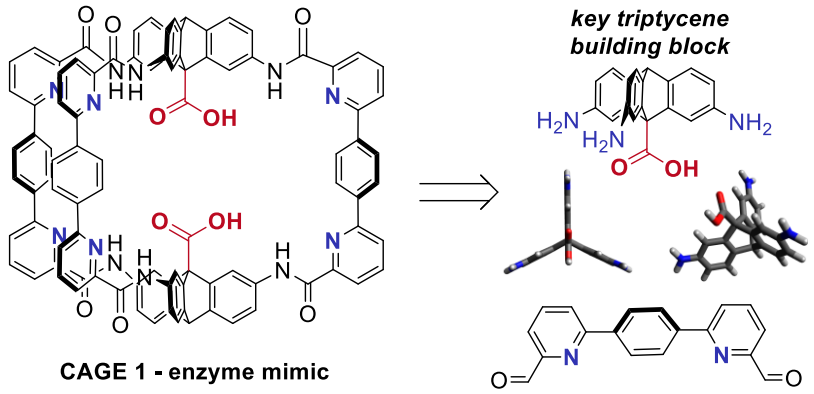
Synthesis of Novel Triptycene Building Blocks for Supramolecular Catalysis

PI: Dr Keith G. Andrews *Student: Michael Heron* *Co-supervisor: Dr Luke O'Driscoll*

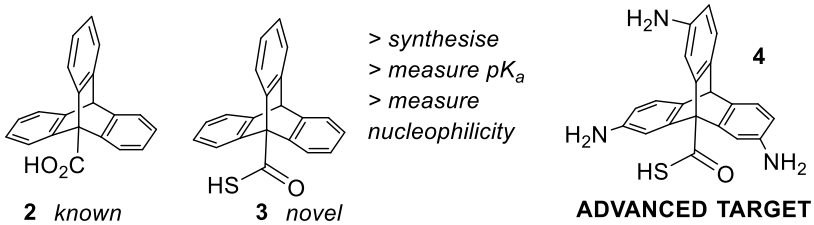
Abstract: In this synthetic organic chemistry summer project, we propose to synthesise a novel thioacid-containing triptycene for use in a class of self-assembled supramolecular catalysts. The new building block is predicted to be more nucleophilic and more acidic than a fragment previously used, which will benefit the catalysis, so the project hopes to establish a synthetic route and to determine the physical organic properties of the variant molecule.

Background and motivation: Macromolecular cages such as **1** (Fig 1) have recently been reported by the Andrews group as organocatalysts for acyl transfer reactions.[1] The unique 3D cavity environment in the cage shows promise for regioselective transformations of biofeedstocks (e.g. lipids). Catalysis is contingent on the co-aligned pair of internal carboxylic acid groups in the cavity, which mimic the active site of aspartyl proteases and glycoside hydrolase enzymes, showing rate accelerations >10^4 over background. Since the acid groups act as nucleophiles and acids, we have hypothesised that replacement with thioacids will lead to a rate-enhancement in the catalysis. This project will investigate conversion of triptycene-9-carboxylic acid **2** into novel thioacid **3**, for development and ultimately incorporation into the cage catalysts. The pK_a and nucleophilicity of the novel thioacid triptycene **3** will be measured and compared to the original acid **2**.

FIGURE 1 **(a) Macromolecular cage that performs enzyme-like acyl transfer catalysis, and the key functionalised triptycene building block.**



(b) THIS PROJECT: Synthesis of novel, functionalised triptycenes



Aims of the project: *To synthesise, isolate, and characterise a novel, functionalised triptycene for incorporation into a macromolecular cage. To learn advanced NMR characterisation techniques. To practice manual and automated chromatography, and analysis techniques such as 2D NMR and mass spectrometry/LCMS. To experience day-to-day group research activities, including supporting and maintaining a productive laboratory. To participate in group meetings. To measure the pK_a of the project target, and compare to DFT calculations. To measure relative nucleophilicities with a simple NMR kinetic experiment. To keep an electronic lab notebook, and present findings to the research group in group seminars.*

The key hypothesis is that the novel thioacid **3** will be a better nucleophile and a stronger acid than carboxylic acid **2**, properties which will benefit our previously reported catalysis. The student will primarily test methods to convert **2** to **3**, and then measure the difference in pK_a between **2** and **3**. Initially, they will perform two highly educational transformations: first, an *in situ* benzyne-mediated cycloaddition, and second, air-sensitive incorporation of CO_2 gas into an alkyl lithium nucleophile.[1]

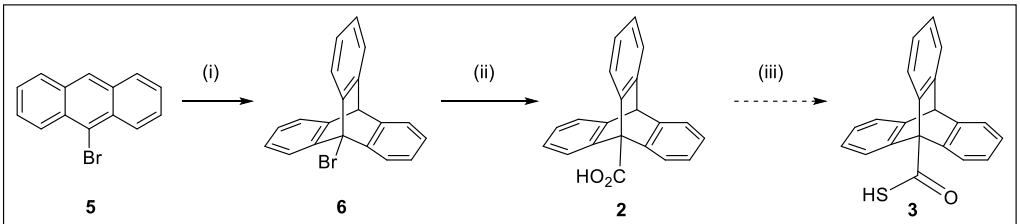


FIGURE 2 Initial project plan: Can known triptycene **2** be converted into novel thioacid **3**?

