we report a highly enantioselective, organocatalytic method for *o*-hydroxylative dearomatization-[4+2] dimerization reactions (Figure 1).[2] Our unique approach employs a chiral oxaziridinium catalyst, which were previously unexplored in dearomative chemistry. Using our novel methodology, the synthesis of (+)-biscarvacrol, and (–)-bis(2,6-xylenol) was achieved with excellent enantioselectivity. Additionally, a range of un-natural bicyclo[2.2.2]octenones were prepared, showing wide tolerance towards an array of phenol substitution patterns.

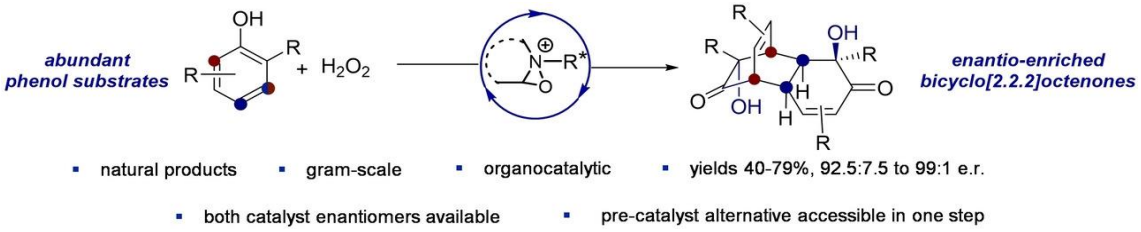

Figure 1: Catalytic Enantioselective Phenol Dearomatization

To compliment the described methodology, we additionally demonstrated a tertiary amine pre-catalyst system, allowing for the use of a more-atom economical catalyst, that can be accessed in a single synthetic step from commercial materials. The utility of the pre-catalyst system was emphasised in a gram-scale synthesis, using only 2.5 mol% loading. In addition to the dearomative methodology, the retro-[4+2]-[4+2] chemistry of *ent*-bis(2,6-xylenol) was investigated, to highlight further downstream modifications of the bicyclo[2.2.2]octenone products into further complex, sp^3-rich scaffolds.

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1. (a) Porco and co-workers *J. Am. Chem. Soc.* **2012**, *134*, 19782-19787; (b) S. Quideau and co-workers *Angew. Chem., Int. Ed.*, **2014**, *126*, 10018–10022.

2. T. D. D'Arcy, M. R.J. Elsegood, and B. R. Buckley *Angew. Chem., Int. Ed.* **2022**, *61*, e202205278.

Lighting the way to new disconnections for amines and azacycles

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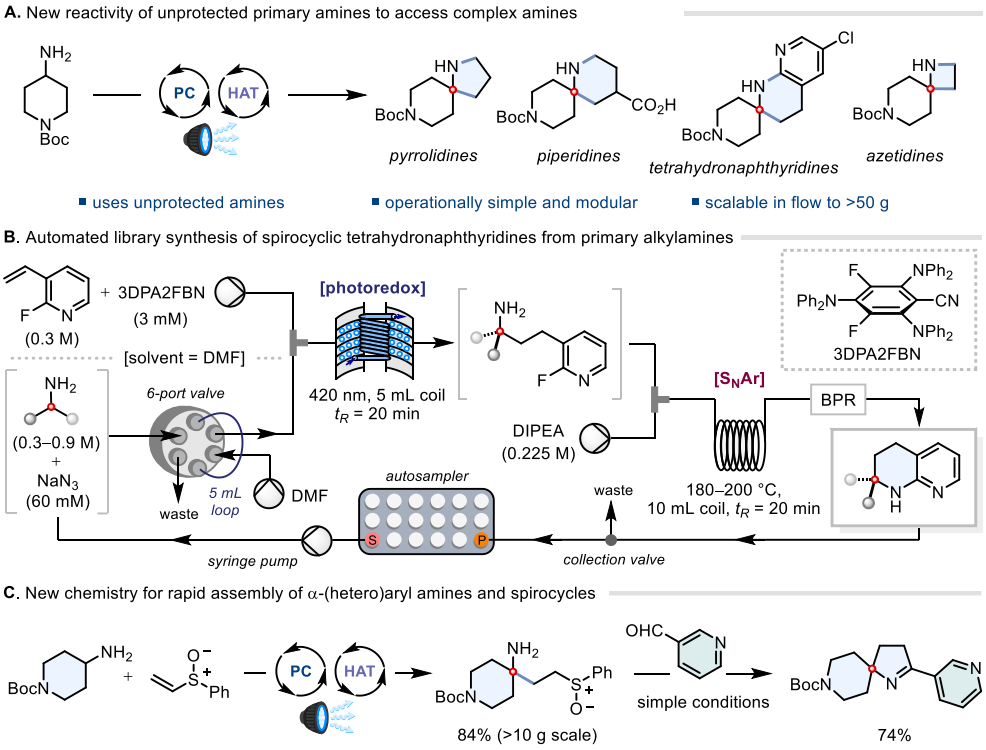
We have uncovered fundamentally new reactivity of unprotected alkylamines, allowing their exploitation not as *N*-nucleophiles but as *C*-nucleophiles for direct C–C bond formation. This highly unconventional approach to amine synthesis – which is reliant on a merger of photoredox and hydrogen atom transfer (HAT) catalysis – allows for rapid assembly of α-tertiary or spirocyclic amine products by α-C–H functionalisation. The methodology is amenable to automation and scale-up in continuous flow, and we anticipate its widespread application in medicinal chemistry.



