

Bath Monash Global PhD Programme in Sustainable Chemical Technologies

Project Title:	Addressing puzzles of enantioselective organocatalysis: A computational and physical organic chemistry approach.
Supervisor at Bath:	Dr Mathew Grayson
Supervisor at Monash:	Prof. David W. Lupton (lead)
Home Institution:	Monash University
Indicative period at Host Institution:	12 months with exact dates to be confirmed

Project Summary

Enantioselective organocatalysis has evolved rapidly and now provides access to a dizzying array of functional materials. Beyond the academic lab organocatalysis being exploited to solve problems in industry. For example, Merck recently employed an amine catalysed Michael addition in the penultimate step of the commercial route to Letemovir, an approved antiviral for cytomegalovirus infections.

Despite significant attention a range of fundamental questions in this field remain. Drawing from recent experiences from the Lupton lab (Monash University) this collaborative project aims to exploit advanced theoretical computational approaches (Grayson, University of Bath), combined with physical organic chemistry to address a series of puzzles common to the field. It is envisaged that based on the interests of the student studies in this project can be focused from fundamental theoretical chemistry, through to physical organic chemistry, and enantioselective reaction discovery. For the computational studies, no prior molecular modelling experience is required. Training can be provided in the use of computational methods to model chemical reactions, a skill useful across all areas of the chemical sciences in both academic and industrial settings. Training in Python, a broadly used and general-purpose programming language, will also be provided for those interested though no programming is necessary for the project.

Specifically, we will focus on two significant problems:

- (1) *Entropy controlled enantioselective transformations.* While enantiodetermining transition states of many reactions are thought to be largely controlled by enthalpy in a number of cases they appear to be entropically controlled, resulting in reactions that are more enantioselective at higher reaction temperatures. While conceptually this can be rationalised, the detail regarding why this is the case, and indeed how this can be exploited to deliver improvements in synthesis, are yet to be developed. Computational methods will be used to calculate the structure and free energy of the transition states of such reactions which will provide a detailed insight into the entropic and enthalpic contributions to the observed selectivity. These insights will then enable rational design of new reactions.
- (2) Electronic sensitivity of enantioselective transformations. The impact of the electronic demand of substrates on enantioselectivity is not fully appreciated. In this topic, we will examine a number of reactions that show profound sensitivity to electronic demand. Does an enhanced understanding on this phenomenon allow the design of new catalysts to overcome these limitations? Computational methods will again be used to understand these observations and to make predictions about the likely selectivity that can be achieved with new generation catalysts.