Approaches to the synthesis and modification of nitrogen-based heterocycles

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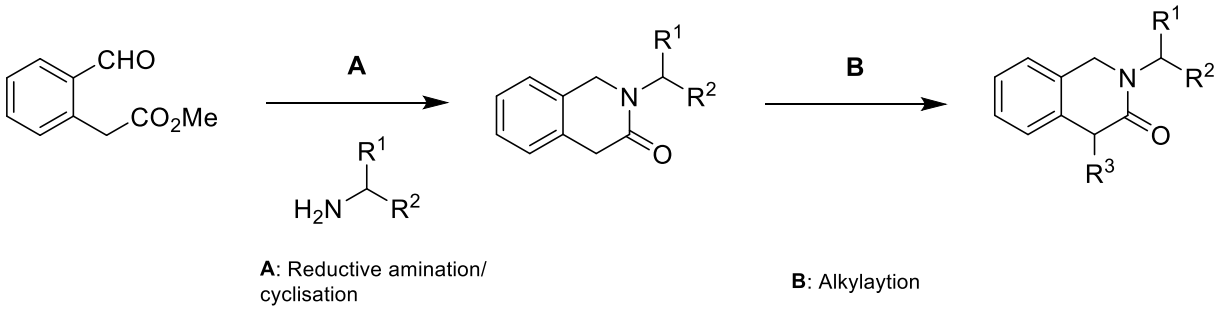
Abstract

This thesis contains an investigation into the synthesis and subsequent modification of nitrogen-based heterocycles, more specifically dihydroisoquinolinone scaffolds. A library of over 30 compounds was developed based on this pathway.

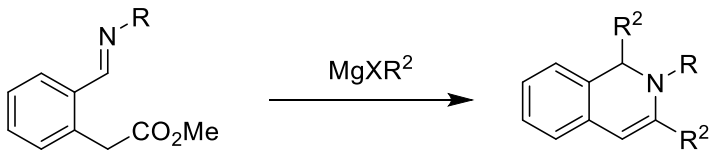


A: Reductive amination/ cyclisation

B: Alkylaytion

The initial aim of the project was to build a compound library based around the compound known as ICG-001; an inhibitor of the human WNT pathway. Several heterocyclic structures analogous to ICG-001 were proposed as target molecules. The final outcome of this project differed somewhat from this initial goal, but modifications had to be made to account for the difficulties encountered during the synthesis of these molecules.

The potential for further modification of the series using Grignard chemistry was also explored:



Overall, this Thesis comprises the successful development of a methodology for generating functionalised dihydroisoquinolinone derivatives. Efforts were also made into generating stereoselective products with limited success. Further modification of these molecules was also explored and yielded some unexpected results.

Abbreviations

AIBN – azisobutyronitrile

BCF – Tris(pentafluorophenyl) borane

CAN – Ceric Ammonium Nitrate

CDI – 1,1'-carbonyldiimidazole

C18 – octadecyl carbon chain bonded silica

DABCO - 1,4-diazabicyclo[2.2.2]octane

DCE – 1,2-dichloroethane

DDQ - 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone

DEA – Diethylamine

DIBAL-H – Diisobutylaluminium hydride

DIC – *N*, *N*'-diisopropylcarbodiimide

DIEA – *N,N'*-diisopropylethylamine

DMF – *N,N'*-dimethylformamide

DMF.DMA – *N,N'*-dimethylformamide dimethyl acetal

DMP – Dess-Martin periodinane

DMSO – Dimethyl Sulfoxide

DPPP – 1.3-Bis(diphenylphosphino)propane

GSK - GlaxoSmithKline

HATU – Hexafluorophosphate Azabenzotriazole Tetramethyl Uronium

HMPA – Hexamethylphosphoramide

HOAt – 1-hydroxy-7-azabenzotriazole

IBX - 2-iodoxybenzoic acid

IC_{50} – Half maximal inhibitory concentration

LCMS – Liquid Chromatography – Mass Spectrometry

m-CPBA – *Meta*-chloroperoxybenzoic acid

NBS – *N*-bromosuccinimide

NIS – *N*-Iodosuccinimide

NMR – Nuclear Magnetic Resonance

PMB – *Para*-methoxybenzene

PPA – Polyphosphoric acid

p-TsOH – *para*-toluenesulfonic acid

SAR – Structure Activity Relationship

S_nAr – Nucleophilic aromatic substitution

STAB – Sodium triacetoxy borohydride

TFA – Trifluoroacetic acid

TFAA – Trifluoroacetic anhydride

THF – Tetrahydrofuran

TMS – Trimethylsilyl

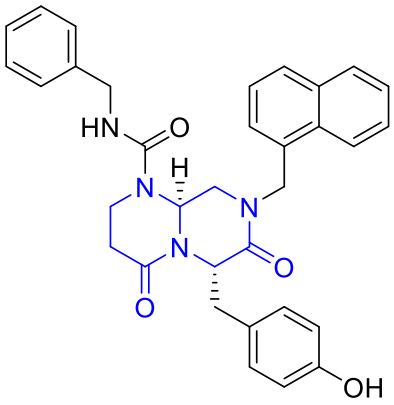
UV – Ultraviolet

WNT – Wingless-Related Integration Site

Contents

Chapter 1: Introduction

The initial aim of this project was to develop a "Fibrosis Toolbox" i.e. a library of easily modifiable analogues designed to have potential activity in fibrotic biological pathways. The toolbox in this case was to be a library of molecules analogous to the known drug molecule ICG-001 (**1**).



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1.1 Project Basis -ICG-001

ICG-001 is a relatively complex molecule containing a tetrahydro-2H-pyrazino-[1,2-a]-pyrimidine-4,7-dione core (highlighted in blue above). It is a beta turn mimetic[1] with a rigid core structure.

- Activity in WNT pathway[2] – IC_{50} = 3µM
- Selectively inhibits the WNT/Beta-catenin pathway
- High molecular weight small molecule - 548
- Two stereogenic centres
- Relatively rigid core with complex nitrogen enrichment
- Contains amino acid derivatives which should ease synthesis

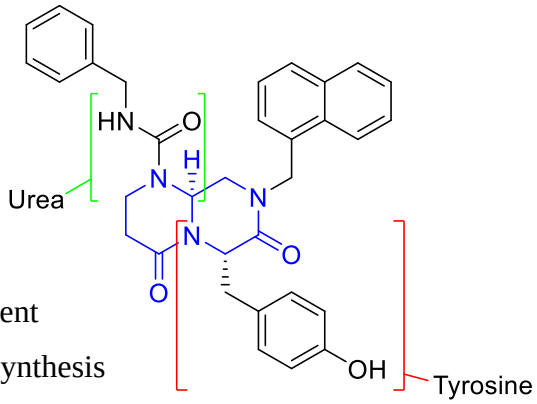
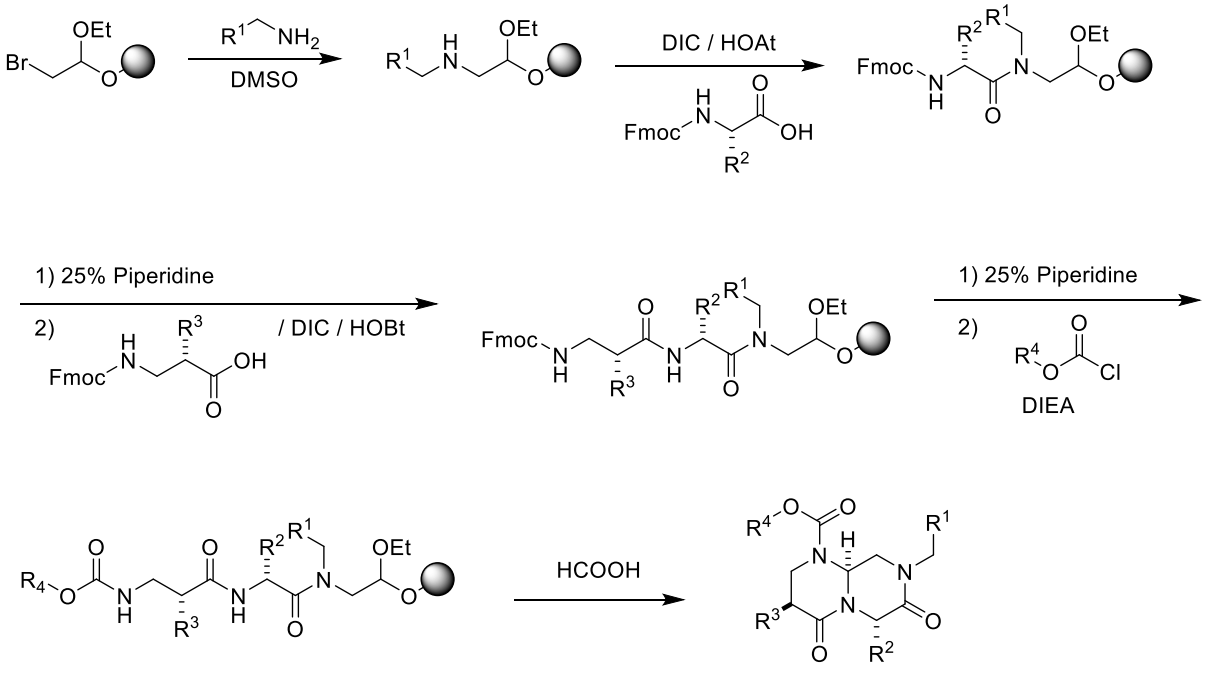


Fig. 1.1 *– ICG-001 and its properties*

ICG-001 was first developed by Kahn *et al.*[3] as a potential drug for colorectal cancers. It was synthesised as part of a library of similar compounds and was found to be the best performing of said compounds, having activity (IC_{50} = 3µM) when targeting a specific point within the WNT/beta-

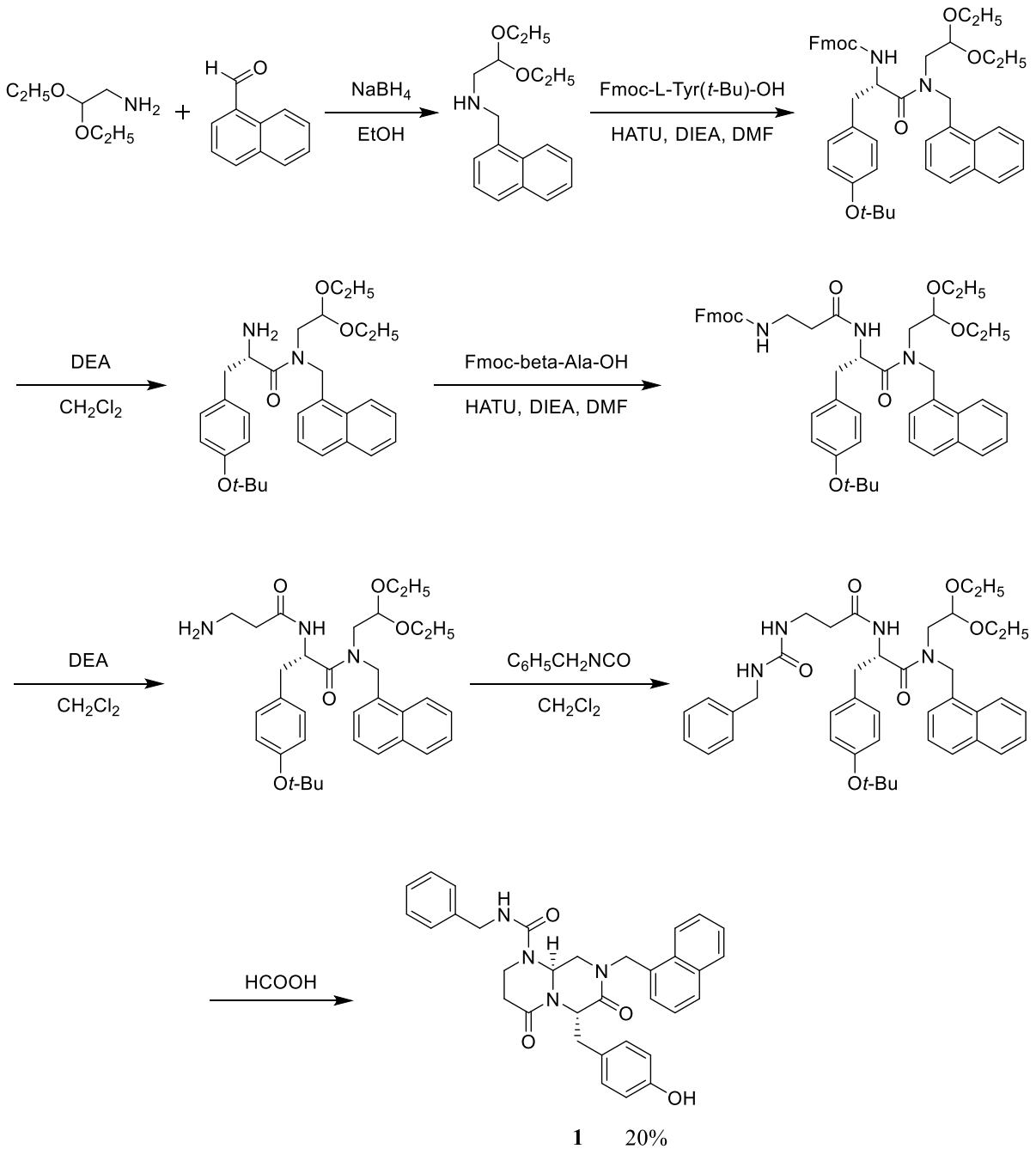
catenin pathway.[4] (IC_{50} is a measure of drug potency. In this case an IC_{50} value of 3 μM means that at this concentration, half of all of the target enzymes in the body have been inhibited) While its lack of potency and high molecular weight makes ICG-001 a (relatively) poor drug molecule in and of itself, it is a very useful starting point given its selectivity and specificity. It was this selectivity that led to it being designated the starting molecule for this project. The initial aim of the PhD was to develop a library of compounds analogous to ICG-001 that could have an effect on the WNT/beta catenin pathway, specifically with a view to having an effect on fibrotic cellular processes.[5–7] The WNT/beta catenin pathway is highly involved in the development of fibroblasts, which lead to collagen deposition and ultimately, scar-tissue formation.[6] This can have adverse effects on biological systems by leading to the replacement of active tissue with scarring, causing that system to malfunction. It was hoped that a new potential lead compound may be discovered from the development of this "toolbox".

The initial synthesis of ICG-001 involved multiple addition and deprotection steps to a resin bound base molecule before acidic conditions facilitated the final release of the cyclised compound.[1] (**Scheme 1.1**) All of the compounds in the initial library that led to the discovery of ICG-001 were synthesised in this manner.



Scheme 1.1

The benefits of this synthesis method were that it allowed for the molecule to be removed from the reaction mixture with ease between each stage of the synthesis, as the resin could be filtered out of the reaction, washed and placed into the next phase of the reaction without going through any arduous purification between synthetic steps. This sort of methodology is very useful when rapidly generating analogues but is less useful when it comes to generating large amounts of a single compound. A solution phase synthesis of the compound, was later developed by Piergentili *et al.*[8] specifically for ICG-001, in order to generate the compound in large enough quantities to study it further. (**Scheme 1.2**)



Scheme 1.2

This methodology resulted in a 20% overall yield of the final product, which is relatively low. The multiple protection/deprotection steps in the synthesis likely only serve to exacerbate this problem. Not only that but attempts to repeat this synthesis in the lab during the course of this PhD led to repeated failure at step 2 of the reaction scheme. Multiple attempts to perform the first amide coupling were attempted using various coupling agents and in all cases, the initial amide coupling product was never recoverable. Thus, the overall synthetic pathway presented by Piergentili *et. al.* is questionable. Clearly an improved methodology for accessing ICG-001 analogues was necessary.

1.2 Beta turn mimetics and the WNT pathway

1.2.1 Beta turn mimetics

A beta turn is defined as a protein structure made up of 4 amino acids in a chain that cause a change of direction in the polypeptide chain. To identify them, each of the amino acids in the sequence is labelled (i, i+1, i+2 and i+3). If a hydrogen bond exists between the carbonyl functional group of the i residue and the amide proton of the i+3 residue, the sequence is said to be a beta turn. Alternatively, if the alpha carbon atoms of residues i and i+3 have a distance of less than 7 Å between them, they are also said to be a beta turn, though this definition is less common.[9] (**Figure 1.2**)

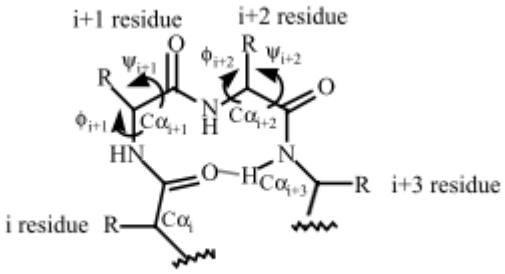


Fig. 1.2 *- General structure of a beta-turn*[10]

Beta turns are a common motif found on the outer edges of protein structures. This is mainly because they provide a method for proteins to fold back in on themselves. They often act as recognition elements for intermolecular interactions that regulate and control biological functions.[11] This, combined with their increased bioavailability and pharmacokinetics when compared to large, peptide based drugs,[12] has led them to receive a great deal of attention from the medicinal research community.[13–19] Any drug which mimics this motif is known as a beta turn mimetic.

1.2.2 WNT pathway

The WNT pathway is a highly conserved and incredibly important biological pathway that plays a variety of vital roles in the body. (**Figure 1.3**) In the broadest terms, it is responsible for the regulation of cell proliferation, maintaining tissue homeostasis and for the differentiation of cell lines in embryonic development.[20] It is very well-studied and largely well understood, however the development of drug molecules that can target the WNT pathway has proved very difficult. The pathway has many methods of circumnavigating interruptions to its processes through it's the fact that it has numerous redundancy pathways, and not all of these are fully understood.[21] Amongst the vast number of conditions that have been linked to malfunctions on the WNT pathway are cancer,[22,23] early onset osteoporosis, aortic calcification,[23] system sclerosis[24] and it has even been found to have an involvement in Alzheimer's disease.[25]

β-catenin is part of the cells transcription regulation machinery. Under normal circumstances, β-catenin is readily phosphorylated in the cell by a complex formed of glycogen synthase kinase 3 (GSK3) casein kinase 1-α (CK1α) Axin, and the tumor suppressor, adenomatous polyposis coli (APC), marking for proteasomal degradation.[26] This prevents it building up and causing unwanted cell proliferation. Mutations in the cell, commonly linked to cancer,[27] cause the activation of the WNT signalling pathway. This, in turn, causes the GSK3 complex to be recruited elsewhere in the cell, meaning it no longer phosphorylates β-catenin. As a result, there is a large increase in the levels of β-catenin in the cell cytoplasm, which then translocates to the nucleus. Once inside the nucleus, it forms a complex with the T-Cell factor (TCF) and causes the activation of genes under the control of TCF, most of which are involved in controlling the proliferation and differentiation of cells.[1,28] Thus increased amounts of β-catenin have the effect of causing cell proliferation. Increased levels of β-catenin in the cell have been linked to numerous diseases.[29] ICG-001 targets this pathway by preventing the formation of the β-catenin/TCF complex, with the aim of preventing its build-up and the subsequent diseases that form as a result.

It has been demonstrated that in various fibrotic diseases that inhibitors of the WNT/beta catenin pathway are downregulated.[30] This leads to increasing amounts of β-catenin being translocated to the nucleus and activating the various transcription pathways that lead to cell proliferation. In many cases this occurs after an injury, and so the natural process with which the body creates extra tissue for wound healing can go out of control and lead to the out of control proliferation of fibrotic tissue. This event has been demonstrated in mouse models,[31] where it has been shown that increased activity of the pathway can interrupt the normal formation of muscle tissue in favour of fibroblast formation.

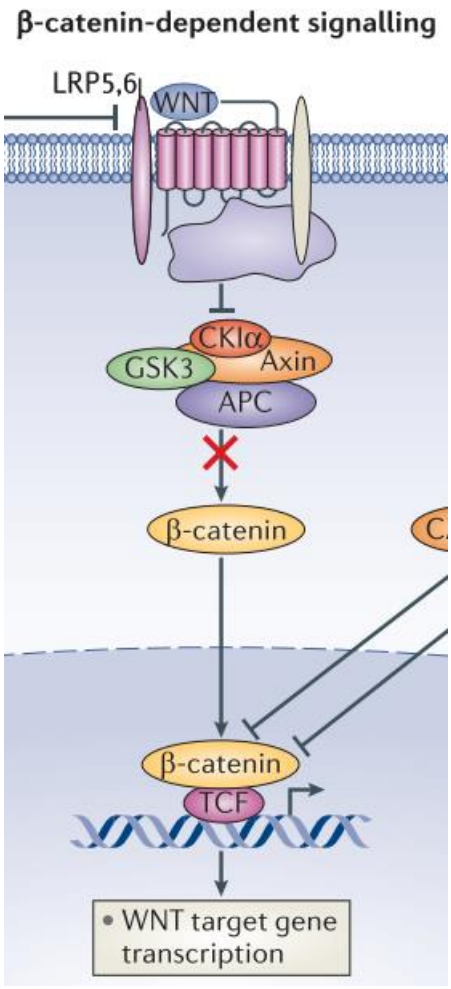


Fig. 1.3 *– The WNT pathway*[28]

1.3 Project Targets – Core Structures

A series of "core structures" were proposed by medicinal chemists at GSK (**Figure 1.4**) that were analogous to the core structure of ICG-001 (highlighted in blue above), retaining the multiple potential points of variance while also introducing aromaticity to the core structure. All of them are heterocycles, mimicking the nitrogen enrichment of the original structure.

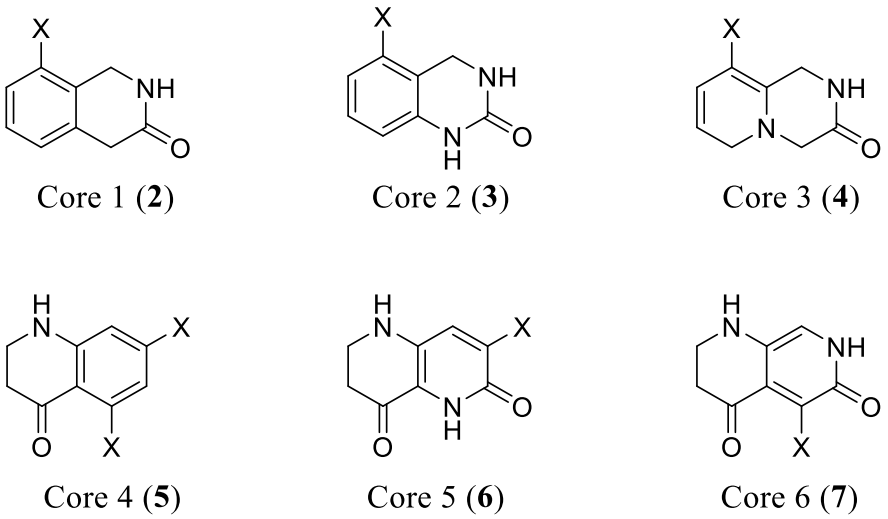


Fig. 1.4 *– Structures of the target cores*

Part of the reason these cores were also chosen was due to the general lack of clinical data of drugs containing these types of structures in the literature, meaning the project had a very high potential to produce novel compounds. While some of the base core structures had been synthesised before (Core 1 (**2**),[32] Core 2 (**3**)[33] and Core 4 (**5**)[34] specifically), functionalisation of said cores was much less common.

Because there was relevant literature around their synthesis, Core 1 (**2**), Core 2 (**3**) and Core 4 (**5**) were initially chosen as the starting points for the project. The previous work on the development of these structures - and the methodologies used for attempting to replicate and modify these syntheses - is explored in greater detail in the relevant chapters of this thesis.

1.3.1 Core structure precedent

When it comes to pharmaceutical precedent for the development of these cores, there is some evidence that compounds analogous to the cores chosen have the potential to make good drug molecules.

1.3.1.1 What makes a good drug molecule?

When it comes to small molecule drugs, a good starting point for their development is to observe Lipinski's Rule of Five.[35] This rule was developed in the early 2000's by a group of researchers at Pfizer and has gone on to form the basis of drug development the world over (as evidenced by the

fact the original paper was cited more than 1000 times in the three years following its initial publication[36]).

The Rule of Five states that when developing drug molecules, difficulties with cell permeation and general absorption are much more likely if the molecule contains more than five H-bond donors, more than 10 H-bond acceptors, a molecular weight greater than 500 and a partition co-efficient (octanol-water) (Log*P*) greater than five.

While there have been many amendments to this rule set over the years (for example, the addition of the Ghose filter[37] and Veber's Rule[38]), Lipinski's rules are treated as a useful jumping off point. To that end, ICG-001 satisfies all but one of Lipinski's rules: it has two H-bond donors, eight H-bond acceptors and a calculated Log*P* of 4.48.[39] It's molecular weight is high at 548, but despite this the molecule still performs as desired.

The one issue it has is its dosage requirements. ICG-001 shows activity in μM concentrations,[1] however it is often the case that drug potency is expected to be in the nM region even in the early stages of development.[40–42] This means that a larger dose of ICG-001 is required to have the desired effect. Larger doses increase the potential for side-effects and so it is often desirable to develop drugs that show potency at low dosages. This reduces the amount of drug given to the patient, therefore reducing the danger of side-effects.

It is likely that the nitrogen atoms spread throughout the core drug structure influence ICG-001's selectivity, as all are H-bond acceptors. It makes sense then, that when designing analogues of this compound an effort should be made to retain as many of the nitrogen atoms as possible. That or to rearrange them slightly and see what effect this has (if any) on the molecule's potency. All six of the new cores retain the positioning of at least one of the three nitrogen atoms in the original core structure. Not only that, but the new cores also seek to introduce aromaticity to the system. This could prove useful in increasing the molecules potency, as aromatic rings can have Van der Waals interactions with hydrophobic binding regions in a target site,[43] potentially increasing the affinity of the drug for its target and therefore lowering the dose required to have an effect. Aromatic rings are also much smaller than cyclohexane rings, and so may fit into an active site better.[43]

Both of these changes are simple yet effective methods of developing analogues that can retain and potentially improve on the potency of the original molecule, and so the selection of these 6 cores makes sense not only from a novelty perspective, but also a drug-design perspective.

Finally, part of the reason for paring back the structure of ICG-001 to its core and building outwards from there is the principle of fragment-based lead discovery. When dealing with smaller fragments, a "Rule of Three" has been suggested by Jhoti *et al.*[44] This rule states that when performing fragment-

based drug discovery, the fragments used should: have a molecular weight < 300, have no more than three H-bond acceptors, have no more than three H-bond donors, have a calculated Log*P* = 3, have no more than three rotatable bonds and have a polar surface area of 60 $Å^2$.

Building on this, Churcher *et al.*[45] from GSK have touted the idea of "Lead-Oriented Synthesis". This idea takes all the lessons learned by medicinal chemists over the years and suggests that, when searching for lead compounds, a certain list of criteria should be adhered to that will make said lead compounds more likely to result in successful drug candidates.

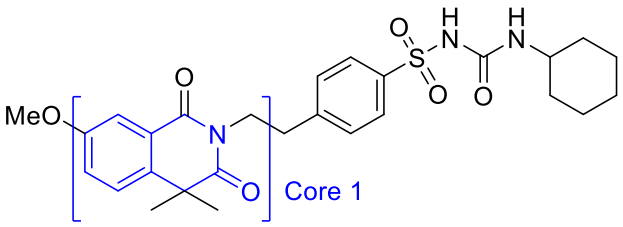
According to them, lead-oriented synthesis should:

- Be able to produce a wide-range of lead-like chemical structures.
- Use cheap reagents and conditions to allow wide utilisation in array formats.
- Not be susceptible to excessive Log*P* drift.
- Be tolerant to a wide range of polar functional groups.
- Produce molecules without residual electrophilic or otherwise reactive centres.

When taking these rules into account, reducing the target to the core structure and lowering the number of heteroatoms present therein makes good sense when searching for lead-like compounds. The idea of making these structures using cheap and widely available reagents was also of great importance, as it means that when it comes to diversifying libraries later, the synthesis is straightforward, and results can be achieved quickly. This was a core goal behind the synthetic methodologies developed in this thesis, as the aim was to be able to develop expanded sets using array chemistry. This goal was achieved in the case of one of the cores and shall be explored in greater detail later in the thesis.

1.3.2 Examples of drugs containing the core structures

Gliquidone (**8**) is a commonly used drug in the treatment of Type 2 diabetes, where it can stimulate the release of insulin in patients. Though it is classed as a tetrahydroisoquinoline as opposed to a tetrahydroisoquinolinone, it is analogous to Core 1 (**2**).



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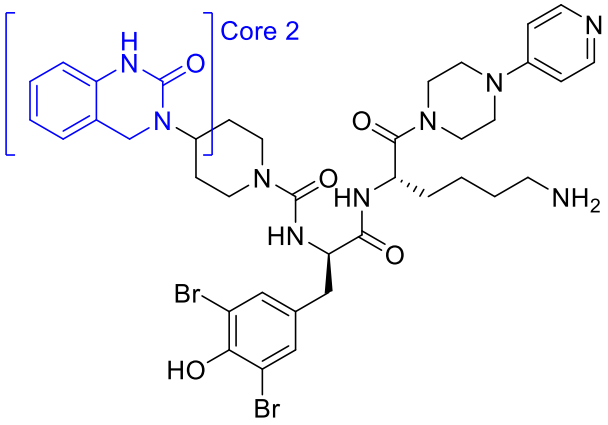
It has a high efficacy and proven safety and metabolic profiles and is estimated to be have been prescribed to around two million patients per month in the early 2000's.[46] This compounds financial success shows that analogues of core 1 at least have the potential to be developed into blockbuster compounds, giving increased validity to the investigation of the core in this thesis.

Another pharmaceutical compound, this time analogous to Core 2 (**3**), known as Olcegepant (**9**) is currently in Phase 2 trials as a treatment for migraines.[47]

The drug is an antagonist of the Calcitonin gene–related peptide (CGRP) receptor. CGRP is a potent vasodilator[48] that is known to be found in increased levels in patients suffering from migraine.[49] Olcegepant aims to prevent migraines by inhibiting the ability of CGRP to bind to its relevant receptor protein and has been shown to be effective.[50]



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Of the other 4 core structures, no current drug molecules are known that are in any stage of experimentation. Searching for the molecules in SciFinder also showed that Core 1 (**2**), Core 2 (**3**) and Core 4 (**5**) were the only ones to have any significant presence in the literature. The other three cores were particularly rare, with Core 5 (**6**) and Core 6 (**7**) only producing three and one results respectively when put through a similarity search. If nothing else, this made the case for pursuing the cores based on their novelty.

1.4 Change in project direction

The original goal was to develop methodologies for the synthesis of all six cores that allowed for easy, late-stage functionalisation. This would allow for the rapid building of a compound library that could potentially be tested for their biological activity. SAR data would then guide the development of new, functionalised molecules to the ultimate end of finding a potential lead compound for the treatment of fibrosis.

To start with, initial synthetic pathways for each of the cores were proposed. From these initial pathways, cores 1 and 2 (compounds **2** and **4**) were selected for prioritisation due to possible ease of synthesis and access to start materials.

As will be elaborated on in the subsequent chapters of this thesis, this plan was quickly amended, as the sheer scale of the task became apparent. The process of synthesising just one of the core molecules with any degree of easy late-stage functionalisation was incredibly arduous, and so the aim of the project was changed.

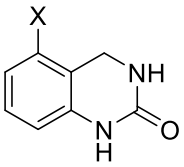
The project then became an investigation into the synthesis and functionalisation of heterocycles, specifically tetrahydroisoquinolinones (Core 1 (**2**)).

The reframing of the thesis meant that the bulk of the work performed no longer incorporated many of the cores, abandoning the toolbox concept. Instead the focus became the synthesis of tetrahydroisoquinolinones, their subsequent functionalisation, and the use of chiral auxiliaries and organometallic chemistry to attempt to direct the stereoselectivity of these functionalisations.

Chapter 2: Early investigations – Core 2 and Core 4

This chapter shall examine the work on Cores 2 and 4 (compounds **3** and **5**). In the early days of the investigation, the synthetic routes for multiple cores were being studied in parallel. Though ultimately Core 1 was the most successful, a large body of work was put into both cores 2 and 4. In this chapter the synthetic methodology and rationale behind the investigations into cores 2 and 4 and the successes and failures that came with them shall be discussed.

Part 1: Core 2: 3,4-dihydroquinazolin-2(1*H*)-one



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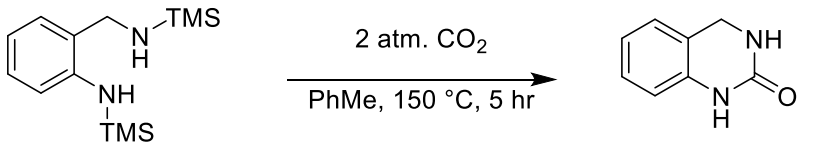
2.1 General Chemistry:

Core 2 (**3**) is a halogenated 3,4-dihydroquinazolin-2(1H)-one scaffold. Typically, 3,4-dihydroquinazolin-2(1*H*)-ones themselves are not that synthetically difficult to make, though they do require the use of some sort of carbonylation reaction of a diamine species to produce the urea moiety. Stephan *et al.* synthesised the bare core molecule (**10**) by heating a TMS protected diamine species in the presence of several atmospheres of CO_2.[51] (**Scheme 2.01**)

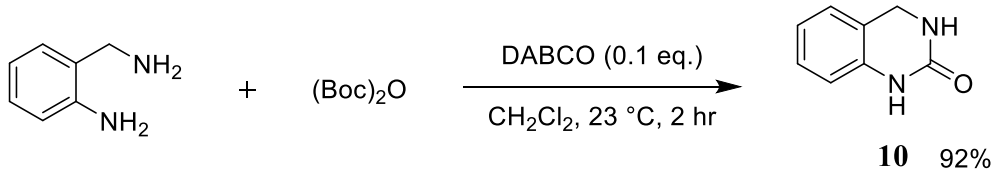


10 78%

Scheme 2.01

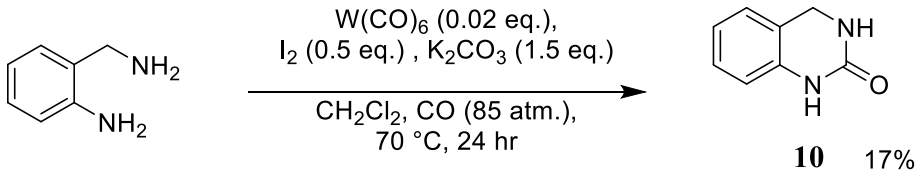
Wang *et al.* used a less harsh approach to making this core structure.[34] The source of CO in this case was Boc-anhydride. Using DABCO as a catalyst, they reacted a diamine species with Boc-anhydride.

This allowed them to generate either an isocyanate or a carbamate (on this point they weren't sure) which was then attacked by the second amine moiety to close the ring and form the urea. (**Scheme 2.02**)



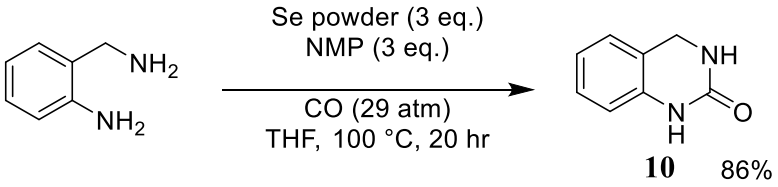
Scheme 2.02

White *et al.* used CO gas itself for carbonylation,[52] while also using a tungsten complex to catalyse the reaction. Their methodology was very tolerant of functional groups, but the conditions require specialist equipment and large quantities of CO gas as well as both iodine and potassium carbonate. As a result, the route has very poor atom economy. The yield was also incredibly low. It is however, a large improvement on previous transition metal catalysed processes for making ureas which tended to use cobalt[53] and nickel[54] complexes (which are well known for their propensity to be highly toxic), as their tungsten catalyst is cheap and has a much higher boiling point than many of its' contemporaries, making it somewhat safer to handle and use. (**Scheme 2.03**)



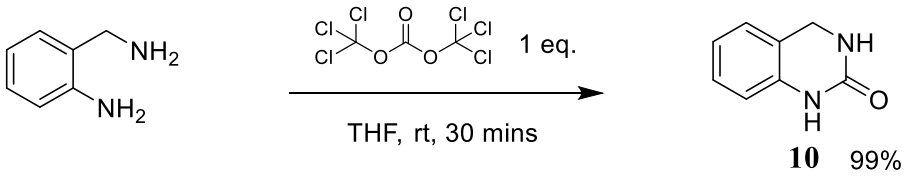
Scheme 2.03

Another methodology using CO gas was developed by Sonoda *et al.*[55] in the 1980's. Their methodology uses selenium metal and a strong, sustained positive pressure of CO (30 kg/cm^2). Once again, the high pressures and relative toxicities of the materials used made this approach somewhat less desirable. (**Scheme 2.04**)



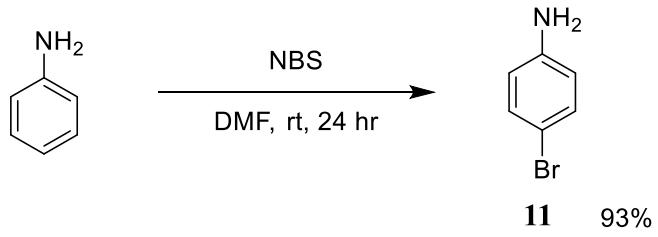
Scheme 2.04

One final possible methodology, as shown by Hartmann *et al.*, is the use of triphosgene as the CO source.[56] While this would no doubt be a viable route, triphosgene is one of the nastier chemicals in a synthetic chemists' arsenal, and as such is best avoided if at all possible (**Scheme 2.05)**



Scheme 2.05

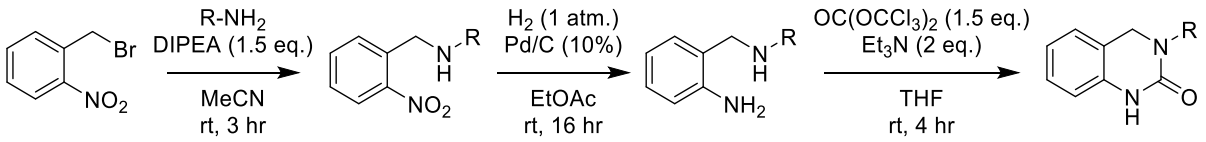
While clearly there is no shortage of methods to make the general core structure, these methodologies present some issues when attempting to apply them to the target molecule. For one, selectively substituting one nitrogen over the other post core synthesis would be difficult. For another, none of these methods have a halogen built into the system, which will be necessary later on in the synthesis to allow for the addition of further side-chains to mimic the overall structure of ICG-001. The Hartmann group did demonstrate that halogenation of the aromatic system was possible using NBS and DMF, but this added the bromine to the *para* position on the ring instead of the *meta* position as required for the synthesis of the core. (**Scheme 2.06**) This is perhaps unsurprising given that it has been previously demonstrated that this bromination method is *para*-selective when aniline is used as a substrate, explaining the selectivity here.[57]



Scheme 2.06

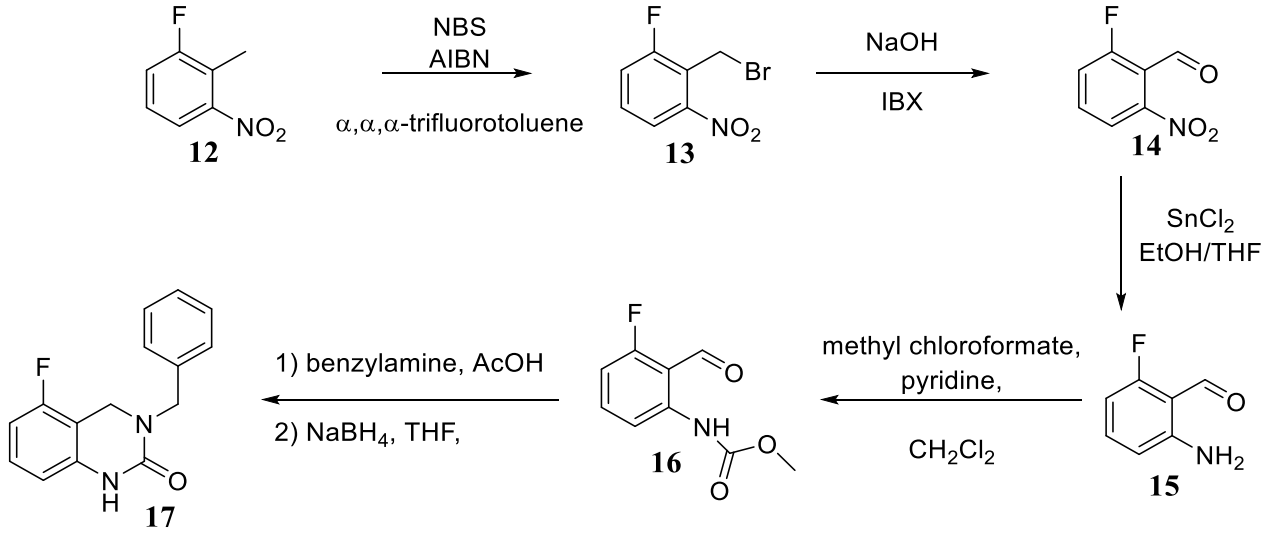
A review of the literature through SciFinder showed that there is not a huge volume of examples of 3,4-dihydroquinazolin-2(1*H*)-ones with a halogen substitution at the correct position that would allow for varied modification post synthesis. Many are synthesised with substituents already in place on one or both of the nitrogen atoms that would be difficult to remove, with only 2 examples containing classic protecting groups. Also, almost all of the methodologies for the synthesis of these compounds involve the use of triphosgene in some capacity (some use CDI instead, but this comes with its own set of issues, and the vast majority are from patents). Many of the routes go *via* a

nucleophilic substitution of a 2-nitrobenzyl halide with an amino group, followed by the reduction of the nitro group to an amine to form a diamine species and finally carbonylation as demonstrated by Herz *et al.*[58] (**Scheme 2.07**)



Scheme 2.07

Using this information, a similar methodology was followed for the synthetic route to core 2. The decision was made to try and avoid using triphosgene. It was also hoped that by getting as far as possible through the synthesis before introducing amine side-chains, it would allow for ease of telescoping the series by batch synthesising the starting material and then varying the amine substituents through simple, straightforward means as outlined in **Scheme 2.08**:



Scheme 2.08

2.2 Step 1: Bromination of the methyl group on **12**

The initial step, the bromination of the methyl group of **12**, proved to be more challenging than originally anticipated. The original plan was to make use of a radical reaction using NBS with azobisisobutyronitrile (AIBN) as the radical initiator.[59] To begin with, the reaction was attempted using CCl_4 as the solvent as that was the most commonly used solvent in the literature. This resulted in an apparent conversion to a mixture of 37% mono-substituted material (**13**) to 48% di-substituted material (**18**) with 15% starting material (**12**) left over, based on the appearance of peaks in the NMR consistent with the positions highlighted (once the integrals have been adjusted to reflect the number of protons they represent) (**Figure 2.1**).

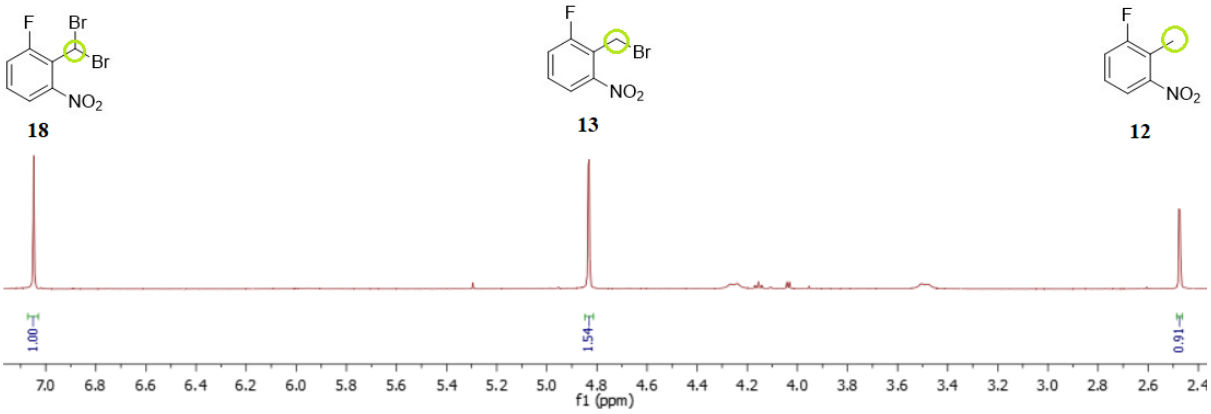
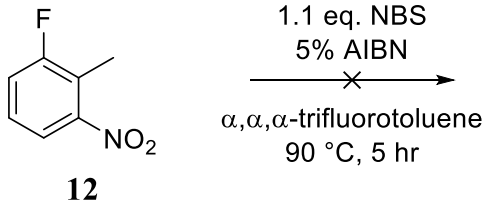


Fig. 2.1 *– NMR spectrum containing compounds* ***13***, ***18*** *and* ***12***

Encouraged by this result, it was decided to switch the solvent to α, α, α-trifluorotoluene, as it is relatively high boiling (102 °C) when compared to other halogenated solvent alternatives such as dichloromethane (40 °C), and should be inert to the reaction conditions when toluene wouldn't be. The reasoning behind the switch was that CCl_4 is well known for its' serious adverse environmental[60] and health[61] effects and therefore is highly unlikely to be used in an industrial synthetic route.

However, the solvent switch was not effective. It failed to produce any bromination at all, as only starting material **12** was recovered. (**Scheme 2.09**)

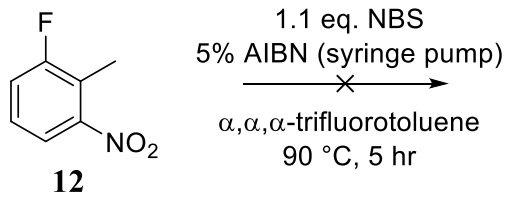


Scheme 2.09

Several reasons for this failure were postulated and investigations began into elucidating which of them was the most likely culprit.

2.2.1 First Attempt

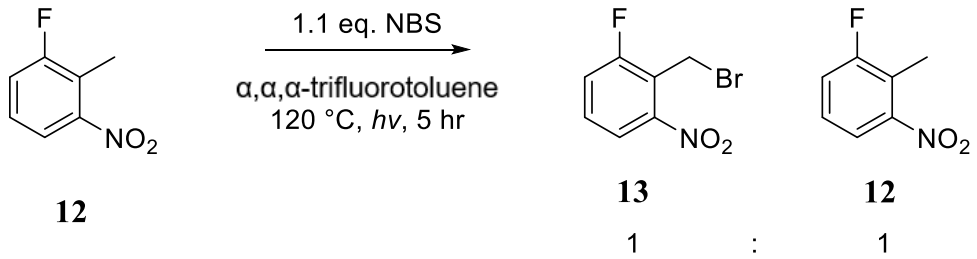
It was possible that the AIBN was being used up too quickly and that this was preventing the reaction from progressing. To counteract this, a slow addition of AIBN was attempted *via* syringe pump over the course of 5 hours. This however, had little effect on the reaction outcome. Once again only starting material **12** was recovered. (**Scheme 2.10**)



Scheme 2.10

2.2.2 Second Attempt

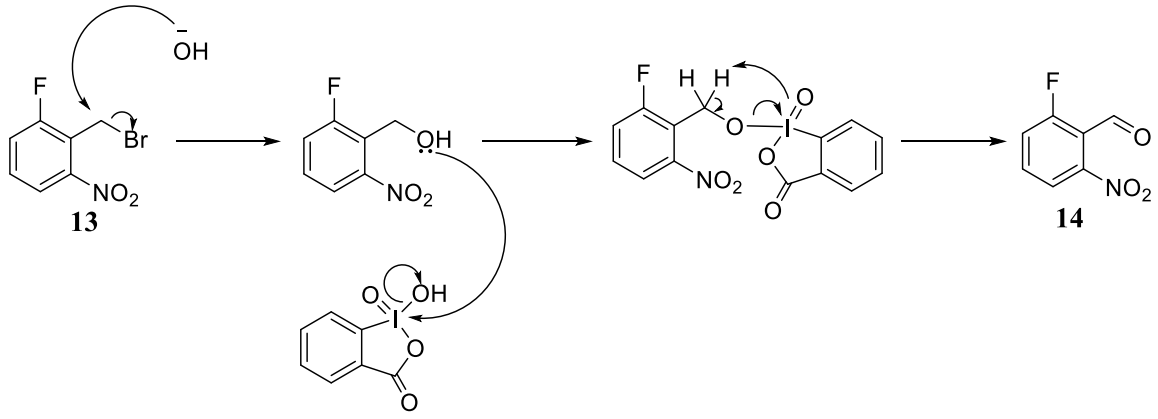
The reaction was then attempted using UV radiation as an initiator instead of AIBN, while also heating the solvent to reflux.[62] This resulted in a 50% conversion to the mono-brominated product **13** with 50% starting material **12** remaining (by NMR). (**Scheme 2.11**) This reaction was successful to some degree, but there were severe reproducibility issues. The lamp used to provide UV radiation was large and difficult to direct while also generating huge amounts of heat. As a result, the addition of UV radiation to the system was uneven and the temperature of the reaction virtually impossible to control. This lack of control was undesirable as it would lead to inconsistent results and reproducibility issues when it came to any sort of scale up. This fact, coupled with the lack of photochemical equipment available in the lab, led to a rethink of the synthetic route.



Scheme 2.11

Since this methodology failed to achieve the results desired, another method was sought out. The initial plan had been to convert the benzyl bromide in compound **13** to a primary alcohol and then to

the oxidise this group to the aldehyde **14** by use of IBX (**Scheme 2.12**). Since this was no longer a viable route due to the aforementioned issues, alternative methods for the direct conversion of the methyl group to an aldehyde were researched.

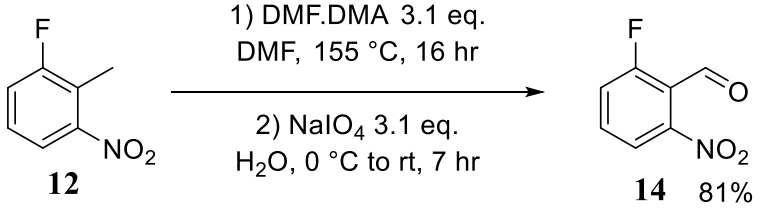


Scheme 2.12

2.3 Synthesis of aldehyde 14

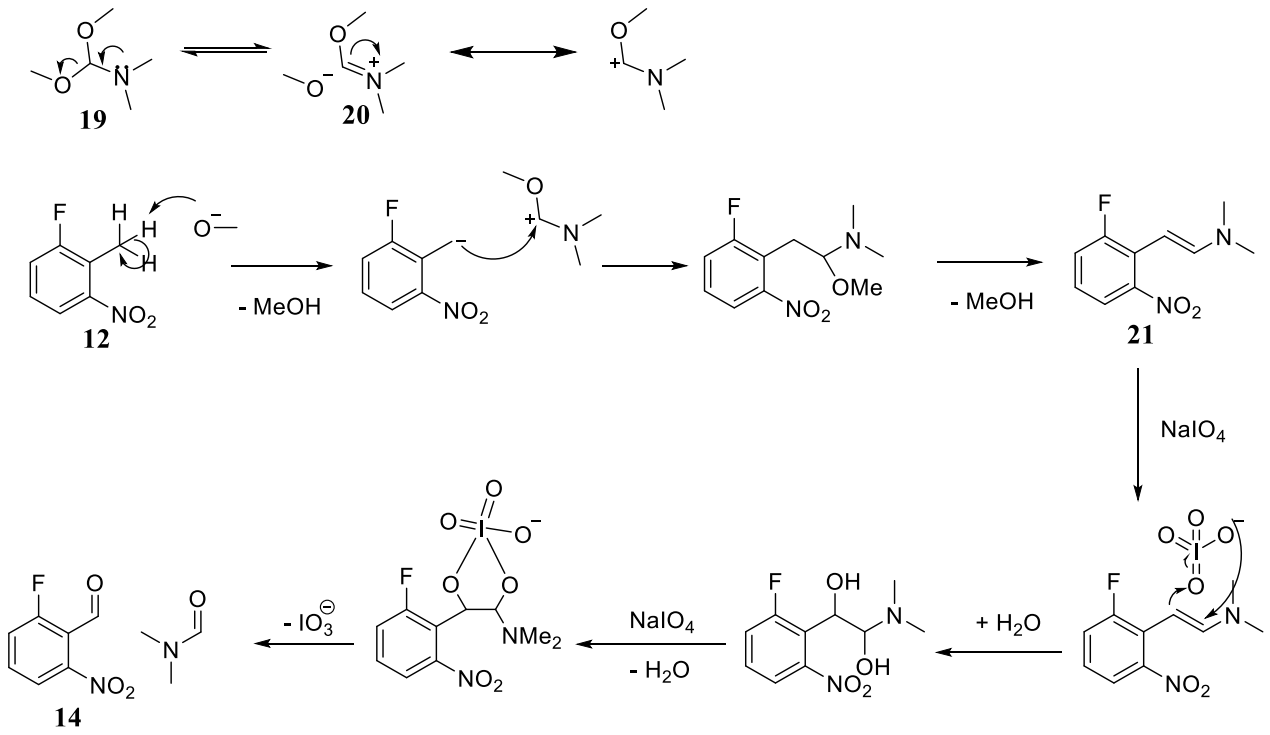
A paper from the Carter group at Oregon State University showed a very simple method for forming an aldehyde directly from the tolyl methyl group of the bromide equivalent of **12**.[63] The paper used *N*,*N*-dimethylformamide dimethyl acetal (DMF.DMA) to form an enamine which was subsequently oxidised to an aldehyde using sodium periodate.

This reaction proved highly successful, generating an 80% isolated yield of the desired product **14**. (**Scheme 2.13**)



Scheme 2.13

The mechanism for this reaction, as proposed by Levacher *et al.*,[64] is interesting. It relies on the immediate formation of the iminium **20** from DMF.DMA (**19**), allowing for the release of a methoxide ion which removes the proton from the methyl group of **12**. Once the enamine **21** is formed, the periodate performs its oxidation on the double bond, generating the desired aldehyde product **14** and DMF as a side product. (**Scheme 2.14**)

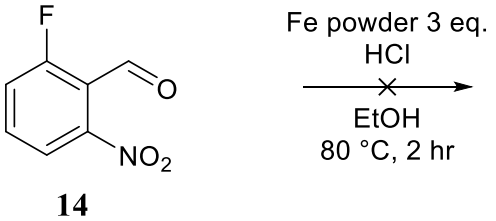


Scheme 2.14

2.4 Nitro Group Reduction

2.4.1 First Attempt

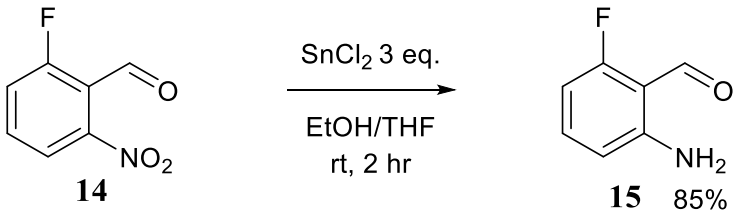
The step following the formation of the aldehyde required the reduction of the nitro group on compound **14** to the amine equivalent **15**. Again, several sets of conditions were attempted. Iron chloride was initially generated *in situ* by the reaction of iron with aqueous HCl.[65] However, this reaction proved to be somewhat difficult, as the iron was incredibly hard to remove at the end of the reaction, requiring the use of a siderophore (in this case catechol) to fully extract it from the reaction mixture. Not only that, but the reaction itself was unexpectedly unsuccessful, as no product material was formed and only a 50% recovery of the starting material was obtained. (**Scheme 2.15**)



Scheme 2.15

2.4.2 Second Attempt

Alternate conditions using anhydrous tin (II) chloride as the reducing agent were found.[66] This new method requires no heating and can be performed under air to no detrimental effect, making it an incredibly mild reaction. (**Scheme 2.16**) This reaction has been performed on up to an 800 mg scale in the laboratory and consistently gave yields in the region of 85%.



Scheme 2.16

As can be seen in **Figure 2.2**, the difference between the 2 compounds is easily distinguished by ^{1}H NMR, as the lack of the nitro group makes the aromatic protons shift upfield.

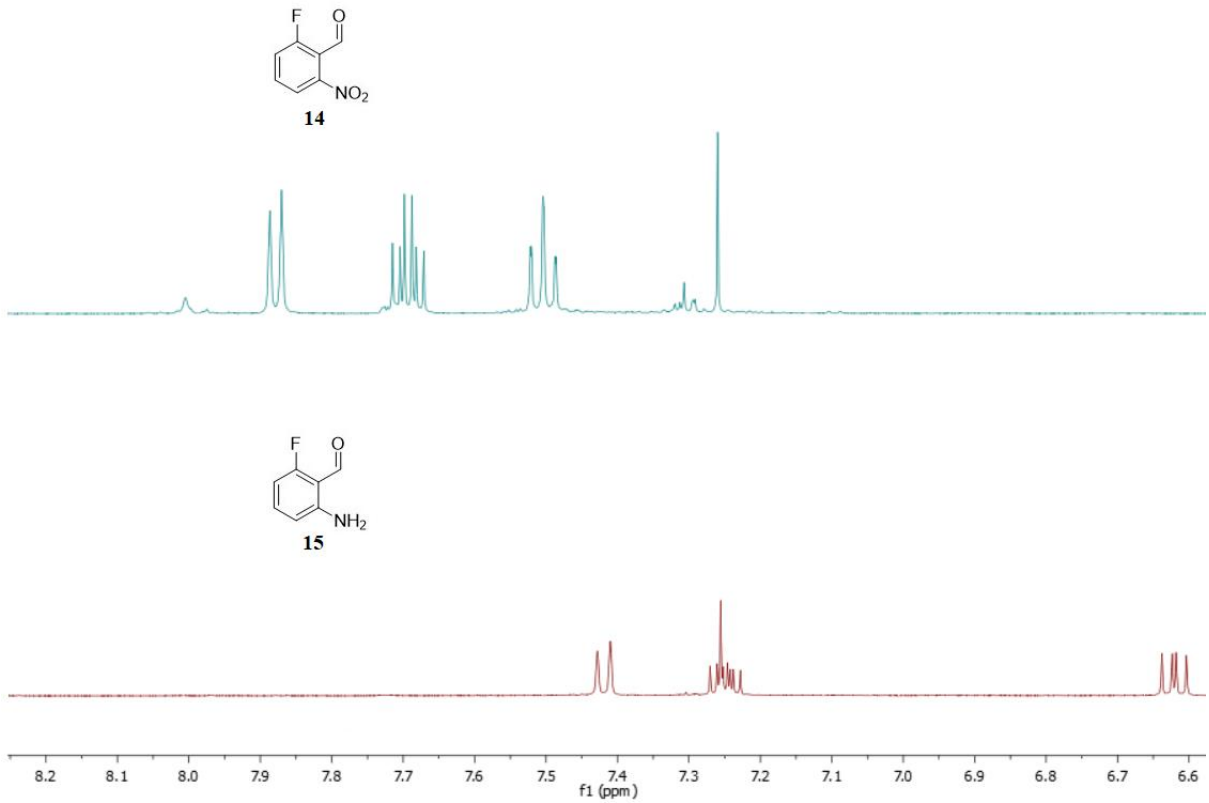


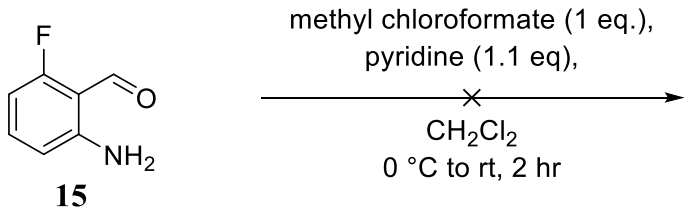
Fig. 2.2** – Differences in NMR spectra between **14** and **15

2.5 Addition of methyl chloroformate

The next step involved the addition of methyl chloroformate (largely because it was readily available in the lab) to **15** to form a carbamate **16** through a simple N-alkylation reaction.

2.5.1 First Attempt

To begin with, the plan was to use methyl chloroformate as a carbonylation agent and pyridine as a base to neutralise HCl generation in the reaction mixture. (**Scheme 2.17**)

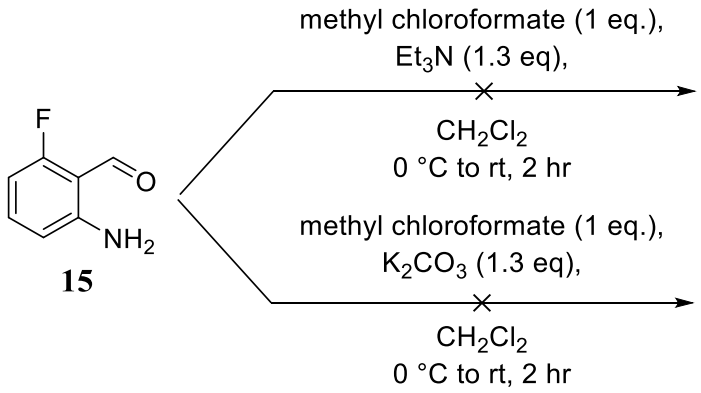


Scheme 2.17

This reaction was largely unsuccessful and large amounts of starting material were left over. TLC analysis failed to conclusively show any formation of a new product and NMR analysis was inconclusive at best. This trend continued even after the methyl chloroformate had been distilled over calcium hydride to ensure it was dry. It was decided to attempt the reaction with alternative bases to see if the reaction could be improved at all.

2.5.2 Second Attempt

It was possible that the problem with the reaction was the base used, and so alternative bases were trialled. In this case, both triethylamine and potassium carbonate were used, and the reactions performed in parallel. Neither of these reactions succeeded in producing any product formation. (**Scheme 2.18**)

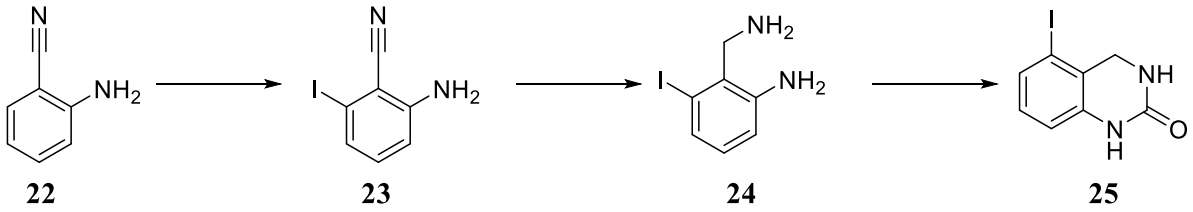


Scheme 2.18

It was at this point that the difficulties associated with this pathway led to a rethink of the synthesis of this core.

2.6 Alternative direction - Nitrile route

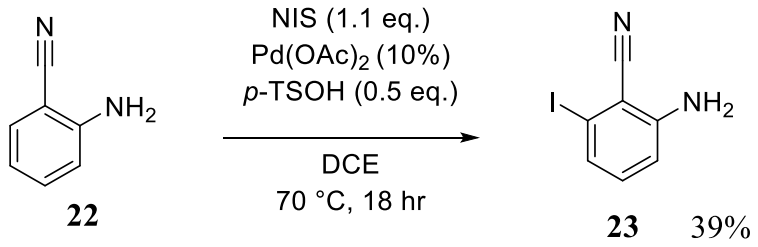
A possible alternative route was developed which employed the reduction of a benzonitrile group to place the benzylic amino group into the molecule instead of going to the trouble of generating an aldehyde to perform a reductive amination. However, a halogen would still need to be installed on the aromatic ring. In order to do this, conditions developed by Sun *et al.*[67] could be employed. This would allow the introduction of a halogen *ortho* to the nitrile group of 2-aminobenzonitrile (**22**). The nitrile could subsequently be reduced and carbonylation could then be used to close the ring system. (**Scheme 2.19**) This route was also nice as the nitrile group on **22** was required for the introduction of the halogen in the first place, so the methodology uses existing functional groups to affect reactions without needing to add to many extra reagents or directing groups.



