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**Marie Curie International Incoming Fellowships (IIF)**

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| **Project No.**: | 625471 |
| **Acronym**: | ARNIIF |
| **Full Title**: | Asymmetric reactions of nitrile compounds: an approach to the synthesis of bioactive molecules |
| **Research Fellow**: | Dr Arghya Sadhukhan |

# PROJECT FINAL REPORT

**Period covered**: 01/10/2014 – 30/09/2016

**Years 1 and 2 of 2**

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| **Start date of project**: | 01/10/2014 |
| **Project Coordinator**: | Professor Iain Coldham |
| **Contact details**: | i.coldham@sheffield.ac.uk |
| **Organisation name**: | University of Sheffield, UK |
| **Organisation PIC**: | 999976881 |

**Date of submission of mid-term report**: 08/10/2015

**Project website address**: http://icoldham.staff.shef.ac.uk/research_nitriles.html

# Final Report

## CONTENTS

# 1. Final publishable summary report

## 1.1 An executive summary

Synthetic chemistry plays a key role in the preparation of new molecules that can find use as new drugs, agrochemicals, fine chemicals, polymers, or high value materials. Of particular importance is the ability to form carbon-carbon bonds in a controlled manner, as this allows the construction of the carbon frameworks in the desired molecules. With this bond formation often comes the necessity to control the absolute configuration at the carbon atom, in other words, which mirror image of the product is formed. This is crucial in drugs as different mirror images of small molecules often have different biological properties, since they interact with the large biomolecules of nature (enzymes) that themselves exist as single mirror image forms. An important method to prepare carbon-carbon bonds is to remove a proton from a compound using a base (usually a group I or group II metal species) and to react the new metallated intermediate with an electrophile. A useful compound that is very amenable to this deprotonation is a nitrile and good yields of the substituted compound with a new carbon-carbon bond can be formed. However these products are formed as mixtures of mirror images and it is seen as a huge challenge in the synthetic chemistry community to be able to transfer the optical purity from the nitrile to the product.

This Marie Curie International Incoming Fellowship commenced in October 2014 and ran for two years. The objectives of the Fellow (Dr Arghya Sadhukhan) were to investigate whether it was possible to perform selective reactions with optically active metallated nitriles. Six workpackages were studied, involving WP1 and 2: the preparation of chiral nitriles and their metallation; WP3: the rate at which the metallated mirror images interconvert; WP4: a study of their structures; WP5: their ability to undergo further transformations; WP6: any selectivity in the presence of chiral ligands. All six workpackages were studied and we were delighted to find that highly selective reactions were discovered. Workpackages 1–4 were most successful and allowed the formation of products without significant loss of optical activity and we were able to quantify the rates of interconversion, together with proposing plausible structures.

The Marie Curie Fellowship allowed Dr Sadhukhan to enhance his strengths in research, to experience the European research environment, and to transfer knowledge and skill to other researchers, particularly through the co-supervision of two PhD students. In addition, the Fellow attended personal development and training events. The results of the research have been published in a high impact journal and by presentations at conferences.

## 1.2 A summary description of project context and objectives

The central theme of the research was a study of the configurational stability and reactivity of metallated nitrile compounds. Nitriles are compounds containing a carbon-nitrogen triple bond and have potential as building blocks for pharmaceutically relevant drugs and the Fellow joining the project, Dr Sadhukhan, had experience in handling this type of compound in single mirror image form. At the University of Sheffield, we had some preliminary results that suggested that metallated nitriles could have configurational stability, so Dr Sadhukhan was a good match for this study.

The original objectives discussed the chemistry of metallated nitriles and noted that there were currently few approaches known for their asymmetric alkylation. We stated that 'the primary objective of this research is to develop a new, general method to achieve the asymmetric alkylation of metallated nitriles.'

We proposed two main approaches:

(i) Taking a chiral, enantiomerically pure, nitrile precursor and formation of a chiral, configurationally stable metallated nitrile, which is quenched by an electrophile.

(ii) Taking a racemic nitrile and formation of a chiral metallated nitrile that is resolved by a chiral ligand, followed by quenching with an electrophile.