References: [1] "Photocatalytic Hydroaminoalkylation of Styrenes with Unprotected Primary Alkylamines" *J. Am. Chem. Soc.* **2021**, *143*, 15936. [2] "γ-Amino Phosphonates via the Photocatalytic α-C–H Alkylation of Primary Amines" *Tetrahedron* **2021**, *81*, 131896. [3] "Photocatalytic α-Tertiary Amine Synthesis *via* C–H Alkylation of Unmasked Primary Amines" *Angew. Chem. Int. Ed.* **2020**, *59*, 14986. [4] "Modular, Automated Synthesis of Spirocyclic Tetrahydronaphthyridines from Primary Alkylamines" *Commun. Chem.* **2023**, *6*, 215.

Different sensing strategies for the fluorescent detection of biomolecules in cellular systems

Professor Steven Bull

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The presentation will describe our efforts into developing fluorescent chemical sensors as investigational tools for probing complex biological processes in cellular systems, including for the real-time detection of osteocyte bone resorbing activity in deep bone cavities, imaging of amyloid-beta plaques in mice brains and visualization of drug induced liver damage.

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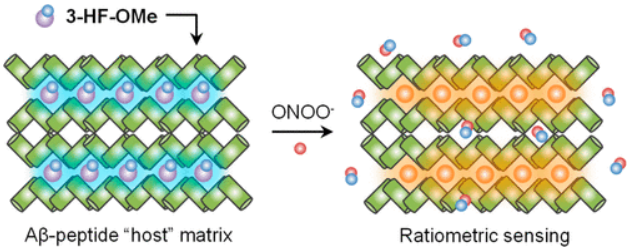

An ESIPT based fluorescence sensor for visualising Ab-amyloid plaques in mice brains

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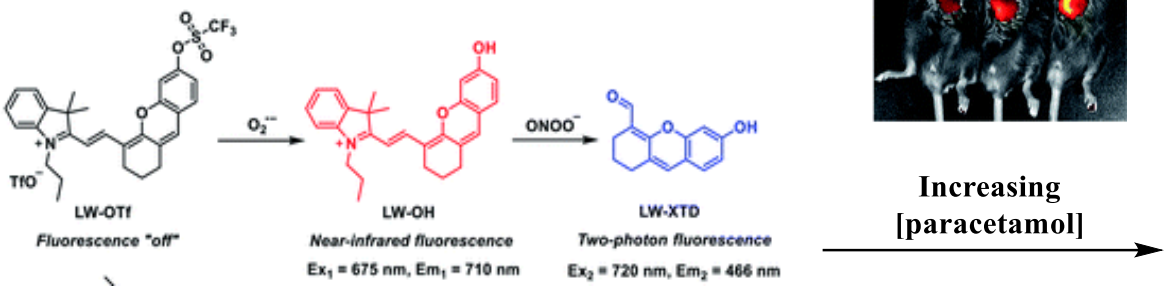

Two Photon Fluorescent

Imaging of Superoxide and Peroxynitrite in Drug Induced Liver Injury

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