Scheme 2.19

2.6.1 Iodination Reaction

The first step was the iodination of **22** to produce **23**. Using conditions derived from Sun *et al.* some success in generating the desired product was achieved. (**Scheme 2.20**)

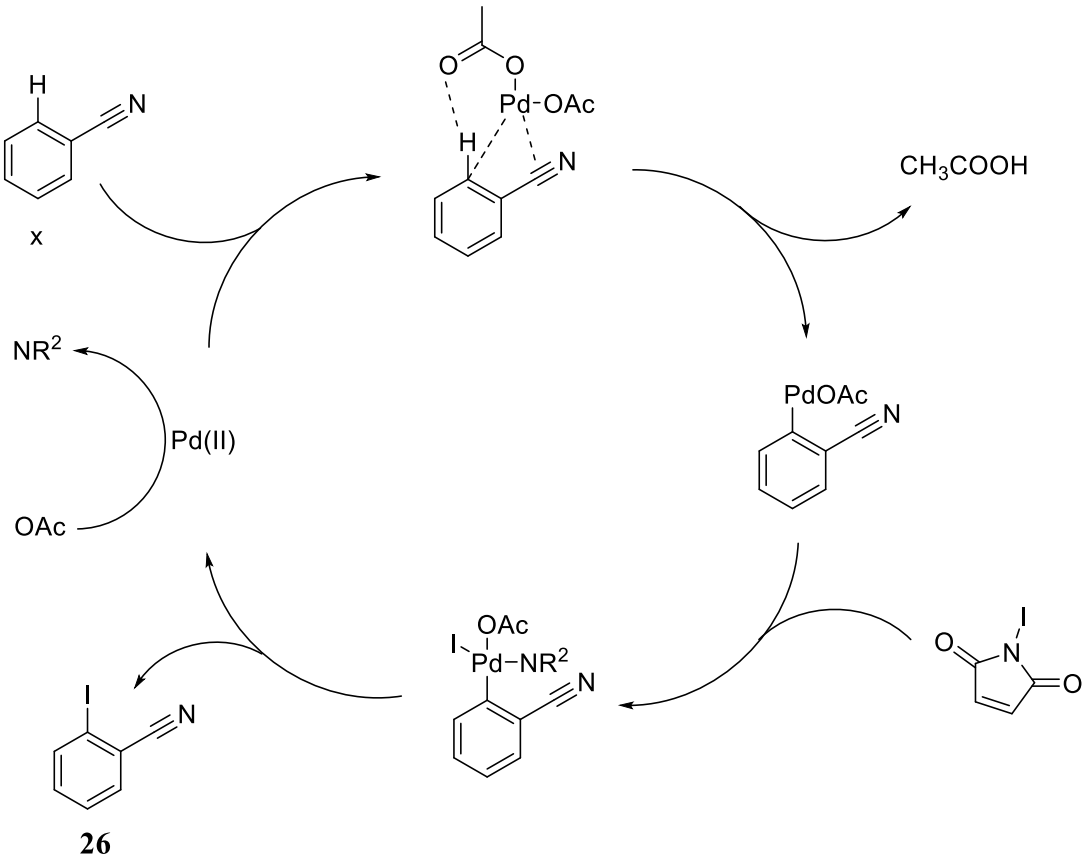


Scheme 2.20

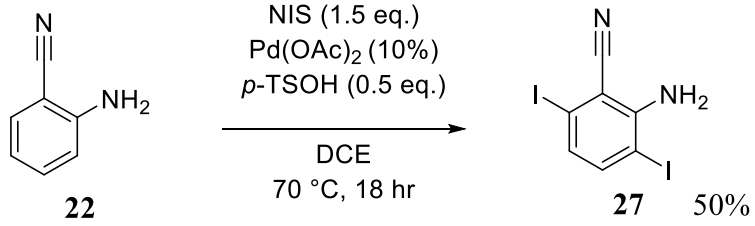
The appearance of a peak at 98.5 Hz in the ^{13}C NMR spectrum is indicative of the heavy-atom effect causing the carbon attached to a halogen to appear at a much lower than expected chemical shift[68], thus providing evidence for the addition of iodine to the compound. In the Sun's proposed reaction mechanism, they posit that the palladium co-ordinates to the nitrile bond, allowing palladium C-H *ortho* insertion to occur. Oxidative addition of the NIS follows before reductive elimination releases the iodinated product **26**. The Pd catalyst then undergoes NR_2/OAc ligand exchange to expel succinimide and regenerate the catalyst to begin the cycle anew. (**Scheme 2.21**)

While largely successful, this reaction isn't perfect, as it only ever progresses to 75% completion at most and the separation of any leftover starting material is very difficult as both **22** and **23** tend to co-elute on a column. However, it is likely that if further modifications were performed on the system, it would be possible to separate the two compounds at a later stage.

To counteract the problem of leftover start material, the equivalents of NIS used were increased from 1.1 to 1.5. This, however, led to an entirely new issue arising. The presence of 2 doublets in the aromatic region of the NMR spectrum, integrating for 1 proton each and both with a coupling constant of 1.9 Hz, indicated that there were only 2 aromatic protons left and that both were next to each other. The low coupling constant is a common occurrence in proton NMR analysis of iodo-aryl species.[69] To contrast this, the mono-iodo substituted material **23** has the low coupling constant character noted in the di-iodo species (2.1 Hz), but also has a doublet with a standard aromatic coupling constant (8.7 Hz), likely the proton *ortho* to the amino group, as this will not be under any influence from iodine. The presence of a double-doublet with both of the above coupling constants represent the proton *para* to the nitrile group (**Figure 2.3**) This evidence led to the conclusion that the reaction had exclusively formed the compound **27**. (**Scheme 2.22**)



Scheme 2.21



Scheme 2.22

It is entirely possible that by increasing the amount of NIS present, the standard iodination reaction NIS is known to perform was being promoted *i.e.* once the starting material had been iodinated *via* the palladium catalysed method, the NIS continued to react with the material of its own accord. From this it was concluded that in future it would be best to simply take the semi-impure material that comes from using 1.1 equivalents of NIS and carry it through, as further iteration later in the synthesis should allow the separation of any side-products that form.

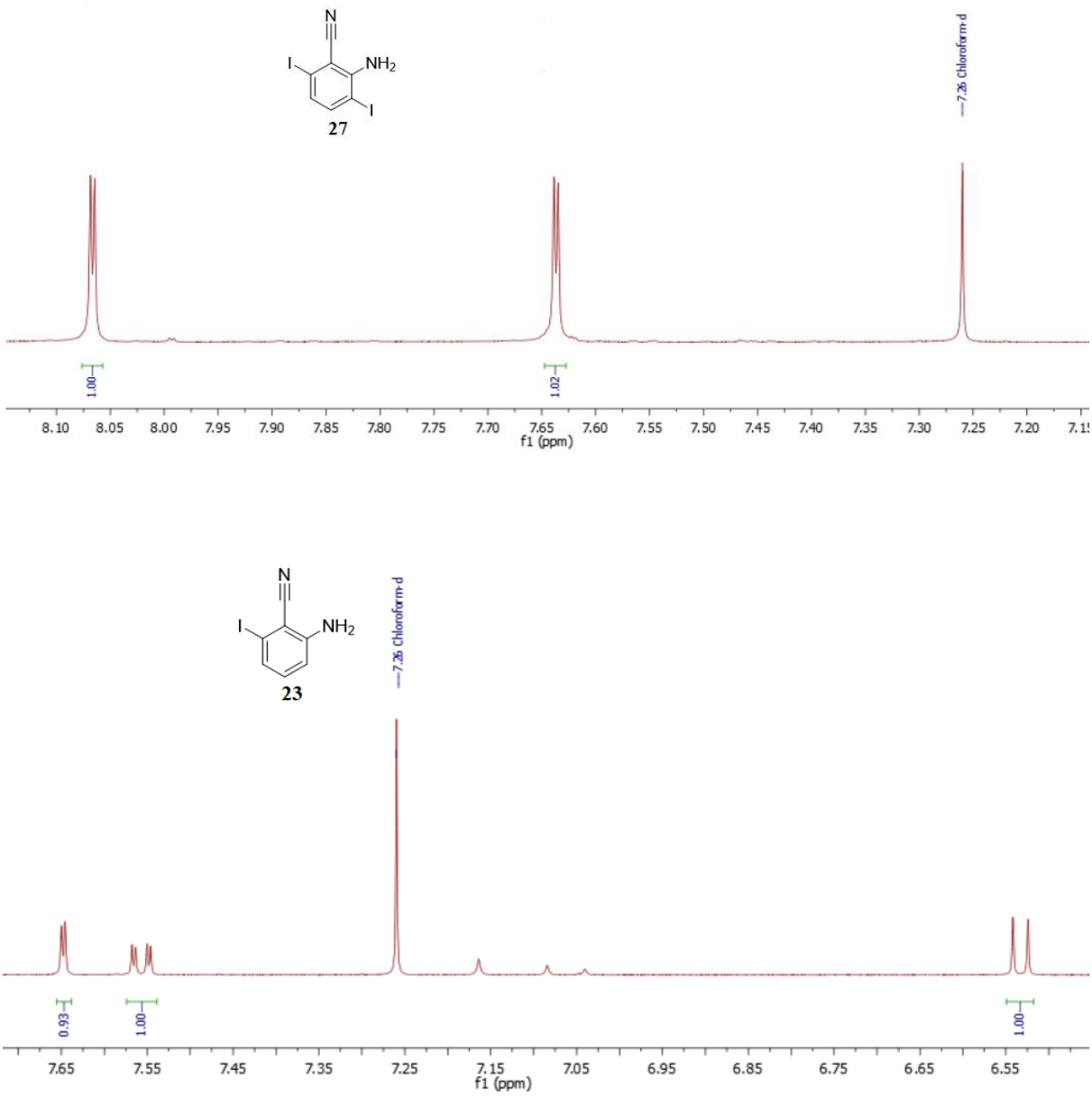
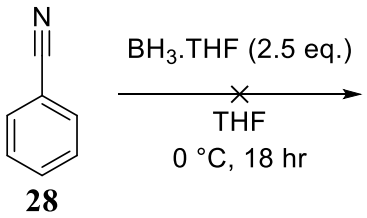


Fig. 2.3 *– ^{1}H NMR spectra and comparison of splitting patterns of* ***23*** *and* ***27***

2.7 Reduction of the nitrile

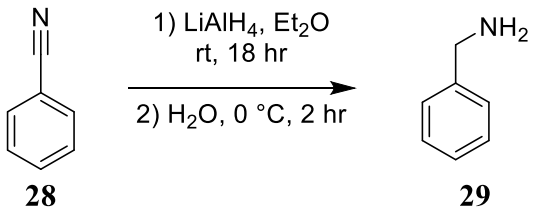
2.7.1 Reduction to amine

The next step was to find suitable conditions for nitrile reduction on these types of compounds. It was decided to trial conditions on plain benzonitrile (**28**) to begin with as plenty of the material was to hand in the lab and it would provide the ability to test a wide set of conditions very quickly. Initially the reduction of **28** directly to the amine (**29**) using BH_3.THF as proposed by De Vos *et. al.* was attempted.[70] (**Scheme 2.23**)



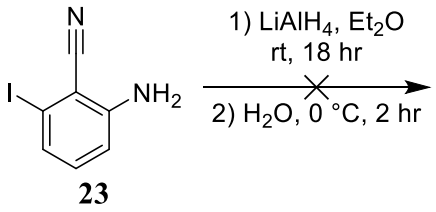
Scheme 2.23

Interestinglyly, this reaction failed to progress at all. Only the starting nitrile **28** was extracted from the reaction mixture. It was decided to investigate more severe reducing agents, moving to attempt this reaction using $LiAlH_4$ instead. (**Scheme 2.24**)



Scheme 2.24

^{1}H NMR analysis concluded that this reaction had worked. The appearance of a peak at 3.86 ppm integrating for 2 protons is indicative of the benzylic position being present. This would seem to imply that the nitrile is relatively stable and requires somewhat forcing conditions in order to undergo reduction. This approach was then applied to compound **23**. (**Scheme 2.25**)

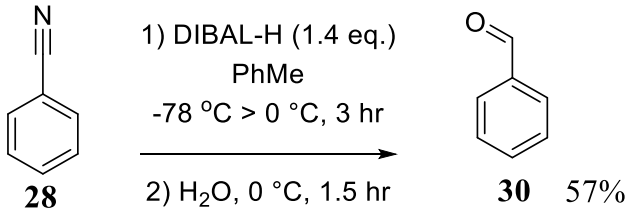


Scheme 2.25

This reaction failed to produce any of the desired product whatsoever, instead returning some starting materials and a few minor by-products.

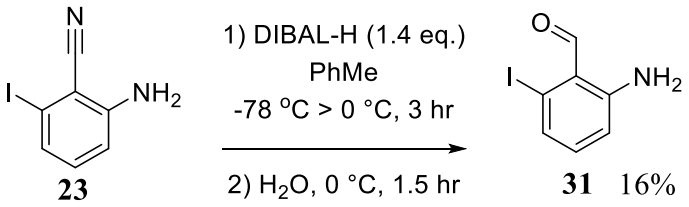
2.7.2 Reduction to aldehyde

The lack of a workable nitrile reduction led to a rethink and it was decided that a change of approach was needed. Perhaps converting the nitrile to the aldehyde (**30**) instead would yield better results? For this reaction, DIBAL-H[71] was chosen as the reducing agent due to its relatively low cost and wide availability. (**Scheme 2.26**)



Scheme 2.26

After the warming of the reaction mixture to 0 °C over the course of 3 hours, distilled water was added to the reaction mixture and it was kept stirring at 0 °C. This allowed for hydrolysis of the aluminium complex to occur and give benzaldehyde. After purification by column chromatography, a 57% yield of **30** was obtained. While this yield was less than ideal, it did provide some encouragement. This reaction was then attempted on the iodinated material **23**. (**Scheme 2.27**)

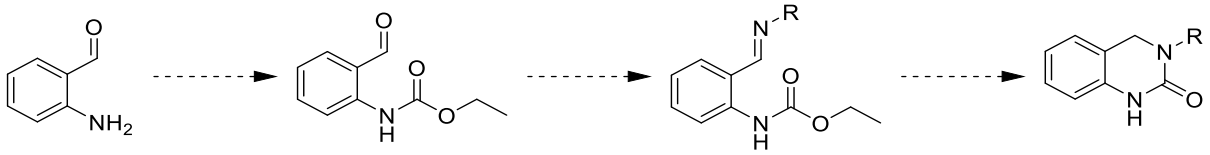


Scheme 2.27

The reaction did not even lead to a recovery of starting material, simply the product **31** in a 16% yield and some indecipherable additional products. The yield was also very disappointing and seriously brought the viability of the route into question. It would prove very inefficient and heavy on materials to synthesise enough of compound **31** to take through to subsequent steps. Also, since the ultimate goal of this project is the development of these compounds for use in medicinal chemistry research, it would be beneficial for the reactions to be high yielding so as to minimise waste and make the reactions scalable to manufacturing levels. The principles of Lead-Oriented Synthesis also apply here, and the low yield means this route doesn't follow the principles well.

2.8 Series rethink

One final rethink of the series was adopted (**Scheme 2.28**). Simplifying the core back to its non-halogenated form, the following synthetic route was proposed based on the work discussed in Chapter 4 of this thesis:

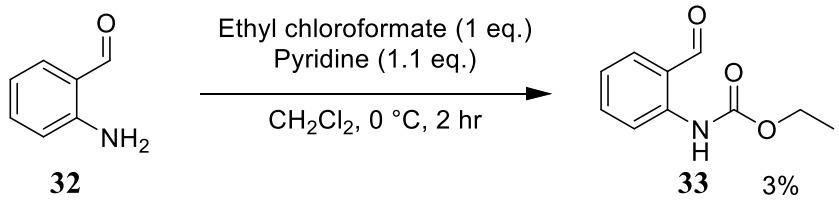


Scheme 2.28

The initial step would use the formation of a carbamate (as attempted in **Scheme 2.17)** to see if removing the halogen increased the yield to any degree. Ethyl chloroformate was used at this point, as methyl chloroformate was designated as restricted at GSK due to its toxicity and potent action as an alkylating agent. As a result, it was much more difficult to access and so ethyl chloroformate was chosen as an alternative.

2.8.1 Initial synthesis

The initial step used the conditions as seen before, alkylation with ethyl chloroformate at the amine position using pyridine as a base to neutralise excess HCl generated by the reaction: (**Scheme 2.29**)

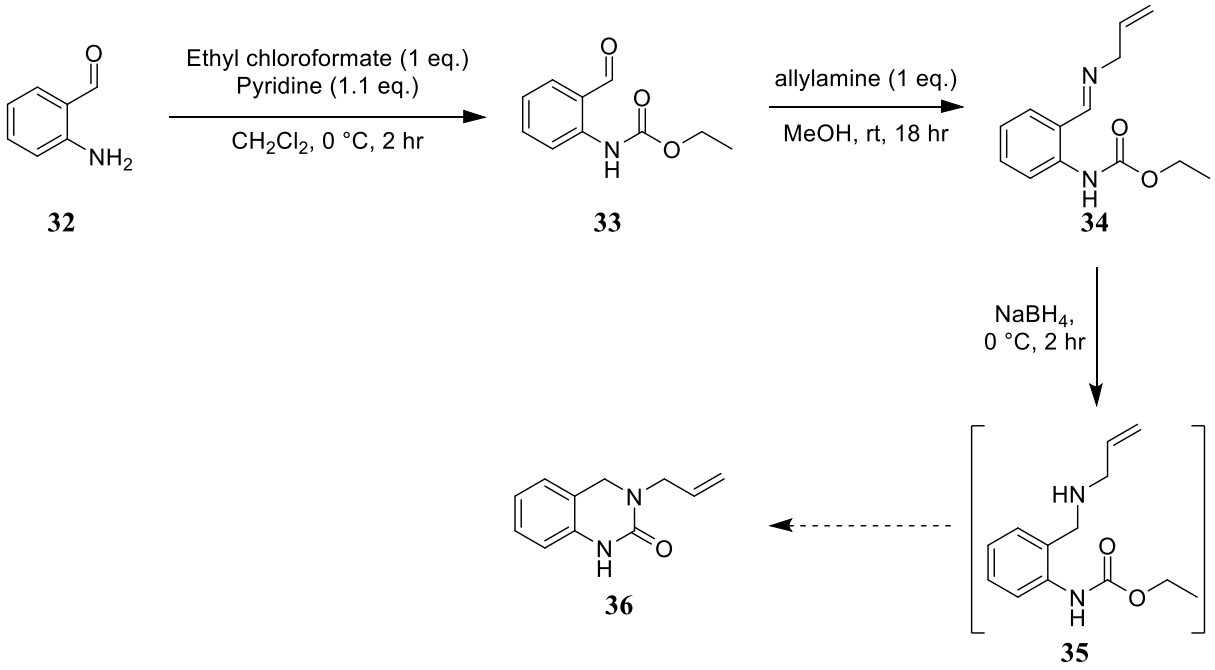


32 **33** 3%

Scheme 2.29

Though this reaction appeared to have been successful by NMR given the appearance of peaks corresponding to the ethyl group at 4.25 and 1.34 ppm that integrated to the correct amounts, it had an incredibly low yield. This was thought to be largely due to the possibility that the product **33** is soluble in water due to the presence of the carbamate group, and so the aqueous workup resulted in the loss of some of the product from the organic layer. This theory was backed up by a doubling of the yield when the aqueous layer was re-extracted with a large excess of EtOAc.

Upon re-attempting the reaction, the decision was made to skip the aqueous workup phase for this step entirely. The solvent was simply removed, and the raw material was carried straight through to the reductive amination step (**Scheme 2.30**). It was hoped that, if the reductive amination work as planned, the secondary amine formed would attack the carbamate carbonyl and eliminate ethanol to form the desired core structure **36**.



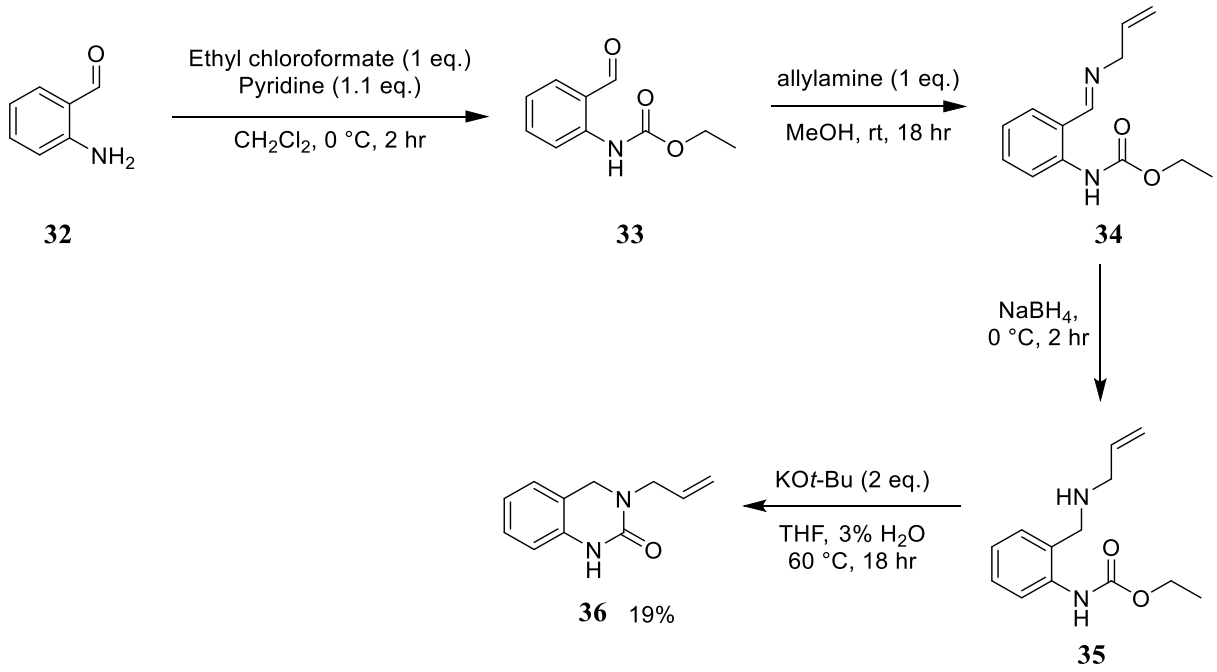
Scheme 2.30

Before attempting the reduction, extra MeOH had to be added to the reaction, as it had turned biphasic and cloudy. This alleviated the problem and the synthesis was continued with the reductive amination step, eventually yielding a yellow oil. NMR analysis after the reduction step indicated that the that the reaction hadn't gone to completion. The mixture was re-dissolved in fresh MeOH and sodium borohydride added to attempt the reduction once more. Almost all of the material was again recovered as a yellow oil and ^{1}H NMR analysis indicated that the ethyl group was still present. It was believed that the reduction had indeed taken place, but the cyclisation was not occurring. This hypothesis was backed up by LCMS data, which registered an M+H^{+} of 235, consistent with the reduced secondary amine product **35**. Upon heating the reaction to 60 °C in MeOH, no change was observed, which suggested the reaction was going to need some form of assistance in order to form the urea N-CO bond.

2.8.2 Amide formation assistance

A paper by Yoon *et al.*[72] was noted, showing that potassium *tert*-butoxide in THF could facilitate the formation of amide bonds from amines and esters. These conditions were attempted, initially using dry THF and 2 equivalents of KO*t*-Bu at room temperature under air. This failed to produce any cyclisation. At this point it was noted that the paper specified the use of technical grade THF as opposed to dry solvent, indicating that the presence of some water was necessary for the reaction to progress. Upon spotting this, the reaction was reattempted, adding 3% water to the dry THF. When

the reaction was left stirring in this mixture overnight at room temperature, it began to show some progression. To attempt to speed up the reaction, the conditions were repeated (2 eq. KO*t*-Bu, THF (3% H_2O)) and the reaction temperature increased to 60 °C. Upon being left overnight, the reaction finally appeared to have worked. After working the reaction up, the residue was purified *via* reverse-phase chromatography on an C18 column using an acetonitrile/water solvent mixture and an ammonium carbonate modifier. Drying the fractions under a stream of nitrogen on a heating mantle set to 40 °C overnight finally afforded the product **36** as a white solid, with an overall yield of 19%. NMR spectroscopy, IR and HRMS (confirmed $[M+H]^+$ = 189.1029) analyses were used to confirm that the reaction had been successful. The full reaction scheme is outlined below: (**Scheme 2.31**)

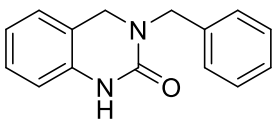


Scheme 2.31

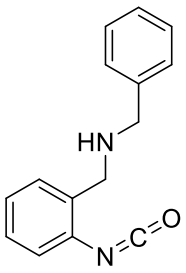
2.8.3 Telescoping the reaction

Bolstered by this success, it was decided to attempt the chemistry using a different amine, in this case benzylamine, and to test whether the methodology could be applied to a host of amine substrates. This reaction appeared to be progressing well, with initial LCMS monitoring of the final step of the reaction indicating that the product **37** was beginning to form. However, upon leaving the reaction overnight, LCMS showed only a 25% conversion to **37**. Upon attempting to work up the reaction, a noticeably pungent smell was observed. A quick investigation revealed that the initial assessment of the reactions' progression may have been misinformed. The isocyanate **38** has the same mass as the

desired product **37** and the odour observed seemed to indicate that it was the isocyanate that had formed. It was attempted to force the reaction by heating it further. The THF was swapped out for 1,4-dioxane and the *tert*-butoxide conditions were repeated, increasing the temperature to 100 °C overnight. This provided no change whatsoever and so this course was abandoned.



37



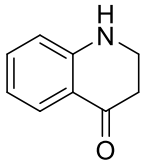
38

2.9 Series conclusions

There was a final attempt to reproduce the methodology that led to compound **36**, however on this occasion the yield was reduced to 2%. The clear evidence of reproducibility issues and problems with replacing the amine substrate meant that this methodology was not suitable for the desired purpose.

At this point, the multiple failures associated with this core led to the conclusion that it was probably best to cease investigations into the area at this point. Several avenues had been explored and none had achieved any usable or even reproducible results. Efforts would most likely be better focused elsewhere.

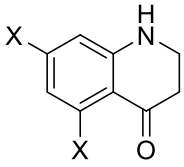
Part 2: Core 4: 2,3-dihydro-4(1H)-quinolinone



39

2.10 General Chemistry

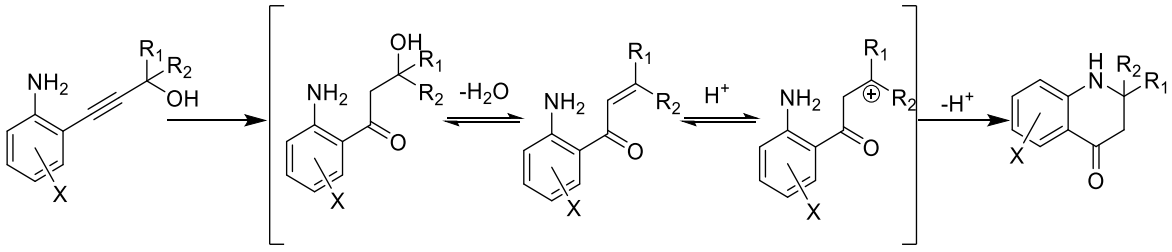
Core 4 was designed as a 5,7-dihalo-2,3-dihydro-4(1H)-quinolinone (**5**). Ideally, both halogenated positions would be different halogen substituents to allow for exploitation of differential reactivity later in the synthesis to selectively substitute one position over the other. Simple alkylation chemistry could be used to modify the substituent at the nitrogen position. Through this methodology it should be possible to introduce 3 points of difference to the molecule.



5

The general synthesis of this core is less varied than that of Core 2. The methodologies available in the literature have very few points of difference and are often performed on molecules that have far more complex substituent groups. Any variations to the methods spoken about below tend to simply iterate on the existing methodologies by either: altering reagents to achieve multiple steps at once or, using slightly different reagents with the same reacting partners to achieve the same results.

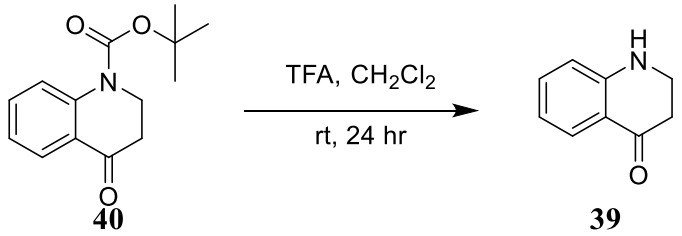
One synthetic method demonstrated by Politanskaya *et al.*[33] starts with 2-iodoaniline, performs a Sonagahira coupling with an alkynyl alcohol species and then hydrates across the triple bond using *para*-toluenesulfonic acid monohydrade as a catalyst. The acidic environment then allows for the terminal alcohol group to leave as water, generating a carbocation that is quenched by the nitrogen lone pair, closing the ring system. (**Scheme 2.32**)



Scheme 2.32

This method allowed the generation of both the parent core molecule **39** and the di-fluoro species with the substitution pattern desired. However, in both cases the yield was 10% or lower. Also, though C-C cross coupling reactions are powerful, it would be better if they could be avoided this early in the synthesis.

Other methods of generating the core have been as simple as buying the commercially available boc-protected amine and de-protecting it using acidic conditions, as is standard for this protecting group.[73] (**Scheme 2.33**)

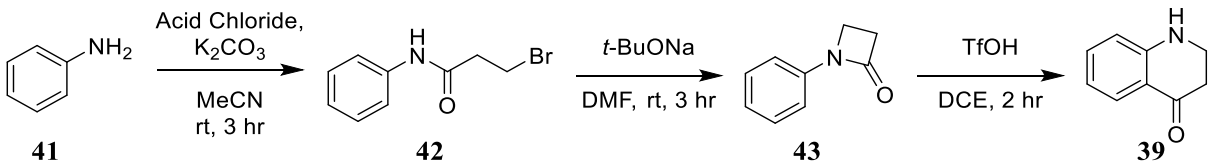


40 **39**

Scheme 2.33

Though quick and easy, the protected amine species is almost £100 per gram, which is rather expensive for a small organic heterocycle. On top of this, this methodology seems largely pointless as the difference in price between **40** and **39** is not very large and varies by supplier. Halogenation of the ring from this point on would also not be a trivial task, so any time saved by this methodology will likely be made up for elsewhere.

Another methodology developed by Wang *et al.*[74] was to take aniline and perform an amide coupling with a bromo-alkyl acid chloride species. The bromo alkane was then used to alkylate the secondary amide and form a β-lactam species. This species then freely underwent the Fries rearrangement in the presence of triflic acid to yield the desired core. (**Scheme 2.34**)



41 **42** **43** **39**

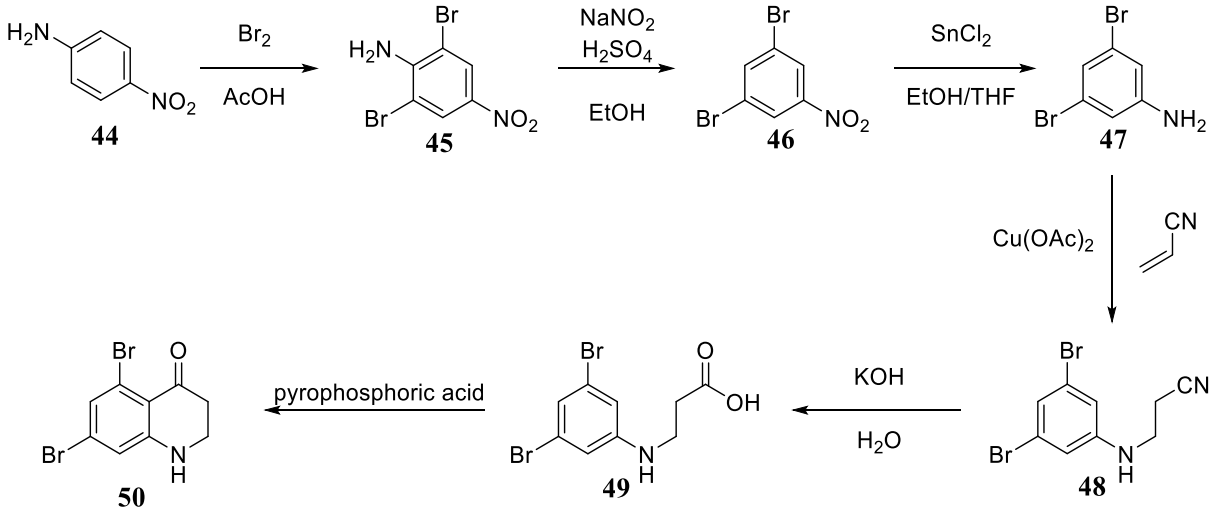
Scheme 2.34

Investigations into possible late-stage selective introduction of halogens at specific points on the aromatic ring of **39** showed that this method would also prove to be difficult, as little to no evidence exists for such reactions being successful. As such, it was decided that the best way to approach this core was to have the halogens in place on the aromatic ring before attempting any further derivatisation.

Examples of both the dichloro[75] and difluoro[33] forms of **5** exist in the literature but neither is as desirable as the dibromo. Fluorine is generally inert to most C-C bond forming reactions while chlorine is much more limited in its reaction scope. For example, the Suzuki-Miyaura cross coupling reaction will work for aryl chlorides, but their reaction rate is much slower than for aryl bromides, meaning reactions will either require higher temperatures, elongated reaction times or bulky, electron-rich ligands to achieve the same result.

A combination of methods was put forward to achieve the desired results. First, the generation of dibromoaniline (**47**) using the methodology developed by Malik *et al.*[76] and then plugging this into the diazotisation conditions developed by Chandrasekhar *et al.*[75] which had already been shown to work with the dichloro species. Since the general reactivity of the dibromo should be similar, this approach was deemed the most likely to have success. Difficulties in selecting the site of reaction for C-C bond forming reactions could be focused on once the core was synthesised.

The planned synthetic route is outlined in **Scheme 2.35**:

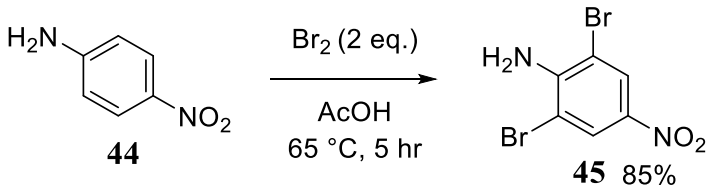


Scheme 2.35

2.11 Step 1: Synthesis of 3,5-dibromoaniline

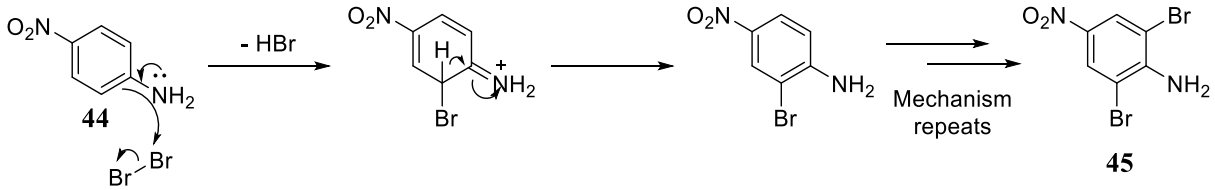
2.11.1 Bromination reaction

The first step of this synthesis was to brominate *p*-nitroaniline **44** to give the product **45** using the methodology as described by Malik *et al.*[76] (**Scheme 2.36**)



Scheme 2.36

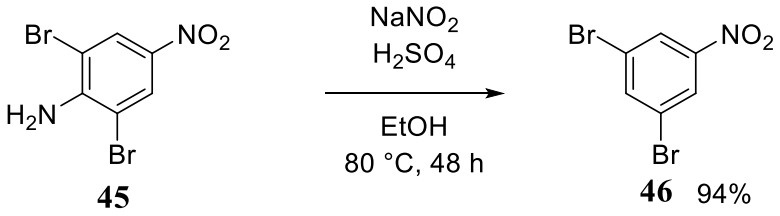
This reaction was successfully performed on a 10 g scale in the laboratory. The bromine was added dropwise initially to ensure a runaway reaction didn't occur and generate a large amount of heat and pressure. After about one third of the bromine was added, a precipitate began to form in the reaction vessel, likely due to the formation of HBr salts in the reaction. This necessitated the addition of hot water to assist in dissolving said precipitate before adding the final portion of the bromine and allowing the reaction to stir for the remaining portion of the allotted 5 hours. It should also be mentioned that using saturated sodium bicarbonate solution to quench the reaction should be avoided if possible, as it leads to the generation of a large quantity of viscous yellow foam that is difficult to extract product from. The mechanism for the reaction is given in **Scheme 2.37**:



Scheme 2.37

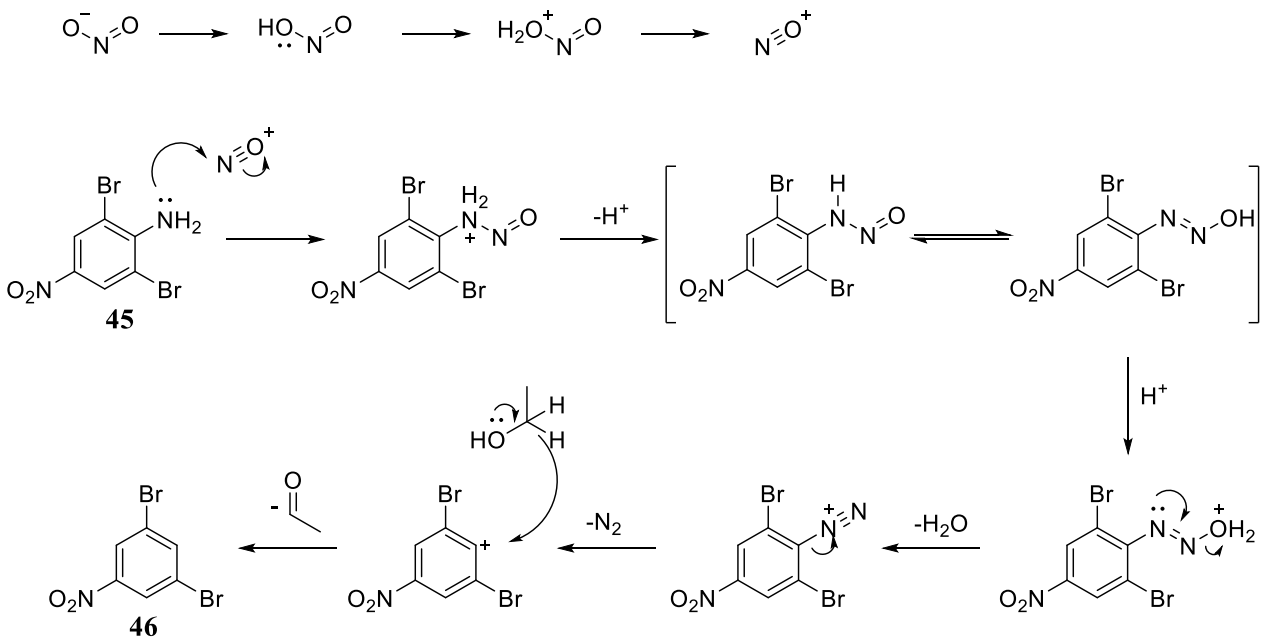
2.11.2 Removal of amino group

The next step was the conversion of **45** to **46** by removal of the amino group. This was accomplished through the use of a diazotisation reaction. (**Scheme 2.38**) This reaction worked incredibly well, giving a 94% yield after recrystallization from ethanol.



Scheme 2.38

As per standard diazotisation methods, sodium nitrite is used to affect the addition of NO^+ to the amino group of **45**. This subsequently loses water to give an N_2^+ substituent on the ring. N_2^+ is well known for its useful propensity as a leaving group as nitrogen gas is incredibly stable. The loss of nitrogen gas is driven by the strength of the N-N triple-bond. This reaction is also irreversible as a result, as it is much more entropically favourable for N_2 to exist on its own. The positive charge on the ring is then quenched by a hydride from the α-carbon of the ethanol, generating acetaldehyde as a side product and giving the final compound **46**. (**Scheme 2.39**)



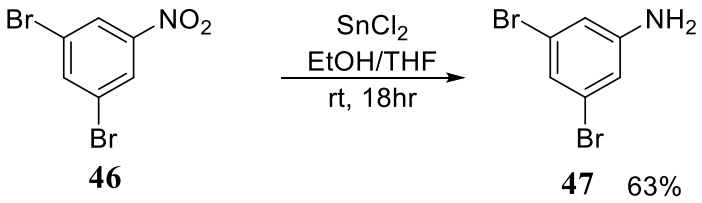
Scheme 2.39

Care had to be taken with this reaction as the diazotisation is both fast and potentially dangerous. The rapid evolution of nitrogen gas from the reaction as shown in **Scheme 2.39** could be very easily classed as an explosive reaction, and so the addition of the sodium nitrite had to be undertaken with the flask open to the air. The slow addition of the sodium nitrite was also used to assist in reducing

the reactions aggression. The generation of acetaldehyde as the side product of the reaction was also a large benefit as it has a boiling point of 20°C, meaning that under the standard reaction conditions, it boils and gets removed from the reaction, preventing any build up and consequently, preventing the slowing down of the reaction. This eases clean-up at the end of the reaction and makes the final compound easier to purify and handle.

2.11.3 Reduction of the nitro group

The next step was to reduce the nitro group of compound **46** to give the aniline compound **47**. This was achieved by using the same conditions as were used in the reduction of the nitro group in core 2; anhydrous tin chloride in an ethanol / tetrahydrofuran mix. (**Scheme 2.40**) This method was chosen once again as it was incredibly mild and worked at room temperature.



46 **47** 63%

Scheme 2.40

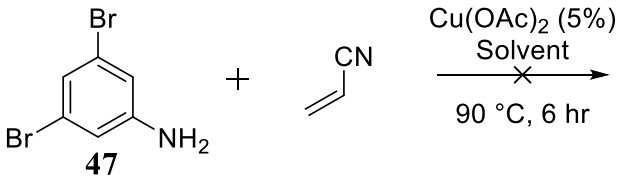
Upon completion, the reaction was stirred with a 1M NaOH solution to neutralise before extraction, with the final compound **47** being purified with silica gel column chromatography. Thankfully it seems that this reaction works almost as well as suggested in the literature.[76] Unfortunately, as is common with organic chemistry and research in general, this ease was not to follow through to other stages of the synthesis.

2.12 Addition of nitrile

Following on from this success, the next task was the alkylation of **47** using acrylonitrile with a copper (II) catalyst, using the conditions developed by Chandrasekhar *et al.*[75] The issue with this method was that the reaction provided in the paper was performed on a very large scale (10 kg) and used neat acrylonitrile as both a reactant and the reaction solvent. It was believed that this may prove problematic when performing the reaction on a small (50 mg) scale in the lab and so initially the reaction was trialled using various solvents in parallel.

2.12.1 First Attempt

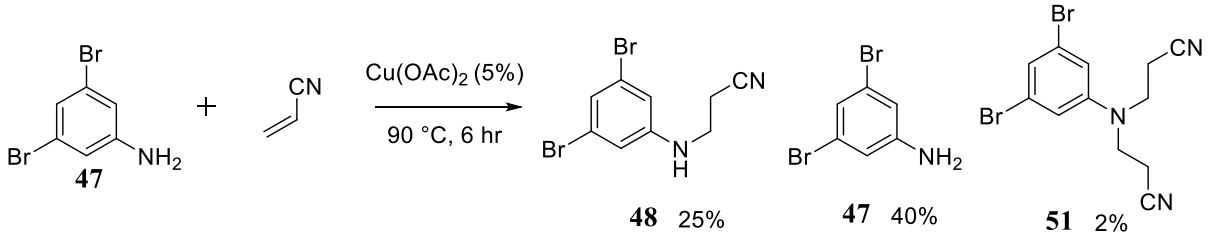
The solvents selected for this attempt were DMF, toluene, water and 1,4-dioxane. These solvents were selected as they have boiling points above the 90°C temperature point as used in the paper. (**Scheme 2.41**)



Scheme 2.41

All of the reactions performed in solvent failed to produce any product, leaving only starting material behind. It was evident from this that the reaction was not likely to work in the presence of a solvent. As a result, the reaction was attempted in neat acrylonitrile on a small scale. (**Scheme 2.42**)

2.12.2 Second Attempt



Scheme 2.42

This reaction worked, though not very well. 3 separate compounds were isolated from the reaction. Just as noted by Chandrasekhar *et al.*, there was a small quantity of compound **51** present in the product mixture, the di-addition product of the reaction. **51** was easily distinguishable from **48** by ^{1}H NMR spectroscopy for several reasons. For one, the amine proton alpha to the first CH_2 group in **48** causes the signal to split in the ^{1}H NMR spectrum which results in a quartet instead of a triplet. There is also the presence of a broad peak corresponding to the amine proton at 4.18 ppm for compound

48. Since **51** doesn't have an amine proton, both of the CH_2 groups appear as triplets. There is also a noticeable difference in chemical shift between the 2 products: (**Figure 2.4**)

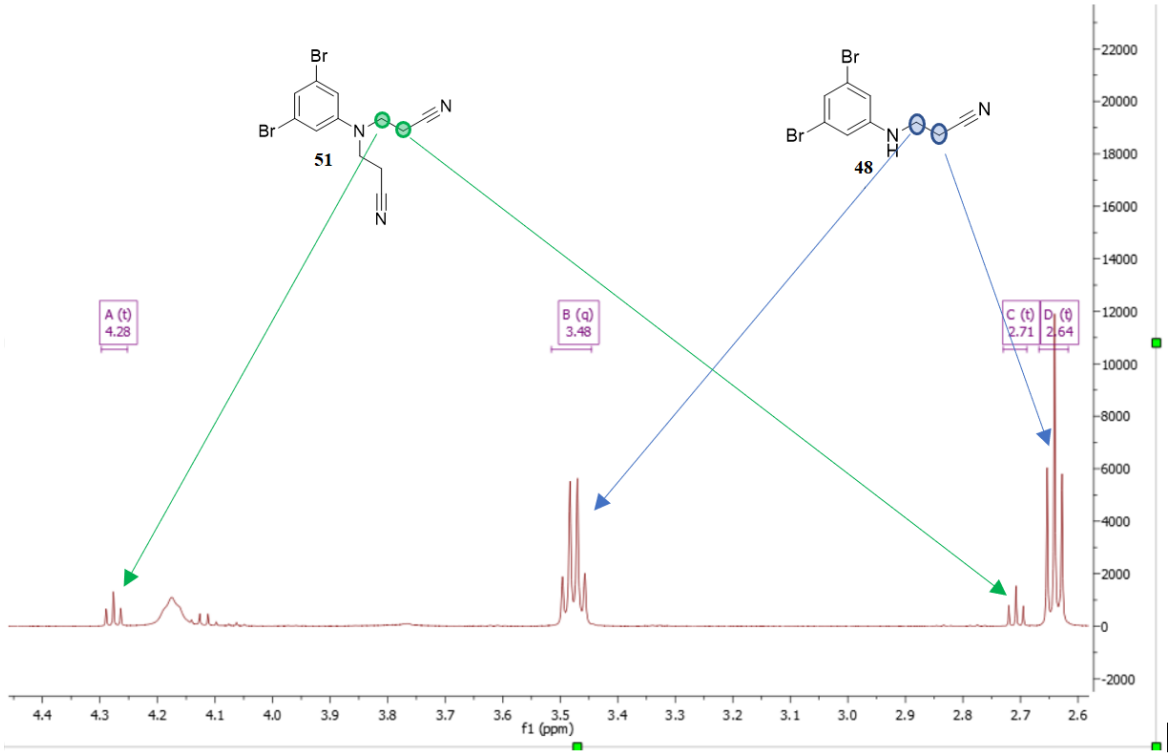
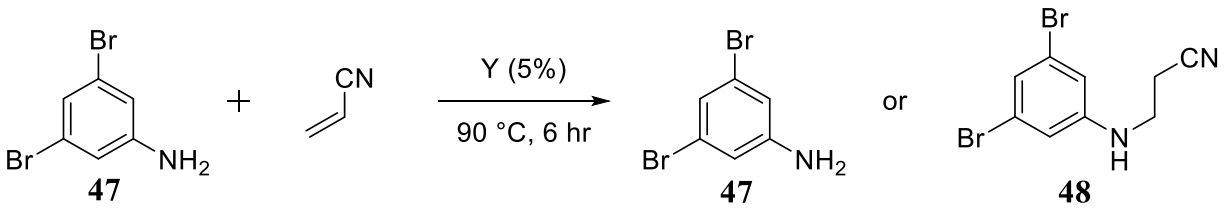


Fig. 2.4 *– Differences between* ***48*** *and* ***51*** *by* ^{1}*H NMR*

2.12.3 Third Attempt

The reaction was attempted with different copper sources to see if these had any effect on the reaction. A range of both copper (I) and copper (II) sources were attempted: (**Scheme 2.43**)



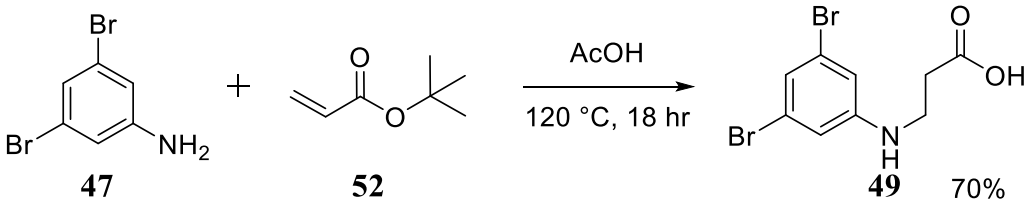
Y = CuI, $Cu(NO_3)_2$, $CuBr_2$, $[Cu(CH_3CN)_4]PF_6$

Scheme 2.43

Almost all of the copper species failed to produce any reaction at all. The lone exception was copper (II) bromide, which generated the addition product **48** in only a 14% yield by ^{1}H NMR.

2.12.4 Acrylate addition

A workaround was proposed, using chemistry from Pinney *et al.*[77] This method used Michael-addition type chemistry to add an acrylate moiety to an aniline. This chemistry was used to attempt the addition of *tert*-butyl acrylate (**52**) to **47** to generate the *tert*-butyl ester protected version of product **49**. (**Scheme 2.44**)

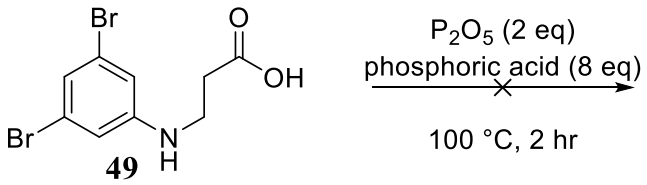


Scheme 2.44

The reaction initially appeared to be successful by ^{1}H NMR, giving the presence of two new triplets at 3.41 and 2.65 ppm, indicating the presence of two methylene groups next to one another. It was discovered however that the reaction conditions were acidic enough to successfully remove the *tert*-butyl protecting group from the acrylate, leaving compound **49** as the actual isolated product. This was unsurprising given that the conditions required for the removal of a *tert*-butyl group normally involve using concentrated sulfuric acid as demonstrated by Strazzolini *et al.*[78] This was not detrimental to the synthesis however, as the cyclisation step for the reaction requires the presence of a carboxylic acid and so, unintentionally, two stages of the reaction had been performed in the same step.

2.13 Cyclisation reaction

The final stage of this process was to use the conditions provided by Watanabe *et al.*[32] to affect a Friedel-Crafts type intramolecular cyclisation. This was a worry however, as it was already known from previous experience that the conditions were very harsh and were likely to destroy the starting material **49**. (**Scheme 2.45**)



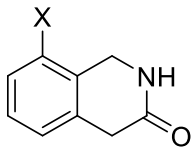
Scheme 2.45

As expected, the reaction failed, generating an incomprehensible mess of products that were most likely breakdown products of **49**. The presence of the aniline in **49** is a problem, as it is within reason that under highly acidic conditions such as those used here, it becomes highly protonated and breaks down, tearing the compound apart before it even has a chance to cyclise as desired.

Conclusions

A significant amount of work was put into both cores 2 and 4 as evidenced by the account given above. Ultimately however, the project came down to priority management. Before the endpoint of these syntheses had been as described, success had been achieved with core 1 and so it was decided to devote efforts entirely to achieving success on that route. This is not to say the work above is insignificant or inconsequential, however. A large amount of time and effort was put into the work above and success was within a few months reached in both cases, particularly with core 2. The synthesis developed for this core in **Scheme 2.31**, while not successfully applied to amines besides allylamine, could likely be optimised within a short period of intense, full-time study. If this project were to be iterated on in the future, it is believed that enough work has been done such that future researchers should find early investigations into the area to be relatively straightforward and should be able to achieve significant results early on in their studies.

Chapter 3: Early investigations – Core 1



2

Core 1 (**2**) is based on a 1,4-dihydro-3(2H)-isoquinolinone scaffold. These types of structures have been made before, though the methodologies involved differ greatly from one another and have varying results. The bromo derivative of **2** has been synthesised to completion before, and this played a role in the decision to pursue this core early in the project.

Once core synthesis was complete, simple alkylation chemistry was theorised to be enough to substitute the nitrogen on the ring, while the carbon atom alpha to the carbonyl group would also likely be susceptible to deprotonation and so could be substituted with an electrophile. The halogen could then be used to facilitate C-C bond forming reactions e.g. palladium cross coupling reactions. In this manner it was theorised that the core could be rapidly functionalised, allowing for the quick and straightforward synthesis of a large library of compounds.

3.1 Previous Syntheses

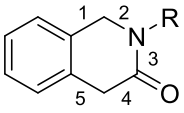
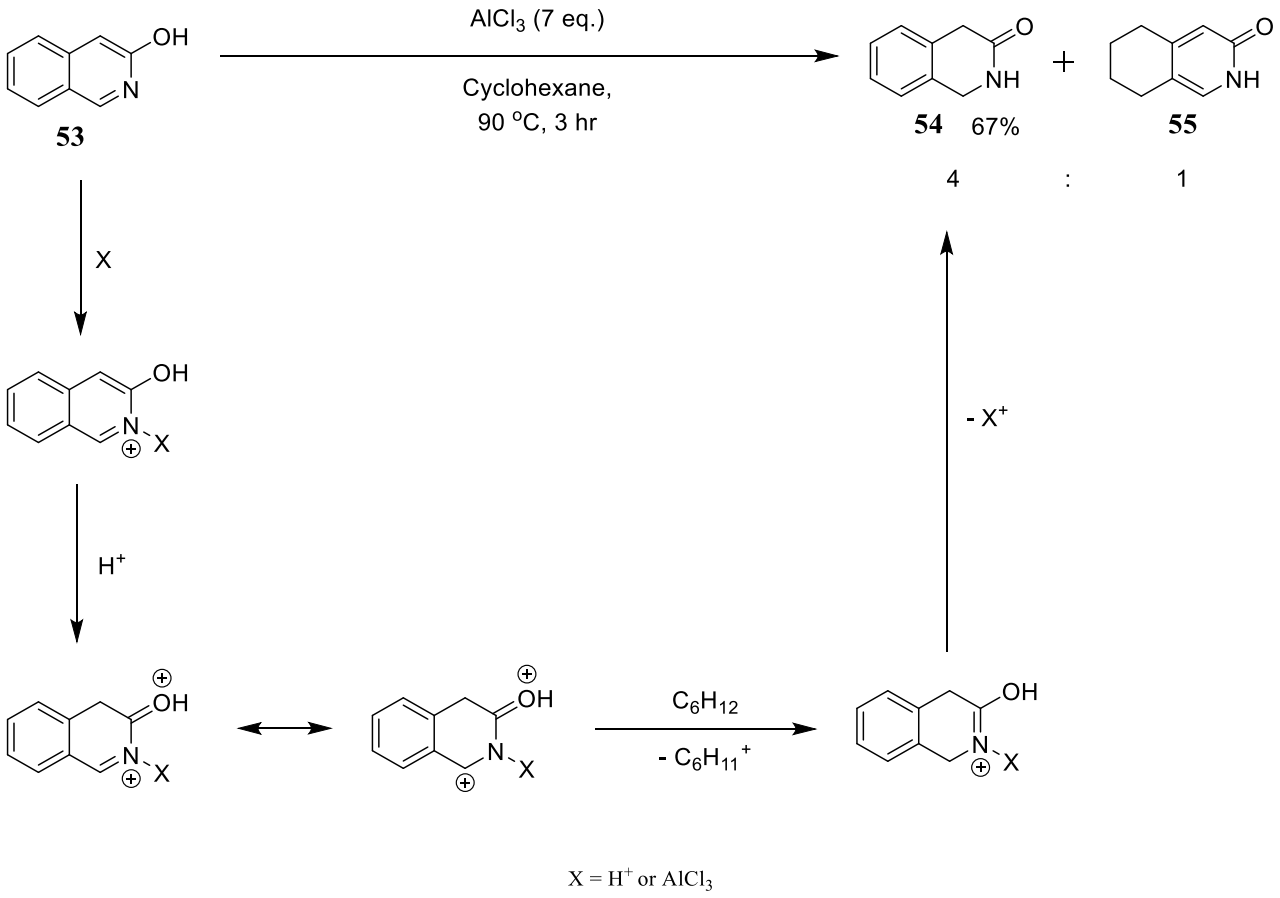


Fig 3.1 *– Structure of Core 1 with labelled bonds*

The core structure **54** without any halogenated substituents was synthesised by the Olah group.[79] They used $AlCl_3$ (in a large excess) on 3-isoquinolinol (**53**) in cyclohexane and heated the mixture to 90 °C for 3 hours to generate their product. The $AlCl_3$ behaves as a superacid in this reaction, resulting in formation of a positive charge on the alcohol group and the formation of a cationic nitrogen species. The cyclohexane then allows for ionic hydrogenation to occur to generate the final product. This process also resulted in the production of **55** as the by-product of the reaction in a ratio of 1:4 with **54**. (**Scheme 3.01**)



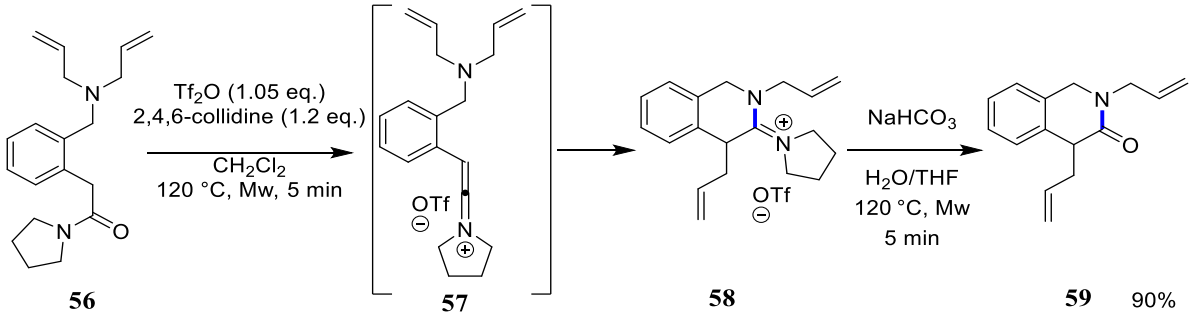
Scheme 3.01

3.1.1 Synthesis of **54** by the formation of Bond 1

A methodology for synthesising the core *via* the formation of bond 1 was developed by Watanabe *et al.*[32] This particular synthesis shall be explored in greater detail further on in this chapter.

3.1.2 Synthesis of **54** by the formation of Bond 3

By the formation of bond 3, Marques *et al.*[80] managed to create a substituted version of the core (**59**) but had no method of differentiating the side chains attached to said core. This consequentially meant that the positioning of the sidechains in the final product could not be directed. They achieved this by generating a tertiary amide from pyrrolidine (**56**) and using this to generate a keteniminium triflate salt intermediate (**57**) which underwent a rearrangement to form **58**. Subsequent hydrolysis afforded the product **59**. (**Scheme 3.02**)

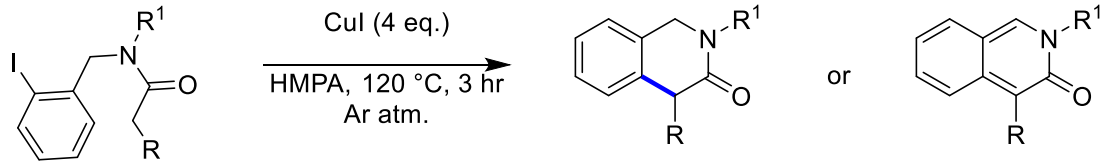


Scheme 3.02

While this reaction is neat and the later steps give high yields, it requires several steps to even generate **56** in the first place and only a 29% yield of this compound was achieved. The multiple steps and lack of ability to differentiate sidechains meant that this route was unattractive.

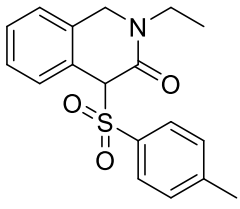
3.1.3 Synthesis of **54** by the formation of Bond 5

Suzuki *et al.*[81] used copper iodide on a preformed substituted amide species with a halogen in place on the ring to form cyclised products. (**Scheme 3.03**)



Scheme 3.03

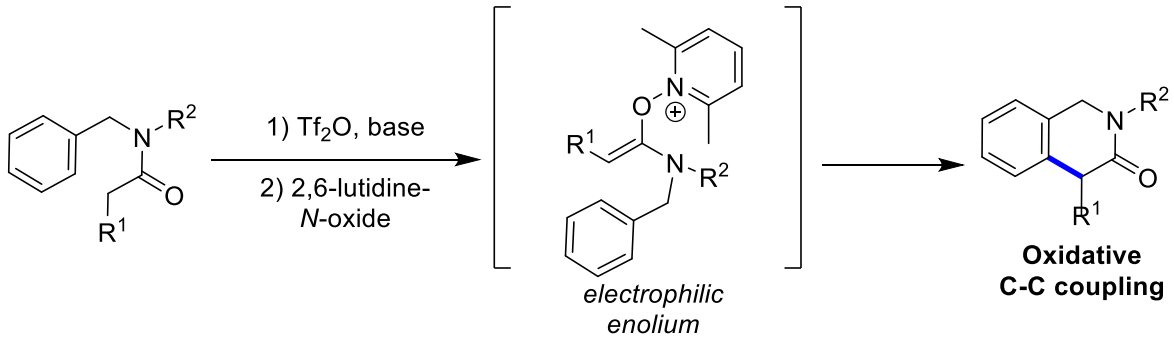
However, they mostly formed fully aromatic species and in only one case did a compound resembling the desired product form (**60**), meaning the reaction was not well tolerated by various functional groups which, again, made this route unattractive.



60

Maulide *et. al.*[82] did come up with a useful and consistent methodology for synthesising the core structure with substituents attached *via* the use of an electrophilic enolium species, which reversed

the polarity of the α-carbonyl position of an amide and allowed for oxidative C-C coupling at that position. (**Scheme 3.04**)

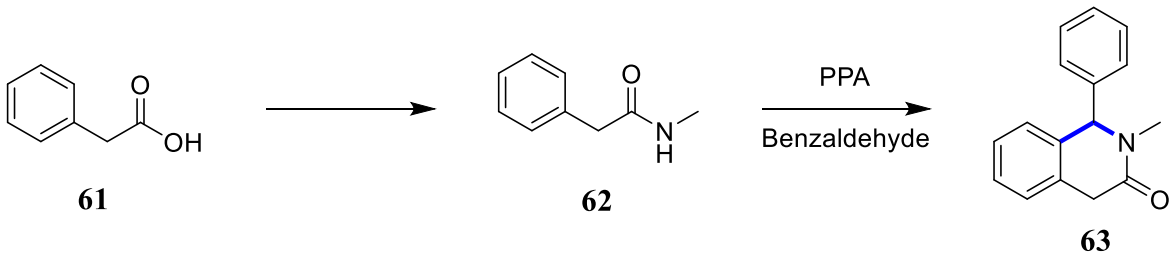


Scheme 3.04

While versatile and tolerant of various functionalised aromatic groups, the *N*-substituent is either a benzyl or an alkyl group in all examples in the paper. It also requires the use of lutidine-*N*-oxide as a reacting partner, which serves no other purpose in the reaction. This makes the overall atom economy of the reaction quite low.