The original application described some known structures of metallated nitriles, in which lithium counterions prefer to reside on the nitrogen atom, but softer metals prefer to reside on the carbon atom. We had obtained some preliminary results with a magnesium counterion, which should prefer to reside on carbon, that had allowed good enantiomer ratios with an alpha-oxygenated nitrile compound (*Angew. Chem. Int. Ed.* **2013**, 7700).

The research plan in the proposal then outlined chemistry to explore this objective. Six workpackages were described in the original application and all six were investigated during this Fellowship. The results are described in the next Section.

## 1.3 A description of the main S&T results/foregrounds

*Work package 1*: Deprotonation of chiral nitriles

Milestone 1 aimed to prepare chiral nitrile compounds with a focus on α-amino nitriles due to Dr Sadhukhan's experience in this area. We therefore started the project with the preparation of the α-amino nitrile N-Boc-2-cyanopiperidine from pipecolic acid. This was compound **15** in the original proposal and was made as a racemic mixture and as a single mirror image (S enantiomer).

Milestone 2 aimed to prepare other chiral nitriles by a linked PhD student. Although the original suggestion was to prepare α-oxygenated nitriles, we had previously tested carbamates (compound **10** in the original proposal, which led to a publication in *Angewandte Chemie Int. Ed.* **2013**, 7700) and before Dr Sadhukhan arrived, we tested other derivatives and the ether **11**, which gave lower selectivity (manuscript submitted Sep 2016 to the journal *Comptes Rendus Chimie* – this has just been accepted in Nov 2016). We decided that it would be better to use the success with the piperidine and to extend this to the related benzene-fused derivative (N-Boc-2-cyano-tetrahydroisoquinoline). This was prepared successfully by the PhD student from the corresponding carboxylic acid. Therefore ***we prepared a selection of chiral nitriles, as described in Milestones 1 and 2***.

Milestone 3 involved the deprotonation of these nitriles and a study of their reaction and selectivity. The chiral nitrile N-Boc-2-cyanopiperidine was treated with a base and the progress of the metallation was followed by React-IR spectroscopy. We found that the best results were obtained by adding at least two equivalents of the base TMPMgCl. By using the base LDA, racemic products were obtained after electrophilic quench. However we were pleased to find that enantiomerically enriched products could be isolated from the magnesiated intermediate. Other bases were also tested together with different temperatures and we selected as the optimum method the use of three equivalents of TMPMgCl at –104 °C in THF. By using a variety of electrophiles this allowed us to prepare enantiomerically enriched 2,2-disubstituted piperidine products with reasonable yields (about 60%) and enantioselectivities (about er 90:10). Some electrophiles could be added in situ but the chemistry was remarkably successful even by allowing initial deprotonation followed by subsequent electrophilic quench. Under these conditions one might expect significant loss of selectivity due to the lability of the intermediate metallated species.

We later found that improved results could be obtained by changing the solvent to diethyl ether. Under these conditions the metallated nitrile was noticeably more configurationally stable and ***we were able to improve the selectivities up to 98:2. These were excellent results that demonstrated the feasibility of the proposed work (Milestone 3).***
The majority of the grant was spent working on this chemistry and optimising the conditions, determining the selectivities, and the absolute configurations of the products. **This work has been written for publication and was submitted to the journal *Chemical Science* in August 2016. It was accepted for publication in October 2016 and is now available on-line (http://dx.doi.org/10.1039/C6SC03712G).**

In year two, when a good number of successful results had been obtained with the 6-membered ring, Dr Sadhukhan investigated some different nitriles (the corresponding 4- and 5-membered ring compounds). Although these could be prepared, we were surprised to find that attempted metallation of the 4-membered ring compound did not give any product, even using LDA as the base. The 5-membered ring (compound **14** in the original proposal) looks more promising but yields have been low so far and this will require further work in future.

Milestone 4 described the deprotonation of the nitriles prepared by the PhD student. This proved much more difficult than expected and only a low yield with one electrophile was obtained and the selectivity was poor. We do not understand the reasons for this as the substrate is quite similar to that used by Dr Sadhukhan.
Both Dr Sadhukhan and the linked PhD student then moved to prepare some more chiral nitrile compounds. In particular, they prepared some acyclic nitriles. A simple chiral alkyl nitrile (compound **19** in the original proposal) was prepared successfully, as were some chiral nitriles derived from the alpha-amino-acids phenylalanine and from alanine (for example compound **16** in the original proposal) and these represent yet further examples of Milestones 1 and 2. Compound **19** did not undergo metallation with TMPMgCl. We are in the process of testing the deprotonation and reaction of the acyclic alpha-amino nitriles (further examples of Milestones 3 and 4). This is now the subject of current work by the linked PhD student as Dr Sadhukhan has finished on the project.

