

Bath Monash Global PhD Programme in Sustainable & Circular Technologies

Project Title:	Sodium: an abundant workhorse metal for the enantioselective synthesis of bioactive heterocycles
Supervisors at Bath:	Prof Steve Bull
Supervisors at Monash:	Prof Phil Andrews (lead) and Dr Vicki Blair
Home Institution:	Monash
Indicative period at Host Institution:	12-18 months

Project Summary

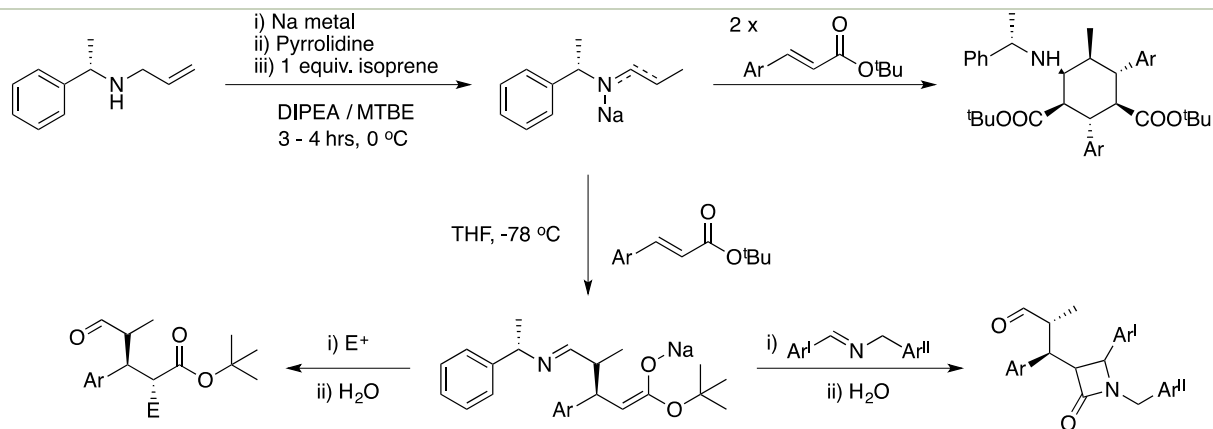
While the first organometallic compounds were comprised of sodium, synthetic implementation of organosodium reagents has idled when compared to their lithium equivalents. Application in synthesis has been hampered by hazardous preparative methods,<sup>1,2</sup> as well as generally inferior atom economy.

However, there are considerable environmental advantages that Na metal boasts over its counterparts.<sup>3-5</sup> In particular, it is easily obtainable from ocean water given its abundance is approximately nine times greater than Mg and more than  $3 \times 10^4$  that of Li, making it effectively an infinite resource on which organometallic chemists can rely upon.

Recent promising developments have shown convenient preparation of strong bases, such as Na diisopropylamide, can be obtained directly from Na metal using electron carriers, such as isoprene.<sup>6,7</sup> This method is completely halogen free and effectively reduces the number of metal atoms required per equivalent of base, by half. Furthermore, an altered form of this method has proven effective in preparation of sodium (*S*)-*N*-( $\alpha$ -methylbenzyl)propylamide- a precursor that can be used in a highly efficient diastereoselective cascade reaction.<sup>8</sup> This procedure yields **six** new contiguous chiral centers from two consecutive Michael additions followed by a ring annulation step, with this highly stereoselective methodology having been used to generate a diverse library of novel chiral cyclohexylamine derivatives.

Recent expansion of this work has shown this type of reactive Na enolate intermediate to be highly versatile that can be used for the convenient preparation of highly functionalised aldehydes with a high degree of stereocontrol. Of particular interest is the potential to trap the intermediate with imines to allow for a three component, one-pot synthesis of a series of novel antibacterial  $\beta$ -lactam rings that can be further functionalised via their synthetically versatile aldehyde functional groups.