3.1.4 Synthesis of 54 by the formation of Bonds 1 and 2

Brossi *et. al.*[83] synthesised the core (albeit with a phenyl substituent attached) by creating both bonds 1 and 2 simultaneously. Starting with phenylacetic acid (**61**), they converted this into *N*-methylphenylacetamide (**62**), before reacting this with benzaldehyde in polyphosphoric acid to generate both bonds 1 and 2 *in situ* (**63**). (**Scheme 3.05**)

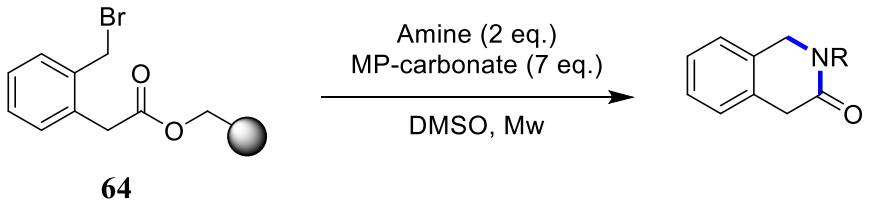


Scheme 3.05

While somewhat useful, this methodology was improved upon by Watanabe *et. al.*[32] in their later paper, removing the requirement for benzaldehyde to be used to introduce a new carbon atom into the ring, and generating an amide without an *N*-substituent already present. Watanabe's chemistry was employed as part of this thesis. (**Scheme 3.20**)

3.1.5 Synthesis of **54** by the formation of Bonds 2 and 3

Dolle *et al.*[84] used a resin-bound benzyl halide species (**64**) to first undergo nucleophilic attack by an amine before heating to release it from the resin to generate the final product. (**Scheme 3.06**)



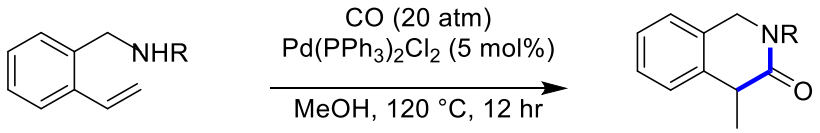
64

Scheme 3.06

This methodology worked well, however it rarely resulted in yields higher than 40%. The combination of low yields and the lack of general experience with resin chemistry in the lab made this methodology somewhat unattractive, and so it wasn't pursued in this format. This chemistry was used in a slightly different format however at one point of the project and shall be explored later in the thesis.

3.1.6 Synthesis of **54** by the formation of Bonds 3 and 4

Huang *et al.*[85] developed a methodology to form both bonds 3 and 4, this time utilising palladium catalysis. In their methodology, a benzylic amine and an alkene underwent a carbonylation reaction to generate the final cyclised species. (**Scheme 3.07**)

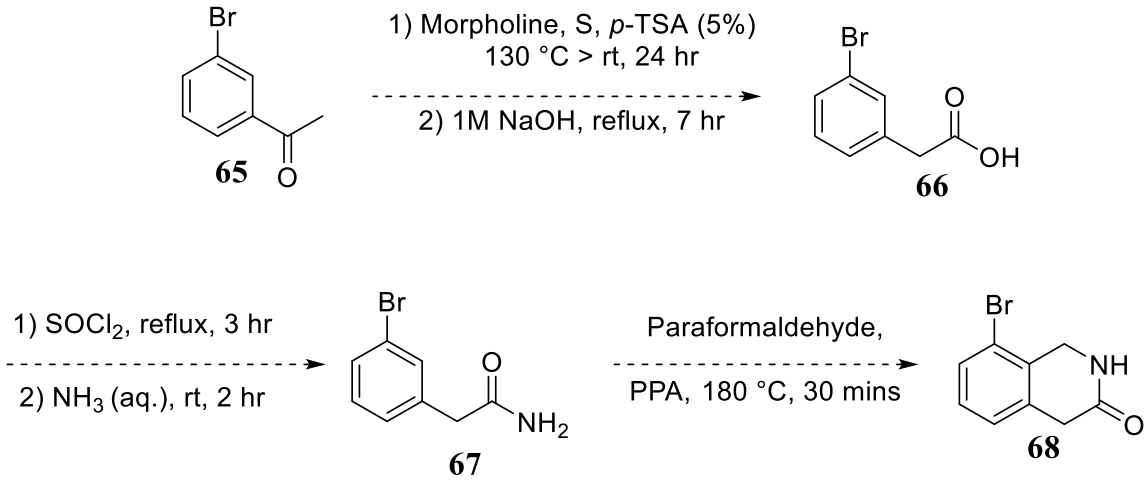


Scheme 3.07

While the number of examples in this paper is large, it always resulted in a sidechain of some sort being attached at the α-carbonyl position. The reaction conditions also called for 20 atmospheres of CO, which was not safe or practical in the lab this work was carried out in.

3.2 Synthesis of **68** – Formation of bonds 1 and 2

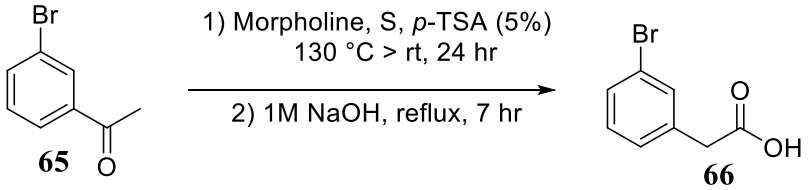
It was decided to attempt to synthesis **68** through the formation of bonds 1 and 2 as previously described on **54**. The initial proposed reaction scheme is shown in **Scheme 3.08** below. The first step employs the use of the Willgerodt-Kindler reaction[86] to synthesise compound **66**. This could then be converted to the amide (**67**) by conversion to the acid chloride and reacting this with aqueous ammonia. The final step could be achieved using the conditions developed by Watanabe *et al.*[32], using paraformaldehyde as a source of carbon and pyrophosphoric acid to facilitate the formation of the final product **68**.



Scheme 3.08

3.2.1 First step

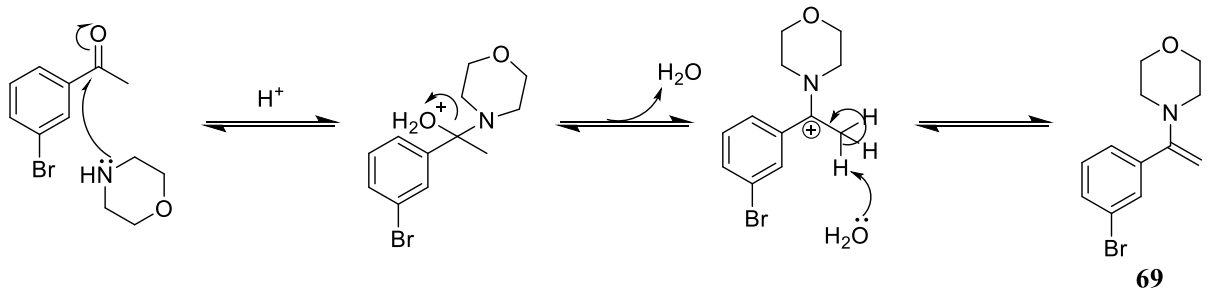
The Willgerodt-Kindler reaction is an under-utilised but incredibly powerful reaction. It has largely fallen by the wayside in modern organic synthesis, but this is surprising given both its power and ease of use. The reaction uses elemental sulfur and a secondary amine to turn acetophenone species into terminal thioamides that can undergo a variety of other functional group conversions. In this case, hydrolysis to the carboxylic acid. **(Scheme 3.09)**



Scheme 3.09

Before discussing the reaction mechanism, it should be noted that this was initially elucidated by Carmack *et al.*[87] in the 1980's and that quite a few of the intermediated have not been confirmed experimentally. However, Bolm *et al.*[88] have stated that this is the widely accepted mechanism for the reaction, and elements of the mechanism have been confirmed by Peng *et al.*[89] using C^{14} labelling experiments.

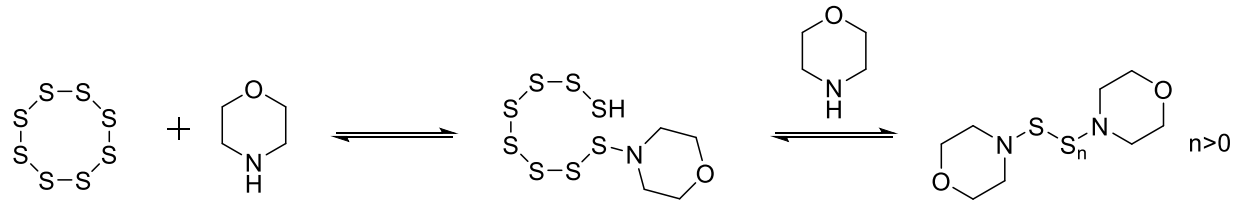
The initial step of the reaction involves the formation of an enamine species **69**. (**Scheme 3.10**)



69

Scheme 3.10

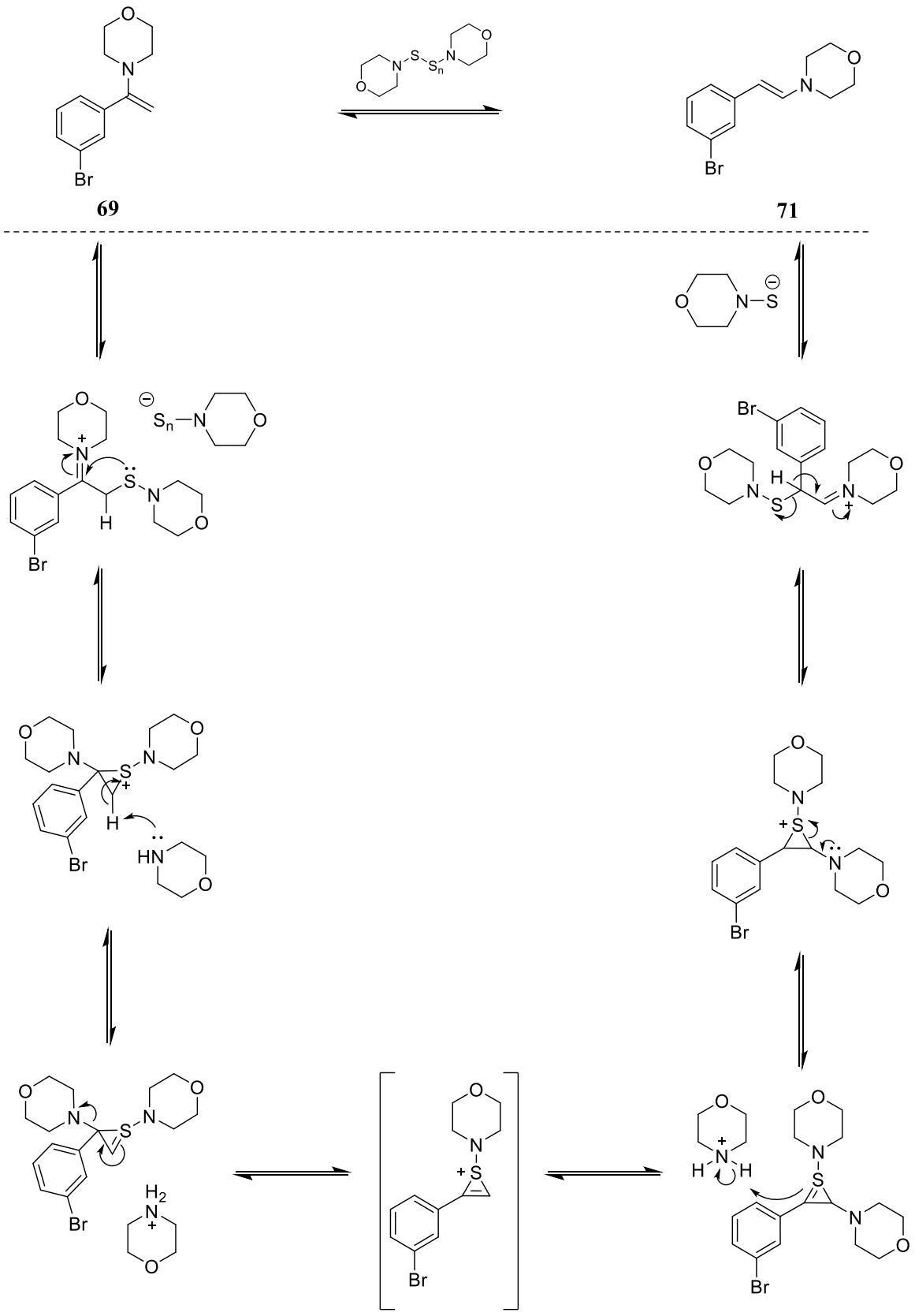
The morpholine and elemental sulfur also react to generate the amino-sulfur species **70**. (**Scheme 3.11**)



70

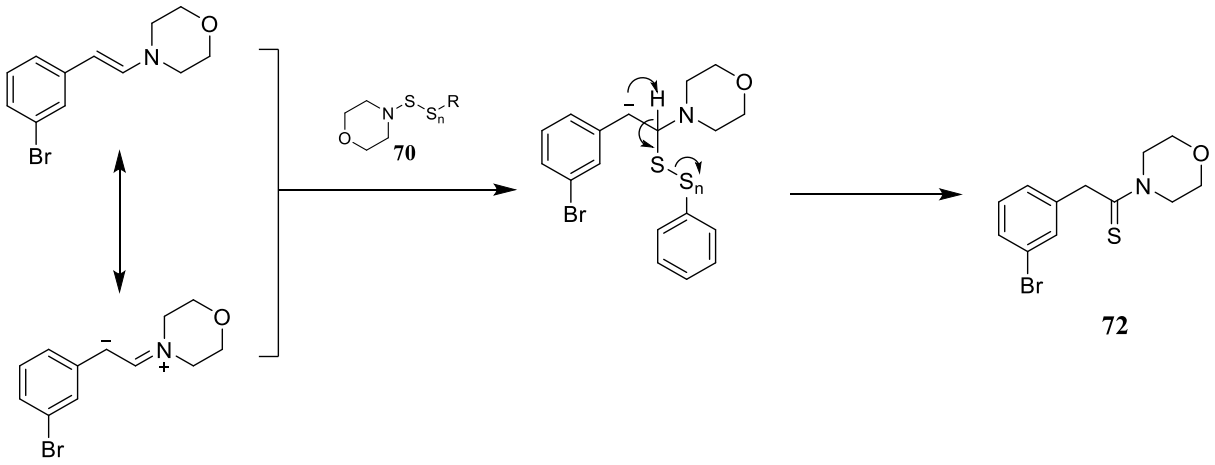
Scheme 3.11

70 then promotes the isomerisation of **69** to form enamine **71**, the mechanism for this process is outlined in the following scheme: (**Scheme 3.12**)



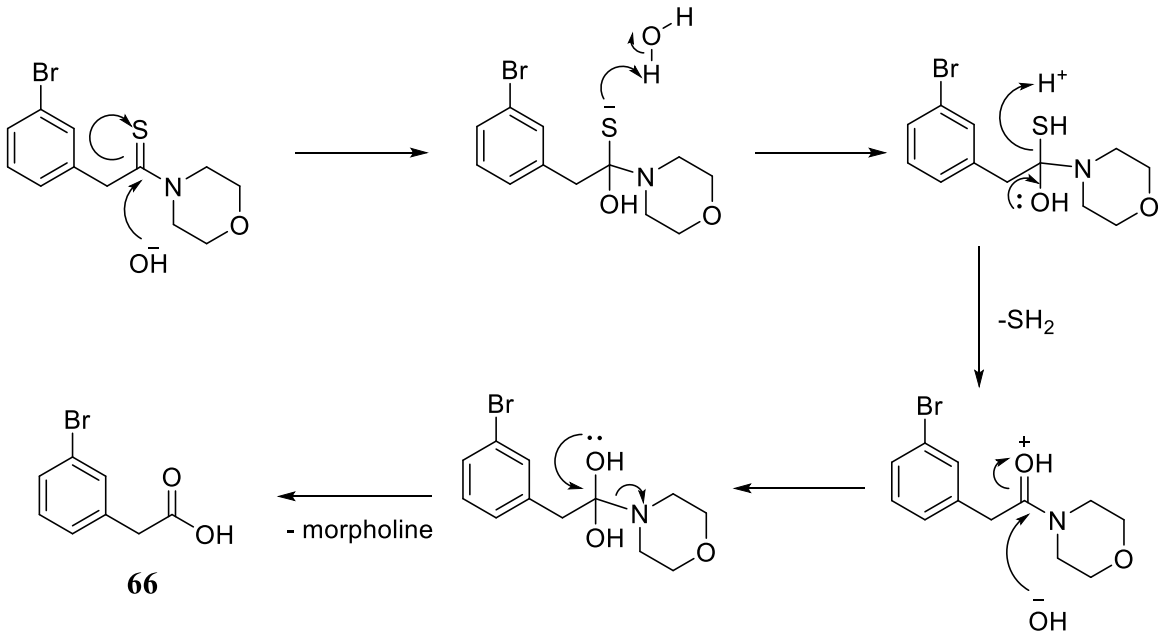
Scheme 3.12

This enamine species is then oxidised to the thioamide (**72**) by the amino-sulfur compound **70**. (**Scheme 3.13**)



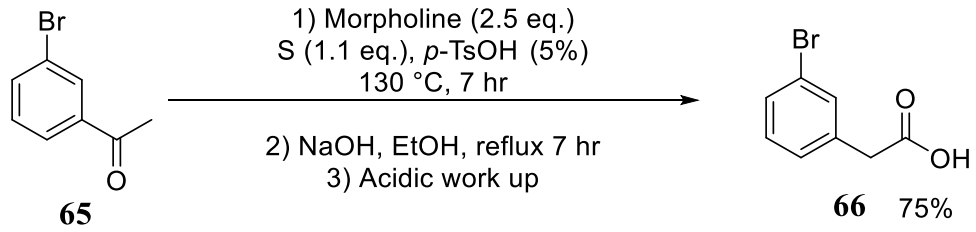
Scheme 3.13

This marks the endpoint of the standard Willgerodt-Kindler reaction. From here, hydrolysis in the presence of an aqueous base affords the final carboxylic acid **66**. (**Scheme 3.14)**



Scheme 3.14

Upon performing the reaction in the laboratory, product **66** was generated with an isolated yield of 75%. (**Scheme 3.15**) Any remaining starting material (**65**) was easily extracted from the reaction mixture with diethyl ether before the acidic workup, as the product **66** was deprotonated and water soluble at this stage.



Scheme 3.15

The compounds were easily distinguishable from one another as the CH_2 in **66** appears at 3.63 ppm in the ^1H NMR while the CH_3 of start material **65** appears at 2.57 ppm.

These findings also held true on scale. The reaction proved successful even up to larger scales (1.5 g) and the ease with which the compound was purified (simple acidic workup) meant that the reaction was also incredibly clean as it didn't require any further purification.

3.2.2 Conversion of carboxylic acid 66 to amide 67

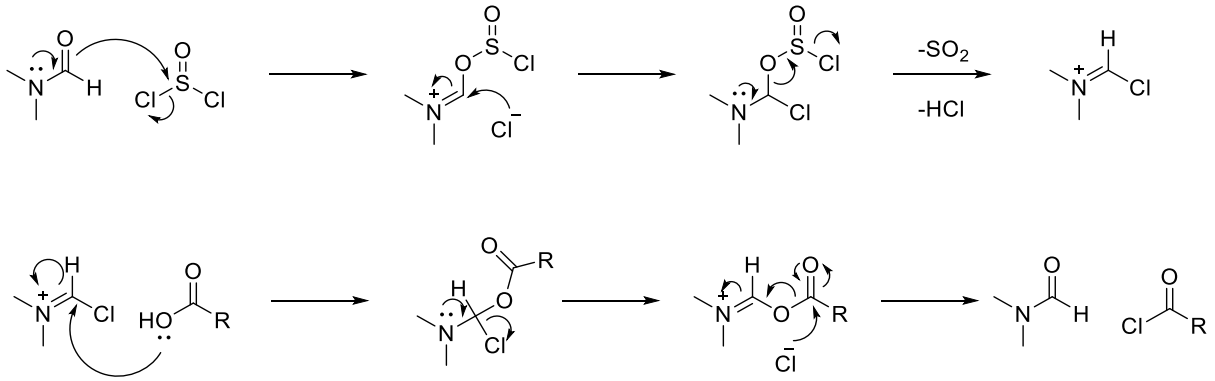
The next step involved the conversion of **66** to the corresponding acid chloride. The acid chloride was then to be converted to the amide **67** by stirring it in the presence of aqueous ammonia. This step should have been straightforward. As is often the case however, there were some unexpected results and the reaction required some optimisation. Several methods to achieve the desired product **67** simply failed to produce any results.

3.2.2.1 First attempt

The first attempt at the synthesis of **67** involved dissolving **66** in neat thionyl chloride with a catalytic amount of DMF. This was quenched with 25% aqueous ammonia.[90] (**Scheme 3.16**) The mechanism for the conversion to the acid chloride is given in **Scheme 3.17**. This returned almost exclusively starting material however, which was unusual and disappointing given that acid chlorides are very reactive species[91] and should convert to amides with little to no difficulty. It appeared that thionyl chloride was simply no going to perform this reaction as desired and so, alternative methods of synthesising the acid chloride intermediate were attempted.

66

Scheme 3.16

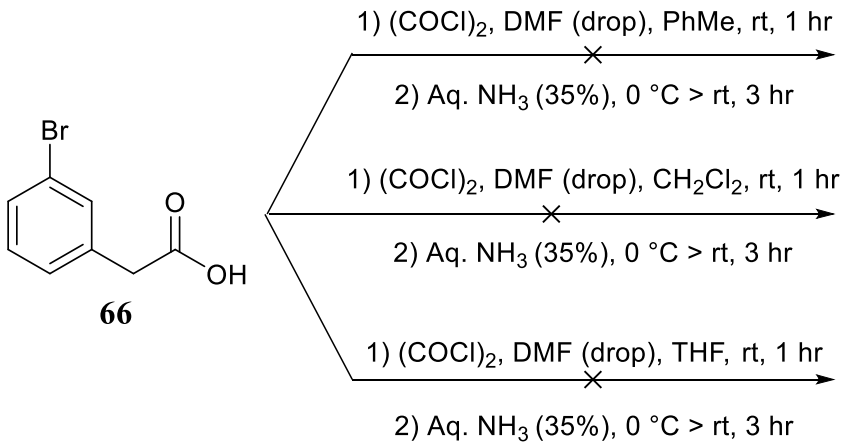


Scheme 3.17

3.2.2.2 Second Attempt

The second attempt used conditions from Williamson *et al*.[92] (**Scheme 3.18**) Oxalyl chloride was used in place of thionyl chloride, and instead of performing the reaction neat, it was trialled in various dry solvents. It was also kept at a much cooler temperature, starting from 0 ˚C before allowing the reaction to come up to room temperature over an extended period.

Oxalyl chloride was chosen as an alternative for its sheer reactivity, as it is well known for producing acid chlorides with very little intervention.[93] Because the reaction is exothermic, it was cooled to slow the reaction to manageable speeds and prevent the oxalyl chloride from boiling out of the system. It was hoped that using oxalyl chloride would also help with purification afterwards, as it breaks down to give CO_2 and CO which are released from the reaction.

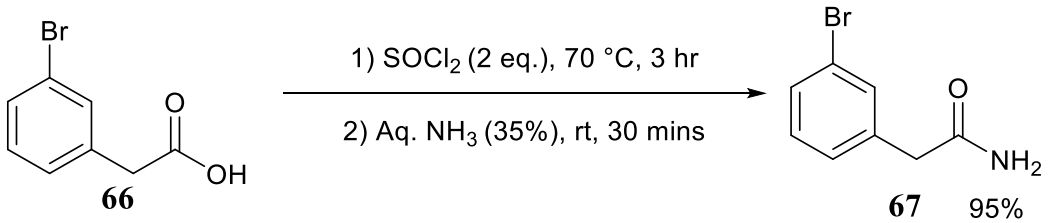


Scheme 3.18

Once again, the reactions failed to generate any product, with **66** being recovered from every reaction unchanged. At this point it was believed that perhaps the issue was the speed of formation of the acid chloride and not the reagents being used. By leaving the reaction for longer, it was hoped that the desired results could be achieved. There was also the possibility that the temperature at which the oxalyl chloride reactions were performed was simply too low. The lack of formation of gas bubbles in the reaction backed up this theory, as if the reaction was progressing it would be generating CO and CO_2 as side products.

3.2.2.3 Third Attempt

A further set of alternative conditions were found,[94] once again using neat thionyl chloride but refluxing for longer and a using a higher concentration of ammonia for the quench (35% instead of 25%). (**Scheme 3.19**)

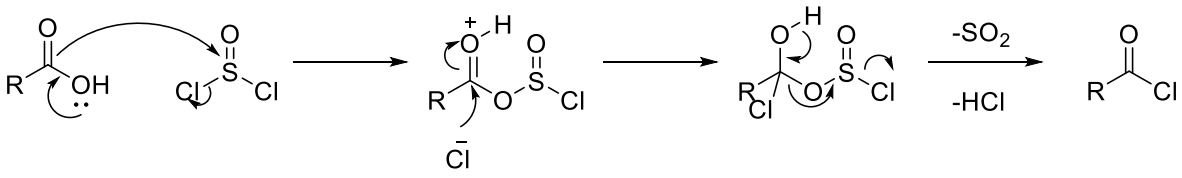


Scheme 3.19

This reaction proved very successful and resulted in an isolated yield of 95% of the amide product **67**. Using ^{1}H NMR spectroscopy to identify the difference between compounds **66** and **67** was not particularly useful as the change in the chemical shift of the CH_2 group is so small (0.08 ppm). FTIR

spectroscopy was used to confirm the presence of the amide functional group in compound **67**, giving confirmation that the reaction had indeed worked correctly. The appearance of a peak at 3346 cm^{-1} is indicative of the amide NH stretches while a peak at 1634 cm^{-1} represents the amide carbonyl stretch. The lack of a carboxylic acid CO (at 1696 cm^{-1}) or OH (at 3000 cm^{-1}) group suggests complete conversion to the amide **67**.

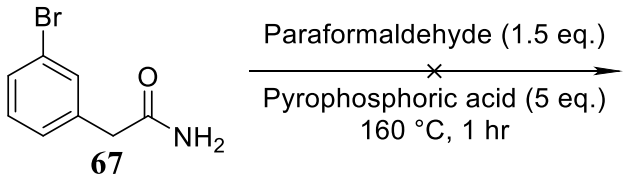
This reaction also had the added benefit of not requiring DMF as a catalyst, simplifying the reaction conditions somewhat and making solvent removal easier. The mechanism is provided in **Scheme 3.20**.



Scheme 3.20

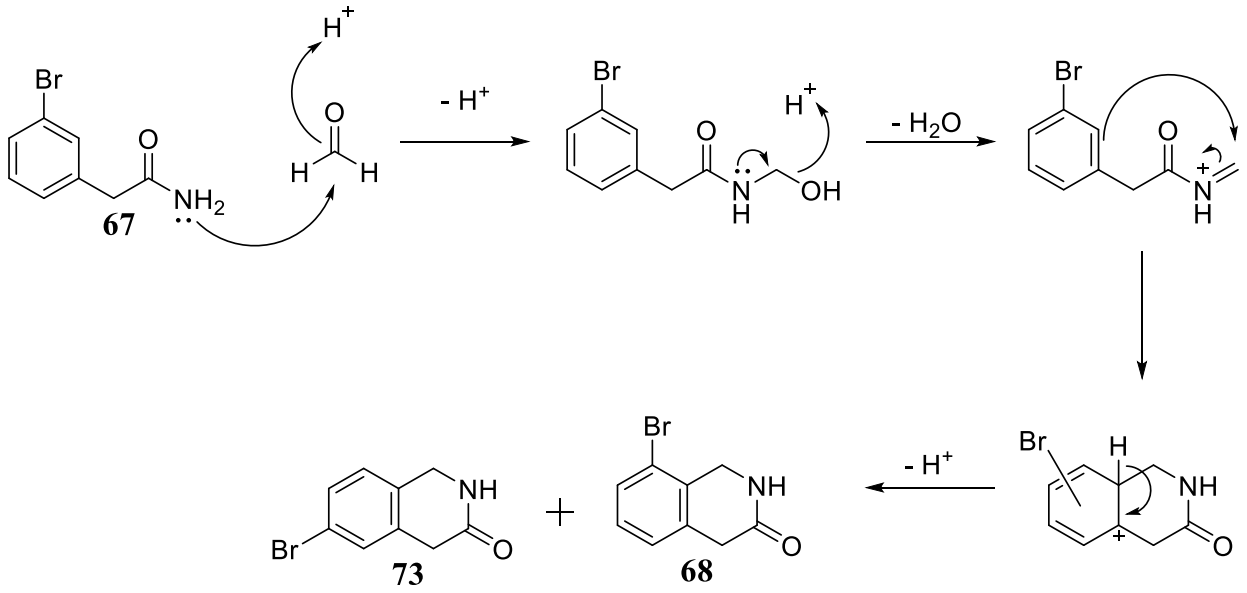
3.2.3 Cyclisation to form 68

Following the success of this step, the final stage of the synthesis was to perform a cyclisation reaction using the primary amide **67** to generate the 1,4-dihydro-3(2H)-isoquinolinone **68**. This reaction was attempted using the conditions developed by Watanabe *et al.*[32] Paraformaldehyde was used as the carbon source needed to generate the six-membered ring. (**Scheme 3.21**) This was an improvement on the methodology previously developed by Brossi *et al.*[83]



Scheme 3.21

The proposed mechanism for the reaction attempted is given in **Scheme 3.22**. It should be noted that there was potentially little control over which of the two final products (**68** and **73)** was the preferred product of the synthesis.



Scheme 3.22

Disappointingly, this reaction failed when attempted in the lab. What came out of the reaction was invariably a black tar. ^{1}H NMR data also proved to be almost indecipherable. From this it was determined that the reaction conditions were harsh enough to destroy starting material **67**, and that the difficult to analyse ^{1}H NMR data was most likely caused by an amalgamation of breakdown products. Heating **67** in neat pyrophosphoric acid was very likely not going to provide a successful outcome and so alternatives had to be found.

According to Watanabe's original paper, the cyclisation reaction to generate **68** could also be performed on a nitrile starting material to achieve the same results using the same conditions. This led to an attempt to change the starting amide (**67**) to the corresponding nitrile (**74**), which would then be placed under the same reaction conditions to hopefully achieve the desired result. This plan was also backed up by a Merck patent in which this very reaction had been performed[95] on the same substrate (**74**).

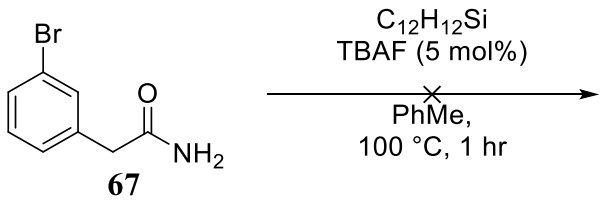
Several methods to convert **67** to **74** were attempted with varying levels of success.

3.2.4 Conversion of amide 67 to nitrile 74

3.2.4.1 First Attempt

Initially, conditions from Beller *et al.*[96] were attempted. (**Scheme 3.23**) In their paper, the group showed that they had tested this reaction on multiple substrates. Using TBAF to provide a catalytic amount of fluoride to the reaction, they used various aryl and alkyl hydrosilanes to convert amides

to nitriles. The benefit of this method was that it did away with the use of stoichiometric amounts of metal such as those used in the Sandmeyer reaction,[97] making it more synthetically attractive. Diphenyl silane was chosen as the hydrosilane as it was readily available in the lab and had also performed quite successfully in the paper.

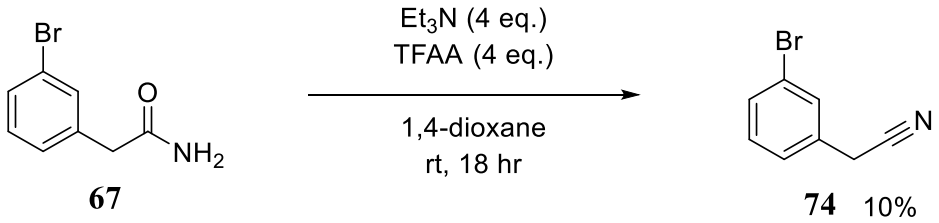


Scheme 3.23

Unfortunately, this method was unsuccessful when performed on amide **67** in the laboratory. The crude ^{1}H NMR of the mixture showed a large amount of contamination in the aromatic region of the spectrum. Upon purification by column chromatography, four separate fractions were obtained, each containing highly complex aromatic regions. It appeared that the diphenyl silane had broken down to form some aromatic products that completely contaminated the reaction.

3.2.4.2 Second Attempt

The next set of conditions trialled used trifluoroacetic anhydride as a method of dehydrating the amide with triethylamine present to neutralise the trifluoroacetic acid generated in the reaction. (**Scheme 3.24**)



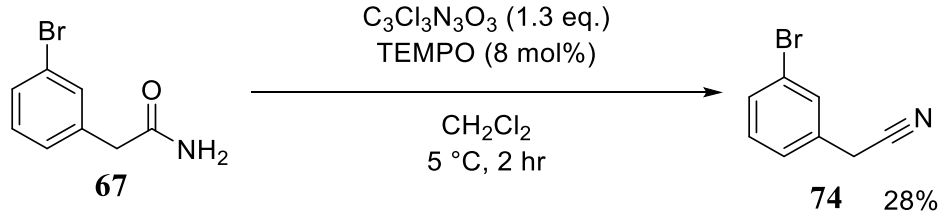
Scheme 3.24

This reaction afforded a 10% conversion to the desired nitrile **74** after being purified by column chromatography. The reaction also generated what appeared to be a large amount of TFA.Et_3N salts, indicating that the acid was being removed from the reaction as fast as it was being generated. This removal process appeared to be much faster than the rate of conversion to **74** and so it seemed that

the reactive species was being used up before it could perform the work required. This is perhaps unsurprising given the large excess of TFAA and Et_3N that were required for the reaction. Alternative methods were sought after this failure.

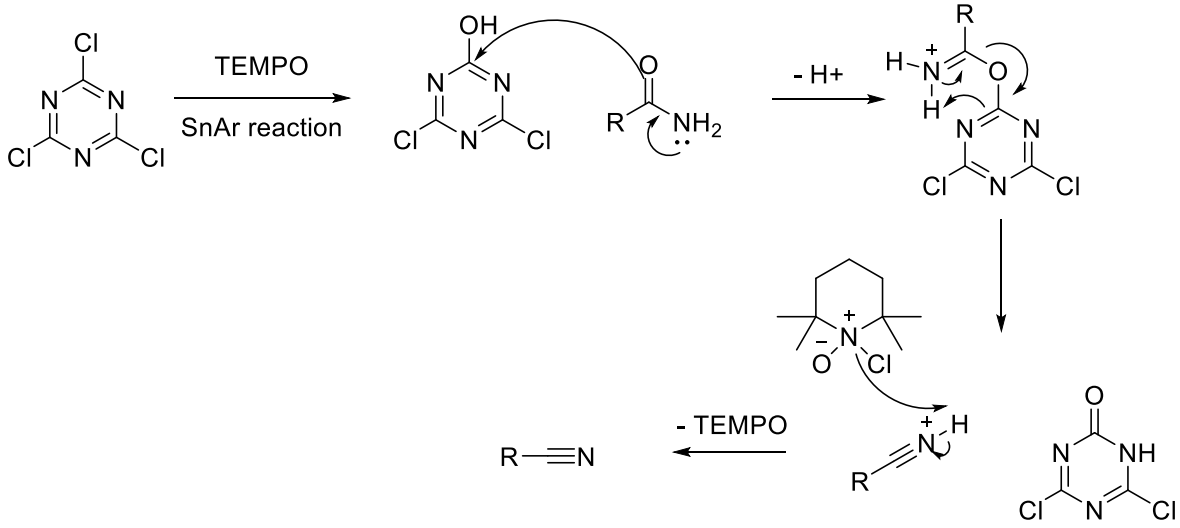
3.2.4.3 Third Attempt

Chen *et al.*[98] discovered conditions using the cheap and commercially available trichloroisocyanuric acid to convert amides to nitriles using TEMPO as a catalytic initiator. (**Scheme 3.25**)



Scheme 3.25

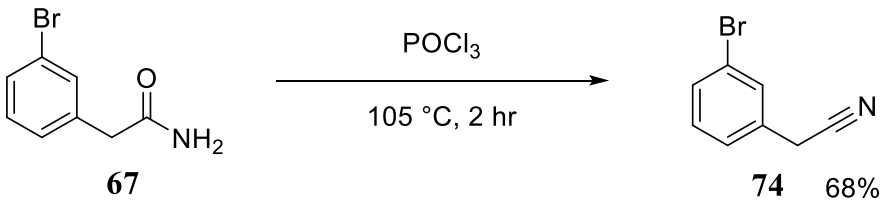
The reaction conditions were relatively mild and provided a 28% yield of the desired nitrile **74**. However, this was still quite a low yield and so alternative methods of achieving the desired conversion were sought out. The mechanism for this reaction is provided in **Scheme 3.26**.



Scheme 3.26

3.2.4.4 Fourth Attempt

Standard[99] amide dehydration conditions were used next. Amide **67** was heated in neat $POCl_3$ to generate the nitrile **74**. (**Scheme 3.27**)

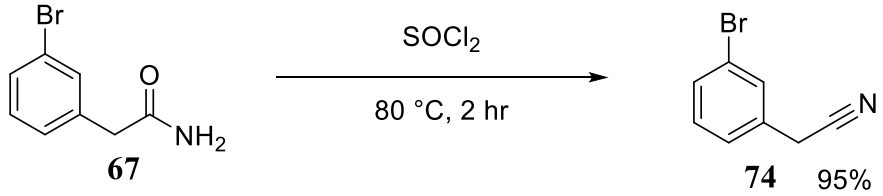


Scheme 3.27

This reaction was quite successful, giving a 68% yield of the desired product **74**; a much-needed improvement on the results that had been previously obtained.

3.2.4.5 Fifth Attempt

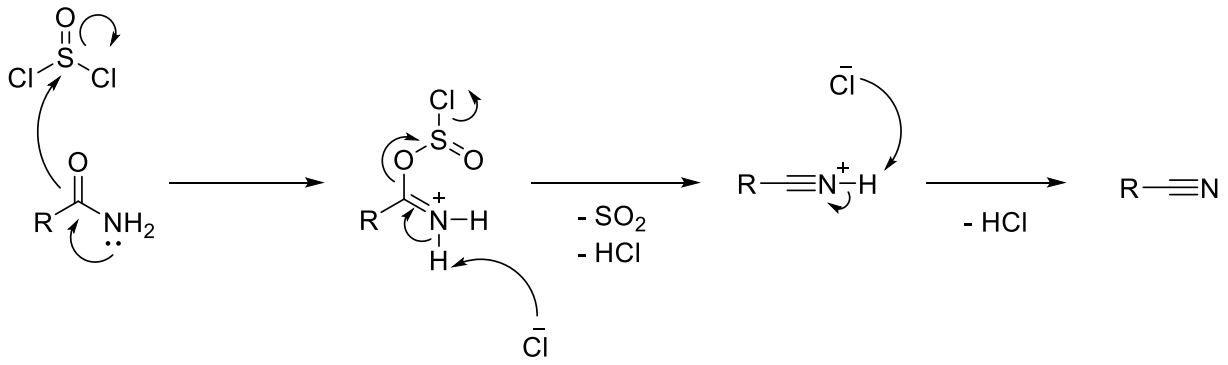
In parallel to the method used for the fourth attempt, the reaction was also attempted in neat thionyl chloride.[100] (**Scheme 3.28**)



Scheme 3.28

This gave the best result, with a 95% conversion to the desired product **74**. It was also useful in that it was relatively easy to remove the thionyl chloride under vacuum, making purification of the final compound much easier. The presence of the nitrile was confirmed by ^{1}H NMR and FTIR spectroscopy. In the ^{1}H NMR spectrum, the CH_2 signal shifted from 3.55 ppm to 3.74 ppm when compared to the amide **74**. In the FTIR spectrum, the peaks representative of the amide group of **67** were gone and replaced by a medium strength peak at 2257 cm^{-1}, confirming the presence of a nitrile.

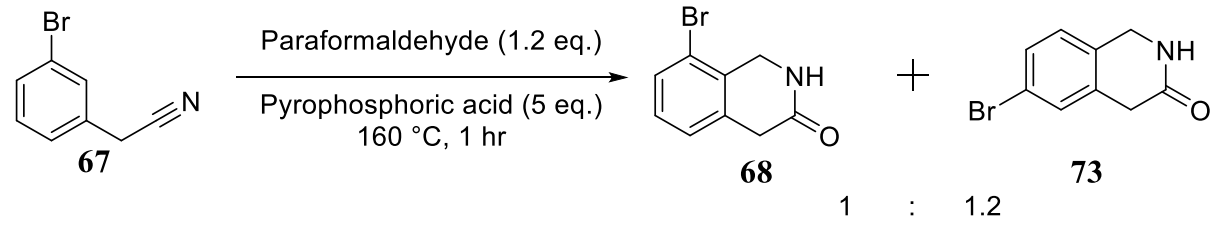
This then became the preferred method of generating the nitrile **74**. The mechanism for this reaction is given in **Scheme 3.29** below.



Scheme 3.29

3.2.5 Cyclisation of 74 to form 68

Following the successful synthesis of nitrile **74**, the cyclisation reaction was reattempted using the conditions from the previous reaction as suggested by Watanabe *et al*.[32] (**Scheme 3.30**)



Scheme 3.30

This method was indeed successful, but it came at a cost. The reaction never yielded more than a 50% combined yield of compounds **68** and **73** and this worsened when the reaction was scaled up. For example, starting with 250 mg of **67** would yield at most 50 mg of combined products **68** and **73**. Once again, it is believed the harsh reaction conditions are a major part of the problem here. Unfortunately, compound **68** was inseparable from compound **73** by silica gel column chromatography. There was also the added issue that the reaction favoured the formation of compound **73** over **68** in a 1.2 : 1 ratio, which was not desirable. The products had previously been characterised in a patent[101] and the NMR spectroscopy results reported therein allowed for the confirmation of which peaks in the NMR spectrum represented which product. The methylene peaks of **68** appeared at 4.56 and 3.62 ppm while the corresponding peaks for **73** appeared at 4.46 and 3.57

ppm. This correlated with what was previously noted by others attempting the reaction, where it was almost always a approximately 1:1 mixture of the two products that was generated.[101] (**Figure 3.2**)

The persistent difficulties with this supposedly straightforward series and the low yields obtained led to a rethink of the entire pathway and a new route was devised.

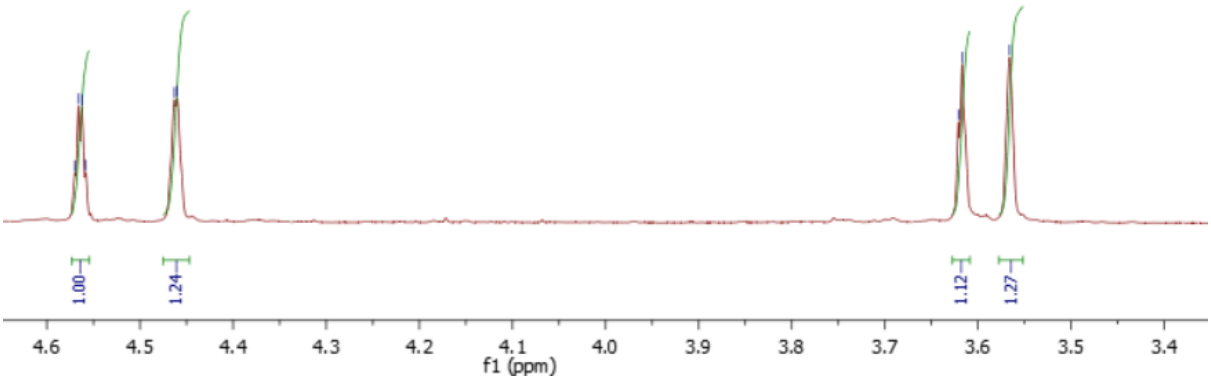
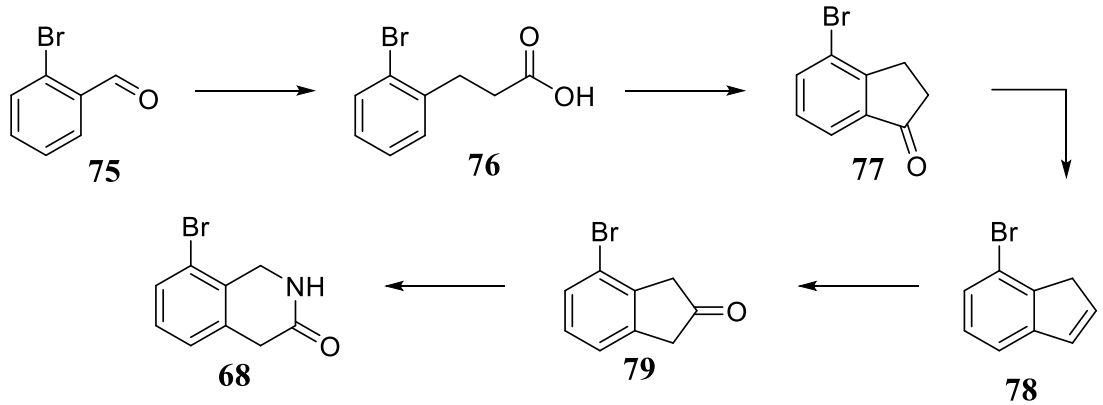


Fig. 3.2 *– ^{1}H NMR spectrum containing a mixture of compounds **68** and **73***

3.3 New route to **68**

This route involved the generation of an indanone **77** before using various reduction and oxidation steps to rearrange the position of the carbonyl, giving compound **79**, before finally generating compound **68** through a nitrogen insertion step. (**Scheme 3.31**)



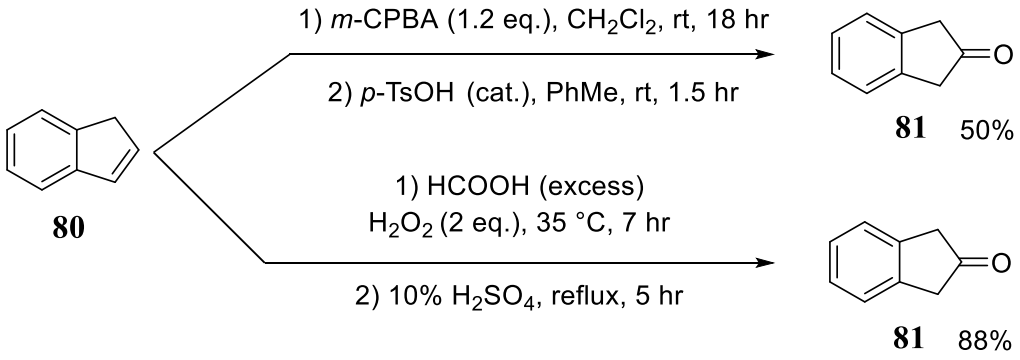
Scheme 3.31

Before initiating this synthesis, it was deemed important to establish that some of the proposed reactions were going to be synthetically viable. This would help to prevent wasted time on reaction

optimisation later in the synthetic pathway. To this end, the final two steps were performed on relevant, but non-halogenated analogues of the materials proposed in the pathway as a proof of concept for the planned route as a whole.

3.3.1 First test – Indene 80 to Indanone 81

To begin with, the conversion of indene **80** to indanone **81** was tested. Two differing sets of conditions were trialled with the conditions used by Streitwieser *et al*. using excess formic acid and hydrogen peroxide proving to be the most successful.[102,103] (**Scheme 3.32**)

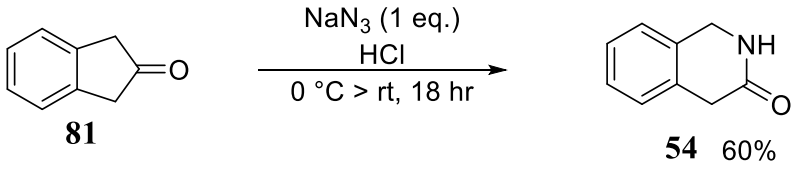


Scheme 3.32

Both reactions succeeded in transforming **80** into **81**, however the *m*-CPBA/CH_2Cl_2 reaction was much lower yielding and led to the generation of more side products. Most likely, this was due to the lower reactivity of the *m*-CPBA and its limited solubility in the reaction solvent. The side products generated were likely benzene ring containing breakdown products of the *m*-CPBA. The formic acid / hydrogen peroxide reaction, however, has a much lower propensity for leaving by-products in the reaction mixture as the reagents used are small in terms of molecular weight and any breakdown products will likely be volatile. This mixture generates performic acid *in situ*, which is an incredibly good oxidising agent typically used in biological studies.[104] The product was easily differentiated from the starting material by ^{1}H NMR spectroscopy. Compound **81** has a singlet, non-aromatic peak at 3.57 ppm that integrates for four protons while **80** has signals at 6.88 ppm, 6.55 ppm and 3.39 ppm representing its CH and CH_2 groups respectively.

3.3.2 Second test –conversion of indanone 81 to lactam 54

The reaction to generate compound **54** (**Scheme 3.33**) was performed using conditions from Kanai *et al.*[105] These conditions are very clearly less harsh than the conditions employed in **Scheme 3.30** and the success of the reaction gave some hope that the pathway was a viable alternative to the originally proposed synthetic route.



81 **54** 60%

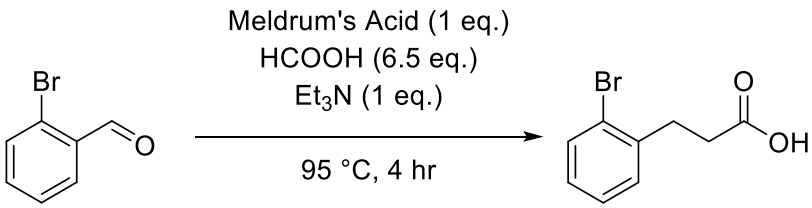
Scheme 3.33

The change of **81**'s singlet at 3.57 ppm in the ^{1}H NMR spectrum into two separate peaks at 4.50 ppm and 3.59 ppm (indicating the CH_2 groups next to the amine and carbonyl respectively) each integrating for two protons confirmed that the product **54** had been formed. The NH peak appeared at 7.3 ppm, which is unsurprising given that the proton is on an amide species. It does differ to the literature value for **54** however,[106] and this phenomenon is explored further in Chapter 5.

After proving that the last steps of the pathway were indeed viable, a full synthesis of the route was begun.

3.3.3 Synthesis of carboxylic acid 76

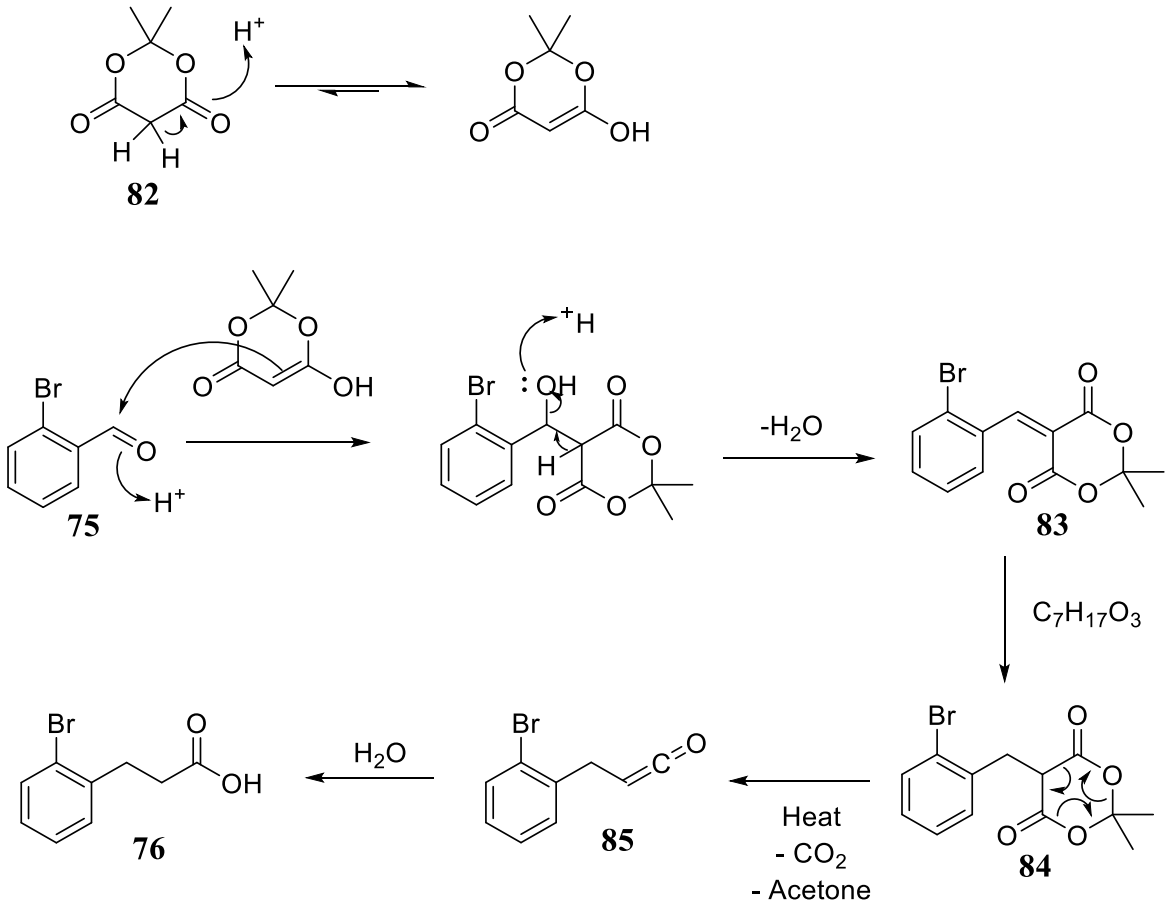
The carboxylic acid **76** was synthesised from **75** using Meldrum's acid (**82**) and triethylammonium formate (generated *in situ*) as a reducing agent in a very straightforward reaction with a decent yield[107] (**Scheme 3.34**)



75 **76** 60%

Scheme 3.34

The mechanism for this reaction is shown in **Scheme 3.35**. Formic acid and triethylamine combine *in situ* to generate triethylammonium formate, a reducing agent.[108] This allows for the reduction of the alkene group in **83** generated after the addition of Meldrum's acid to the molecule and its subsequent dehydration. The Meldrum's acid adduct **84** then undergoes rearrangement to generate CO_2 and acetone. The reaction was performed under air and without first drying any of the solvents or reagents, which provided the water necessary for the hydrolysis of the ketene **85** to the final carboxylic acid product **76**.

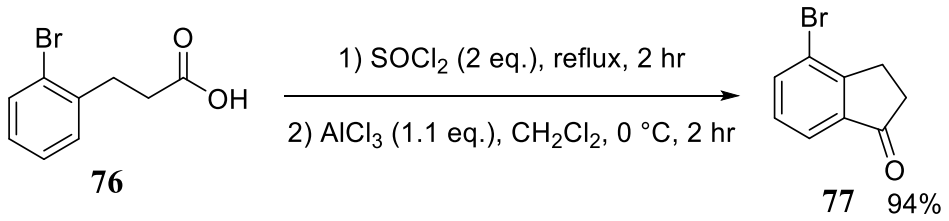


Scheme 3.35

3.3.4 Synthesis of indanones

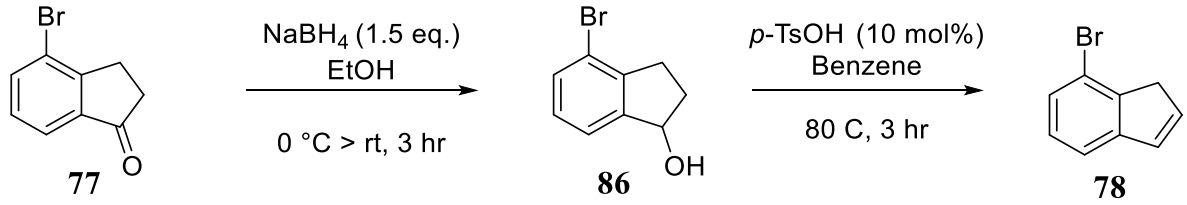
Following the success of this step, the carboxylic acid product **76** was converted to the corresponding acid chloride, using the same conditions established previously (as shown in **Scheme 3.17**). This allowed for the subsequent formation of **77** via an intramolecular Friedel-Crafts cyclisation

reaction.[109] The reaction generated the indanone product **77** in an excellent 94% yield. (**Scheme 3.36**).



Scheme 3.36

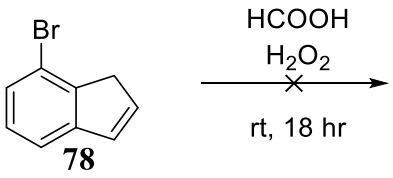
Following this, the next step was to reduce ketone **77** to the alcohol **86** and then, following the elimination of water, (**Scheme 3.37**) to re-oxidise the resulting indene **78** to generate the indanone **79**.[110] (**Scheme 3.38**)



Scheme 3.37

This reaction used sodium borohydride to reduce the indanone **77** to the alcohol **86.** Water was then eliminated to generate the indene **78.** This method used an acid, in this case *p*-TsOH, to protonate the alcohol on **86** and produce a good leaving group. Though the reaction was partially successful by ^{1}H NMR, product **78** could not be separated from the reaction mixture after two separate rounds of silica gel column chromatography.

This lack of purity appears to have affected the next step of the reaction also. The oxidation conditions proposed by Streitwieser *et al.*[102] failed to produce a result in the case of compound **78**, despite having been successful on the unsubstituted indene **80**. (**Scheme 3.38**)

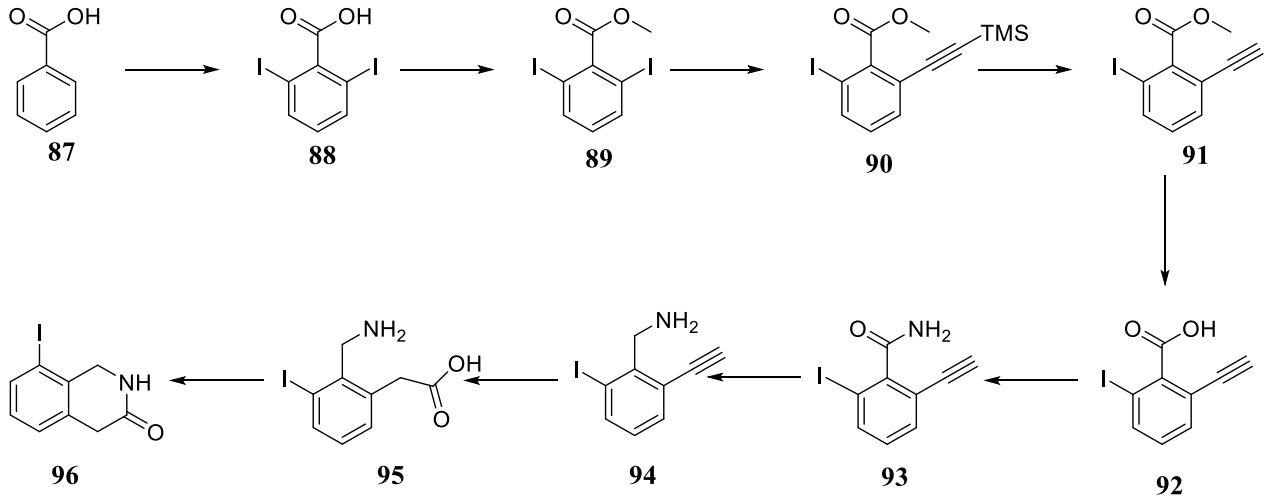


Scheme 3.38

The issues that have developed with this particular route led to the conclusion that it may not be a viable pathway. The difficulty in getting steps to work cleanly and the uncertainty around the selectivity of the Beckmann rearrangement did not look promising and so alternative methodologies were once again sought out.

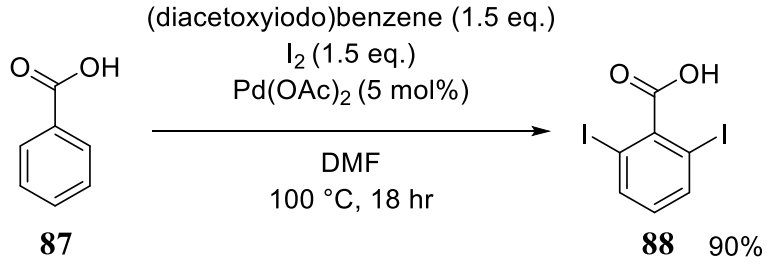
3.4 Iodobenzoic acid route

A freshly proposed route to **2** used multiple common synthesis techniques to achieve a disubstituted ring structure and end with a pair of reactive species located next to one another on the aromatic ring. In this way, problems associated with the harsh cyclisation conditions employed thus far could be avoided. The proposed pathway is shown in **Scheme 3.39**. This pathway makes use of abundantly available benzoic acid (**87**). A di-iodination is performed to place iodine atoms at either side of the carboxylic acid group (**88**). A series of reactions could then be performed to modify the structure until an amine and a carboxylic acid sit next to one another on the ring (**95**), allowing for a simple amide coupling to close the ring and generate the ring structure required for core 1 (**96**).



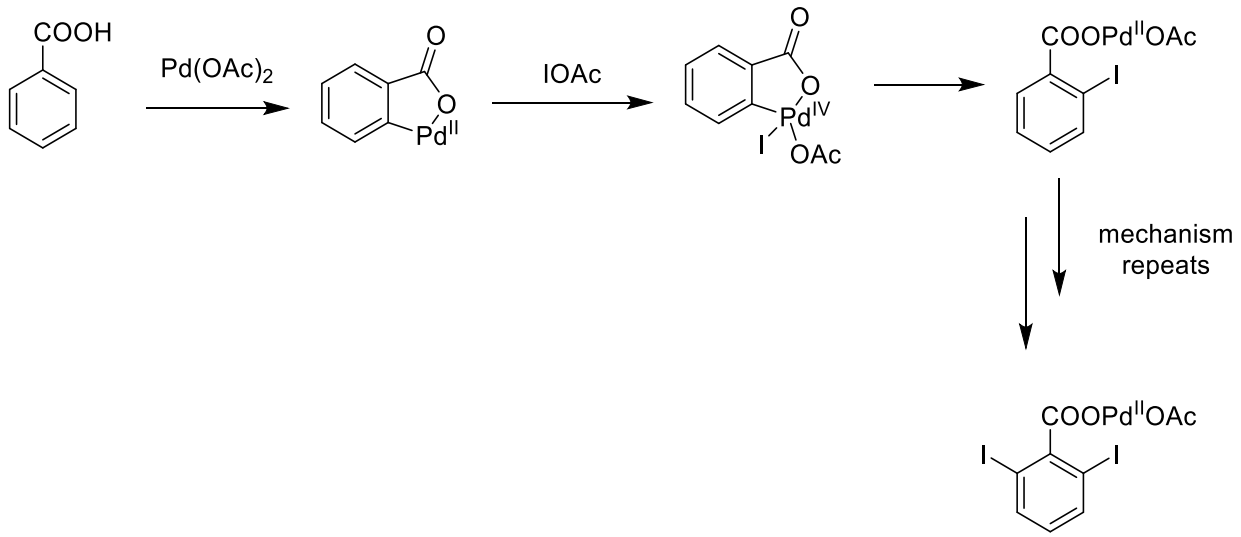
Scheme 3.39

3.4.1 Iodination reaction



Scheme 3.40

The initial iodination reaction to produce **88** was performed in the laboratory using conditions from Yu *et al.*[111] who had successfully performed this reaction previously. (**Scheme 3.40**) In their proposed mechanism, the Pd centre co-ordinates to a carboxylate and the *ortho* position on the ring to give a palladacycle. The addition of IOAc oxidises the Pd(II) centre to Pd(IV) before the iodine atom is transferred to the ring and reductive elimination regenerates Pd(II). (**Scheme 3.41**)

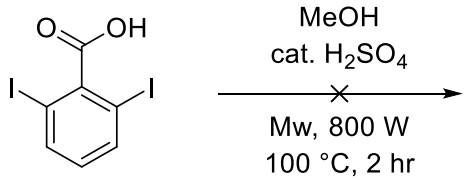


Scheme 3.41

This reaction worked particularly well, achieving a 90% yield. The next step in the series was the esterification of the carboxylic acid group, both to protect the substituent and to make it easier to handle, as the carboxylic acid may cause issues when it came to purification given its acidity.