*Work package 2*: Sulfide–magnesium exchange study
Milestone 5 aimed to prepare chiral sulfides with the stereocentre alpha to the nitrile. This was achieved successfully with the 2-cyanopiperidine. Although the parent S-phenyl compound (related to structure **24** in the original proposal) did not undergo sulfide–

magnesium exchange with isopropyl magnesium chloride, we were pleased to find that the corresponding 2-methoxyarylsulfide was amenable to this chemistry. The methoxy group probably helps to coordinate the magnesium to effect the sulfide–magnesium exchange. We were able to obtain different substituted products after electrophile quench. The key question in this research is whether the exchange and quench occur stereospecifically, or if the exchange promotes racemisation. ***It was noteworthy to discover that there was a high level of stereoretention in the chemistry (Milestone 5).*** The yields of the products were moderate and there was only partial loss of selectivity (enantiomer ratio dropped from 85:15 to about 80:20). The discovery of the ability to conduct such a transformation could open a new way to prepare metallated nitriles selectively. This has potential for synthesis, particularly if a stereoselective method to prepare alpha-thio-nitriles is developed that does not arise from simple deprotonation then quench with a sulfur-based electrophile. The results of this study were included in the *Chemical Science* publication.

*Work package 3*: Kinetic studies determination of the configurational stabilities
Milestone 6 described some physical organic chemistry to determine how fast the metallated intermediate racemises. It is clearly important to know such information to avoid loss of selectivity. Ideally the magnesiated intermediate would have good configurational stability, at least at low temperatures. By quenching this intermediate after different time periods, ***Dr Sadhukhan obtained good kinetic data on the configurational stability*** in THF and in diethyl ether. The first order log plots gave good straight lines from which we obtained the gradient and hence the rate constants. We found that the rate of inversion was relatively fast, even at –104 °C, with rate constants of $k = 6.5 \times 10^{-3}\ \text{s}^{-1}$ in THF and $4 \times 10^{-3}\ \text{s}^{-1}$ in diethyl ether. These equate to a half-life for enantiomerisation of only 2 min in THF and 3 min in diethyl ether. Therefore ***the intermediate organomagnesium species has low configurational stability. These data demonstrate successful achievement of Milestone 6*** for this compound. The results of these kinetic studies were included in the *Chemical Science* publication. In future we plan to obtain kinetic data for other chiral metallated nitriles.

*Work package 4*: Structural and computational studies
Milestone 8 planned to collaborate with Professor Hevia (University of Strathclyde, UK) and with Dr Meijer (University of Sheffield, UK) to gain information on the structures of the metallated intermediates. Dr Sadhukhan and I met with Professor Hevia at the 11th International Symposium on Carbanion Chemistry this year and discussed the possibility of

carrying out spectroscopic studies on the organomagnesium intermediate(s). In the chemistry, we do not observe crystalline intermediates in THF or ether (necessary for TMPMgCl formation), so no X-ray would be possible. As an alternative, 1H DOSY NMR was discussed and this could be helpful. However this would not be possible at the very low temperatures that are required to maintain the selectivity, particularly with the short half-life for enantiomerisation. It is quite possible that a different organometallic species is present prior to enantiomerisation, as the metal may relocate to the nitrogen atom of the nitrile over time or on warming. Therefore carrying out DOSY NMR on the racemic compound alone is unlikely to provide the information that is relevant to the enantioselective reactions and we decided therefore not to spend the time to attempt this in Strathclyde.

We did discuss the chemistry and possible structures with the computational chemist Dr Meijer. Density functional theory calculations on possible magnesiated intermediates were carried out in collaboration with Dr Meijer. We were pleased to obtain some energy-minimised structures that seemed plausible (and were different – and lower energy – from the bridged structures suggested by Prof Carlier on a different magnesiated nitrile). These structures place a magnesium ion on the carbon alpha to the nitrile together with another magnesium ion on the nitrogen atom of the nitrile. This fits with our experimental work in which we have shown that two equivalents of base are required. ***The computational studies have therefore given insight into possible structures (Milestone 8).*** The results of these DFT studies were included in the *Chemical Science* publication.