(i) anthranilic acid, isoamyl nitrate, CH_2Cl_2; (ii) n-BuLi, CO_2, Et_2O; (iii) thioacetic acid (see text for alternative methods)

In detail: readily available bromide **5** will undergo reaction with benzyne (generated *in situ*) to form triptycene **6**, which is isolated by crystallisation (Fig 2). Next, bromide **6** undergoes lithium exchange and is quenched by

bubbling gaseous CO_2 generated from dry ice through the reaction to give acid **2**, which is purified by crystallisation or chromatography.[1] The student encounters *n*-BuLi and chromatography in year 3 at Durham, so these will be advanced versions of known chemistry. The student will then explore various chemical methods to access thioacid **3** from **2** (avoiding use of CS_2). Possibilities include anhydride formation/hydrolysis with thioacetic acid, Lawesson's reagent, thioester formation/hydrolysis, acyl chloride formation and quenching with thiourea, and atom exchange with sodium hydrosulfide, among others.[2] This route selection dilemma will train the student in researching routes to balance sustainability, safety, and practicability in organic synthesis. The synthesis and associated materials will be provisioned from current funding available to the PhD students, since the molecules from this project will be trialled directly in their studies. If the student is successful, we will characterise **3**, measure the pK_a (non-aqueous potentiometric or NMR titration, DMSO) and compare it to **2**, and attempt the successful conditions on the precursor to key "advanced target" triptycene **4** (Fig 1).

Supervision

The laboratory work will be conducted under the supervision of Dr Keith Andrews, Dr Luke O'Driscoll, and two PhD students working on macromolecular cage development in a brand-new laboratory. Andrews is a lab-active PI, and so supervision will typically be direct. O'Driscoll will be available for additional supervision where necessary (or for cover) as an expert in organosulfur chemistry, and the student will benefit from a shared group office and PhD students with direct expertise of the relevant triptycene chemistry. Additional training and supervision will be available from the analytical services staff. The student will discuss their work daily to reflect on learning points.

Training

The student will learn advanced organic chemistry research and synthesis techniques, including: use of electronic lab notebooks; planning experiments; researching reaction conditions; safety COSHH assessments; Schlenk technique; handling air sensitive reagents; NMR-analysis, including training using the educational SimpleNMR software developed at Durham;[3] manual and automated chromatography; working in a research team; presenting research results; writing a research report; analysing mixtures, advanced TLC, mass spectrometry/LCMS; measuring pK_a values; error analysis; time management; independent project steering. This training will be provided "on the job", from two experienced demonstrators (PI, co-I) and two PhD students, and will perfectly prepare the student for a successful MChem project and beyond. Since the student has expressed a desire to learn/explore computational methods, they will be exposed to the department HPC cluster (Hamilton) for running DFT experiments to calculate the pK_a of the acid/thioacid. Finally, the student will be expected to write a report of their work, and present their project to the research group.

Timescale

Week1	Week2	Week3	Week4	Week5	Week6	Week7	Week8
Safety, familiarisation, lab book training; experiment planning	Synthesise **6** & **2**; route planning for **3**; submit HPC calculations		Screen conditions to form **5**. Characterise **5**. Analyse DFT data. Plan pK_a experiments		Measure pK_a values. If time, apply new route to synthesise **advanced target**, or measure kinetics of alkylation (nucleophilicity).		Write report; present work to group.

The schedule has ample contingency time/extra experiments built in, since lab projects can ebb and flow. Following induction, the student will have three key synthetic steps to master over 7 weeks. If they excel, there will be scope for extending the methodology, and measuring physical chemical properties of the made compounds. Most of the training will be provided by demonstration in practical conditions, but weeks 1 and 8 are set aside for lab-adjacent skills development.

Key objectives

- Learn advanced techniques to master the synthesis of **6** and **2**, which are useful for the group.
- Plan, discuss, and execute a sustainable route to novel triptycene **3** from **2**.
- Measure the pK_a and relative nucleophilicity of **3** compared to **2**.
- Use DFT to optimise the geometry and calculate the pK_a of **3** and **2** on the supercomputer.
- Bonus: Apply successful conditions to access the "advanced target" triptycene, ready to be incorporated into a cage catalyst.
- This data will form part of a future publication.

References

1 K. G. Andrews, T. K. Piskorz, P. N. Horton and S. J. Coles, *J Am Chem Soc*, 2024, **146**, 17887–17897.

2 S. M. Mali and H. N. Gopi, *J Org Chem*, 2014, **79**, 2377–2383.

3 E. Hughes and A. M. Kenwright, *MRC*, 2024, **62**, 556–565.