3.4.2 Esterification

Initially, a standard method of esterifying benzoic acid was trialled; heating **88** in methanol in the presence of a catalytic amount of sulfuric acid. (**Scheme 3.42**)

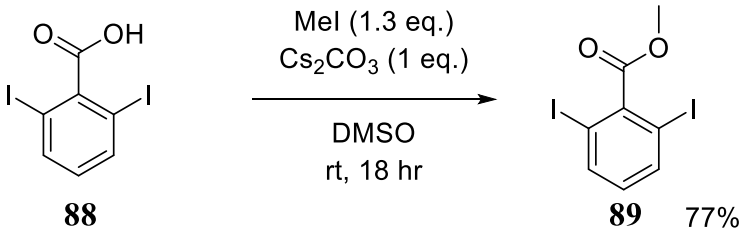


88

Scheme 3.42

This proved unsuccessful. It is likely that the reason for this was that the sheer size of the iodine groups next to the acid was preventing the reagents from getting near the acid group. An alternative method of esterifying the carboxylic acid had to be found. A set of methylation conditions were

discovered from a patent[112] (but are fairly standard) that used methyl iodide and caesium carbonate to perform the methylation. (**Scheme 3.43**)



88 **89** 77%

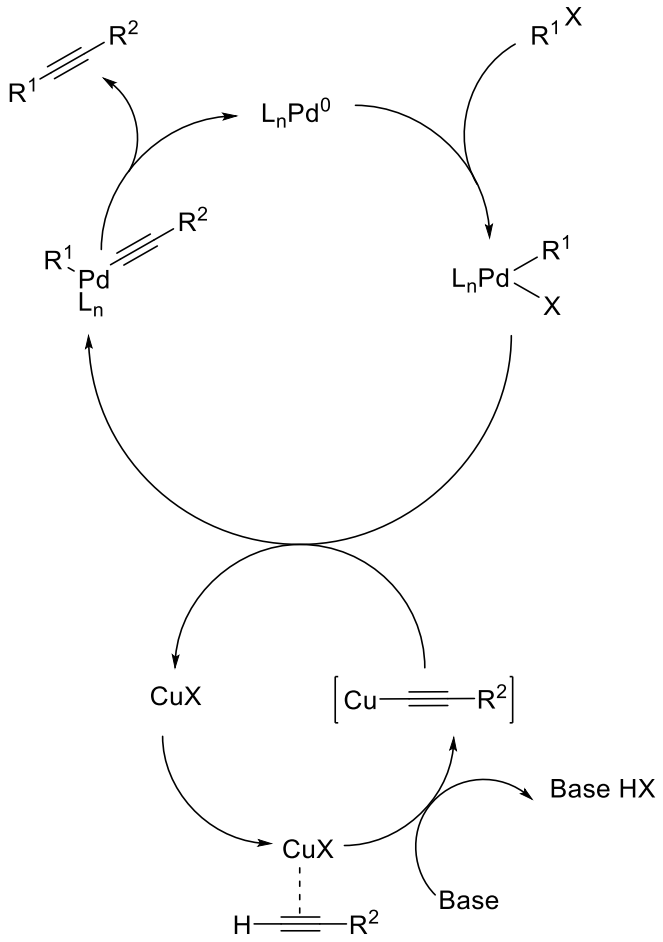
Scheme 3.43

This reaction proved highly successful, generating a 77% yield of **89** when performed on a 250 mg scale. The reaction was useful in that the product precipitates out of solution on the addition of water and so can be filtered from the reaction mixture without the need for further purification. The only difficulty was fully removing the DMSO from the compound, which required multiple washes with distilled water.

The next step was to perform a Sonogashira reaction on **89**.

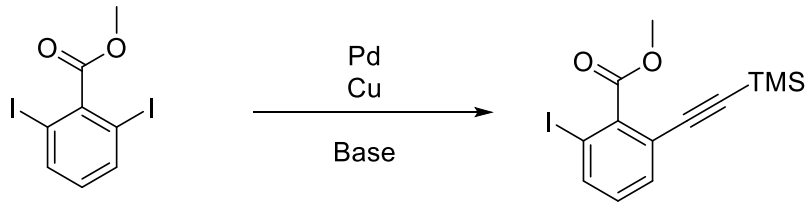
3.4.3 Sonogashira coupling

The Sonogashira reaction is a well-known and well utilised C-C bond forming reaction developed in the 1970's that uses a Pd catalyst in conjunction with a Cu(I) salt to generate bonds between sp^2 carbon-halides and terminal acetylenes.[113,114] The Pd catalyst used is typically in an oxidation state of zero and are typically triphenylphosphine complexes, with $Pd(PPh_3)_4$ being one of the most common catalysts used. A drawback is that these catalysts typically require higher loadings (around 5 mol%).[115] The catalytic cycle for the reaction is laid out in **Scheme 3.44** below:



Scheme 3.44

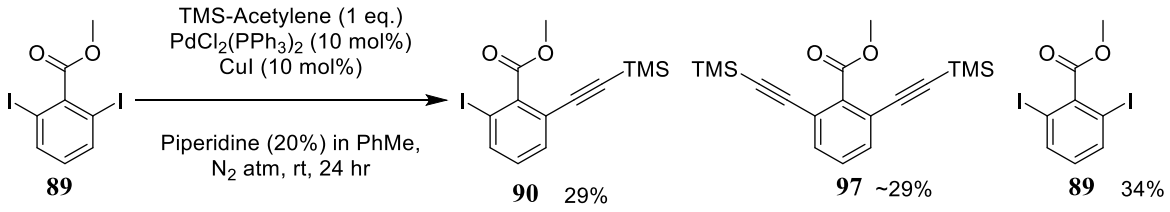
The general transformation that was being aimed for with the application of the Sonogashira coupling in this instance in detailed in **Scheme 3.45** below:



89 **90**

Scheme 3.45

It was hoped that by adding only one equivalent of the alkyne, a single coupling reaction could be achieved leaving one of the iodine atoms unreacted on the compound. This was not the case when the reaction was performed, however. (**Scheme 3.46**)



Scheme 3.46

The reaction yielded a mixture of products. Looking at the crude ^{1}H NMR data, a small portion of the starting material remained unreacted. Of the material that did react, the attempt at controlling the reactivity was a failure. Though only a single equivalent of TMS-acetylene was added to the reaction, it appears that almost a 50:50 mix of the mono (**90**) and di-substitution (**97**) products was formed indicating that rate of reaction at both iodines was similar products were easily differentiated by ^{1}H NMR spectroscopy. (**Figure 3.3**)

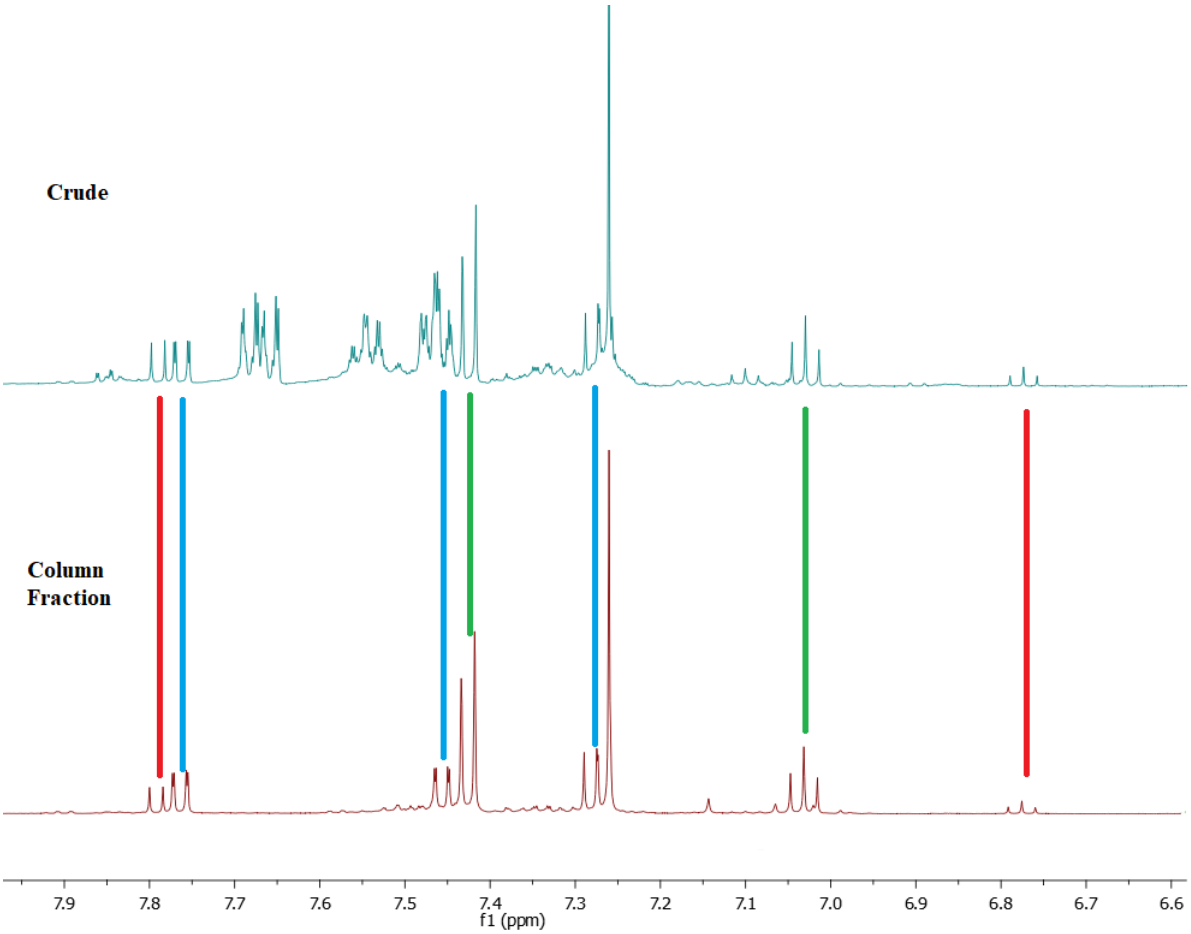


Fig. 3.3 *–Crude and purified ^{1}H NMR Spectra containing **89** (red), **90** (blue) and **97** (green)*

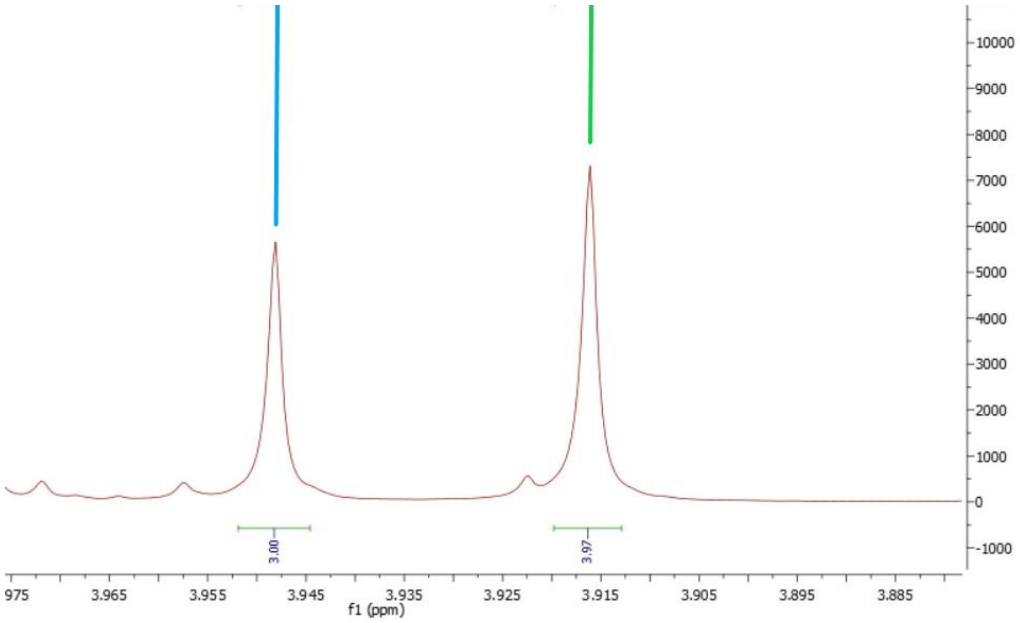


Fig. 3.4 *– ^{1}H NMR of methyl peaks in **90** (blue) and **97** (green)*

The ^{1}H NMR spectra shown in **Figure 3.3** show the crude NMR mixture, followed by a single fraction from the silica gel column performed to clean up the reaction. As can be seen from this aromatic region, there are three separate species present. Though most of the starting material **89** had been extracted in the previous fraction, a small amount co-eluted. The doublet and triplet marked with the red lines belong to the starting material (**89**). The green lines correspond to the di-substitution product (**97**). As can be seen, this shares the same splitting pattern as **89**. This is unsurprising as both iodine groups have been replaced, resulting in the aromatic C-H protons *ortho* to the alkynes groups being chemically equivalent just as they were in the starting material **89**. The blue lines show the aromatic C-H protons in the mono-addition product **90**. As this molecule doesn't have any protons in a chemically equivalent environment due to the loss of its symmetry, the splitting pattern is more complex. This analysis is borne out in the methyl groups also, as these occur in the same general region of the spectrum but have different chemical shifts, again showing an almost 50:50 split between **90** and **97**. (**Figure 3.4**) When taking into account the mass of the products retrieved from the reaction and their relative concentration by NMR spectroscopy, it became apparent that the reaction had formed a statistical mixture i.e. a 1:1:1 ratio of products was achieved. This indicated that the reaction was very non-selective.

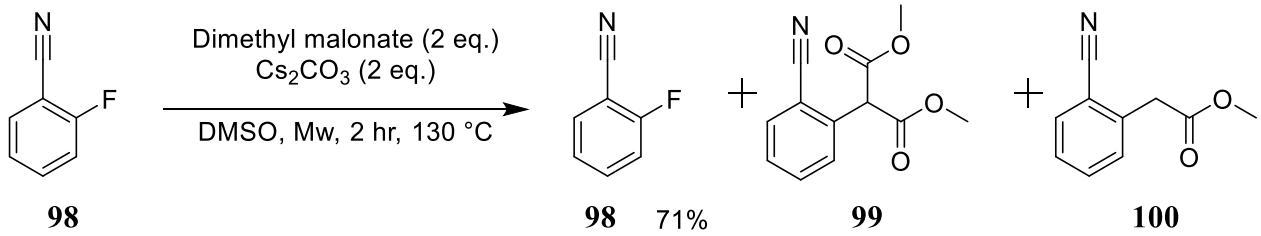
A different approach was sought at this point given the lack of success here. The initial plan had been to convert the alkynyl group to a carboxylic acid towards the end of the synthesis, (**Scheme 3.39**)

instead an attempt was made to incorporate the carboxylic acid into the system earlier and through simpler means, thus negating the necessity for a Sonogashira coupling.

3.4.4 Alternate route to carboxylic acid

3.4.4.1 Initial test

To test the proposed route, 2-fluorobenzonitrile (**98**) was chosen as the starting material. Using an S_NAr type reaction, a malonate group could be introduced, and this could be converted into an ester by simple decarboxylation. In practice, this process was only somewhat successful. After 2 hours in the microwave, the reaction yielded a recovery of 71% of the starting material **98**. (**Scheme 3.47**) Of the remaining material, it was found to be an almost 50:50 mix of the malonate product (**99**) and the decarboxylated product (**100**) by ^{1}H NMR spectroscopy.



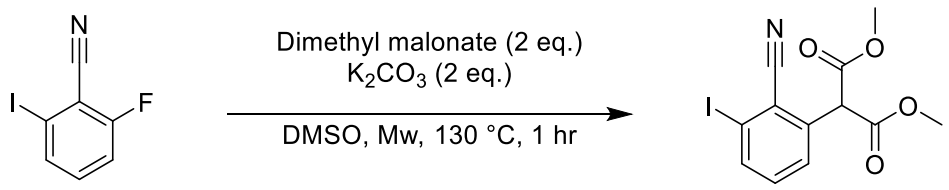
Scheme 3.47

Though the methodology wasn't perfect, the reaction's simplicity meant that it was easy to trial on a di-halogenated material more closely resembling compound **89**.

3.4.4.2 Attempt with halogenated material

The reaction was reattempted using the commercially available 2-fluoro-6-iodobenzonitrile (**101**) as the starting material. Both Cs_2CO_3 and K_2CO_3 were trialled as bases for the reaction. Both reactions were successful, generating the product **102** in quantitative yields with no sign of the decarboxylated product (**Scheme 3.48**). K_2CO_3 was used as the base for this reaction going forward as there were large quantities of it available in the lab. This yield was reduced from quantitative to 66% when

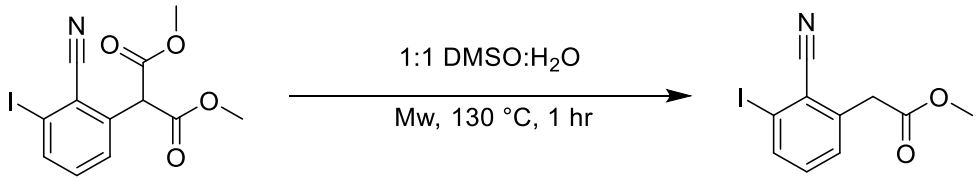
scaled up to 1 gram of starting material, but this is still a large improvement over the result shown in **Scheme 3.47**.



101 **102**

Scheme 3.48

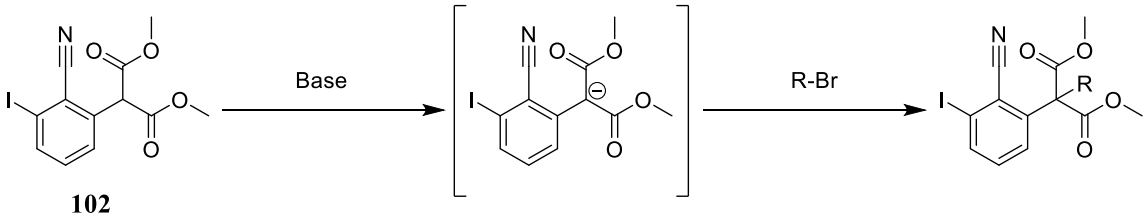
Decarboxylation of this material proved to be a simple task. Using a solvent mixture of 1:1 DMSO to water[116] and heating in a microwave was enough to fully remove one of the carbonyl groups, resulting in the generation of **103** quantitatively and without any hydrolysis of the ester. (**Scheme 3.49**)



102 **103**

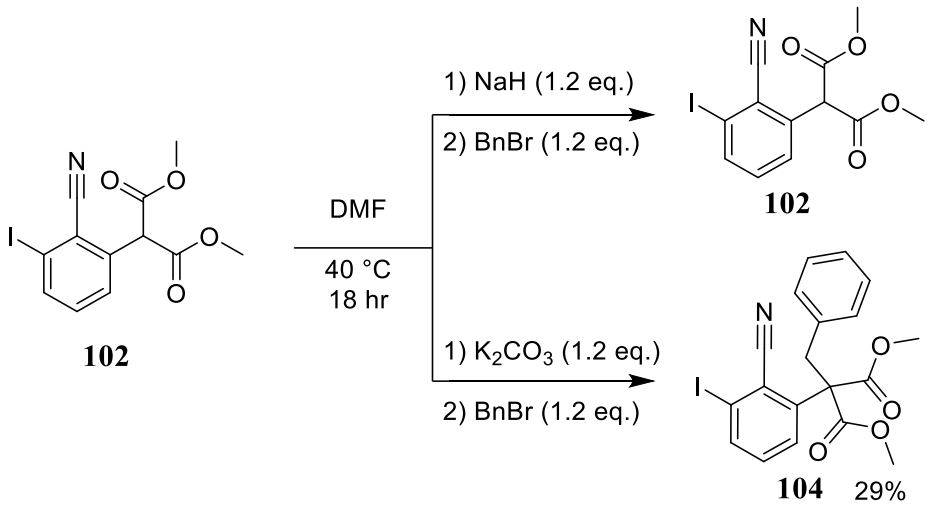
Scheme 3.49

The possibility of exploiting the acidity of the single proton at the centre of the malonate sidechain was explored, as it could allow for the introduction of chemical diversity in the final molecule. By treating **102** with a base, the proton should be removable, and the negative charge stabilised across the adjacent esters, making subsequent alkylation with an electrophile an easy task. (**Scheme 3.50**)



Scheme 3.50

Initially, both NaH and K_2CO_3 were trialled as potential bases, with DMF used as the solvent. From this it was concluded that K_2CO_3 was the base to use, as only starting material **102** was recovered from the NaH reaction. (**Scheme 3.51**) The failure of the NaH reaction may simply be down to the chemicals age, or the presence of mineral oil in the powder. Regardless, K_2CO_3 is easier to handle and worked well so it was chosen as the base for this reaction going forward.

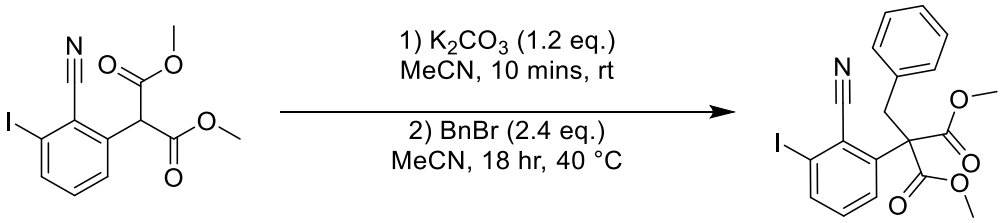


Scheme 3.51

The reaction was repeated on a larger scale and it was found by TLC analysis that after the initial 18-hour timeframe, the reaction was not yet completed. An additional equivalent of benzyl bromide was added, and the reaction left for a further 18 hours, at which point it was judged to be complete by TLC analysis. ^{1}H NMR analysis confirmed that the single proton on the malonate side chain was no longer present and a new singlet integrating for two protons had appeared at 3.7 ppm. The aromatic region had also become vastly more complex, with all integrations and multiplets pointed to the product **104** having been formed.

The yield for this reaction was relatively low (at 29%). The impression that the TLC provided that the reaction had gone to completion may have been a false positive, as if the deprotonation had been

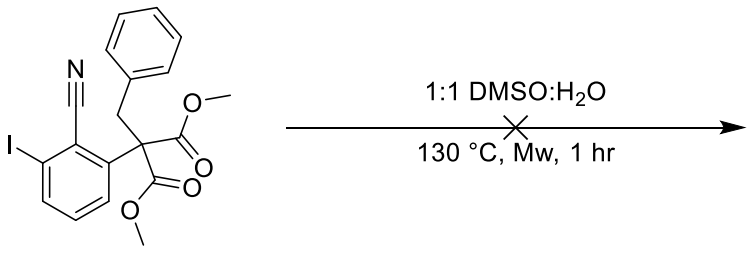
successful but the alkylation had yet to occur, the charged species would sit on the baseline, giving the impression that the reaction had finished when in reality it had only partially progressed. The decision was made to attempt the reaction in different solvents to see if this made any difference. Both THF and MeCN were attempted (both being polar aprotic solvents with lower boiling points than DMF, making them easier to remove after the reactions completion), with MeCN proving to be a much better solvent for the reaction, with the yield increasing from 37% in THF to 79% in MeCN. Thus, the reaction can be summed up in **Scheme 3.52**.



102 **104** 79%

Scheme 3.52

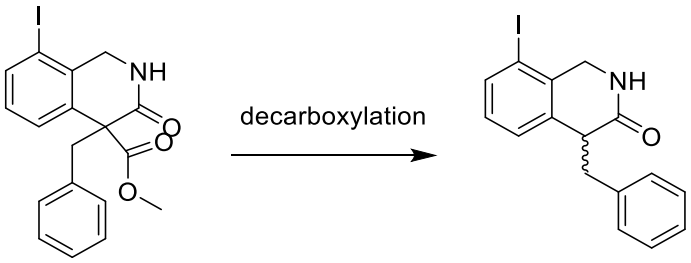
The decarboxylation reaction was then attempted on this material but to no avail. It appeared that addition of the benzyl group in **104** stabilised the ester group to hydrolysis, which was the required first step of the decarboxylation reaction. (**Scheme 3.53**)



104

Scheme 3.53

This was disappointing but not a terrible outcome. As long as the nitrile reduction and subsequent cyclisation could be performed successfully, the subsequent mixture of enantiomers that would result from the cyclisation (**106**) would likely readily decarboxylate to give **107,** also as a racemic mixture. (**Scheme 3.54**)



106 **107**

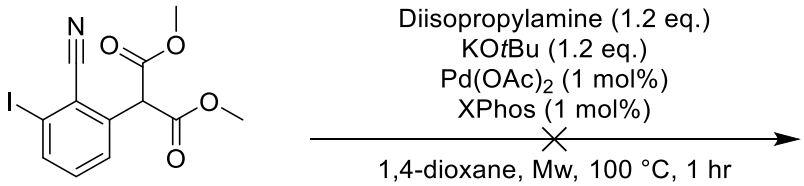
Scheme 3.54

At the same time, investigations began into using the halogen moiety to facilitate C-C bond-forming reactions.

3.4.5 Palladium cross coupling reactions

3.4.5.1 Buchwald-Hartwig

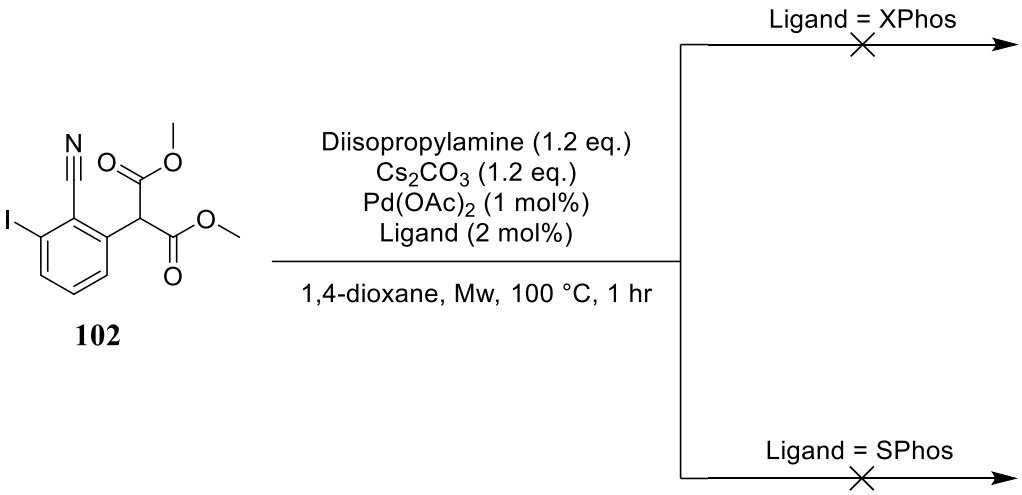
Initially, Buchwald-Hartwig conditions were trialled on **102**. To begin with, potassium *tert*-butoxide was used as a base. (**Scheme 3.55**)



102

Scheme 3.55

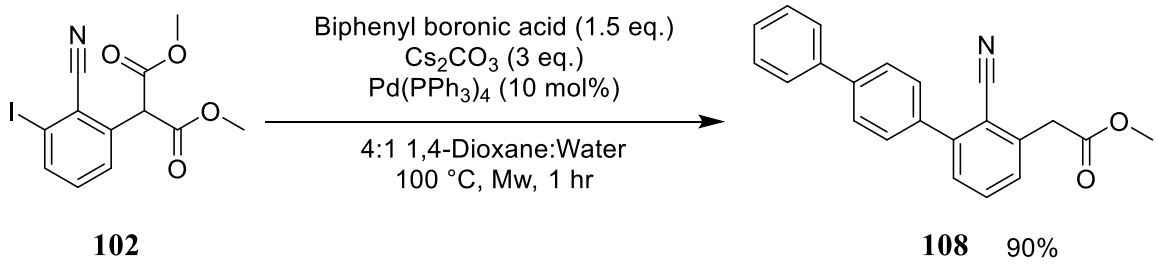
This proved unsuccessful however, as only starting material was recovered post-workup. It was postulated that the acidity of the malonate alpha proton, as exploited above, could have interfered with the reaction by mopping up the base and generating a charged species that would not react as planned. To counteract this, alternate conditions developed by Buchwald[117] using Cs_2CO_3 as the base for the reaction were trialled, as this was supposed to facilitate the Buchwald reaction in the presence of functional groups such as esters. Though separate reactions using both X-Phos (2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl) and S-Phos (2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl) as ligands were attempted, no change to **102** was observed. (**Scheme 3.56**)



Scheme 3.56

3.4.5.2 Suzuki-Miyaura

Instead of Buchwald-Hartwig conditions, Suzuki-Miyaura coupling was also trialled. This proved to be more successful. An initial trial run of the conditions was performed on **102**: (**Scheme 3.57**)



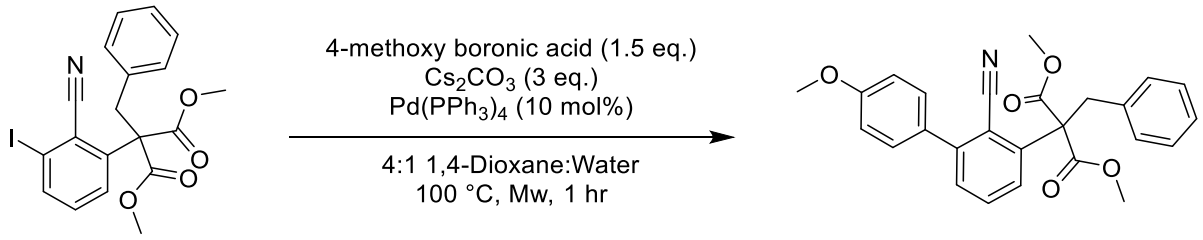
Scheme 3.57

As can be seen from the scheme above, the reaction conditions also cause the decarboxylation of the malonate group. This was not an unwelcome result as this would have been the next step of the process anyway. Initially only 46% of **108** was recovered cleanly. After chromatography, there was a separate fraction which contained both **108** and its malonate form in what appeared to be equal amounts. Treating this mixture with the decarboxylation conditions from **Scheme 3.49** resulted in the material being fully converted into the decarboxylated product **108**, resulting in an overall yield of 90% for the reaction.

Though biphenyl boronic acid may seem like an unusual choice, it was selected for a few reasons. Due to the possible interference of the malonate group as noted in the Buchwald-Hartwig conditions, a boronic acid with limited functionality was desired for this initial test, as amines, amides or any oxygenated functional groups could interfere with the reaction and the goal was to prove the

conditions worked. Biphenyl boronic acid was the only boronic acid on hand in the lab that satisfied these requirements and so it was chosen for this test run.

Having already generated a decent amount of **104** previously, this was then put through the Suzuki-Miyaura conditions. In this instance, a different boronic acid was chosen. 4-Methoxy boronic acid was likely to have relatively little potential to cause side reactions. On top of this, the issue of the acidic malonate proton was no longer a concern when using **104** as the starting material. The methoxy group should also be clearly visible in the ^{1}H NMR, making identification of the product easier. (**Scheme 3.58**)



104 **109** quant.

Scheme 3.58

This reaction resulted in the quantitative yield of **109**. After recrystallisation of the product from MeOH, an X-ray structure of the material was determined. (**Figure 3.5**)

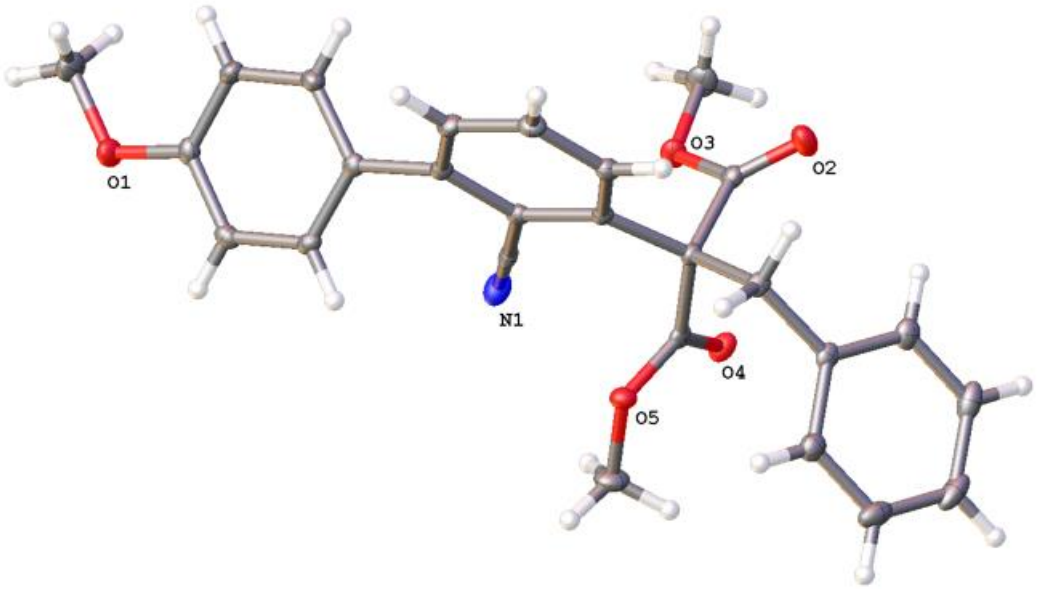


Fig 3.5 *– Crystal structure of compound* ***109***

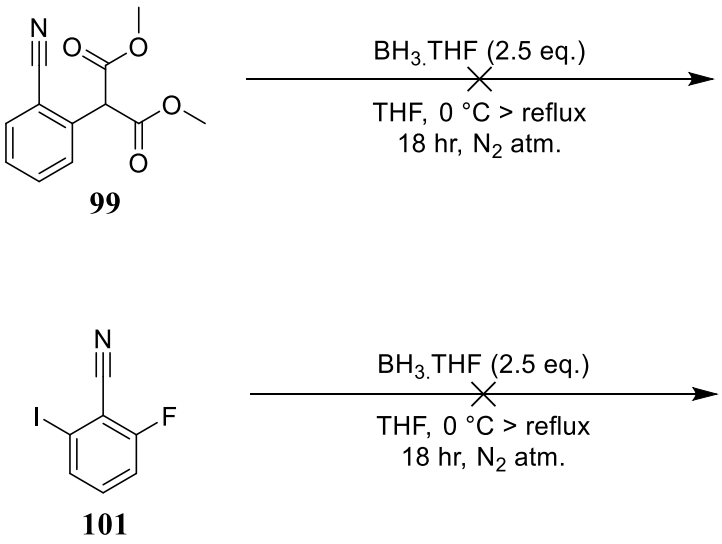
Unsurprisingly, the benzylic and anisole aromatic rings are almost perpendicular to that of the central benzonitrile and the arms of the malonate group extend outwards, filling into empty space. This proximity would likely be the eventual downfall of this route, however.

3.4.6 Nitrile reduction

The next item on the agenda was the reduction of the nitrile group. Multiple sets of conditions for this were trialled.

3.4.6.1 First Attempt - Boranes

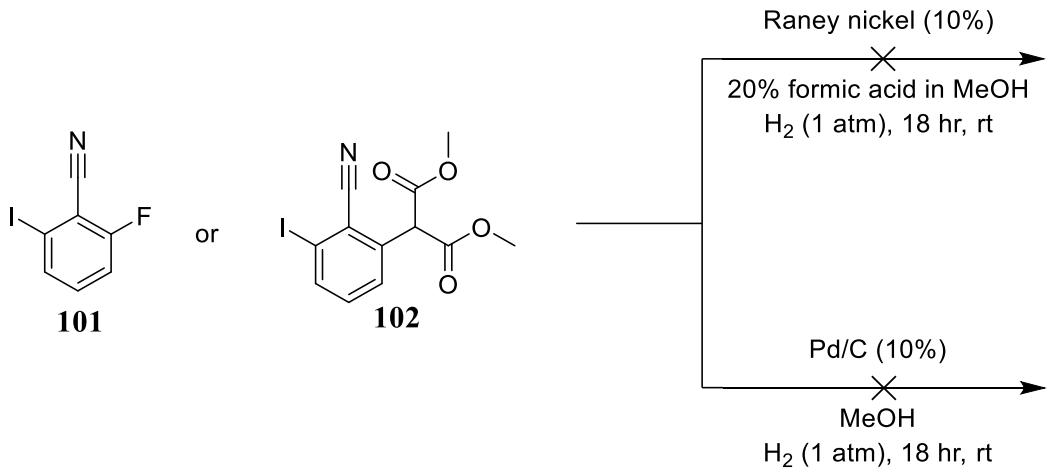
The first set of conditions trialled used BH_3.THF. (**Scheme 3.59**) After this reaction however, no trace remained of the malonate group of **99** and the aromatic region was very complex. Given boron's affinity to oxygen, it likely attacked the malonate group instead of the nitrile. When the reaction was trialled on **101** which had no malonate group it resulted in a mix of products by ^{1}H NMR, none of which appeared to be the amine product, as there was no appearance of a peak representing a benzylic CH_2 in the spectrum.



Scheme 3.59

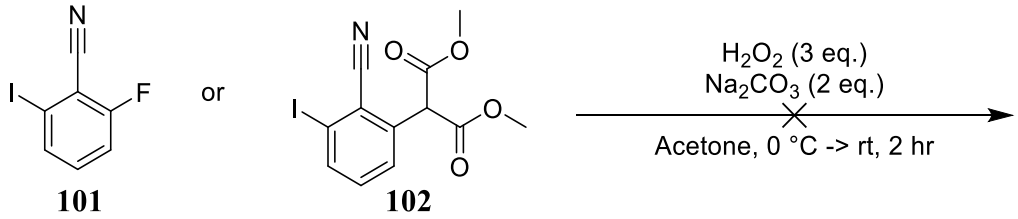
3.4.6.2 Next attempt - Hydrogenation

Both Raney nickel and Pd/C with a H_2 atmosphere were then attempted, each to no avail when used on both **101** and **102**. (**Scheme 3.60**)



Scheme 3.60

The direct reduction of the nitrile to the amine was proving difficult, and so the possibility of generating the amide first *via* hydrolysis and then converting this to the amine was investigated. Perhaps the amide would be more amenable to reduction than the nitrile? This idea didn't last long however, as the oxidation conditions used to achieve the formation of the amide failed to produce any results,[118] (**Scheme 3.61**) with only starting material being recovered in both cases.

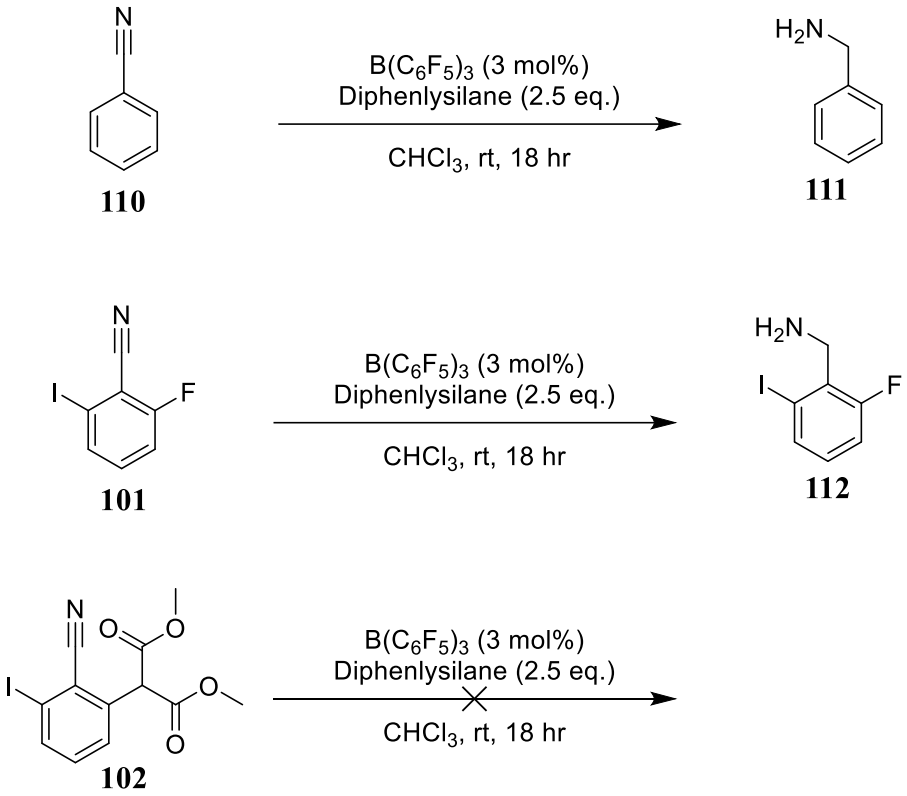


Scheme 3.61

3.4.6.3 Tris(pentafluorophenyl)borane (BCF) reduction

While searching for possible alternative methods of reduction, a paper from Chang *et al.*[119] stood out. Under these conditions, nitriles could undergo hydrosilylation using tris(pentafluorophenyl) borane (BCF) as a catalyst. A simple acidic workup would then remove the silyl groups leaving just the amine species. The real attraction of this paper was that they used benzonitrile as their base molecule for the reaction, which had obvious links to the work in this project. They had also demonstrated the reaction functioned well on a variety of substrates though, perhaps notably, there were few examples of *ortho*-substituted benzonitriles.

The reaction was attempted, and three reactions were set-up in parallel. The first used benzonitrile (**110**) as the substrate with the other two substrates being **101** and **102**. The benzonitrile reaction was used to confirm whether the paper was reproducible, while the others could be used as direct comparisons to all the work carried out above. (**Scheme 3.62**)



Scheme 3.62

The reaction was certainly reproducible and, pleasingly, in the case of **110** the reaction produced **111** quantitatively. The disappointment came with **102**, which failed to react at all. Boron's affinity for oxygen was likely the problem here, and if the boron was co-ordinating to the malonate group it wouldn't be able to function as the catalyst for the hydrosilylation reaction.

3.4.6.4 Metal co-ordination attempts

If co-ordination was the root cause of the lack of reactivity, it was possible that by introducing a metal into the reaction before the addition of BCF, it could co-ordinate to the malonate group and effectively block it, allowing the BCF to act on the nitrile. This was tested simply by adding various

metal salts to a sample of **102** and examining the samples by ^{1}H NMR. A 1:1 ratio of **102** to the appropriate metal salt was used in each case (56 µmol of each) and the samples were each dissolved in 0.5 mL $CDCl_3$. (**Figure 3.6**)

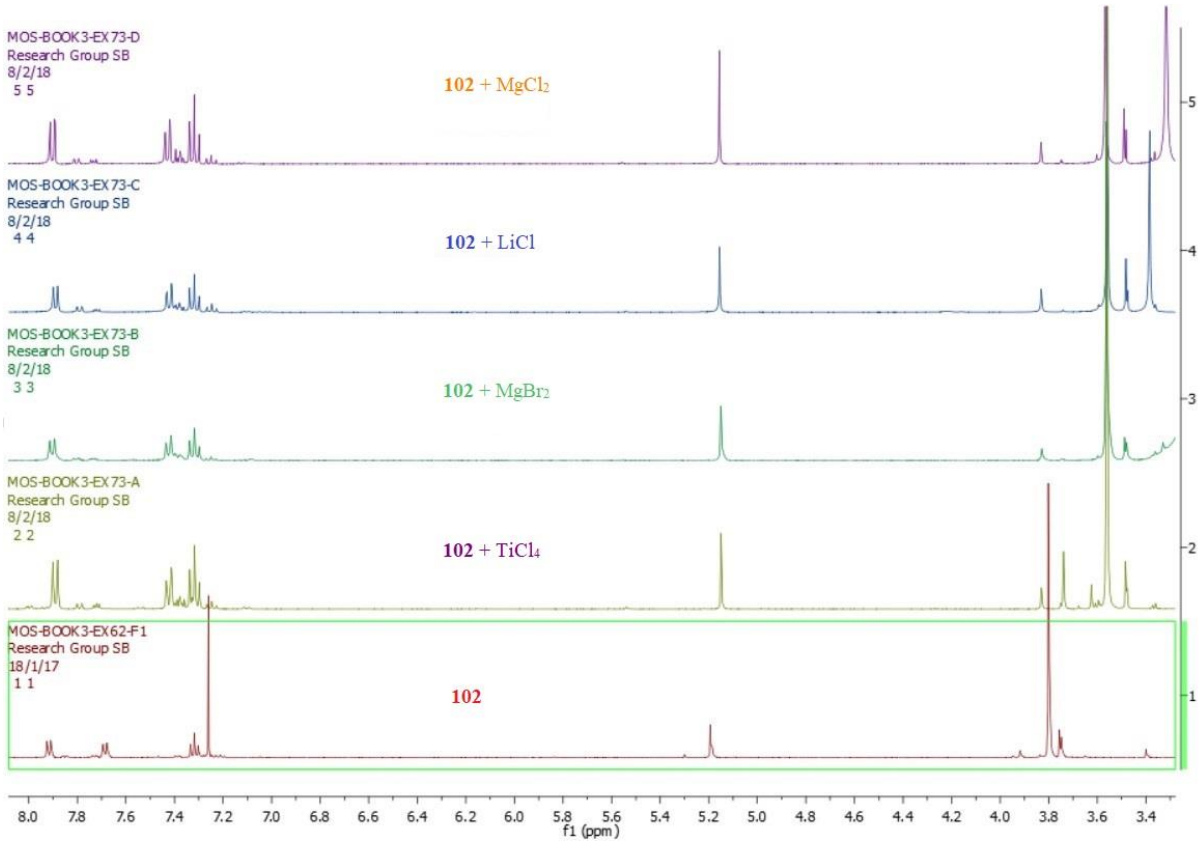


Fig. 3.6 *– ^{1}H NMR spectrum of **102** with different metal salts added*

There is a notable shift in all the above examples, particularly in the aromatic region and with the malonate methyl groups. This result was later explained with the aid of their ^{13}C NMR spectra. (**Figure 3.7**)

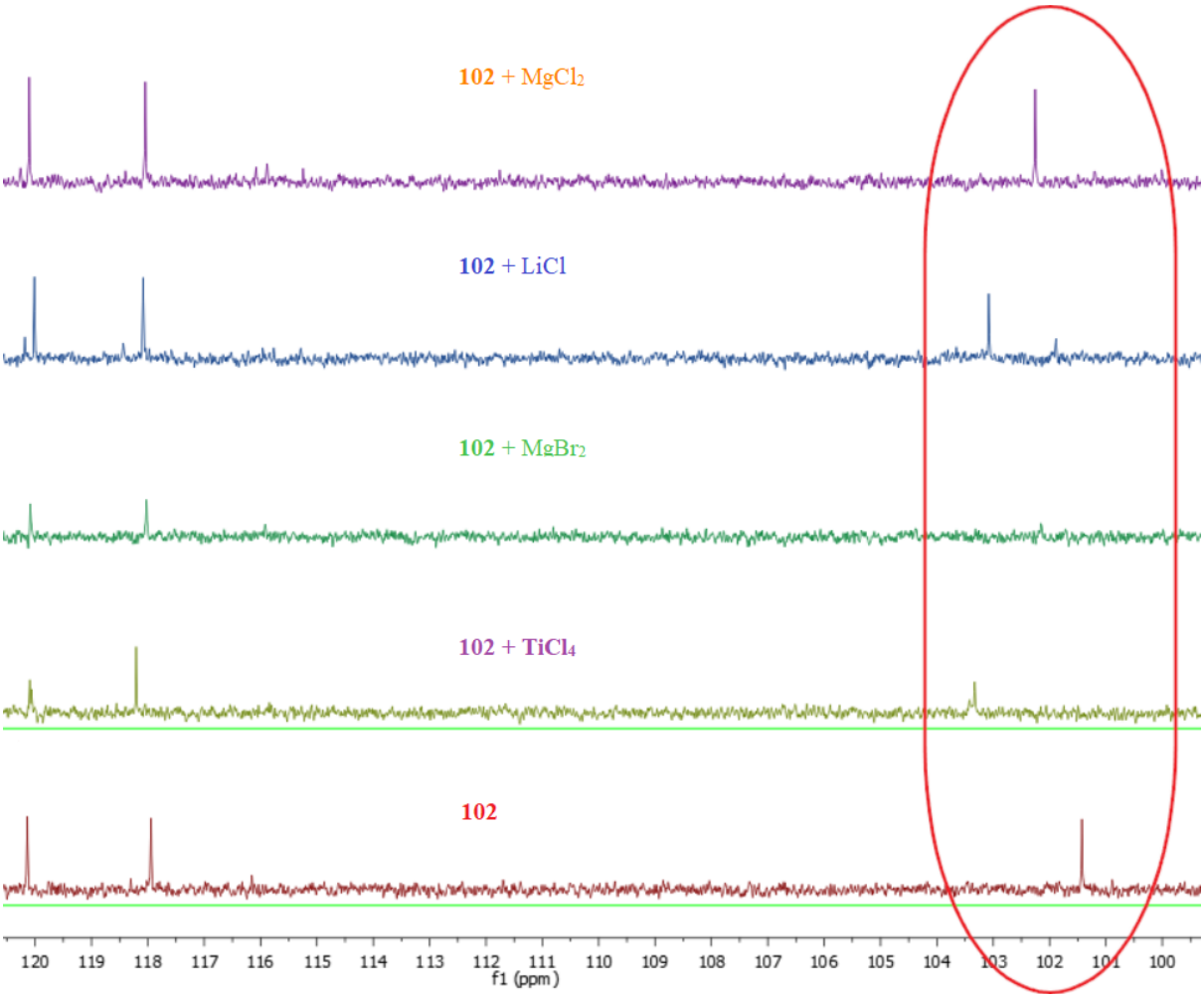


Fig. 3.7 *– ^{13}C NMR spectrum of* ***102*** *with metal salts added*

In these spectra, there was a difference between the positions of the carbon atoms attached to the iodine in **102**, with all other carbons remaining the same. The most plausible conclusion here is that there is some form of halo-metal exchange occurring at the iodine position. This also explains the aromatic proton shifts seen earlier, as the iodine is directly bound to the ring, so any change in its state would alter the chemical shifts of the neighbouring protons.

To counteract this, the co-ordination study was attempted using some of the same metal salts and **99**, which no longer contained an iodine atom. (**Figure 3.8**)

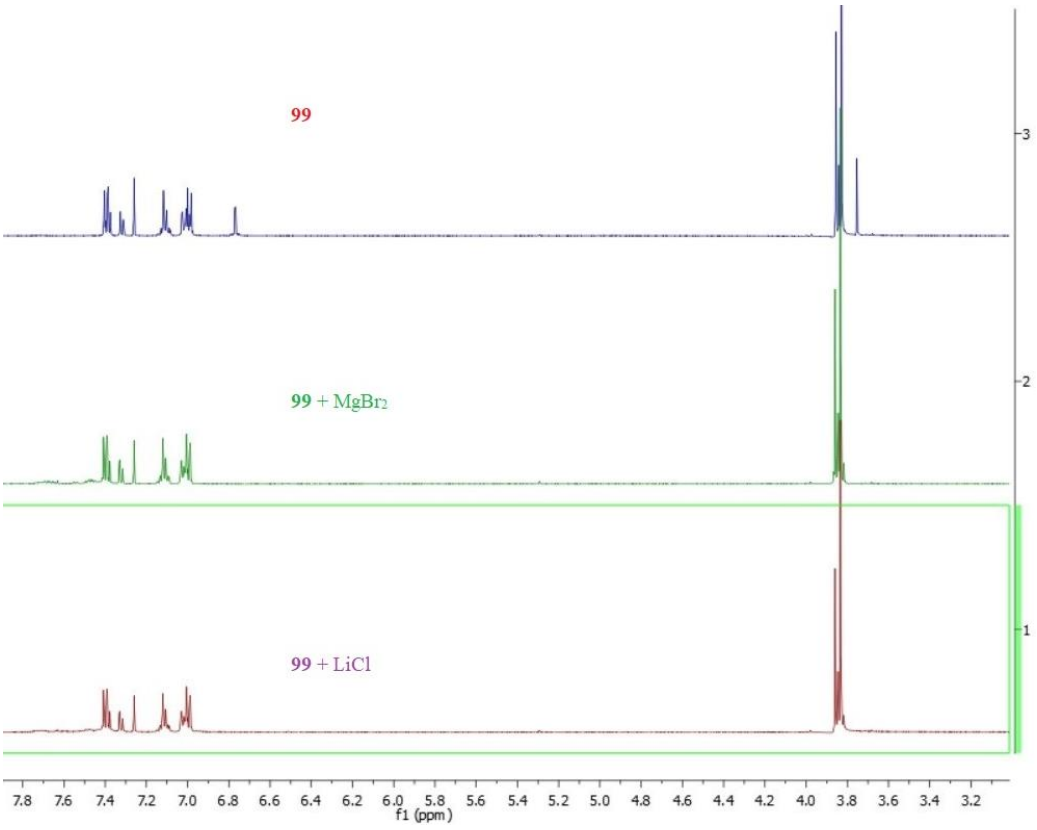


Fig 3.8 *– ^{1}H NMR spectrum of* ***99*** *with metal salts added*

There was no shift at all as can be seen above, indicating that the metals don't co-ordinate to the malonate group and so would not be capable of blocking it off from attack on the malonate group by BCF.

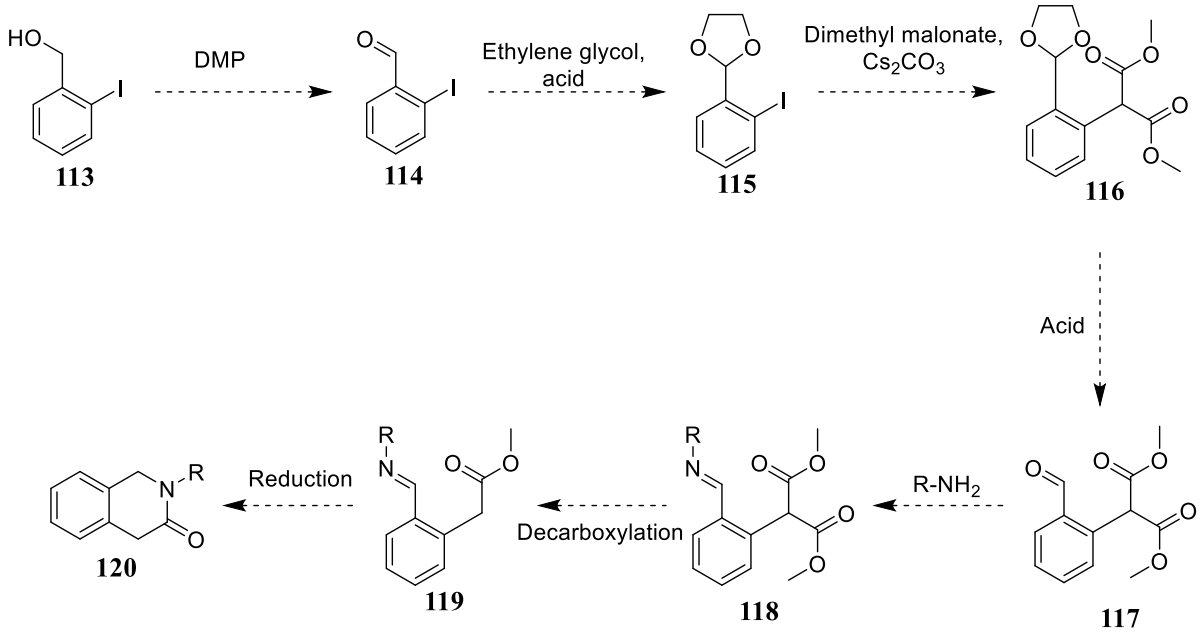
At this stage it was felt that most logical avenues had been exhausted when it came to this route. Though the route had almost been completed, the final step was elusive and without an effective method for nitrile reduction, success was unlikely.

A final change in direction was needed.

3.5 Aldehyde route

It was thought that by going *via* the aldehyde instead, reductive amination could be used as a method for incorporating nitrogen substituents. This would also allow the introduction of functionality through the addition of an amine to the reaction directly as opposed to later alkylating the amine species generated by the reduction of a nitrile. This is useful as amines are one of the most commonly available chemicals to an organic chemist. To add to this, the reaction conditions required to carry out a reductive amination typically involve the use of sodium borohydride or a related derivative. Sodium borohydride doesn't typically reduce esters[120] which means it could be used safely in the presence of the malonate group without any fear of side reactions taking place.

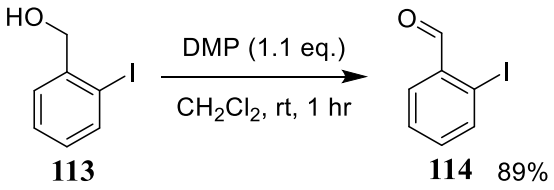
As removal of the halogen from the general core structure had in the past yielded some success, it was decided to apply this principle here also as it could aid with the simplification of the route. To that end, the following new route was developed. (**Scheme 3.63**)



Scheme 3.63

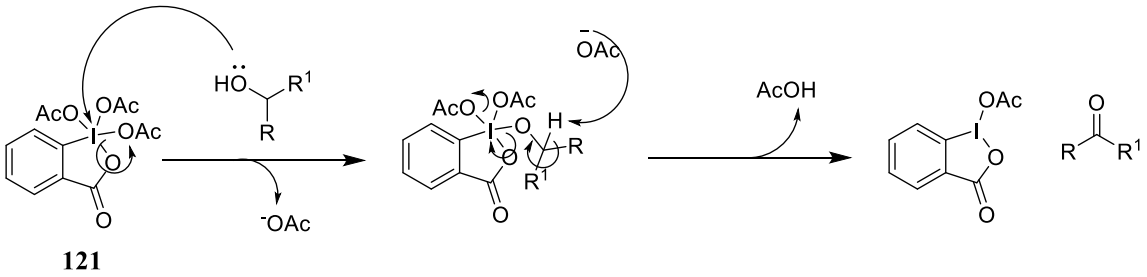
3.5.1 Initial aldehyde generation

113 was chosen as the starting material because it is commercially available. The conversion of **113** to the aldehyde **114** was rather simple, employing Dess-Martin periodinane (DMP) with an 89% yield. (**Scheme 3.64**)



Scheme 3.64

DMP (**121**) makes use of hypervalent iodine to co-ordinate to the alcohol group, allowing an acetate anion to deprotonate the benzylic position, resulting in a cascade that releases the aldehyde and acetic acid while simultaneously reducing the iodine from iodine (V) to iodine (III).[121] (**Scheme 3.65**)



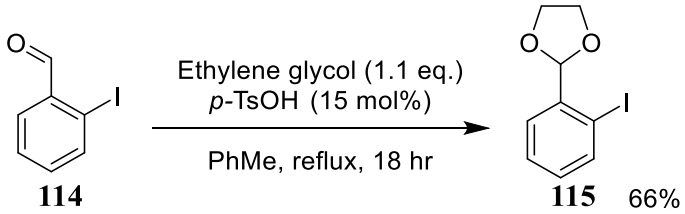
Scheme 3.65

The next stage was the protection of the aldehyde group.

3.5.2 Protecting the aldehyde

The protection of the aldehyde at this point was necessary to prevent the group from reacting with dimethyl malonate in the next step. This was once again a relatively simple process. **114** was heated in the presence of ethylene glycol in an acidic environment to generate the acetal product **115**.[122] This reaction is very dependent on the ability to drive off water as it's formed however, and so even when using a Dean-Stark apparatus to collect water as it was formed and boiled off, a maximum

yield of 66% was achieved. (**Scheme 3.66**) Starting material **114** survived the process unscathed however, and so could be separated from the mixture of products and re-used.

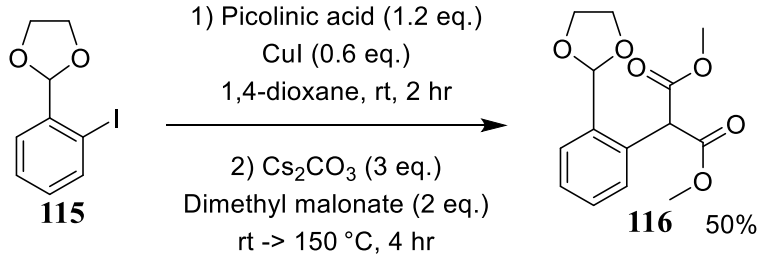


Scheme 3.66

3.5.3 Malonate addition

Following conditions developed by Kwong *et al.*[123] the addition of a malonate group was attempted. The conditions had been successfully performed on esters, alkoxides and heterocycles in their paper. The paper stated that room temperature should be enough for the reaction to progress. However, it was found that the reaction had to be heated to 150 °C for several hours before any success was achieved using substrate **115**. Also, the increase to 150 °C had to be gradual, as starting the reaction off at this temperature appeared to cause degradation of the materials and effectively kill the reaction.

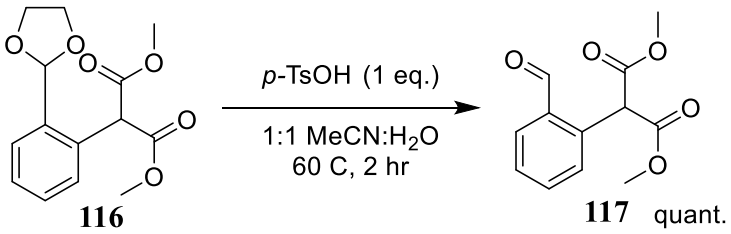
The order of addition was also altered to attempt to maximise the yield from the reaction. Picolinic acid and CuI were first allowed to stir together for 15 minutes to give the catalytic intermediate time to form. In a separate vessel, the dimethyl malonate and Cs_2CO_3 were mixed to generate the deprotonated species in as large a quantity as possible to prevent possible side reactions with the base. **115** was then added to the reaction vessel with the picolinic acid/CuI catalyst and left to stir for 2 hours before the addition of the dimethyl malonate anion. (**Scheme 3.67**)



Scheme 3.67

This resulted in a maximum yield of 50% with none of **115** remaining, likely due to thermal decomposition under the reaction conditions.

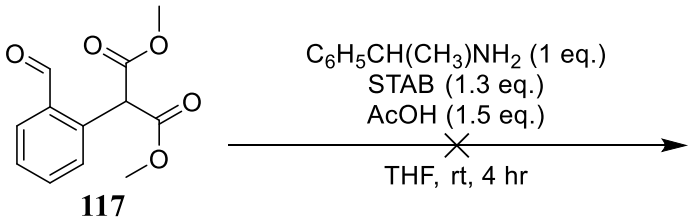
Nevertheless, the series was continued. The deprotection of the acetal group was a very simple affair, requiring the use of an acid and water. (**Scheme 3.68**) This gave **117** in a quantitative yield.



Scheme 3.68

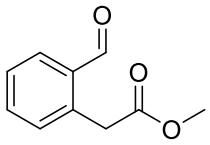
3.5.4 Reductive amination

An initial test of reductive amination conditions was trialled using conditions from one of the most well cited papers on the topic from Abdel-Magid *et al.*[124] The methodology in this paper uses sodium triacetoxyborohydride (STAB) as the reducing agent in the presence of a small amount of acetic acid and is a widely used method for reductive amination. As is the recurring theme of this thesis thus far however, the results achieved here said otherwise, as the reaction failed to progress. (**Scheme 3.69**)



Scheme 3.69

At this stage, the myriad issues that had been occurring led to the purchase of commercially available **122**, which effectively rendered this route null. On top of that, **122** ended up being a game changer, and will form the basis for the rest of this thesis. At this point, no further work was performed on this route.



122

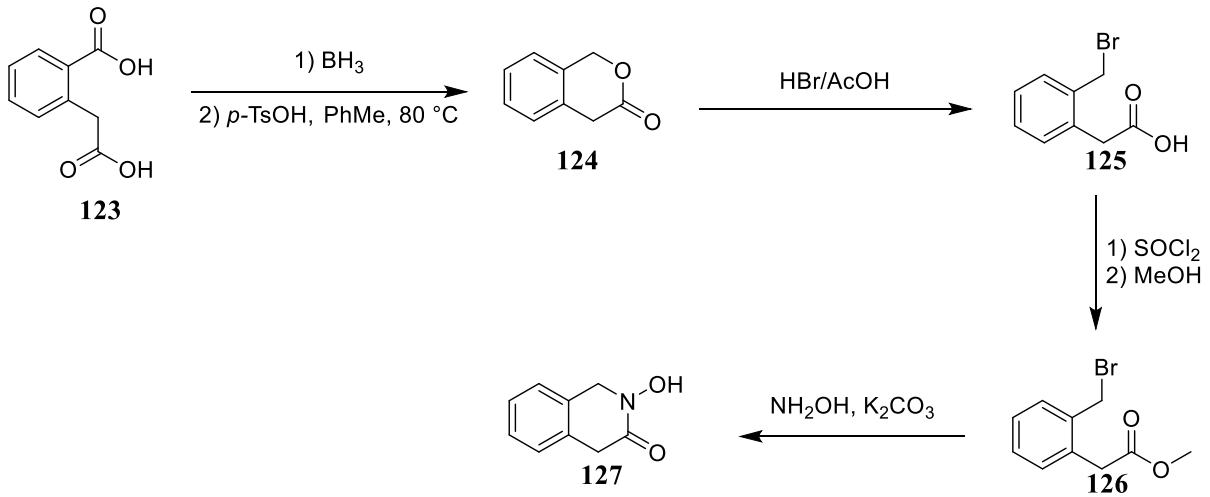
Conclusion

Many different approaches were employed in order to achieve the synthesis of core 1. Though some approaches showed some success, on almost every occasion a point was reached which made progressing further difficult or even impossible. Often this point was close to the endpoint of the entire synthesis, or in the case of compound **68**, achieved the desired result but at significant cost. While at times frustrating, this chapter shows a relatively exhaustive and creative exercise in synthetic workarounds. Regardless of the success of these syntheses, the lessons learned here would apply to the rest of the project and likely resulted in an overall improvement in the synthetic chemistry skills used throughout the rest of this thesis.