*Work package 5*: Application in total synthesis of bioactive compounds

Milestone 9 related to applying the chemistry for the synthesis of biologically relevant compounds. We stated in the original proposal that this will build on earlier parts. Indeed we would need to test the chemistry with some more nitriles before we could properly investigate this aspect. However we did study the conversion of some of the products to other derivatives, as would be necessary for the synthesis of biologically relevant targets. We found that the nitrile group in the product was very inert to reaction and we were unable to reduce or hydrolyse it. This was surprising given the wealth of related examples in the literature and may be due to the location of the nitrile in a hindered axial position at a quaternary centre. We did find that the S-pyridyl product could be converted to the alkene by simple heating and this chemistry could form the basis for the preparation of unsaturated nitriles. So Dr Sadhukhan spent some time attempting related elimination chemistry with other nitriles, but this was unsuccessful (the anion of cyclohexanenitrile did not quench with S-pyridyl benzenesulfonate although it was reactive to other electrophiles). The application of the chemistry will therefore require future work.

We did submit some of the nitrile compounds for biological screening. This is being carried out by Dr S. Baxendale in the Department of Biomedical Science at the University of Sheffield. There is expertise in the University with in vivo zebrafish screens and the plan is to test for modulators of versican expression and to test as anti-convulsants. We hope that this will lead to further collaboration with Biomedical Science in future to prepare related compounds that would be designed to give improved properties.

*Work package 6*: Dynamic resolution studies

Milestone 7 planned to make use of the kinetic data on the rates of enantiomerisation to carry out dynamic resolution with chiral ligands. We were aware that the chiral organomagnesium intermediate can undergo ready inversion. Therefore preparing the racemic mixture and addition of a chiral ligand that complexes to the metal would lead to diastereomeric intermediates that could have different reactivities or thermodynamic stabilities. This could allow us to resolve them by dynamic resolution under kinetic or under thermodynamic control. Dr Sadhukhan attempted to resolve the magnesiated intermediate with the chiral ligand sparteine. After electrophile quench the product obtained was always racemic, despite varying the conditions to attempt a kinetic resolution (slow quench) or thermodynamic resolution (low temperature quench). A different chiral ligand may be required but at present this approach has been unsuccessful. It is a potentially powerful way to make enantiomerically enriched nitriles so some further effort in this area would be worthwhile.

We also attempted to use a zinc or a copper base to effect the chemistry. However these did not deprotonate the nitrile. Therefore we would have to use a more basic zinc species in future if we explore this chemistry further.

Overall, ***the chemistry did not deviate from the proposed work in the original application. We were able to investigate all the aspects described, with particular emphasis on the first four (out of the six) work packages***. The fundamental chemistry (involving formation, deprotonation, and stereospecific electrophile quench) was successful for a 2-cyanopiperidine substrate. We investigated other substrates that were not successful and we are currently exploring the chemistry of other acyclic analogues. The resources were deployed as planned in terms of person-months (24 month position for Dr Sadhukhan) and costs for the research, although these were expended well in advance of the duration of the grant.

## 1.4 The potential impact and the main dissemination activities

This project has had a significant impact on the area of research of nitrile anion chemistry. For example, a recent e-mail (7 November 2016) from Professor Opatz (University of Mainz) who spotted our advanced article publication commented 'congratulations on your very nice paper in Chem. Sci. – with the structural analysis of Enders and Boche in mind, I would have never guessed that this can work!'

In addition, the project has made a huge impact on the research fellow, Dr Sadhukhan. He has benefitted from scientific and technical training in activities directly related to the project and has gained very valuable experience in the EU. He supervised two PhD students and helped to run a research laboratory. These activities have helped him to mature as an individual and as a research leader, by strengthening his ability to direct projects and manage a team. These aspects will impact the future employment that Dr Sadhukhan will undertake.