$\beta$ -lactams are critical component of families of antibiotics such as cephalosporins, carbapenems and carbacephems that are key for treating many chronic bacterial infections. Unfortunately, many of these  $\beta$ -lactams have developed drug resistance in bacteria emanating from the evolution of bacterial metallo-lactamases. Therefore, new designer  $\beta$ -lactam drugs are needed which are not affected by this enzyme and so this new synthetic approach has the potential to provide a vital new weapon in the armoury of antimicrobials available for clinicians.



1. M. Schlosser, *Angewandte Chemie International Edition in English*, 1964, **3**, 362-373.
2. M. Schlosser, *Angewandte Chemie International Edition in English*, 1964, **3**, 287-306.
3. T. C. Wanger, *Conservation Letters*, 2011, **4**, 202-206.
4. V. Flexer, C. F. Baspineiro and C. I. Galli, *Sci. Total Environ.*, 2018, **639**, 1188-1204.
5. C. Grosjean, P. H. Miranda, M. Perrin and P. Poggi, *Renewable and Sustainable Energy Reviews*, 2012, **16**, 1735-1744.
6. P. C. Andrews, N. D. R. Barnett, R. E. Mulvey, W. Clegg, P. A. O'Neil, D. Barr, L. Cowton, A. J. Dawson and B. J. Wakefield, *J. Organomet. Chem.*, 1996, **518**, 85-95.
7. D. Barr, A. J. Dawson and B. J. Wakefield, *J. Chem. Soc., Chem. Commun.*, 1992, 204-204.
8. M. Koutsaplis, P. C. Andrews, S. D. Bull, P. J. Duggan, B. H. Fraser and P. Jensen, *Chem. Commun.*, 2007, 3580-3582.

#### Features of the programme

- PhD researchers will be registered at both institutions and will be awarded a joint PhD degree.
- PhD researchers will be jointly supervised by academics from both Monash and Bath Universities.
- All PhD researchers in the joint programme will also undertake a bespoke advanced training plan covering a range of topics focusing on sustainability.
- Applicants can apply to either Monash University or the University of Bath as their nominated home institution.
- PhD researchers will undertake a period of no less than 12 months at the partner institution.
- Up to four scholarships/studentships will be offered. Additional and suitably qualified applicants who can access a scholarship/studentship from other sources will be also considered. Evidence of funding must be provided.
- The scholarships/studentships include:
  - a *full tuition fee sponsorship* provided by Monash or Bath for the course duration (up to a maximum 42 months). Note, however, that studentships for Bath-based projects will provide cover for UK/EU tuition fees ONLY.
  - a *living allowance (stipend)* provided by Monash or Bath Universities.

Note: Overseas Student Health Cover (OSHC) must be paid by the student, unless covered by the university.

#### How to apply

You MUST express interest for three projects in order of preference. Please submit your application at the Home institution of your preferred project ('Home' institution details can be found in the project summary).

However, please note that you are applying for a joint PhD programme and applications will be processed as such.

**The deadline to submit applications is 11th April 2021**

### ***Monash University***

Expressions of interest (Eoi) can be lodged through <https://www.monash.edu/science/bath-monash-program>. The Eoi should provide the following information:

CV including details of citizenship, your Official Academic Transcripts, key to grades/grading scale of your transcripts, evidence of English language proficiency (IELTS or TOEFL, for full requirements see: <https://www.monash.edu/graduate-research/faqs-and-resources/content/chapter-two/2-2>), and two referees and contact details (optional). You must provide a link to these documents in Section 8 using Google Drive (Instructions in Section 8).

### ***University of Bath***

Please submit your application through the following link: <https://www.csct.ac.uk/bath-monash-global-phd-programme/>

Please make sure to mention in the “finance” section of your application that you are applying for funding through the joint Bath/Monash PhD programme for your specified projects.

In the “research interests” section of your application, please name the three projects you are interested in and rank them in order of preference. Please also include the names of the Bath lead supervisors.