Chapter 4 – Reductive amination

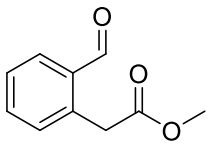
4.1 Introduction

The lack of success, as documented in the previous chapters, led to the conclusion that perhaps a new approach was needed. For instance, Haeggström *et al.*[125] used a nucleophilic substitution reaction on a benzyl halide species to generate an amine species. This species subsequently spontaneously reacted with the *ortho*-ester moiety to produce the end isoquinolinone. (**Scheme 4.01**)



Scheme 4.01

This process started with homophthalic acid (**123**) however, which required conversion to isochromanone (**124**) before being subjected to HBr to generate the benzyl bromide species (**125**). This species then had to be converted to the methyl ester (**126**) before nucleophilic substitution could be used to yield the desired product (**127**) The many steps required simply to generate the required starting material was somewhat concerning. Rather than going down another long synthetic route only to have it ultimately be deemed unsuccessful once more, it was decided to purchase methyl-2-(2-formylphenyl)acetate (**122**) from commercial suppliers.



122

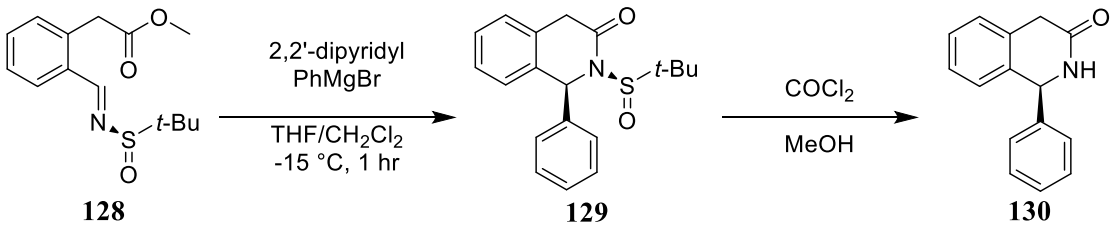
This proved to be something of a game changer and led to the development of the chemistry discussed for the rest for this thesis.

It was believed that the chemistry in **Scheme 4.01** above could be applied to this species. If a secondary amine was to be produced by reductive amination, it should spontaneously cyclise to give the desired core structure.

4.1.1 Alkylation after cyclisation

Once the cyclisation of the compounds was achieved, the next logical step was the derivatisation of the series. Of particular interest was the possibility of alkylation chemistry being used to attach sidechains to both of the benzylic positions of the final cyclised structure.

Substitutions have been made at the *alpha* position next to the amine on similar cyclised structures before[126] but this required the introduction of a chiral auxiliary at the imine stage of the synthesis, and the use of a Grignard reagent to effect the substitution (notably, this reaction is an example of asymmetric synthesis, which will be explored in more detail in Chapter 5 of this thesis). The auxiliary later had to be removed and Grignard reagents, while available commercially, are known for their short shelf life, making them less desirable for use in derivatisation. (**Scheme 4.02**)

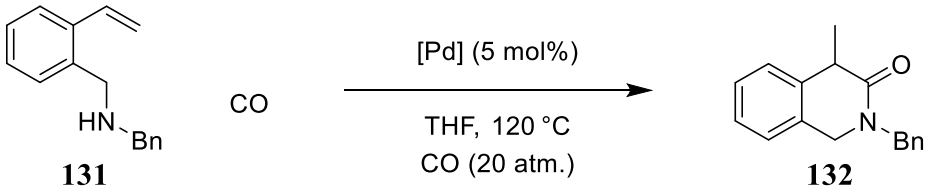


128 **129** **130**

Scheme 4.02

Work has also been done to substitute *alpha* to the carbonyl,[85] though this necessitated starting from a 2-vinyl benzylamine species (**131**) and using a palladium catalyst under a pressurised atmosphere

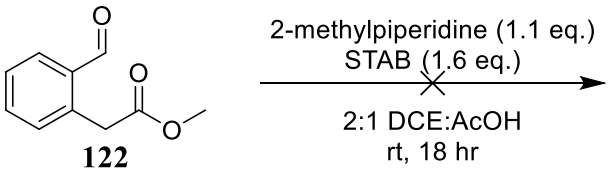
of carbon monoxide, (**Scheme 4.03**) which is not a synthetic methodology that the majority of researchers would have the capability of following.



Scheme 4.03

4.2 Reductive amination

In order for this route to be successful, **122** first had to be able to undergo reductive amination. A simple reaction was performed to test the conditions required for this step. (**Scheme 4.04**)



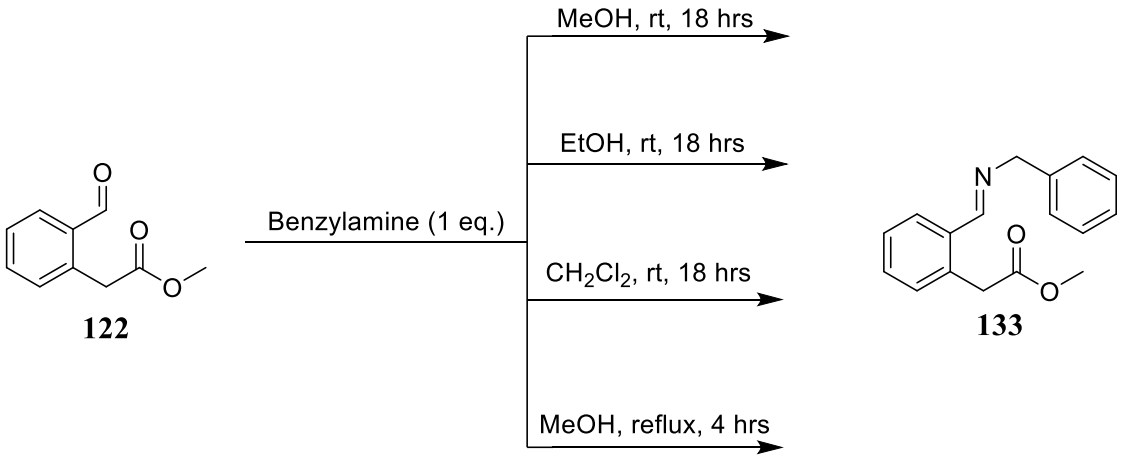
Scheme 4.04

2-Methylpiperidine was used as the amine source for 2 reasons: its methyl group should be easily distinguishable by ^{1}H NMR spectroscopy and the product it generates is a tertiary amine, which should not react with the ester group and cyclise. Unexpectedly, this was a failure. ^{1}H NMR spectroscopy analysis of the product of the reaction showed 2 non-aromatic singlet peaks, each integrating for 2 protons, at 5.32 ppm and 3.72 ppm respectively, with no incorporation of the methylpiperidine. This led to the conclusion that the product formed was actually isochromanone (**124**), which appeared to indicate that the reduction of the carboxyl groups was taking place before an imine species was being formed. It was unclear whether the imine in this case would even form at all, and so a different test was devised.

4.2.1 Imine formation

The conditions for imine formation were tested. In this case, benzylamine was used. The idea behind this switch in reagents was that, should the imine formation be successful, reduction conditions could immediately be tested on the imine.

The study was relatively simple, basically comprising of a solvent study. (**Scheme 4.05**)



Scheme 4.05

Pleasingly, all of these reactions successfully formed the imine **133**. ^{1}H NMR analysis showed the complete disappearance of the aldehyde peak at 10.1 ppm and the appearance of a singlet peak corresponding to the imine alkene proton at 8.6 ppm. (**Figure 4.1**)

It should be noted that while 2 imine isomers are possible here (*E* and *Z*), one is clearly formed as the major product.

Due to the fact that the *Z*-isomer in this case would result in quite a large amount of steric clash between the aromatic ring systems, it is almost certain that the major isomer formed here is the *E*-isomer. The formation of the Z-isomer appears to be present in all cases (imine peak at 8.4 ppm), however the amount of it present varies with the solvent used and is decreased when the reaction is heated. (7% in EtOH and MeOH, 12% in CH_2Cl_2 and 19% in refluxing MeOH)

This result would appear to suggest that the issue with the reaction in **Scheme 4.04** was that the rate of formation of the iminium ion was too slow, allowing reduction of aldehyde to occur instead. This is perhaps unsurprising given that the formation of a cationic iminium species (**134**) in this case is

likely not kinetically favourable, as it results in the formation of a charged species with little option for resonance, as so would likely only form under extremely forcing conditions.

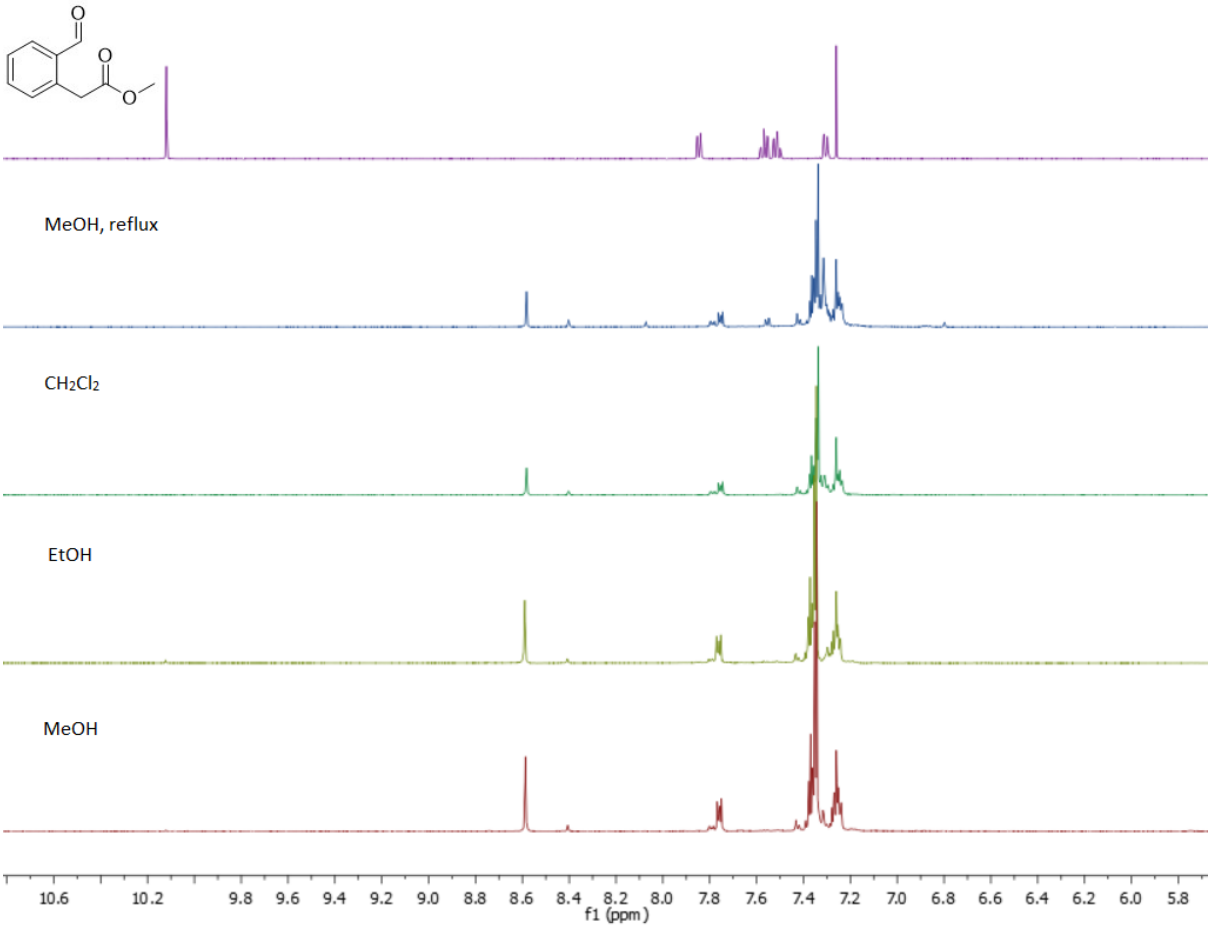
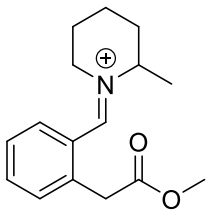


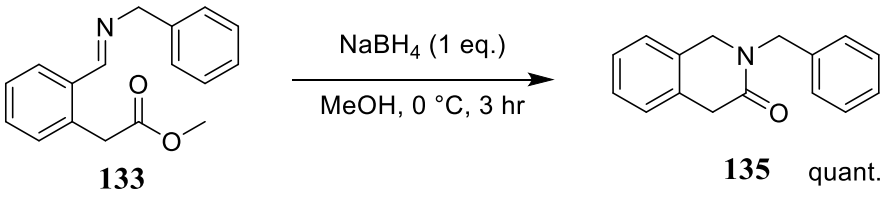
Fig. 4.1 *– ^{1}H NMR analysis of the formation of imine* ***133***



134

4.2.2 Reduction

To perform the reduction step, the imine formation reaction in **Scheme 4.05** that was stirred at room temperature overnight in methanol, was then cooled to 0 °C and treated with a single equivalent of sodium borohydride. (**Scheme 4.06**)



133 **135** quant.

Scheme 4.06

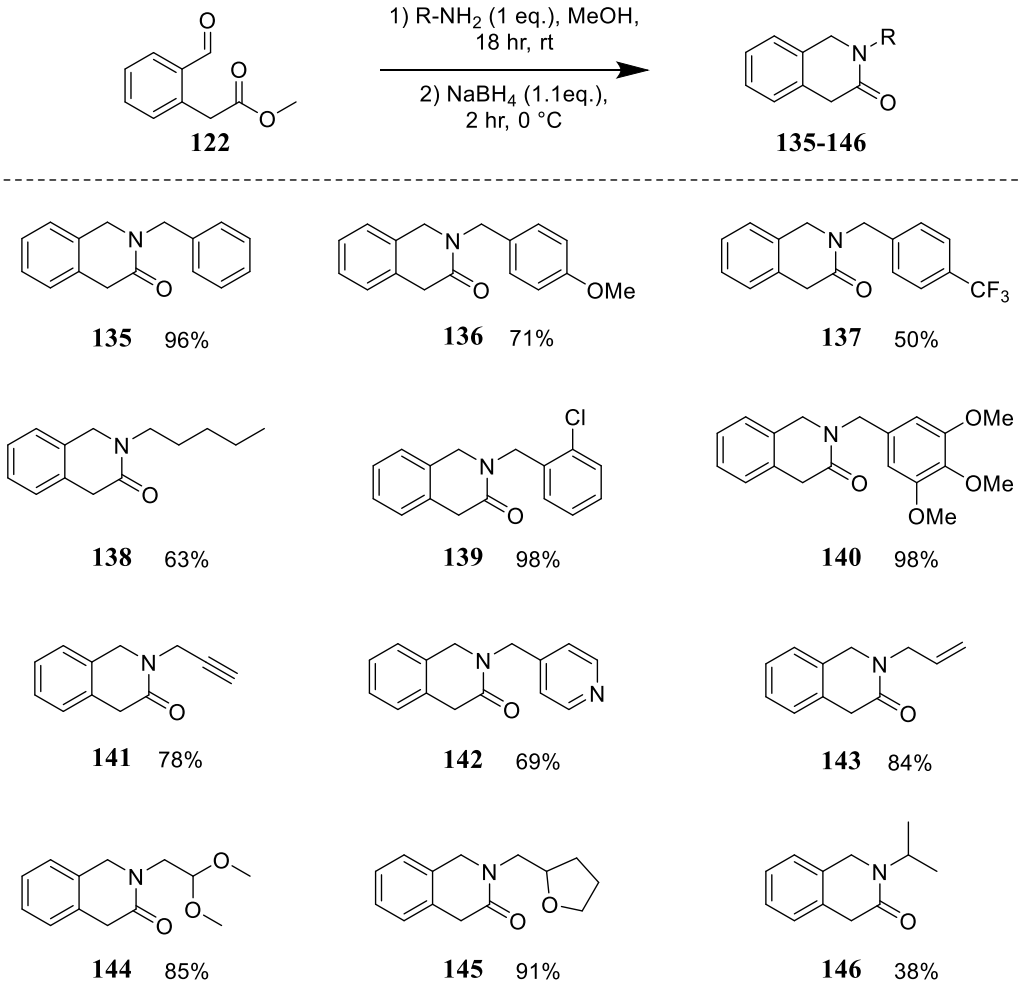
This led to a quantitative yield of **135**, easily characterised by the appearance of three singlet peaks in the ^{1}H NMR at 4.8, 4.4 and 3.7 ppm. All of these integrated for 2 protons each, indicating they represented the CH_2 groups. The test reaction had been carried out on a very small scale (20 mg / 0.11 mmol of aldehyde **122**) and so the reaction was scaled up to 250 mg of **122**. After the reaction was finished, the final product was purified using silica gel column chromatography (4:1 CH_2Cl_2:EtOAc) to give **135** in a 96% yield.

This was a major success, as it allowed for the formation of the ring under very mild conditions and using reagents available in most every synthetic chemistry lab. The next test was to see if the reaction could be repeated using different amine substrates. A large set of primary amines were obtained that had plenty of variance in their functionality in order to determine the substrate scope of the reaction conditions.

The initial imine formation was also studied to determine just how long it actually took to form the imine under the standard conditions, as until this point it had simply been left overnight. A ^{1}H NMR study showed that the imine formation reached completion in 3 hours, but the reactions were often left overnight for convenience.

This led to the development of a one-pot synthetic methodology for the formation of *N*-substituted 1,4-dihydro-3(2H)-isoquinolinones. The successful reactions are summarised in **Table 4.1**:

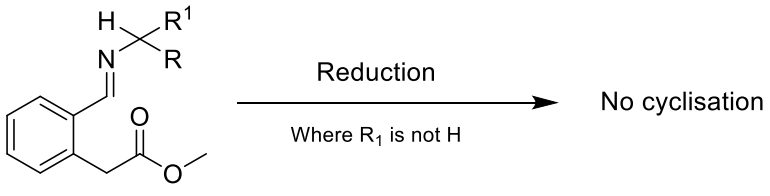
Table 4.1 *- N-substituted 1,4-dihydro-3(2H)-isoquinolinones*



As can be seen from **Table 4.1**, the amine substituents chosen varied from heterocycles, to alkyl chains, to substituted aromatic rings. In general, this reaction was very successful across a variety of substrates. A consistent trend was noticed throughout the series when it came to identification of the compounds by ^{1}H NMR spectroscopy, as 2 singlet peaks representing the two benzylic positions consistently appeared in the regions of 4.4 ppm and 3.7 ppm respectively.

The one major outlier is the isopropylamine derived species **146**. All of the other successful reactions had a methylene group in the *alpha* position to the amine. **146** was the only compound that was successfully derived from an amine species that didn't have this stipulation. Though successful, the yield was incredibly poor in comparison to all the other compounds in the series. When other amines of a similar substitution pattern to isopropylamine were trialled (such as α-methylbenzylamine, any amino acids or benzhydrylamine), they failed to produce any product.

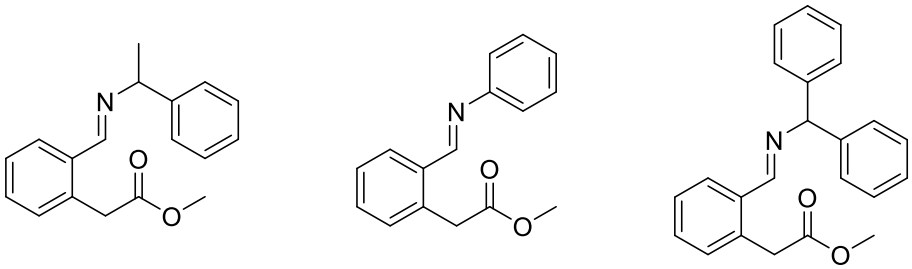
This trend is summarised in **Scheme 4.07**, though it should be noted that isopropylamine appears to be the exception to this rule.



Scheme 4.07

Because the reaction was one-pot, it was unclear at which point the reaction was failing. Perhaps the imine wasn't forming at all in the substrates that were unsuccessful and so the reaction was not going to be possible *via* this route. To test this, a study of imine formation was performed. Aldehyde **122** and a single equivalent of 4 different amines (α-methyl benzylamine, aniline, benzhydrylamine and alanine methyl ester hydrochloride) were left stirring in MeOH and samples taken hourly to be studied using ^{1}H NMR spectroscopy. What was discovered was that the imine formed successfully in almost all cases within 3 hours. The exception to this was when using alanine methyl ester hydrochloride. This reaction required the addition of a single equivalent of base (typically Et_3N) in order to free the amine species, and it then had to be left stirring overnight in order to completely form the imine.

Three of these imines were isolated and fully characterised. (**Figure 4.2**)



147 **148** **149**

Fig. 4.2 *– imines formed from α-substituted amines*

Clearly the imine formation was not the issue with the non-progression of these substrates to completed ring systems. The issue was the reductive amination. The logical next step was to change the reagents used for the reductive amination. A large number of reductive conditions were trialled

on **147**, the α-methylbenzylamine derived imine, as the imine was perfectly stable when stored in the fridge, making it easy to synthesise a large batch for use across multiple reactions.

The results of this study are summarised in **Table 4.2**.

Surprisingly, not even heating the imine in the presence of $LiAlH_4$ resulted in any reduction of the imine. The only changes that were observed were that hydrolysis sometimes occurred when using STAB, usually when an acid was added to the reaction. This is a known side reaction of this reagent[124] and was also likely due to the fact the acids weren't stored in anhydrous conditions and so some water was introduced to the reaction upon their addition. Also, in the case of the final entry on the table, it was observed that the methyl peak for the ester group of **147** was disappearing from the ^1H NMR spectrum, indicating that the ester group was being reduced instead of the imine.

Table 4.2 *– Reduction attempts on imine* ***147***

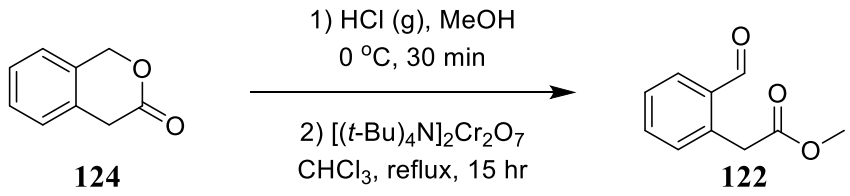
Reducing agent	**Solvent**	**Temp**	**Reduction (Y/N)**	**Hydrolysis (Y/N)**
H_2, Pd/C (10 mol%)	MeOH	rt	No	No
Picoline borane (1 eq.)	CH_2Cl_2	rt	No	No
$NaBH_4$ (1.1 eq.)	MeOH	0°C	No	No
$NaBH(OAc)_3$ (1 eq.)	MeOH	0°C	No	No
$NaBH(OAc)_3$ (1 eq.)	CH_2Cl_2	rt	No	Yes[a]
$NaBH(OAc)_3$ (1 eq.)	THF	rt	No	Yes[a]
$NaBH(OAc)_3$ (1 eq.)	CH_2Cl_2	rt	No	Yes[b]
DIBAL-H (1.1 eq.)	THF	0°C	No	No
$LiAlH_4$ (excess)	THF	0°C	No	No
$LiAlH_4$ (excess)	THF	reflux	No	No

[a] 1.5eq of acetic acid added

[b] 3eq TFA added

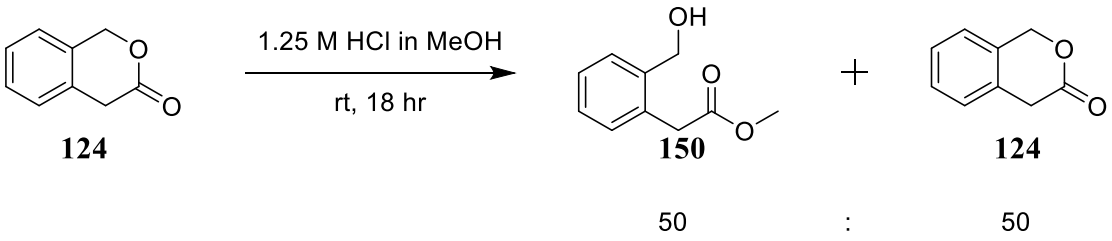
4.3 Synthesis of **122** from isochromanone

In parallel to the above attempts at reduction, an attempt was made to synthesise the aldehyde **122** from isochromanone (**124**), as one issue with the methodology that had been developed was the cost of **122**. This had been achieved previously[127] (**Scheme 4.08**) and the methodology was reattempted.



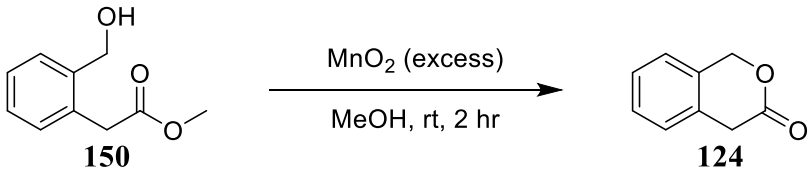
Scheme 4.08

Initially **124** was dissolved in a commercially bought, 1.25 M solution of HCl in MeOH and stirred at room temperature overnight. (**Scheme 4.09**)



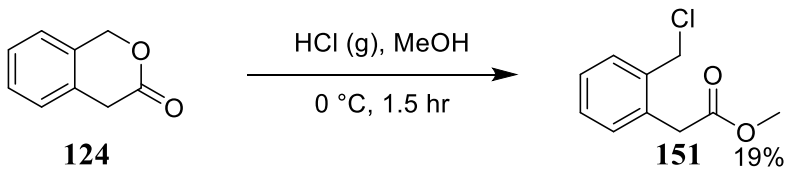
Scheme 4.09

^{1}H NMR analysis showed that this generated an almost 50:50 mixture of **124** to the alcohol product (**150**) in the best case. The results were very inconsistent however, often levelling off at around 35:65 alcohol **150** to **124**. It was decided to go with a different oxidation method for an initial trial of the route, as bis(tetrabutylammonium) dichromate is very toxic and milder oxidation reagents were already on hand in the lab. An initial test of the oxidation of the alcohol group to the aldehyde using MnO_2 appeared to only succeed in performing hydrolysis of the ester, which resulted in the reformation of **124**, as confirmed by ^{1}H NMR analysis. (**Scheme 4.10**)



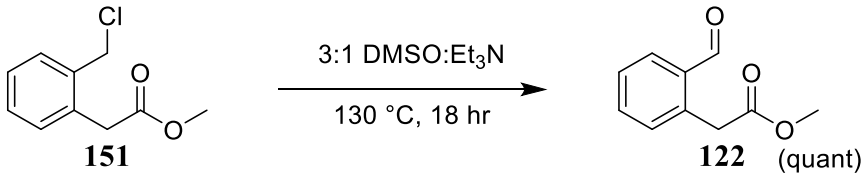
Scheme 4.10

The results with commercial HCl solutions were so inconsistent it was decided to attempt generating HCl *in situ* and using that to open the lactone. This was achieved by dissolving **124** in MeOH and fitting the flask with a bubbler, then cooling the solution to 0 °C. The bubbler was connected to a flask containing $CaCl_2$. Concentrated HCl (~36%) was dropped onto the $CaCl_2$, immediately dehydrating the solution and liberating HCl gas, which was then passed through the MeOH solution. After 1.5 hours the solution had gone from orange in colour to yellow/brown. ^{1}H NMR analysis of the product showed this to be a different product to **150** as derived from the previous reaction. The methylene peak for the benzyl alcohol group had shifted from 3.77 ppm to 3.81 ppm, while the other peaks had shifted but only very slightly. This led to the belief that a different product had been generated. The ^{1}H NMR data recorded matched those previously reported for the benzyl chloride species **151**,[125] and so it was believed that this was the actual product that had been generated, albeit in a very low yield. (**Scheme 4.11**)



Scheme 4.11

If this was the case, the benzyl chloride should be susceptible to the Kornblum oxidation[128] which would allow for the synthesis of the aldehyde **122**. This proved to be successful, quantitatively generating **122** from **151**. (**Scheme 4.12**)



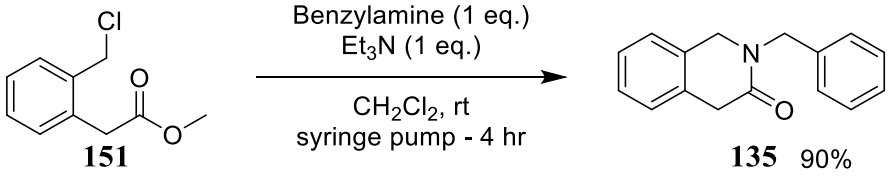
Scheme 4.12

Upon repeating the reaction on a larger scale however, it was found that it was very difficult to push the initial step to generate more than 50% of **151**. Scale once again appeared to be an issue with this methodology.

The successful generation of **151** did however lead to some interesting possibilities.

4.4 Secondary amines from **151**

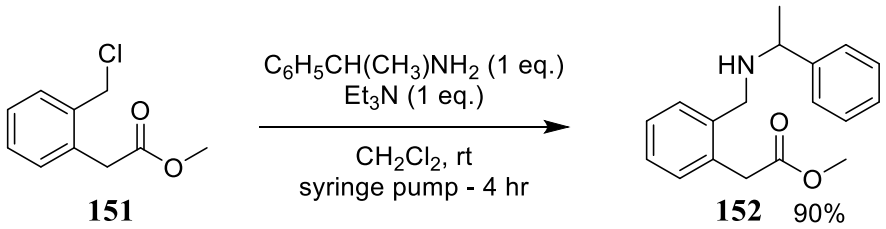
It was realised that the benzyl chloride **151** could directly undergo nucleophilic substitution with an amine species as demonstrated by Dolle *et al.*[84] Perhaps this would mean that **151** could be used to get around the issue of the amines that had failed to cyclise previously, as there would be no need for a reduction step. To test this, **151** was reacted with an equivalent of benzylamine (with Et_3N present to neutralise any HCl generated by the reaction). **151** was added to a mixture of benzylamine and Et_3N using a syringe pump over 4 hours to attempt to control excess alkylation of benzylamine. This resulted in the formation of **135** with a 90% yield. (**Scheme 4.13**)



151 **135** 90%

Scheme 4.13

This showed that the cyclisation reaction should take place immediately after the formation of the secondary amine species. It was hoped that the same would hold true for the species that had failed to react under the previous reductive amination conditions. (**Scheme 4.06** above) To test this, the reaction was reattempted using α-methylbenzylamine as the reactant. Unfortunately, while the secondary amine did form, it failed to cyclise. (**Scheme 4.14**)



Scheme 4.14

This product was clearly visible by ^{1}H NMR spectroscopy, as the benzylic protons on the amine substituent had now become diastereotopic with the introduction of the stereocentre into the molecule. This resulted in the appearance of two doublets at 3.73 and 3.69 ppm with a large coupling constant of 15.70 Hz, consistent with geminal coupling. (**Figure 4.3**)

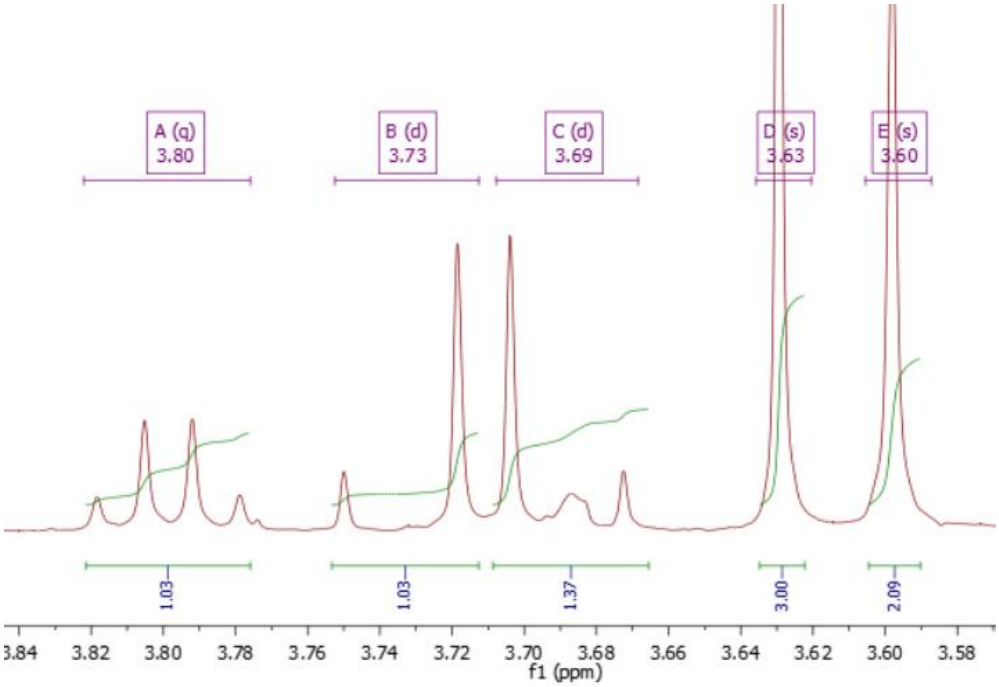


Fig. 4.3 *– ^{1}H NMR evidence for* ***151***

Repeating the reaction at a higher temperature (40 °C) yielded the same result.

4.4.1 GSK and hydrogenator

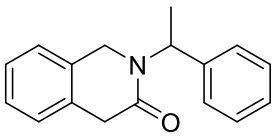
The failure of some compounds to cyclise was a major disappointment, as it meant that amino acids and other varied amines would be impossible to incorporate into the synthesis. Amino acids are a commonly used source of stereochemical purity when building molecules and the lack of ability to

incorporate them was a major setback. Though a fairly exhaustive list of reduction methods had been attempted on the imine, there was still one method that had yet to be attempted. GSK have access to a piece of equipment known as a H-cube, a flow hydrogenation system that allows for varied temperature and pressure conditions to be applied to the flow reactor. This was seen as the last attempt at reducing the imine, though given the result from **Scheme 4.14,** it was unclear if, even if the imine was reduced, the cyclisation would occur.

In any case, the H-cube method was attempted.

To begin with, the conditions were set to a temperature of 40 °C, a flow rate of 1 mL/min and 1 atm. of H_2 with a 10% Pd/C catalyst. The imine **147** was dissolved in MeOH and allowed to flow through the system. The product was collected, and samples were removed for LCMS analysis. Surprisingly, the LCMS analysis indicated that the hydrogenation had been successful in generating the secondary amine **152** after a single pass through the system. There was no evidence that the cyclisation had occurred, but this was at least a step forward. Given that the compound is a secondary amine and the chromatography columns available at GSK were all pre-packed and automated, it was decided to go with a reverse-phase column instead, so as not to risk the silica degrading the compound. Though the compound had been purified over silica before (in the presence of Et_3N), GSK had easy access to reverse-phase purification systems, and it was decided this would be the best method for purification.

What was isolated from the reverse-phase purification, however, came as quite the surprise. Upon analysing the products, it was found that the major isolated product was indeed the cyclised product **153**, albeit at a very reduced yield (10%).



153

Compound **153** was easily identified through the appearance of a set of roofed doublets at 4.27 and 3.98 ppm, as these represented the benzylic position *alpha* to the nitrogen atom. The 2H atoms alpha to the nitrogen are being influenced by the introduction of the stereogenic centre on the nitrogen substituent, causing them to become diastereotopic. The large coupling constant of 15.41 Hz is consistent with geminal coupling, and the appearance of a singlet peak representing the position alpha to the carbonyl at 3.71 ppm was consistent with other cyclised molecules in the series, indicating that the reaction had been successful. (**Figure 4.4**)

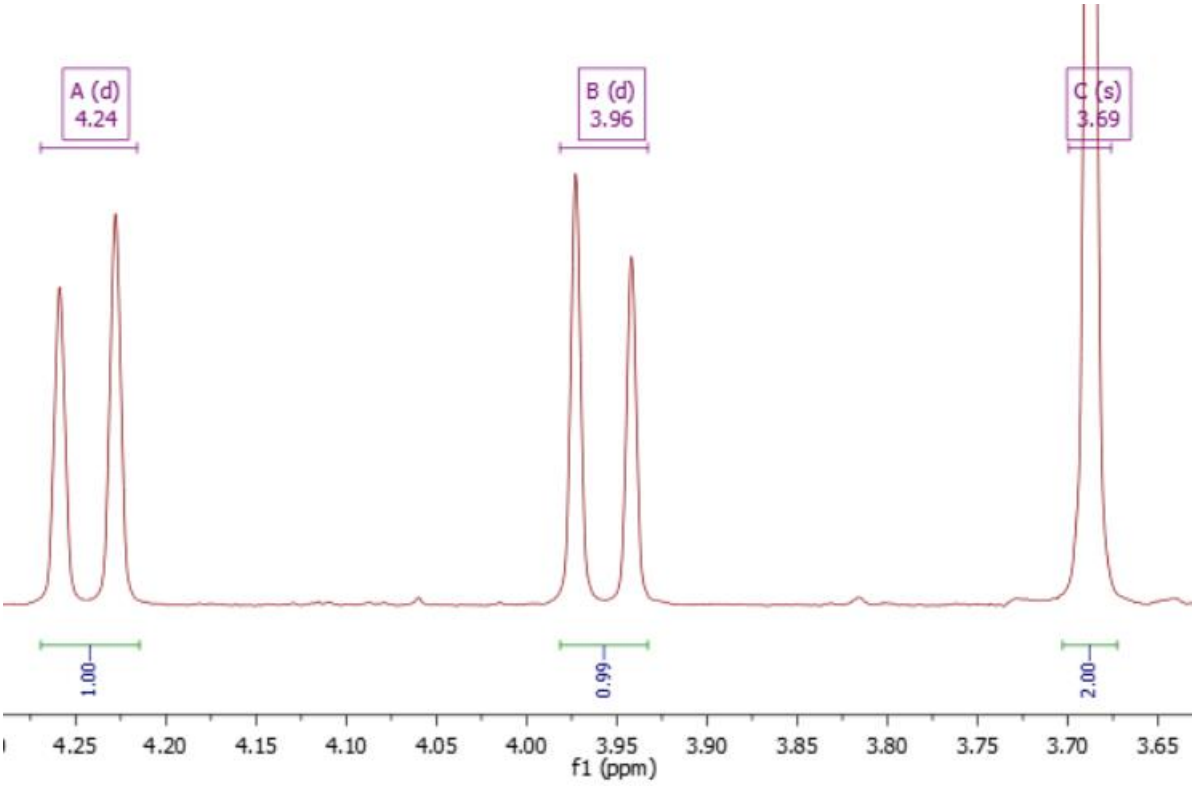


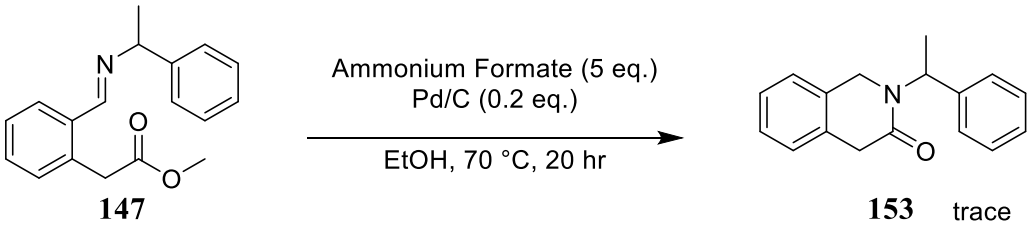
Fig. 4.4 *– ^{1}H NMR evidence for the formation of* ***153***

It appeared that a condition used in the purification of the molecule had caused the cyclisation, though it was unclear what exactly had caused it. Nevertheless, this was a major breakthrough.

4.5 Transfer Hydrogenation

It was now determined that the best reduction method for the imine was hydrogenation and that it appeared the resulting secondary amine needed specific conditions to cyclise. After discussions with some of the scientists at GSK, conditions for transfer hydrogenation[129] were sourced in-house. Transfer hydrogenation appeared to be ideal as it would allow for the *in situ* generation of H_2 in the presence of Pd/C, which was now confirmed to reduce the imine, and the higher temperatures involved may be enough to facilitate the cyclisation reaction. Due to internal company safety mandates, transfer hydrogenations were not allowed to be carried out in methanol, as this had the

potential to result in an explosion. Ethanol was chosen as the solvent instead for this reaction. (**Scheme 4.15**)

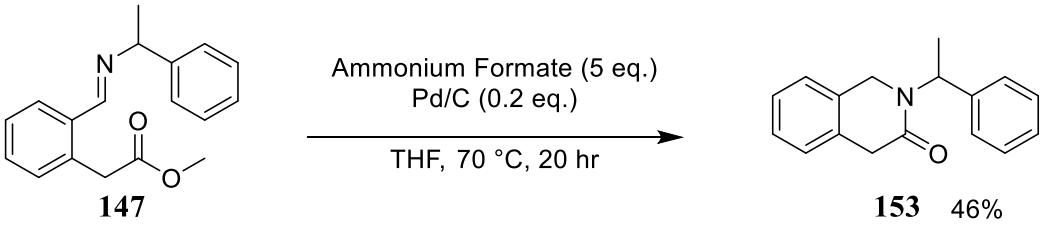


147 **153** trace

Scheme 4.15

This reaction was somewhat successful, LCMS analysis showed the formation of **153** had indeed occurred however, ^{1}H NMR analysis failed to confirm this result as it appeared to be too weak. The simplest thing to change in an effort to improve the yield was the solvent, and so a solvent swap was performed. THF was chosen as a suitable alternative as it had no bonds that could undergo hydrogenation and had a similar boiling point to ethanol.

The reaction was performed as before after swapping the solvent. (**Scheme 4.16**)



147 **153** 46%

Scheme 4.16

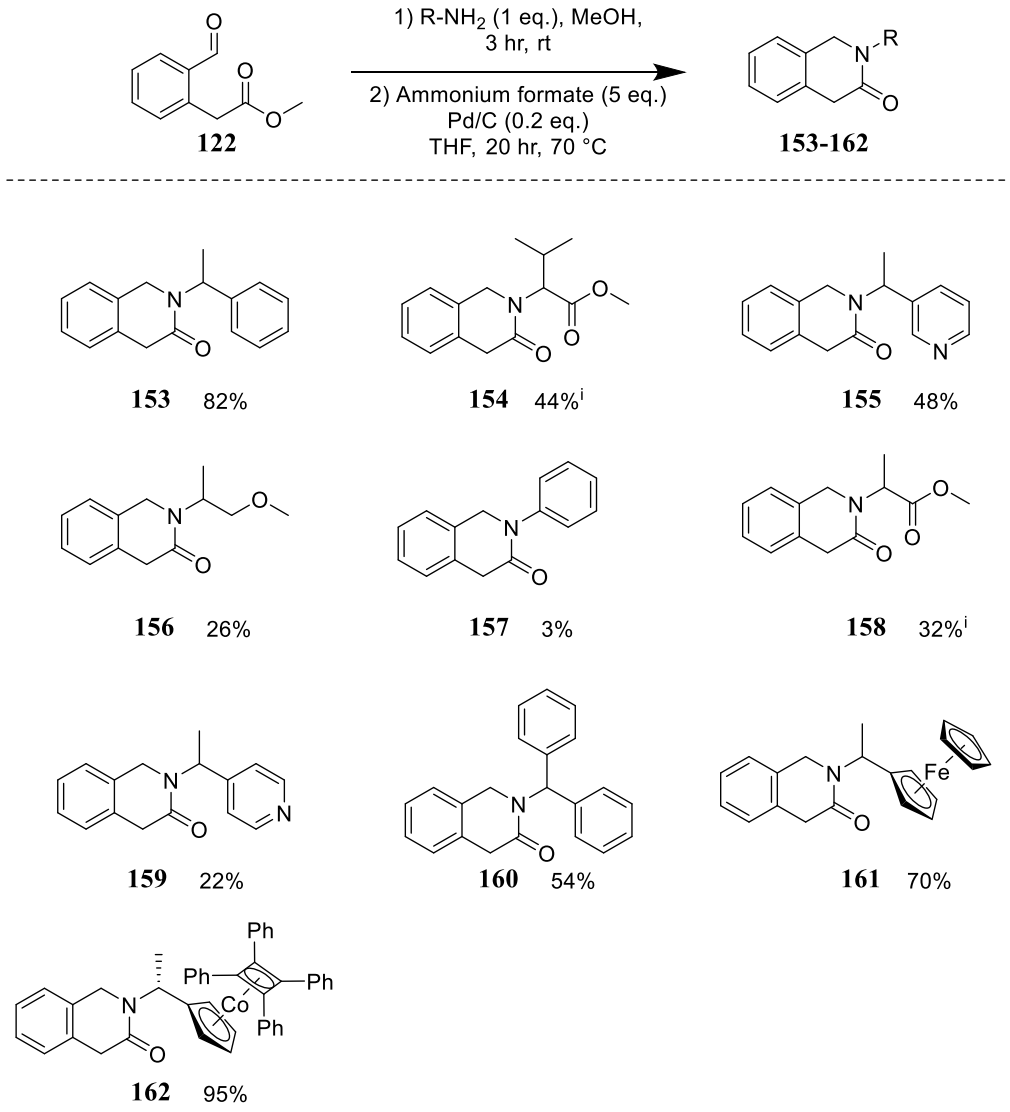
This change resulted in the isolation of a large enough amount of the product to perform all the necessary analyses to confirm its presence.

Bolstered by this success, the reaction was exemplified using the small-scale array chemistry capabilities at GSK. (**Table 4.3**) This methodology, while allowing for rapid synthesis, is costly in terms of material and often leads to some losses, which likely explains the low yields of the series overall.

Using a 24-well heating mantle plate, reactions were set up on a small scale in glass vials, each fitted with a stirrer bar, and so were subjected to the same conditions over the same time period. The samples were then all filtered, dried, dissolved in DMSO and purified via Mass Directed Auto-Prep, a Reverse Phase purification technique that uses a mass spectrometer to detect when the product is eluting. All of the samples can be loaded into the purification system at once, allowing for minimal

manual interference and ease of purification. This technique is typically used when synthesising compounds for testing to elucidate the Structural Activity Relationship of an active target site for a drug compound, and so is geared more towards isolating at least some product rather than maximising yields. As such, yields are often lower than they would have been had each compound been synthesised and purified normally.

Table 4.3 *– N-substituted 1,4-dihydro-3(2H)-isoquinolinones with α-substituents*



[i]Starting amine added as hydrochloride salt and 1 eq. Et_3N added to generate free base

Still, it was found that amino acids were not compatible with this chemistry. However, if they were added as the methyl-ester hydrochloride salt and allowed to generate the free-base *in-situ*, they could be used with this chemistry successfully. The initial reaction was performed on a 2g scale and this

actually improved the yield greatly, resulting in an isolated yield of 82% of **153**. (**Table 4.3, entry 1**)

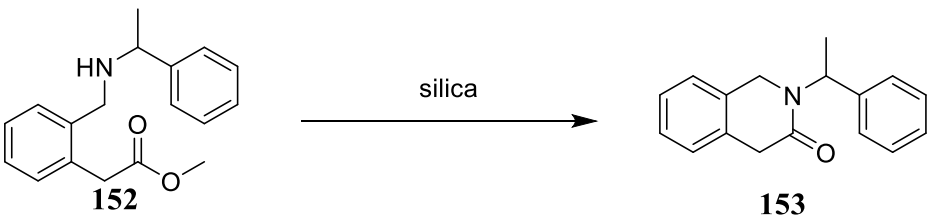
Once again, a consistent pattern was noted with the ^{1}H NMR spectra of these products. A singlet representing the position alpha to the carbonyl consistently appeared at around 3.7 ppm while a set of doublets representing benzylic CH_2 next to the nitrogen atom consistently appeared between 4.5 ppm and 3.9 ppm, with a high coupling constant (~15 Hz) consistent with geminal coupling.

A trend was also noticed when it came to the type of amines that would react. As can be seen in example **157**, it appeared the reaction did not work well when the amine was directly attached to an aromatic ring. This carried over to non-aromatic groups also, as cyclohexylamine failed to produce any product. It is possible that a degree of flexibility is required for the cyclisation to occur, which structures like aniline and cyclohexylamine don't allow.

Cyclised products **161** and **162** are included in the table here but are not relevant to this section and shall be discussed in more detail in the next chapter.

A question remained when it came to the cyclisation, however. It was still unclear which of the stages of the synthesis was the greatest barrier to the cyclisation reaction. Was it the reduction of the imine or the cyclisation step itself? The fact that secondary amine **152** had cyclised upon purification previously indicated that the conditions necessary to force the final cyclisation were quite mild, and that it was the imine reduction that had was the major barrier to performing the cyclisation reactions.

To test this theory, a small sample of **152** was placed in a vial, dissolved in CH_2Cl_2, and a spatula tip-full of standard silica was added to the solution, before stirring at room temperature overnight. The sample was analysed the next day and was found to have cyclised to form **153**. Further work found that, if **152** was mounted onto a silica gel column for chromatography, what eluted from the column was the product **153**. The mildly acidic silica was enough to facilitate the cyclisation step, confirming that the greatest hurdle to this chemistry is the imine reduction. (**Scheme 4.17**)



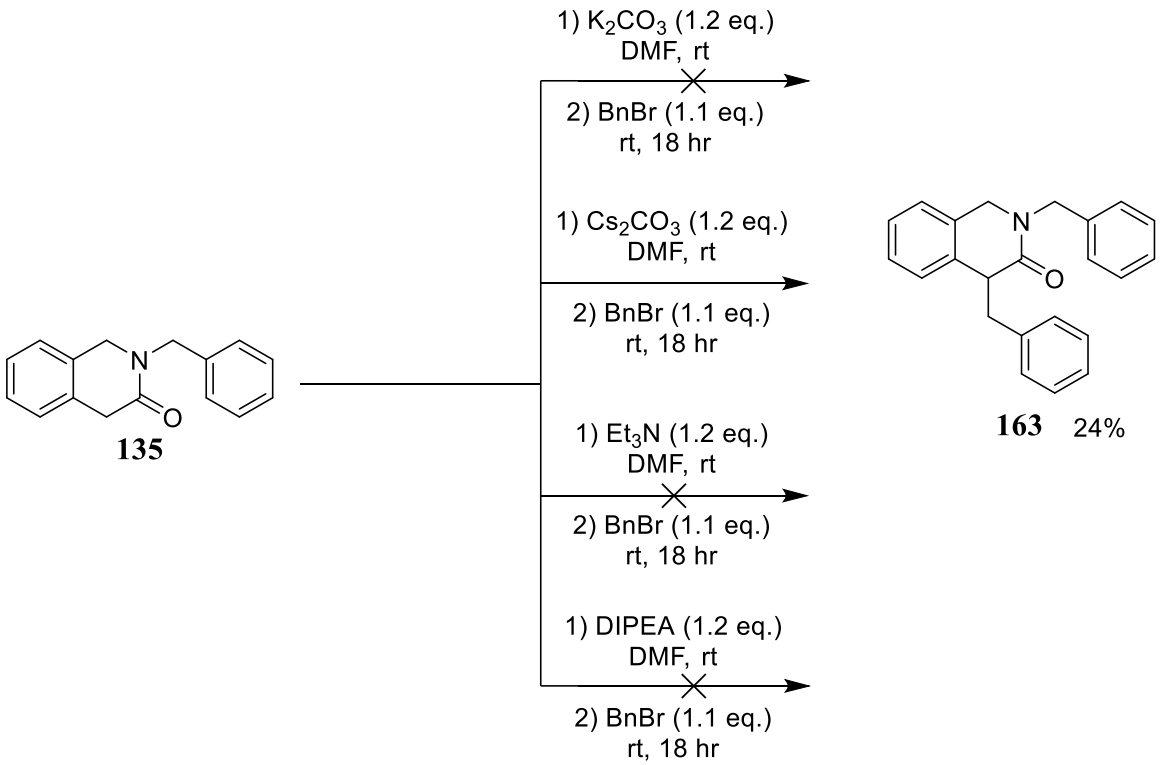
Scheme 4.17

4.6 Alkylation

The next logical step was to attempt further derivatisation of the core structure.

Because of the success had with the cyclisation, it was decided to attempt a different method of derivatisation. The position alpha to the carbonyl would be expected to have a pKa of ~18[130] and so should be susceptible to deprotonation by a base. This would allow the addition of an electrophile to perform the alkylation reaction.

The first bases tested were chosen for their ease of use and general availability. Bases K_2CO_3, Cs_2CO_3, Et_3N and DIPEA are found in most, if not all, synthetic chemistry labs and so were the logical bases to trial initially. To begin with, the bases were added to the starting material **135** in DMF and the alkylating agent (in this case, benzyl bromide) was added 10 minutes after the addition of the base. The reactions were then left stirring overnight. (**Scheme 4.18**)

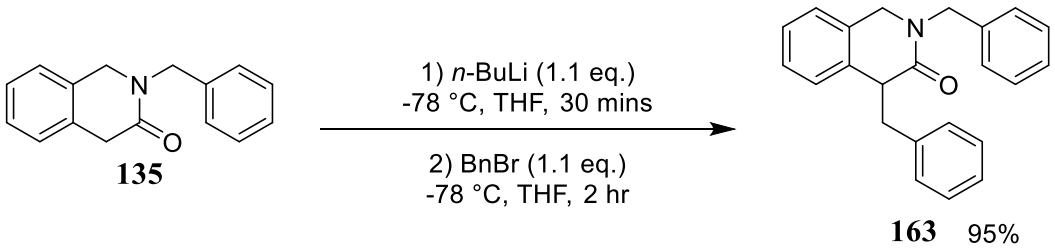


Scheme 4.18

The only reaction that showed any progression was the Cs_2CO_3 reaction and even then, the reaction had only achieved 24% completion as determined by ^1H NMR. Though the conjugate acids of all of

the bases used had a similar pKa value (~10), Cs_2CO_3 is known to be much more soluble in aprotic solvents than other inorganic bases,[131] and this likely contributed to the minor success of the reaction as seen here. Even with this success, it seemed a stronger base was necessary. The base chosen next was *n*-BuLi, as it is commonly available and almost certainly strong enough to cause deprotonation to occur (pKa = 50). This required a change in the methodology however, as the reactivity of *n*-BuLi needs to be modulated by temperature. The solvent was changed to THF and a dry ice/acetone bath was used to drop the temperature to -78 °C. Compound **135** was dissolved in the THF under a nitrogen atmosphere before being placed in the bath with stirring. After 10 minutes, *n*-BuLi was added. This caused the reaction to turn a deep red colour, indicating the lithiation reaction was taking place. After 30 minutes, benzyl bromide was added to the reaction and the temperature was maintained for 2 hours. After 3 hours, the reaction was allowed to come up to room temperature before being quenched with water and extracted into organic solvent.

After purification through a silica column, the product **163** was isolated in a 95% yield. (**Scheme 4.19**)



Scheme 4.19

The compound was easily identifiable by ^{1}H NMR spectroscopy as the singlet peak that normally represent the protons alpha to the carbonyl at ~3.7 ppm was gone, having been replaced by an apparent triplet at 3.99 ppm representing the single proton remaining at that position (a double doublet was expected). A new set of doublets at 4.77 and 4.46 ppm appeared, representing the protons of the CH_2 group alpha to the nitrogen in the bicyclic system. This was to be expected as the compound is now chiral and so the protons have become diastereotopic. The new benzylic CH_2 position generated through this reaction resulted in the appearance of another set of doublets at 3.87 and 3.46 ppm respectively, both with coupling constants of 15.5 Hz, consistent with the geminal coupling of diastereotopic benzylic hydrogens. (**Figure 4.5**)

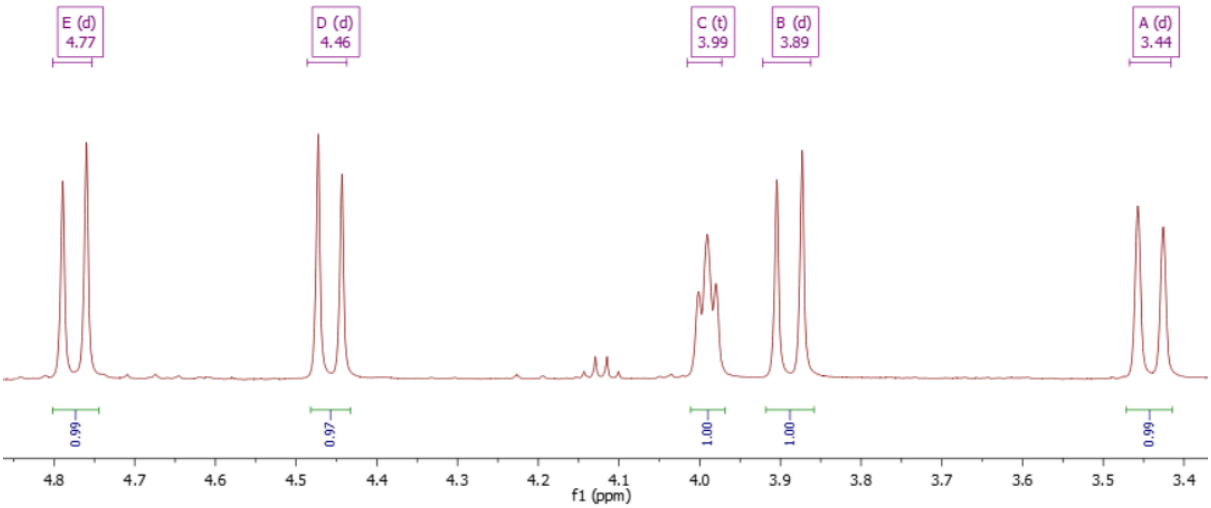
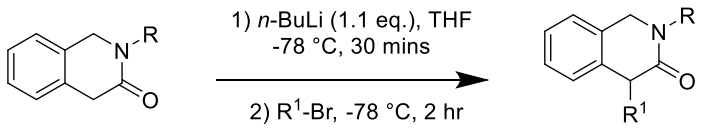


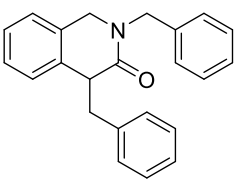
Fig. 4.5 *– ^{1}H NMR evidence for the formation of* ***163***

The success of this reaction led to the conclusion that this methodology was the best to use. The set was expanded to include various functional groups and some variance in the starting isoquinolinone used. (**Table 4.4**)

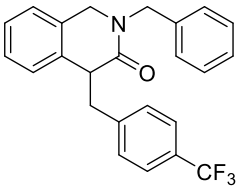
The alkylating agents used were again, chosen for their variance. The set includes aromatic rings, alkenes, alkynes and ether chains. All of them achieving at least a decent rate of success and maintaining the same ^{1}H NMR patterns as had been seen in **Figure 4.5** above, allowing for easy identification of the products. The one exception to this was compound **166**, which will now be looked at in greater detail.

Table 4.4 *– Alkylation of N-substituted 1,4-dihydro-3(2H)-isoquinolinones*

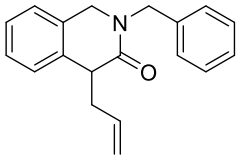




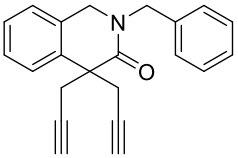
163 95%



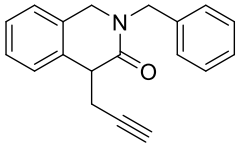
164 40%



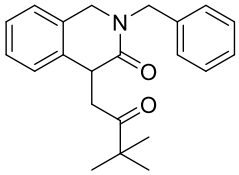
165 58%



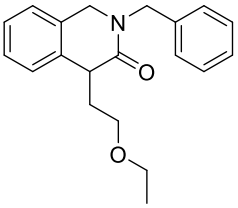
166 29%



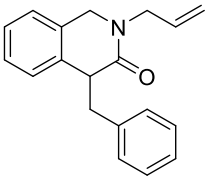
167 83%[i]



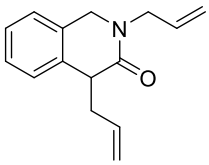
168 81%



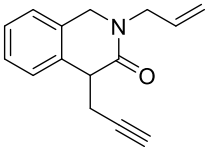
169 58%



170 95%



59 98%

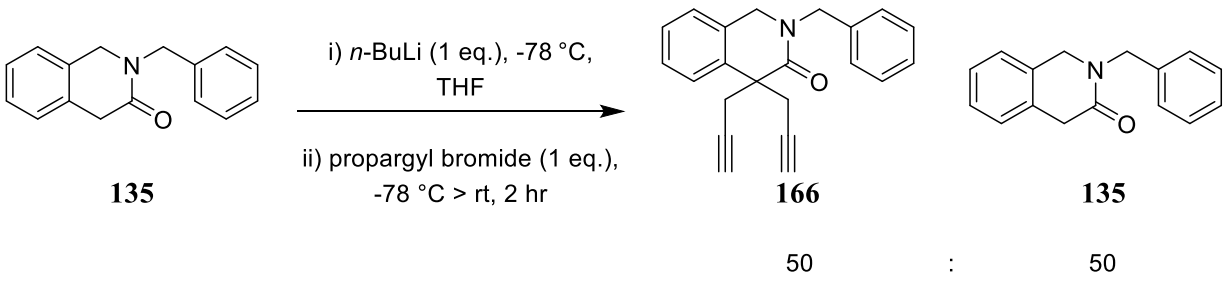


171 79%

[i] 5 eq. propargyl bromide, immediately removed from -78 °C bath and brought up to room temperature upon addition.

4.6.1 The propargyl bromide issue

There is clear outlier in the set shown in **Table 4.4** above. Product **166** is the di-addition product from the reaction and is also the lowest yielding of the entire series. This was interesting as it was found that by using the standard reaction conditions, **166** was exclusively formed, with the starting material (**135**) also being isolated from the reaction mixture. (**Scheme 4.20**)

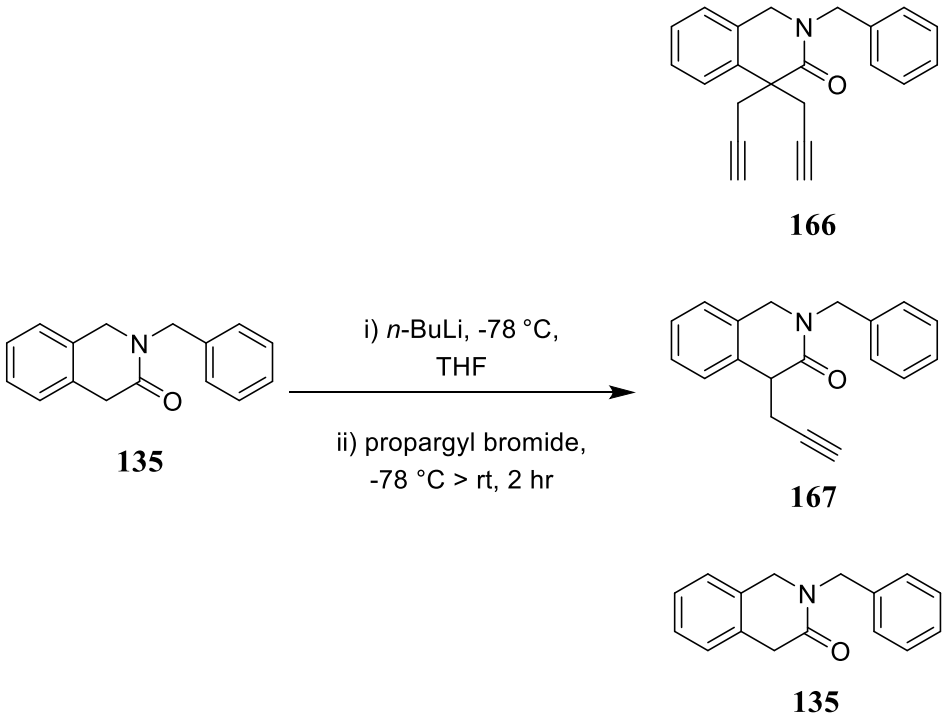


Scheme 4.20

This was the only case in which this di-addition was observed. The reaction was also tested using the allyl derivative (**143**) as the starting material. As can be seen from **Table 4.4** above, this readily formed the mono-addition product in a relatively high yield. It appeared that this unusual process was exclusive to the benzylic derivative.