The main dissemination activities have been the reporting of the results through the presentation of the results at conferences and, in particular, through a very high impact publication in the scientific literature. This publication is in one of the top-ranking journals in chemistry (*Chemical Science*) with a very high impact factor and is highly regarded internationally. The work is open access and can be found at:

http://dx.doi.org/10.1039/C6SC03712G

Both Dr Sadhukhan and Prof Coldham disseminated the results of the research at several conferences. Dr Sadhukhan also presented his results at regular research group meetings and to visitors to the Department, thereby improving his communication skills. The results of the metallated nitrile chemistry have so far been presented at three international conferences and one national conference during the period of this grant. A highlight was the international symposium on carbanion chemistry in France, where Dr Sadhukhan was given the opportunity to present his work as a poster and to meet academics and industrial chemists from across the world. At the same meeting, Prof Coldham presented the results as a plenary lecture presentation. It is hoped from all these dissemination activities that particular interest in this science will be stimulated to lead to further work in this area.

## 1.5 The address of the project public website

http://icoldham.staff.shef.ac.uk/research_nitriles.html

# 2. Use and dissemination of foreground

## 2.1 Section A

We have disseminated the results of the research in one scientific refereed publication so far, together with presentations at several conferences (national and international), as outlined below. The journal *Chemical Science* is a highly respected internationally leading journal with impact factor 9.1 for 2015.

(i) List of scientific publications

**TEMPLATE A1: LIST OF SCIENTIFIC (PEER REVIEWED) PUBLICATIONS**

| no. | Title | Authors | Title of periodical | Publisher | Place | Date / Year | Pages | Permanent identifiers / DOI | Open access ? |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Highly enantioselective metallation–substitution alpha to a chiral nitrile | A. Sadhukhan, M. C. Hobbs, A. J. H. M. Meijer, I. Coldham | Chemical Science | Royal Society of Chemistry | Cambridge, UK | Oct 2016 | in press | 10.1039/C6SC03712G | Yes |

(ii) List of all dissemination activities

**TEMPLATE A2: LIST OF DISSEMINATION ACTIVITIES**

| NO. | Type of activities | Main leader | Title | Date/Period | Place | Type of audience | Size of audience | Countries addressed |
|---|---|---|---|---|---|---|---|---|
| 1 | Web site | I. Coldham | The importance of nitriles in chemistry | Jul 2015–present | USFD | all | global | worldwide |
| 2 | Talk at international Anatolian Conference | I. Coldham | Asymmetric Organometallic Reactions aided by *in situ* IR Spectroscopy | 18/03/2015 | Antalya, Turkey | academic and industrial chemists including PhD students | 250 | worldwide |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 3 | Poster at national conference RSC Midlands meeting | A. Sadhukhan | Enantioselective metallation–substitution alpha to a chiral nitrile | 11/04/2016 | Birmingham, UK | academic and industrial chemists including PhD students | 80 | UK |
| 4 | Talk at international conference ISCC-11 | I. Coldham | Synthesis and Reactions of Chiral Organometallics of Saturated Nitrogen Heterocycles | 18/07/2016 | Rouen, France | academic and industrial chemists including PhD students | 120 | worldwide |
| 5 | Poster at international conference ISCC-11 | A. Sadhukhan | Enantioselective metallation–substitution alpha to a chiral nitrile | 18–21/07/2016 | Rouen, France | academic and industrial chemists including PhD students | 120 | worldwide |
| 6 | Poster at international conference SAHOC | A. Sadhukhan | Enantioselective metallation–substitution alpha to a chiral nitrile | 01–02/09/2016 | Sheffield, UK | academic and industrial chemists including PhD students | 100 | worldwide |

## 2.2 Section B

(A) There are no intellectual property rights (patents, trade marks, registered designs, utility models, or other) applied for as as results of this research. All the results are openly available to the public domain. The results above have been made available on the web, at conferences, and in open access format in the journal *Chemical Science* which is freely available for anyone in the public to download and read. Any further results will be published in the scientific literature and made available.

(B) There is no confidential information in this project. The main results of the work have now been published in the journal *Chemical Science* and are freely available. Further results may lead to work that could be exploited in the pharmaceutical or fine chemical sectors. If results are obtained that have potential for exploitation then these will be discussed with the University of Sheffield commercialisation team that deals with intellectual property and business development (https://www.sheffield.ac.uk/ris/contacts/commercial).