Innovative Enantioselective Methodology for Novel

*Introduce a new concept in catalytic enantioselective reactions using hypervalent iodine (III) reagents and chiral hydrogen bond donors*

*Generate a range of chiral fluorinated heterocycles for drug discovery*

*Use mechanistic studies to understand the key influences on the enantiodetermining step*

Project Description

An important strategy in the development of new pharmaceutical products is the incorporation of fluorine because of its beneficial influence on the metabolic stability, lipophilicity and bioavailability of biologically active molecules. Since heterocycles often form the core structure in drug candidate molecules, fluorinated heterocycles are highly desirable targets and there is a demand for molecules containing a fluorine substituent on a stereogenic carbon. Most of the substantial advances in enantioselective fluorinations have focussed on using expensive electrophilic fluorinating reagents which are made from elemental fluorine. In contrast, enantioselective catalysis with nucleophilic fluoride sources has progressed at a much slower rate.

In 2013 we reported the preparation of the hypervalent iodine(III) reagent 1 from cheap sources of nucleophilic fluoride and its application as a new fluorinating reagent. Since then, the reaction scope of 1 has extended significantly and it is now commercially available. Furthermore, 1 offers new regioselectivity and access to novel fluorinated heterocycles which cannot be prepared from established electrophilic fluorinating reagents such as Selectfluor (Scheme 1). However, these reactions normally require a transition metal to activate 1 by coordinating to the fluorine atom.

More recently, we reported that 1 can be activated by hydrogen bonding to hexafluoroisopropanol and crucially, it removed the need for transition metals. In unpublished studies we have now established that only 10 mole% of a bidentate urea is required to activate 1 in its reaction with an unsaturated hydrazone to generate a new fluorinated heterocycle in 75% yield.

The aim of this research proposal is to establish a new concept in catalytic enantioselective fluoro cyclisation which combines chiral hydrogen bond donors with the fluoride-derived iodine(III) reagent 1 for the first time (Scheme 2). The fluoro cyclisation of alkenes with 1 is an attractive single step procedure for constructing new fluorinated...
heterocycles and an enantioselective version would enable the preparation of carbon-fluorine quaternary stereogenic centres, which is one of the most challenging tasks in organofluorine chemistry.

Methodology

This project will provide training in a broad range of modern synthetic organic chemistry, particularly enantioselective catalysis, air- and moisture-sensitive reactions, and a full range of analytical techniques (multinuclear NMR spectroscopy, chiral GC, chiral HPLC, mass spectrometry and chromatography). As part of the project, the student will gain comprehensive knowledge in organofluorine chemistry and organocatalysis.

Furthermore, the student will develop good organisational, problem-solving and communication skills, both written and verbal. The Synthesis and Catalysis weekly research group meetings provide the opportunity to present work, discuss the latest chemistry research and learn about new areas of synthetic chemistry. The student will attend national RSC meetings where they will be expected to present posters (2nd and 3rd years) and to deliver an oral presentation at the RSC Fluorine Postgraduate Meeting (4th year).

Advantages:
- New fluorinated heterocycles
- High value, chiral products
- Operationally simple
- No toxic transition metals

A new concept in catalytic enantioselective fluorocyclisations will be established by combining chiral hydrogen bond donors with the hypervalent iodine(III) reagent 1 for the first time.

Further Reading


Application Instructions

When applying, please ensure we have received all of the following required documents by Tuesday 4th February 2020:

- Please submit your PhD application using the Apply Button at the bottom of the funding page.
- Include with your application:
• 2 academic references - if you have reference letters please upload in the space provided. If not please enter the contact details, including email address, of your referees in the text boxes provided. Please advise your referees of the application closing date.
• CV
• Personal statement explaining why you want to be considered
• Undergraduate transcripts
• If you have completed your undergraduate degree, we will also require your undergraduate degree certificate
• If you have completed a postgraduate degree, we will also require your transcripts and degree certificate
• Evidence of English proficiency if applicable and available.

In the funding section of the application please select Studentship and in the drop down menu select GTA.

In the Proposal section please enter the supervisor’s name and project title you are applying for. If you want to be considered for more than one project enter details of both projects - you do not need to submit more than one online application.

If we do not have the required documents by the closing date, your application may not be considered for the studentship.