To investigate how this was occurring, various alterations were made to the synthetic process for this reaction. (**Table 4.5**) This resulted in the formation of both the mono and di-addition products to varying degrees. (**Scheme 4.21**)

What was discovered through these investigations was that **166** was the kinetically favoured product. Once the initial addition step has completed, an enolate species of **167** exists (**172**) that reacts faster with propargyl bromide than the initial lithiated species, leading to di-addition occurring instead of mono-addition. This species is likely stabilised by the cold temperature of the reaction.



Scheme 4.21

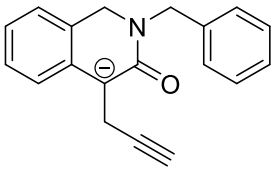
Table 4.5 *– Conditions for alkylating* ***135*** *with propargyl bromide*

	nBuLi eq.	**Propargyl bromide eq.**	**Temp (°C)**	**166 (% by NMR)**	**167 (% by NMR)**	**135 (% by NMR)**
1	1.1[i]	1	-78	50	0	50
2	1.1	2	-78	55	22	23
3	1.1	1	-78[ii]	28	64	8
4	2	2	-78	100	0	0
5	1.1	5	-78	23	65[iii]	12

[i] Standard reaction conditions

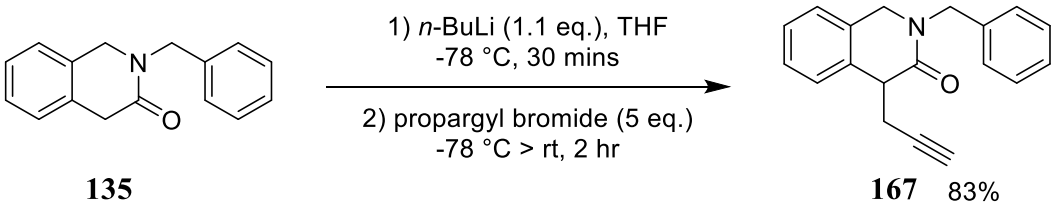
[ii] Reaction was removed from cold bath immediately after the addition of the propargyl bromide

[iii] This value was found in initial crude NMR test run. Yield increased to 83% when repeated on scale as shown in table 4.4



172

On further investigation of this reaction it was found that the mono-propargyl derivative **172** was formed almost exclusively following the addition at -78 °C of 5 equivalents of propargyl bromide to the initially formed lithium enolate, and immediate warming of the reaction mixture to room temperature. As propargylation of N-allyl substrate **143** proceeded readily without this complication (**Table 4.4**, **171**), as otherwise did the alkylation of **135** (**Table 4.4**, **163**–**165**, **168**, **169**), it is the specific combination of N-benzyl and C(1)-propargyl substituents that promote the formation of **166**. This can be accounted for by the greater stability of the enolate derived from **167**, although the synergistic influence of the substituents that results in this effect is not clear.



Scheme 4.22

Conclusion

The purchase of **122** led to a period of great success in this project, allowing for the complete synthesis of one of the original core structures and providing plenty of potential for derivatisation. A total of 32 separate compounds (the vast majority of which were novel) were synthesised *via* the route developed herein, spanning a wide array of functional groups. This chemistry is straightforward and reliable and may form the basis for further work in the future, particularly in the field of medicinal chemistry, as it provides quick access to highly functionalised molecules using a simple methodology that can be applied to large sets (as demonstrated by the array chemistry performed here), making it ideal for exploring SAR when developing new drug candidates.

Chapter 5 – Protecting group development and Grignard addition

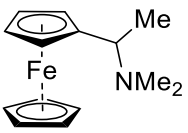
5.1 Introduction

When originally coming up against issues with the cyclisation step, particularly when it came to substrates with substitution at the α position, a potential workaround was proposed. The idea was to perform the cyclisation step using an amine that could be removed afterwards, leaving a free amino group that could undergo substitution afterwards, potentially allowing for access to the molecules that failed to be synthesised from the developed cyclisation method. The easiest method of doing this would be to incorporate a substrate that would traditionally be used as a "protecting group" as the methods for removal of these groups are usually very straightforward, making them ideal candidates. It was also proposed that some of these "protecting groups" could be used as directing groups and allow for the development of single enantiomers of some of the molecules that were previously synthesised as racemates.

5.1.1 Ugi's amine – potential "protecting group" and director

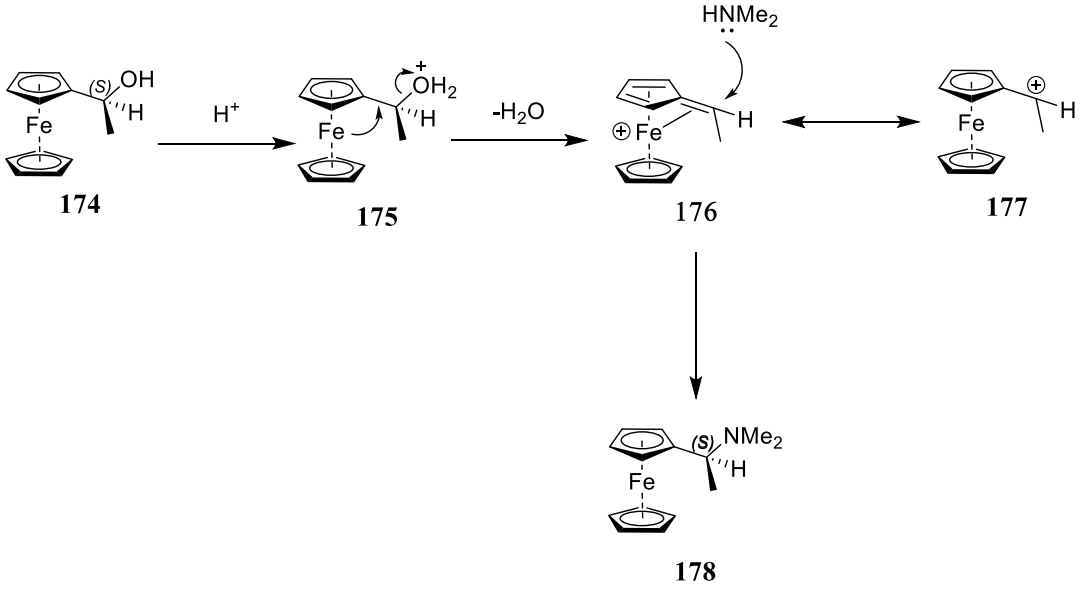
Ugi's amine (*N*,*N*-dimethyl-1-ferrocenylethylamine) (**173**) was developed by Ivar Ugi in 1970 and has become widely known for its utility as a precursor molecule in the development of metal ligands that contain planar chirality.[132–135]

Ferrocene compounds of this sort are notable in that when a suitable leaving group is present under acidic conditions, it allows for the formation of a stable carbocation delocalised to the metal centre,[136] (**Scheme 5.01)** a fact that could be exploited in order to use it as a "protecting group".



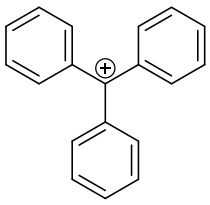
173

The formation of this carbocation makes the group functionally similar to a trityl protecting group which is able to stabilise a positive charge on the carbon in the centre of its three aromatic rings by forming a tritylcation. (**179**)



174 **175** 176 **177** **178**

Scheme 5.01



179

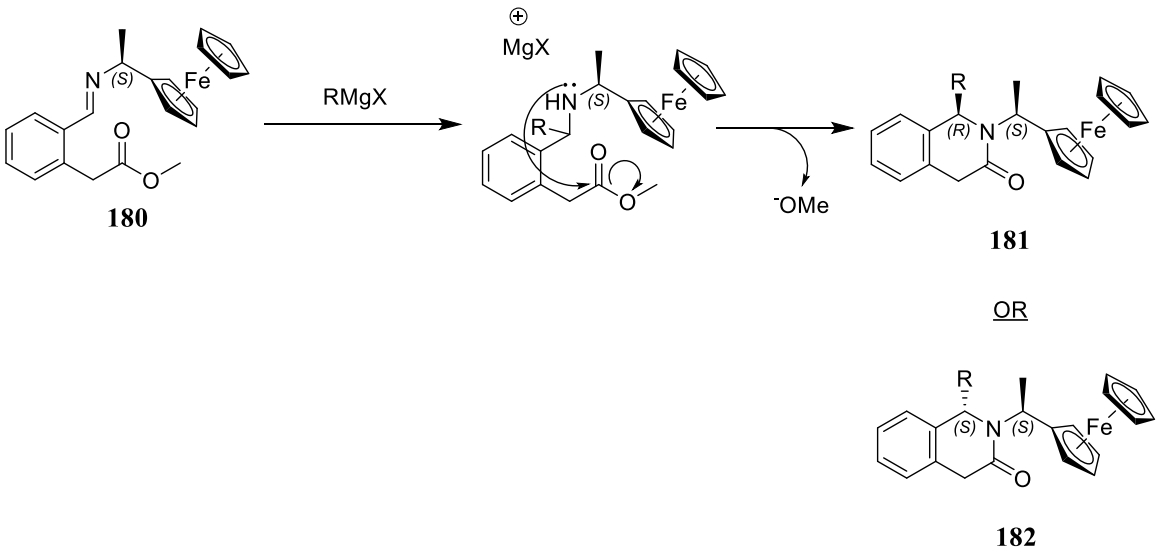
The similarities in charge stabilisation between the two groups, mean that it could be possible to remove the ferrocenyl moiety under the acidic conditions used for trityl removal.[137] Not only this, but the synthesis of Ugi's amine progresses with the retention of stereochemistry, so if a single enantiomer of **174** is used in the synthesis of Ugi's amine, it is possible to control the stereochemistry of the final product. This makes Ugi's amine particularly interesting when it comes to use as a potential auxiliary, as both enantiomers can be easily synthesised according to requirements.

The trityl protecting group would likely not be suitable for the reductive amination and cyclisation reaction, given the challenges involved in performing reductive amination chemistry on such a large, hindered group. This was evidenced in the previous chapter, as the nearest analogue to the trityl group studied - the benzhydrylamine derived **160** - only achieved a 54% yield under the optimised

conditions. This would likely decrease significantly if another ring system were to be added to the amine species, making the insertion of a trityl amine unlikely to be successful. While Ugi's amine is large, it only contains a large functional group on one side, with the other arm being a methyl group. This gives it much less chance of being unsuccessful due to sterics.

5.1.2 Grignard addition to imines

To further the derivatisation of the tetrahydroisoquinolinone structures, one possible method was the potential for performing an alkylation on the imine itself. This would allow for another point of difference in the synthesis and help to further diversify the series. In this regard, the potential of Grignard reagents was investigated. There was also the potential for stereoselective reactions at this point of the molecule if the imine is derived from a chiral amine, such as Ugi's amine, as the proximity of the imine to the side-chain group would likely influence the final addition to the imines diastereotopic faces. (**Scheme 5.02**)

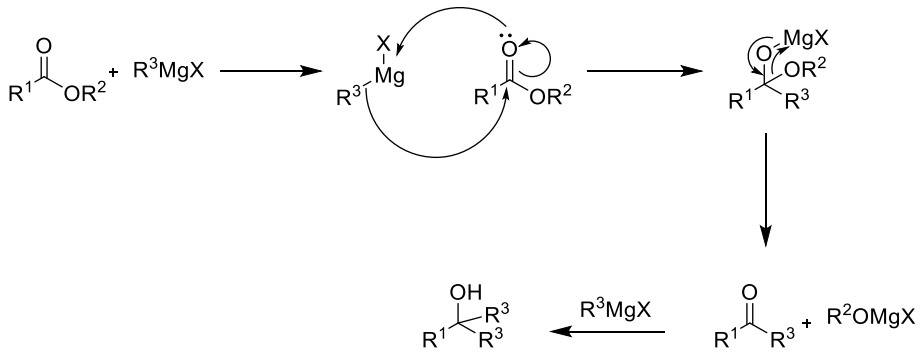


Scheme 5.02

Typically, the addition of Grignard reagents to imines is somewhat difficult. Though the alkylation of imines has been reported several times using organometallic reagents containing metals such as Li, Zn, B and Zr,[138] examples using Grignard reagents are much less common.

Many examples simply show that Grignard reagents don't appear to be reactive to imines at all without the presence of a catalyst,[139,140] which often takes the form of a Lewis acid. Ishihara *et al.*[141] found that the reaction did indeed progress in some cases. However, the addition of a catalyst (which in this case was simply $ZnCl_2$) dramatically increased the effectiveness of the reaction, more than doubling the yield in some cases.

The addition of Grignard reagents to ester groups is already a well-understood reaction[142] and is routinely taught at undergraduate level. (**Scheme 5.03**)



Scheme 5.03

It is likely then, that the ester group contained within the imine compounds produced in this thesis would interfere with any attempt to alkylate the imine moiety. Nevertheless, it was worth attempting, and this led to one of the more interesting discoveries of the project, albeit at a very late stage.

5.2 Protecting group

This section details the methodologies used to try and exploit "protecting group" chemistry to synthesise more complex molecules, starting from some compounds that were already available in the compound library before moving on to the ferrocene based chemistry.

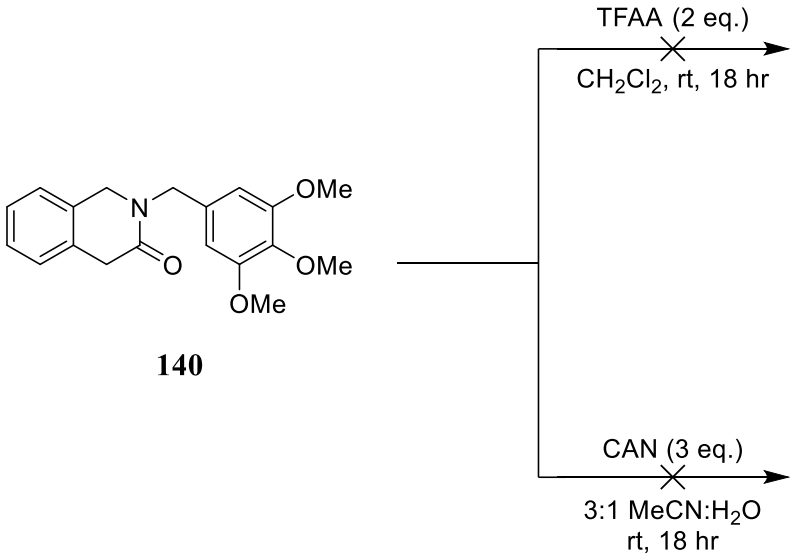
5.2.1 Removal of N-substituent

The first task was to see if the sidechains attached to the nitrogen could be removed, this could prove additionally useful at a point in the future if chiral auxiliary chemistry became an area of interest.

Para-methoxybenzene (PMB) is a well-known and well-studied protecting group that can be removed *via* several methods. For instance it is known to be labile in the presence of strong acids[143] and also susceptible to oxidative cleavage in the presence of compound such as DDQ[144] and CAN[145].

A PMB derivative (**136**) was synthesised as part of this project, however the 3,4,5-trimethoxy version (**140**) had also been synthesised in a decent quantity. CAN is a known single electron oxidant[146], and is often used in the removal of PMB protecting groups. It was hoped that the presence of the extra methoxy groups on the ring could stabilise the resultant radical and make it easier to affect the removal of the group. So **140** was chosen to test removal conditions.

2 sets of conditions were trialled. (**Scheme 5.04**)

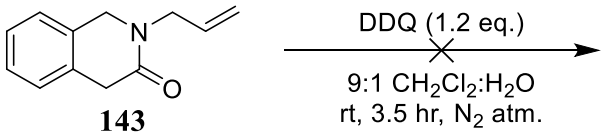


140

Scheme 5.04

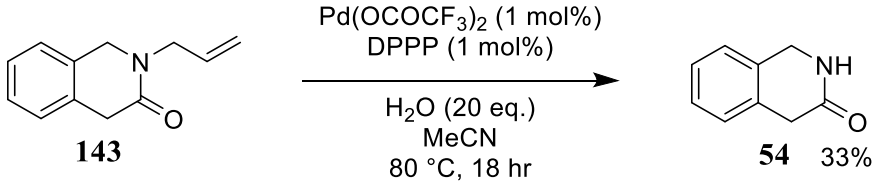
Neither strong acid (in this case Trifluoroacetic anhydride (TFAA)) nor CAN were successful in removing the sidechain. Starting material **140** was recovered from both reactions completely untouched.

After this failure, the potential of another compound from the library was explored. Compound **143** contained an allyl group. Though more commonly used as alcohol protecting groups, allyl chains are nonetheless well-known protecting groups.[137] Kumar *et al.*[147] had had success with the removal of the allyl group from amines using DDQ, and so the conditions used were attempted here. (**Scheme 5.05**)



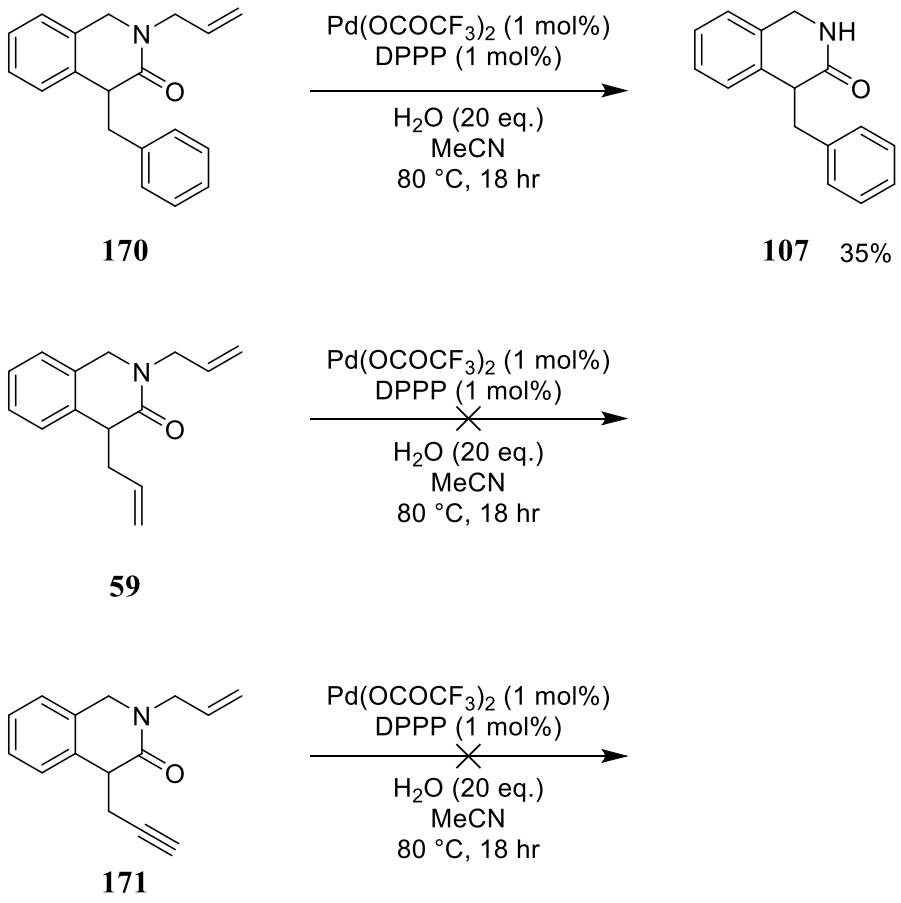
Scheme 5.05

The reaction was monitored by TLC and after 3.5 hours, the spot representing **143** was judged to have disappeared and thus the reaction was deemed complete. This was a false positive however, as the reaction had failed to progress at all and **143** was recovered from the reaction mixture. The chemistry was developed for an allyl amine species as opposed to the allyl amide present here. Tokunaga *et al.*[148] developed Pd catalysed methods for the de-allylation of amides. The conditions had been shown to work on lactam species and so these conditions were attempted next. (**Scheme 5.06**)



Scheme 5.06

This resulted in a 33% yield of **54**, which was low but at least showed some success. The de-allylation conditions were then trialled on various alkylated substrates of **143** to see if the chemistry could be applied across multiple compounds. (**Scheme 5.07**)



Scheme 5.07

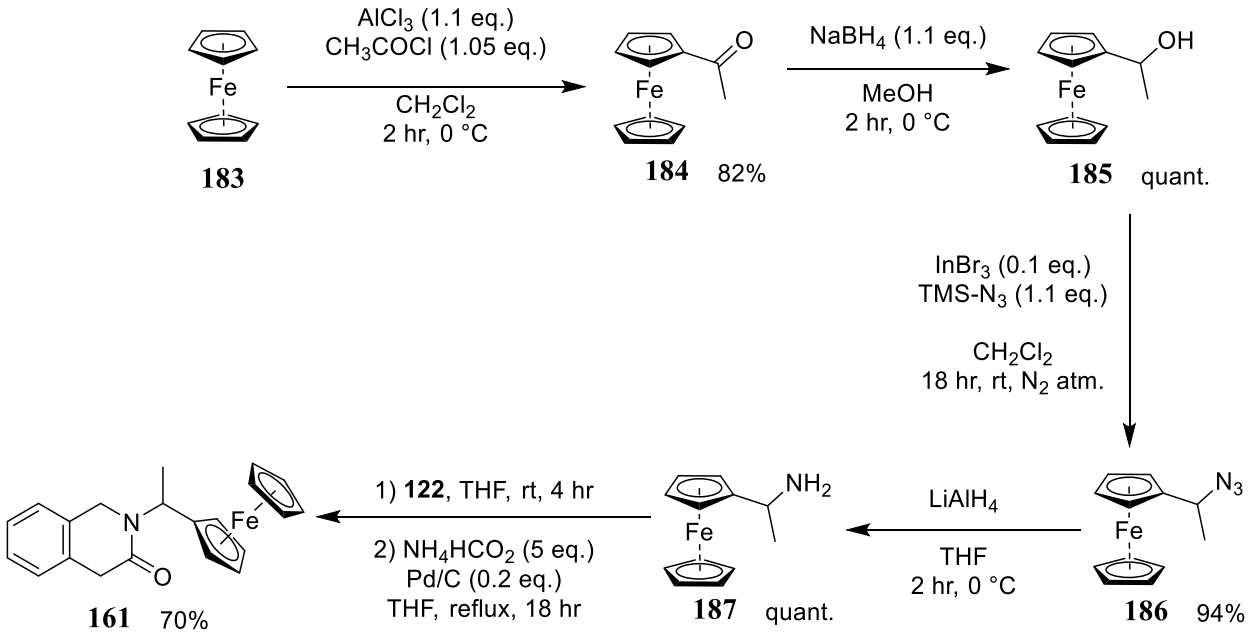
The reaction was successful on the benzylated compound **170** to almost the same degree as it had been on the base material **143**. This result didn't come without difficulty however, as it took multiple rounds of purification to finally isolate the compound. When the α-carbonyl substituent was altered, things got worse. The LCMS traces of both the failed reactions appeared to show the presence of the de-allylated products in their respective crude mixtures, but no amount of purification managed to isolate any product. The chemistry was deemed not useful for the purposes of this project at this stage as it could not achieve reliable results.

The failure of this chemistry led to the development of a ferrocene based protecting group.

5.2.2 Protecting group - Synthesis of 161

The synthetic route to amine **187** and its' subsequent transformation into compound **160** is shown in **Scheme 5.08** below. The first step was a simple acylation of ferrocene (**183**) to generate

acetylferrocene (**184**) in a high yield. This then underwent a straightforward sodium borohydride reduction to the alcohol **185** in a quantitative yield. Using chemistry developed by Cozzi *et al*.[149] the nucleophilic substitution of the alcohol was achieved *via* indium catalysis, generating the azide **186**. This step proceeds *via* the ferrocene cation (**176**) and should therefore go with retention of stereochemistry if the starting alcohol is a single enantiomer. Finally, $LiAlH_4$ was used to reduce the azide to form the amine species **187** which is analogous to Ugi's amine. The benefit of this compound is that it effectively replaces the phenyl group from α-methylbenzylamine with a ferrocene group, and so the chemistry developed to achieve the reductive amination of the α-methylbenzylamine derived imine, should also apply to **187**. This indeed proved to be the case, as the cyclised product **161** was successfully generated in a 70% yield using the previously developed chemistry from Chapter 4.



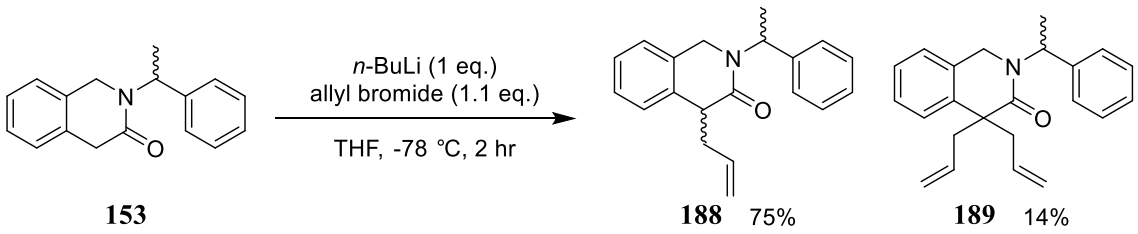
Scheme 5.08

The successful synthesis of **161** generated two avenues of exploration. The first; removal of the ferrocenyl group to begin generating new structures. The second: using the ferrocene as a type of chiral auxiliary to direct stereoselectivity when adding groups to other parts of the molecule.

5.3 Stereoselectivity

If stereoselectivity was going to be explored, the obvious choice based on the work developed thus far, was to try and affect the stereoselectivity of the alkylation step developed in the previous chapter. The ideal candidate to use as a baseline for this was the α-methylbenzylamine derived species **153**, as it had a simple stereogenic centre in place that could serve as a good baseline for further comparison when increasing the complexity of the sidechain.

The test for this was very simple, as a **153** had been synthesised as a racemate and in a large quantity. (**Scheme 5.09**)



153 **188** 75% **189** 14%

Scheme 5.09

While some di-addition product (**189**) was observed, the major product was the mono-addition product **188**. Of a potential of 4, the formation of 2 diastereomers of **188** were observed as the major product of the reaction. This is unsurprising, as a racemic mixture of enantiomers were generated in each case. The enantiomers will appear as a single species in the NMR, resulting in the appearance of what appear to be 2 separate species that are actually 2 sets of racemates. The enantiomers were easily distinguished in the ^{1}H NMR spectrum as the methyl peak appeared in different places in the spectrum; in this case, at 1.60 and 1.54 ppm respectively. (**Figure 5.1**)

When both peaks are integrated and the combined total set to 100, the percentage of each compound present can be elucidated. This is shown in **Figure 5.1** above. The split is 51:49, meaning the reaction can in no way be considered selective. The effect of the stereogenic centre in **153** is negligible when it comes to influencing stereoselectivity at the α-carbonyl position.

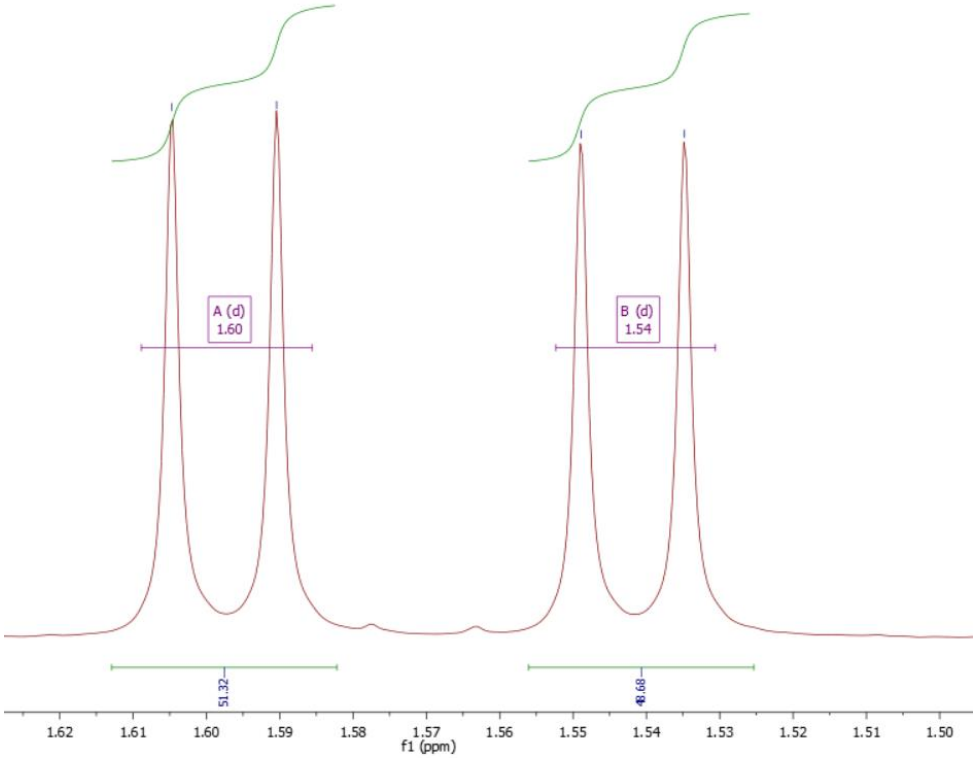
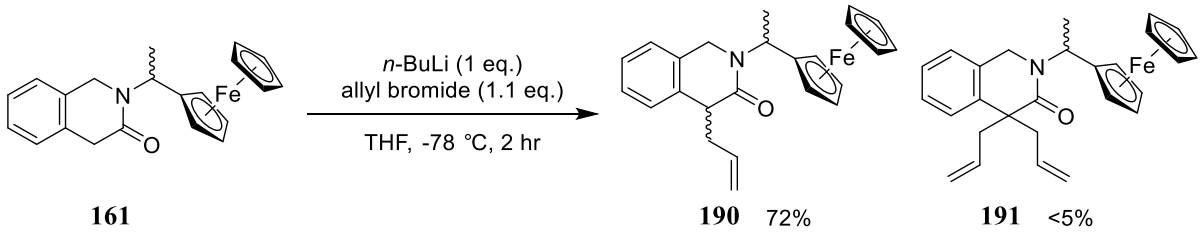


Fig. 5.1 *– ^{1}H NMR spectrum showing CH_3 groups for both diastereomers of* ***188***

This was where the usefulness of the ferrocene derived compound **161** came into full effect. Ferrocene is considerably larger than the simple phenyl ring in **153**. This should mean that if it was possible to direct stereoselectivity at the α-carbonyl position of the molecule using a chiral auxiliary at the *N*-position, **161** should provide some evidence of this effect.

The reaction from **Scheme 5.09** was repeated using **161** as the starting material. (**Scheme 5.10**)



161 **190** 72% **191** <5%

Scheme 5.10

A negligible amount of the di-addition product **191** was obtained, while once again the mono-addition product **190** was isolated as a mix of 2 diastereomers. The ^{1}H NMR spectrum showed that

the methyl peaks appeared much closer together this time - at 1.51 and 1.48 ppm respectively – but nonetheless showed that 2 separate diastereomers of **190** were present. (**Figure 5.2**)

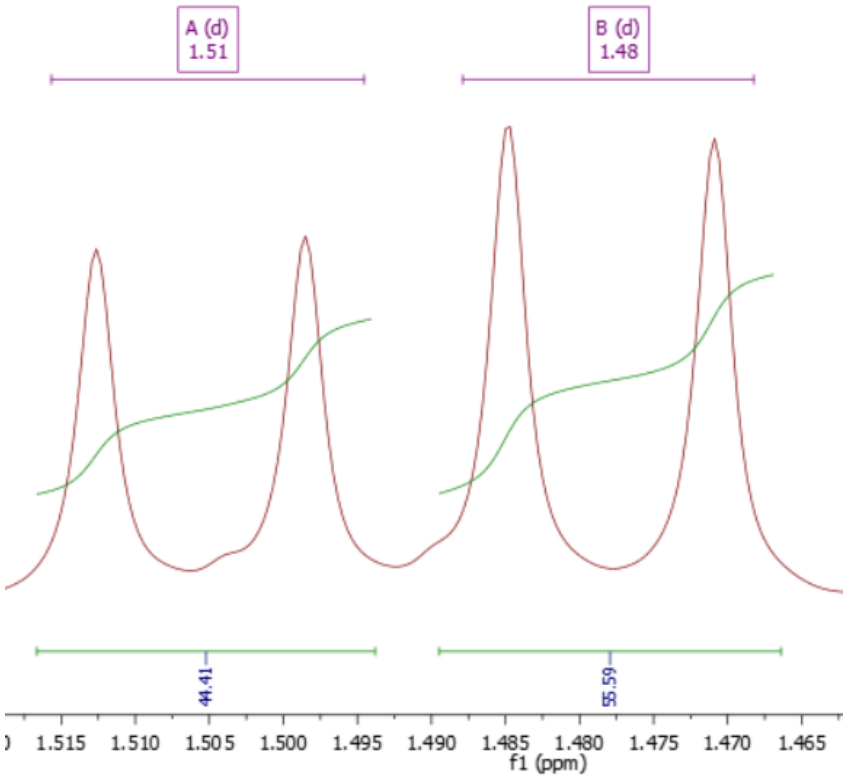


Fig. 5.2 *– ^{1}H NMR spectrum showing CH_3 groups for both diastereomers of* ***190***

As can be seen in **Figure 5.2**, the diastereomers exist in a 56:44 ratio in this case. This was disappointing, as it is too small of a difference to be of any demonstrable significance. Clearly the ferrocene derived **161** was simply not capable of significantly affecting stereoselectivity at the bottom position of the ring system.

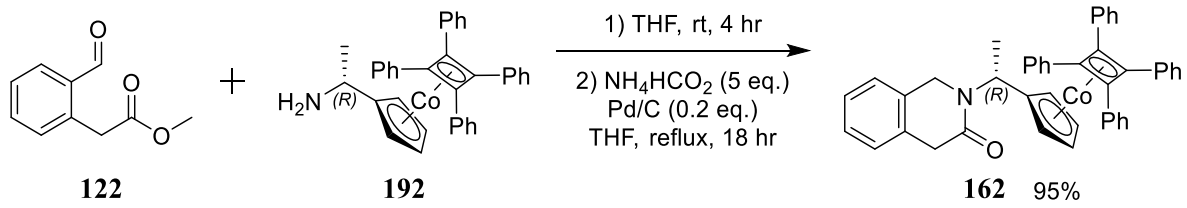
To ensure this wasn't a solvent issue, the reaction was repeated using both **153** and **161**, keeping all conditions the same and swapping the solvent for dry Et_2O. This resulted in no significant change in diastereoselectivity, indicating solvent was not a factor, as had been suspected.

This led to 2 possible conclusions: that the sidechain wasn't large enough to affect the molecule from such a distance away, or that it isn't possible to influence the stereochemistry of these systems in this manner.

To prove that the side-chain size wasn't an issue, a molecule developed by another researcher in the lab was used.[150] The single *R* enantiomer amino cobalt sandwich complex **192**. This molecule was significantly larger than **187** with the cyclcopentadiene ring having been replaced by a tetraphenyl

cyclobutadiene ring, which takes up significantly more space. This massive increase in size should hopefully have the effect of completely "blocking" one side of the molecule from attack by the alkylating agent at the α-carbonyl position, and determine once and for all whether the side-chain size had any impact on the selectivity of the reaction.

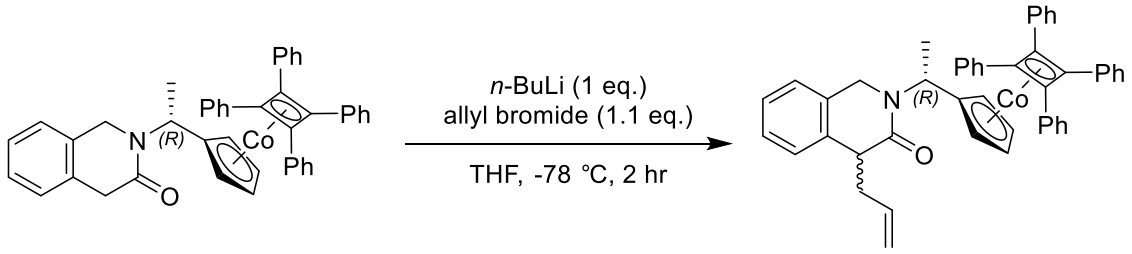
Firstly, the cyclised product had to be formed as before. (**Scheme 5.11**) This reaction was very successful, generating a 95% yield of the product **162**.



122 **192** **162**

Scheme 5.11

Following on from this, the alkylation reaction was repeated as before. (**Scheme 5.12**)



162 **193**

Scheme 5.12

Once again, ^{1}H NMR spectroscopy allowed for the differentiation of different diastereomers, using the methyl peaks at 0.85 ppm and 0.79 ppm as reference points. (**Figure 5.3**) This analysis showed a 55:45 mix of diastereomers.

This lack of improvement in the diastereomeric ratio despite the massive increase in side-chain size indicated that it was going to be impossible to use the sidechain as a chiral auxiliary in this manner.

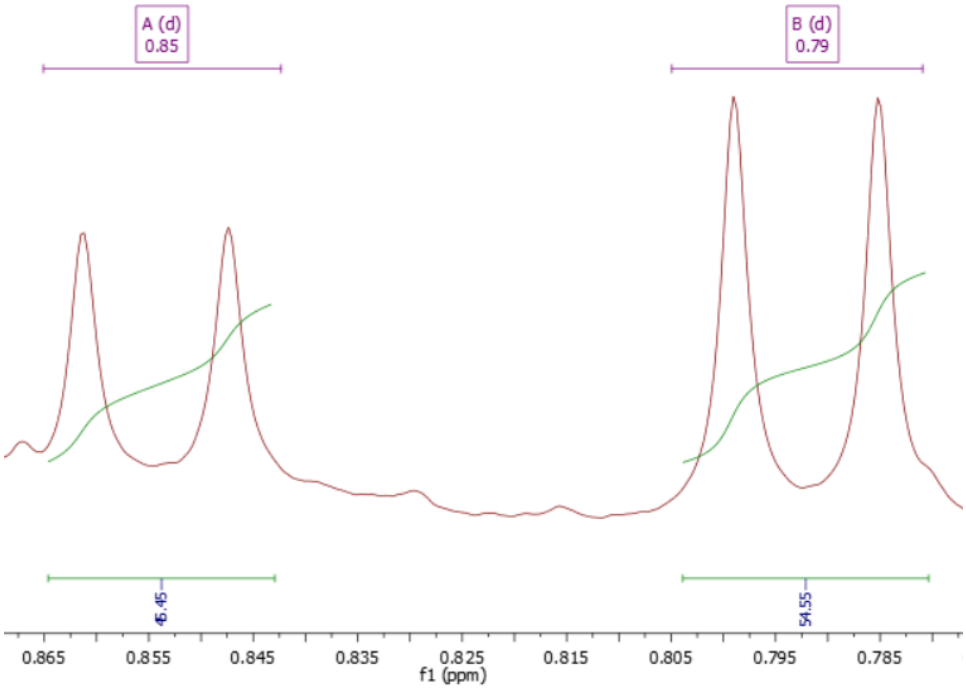


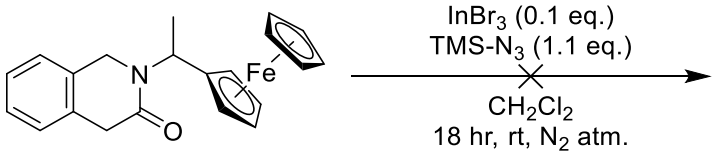
Fig. 5.3 *– ^{1}H NMR spectrum showing CH_3 groups for both diastereomers of* ***193***

There was still the possible utility of **187** as a protecting group to consider, however. Protecting groups need a method of removal, and so methods of removing the ferrocene moiety were investigated.

5.4 Protecting group removal

Though, like trityl protecting groups, the ferrocenyl group should be easily removable using acid,[137] initially it was decided that the chemistry employed in the developed of the ferrocenyl side chain could be reused to potentially regenerate an intermediate in the process (specifically, intermediate **186**). This would allow for material to be recovered and put back into the synthesis of the starting material at a later point, further expanding the potential of this chemistry by increasing its atom economy. In this case, the indium chemistry developed by Cozzi *et al.*[149] was employed. (**Scheme 5.13**) Instead of an alcohol, the leaving group would be the tetrahydroisoquinolinone ring instead.

This would also allow the regeneration of the ferrocenyl azide **186**, which could easily be recycled to be used as a protecting group once more.



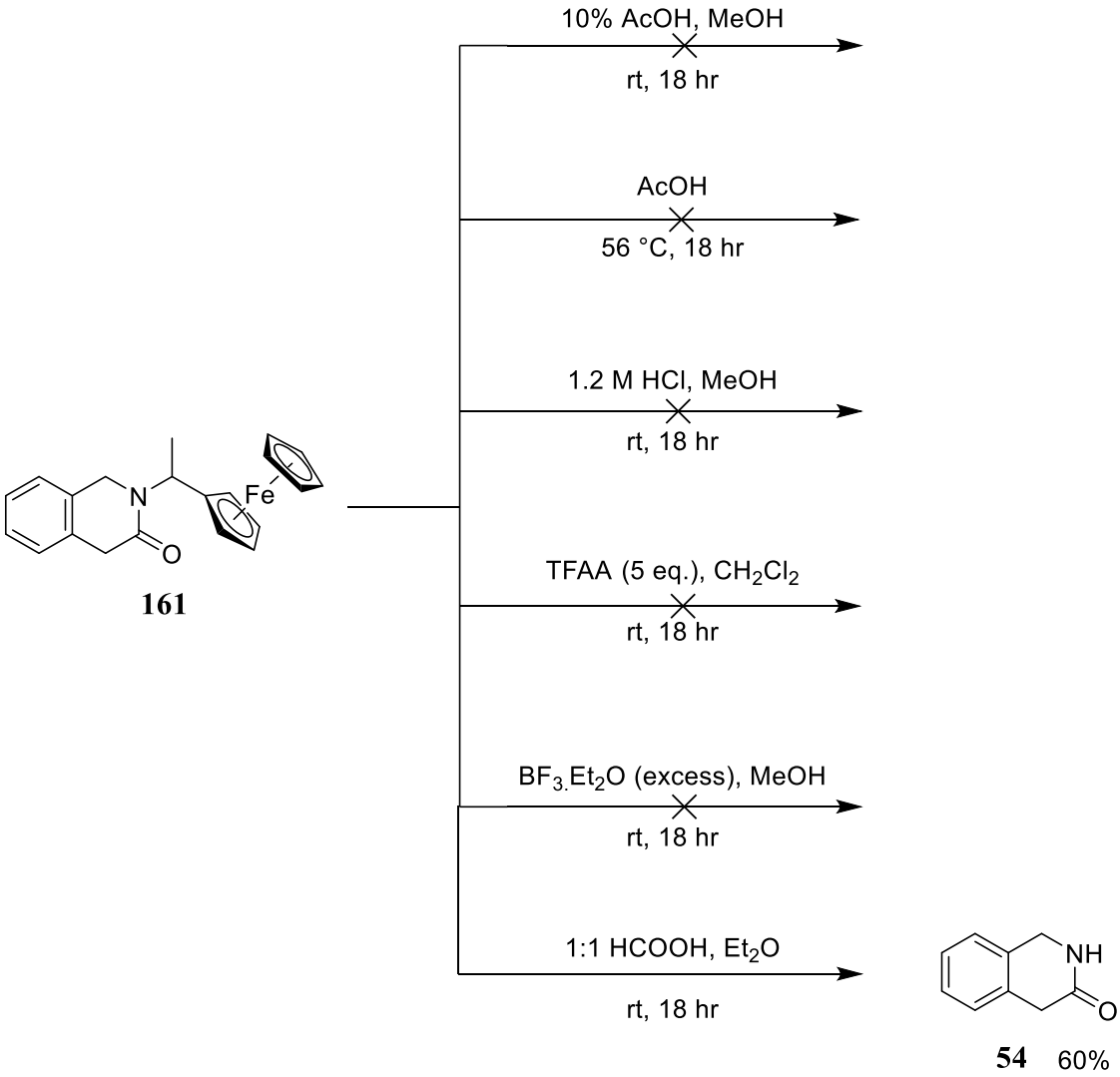
161

Scheme 5.13

This proved to be a failure, with the starting material **161** being recovered untouched from the reaction mixture. It appeared that the tetrahydroisoquinolinone ring was not a good enough leaving group for the chemistry to function. This is perhaps unsurprising, given that the only leaving group employed for this chemistry in the paper on which it was based was an OH group. In fact, indium was chosen to catalyse this reaction specifically because it worked on ferrocenes with an OH group by acting as a Lewis acid and coordinating to the OH group to make it a good leaving group.[151–153] While the same principle applies here as the oxygen in the lactam ring should be susceptible to coordination, it seemed that $InBr_3$ was not a strong enough Lewis acid to achieve the desired result in this case.

Thus, the standard acidic methods of trityl group removal were trialled. (**Scheme 5.14**)

As shown in **Scheme 5.14**, various acids were used, including a Lewis acid in the form of $BF_3.Et_2O$. In the end, the only successful set of conditions were the use of 1:1 formic acid in Et_2O, which resulted in a 60% isolated yield of the product **54**. Comparison of the ^1H NMR to the product of **Scheme 3.32** earlier in the thesis confirmed the product had formed.



161

54 60%

Scheme 5.14

Interestingly but perhaps unsurprisingly, comparison to the ^{1}H NMR spectrum of **54** showed that the NH peak had moved quite a significant distance (from 7.34 ppm in the original to 6.49 ppm in the new product). It was theorised that this was likely an issue of the chemicals' overall environment but, to be absolutely certain, the new sample was spiked with some of the original pure sample and ^{1}H NMR analysis performed once again. Sure enough, the NH peak moved from 6.49 ppm to 6.59 ppm when the sample was spiked with pure material, indicating that the NH proton would show up at different positions depending on factors such as sample concentration etc. (**Figure 5.4**)

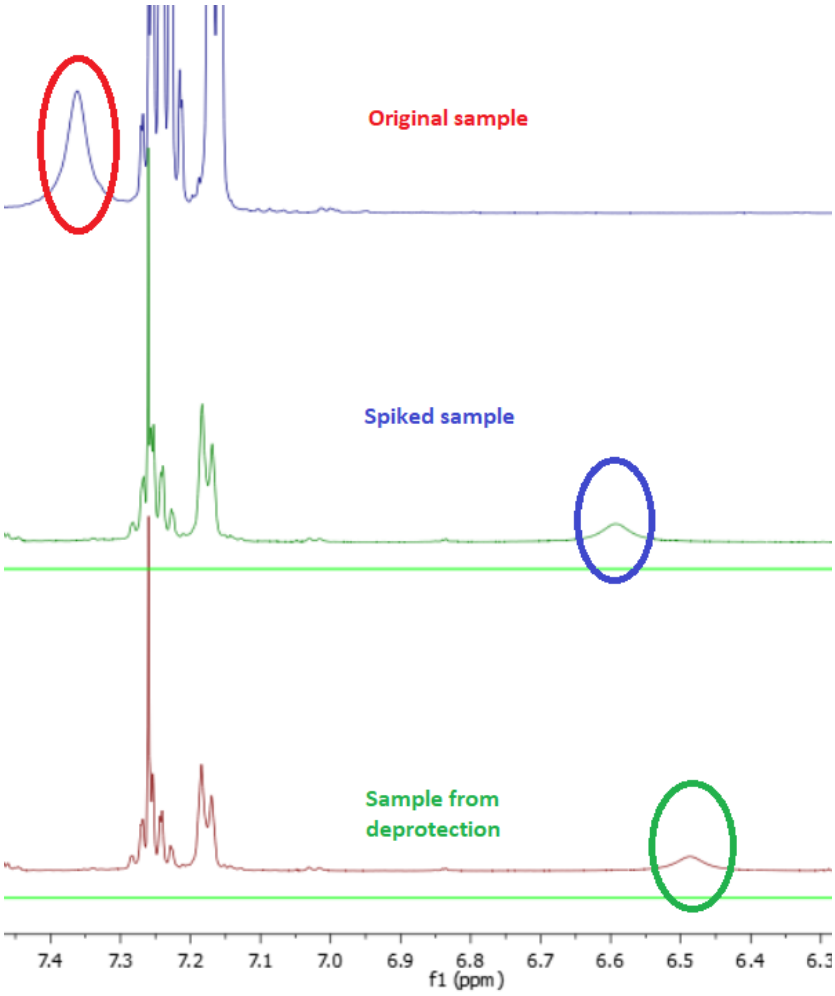
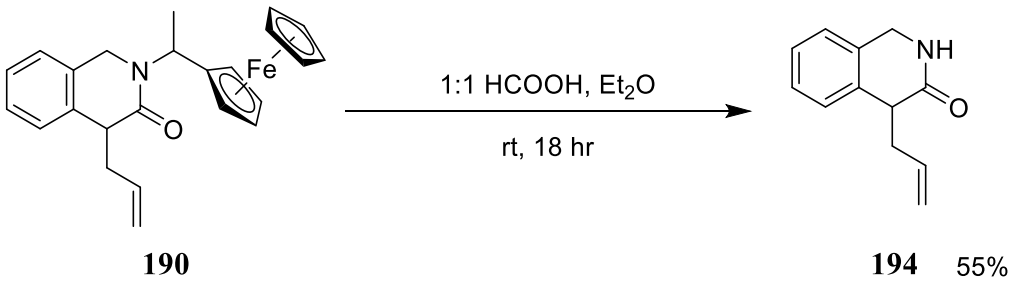


Fig. 5.4 *– Comparison of NH position in* ^{1}H *spectra of* ***54***

Knowing the conditions required for the removal of the ferrocenyl sidechain, the removal was attempted on an already allylated form of the compound, **190**. Under the same conditions as before, the deprotected form **194** was recovered in a 55% yield. (**Scheme 5.15**)

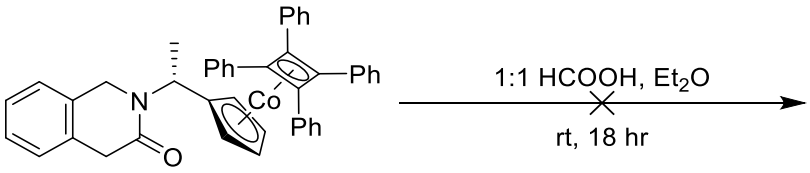


190 **194** 55%

Scheme 5.15

The appearance of a broad singlet peak at 6.41 ppm in the ^{1}H NMR spectrum indicated the presence of a free NH, and subsequent HRMS analysis also confirmed that the product had formed ($M+H^{+}$ = 188.1069)

As a final step, the removal conditions were trialled on the cobalt sandwich complex **162**. (**Scheme 5.16**) The reaction was unsuccessful, with the starting material remaining completely untouched by the reaction conditions. This was surprising, as it had been previously shown that cobalt sandwich complexes of this type readily stabilise carbocations[150] and so should be susceptible to removal under acidic conditions.



162

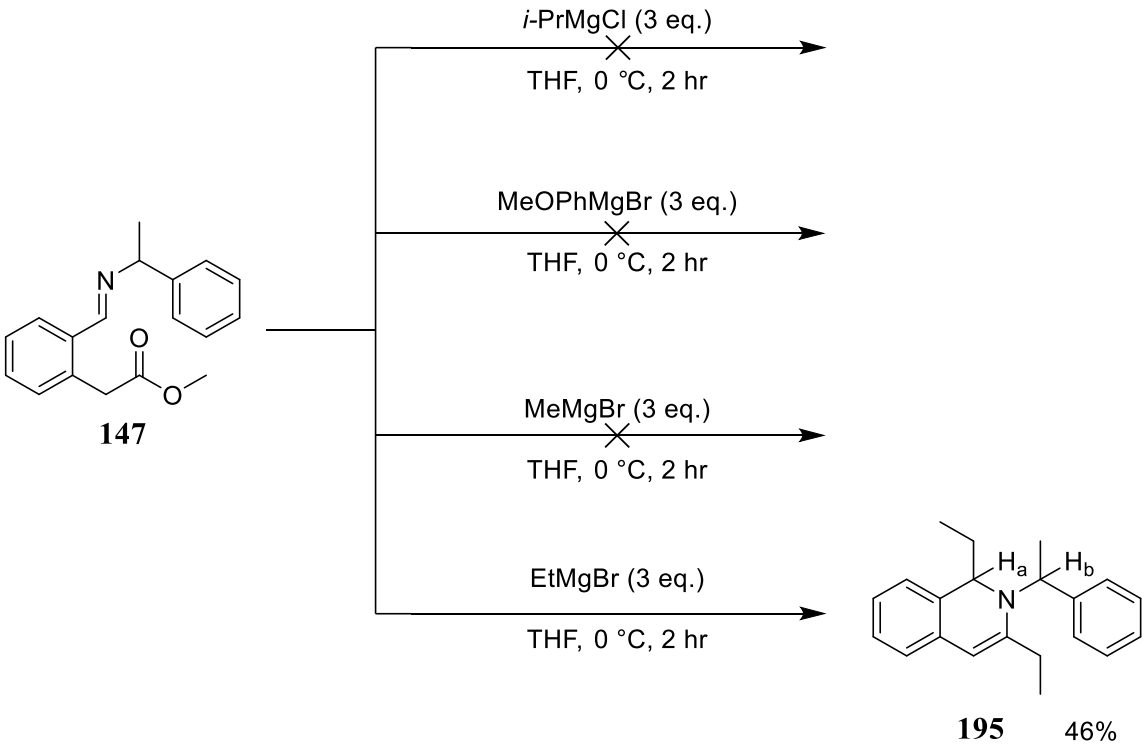
Scheme 5.16

While this chemistry successfully led to the discovery of a functioning protecting group for the tetrahydroisoquinolinone series in the form of a ferrocenyl derived side-chain that could be easily removed under acidic conditions, any hopes that the same group could be used as a chiral auxiliary were dashed by the results. Even upon massively increasing the size of the sidechain to an bulky cobalt sandwich complex, there was little to no influence on the selectivity of alkylation chemistry at the diastereotopic α-carbonyl position. However, this chemistry was not without its successes. This project has succeeded in developing a simple route to a wide series of varied tetrahydroisoquinolinones; and developed a simple methodology for their subsequent modification along with the development of a useful protecting group for the series.

5.5 Grignard chemistry – Addition to imine

From here, the chemistry returned to the tetrahydroisoquinolinone synthesis, with the addition of a Grignard reagent to the imine being explored. Imine **147** was chosen as the base molecule for this investigation once again, as it was both chemically simple and contained a stereogenic centre. This would help in quickly proving whether Grignard reagents had any utility in this area.

Initially, imine **147** was reacted with 4 varied Grignard reagents that were readily available in the lab. (**Scheme 5.17**)



Scheme 5.17

This led to an unexpected discovery. The majority of the Grignard reagents attempted failed to produce any reaction, and the starting imine **147** was hydrolysed back into aldehyde **122** by the aqueous workup. In the case of ethyl magnesium bromide however, the addition reaction did indeed take place. The product that came from this reaction was unexpected and required a bit of investigation to assign the structure of the molecule as being compound **195**.

There were 3 separate CH_3 groups present in the ^1H NMR spectrum as well as a singlet appearing in the region of the spectrum where an alkene would be expected, along with two separate CH_2 groups. This led to the conclusion that the ethyl Grignard had attacked the molecule twice, with the second

addition likely to be at the carbonyl. The elimination of water thereafter would generate the alkene to give the final structure **195**.

The singlet at 5.55 ppm is indicative of the alkene proton while the doublet of doublets at 4.02 ppm represents the proton labelled H_a in **Scheme 5.17** above. The fact that this proton is a doublet of doublets indicates that the adjacent protons, in this case the ethyl CH_2 protons, are diastereotopic, as the signal would otherwise be a triplet. Diastereomers are different molecules, and the lack of any other observable molecule in the ^1H NMR spectrum with a similar splitting pattern indicates that a single diastereomer has been formed. (**Figure 5.5**)

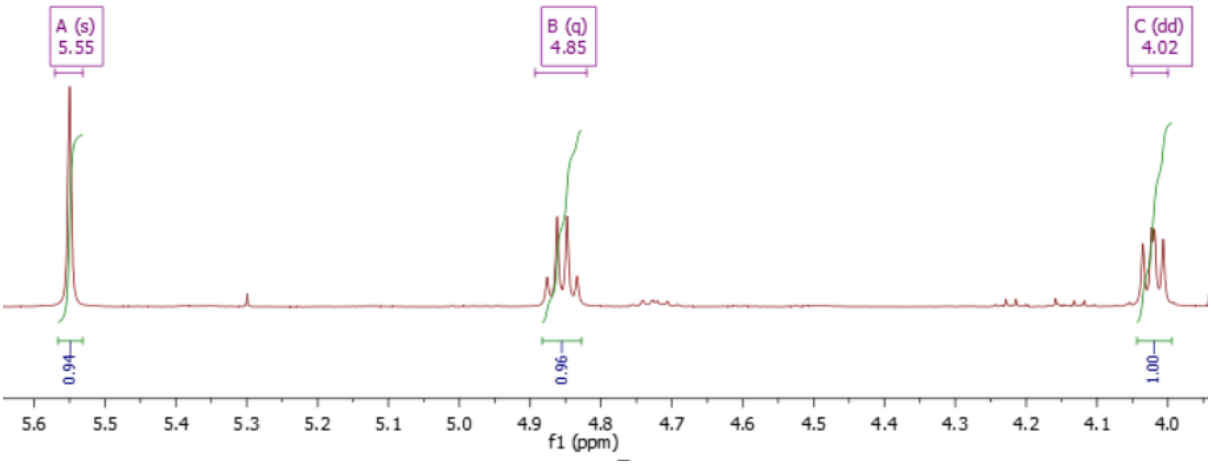
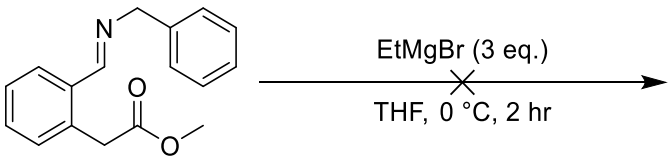


Fig 5.5** – ^1H NMR spectrum of **195

Buoyed by this unexpected success, the next step was to see if the removal of the stereogenic centre from the imine - by use of the simpler benzylamine derived imine **196 -** would be successful. (**Scheme 5.18**)

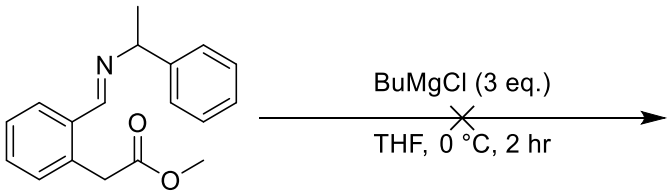


196

Scheme 5.18

Surprisingly, this reaction was an abject failure. The only identifiable product recovered from the reaction mixture was the hydrolysed aldehyde **122**. The molecule appeared to have otherwise been destroyed by the reaction conditions. Even when reducing the amount of Grignard used to a single equivalent, the imine either failed to react or was destroyed by the reaction conditions. On reflection, this was perhaps unsurprising given that there has been so much difficulty in attempting this type of reaction in the past.[141]

The reaction was reattempted on imine **147**, this time using butylmagnesium chloride as the Grignard reagent. (**Scheme 5.19**)

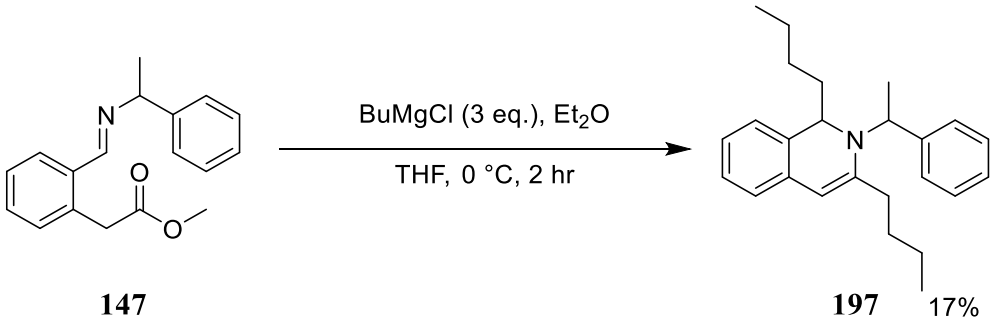


147

Scheme 5.19

This reaction failed to produce any cyclised product. There were only 2 major differences between this reaction and the ethyl Grignard reaction (besides the active reagent); that the Grignard in question was the magnesium chloride species instead of the bromide, and that the ethyl Grignard was added as a solution in Et_2O (3M) while the butyl was in THF (2M).

To test whether solvent was a factor, the butyl Grignard reaction was repeated. However, this time a volume of Et_2O was added. (**Scheme 5.20**) The ratio of Et_2O to THF in the original ethyl Grignard reaction was calculated and the volume of Et_2O added to the butyl Grignard reaction was calculated to match. This meant that the solvent concentrations were the same, ensuring that the only variable was the Grignard added.



Scheme 5.20

This resulted in the successful production of compound **197**, once again as a single diastereomer as indicated in part, by the appearance of a single doublet of doublets at 4.11 ppm in the ^{1}H NMR spectrum. (**Figure 5.6**) The appearance of a singlet in the alkene region (5.55 ppm) and the presence of 3 methyl groups also helped to confirm that the product **197** had formed.

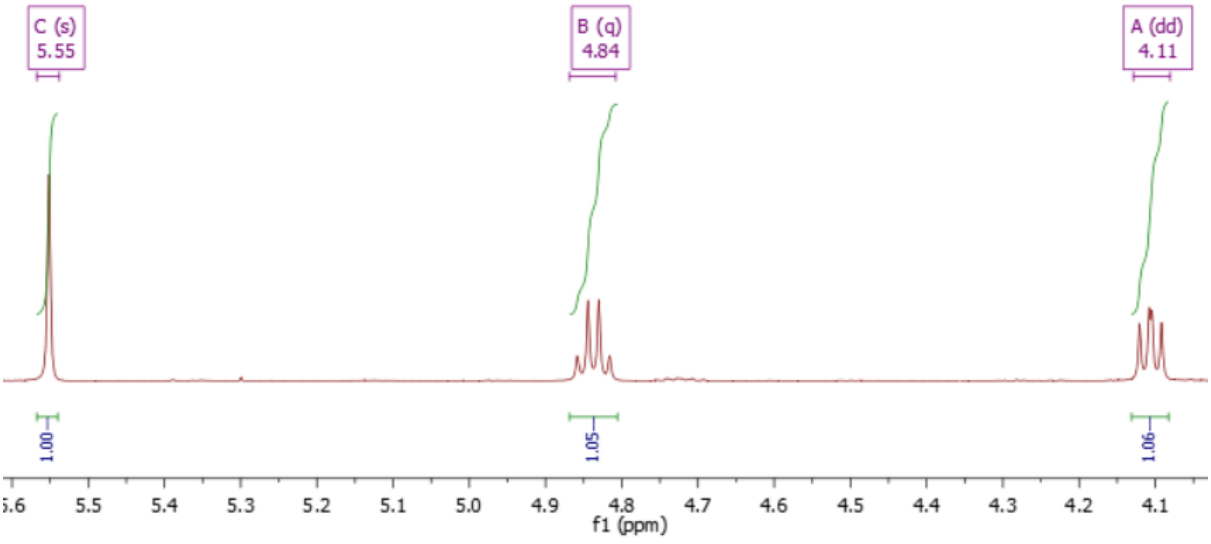
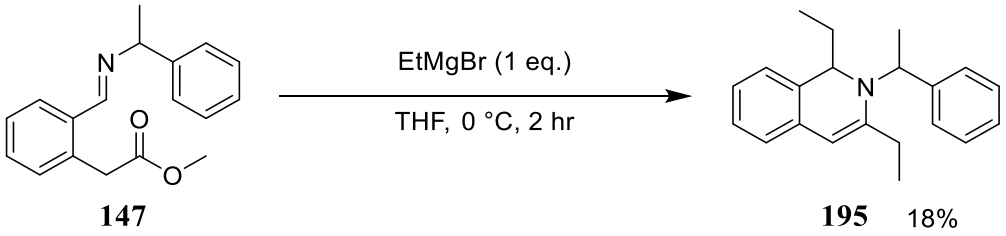


Fig 5.6** – ^{1}H NMR spectrum of **197

The fact that the Grignard reagent attacked twice indicated that there was more going on with the reaction mechanism that had initially been anticipated. The equivalents of Grignard used were reduced to 1 eq. in order to determine whether the excess Grignard reagent was causing the over-alkylation. (**Scheme 5.21**)



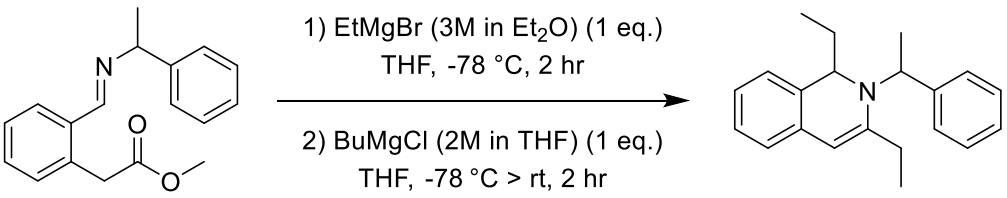
147 **195** 18%

Scheme 5.21

The reaction exclusively produced the di-addition product **195**, while any leftover imine was hydrolysed to the aldehyde as a result of the workup. This was taken to indicate that the di-addition product was the preferred product of the reaction.

It was thought that by reducing the temperature, the reaction could be slowed enough to the point where perhaps one addition would take place but the second would not. By introducing a second Grignard reagent at this point and allowing the reaction to come up to room temperature slowly, analysing the final product produced would allow for the elucidation of the reactions order of events. If ethyl Grignard was used initially, the position at which the ethyl Grignard was incorporated could be deemed the initial point of reaction, and therefore help to figure out the mechanism of the reaction.

Ethyl Grignard and butyl Grignard were used for this reaction as there was confidence in the ability of both to function under these conditions. Additionally, the ethyl Grignard being a solution in Et_2O meant that there should be no need to add Et_2O to the reaction to assist in the butyl Grignard reaction, as it would have already been introduced. (**Scheme 5.22**)

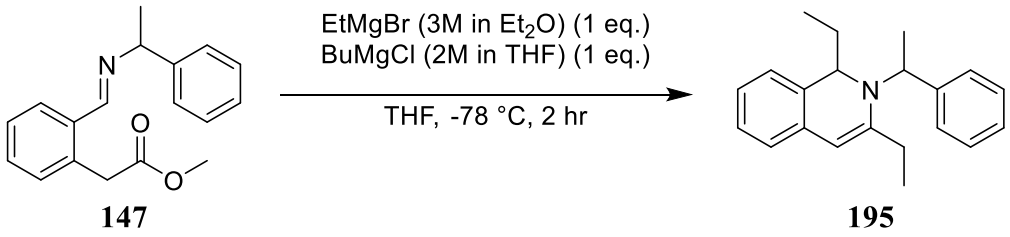


147 **195**

Scheme 5.22

Analysis of the crude ^{1}H NMR spectrum showed that the only product formed in the reaction was the di-ethyl product **195**, with no sign of any butyl incorporation.

Following this, the ethyl and butyl Grignard reagents were added at the same time at -78 °C. If the reagents could be forced to compete with one another, perhaps a different result would be observed that could shed some light on the reaction. Once again however, analysis of the crude ^{1}H NMR spectrum showed only the di-ethyl product **195** had formed in the reaction mixture. (**Scheme 5.23**)

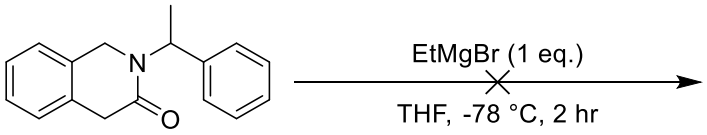


147 **195**

Scheme 5.23

From this, it was concluded that the second addition to the molecule is incredibly fast and that the ethyl is clearly more reactive than the butyl Grignard reagent. The fact that ethyl Grignard is incorporated into both positions without any sign of butyl incorporation indicates that once the initial Grignard addition occurs, the second addition and subsequent cyclisation reaction is even faster than the initial reaction. Ethyl Grignard being more reactive means that it is the preferred reaction partner for this step, and so the diethyl species is formed incredibly quickly, using up all of the ethyl Grignard present in the reaction before the butyl even has a chance to react. There could also be alternative explanations: the reactivity of the Grignards in their various solvents, aggregation of compounds etc. but there wasn't enough time available to fully explore these possibilities.

Finally, the already cyclised tetrahydroisoquinolinone product **153** was subjected to the Grignard conditions. This would help to elucidate whether the addition of the Grignard to the carbonyl occurred after the cyclisation step or before it. (**Scheme 5.24**) If the Grignard addition occurred at the imine position first, the cyclisation reaction should occur as normal and the second addition would be to the carbonyl position of the cyclised lactam. This meant that if the Grignard attacked the carbonyl position of an already cyclised compound, it could be posited that the imine was the point of initial attack.



153

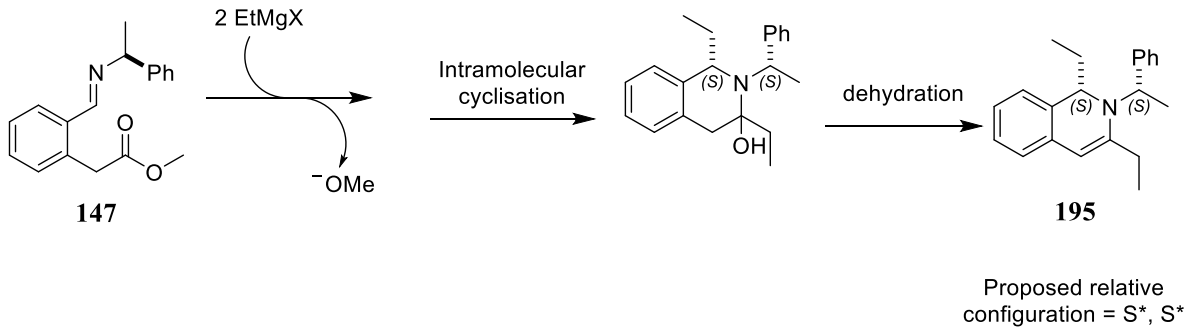
Scheme 5.24

Unsurprisingly, this reaction failed completely. This was taken as proof that the addition to the carbonyl took place before the cyclisation had occurred, and given the already known difficulties associated with the addition of Grignard reagents to imine species[139,140], it was highly likely that the Grignard attacked the carbonyl position first.

Taken as a whole, these results led to the development of a working theory as to how this reaction was progressing.

The general reactivity of imines versus esters when it comes to Grignard reactions, would indicate that the first step of the reaction is the attack of the Grignard into the ester group, resulting in a ketone. Given that previous work has indicated that a catalyst of some sort is necessary[139–141] for the addition of a Grignard to an imine, and the general lack of difficulty with that process here, it would seem likely that a magnesium salt is acting as a sort of Lewis acid for the reaction, likely chelating to both the keto oxygen and the imino nitrogen.

This would also help to explain the reactions diastereoselectivity. By chelating to the nitrogen and oxygen, the magnesium could lock the conformation of the molecule. This would result in Grignard addition to the imine to occur on the less sterically hindered side of the molecule (as dictated by the auxiliary, where the smallest group (hydrogen) is pointing towards the coordinated magnesium). Once the addition occurred, the amine produced could perform the cyclisation. Following this, a dehydration would produce the alkene and result in the final product being generated as a single diastereomer. (**Scheme 5.25**) The production of an equivalent of water through this method could also help to explain the complete lack of any reaction of the butyl Grignard once the ethyl Grignard had already been introduced, as this would undoubtedly hydrolyse any Grignard reagent it came into contact with.



Scheme 5.25

Conclusion

Throughout this chapter, the idea of stereoselective additions to the core tetrahydroisoquinolinone structure was explored. Several strategies were investigated, from using a chiral auxiliary attached through the amino position, through to using Grignard additions to affect stereoselective addition to the imine.

Though many of the discoveries related to the Grignard chemistry were made in the closing days of the project (and thus are somewhat lacking in absolute evidence), a plausible hypothesis has been put forward for how the cyclisation of the imino-ester starting products occurs in the presence of a Grignard reagent, resulting in a single diastereomeric product.

All in all, while not perfect, the results obtained in this chapter point to the conclusion that it is possible to further derivatise the tetrahydroisoquinolinone structure in a stereoselective manner (albeit only in specific positions) and this work has also succeeded in developing an easily removal protecting group that could be used to generated secondary amide structures. All of this proves that the chemistry developed throughout this thesis is versatile and resilient, with industry-wide applications as it provides simple and controllable access to a vast array of compounds that were previously quite difficult to synthesis effectively.

Final conclusions

Though the project initially aimed to build a large “toolbox” of compounds across a varied set of core structures, ultimately this wasn’t what the project achieved. As detailed throughout this thesis, numerous challenges and difficulties meant that in the end, only two of the six initial proposed cores

were synthesised to completion. Of these two, only one was telescoped to the development of a significant compound library.

Early chapters explore the many and varied approaches that were taken in an attempt to synthesise the target molecules. While the majority of these routes ended in failure, what was discovered throughout the process was evidence as to why the core structures proposed at the beginning of the project were worth pursuing in the first place. If a strong and robust methodology to develop a library of compounds based on any of the core structures could be achieved, this would be a significant contribution to chemistry, as it would allow synthetic chemists everywhere access to a group of compounds that were previously incredibly difficult to reliably synthesise without very specialised equipment or chemical reagents.

In the case of the dihydroisoquinolinone series, one such strong and robust methodology was indeed developed, leading to the synthesis of a diverse array of more than 30 compounds. The methodology developed is straightforward and makes use of standard laboratory reagents. This means the work should be repeatable in any synthetic chemistry lab, regardless of access to equipment and materials. This was a major success, and justified the effort put into its development, regardless of the lack of results with other targets. Not only that, but significant barriers to the series' usefulness (i.e. the inability of sodium borohydride to reduce certain types of imines in the series) were overcome, ultimately strengthening the overall method.

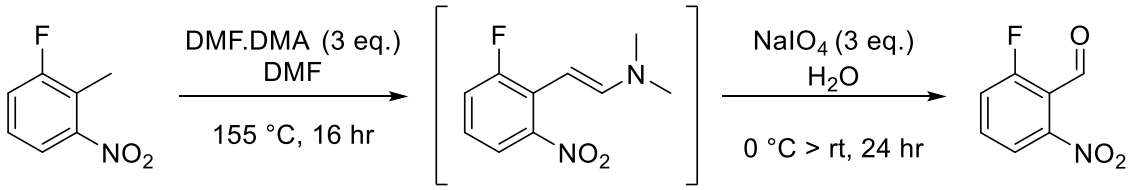
While a new route was indeed developed, significant exploratory work was also performed in developing methods for introducing chirality into the products of this methodology. Though the use of chiral auxiliaries was ultimately unsuccessful, later success with the use of Grignard reagents showed that it may indeed be possible to develop methodologies to produce single enantiomers, or even diastereomers, of compounds based on the dihydroisoquinolinone scaffold.

To conclude, while this project may not have achieved the goals that it initially aimed for; what was achieved instead was the development of a powerful methodology to synthesise a group of heterocycles that could be of great used to synthetic chemists the world over. The project also laid the groundwork for future projects to look at introducing chirality into this series, and in doing so, greatly expand the possibilities of what could be achieved with this chemistry.

Experimental

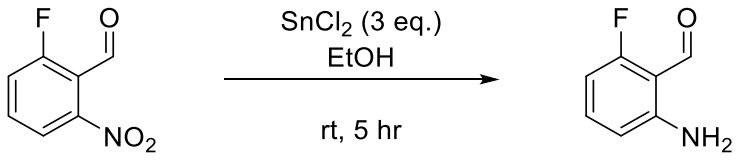
All commercial compounds were used as provided. All ^{1}H NMR and ^{13}C NMR spectra were recorded on 400 MHz or 500 MHz Bruker NMR machines. Chemical shift values are expressed in δ units relative to tetramethylsilane (TMS) signal as internal reference in d_6-DMSO or $CDCl_3$. IR spectra were recorded neat or as KBr disc. All solvents were purchased from commercial sources and used without further purification. Wherever necessary the solvents were dried by standard literature procedures. Silica gel (60 Å pore size, 40 - 63 µm technical grade) was used for chromatography. All TLC plates were visualised using $KMnO_4$ as a stain.

*2-Fluoro-6-nitrobenzaldehyde (**14**)*



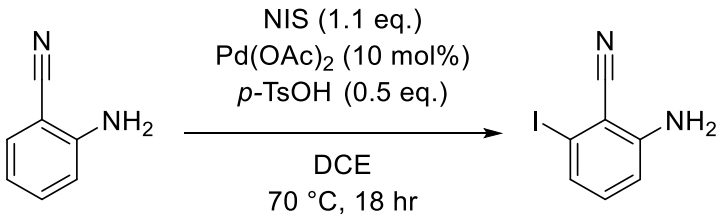
To a flame dried 2 mL microwave tube equipped with a stirrer bar under a nitrogen atmosphere was added 2-fluoro-6-nitrotoluene (100 mg, 0.64 mmol) and *N*,*N*-dimethylformamide (1 mL). To the stirred solution was added dimethylformamide dimethyl acetal (236 mg, 1.98 mmol). The reaction was stirred at 155 °C in an oil bath for 16 hr before being cooled to 0 °C in an ice bath and added to a rapidly stirring solution of sodium metaperiodate (424 mg, 1.98 mmol) in distilled water (2 mL). The reaction was stirred at 0 °C for a further 4 hours before being allowed to warm to room temperature and stirred at room temperature for a further 18 hours. The dark red mixture was filtered over a celite pad and washed with ethyl acetate (10 mL) before being transferred to a 50 mL separating funnel. The organic layer was washed (in order) with brine (3 x 10mL) and distilled water (3 x 10mL), dried over magnesium sulfate, filtered and the solvent removed under reduced pressure to yield **14** as an orange oil (88 mg, 0.52 mmol, 81% yield). ^{1}H NMR analysis consistent with literature values.[154] ^{1}H NMR (500 MHz, Chloroform-d) δ 10.31 (s, 1H, C*H*O), 7.88 (d, *J* = 8.4 Hz, 1H, H^{AR}), 7.69 (td, *J* = 8.4, 5.3 Hz, 1H, H^{AR}), 7.50 (t, *J* = 8.4 Hz, 1H, H^{AR})

*2-Amino-6-fluorobenzaldehyde (**15**)*



To a 20 mL round-bottomed flask equipped with a stirrer bar under air was added 2-fluoro-6-nitrobenzaldehyde (200 mg, 1.2 mmol) and absolute ethanol (3 mL). Anhydrous tin (II) chloride (683 mg, 3.6 mmol) was added and the reaction was stirred at room temperature for several hours. The reaction was monitored by TLC (4:1 petroleum ether (40-60) : ethyl acetate) and upon completion, 1M KOH (2 mL) was added to neutralise and the reaction was stirred at room temperature for 30 minutes. It was then diluted with diethyl ether (10 mL), transferred to a 50 mL separating funnel and washed with distilled water (3 x 10 mL). The organic layer dried over magnesium sulfate, filtered and solvent removed under reduced pressure to yield **15** as a dark red oil (107 mg, 0.8 mmol, 64% yield) ^{1}H NMR analysis consistent with literature values.[155] ^{1}H NMR (500 MHz, Chloroform-d) δ 9.21 (s, 1H, C*H*O), 7.43 (d, *J* = 9.0 Hz, 1H, H^{AR}), 7.28 – 7.23 (ddd, *J* = 9.0, 7.2, 5.0 Hz, 1H, H^{AR}), 6.63 (dd, *J* = 9.0, 7.2 Hz, 1H, H^{AR}).

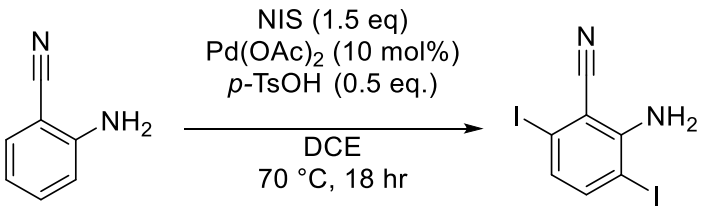
*2-Amino-6-iodobenzonitrile (**23**)*



To a flame dried 5 mL microwave tube equipped with a stirrer bar under a nitrogen atmosphere was added 2-aminobenzonitrile (59 mg, 0.5 mmol), palladium (II) acetate (30 mg, 10 mol%), N-iodosuccinimide (124 mg, 0.6 mmol), p-toluenesulfonic acid monohydrate (48 mg, 0.25 mmol) and 1,2-dichloroethane (2 mL). The reaction was stirred at 70 °C in an oil bath for 18 hours before being diluted with dichloromethane (5 mL) and transferred to a 25 mL separating funnel. The organic layer was washed with saturated sodium bicarbonate solution (5 mL) and distilled water (5 mL) before being dried over magnesium sulfate, filtered and solvent removed under reduced pressure to yield a yellow oil. The oil was purified by column chromatography (4:1 petroleum ether (40-60) : ethyl acetate, R_f = 0.45) to yield a yellow/white solid (53 mg, 0.22 mmol, 43% yield). The compound was then recrystalised from ethanol to yield **23** as yellow crystals (48 mg, 0.2 mmol, 39% yield). Melting

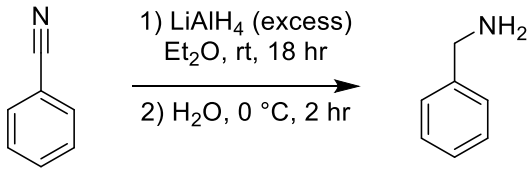
point analysis consistent with literature values. Literature Melting Point 136 – 137 °C.[156] Melting point: 134 – 137 °C. FT-IR (thin film cm^{-1}) 3370, 3459, 2924, 2218, 1485. ^{1}H NMR (500 MHz, Chloroform-d) δ 7.65 (d, *J* = 2.0 Hz, 1H, H^{AR}), 7.56 (dd, *J* = 8.7, 2.0 Hz, 1H, H^{AR}), 6.53 (d, *J* = 8.7 Hz, 1H, H^{AR}), 4.45 (br s, 2H, NH_2). ^{13}C NMR (126 MHz, Chloroform-d) δ 149.2, 142.7, 140.1, 136.7, 117.2, 116.2, 98.5.

*2-Amino-3,6-diiodobenzonitrile (**27**)*



To a flame dried 10 mL microwave tube equipped with a stirrer bar under a nitrogen atmosphere was added 2-aminobenzonitrile (205mg, 2.1 mmol), palladium (II) acetate (141 mg, 10 mol%), N-iodosuccinimide (709 mg, 3.2 mmol), p-toluenesulfonic acid monohydrate (200 mg, 1.1 mmol) and 1,2-dichloroethane (5 mL). The reaction was stirred at 70 °C in an oil bath for 18 hours before being diluted with dichloromethane (10 mL) and transferred to a 50 mL separating funnel. The organic layer was washed with saturated sodium bicarbonate solution (10 mL) and distilled water (10 mL) before being dried over magnesium sulfate, filtered and solvent removed under reduced pressure to yield **27** as a yellow/white solid (387 mg, 76%, 1.6 mmol). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (d, *J* = 1.9 Hz, 1H, H^{AR}), 7.64 (d, *J* = 1.9 Hz, 1H, H^{AR}), 4.93 (br, s, 2H, NH_2). ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.8, 149.0, 140.4, 115.7, 97.0, 84.3, 84.2.

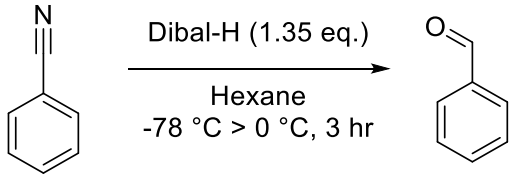
*Benzylamine (**29**)*



To a flame dried 2 mL microwave tube equipped with a stirrer bar under a nitrogen atmosphere was added benzonitrile (50 mg, 0.5 mmol) and diethyl ether (0.5 mL). Cooled to 0 °C in an ice-bath. $LiAlH_4$ (excess) added slowly to the reaction with stirring. Reaction stirred at 0 °C for one hour before being allowed to come up to room temperature. Quenched by the slow addition of distilled

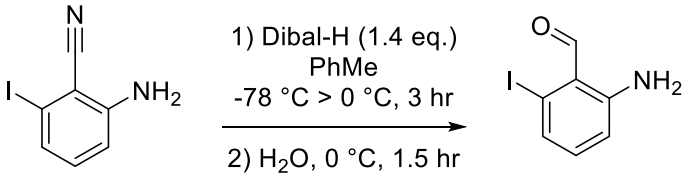
water before being diluted with Et_2O and the organic and aqueous layers separated. Organic layer dried over $MgSO_4$ and the solvent removed. Yielded **29** as an oil. Crude NMR analysis was consistent with literature values.[157] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.29 (m, 5H, H^{AR}), 3.86 (s, 2H, NH_2), 2.23 (s, 2H, CH_2).

*Benzaldehyde (**30**)*



To a flame dried and sealed 2 mL microwave tube equipped with a stirrer bar under a nitrogen atmosphere was added benzonitrile (50 mg, 0.48 mmol) and dry hexane (0.5 mL). The reaction was cooled to -78°C in an acetone/dry ice bath before 1M Dibal-H in hexanes (0.65 mL, 0.65 mmol) was added dropwise *via* syringe with stirring. Once the addition was complete, the reaction was allowed to warm to 0 °C over 3 hours with further stirring. Distilled water (0.2 mL) was then added and the reaction was stirred at 0 °C in an ice bath for 1.5 hours before solid potassium carbonate was added to basify (red litmus paper turned blue). The reaction was then diluted with dichloromethane (5 mL) and transferred to a 25 mL separating funnel. The organic layer was washed with a saturated Rochelle's salt solution (5 mL) and brine (5 mL), extracted and dried over magnesium sulfate. The organic layer was filtered and the solvent was removed under reduced pressure to yield an opaque oil. The oil was purified via silica gel column chromatography (4:1 petroleum ether (40-60) : ethyl acetate, R_f = 0.6) to yield **30** as a clear oil (29 mg, 0.27 mmol, 57% yield) ^{1}H NMR analysis consistent with literature values.[158] ^{1}H NMR (500 MHz, Chloroform-*d*) δ 10.02 (s, 1H, CHO), 7.88 (d, *J* = 7.5 Hz, 2H, H^{AR}), 7.63 (t, *J* = 7.5 Hz, 2H, H^{AR}), 7.53 (t, *J* = 7.1 Hz, 1H, H^{AR}).

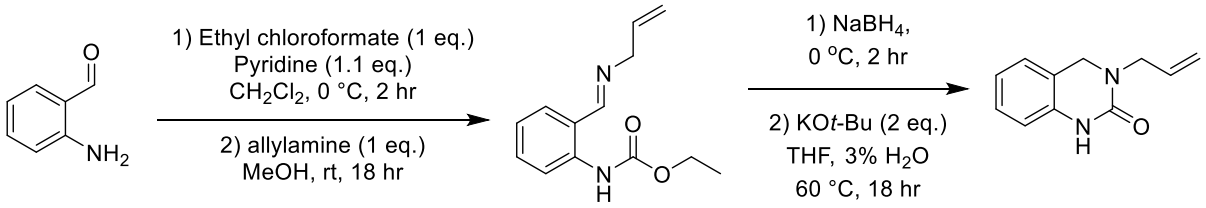
*2-Amino-6-iodobenzaldehyde (**31**)*



To an oven-dried 5mL microwave tube equipped with a stirrer bar under a nitrogen atmosphere was added 2-amino-6-iodobenzonitrile (48 mg, 0.2 mmol) and dry PhMe (0.5 mL). The reaction vessel was sealed and cooled to -78 °C. DIBAL-H (28 µL, 0.3 mmol, 1M in PhMe) was added and the

reaction allowed to warm to 0 °C over 3 hours. After 3 hours, 0.5 mL distilled water was added and the reaction was allowed to stir at 0 °C for a further 1.5 hours. The reaction mixture was diluted with EtOAc and washed with saturated Rochelle's salt solution (5 mL) and brine (5 mL). The organic layer was extracted and dried over $MgSO_4$ before filtering and removing the solvent under reduced pressure. Yielded a yellow oil (36 mg). Purified by silica gel column chromatography (5:1 petroleum ether (40-60) : ethyl acetate, $R_f = 0.39$) to yield **31** as a yellow oil (21 mg, 43%, 0.09 mmol). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.79 (d, *J* = 0.5 Hz, 1H, C*H*O), 7.75 (d, *J* = 2.1 Hz, 1H, H^{AR}), 7.51 (dt, *J* = 17.9, 8.9 Hz, 1H, H^{AR}), 6.47 (d, *J* = 8.7 Hz, 1H, H^{AR}), 6.15 (s, 2H, NH_2).

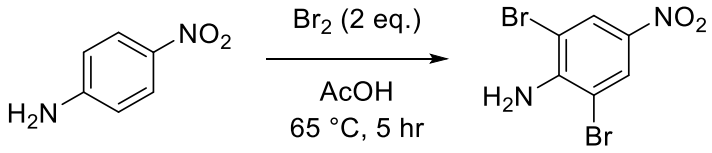
*3-Allyl-3,4-dihydroquinazolin-2(1H)-one (**36**)*



2-Aminobenzaldehyde (100 mg, 0.825 mmol) was dissolved in CH_2Cl_2 (2 mL) and pyridine (0.067 mL, 0.825 mmol) under an N_2 atmosphere in a 5 mL microwave tube. The reaction was cooled to 0 °C in an ice-bath. Ethyl chloroformate (0.079 mL, 0.825 mmol) was added and the reaction vessel sealed and stirred at 0 °C for 2 hr. After 2 hr, the reaction was allowed to warm to room temperature and allylamine (0.074 mL, 0.991 mmol) added (reaction was biphasic so Methanol (1.5 mL) added). Stirred overnight. The reaction was cooled to 0 °C in an ice-bath. 1 mL MeOH added followed by sodium borohydride (95 mg, 1.98 mmol) and the reaction was left stirring for 2 hours before being allowed to warm to room temperature. Diluted with CH_2Cl_2 (~25 mL) and then washed with distilled water (~25 mL) and brine (~25 mL) before passing the organic layer through an Isolute Phase Separator. The solvent was removed in vacuo to yield 138 mg of a yellow oil. Worked up by diluting with EtOAc (10 mL) and washing with distilled water (10 mL) and brine (10 mL). The organic layer was passed through an Isolute Phase Separator. The solvent was removed in vacuo to yield a pale yellow oil (131 mg). LCMS confirmed ethyl group still present ($M+H^+$=235). The compound was dissolved in THF (2 mL) and sodium tert-butoxide (180 mg) was added, followed by 50 µL of distilled water. The reaction was heated to 60 °C overnight. Reaction turned orange overnight. LCMS obtained (WF107583 HpH). Appeared to show product had formed. The reaction mixture was passed through an Isolute Phase Separator and diluted with EtOAc (20 mL). The solvent was removed in vacuo to give 251 mg of an orange/white solid. The solid was dissolved in EtOAc (20 mL) and washed with distilled water (10 mL) and brine (10 mL). The organic layer was passed through an Isolute Phase Separator and the solvent removed in vacuo to yield 70 mg of an orange oil. The sample

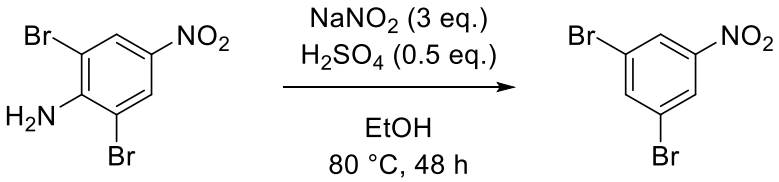
was dissolved in DMSO (1 mL) and purified by EZ Prep on Xselect CSH C18 30x150mm 5um using Acetonitrile Water with an ammonium carbonate modifier. The solvent was dried under a stream of nitrogen in the Radleys blowdown apparatus to give **36** as a white solid (34 mg, 20%, 0.17 mmol). IR (thin film) cm^{-1}: 3199, 3122, 3062, 2915, 1661, 1607, 1504, 1483, 1431, 1416. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.53 (br s, 1 H), 7.17 (tt, *J* = 7.7, 0.7 Hz, 1 H), 7.03 (d, *J* = 7.6 Hz, 1 H), 6.93 (td, *J*=7.3, 1.0 Hz, 1 H), 6.79 (dd, *J* = 7.8, 0.7 Hz, 1 H), 5.87 (ddt, *J* = 17.1, 10.2, 6.1, 6.1 Hz, 1 H), 5.24 - 5.33 (m, 2 H), 4.42 (s, 2 H), 4.12 (dt, *J* = 5.9, 1.4 Hz, 2 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 154.7, 137.2, 132.8, 128.1, 125.4, 121.7, 117.9, 117.5, 113.9, 49.4, 48.0. (ESI-Orbitrap) m/z: $[M + H]^+$ calcd for $C_{11}H_{13}N_2O_1$, 189.1028; found, 189.1029.

*2,6-Dibromo-4-nitroaniline (**45**)*



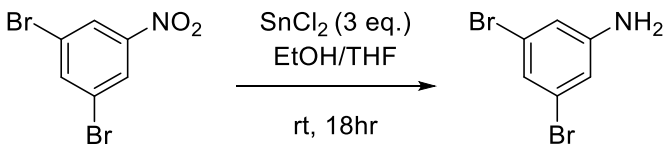
To a flame dried 250 mL three-necked flask equipped with a dropping funnel and a stirrer bar under a nitrogen atmosphere was added *p*-nitroaniline (10 g, 72.4 mmol) and acetic acid (90 mL). The mixture was heated to 65 °C in an oil bath with stirring. Bromine (23 g, 7.42 mL, 144.8 mmol) was then added dropwise to the reaction over a period of 5 hours. After about one-third of the bromine was added, a yellow/orange precipitate formed in the reaction vessel. Bromine addition was halted while hot water (20mL) was added *via* syringe to dissolve the precipitate before the addition of bromine was continued. After 5 hours, the solution was allowed cool to room temperature before being poured over an ice/water slurry with stirring. The reaction was then quenched with the slow addition of saturated sodium bicarbonate solution. This generated an emulsion and so the mixture was transferred to a 250 mL separating funnel and extracted with CH_2Cl_2. The crude material was obtained as a yellow/orange solid (18.138 g, 61.54 mmol, 85% yield). The crude product was recrystallized from chloroform to yield the product a yellow solid (13.990 g, 47.06 mmol, 65% yield) ^{1}H NMR analysis was consistent with literature values.[76] ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.34 (s, 2H, H^{AR}), 5.28 (br s, 2H, NH_2)

*3,5-Dibromonitrobenzene (**46**)*



To a flame dried 250 mL three-necked flask equipped with a dropping funnel and a stirrer bar under a nitrogen atmosphere was added 2,6-dibromo-4-nitroaniline (13.77 g, 47 mmol), conc. sulfuric acid (15 mL, 28.2 mmol) and absolute ethanol (160 mL). The reaction was heated to 80 °C in an oil bath with stirring. Sodium nitrite (9.729 g, 141 mmol) was then added slowly. Once the addition was complete and the foaming had subsided, the reaction was refluxed for 48 hr. The reaction was removed from the heat and allowed to cool to room temperature before being poured over ice. A brown precipitate formed. The solution was then filtered. The residue was dissolved in boiling ethanol, filtered and the solvent was removed under reduced pressure to give a brown solid (12.378 g, 44.2 mmol, 94% yield) ^{1}H NMR analysis consistent with literature values.[76] ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.32 (d, *J* = 1.7 Hz, 2H, H^{AR}), 8.00 (t, *J* = 1.7 Hz, 1H, H^{AR}).

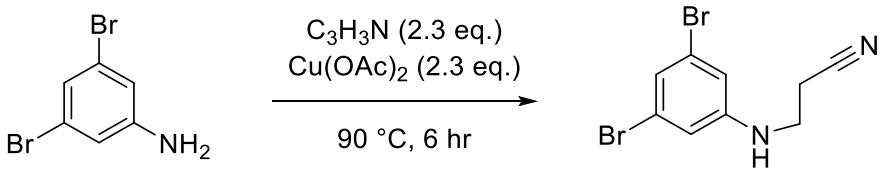
*3,5-Dibromoaniline (**47**)*



To a 100 mL three-necked flask equipped with a dropping funnel and a stirrer bar under an air atmosphere was added 3,5-dibromonitrobenzene (1 g, 3.56 mmol), absolute ethanol (18 mL) and tetrahydrofuran (18 mL). Anhydrous Tin (II) Chloride (2.7 g, 14.24 mmol) was added slowly with stirring and the reaction was left stirring for 18 hr at room temperature. The solvent was removed under reduced pressure and the residue was diluted with 10 mL 1M sodium hydroxide solution before being left to stir for a further 30 mins at room temperature. The reaction was then diluted with diethyl ether (30 mL), transferred to a 250 mL separating funnel and the organic layer separated and extracted. The organic layer was washed with distilled water (2 x 30mL) and brine (1 x 30mL), dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure to yield the crude product as a brown oil (0.952 g). The compound was purified via silica gel column chromatography (8:1 petroleum ether (40-60) : ethyl acetate, R_f = 0.44). Yielded a brown solid (0.56 g, 2.23 mmol, 63% yield) ^{1}H NMR analysis consistent with literature values[76] ^{1}H NMR (500 MHz,

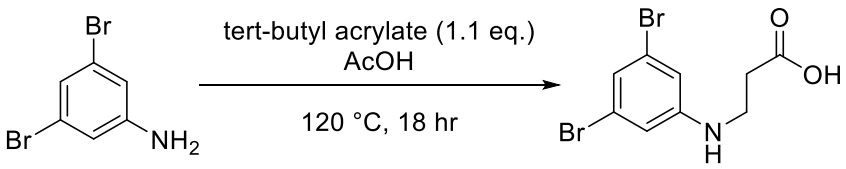
Chloroform-*d*) δ 7.00 (t, *J* = 1.5 Hz, 1H, H^{AR}), 6.70 (d, *J* = 1.6 Hz, 2H, H^{AR}), 3.78 (br s, 2H, NH_2). ^{13}C NMR (126 MHz, Chloroform-d) δ 148.7, 123.8, 123.5, 116.6.

*3-[(3,5-Dibromophenyl)amino]propanenitrile (**48**)*



To a 1 mL microwave tube equipped with a stirrer bar under a nitrogen atmosphere was added 3,5-dibromoaniline (250 mg, 1 mmol), acrylonitrile (12 mg, 2.3 mmol) and $Cu(OAc)_2.H_2O$ (10 mg, 2.3 mmol). The reaction vessel was sealed, and the reaction stirred at 90 °C in an oil bath for 6 hours before being allowed to cool to room temperature. The reaction was then basified with 1M ammonium hydroxide solution (5 mL), diluted with diethyl ether (10 mL), transferred to a 50 mL separating funnel and washed with distilled water (3 x 10mL). The organic layer was dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure to yield the crude product as a brown oil. The crude product was purified by silica gel column chromatography (4:1 petroleum ether (40-60) : ethyl acetate, R_f = 0.34) to yield a brown oil (75 mg, 0.25 mmol, 25% yield) ^{1}H NMR analysis consistent with literature values.[75] ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.03 (t, *J* = 1.6 Hz, 1H, H^{AR}), 6.67 (d, *J* = 1.6 Hz, 2H, H^{AR}), 4.2 (br s, 1H, N*H*), 3.48 (q, *J* = 6.5 Hz, 2H, CH_2), 2.64 (t, *J* = 6.5 Hz, 2H, CH_2).

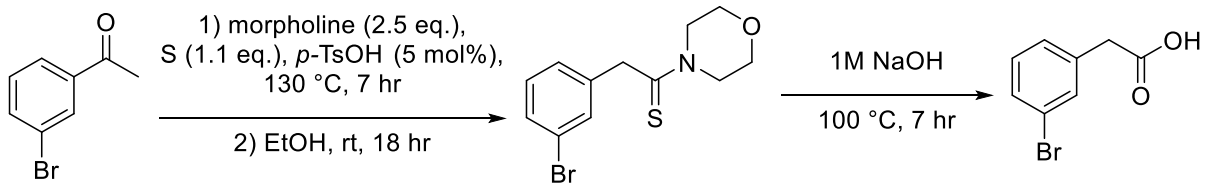
*3-[(3,5-Dibromophenyl)amino]propanoic acid (**49**)*



To a 2 mL microwave tube equipped with a stirrer bar under a nitrogen atmosphere was added 3,5-dibromoaniline (50 mg, 0.2 mmol), tert-butyl acrylate (28.2 mg, 0.22 mmol) and glacial acetic acid (0.5 mL). The reaction vessel was sealed, and the reaction was stirred at 120 °C in an oil bath for 18 hours. The reaction was then allowed to cool to room temperature, diluted with dichloromethane (5 mL), transferred to a 25 mL separating funnel and washed with distilled water (2 x 5 mL). The

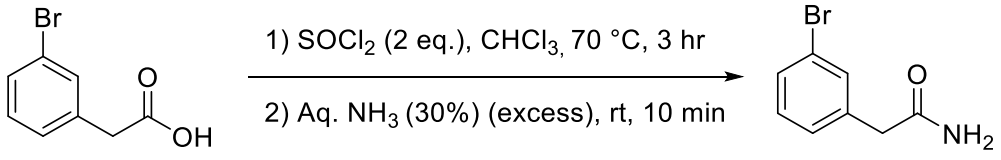
organic layer was dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure to yield a pale orange solid (62 mg, 0.164 mmol, 82% yield) ^{1}H NMR analysis consistent with literature values.[159] ^{1}H NMR (500 MHz, Chloroform-d) δ 7.04 (t, *J* = 1.6 Hz, 1H, H^{AR}), 6.67 (d, *J* = 1.6 Hz, 2H, H^{AR}), 3.48 (t, *J* = 6.2 Hz, 2H, CH_2), 2.64 (t, *J* = 6.2 Hz, 2H, CH_2).

*3-Bromophenylacetic acid (**66**)*



To a flame dried 20 mL round-bottomed flask equipped with a stirrer bar under a nitrogen atmosphere was added 3-bromoacetophenone (1 g, 5.02 mmol), sulfur (176 mg, 5.5 mmol), morpholine (1.09 g, 12.5 mmol) and p-toluenesulfonic acid (47.6 mg, 0.25 mmol). The reaction was heated at 130 °C in an oil bath for 7 hr. Ethanol absolute (2 mL) was added *via* syringe and the reaction was left stirring at room temperature for a further 18 hr. 6M KOH solution (1mL) was then added *via* syringe and heated to reflux for a further 7 hr. The reaction was allowed to cool to room temperature and the solution acidified with 1M hydrochloric acid to yield a yellow/white precipitate. The solid was filtered off to yield a yellow/white solid (667mg, 3.21 mmol, 64% yield). ^{1}H NMR analysis was consistent with literature values.[160] ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.47 – 7.40 (m, 2H, H^{AR}), 7.24 – 7.18 (m, 2H, H^{AR}), 3.63 (s, 2H, CH_2).

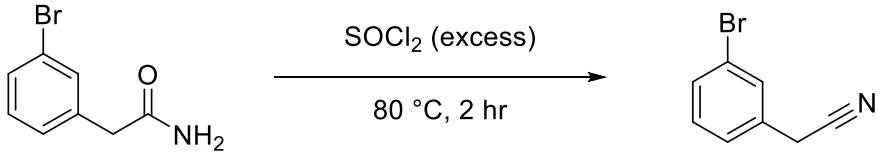
*2-(3-Bromophenyl)acetamide (**67**)*



To a flame dried 10 mL round-bottomed flask equipped with a stirrer bar under a nitrogen atmosphere was added 3-bromophenylacetic acid (100 mg, 0.465 mmol) and chloroform (4 mL). The reaction was cooled to 0 °C in an ice bath and thionyl chloride (110.6 mg, 0.93 mmol) was added dropwise *via* syringe. The solution was stirred at 70 °C in an oil bath for 3 hours before being allowed to cool to room temperature and the solvent was then removed under reduced pressure. To remove all

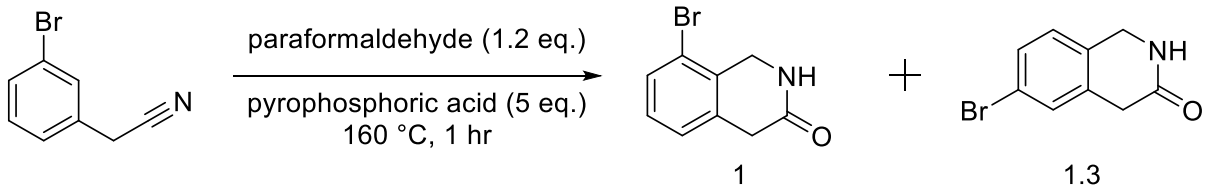
volatiles the residue re-dissolved in chloroform (1 mL) and solvent removed under reduced pressure once again. The reaction was quenched with 30% aqueous ammonia (5 mL) and stirred at room temperature for 10 minutes before being diluted with ethyl acetate (5 mL), transferred to a 25 mL separating funnel and washed (in order) with saturated sodium bicarbonate solution (5 mL), brine (5 mL) and distilled water (5 mL). The organic layer was dried over magnesium sulfate, filtered and the solvent removed under reduced pressure to yield a white solid (95 mg, 0.442 mmol, 95% yield) ^{1}H NMR and FT-IR analysis were consistent with literature values.[161] FT-IR (thin film cm^{-1}) 3347, 2809, 1634, 1570, 1417. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.45 – 7.42 (m, 2H, H^{AR}), 7.24 – 7.21 (m, 2H, H^{AR}), 3.55 (s, 2H, CH_2).

*3-Bromobenzylcyanide (**74**)*



To a flame dried 0.5 mL microwave tube equipped with a stirrer bar under a nitrogen atmosphere cooled to 0°C in an ice bath was added 2-(3-bromophenyl)acetamide (50 mg, 0.23 mmol). Thionyl chloride (0.5mL 6.9 mmol) was added dropwise *via* syringe and the reaction was then heated to 80 °C in an oil bath with monitoring by TLC (4:1 petroleum ether (40-60): ethyl acetate). After 4 hours, the reaction was judged to be complete and it was removed from the oil bath and poured onto ice. It was then diluted with ethyl acetate (5 mL), transferred to a 25 mL separating funnel and washed with distilled water. The organic layer was dried over magnesium sulfate, filtered and the solvent removed under reduced pressure. A brown oil was obtained (45mg, 0.23 mmol, >95% yield). ^{1}H NMR and FT-IR analysis were consistent with literature values.[162] FT-IR (thin film cm^{-1}) 3060, 2919, 2257, 1683, 1595, 1572. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.52 – 7.45 (m, 2H, H^{AR}), 7.26 (m, 2H, H^{AR}), 3.74 (s, 2H, CH_2).

*8-Bromo-1,4-dihydro-3(2H)-isoquinolinone (**68**) and 6-Bromo-1,4-dihydro-3(2H)-isoquinolinone (**73**)*

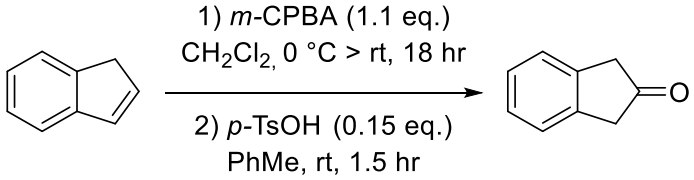


To a flame dried 2 mL microwave tube equipped with a stirrer bar under a nitrogen atmosphere was added 3-bromobenzylcyanide (68 mg, 0.35 mmol), paraformaldehyde (12.6 mg, 0.42 mmol) and pyrophosphoric acid (311 mg, 1.75 mmol). The vessel was sealed, and the reaction was heated at 180 °C in an oil bath for 30 minutes. It was then allowed to cool to room temperature and quenched via the slow addition of saturated sodium bicarbonate solution (10 mL). The reaction was then diluted with ethyl acetate (10 mL) before being transferred to a 50 mL separating funnel and washed with distilled water (10 mL). The organic layer was dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure to yield a dark brown oil (30 mg). Purified by silica gel column chromatography (gradient elution - 0% methanol : CH_2Cl_2 > 10% methanol : CH_2Cl_2, $R_{f\,(CH2Cl2)} = 0.5$). Yielded a yellow solid (17 mg, 0.077 mmol, 22% yield) ^{1}H NMR analysis consistent with literature values for compounds **68**[95] and **73**.[95] FT-IR (**68** and **73** mix) (cm^{-1}) 3445, 1651.

68 ^{1}H NMR (500 MHz, Chloroform-d) δ 7.46 (d, *J* = 6.7 Hz, 1H, H^{AR}), 7.15 – 7.12 (m, 2H, H^{AR}), 4.56 (s, 2H, CH_2), 3.62 (s, 2H, CH_2).

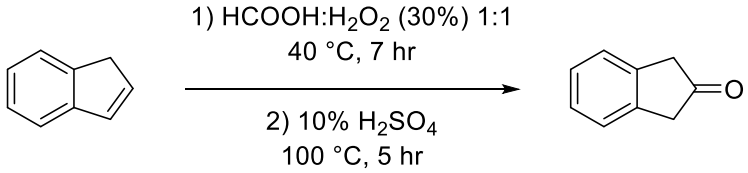
73 ^{1}H NMR (500 MHz, Chloroform-d) δ 7.36 (d, *J* = 8.1 Hz, 1H, H^{AR}), 7.33 (s, 1H, H^{AR}), 7.04 (d, *J* = 8.1 Hz, 1H, H^{AR}), 4.46 (s, 2H, CH_2), 3.57 (s, 2H, CH_2).

*2-Indanone (**81**)*



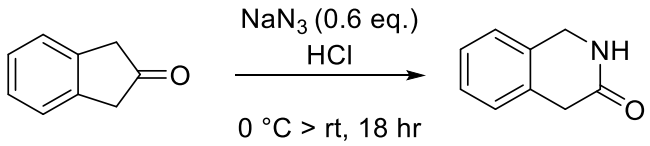
To a 2 mL microwave tube equipped with a stirrer bar under an air atmosphere was added indene (50 mg, 0.4 mmol) and dichloromethane (0.3 mL). The reaction was cooled to 0 °C in an ice bath. *M*-chloroperoxybenzoic acid (90 mg, 0.5 mmol) in dichloromethane (0.7 mL) was added dropwise *via* syringe and the reaction allowed to warm to room temperature before being left to stir for a further

18 hours, after which it was diluted with CH_2Cl_2 (2 mL) and transferred to a 25 mL separating funnel. Washed (in order) with 0.5 M sodium bisulfite solution (2 mL), saturated sodium bicarbonate solution (2 mL) and distilled water (2 mL). The organic layer was dried over magnesium sulfate, filtered and the solvent removed under reduced pressure. The residue was then redissolved in toluene (0.5mL) and *p*-toluenesulfonic acid added (12 mg, 0.06 mmol) before stirring the reaction at room temperature for 1.5 hours. The reaction was then diluted with ethyl acetate (5 mL) and transferred to a 25 mL separating funnel. Washed (in order) with 0.5 M sodium bisulfite solution (2 mL), saturated sodium bicarbonate solution (2 mL) and distilled water (2 mL), before the organic layer was dried over magnesium sulfate, filtered and the solvent removed under reduced pressure to yield a yellow oil (42 mg, 0.32 mmol, 75% yield) ^{1}H NMR analysis was consistent with literature values.[102] ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.32 – 7.26 (m, 4H, H^{AR}), 3.57 (s, 4H, CH_2).



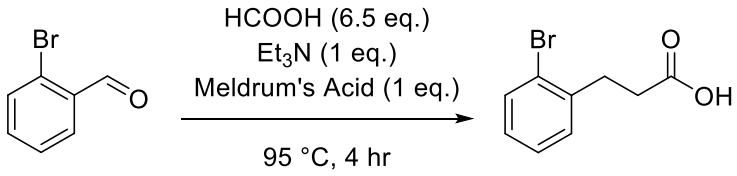
To a 2 mL microwave tube equipped with a stirrer bar under an air atmosphere was added formic acid (0.5 mL, 8.7 mmol) and 30% hydrogen peroxide (20.5 mg, 0.602 mmol). The reaction was heated to 40 °C in an oil bath. Indene (50 mg, 0.3 mmol) was added dropwise *via* syringe over 2 minutes and the reaction stirred at 40 °C in an oil bath for 7 hours. The solvent was then removed under reduced pressure. 10% sulfuric acid (0.5 mL) added to the residue and the reaction heated at 100 °C in an oil bath for a further 5 hours. Monitoring by TLC (4:1 petroleum ether (40-60): ethyl acetate) the reaction was judged to be complete. Quenching with saturated sodium bicarbonate solution (5 mL) and diluting with ethyl acetate (5 mL) the mixture was transferred to a 25 mL separating funnel. The organic layer washed with distilled water (0.5 mL), dried over magnesium sulfate, filtered and the solvent removed under reduced pressure to yield a brown oil (50mg, 0.26 mmol, 88% yield) ^{1}H NMR analysis was consistent with literature values.[102] ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.32 – 7.26 (m, 4H, H^{AR}), 3.57 (s, 4H, CH_2).

*1,4-Dihydro-3(2H)-isoquinolinone (**54**)*



To a flame dried 2 mL microwave tube equipped with a stirrer bar under a nitrogen atmosphere was added 2-indanone (100 mg, 0.76 mmol) and conc. hydrochloric acid (2.5 mL) before cooling the reaction to 0 °C in an ice bath. Sodium azide (98.8 mg, 0.52 mmol) was added slowly and, on complete addition, the reaction was removed from the ice bath and stirred at room temperature for 18 hours. The reaction was monitored by TLC (4:1 petroleum ether (40-60): ethyl acetate) and upon completion, was poured onto ice water. Solid potassium carbonate was added to adjust the solutions pH to 9 (using a pH meter). The reaction was diluted with CH_2Cl_2 (0.5 mL), transferred to a 25 mL separating funnel and washed with distilled water (0.5 mL). The organic layer was dried over magnesium sulfate, filtered and the solvent removed under reduced pressure to yield the crude product as a brown solid. The compound was purified via silica gel column chromatography (1:1 petroleum ether : ethyl acetate) to yield a brown solid (67 mg, 0.46 mmol, 60% yield). ^{1}H NMR analysis consistent with literature.[106] ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.26 (s, 2H, H^{AR}), 7.20 – 7.14 (m, 2H, H^{AR}), 7.01 (s, br, 1H, N*H*), 4.50 (s, 2H, CH_2), 3.59 (s, 2H, CH_2).

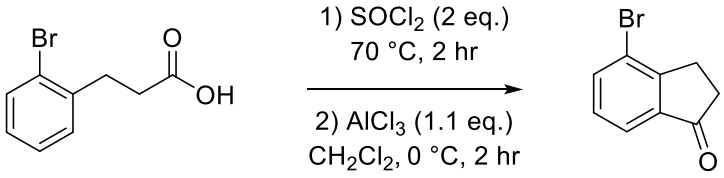
*3-(2-Bromophenyl)propanoic acid (**76**)*



To a 1 mL microwave tube cooled to 0 °C in an ice bath and equipped with a stirrer bar under a nitrogen atmosphere was added triethylamine (27.3 mg, 0.27 mmol) and formic acid (80.8 mg, 1.76 mmol) before stirring the reaction for 15 minutes at 0 °C. Meldrum's Acid (2,2-dimethyl-1,3-dioxane-4,6-dione) (39 mg, 0.27 mmol) and 2-bromobenzaldehyde (50 mg, 0.27 mmol) were added, the reaction was heated to 95 °C in an oil bath and stirred for a further 4 hours. The reaction was monitored by TLC (4:1 petroleum ether (40-60): ethyl acetate) and upon completion, was allowed to cool to room temperature before being poured onto ice water. It was then acidified to pH 1 using 37% aqueous hydrochloric acid (monitored by pH meter) and placed in a fridge overnight. Yellow crystals formed. The crystals were filtered off and re-dissolved in chloroform (1 mL), dried over

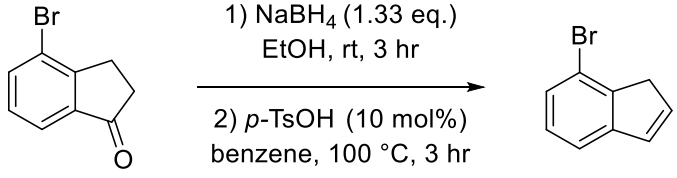
magnesium sulfate, filtered and the solvent removed under reduced pressure to yield a yellow solid (48 mg, 0.21 mmol, 78% yield). ^{1}H NMR analysis consistent with literature values.[107] ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.54 (m, 1H, H^{AR}), 7.29 – 7.22 (m, 2H, H^{AR}), 7.12-7.07 (m, 1H, H^{AR}), 3.08 (m, 2H, CH_2), 2.72 (m, 2H, CH_2).

*4-bromo-indan-1-one (**77**)*



To a flame dried 1 mL microwave tube cooled to 0°C in an ice bath and equipped with a stirrer bar under a nitrogen atmosphere was added 3-(2-bromophenyl)propanoic acid (38 mg, 0.162 mmol) and thionyl chloride (38.5 mg, 0.324 mmol). The reaction was stirred at 70 °C in an oil bath for 2 hours before the thionyl chloride was removed under reduced pressure. The residue was re-dissolved in dry dichloromethane (0.5 mL) and cooled to 0 °C in an ice bath. Aluminium trichloride (24 mg, 0.178 mmol) was added slowly and reaction was left stirring for a further 2 hours at 0°C. It was then poured over ice water, diluted with dichloromethane (5 mL), transferred to a 25 mL separating funnel and the aqueous layer acidified with 3M hydrochloric acid (0.5mL) before washing with distilled water (5 mL). The organic layer was dried over magnesium sulfate, filtered and the solvent removed under reduced pressure to yield a white solid (32mg, 0.152 mmol, 94% yield). ^{1}H NMR analysis was consistent with literature values.[163] ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.76 (d, *J* = 7.7 Hz, 1H), 7.71 (d, *J* = 7.7 Hz, 1H), 7.26 (t, *J* = 7.7 Hz, 1H), 3.10 – 3.06 (m, 2H), 2.76 – 2.71 (m, 2H).

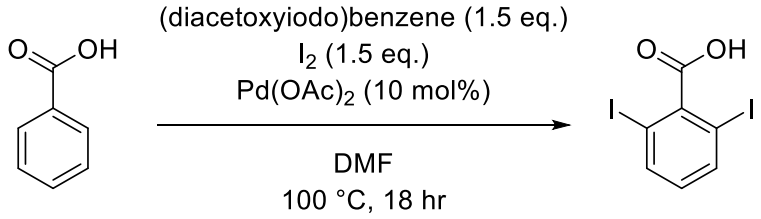
*7-bromo-1H-indene (**78**)*



To a flame dried 2 mL microwave tube cooled to 0 °C in an ice bath and equipped with a stirrer bar under a nitrogen atmosphere was added 4-bromo-indan-1-one (32 mg, 0.152 mmol) and sodium borohydride (8.7 mg, 0.23 mmol). The reaction was then allowed to come up to room temperature and left stirring for 3 hours before removing the solvent under reduced pressure. The residue was re-dissolved in 10% hydrochloric acid (0.5 mL) and stirred at room temperature for a further 30 minutes

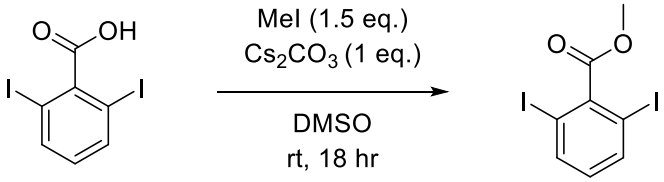
before being diluted with dichloromethane (5 mL), transferred to 25 mL separating funnel and washed with distilled water (5 mL). The organic layer was dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure. The residue was dissolved in benzene (0.5 mL) and *p*-toluenesulfonic acid (3 mg, 10 mol%) was added before heating the reaction to 100 °C in an oil bath with stirring for a further 3 hours. The solvent was again removed under reduced pressure and the residue was dissolved in dichloromethane (5 mL), transferred to a 25 mL separating funnel and washed (in order) with saturated sodium bicarbonate solution (5 mL) and distilled water (5 mL). The organic layer dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure. The compound was purified by silica gel chromatography (petroleum ether, R_f = 0.3) to yield a white solid (10 mg, 0.11 mmol, 72% yield). ^{1}H NMR analysis was consistent with literature values.[163] ^{1}H NMR (500 MHz, Chloroform-d) δ 7.38 – 7.35 (m, 1H, H^{AR}), 7.22 (d, J = 7.4 Hz, 1H, H^{AR}), 7.12 (t, J = 7.8 Hz, 1H, H^{AR}), 3.35 (d, J = 22.9 Hz, 1H, CH_2), 3.24 (d, J = 22.9 Hz, 1H, CH_2) 3.02 – 2.93 (m, 1H, C*H*), 2.55 – 2.46 (m, 1H, C*H*).

*2,6-Diiodobenzoic acid (**88**)*



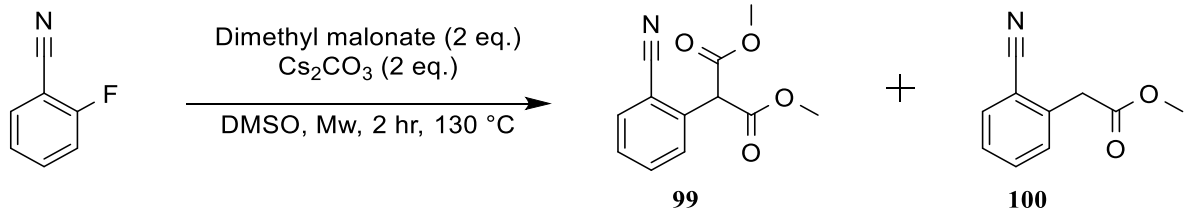
To a flame dried 2 mL microwave tube equipped with a stirrer bar under a nitrogen atmosphere was added benzoic acid (50 mg, 0.4 mmol), (diacetoxyiodo)benzene (193 mg, 0.6 mmol), iodine (76 mg, 0.6 mmol), palladium (II) acetate (4.5 mg, 5 mol%) and dry N,N'-dimethylformamide (1.5 mL). The reaction was stirred at 100 °C in an oil bath for 18 hours with monitoring by TLC (4:1 petroleum ether (40-60) : ethyl acetate). Upon completion, the reaction was allowed to cool to room temperature and diluted with ethyl acetate (5 mL) before being transferred to a 25 mL separating funnel and washed (in order) with 0.5M hydrochloric acid (5 mL), brine (5 mL), saturated sodium thiosulfate solution (5 mL) and 2M sodium hydroxide solution (5 mL). The organic layer was removed, and the aqueous layer was re-acidified using 1M hydrochloric acid (until it turned blue litmus paper red) before being extracted with ethyl acetate. The organic layer was then dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure to yield a dark orange solid (120 mg, 0.32 mmol, 80% yield). ^{1}H NMR analysis consistent with literature values.[164] ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.82 (d, J = 7.9 Hz, 1H, H^{AR}), 6.73 (t, J = 7.9 Hz, 2H, H^{AR}).

*2,6-Diiodomethyl benzoate (**89**)*



To a 5 mL microwave tube equipped with a stirrer bar under a nitrogen atmosphere was added 2,6-diiodobenzoic acid (250 mg, 0.67 mmol), cesium carbonate (218 mg, 0.67 mmol) and dimethylsulfoxide (2.5 mL). While stirring at room temperature, methyl iodide (123 mg, 0.87 mmol) was added dropwise *via* syringe. After complete addition of the methyl iodide, the reaction was stirred at room temperature for a further 18 hours. Distilled water was then added (2 mL) and the reaction stirred for a further 10 minutes as a precipitate formed. The precipitate was filtered off and re-dissolved in acetone, dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure to yield a pale yellow solid (199 mg, 0.52 mmol, 77% yield) The compound was recrystallised from ethanol to yield yellow/white crystals (180mg, 0.46 mmol, 68% yield). MP 113 – 115 °C. FT-IR (thin film cm^{-1}) 3036, 3000, 1727, 1543, 1420. ^{1}H NMR (500 MHz, Chloroform-d) δ 7.78 (d, *J* = 8.0 Hz, 2H, H^{AR}), 6.77 (t, *J* = 8.0 Hz, 1H, H^{AR}), 3.98 (s, 3H, CH_3). ^{13}C NMR (126 MHz, Chloroform-d) δ 169.0, 145.5, 138.6, 132.0, 91.2, 53.3. RMS (ESI- Waters XEVO G2-S) m/z: $[M + H]^+$ calcd for $C_8H_7I_2O_2$, 358.8535; found, 358.8538.

*Dimethyl (2-cyanophenyl)propanedioate (**99**) and Methyl (2-cyanophenyl)acetate (**100**)*



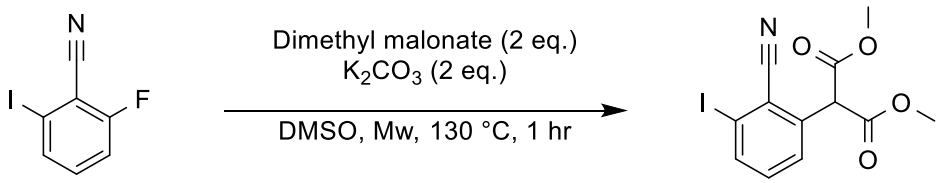
To a 20 mL Microwave tube equipped with a stirrer bar was added 2-fluorobenzonitrile (1.5 mL, 14 mmol), dimethyl malonate (3 mL, 26 mmol), Cs_2CO_3 (8.4g, 26 mmol) and DMSO (10 mL). Heated to 130 °C in a microwave for 2 hours. Diluted with EtOAc (20 mL), transferred to a separating funnel and washed with 5 x 20 mL portions of distilled water. The organic layer was dried over $MgSO_4$ and the solvent removed under vacuum. The residue was purified by silica gel column chromatography (5:1 petroleum ether:EtOAc). Yielded a mixture of **99** and **100** with some residual dimethyl malonate

present. The residue washed with 4M NaOH solution to remove malonate and afford the products **99** and **100**.

99: FTIR (thin film) cm $^{-1}$: 2956, 2922, 2851, 2227, 1736, 1632, 1600, 1489, 1435. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (td, *J* = 7.9, 0.9 Hz, 2H, H^{AR}), 7.64 (td, *J* = 7.8, 1.4 Hz, 1H, H^{AR}), 7.46 (td, *J* = 7.6, 1.3 Hz, 1H, H^{AR}), 5.15 (s, 1H, C*H*), 3.80 (s, 6H, CH_3). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.5, 136.1, 133.2, 133.1, 130.2, 129.0, 117.3, 113.7, 113.7, 55.3, 53.4.

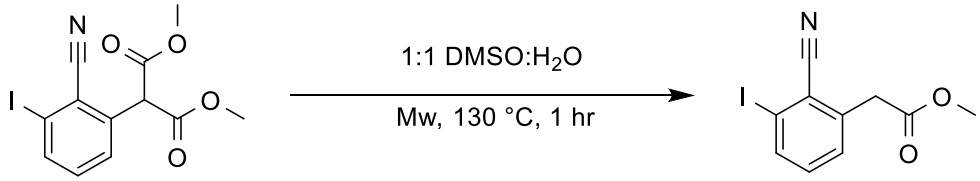
100 ^{1}H NMR analysis consistent with literature values.[165] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (dd, *J* = 7.8, 1.2 Hz, 1H, H^{AR}), 7.57 (td, *J* = 7.7, 1.2 Hz, 1H, H^{AR}), 7.42 (dd, *J* = 7.7, 1.2 Hz, 1H, H^{AR}), 7.39 (td, *J* = 7.7, 1.2 Hz, 1H, H^{AR}), 3.89 (s, 2H, CH_2), 3.74 (s, 3H, CH_3).

*Dimethyl (2-cyano-3-iodophenyl)propanedioate (**102**)*



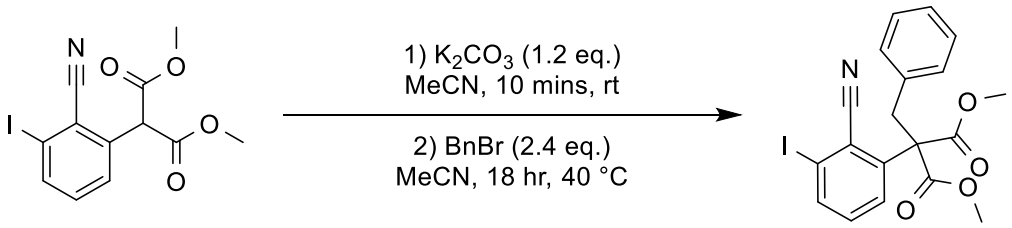
To a flame-dried 5 mL microwave tube equipped with a stirrer bar under an N_2 atmosphere was added 2-fluoro-6-iodobenzonitrile (50 mg, 0.2 mmol), dimethyl malonate (53 mg, 0.4 mmol) and K_2CO_3 (55 mg, 0.4 mmol) before the addition of dry DMSO (0.5 mL). The reaction vessel was sealed and heated to 130 °C in a Microwave for 1 hour. The mixture was partitioned between EtOAc (5 mL) and distilled water (5 mL) and the organic layer washed with 4 x 5 mL portions of distilled water. The organic layer was dried over $MgSO_4$ and the solvent removed under vacuum. Purified by silica gel column chromatography (4:1 Petroleum Ether:EtOAc) to yield the product **102** as a white solid Rf = 0.24, 66 mg (92%). FTIR (thin film) cm $^{-1}$: 2957, 2358, 2225, 1742, 1585, 1559, 1436. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (dd, *J* = 8.0, 0.9 Hz, 1H, H^{AR}), 7.68 (dd, *J* = 8.0, 0.9 Hz, 1H, H^{AR}), 7.32 (t, *J* = 8.0 Hz, 1H, H^{AR}), 5.19 (s, 1H, C*H*), 3.80 (s, 6H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.2, 139.4, 138.5, 133.7, 129.4, 121.6, 118.0, 99.1, 56.0, 53.5. HRMS (ESI- Waters XEVO G2-S) m/z: $[M + H]^+$ calcd for $C_{12}H_{11}I_1N_1O_4$, 359.9733; found, 359.9737.

*Methyl (2-cyano-3-iodophenyl)acetate (**103**)*



To a 5 mL microwave tube equipped with a stirrer bar was added **102** followed by 0.6 mL of 1:1 DMSO:H_2O. The reaction vessel was sealed and heated to 130 °C in a microwave for 1 hour. The mixture was partitioned between EtOAc (5 mL) and distilled water (5 mL) and the organic layer washed with 4 x 5 mL portions of distilled water. The organic layer was dried over $MgSO_4$, filtered and the solvent removed under vacuum. Yielded the product **103** quantitatively. FTIR (thin film) cm $^{-1}$: 2953, 2920, 2850, 2226, 1738, 1585, 1557, 1449, 1434. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (dd, J = 8.0, 1.0 Hz, 1H, H^{AR}), 7.40 – 7.37 (m, 1H, H^{AR}), 7.24 (t, J = 7.9 Hz, 2H, H^{AR}), 3.92 (s, 2H, CH_2), 3.74 (s, 3H, CH_3). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.9, 140.4, 138.4, 133.6, 130.1, 121.6, 118.2, 99.3, 52.7, 40.4. HRMS (ESI- Waters XEVO G2-S) m/z: $[M + H]^+$ calcd for $C_{10}H_9I_1N_1O_2$, 301.9678; found, 301.9677.

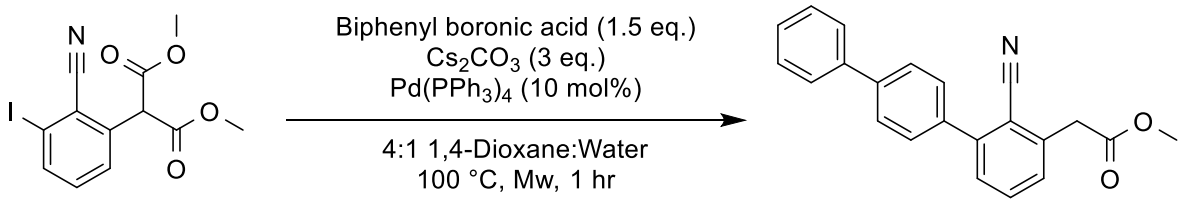
*Dimethyl benzyl(2-cyano-3-iodophenyl)propanedioate (**104**)*



To an oven-dried 5 mL microwave tube equipped with a stirrer bar under an N_2 atmosphere was added **102** (200 mg, 0.56 mmol), K_2CO_3 (92 mg, 0.67 mmol) and dry MeCN (0.6 mL). The reaction vessel was sealed and stirred at room temperature for 10 minutes before the addition of BnBr (229 mg, 1.34 mmol). The reaction was then heated to 40 °C for 18 hours. The reaction was allowed to cool to room temperature before being diluted with EtOAc (5 mL), added to a separating funnel and washed with distilled water (2x5 mL) and brine (5 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent removed under vacuum. Purified by silica gel column chromatography (CH_2Cl_2) Rf = 0.35 to yield the product **104** (198 mg, 79% yield). FTIR (thin film) cm $^{-1}$: 2952, 2227,

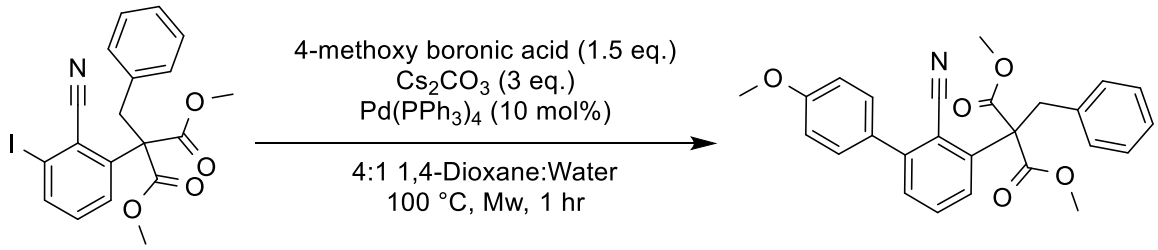
1737, 1580, 1554, 1496, 1449, 1435. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (dd, *J* = 7.2, 1.7 Hz, 1H, H^{AR}), 7.16 – 7.04 (m, 5H, H^{AR}), 6.95 (dd, *J* = 7.7, 1.6 Hz, 2H, H^{AR}), 3.81 (s, 6H, CH_3), 3.77 (s, 2H, CH_2). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.0, 143.2, 138.7, 135.3, 132.6, 130.9, 129.3, 127.9, 127.2, 120.8, 118.3, 101.4, 66.0, 53.6, 41.2. HRMS (ESI- Waters XEVO G2-S) m/z: $[M + H]^+$ calcd for $C_{19}H_{17}I_1N_1O_4$, 450.0202; found, 450.0199.

*Methyl (1^2-cyano[1^1,2^1:2^4,3^1-terphenyl]-1^3-yl)acetate (**108**)*



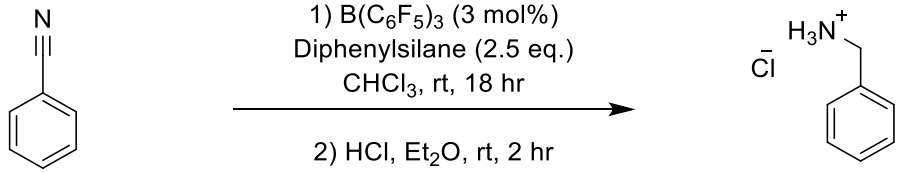
To a 5 mL microwave tube equipped with a stirrer bar was added **102** (50 mg, 0.2 mmol), biphenyl boronic acid (59 mg, 0.3 mmol), Cs_2CO_3 (195 mg, 0.6 mmol) and $Pd(PPh_3)_4$ (23 mg, 0.02 mmol). The reagents were suspended in 4:1 1,4-dioxane:H_2O before the reaction vessel was sealed and heated to 100 °C in a microwave for 1 hour. Once cooled to room temperature, diluted with EtOAc (10 mL) and washed with distilled water (2 x 10 mL) and brine (10 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent removed under vacuum. The residue was purified by silica gel column chromatography (CH_2Cl_2). Rf = 0.55 Yielded **108** as an orange solid (30 mg, 46%). A second fraction containing a mixture of the still carboxylated material and the product was dissolved in 1:1 DMSO H_2O and heated to 130 °C in a microwave for 1 hour to quantitatively produce the product **108** (29 mg, 46%). Products combined to give **108** as an orange solid (59 mg, 90%). FTIR (thin film) cm $^{-1}$: 2918, 2849, 2219, 1729, 1580, 1489, 1459, 1435, 1401. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 – 7.70 (m, 2H, H^{AR}), 7.67 – 7.60 (m, 5H, H^{AR}), 7.49 – 7.45 (m, 3H, H^{AR}), 7.43 – 7.40 (m, 1H, H^{AR}), 7.40 – 7.36 (m, 1H, H^{AR}), 4.00 (s, 2H, CH_2), 3.78 (s, 3H, CH_3). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.6, 146.1, 141.8, 140.5, 139.0, 137.3, 132.7, 129.5, 129.4, 129.1, 129.0, 127.8, 127.5, 127.3, 117.4, 112.6, 52.6, 40.0. HRMS (ESI- Waters XEVO G2-S) m/z: $[M + H]^+$ calcd for $C_{28}H_{18}N_1O_2$, 328.1338; found, 328.1336.

*Dimethyl benzyl(2-cyano-4'-methoxy[1,1'-biphenyl]-3-yl)propanedioate (**109**)*



To a 5 mL microwave tube was added **104** (20 mg, 44.5 µmol), 4-methoxybenzene boronic acid (10 mg, 67 µmol), Cs_2CO_3 (44 mg, 0.134 mmol) and $Pd(PPh_3)_4$ (28 mg, 10 mol%). Suspended in 4:1 1,4-Dioxane:H_2O. The vessel was sealed and heated to 100 °C in a microwave for 1 hour. Once cooled to room temperature, diluted with EtOAc (10 mL) and washed with distilled water (2 x 10 mL) and bring (10 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent removed under vacuum. The residue was purified by silica gel column chromatography (CH_2Cl_2). Yielded the product **109** as an orange solid (19 mg, >95%). Recrystallised from MeOH. Mp = 156-158 °C. FTIR (thin film) cm $^{-1}$: 2950, 2224, 1737, 1610, 1586, 1513, 1494, 1463, 1429. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.37 (m, 3H, H^{AR}), 7.32 (dd, J = 7.8, 1.1 Hz, 1H, H^{AR}), 7.14 – 7.08 (m, 3H, H^{AR}), 7.03 – 6.97 (m, 5H, H^{AR}), 3.86 (s, 3H, CH_3), 3.84 (s, 2H, CH_2), 3.83 (s, 6H, CH_3). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.7, 160.2, 147.4, 141.5, 135.8, 131.7, 131.1, 130.9, 130.5, 129.3, 128.1, 127.8, 127.0, 117.5, 116.2, 114.9, 114.2, 112.1, 66.0, 55.5, 53.5, 41.2. HRMS (ESI- Waters XEVO G2-S) m/z: [M + H]$^+$ calcd for $C_{26}H_{24}N_1O_5$, 430.1654; found, 430.1652.

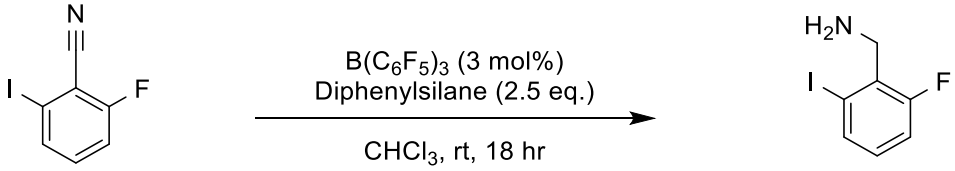
*Benzylamine Hydrochloride (**111**)*



To an oven-dried 5 mL microwave tube equipped with a stirrer bar under an N_2 atmosphere was added benzonitrile (50 mg, 0.48 mmol), diphenyl silane (0.2 mL, 1.2 mmol) and $B(C_6F_5)_3$ (26 mg, 50 µmol). The reactants were suspended in dry $CHCl_3$ (0.5 mL) and stirred at room temperature for 18 hours. Diluted with CH_2Cl_2 (10 mL) and washed with saturated bicarbonate solution (10 mL) and brine (10 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent was removed under vacuum. The residue was suspended in 2M HCl in Et_2O for 1 hour and the white precipitate that formed was then filtered off to give the product **111** as the HCl salt. ^{1}H NMR consistent with

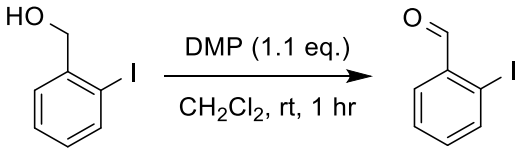
literature values.[166] ^{1}H NMR (500 MHz, DMSO) δ 8.58 (s, 2H, N*H*$_2$), 7.54 – 7.35 (m, 5H, *H*^{AR}), 4.01 (s, 2H, C*H*$_2$).

*1-(2-Fluoro-6-iodophenyl)methanamine (**112**)*



To an oven-dried 5 mL microwave tube equipped with a stirrer bar under an N_2 atmosphere was added 2-fluoro-6-iodobenzonitrile (50 mg, 0.2 mmol), diphenyl silane (86 µL, 0.5 mmol) and $B(C_6F_5)_3$ (11 mg, 21 µmol). The reactants were suspended in dry $CHCl_3$ (0.5 mL) and stirred at room temperature for 18 hours. Diluted with CH_2Cl_2 (10 mL) and washed with saturated bicarbonate solution (10 mL) and brine (10 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent was removed under vacuum. The residue was suspended in 2M HCl in Et_2O for 1 hour and the white precipitate that formed was then filtered off. The solid was then partitioned between EtOAc (10 mL) and saturated sodium bicarbonate solution (10 mL) and washed with bicarbonate solution (2 x 10 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent removed to afford **112** as a colourless oil. ^{1}H NMR (500 MHz, DMSO-d6) δ 7.67 (d, *J* = 7.8 Hz, 1H), 7.35 (t, *J* = 8.4 Hz, 1H), 7.06 (td, *J* = 8.4, 6.0 Hz, 1H), 3.79 (d, *J* = 2.0 Hz, 2H). ^{13}C NMR (126 MHz, DMSO-d6) δ 135.2 (d, *J* = 3.3 Hz), 132.7, 132.6, 115.7, 115.6, 40.8.

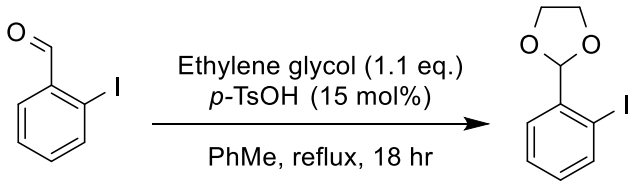
*2-Iodobenzaldehyde (**114**)*



2-iodobenzyl alcohol (150 mg, 0.64 mmol) and DMP (297 mg, 0.7 mmol) were suspended in CH_2Cl_2 (3 mL) and stirred at room temperature for 1 hour. The mixture was then diluted with a further 10 mL of CH_2Cl_2 and washed with distilled water (2 x 10 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent removed under vacuum to yield a solid. Solid was passed through a silica plug (CH_2Cl_2 eluent) and the solvent was removed to yield **114** as a white solid (131 mg, 89%). ^{1}H NMR data consistent with literature values.[167] ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.07 (s, 1H, C*H*O),

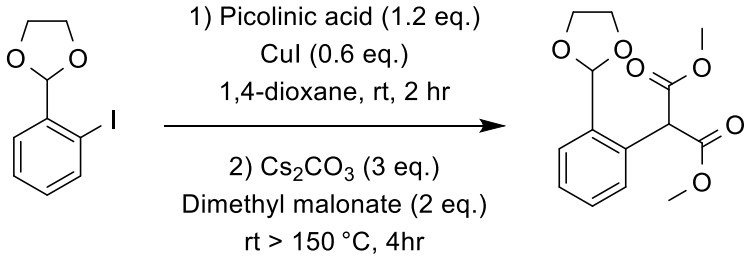
7.96 (d, *J* = 7.9 Hz, 1H, H^{AR}), 7.88 (dd, *J* = 7.7, 1.7 Hz, 1H, H^{AR}), 7.47 (t, *J* = 7.5 Hz, 1H, H^{AR}), 7.29 (td, *J* = 7.6, 1.7 Hz, 1H, H^{AR}).

*2-(2-Iodophenyl)-1,3-dioxolane (**115**)*



2-iodobenzaldehyde (131 mg, 0.56 mmol), ethylene glycol (38 mg, 0.61 mmol) and *p*-TSOH monohydrate (23 mg, 0.12 mmol) were suspended in PhMe (5 mL) and heated to reflux in a Dean-Stark apparatus under an N_2 atmosphere. Left overnight. The reaction mixture was allowed to cool and diluted with EtOAc (10 mL). Washed with brine (10 mL). The organic layer was dried over $MgSO_4$ and the solvent was removed under vacuum. The residue was purified by silica gel column chromatography (3:1 Petroleum ether:CH_2Cl_2) to afford the product **115** as a yellow oil (118 mg, 76%). ^{1}H NMR data consistent with literature values.[168] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (dd, *J* = 7.6, 1.1 Hz, 1H, H^{AR}), 7.55 (dd, *J* = 7.6, 1.7 Hz, 1H, H^{AR}), 7.37 (td, *J* = 7.6, 1.1 Hz, 1H, H^{AR}), 7.06 (td, *J* = 7.6, 1.7 Hz, 1H, H^{AR}), 5.92 (s, 1H, C*H*), 4.20 – 4.05 (m, 4H, CH_2).

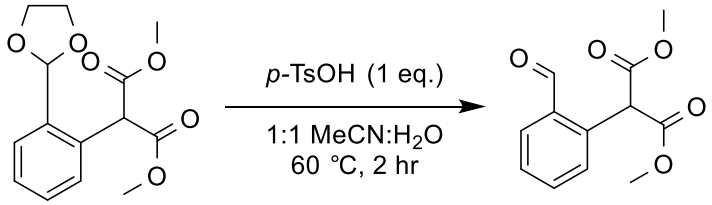
*Dimethyl [2-(1,3-dioxolan-2-yl)phenyl]propanedioate (**116**)*



To an oven-dried 5 mL microwave tube equipped with a stirrer bar under and N_2 atmosphere was added Picolinic acid (11 mg, 86 µmol) and CuI (8 mg, 43 µmol). The reactants were then suspended in dry 1,4-dioxane (0.2 mL) and stirred at room temperature for 2 hours until the suspension became bright orange in colour. 2-iodophenyl-1,3-dioxolane (20 mg, 72 µmol) in dry 1,4-dioxane (0.2 mL) was then added and the reaction was stirred at room temperature for 30 minutes. A mixture of Cs_2CO_3 (72 mg, 0.22 mmol) and dimethyl malonate (37 mg, 0.144 mmol) in dry 1,4-dioxane (0.2 mL) was then added. The reaction temperature was then allowed to increase to 150 °C and stirred for 4 hours. The reaction mixture was cooled to room temperature before being diluted with EtOAc (5 mL) and

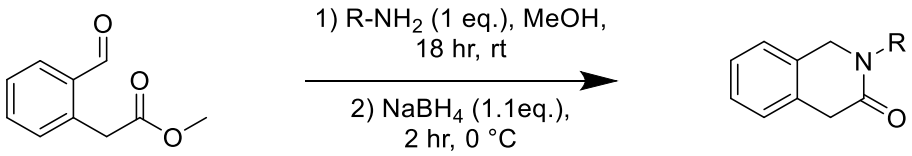
washed with distilled water (5 mL) and brine (5 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent removed under vacuum. The residue was then purified by silica gel column chromatography (4:1 Petroleum ether:EtOAc > 100% EtOAc) to yield the product **116** as a brown oil (10 mg, 50% yield) ^{1}H NMR data consistent with literature values.[169] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (dd, *J* = 7.6, 1.5 Hz, 1H, H^{AR}), 7.45 (dd, *J* = 7.6, 1.5 Hz, 1H, H^{AR}), 7.40 (td, *J* = 7.6, 1.5 Hz, 1H, H^{AR}), 7.35 (td, *J* = 7.6, 1.5 Hz, 1H, H^{AR}), 5.89 (s, 1H, C*H*), 5.32 (s, 1H, C*H*), 4.14 – 4.00 (m, 4H, CH_2), 3.76 (s, 6H, CH_3).

*Dimethyl (2-formylphenyl)propanedioate (**117**)*



To a 1 mL microwave tube equipped with a stirrer bar was added dimethyl [2-(1,3-dioxolan-2-yl)phenyl]propanedioate (12 mg, 43 µmol) and *p*-TsOH monohydrate (8 mg, 43 µmol). The reactants were dissolved in 1:1 MeCN:H_2O (0.4 mL) and the reaction vessel was sealed and heated to 60 °C. After 2 hours, allowed to cool to room temperature and diluted with EtOAc (5 mL). Washed with saturated sodium bicarbonate solution (5 mL) and brine (5 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent removed under vacuum to yield the product 117 as a yellow oil (10 mg, >95% yield). ^{1}H NMR data consistent with literature values.[169] ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.07 (s, 1H), 7.84 (dd, *J* = 7.5, 1.6 Hz, 1H, H^{AR}), 7.63 (td, *J* = 7.5, 1.6 Hz, 1H, H^{AR}), 7.58 (td, *J* = 7.5, 1.6 Hz, 1H, H^{AR}), 7.48 (d, *J* = 8.2 Hz, 1H, H^{AR}), 5.91 (s, 1H, C*H*), 3.78 (s, 6H, CH_3).

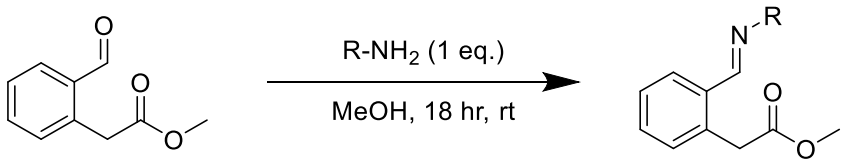
General Procedure A:



To a solution of methyl-2-(2-formylphenyl)acetate (20 mg, 0.11mmol) in methanol (0.2mL) was added an equimolar amount of RNH_2 and stirred for 18 hours at room temperature in a sealed tube. After 18 hours, solution cooled to 0 °C and 1.1 equivalents $NaBH_4$ added while stirring. After 2 hours, distilled water (2 mL) added to quench the reaction and the reaction mixture was diluted with ethyl acetate (5 mL). The organic layer was washed with distilled water (5 mL) and brine (5 mL)

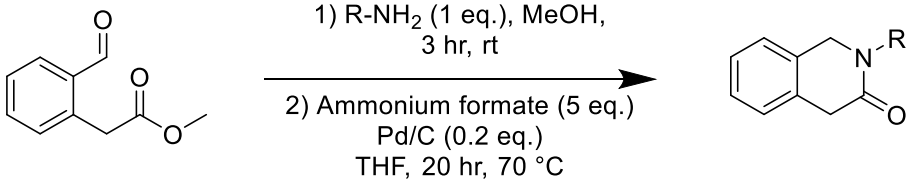
before being dried over $MgSO_4$ and filtered. The solvent was removed via evaporation and the resulting product purified by column chromatography (4:1 CH_2Cl_2: EtOAc)

General Procedure A(i):



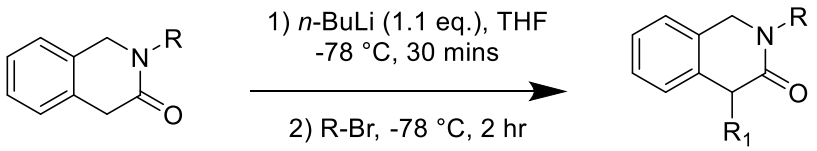
To a solution of methyl-2-(2-formylphenyl) acetate (20 mg, 0.11mmol) in methanol (0.2mL) was added an equimolar amount of RNH_2 and stirred for 3 hours at room temperature in a sealed tube. After 3 hours, solvent was removed to afford the product.

General procedure B:

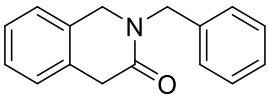


To a sample of methyl 2-(2-formylphenyl)acetate (1 eq.) under a nitrogen atmosphere was added an equimolar amount of amine ($R\text{-}NH_2$) followed by dry Tetrahydrofuran (THF) (~ 0.2M reaction concentration). The reaction was stirred at room temperature for 18 hours. After 18 hours, ammonium formate (5 eq.) and palladium on carbon (0.2 eq.) added to the reaction under a nitrogen atmosphere. The reaction vessel was fitted with a reflux condenser and heated to 70 °C for 18 hours. Allowed to cool to room temperature and poured onto 5% sodium metabisulfite solution before extraction with EtOAc. The organic layer was washed further with brine. Organic layer passed through Isolute Phase Separator and the solvent removed in vacuo. The sample was loaded in CH_2Cl_2 and purified via Combiflash (silica - 80g) using a 0-100% ethyl acetate-cyclohexane mix over 30 mins. The appropriate fractions were combined and evaporated in vacuo to give the product

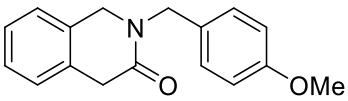
General Procedure C:



Start material lactam (0.28mmol **135** or 0.53mmol **143**) was dissolved in dry THF (0.4mL, 0.6mL), placed under an N_2 atmosphere and cooled to -78 °C with stirring. 1.1 equivalents of *n*-BuLi added and the reaction stirred for a further 10 minutes. 1 equivalent RBr was then added and the solution stirred for a further 2 hours before being allowed to come up to 0 °C. Quenched with the slow addition of distilled water. Diluted with EtOAc and washed with distilled water and brine. Dried over $MgSO_4$ and fitered. The solvent was removed via evaporation and the resulting product purified by column chromatography.

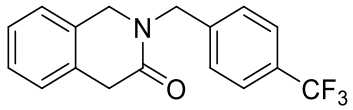


*2-Benzyl-1,2-dihydroisoquinolin-3(4H)-one **135***: Compound was synthesised according to general procedure A. RNH_2 = benzylamine. Rf = 0.45 Product was isolated as a yellow solid (96% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35 – 7.30 (m, 2H, H^{AR}), 7.30 – 7.24 (m, 4H, H^{AR}), 7.19 (dd, J = 11.4, 7.4 Hz, 2H, H^{AR}), 7.07 (d, J = 7.3 Hz, 1H, H^{AR}), 4.76 (s, 2H, CH_2), 4.38 (s, 2H, CH_2), 3.73 (s, 2H, CH_2) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ 169.1, 136.8, 132.3, 131.3, 128.9, 128.1, 127.7, 127.7, 127.4, 126.7, 125.3, 50.4, 50.1, 37.5 ppm. The spectral data were consistent with that reported in the literature.[170]

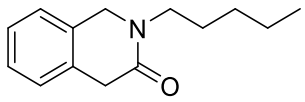


*2-(4-Methoxybenzyl)-1,2-dihydroisoquinolin-3(4H)-one **136***: Compound was synthesised according to general procedure A. RNH_2 = p-methoxybenzylamine. Rf = 0.43. Product was isolated as a yellow oil (63% yield). IR (thin film) cm^{-1}: 2998, 2957, 2931, 2836, 1651, 1611, 1513, 1485, 1458, 1441. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26 – 7.15 (m, 5H, H^{AR}), 7.07 (d, J = 7.5 Hz, 1H, H^{AR}), 6.87-6.83 (m, 2H, H^{AR}), 4.69 (s, 2H, CH_2), 4.36 (s, 2H, CH_2), 3.79 (s, 3H, CH_3), 3.69 (s, 2H, CH_2) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ 169.0, 159.2, 132.3, 131.4, 129.5, 128.8, 127.6, 127.4, 126.7, 125.3,

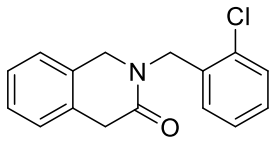
114.3, 55.4, 50.1, 49.5, 37.6 ppm. HRMS (ESI-Orbitrap) m/z: $[M + Na]^+$ calcd for $C_{17}H_{17}N_1O_2Na_1$, 290.1151; found, 290.1143. The spectral data were consistent with that reported in the literature.[171]



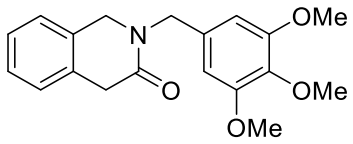
2-(4-(Trifluoromethyl)benzyl)-1,4-dihydroisoquinolin-3(2H)-one ***137***: Compound was synthesised according to general procedure A. RNH_2 = 4-(trifluoromethyl)benzylamine. Purified on a Combiflash Companion using a 0-100% gradient of cyclohexane:EtOAc. Product was isolated as a yellow oil (50% yield). IR (thin film) cm^{-1}: 2911, 1648, 1637, 1617, 1487, 1460, 1438, 1419, 1411. ^1H NMR (400 MHz, $CDCl_3$): δ 7.60 (d, *J* = 8.1 Hz, 2H, H^{AR}), 7.41 (d, *J* = 8.1 Hz, 2H, H^{AR}), 7.20 - 7.32 (m, 3H, H^{AR}), 7.11 (d, *J* = 6.6 Hz, 1H, H^{AR}), 4.83 (s, 2H, CH_2), 4.43 (s, 2H, CH_2), 3.75 (s, 2H, CH_2) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.2, 140.9, 132.1, 130.9, 129.9 (q, *J* = 32.8 Hz, 1 C), 128.1, 127.8, 127.4, 126.7, 125.7 (q, *J* = 3.7 Hz, 2 C), 125.2, 124.1 (br q, *J* = 272.2 Hz, 1 C), 50.6, 49.7, 37.4 ppm. HRMS (ESI- Waters XEVO G2-XS QTof) m/z: $[M + H]^+$ calcd for $C_{17}H_{15}F_3N_1O_1$, 306.1106; found, 306.1106. The spectral data were consistent with that reported in the literature.[171]



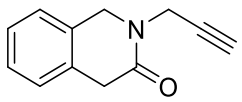
2-Pentyl-1,2-dihydroisoquinolin-3(4H)-one ***138***: Compound was synthesised according to general procedure A. RNH_2 = amylamine. Rf = 0.32. Product was isolated as an oil (63% yield). IR (thin film) cm^{-1}: 2957, 2922, 2859, 1652, 1486, 1458, 1432. ^1H NMR (500 MHz, $CDCl_3$): δ 7.28 – 7.21 (m, 2H, H^{AR}), 7.17 (t, *J* = 6.4 Hz, 2H, H^{AR}), 4.46 (s, 2H, CH_2), 3.61 (s, 2H, CH_2), 3.53 – 3.49 (m, 2H, CH_2) 1.64 – 1.57 (m, 2H, CH_2), 1.38 – 1.27 (m, 4H, CH_2), 0.89 (t, *J* = 7.1 Hz, 3H, CH_3) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ 168.9, 132.7, 131.7, 127.7, 127.4, 126.7, 125.2, 51.0, 47.1, 37.7, 29.2, 27.2, 22.6, 14.1 ppm. HRMS (ESI- Waters XEVO G2-XS QTof) m/z: $[M + H]^+$ calcd for $C_{14}H_{20}N_1O_1$, 218.1545; found, 218.1551.



2-(2-Chlorobenzyl)-1,2-dihydroisoquinolin-3(4H)-one ***139***: Compound was synthesised according to general procedure A. RNH_2 = 2-chlorobenzylamine. Rf = 0.56. Product was isolated as a yellow oil (98% yield). IR (thin film) cm^{-1}: 2922, 1655, 1475, 1443. ^1H NMR (500 MHz, $CDCl_3$): δ 7.40 – 7.37 (m, 1H, H^{AR}), 7.28 (d, J = 6.1 Hz, 1H, H^{AR}), 7.24 – 7.18 (m, 5H, H^{AR}), 7.12 (d, J = 7.5 Hz, 1H, H^{AR}), 4.90 (s, 2H, CH_2), 4.45 (s, 2H, CH_2), 3.73 (s, 2H, CH_2) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ 169.4, 134.2, 133.8, 132.3, 131.3, 129.8, 129.1, 128.9, 127.8, 127.5, 127.4, 126.8, 125.4, 50.9, 47.5, 37.6 ppm. HRMS (ESI- Waters XEVO G2-XS QTof) m/z: $[M + H]^+$ calcd for $C_{16}H_{15}Cl_1N_1O_1$, 272.0842; found, 272.0844.

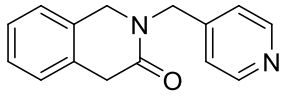


2-(3,4,5-Trimethoxybenzyl)-1,2-dihydroisoquinolin-3(4H)-one ***140***: Compound was synthesised according to general procedure A. RNH_2 = 3,4,5-trimethoxybenzylamine. Rf = 0.34 Product was isolated as a yellow oil (98% yield). IR (thin film) cm^{-1}: 3472, 2939, 2839, 1651, 1592, 1506, 1458, 1421. ^1H NMR (500 MHz, $CDCl_3$): δ 7.28 – 7.18 (m, 3H, H^{AR}), 7.10 (d, J = 7.4 Hz, 1H, H^{AR}), 6.45 (s, 2H, H^{AR}), 4.69 (s, 2H, CH_2), 4.39 (s, 2H, CH_2), 3.82 (s, 3H, CH_3), 3.77 (s, 6H, CH_3), 3.70 (s, 2H, CH_2) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ 169.3, 153.6, 137.5, 132.5, 132.4, 131.6, 127.8, 127.4, 126.8, 125.23, 105.0, 61.0, 56.2, 50.3, 50.2, 37.8 ppm. HRMS (ESI-Orbitrap) m/z: $[M + Na]^+$ calcd for $C_{19}H_{21}N_1O_4Na_1$, 350.1363; found, 350.1356.

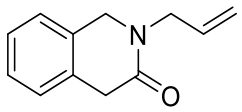


2-(Prop-2-yn-1-yl)-1,2-dihydroisoquinolin-3(4H)-one ***141***: Compound was synthesised according to general procedure A. RNH_2 = propargylamine. Rf = 0.46. Product was isolated as an oil (78% yield). IR (thin film) cm^{-1}: 3297, 3232, 2964, 2923, 2852, 2117, 1738, 1665, 1481, 1459, 1440. ^1H NMR (500 MHz, $CDCl_3$): δ 7.29 – 7.23 (m, 2H, H^{AR}), 7.23 – 7.20 (m, 1H, H^{AR}), 7.18 – 7.15 (m, 1H, H^{AR}), 4.61 (s, 2H, CH_2), 4.40 (d, J = 2.5 Hz, 2H, CH_2), 3.65 (s, 2H, CH_2), 2.26 (t, J = 2.5 Hz, 1H, CH) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ 168.6, 132.0, 131.0, 127.8, 127.5, 126.8, 125.4, 78.3, 72.6,

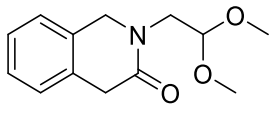
50.1, 37.3, 35.5 ppm. HRMS (ESI-Orbitrap) m/z: $[M + Na]^+$ calcd for $C_{12}H_{11}N_1O_1Na_1$, 208.0733; found, 208.0726.



3-(Pyridine-4-ylmethyl)-1,2-dihydroisoquinolin-3(4H)-one ***142***: Compound was synthesised according to general procedure A. RNH_2 = 4-(aminomethylpyridine). Rf = 0.0 (flushed from column with 10% MeOH in EtOAc) Product was isolated as a green oil (69% yield). IR (thin film) cm^{-1}: 3435, 2075, 1638, 1418. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.55 (s, 2H, H^{AR}), 7.31 – 7.14 (m, 5H, H^{AR}), 7.10 (d, J = 7.4 Hz, 1H, H^{AR}), 4.76 (s, 2H, CH_2), 4.42 (s, 2H, CH_2), 3.73 (s, 2H, CH_2) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ 169.5, 150.3, 145.9, 132.1, 130.9, 128.0, 127.5, 127.0, 125.3, 122.7, 50.9, 49.3, 37.5 ppm. HRMS (ESI-Orbitrap) m/z: $[M + Na]^+$ calcd for $C_{15}H_{14}N_2O_1Na_1$, 261.1004; found, 261.0999.

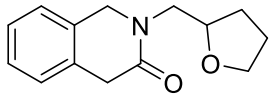


2-Allyl-1,2-dihydroisoquinolin-3(4H)-one ***143***: Compound was synthesised according to general procedure A. RNH_2 = allylamine. Rf = 0.59 Product was isolated as an oil (84% yield). IR (thin film) cm^{-1}: 3051, 1640, 1482, 1459, 1441, 1416. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.21 (m, 2H), 7.15 – 7.11 (m, 2H), 5.81 – 5.72 (m, 1H), 5.20 – 5.16 (m, 2H), 4.40 (s, 2H), 4.13 (dt, J = 5.9, 1.3 Hz, 2H), 3.61 (s, 2H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ 168.6, 132.5, 132.3, 131.4, 127.5, 127.2, 126.6, 125.1, 117.8, 50.1, 49.0, 37.4 ppm. HRMS (ESI-Orbitrap) m/z: $[M + Na]^+$ calcd for $C_{12}H_{13}N_1O_1Na_1$, 210.0889; found, 210.0887.

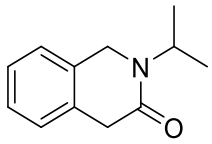


2-(2,2-Dimethoxyethyl)-1,2-dihydroisoquinolin-3(4H)-one ***144****:* Compound was synthesised according to general procedure A. RNH_2 = aminoacetaldehyde dimethyl acetal. Rf = 0.19 Product was isolated as a yellow oil (85% yield). IR (thin film) cm^{-1}: 3463, 2937, 2835, 1653, 1483, 1458. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26 – 7.20 (m, 2H, H^{AR}), 7.18 – 7.14 (m, 2H, H^{AR}), 4.58 (s, 2H, CH_2), 4.53 (t, J = 5.5 Hz, 1H, CH), 3.62 (s, 2H, CH_2), 3.61 (d, J = 5.5 Hz, 2H, CH_2), 3.40 (s, 6H,

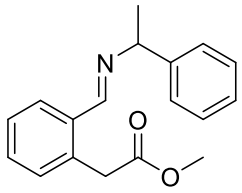
C*H*$_3$) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ 169.5, 132.4, 132.1, 127.6, 127.3, 126.7, 125.2, 103.5, 55.2, 52.9, 49.6, 37.8 ppm. No mass spec as it seemed to break down under the ionisation conditions



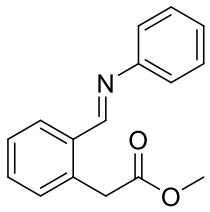
2-((Tetrahydrofuran-2-yl) methyl)-1,2-dihydroisoquinolin-3(4H)-one ***145***: Compound was synthesised according to general procedure A. RNH_2 = tetrahydrofurfurylamine. Rf = 0.20 Product was isolated as a yellow oil (91% yield). IR (thin film) cm^{-1}: 3435, 2075, 1637, 1489. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.25 – 7.20 (m, 2H, *H*^{AR}), 7.19 – 7.12 (m, 2H, *H*^{AR}), 4.71 (d, *J* = 15.7 Hz, 1H, C*H*$_2$), 4.55 (d, *J* = 15.7 Hz, 1H, C*H*$_2$), 4.13 (qd, *J* = 7.1, 3.2 Hz, 1H, C*H*), 3.90 (dd, *J* = 14.1, 3.2 Hz, 1H, C*H*$_2$), 3.88 – 3.83 (m, 1H, C*H*$_2$), 3.87 – 3.83 (m, 1H, C*H*$_2$), 3.74 (dd, *J* = 14.2, 7.2 Hz, 1H, C*H*$_2$), 3.62 (s, 2H, C*H*$_2$), 3.35 (dd, *J* = 14.2, 7.2 Hz, 1H, C*H*$_2$), 2.04 – 1.96 (m, 1H, C*H*$_2$), 1.89 – 1.82 (m, 2H, C*H*$_2$), 1.61 – 1.52 (m, 1H, C*H*) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ 169.7, 132.4, 132.2, 127.6, 127.3, 126.7, 125.2, 78.5, 68.3, 52.7, 50.9, 37.8, 29.2, 25.8 ppm. HRMS (ESI-Orbitrap) m/z: [M + Na]$^+$ calcd for $C_{14}H_{17}N_1O_2Na_1$, 254.1151; found, 254.1144.



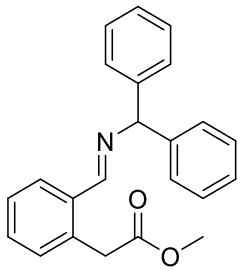
2-Isopropyl-1,2-dihydroisoquinolin-3(4H)-one ***146:*** Compound was synthesised according to general procedure A. RNH_2 = isopropylamine. Rf = 0.39 Product was isolated as a yellow oil (38% yield). IR (thin film) cm^{-1}: 2970, 1725, 1638, 1475, 1457, 1434. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26 – 7.18 (m, 3H, *H*^{AR}), 7.15 (d, *J* = 6.9 Hz, 1H, *H*^{AR}), 4.97 (hept, *J* = 6.9 Hz, 1H, C*H*), 4.30 (s, 2H, C*H*$_2$), 3.58 (s, 2H, C*H*$_2$), 1.17 (d, *J* = 6.9 Hz, 6H, C*H*$_3$) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ 168.6, 132.9, 132.3, 127.6, 127.1, 126.6, 125.1, 43.9, 43.8, 38.5, 19.6 ppm. HRMS (ESI- Waters XEVO G2-XS QTof) m/z: [M + H]$^+$ calcd for $C_{12}H_{16}N_1O_1$, 190.1232; found, 190.1233.



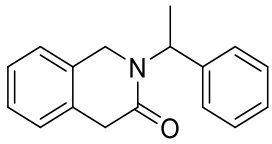
(E)-methyl 2-(2-(((1-phenylethyl)imino)methyl)phenyl) acetate ***147***: Compound was synthesised according to general procedure A(i). RNH_2 = alpha methylbenzylamine. IR (thin film) cm^{-1}: 2970, 2840, 1734, 1643, 1601, 1575, 1492, 1450, 1435, 1406. ^1H NMR (500 MHz, $CDCl_3$): δ 8.57 (s, 1H, =C*H*), 7.71 (dd, *J* = 5.5, 3.6 Hz, 1H, H^{AR}), 7.47 (dd, *J* = 8.2, 1.0 Hz, 2H, H^{AR}), 7.41 – 7.36 (m, 4H, H^{AR}), 7.29 – 7.24 (m, 2H, H^{AR}), 4.52 (q, *J* = 6.6 Hz, 1H, C*H*), 4.10 (d, *J* = 16.3 Hz, 1H, CH_2), 4.01 (d, *J* = 16.3 Hz, 1H, CH_2), 3.62 (s, 3H, OCH_3), 1.61 (d, *J* = 6.6 Hz, 3H, CH_3) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ 172.2, 159.5, 145.1, 134.5, 133.7, 131.9, 130.9, 130.0, 128.4, 127.5, 126.8, 126.6, 70.9, 51.8, 50.2, 40.0, 25.1 ppm. HRMS (ESI-Orbitrap) m/z: $[M + H]^+$ calcd for $C_{18}H_{20}N_1O_2$, 282.1489; found, 282.1498.



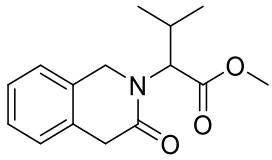
(E)-methyl 2-(2-((phenylimino)methyl)phenyl) acetate ***148****:* Compound was synthesised according to general procedure A(i). RNH_2 = aniline. IR (thin film) cm^{-1}: 3022, 2950, 1733, 1698, 1625, 1590, 1572, 1486, 1450, 1434, 1406. ^1H NMR (500 MHz, $CDCl_3$): δ 8.68 (s, 1H, =C*H*), 7.96 – 7.92 (m, 1H, H^{AR}), 7.46 – 7.40 (m, 4H, H^{AR}), 7.33 – 7.31 (m, 1H, H^{AR}), 7.28 – 7.21 (m, 3H, H^{AR}), 4.08 (s, 2H, CH_2), 3.70 (s, 3H, CH_3) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ 172.0, 159.8, 152.0, 134.6, 134.5, 132.0, 130.9, 130.9, 129.2, 127.8, 126.1, 120.9, 52.1, 39.8 ppm. HRMS (ESI-Orbitrap) m/z: $[M + H]^+$ calcd for $C_{16}H_{16}N_1O_2$, 254.1176; found, 254.1178.



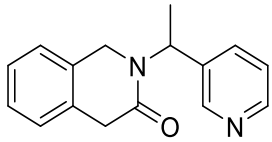
*(E)-methyl 2-(2-((benzhydrylimino)methyl)phenyl) acetate **149***: Compound was synthesised according to general procedure A(i). RNH_2 = benzhydrylamine. IR (thin film) cm^{-1}: 3025, 2950, 2841, 1734, 1639, 1599, 1575, 1492, 1452, 1435, 1406. ^1H NMR (500 MHz, $CDCl_3$): δ 8.64 (s, 1H, =C*H*), 7.77 – 7.72 (m, 1H, H^{AR}), 7.45 – 7.41 (m, 4H, H^{AR}), 7.39 (dd, *J* = 5.7, 3.4 Hz, 2H, H^{AR}), 7.36 (t, *J* = 7.7 Hz, 4H, H^{AR}), 7.29 – 7.22 (m, 3H, H^{AR}), 5.56 (s, 1H, C*H*), 4.11 (s, 2H, CH_2), 3.50 (s, 3H, CH_3) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ 172.1, 161.3, 143.8, 134.4, 134.1, 132.1, 131.7, 130.3, 128.5, 127.7, 127.6, 127.0, 79.6, 51.8, 50.5, 40.2 ppm. HRMS (ESI-Orbitrap) m/z: $[M + H]^+$ calcd for $C_{23}H_{22}N_1O_2$, 344.1645; found, 344.1652.



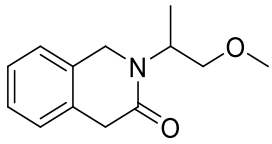
*2-(1-Phenylethyl)-1,4-dihydroisoquinolin-3(2H)-one **153***: Compound was synthesised according to general procedure B. 2g of methyl 2-(2-formylphenyl)acetate. RNH_2 = alpha-methylbenzylamine. 25mL THF. Product was isolated as an off-yellow solid (80% yield) IR (thin film) cm^{-1}: 3029, 2972, 2879, 1636, 1604, 1494, 1468, 1451, 1432. ^1H NMR (400 MHz, $CDCl_3$): δ 7.29 - 7.38 (m, 5H, H^{AR}), 7.24 - 7.27 (m, 1H, H^{AR}), 7.17 - 7.22 (m, H, H^{AR}), 7.04 (d, *J* = 6.9 Hz, 1H, H^{AR}), 6.19 (q, *J* = 7.1 Hz, 1H, C*H*), 4.27 (d, *J* = 15.4 Hz, 1H, CH_2), 3.98 (d, *J* = 15.4 Hz, 1H, CH_2), 3.71 (s, 2H, CH_2), 1.61 (d, *J* = 7.1 Hz, 3H, CH_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.0, 140.0, 132.6, 132.1, 128.6, 127.5, 127.4, 127.2, 127.0, 126.5, 125.1, 50.2, 44.9, 38.3, 15.8 ppm. HRMS (ESI- Waters XEVO G2-XS QTof) m/z: $[M + H]^+$ calcd for $C_{17}H_{18}N_1O_1$, 252.1388; found, 252.1386.[84]



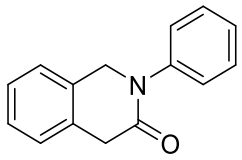
Methyl-3-methyl-2-(3-oxo-3,4-dihydroisoquinolin-2(1H)-yl)butanoate ***154***: Compound was synthesised according to general procedure B. 50mg of methyl 2-(2-formylphenyl)acetate. RNH_2 = valine methyl-ester hydrochloride. 1 eq. Et_3N added to generate free base. 1mL THF. Product was isolated as an oil (44% yield). IR (thin film) cm^{-1}: 2966, 1749, 1718, 1678. ^1H NMR (400 MHz, $CDCl_3$): δ 7.17 - 7.31 (m, 4H, H^{AR}), 5.04 (d, *J* = 10.5 Hz, 1H, C*H*), 4.60 (dd, *J* = 15.7, 1.00 Hz, 1H, CH_2), 4.43 (d, *J* = 15.7 Hz, 1H, CH_2), 3.71 (s, 3H, OCH_3), 3.66 (s, 2H, CH_2), 2.27 - 2.41 (m, 1H, CH_2), 1.04 (d, *J* = 6.7 Hz, 3H, CH_3), 0.84 (d, *J* = 6.7 Hz, 3H, CH_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.5, 170.1, 132.5, 132.4, 127.7, 127.0, 126.7, 125.1, 60.8, 51.9, 46.7, 38.5, 27.8, 19.6, 18.9 ppm. HRMS (ESI- Waters XEVO G2-XS QTof) m/z: $[M + H]^+$ calcd for $C_{15}H_{20}N_1O_3$, 262.1443; found, 262.1439.



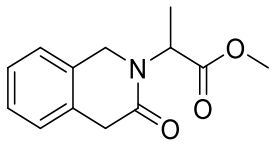
2-(1-(Pyridin-3-yl)ethyl)-1,4-dihydroisoquinolin-3(2H)-one ***155***: Compound was synthesised according to general procedure B. 50mg of methyl 2-(2-formylphenyl)acetate. RNH_2 = α-methyl-3-pyridinemethanamine. 1mL THF. Product was isolated as an oil (48% yield). IR (thin film) cm^{-1}: 2977, 1714, 1646, 1478, 1457, 1424. ^1H NMR (400 MHz, $CDCl_3$): δ 8.57 - 8.60 (m, 1H, H^{AR}), 8.53 (dd, *J* = 4.8, 1.1 Hz, 1H, H^{AR}), 7.58 (m, 1H, H^{AR}), 7.16 - 7.29 (m, 4H, H^{AR}), 7.03 (d, *J* = 7.3 Hz, 1H, H^{AR}), 6.19 (q, *J* = 7.1 Hz, 1H, C*H*), 4.33 (d, *J* = 15.2 Hz, 1H CH_2), 3.98 (d, *J* = 15.2 Hz, 1H, CH_2), 3.69 (s, 2 H), 1.64 (d, *J* = 7.1 Hz, 3H, CH_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.2, 148.9, 148.7, 135.6, 135.0, 132.4, 131.6, 127.7, 127.1, 126.7, 125.1, 123.4, 48.5, 45.0, 38.7, 15.6 ppm. HRMS (ESI- Waters XEVO G2-XS QTof) m/z: $[M + H]^+$ calcd for $C_{16}H_{17}N_2O_1$, 253.1341; found, 253.1336.



2-(1-Methoxypropan-2-yl)-1,4-dihydroisoquinolin-3(2H)-one ***156***: Compound was synthesised according to general procedure B. 50mg of methyl 2-(2-formylphenyl)acetate. RNH_2 = 1-Methoxy-2-propanamine. 1mL THF. Product was isolated as an oil (26% yield). IR (thin film) cm^{-1}: 2987, 2931, 1713, 1668, 1605, 1463. ^1H NMR (400 MHz, $CDCl_3$): δ 7.17 - 7.29 (m, 4H, H^{AR}), 4.98 (m, 1H, C*H*), 4.36 - 4.48 (m, 2H, CH_2), 3.62 - 3.65 (m, 2H, CH_2), 3.54 (dd, *J* = 10.3, 7.1 Hz, 1H, CH_2), 3.44 (dd, *J* = 10.3, 4.9 Hz, 1H, CH_2), 3.34 (s, 3H, OCH_3), 1.22 (d, *J* = 7.1 Hz, 3H, CH_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.3, 132.8, 132.4, 127.5, 127.0, 126.5, 125.0, 74.2, 58.9, 47.7, 45.6, 38.4, 14.1 ppm. HRMS (ESI- Waters XEVO G2-XS QTof) m/z: $[M + H]^+$ calcd for $C_{13}H_{18}N_1O_2$, 220.1338; found, 220.1334.

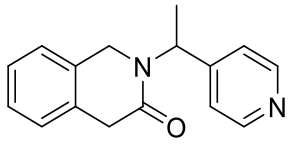


2-Phenyl-1,4-dihydroisoquinolin-3(2H)-one ***157***: Compound was synthesised according to general procedure B. 50mg of methyl 2-(2-formylphenyl)acetate. RNH_2 = Aniline. Product was isolated as an oil (2mg, 3% yield). ^1H NMR (400 MHz, DMSO-d_6): δ 7.45 - 7.2 (m, 9 H, H^{AR}), 4.88 (s, 2H, CH_2), 3.73 (s, 2H, CH_2). The spectral data were consistent with that reported in the literature.[172]

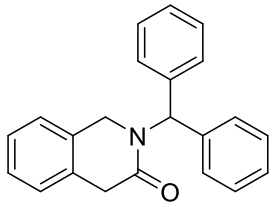


Methyl 2-(3-oxo-3,4-dihydroisoquinolin-2(1H)-yl)propanoate ***158***: Compound was synthesised according to general procedure B. 50mg of methyl 2-(2-formylphenyl)acetate. RNH_2 = Alanine methylester hydrochloride. 1 eq. Et_3N added to generate free base. 1mL THF. Product was isolated as an oil (32% yield). IR (thin film) cm^{-1}: 3037, 2850, 2925, 1655, 1594, 1497, 1460, 1407. ^1H NMR (400 MHz, $CDCl_3$): δ 7.18 - 7.31 (m, 4H, H^{AR}), 5.38 (q, *J* = 7.3 Hz, 1H, C*H*), 4.41 - 4.55 (m, 2H, CH_2), 3.73 (s, 3H, OCH_3), 3.67 (br s, 2H, CH_2), 1.50 (d, *J* = 7.3 Hz, 3H, CH_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 172.1, 169.5, 132.9, 131.8, 127.7, 127.2, 126.7, 125.1, 52.3, 51.5, 47.0, 37.8, 14.5

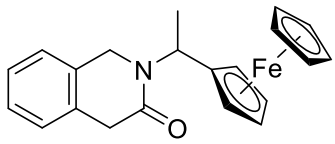
ppm. HRMS (ESI- Waters XEVO G2-XS QTof) m/z: $[M + H]^+$ calcd for $C_{13}H_{16}N_1O_3$, 234.1130; found, 234.1131.



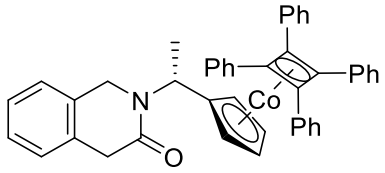
<u>*2-(1-(Pyridin-4-yl)ethyl)-1,4-dihydroisoquinolin-3(2H)-one* ***159***</u>: Compound was synthesised according to general procedure B. 50mg of methyl 2-(2-formylphenyl)acetate. RNH_2 = α-Methyl-4-pyridinemethanamine. 1mL THF. Product was isolated as an oil (22% yield). IR (thin film) cm^{-1}: 3035, 2980, 2940, 1714, 1667, 1599, 1556, 1458, 1414. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.54 - 8.57 (m, 2H, H^{AR}), 7.26 - 7.32 (m, 1H, H^{AR}), 7.16 - 7.24 (m, 4H, H^{AR}), 7.05 (d, J = 7.3 Hz, 1H, H^{AR}), 6.13 (q, J = 7.3 Hz, 1H, C*H*), 4.33 (d, J = 15.4 Hz, 1H, CH_2), 3.97 (d, J = 15.4 Hz, 1H, CH_2), 3.72 (s, 2H, CH_2), 1.62 (d, J = 7.3 Hz, 3H, CH_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.4, 150.1, 149.4, 132.4, 131.6, 127.8, 127.2, 126.8, 125.0, 122.0, 49.5, 45.3, 38.3, 15.5 ppm. HRMS (ESI- Waters XEVO G2-XS QTof) m/z: $[M + H]^+$ calcd for $C_{16}H_{17}N_2O_1$, 253.1341; found, 253.1340.



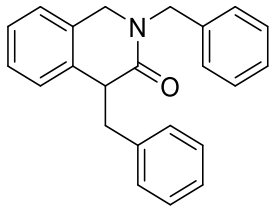
<u>*2-(Diphenylmethyl)-1,4-dihydroisoquinolin-3(2H)-one* ***160***</u>: Compound was synthesised according to general procedure B. 100mg of methyl 2-(2-formylphenyl)acetate. RNH_2 = Benzhydrylamine. 10 mL THF. Product was isolated as a yellow crystalline solid (54% yield). Mp: 159-160°C, IR (thin film) cm^{-1}: 3019, 2915, 1740, 1650, 1601, 1583, 1493, 1468, 1451, 1422. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37 – 7.27 (m, 8H, H^{AR}), 7.25 – 7.20 (m, 6H, H^{AR}), 7.07 (d, J = 7.5 Hz, 1H, C*H*), 4.18 (s, 2H, CH_2), 3.73 (s, 2H, CH_2) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ 169.7, 138.7, 132.8, 132.4, 128.8, 128.7, 127.8, 127.7, 127.2, 126.8, 125.3, 59.9, 47.4, 38.7 ppm. HRMS (ESI- Waters XEVO G2-XS QTof) m/z: $[M + H]^+$ calcd for $C_{22}H_{20}N_1O_1$, 314.1545; found, 314.1541.



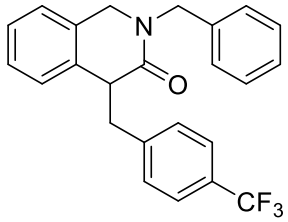
2-(1-Ethyl)ferrocene-1,4-dihydroisoquinolin-3(2H)-one ***161***: Compound was synthesised according to general procedure B. 73mg of methyl 2-(2-formylphenyl)acetate. RNH_2 = 1-(aminoethyl)ferrocene. 10 mL THF. Product was isolated as an orange oil (70% yield). IR (thin film) cm^{-1}: 3082, 2978, 2893, 1739, 1632, 1499, 1471, 1455, 1435. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.21 (dd, *J* = 8.9, 5.5 Hz, 1H, H^{AR}), 7.15 (dd, *J* = 11.4, 7.4 Hz, 2H, H^{AR}), 7.03 (d, *J* = 7.4 Hz, 1H, H^{AR}), 5.92 (q, *J* = 7.0 Hz, 1H, C*H*), 4.27 – 4.24 (m, 1H), 4.18 – 4.10 (m, 9H), 3.98 (d, *J* = 15.6 Hz, 1H), 3.60 (s, 2H, CH_2), 1.50 (d, *J* = 7.0 Hz, 3H, CH_3) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ 168.4, 132.7, 132.3, 127.5, 127.1, 126.6, 125.3, 87.7, 69.1, 68.8 (d, *J* = 2.7 Hz), 67.5, 66.7, 47.9, 44.5, 38.4, 16.5 ppm. HRMS (ESI- Waters XEVO G2-S) m/z: [M] calcd for $C_{21}H_{21}N_1O_1Fe_1$, 357.1019; found, 357.1014.



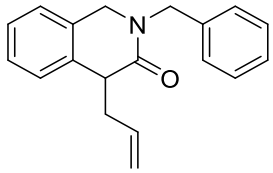
2-(Ethylcyclopentadienyltetraphenylcyclobutadienecobalt)-1,4-dihydroisoquinolin-3(2H)-one ***162***: Compound was synthesised according to general procedure B. 17mg of methyl 2-(2-formylphenyl)acetate. RNH_2 = aminoethylcyclopentadienyltetraphenylcyclobutadienecobalt. 10 mL THF. Product was isolated as a dark orange oil (95 % yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 – 7.44 (m, 8H, H^{AR}), 7.26 – 7.21 (m, 12H, H^{AR}), 7.20 – 7.16 (m, 1H, H^{AR}), 7.11 (dd, *J* = 13.5, 7.3 Hz, 2H, H^{AR}), 6.98 (d, *J* = 7.4 Hz, 1H, H^{AR}), 5.49 (q, *J* = 6.9 Hz, 1H, C*H*), 4.74 – 4.72 (m, 1H, CpC*H*), 4.64 (dd, *J* = 4.1, 2.5 Hz, 1H, CpC*H*), 4.60 (dt, *J* = 2.7, 1.5 Hz, 1H, CH_2), 4.52 (td, *J* = 2.7, 1.5 Hz, 1H, CH_2), 4.08 (d, *J* = 15.6 Hz, 1H, CpC*H*), 3.90 (d, *J* = 15.6 Hz, 1H, CpC*H*), 3.53 (s, 2H, CH_2), 0.85 (d, *J* = 6.9 Hz, 3H, CH_3). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.1, 136.1 (s, 4C), 132.7, 132.3, 128.9 (s, 6C), 128.2 (s, 6C), 127.4, 127.1, 126.6 (s, 4C), 126.5, 125.2, 98.4, 83.9, 82.9, 82.7, 81.6, 75.3 (s, 4C), 45.6, 44.6, 38.3, 15.3. HRMS (ESI- Waters XEVO G2-S) m/z: $[M + H]^+$ calcd for $C_{44}H_{37}Co_1N_1O_1$, 654.2207; found, 654.2210.



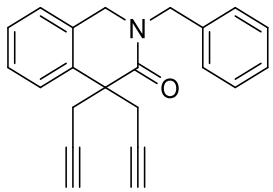
2,4-Dibenzyl-1,2-dihydroisoquinolin-3(4H)-one ***163***: Compound was synthesised according to general procedure C. RBr = benzyl bromide. Rf = 0.18 (4:1 PE:EtOAc) Product was isolated as a yellow oil (95% yield). IR (thin film) cm^{-1}: 3435, 2075, 1643, 1496, 1454. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32 – 7.24 (m, 3H, H^{AR}), 7.24 – 7.19 (m, 3H, H^{AR}), 7.18 – 7.10 (m, 2H, H^{AR}), 7.02 (s, 3H, H^{AR}), 6.90 (d, *J* = 7.1 Hz, 1H, H^{AR}), 6.73 (d, *J* = 7.1 Hz, 2H, H^{AR}), 4.76 (d, *J* = 14.7 Hz, 1H, CH_2), 4.47 (d, *J* = 14.7 Hz, 1H, CH_2), 3.99 (t, *J* = 5.5 Hz, 1H, C*H*), 3.87 (d, *J* = 15.5 Hz, 1H, CH_2), 3.46 (d, *J* = 15.5 Hz, 1H, CH_2), 3.31 (dd, *J* = 6.7 Hz, 1H, CH_2), 3.14 (dd, *J* = 4.4 Hz, 1H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ 137.2, 136.6, 135.2, 131.6, 129.8, 128.7, 128.4, 128.0, 127.9, 127.6, 127.4, 126.7, 125.0, 50.3, 49.6, 48.8, 41.5 ppm. HRMS (ESI-Orbitrap) m/z: $[M + Na]^+$ calcd for $C_{23}H_{21}N_1O_1Na_1$, 350.1515; found, 350.1515. The spectral data were consistent with that reported in the literature[82]



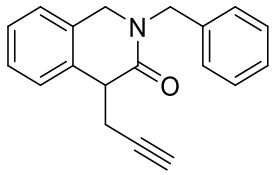
2-Benzyl-4-(4-(trifluoromethyl)benzyl)-1,2-dihydroisoquinolin-3(4H)-one ***164***: Compound was synthesised according to general procedure C. RBr = 4-(trifluoromethyl)benzyl bromide. Rf = 0.68 (4:1 CH_2Cl_2: EtOAc) Product was isolated as a yellow oil (40% yield). IR (thin film) cm^{-1}: 3032, 2928, 1649, 1486, 1455. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34 – 7.28 (m, 3H, H^{AR}), 7.27 – 7.17 (m, 6H, H^{AR}), 7.02 (d, *J* = 7.5 Hz, 1H, H^{AR}), 6.95 (d, *J* = 7.5 Hz, 1H, H^{AR}), 6.81 (d, *J* = 8.0 Hz, 2H, H^{AR}), 4.68 (d, *J* = 14.5 Hz, 1H, CH_2), 4.68 (d, *J* = 14.5 Hz, 1H, CH_2), 4.56 (d, *J* = 14.5 Hz, 1H, CH_2), 4.02 – 3.93 (m, 2H, C*H*,CH_2), 3.51 (d, *J* = 15.8 Hz, 1H, CH_2), 3.38 (dd, *J* = 13.0, 5.6 Hz, 1H, CH_2), 3.18 (dd, *J* = 13.0, 5.6 Hz, 1H, CH_2) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ 170.4, 141.4, 136.3, 134.5, 131.4, 130.0, 128.8, 128.6, 127.8, 127.8, 127.7, 127.0, 125.4, 125.2, 124.8 (q, *J* = 3.8 Hz), 123.2, 50.5, 49.7, 48.1, 41.1 ppm. HRMS (ESI-Orbitrap) m/z: $[M + Na]^+$ calcd for $C_{24}H_{20}F_3N_1O_1Na_1$, 418.1395; found, 418.1394.



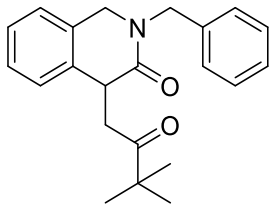
4-Allyl-2-benzyl-1,2-dihydroisoquinolin-3(4H)-one ***165***: Compound was synthesised according to general procedure C. RBr = allyl bromide. Rf = 0.33 (4:1 PE:EtOAc) Product was isolated as a yellow oil (58% yield). IR (thin film) cm^{-1}: 3435, 2075, 1634, 1497, 1453. ^{1}H NMR (500 MHz, $CDCl_3$): δ δ 7.26 (m, 6H, H^{AR}), 7.22 – 7.15 (m, 2H, H^{AR}), 7.06 (d, *J* = 7.5 Hz, 1H, H^{AR}), 5.75 – 5.66 (m, 1H), 5.01 – 4.95 (m, 2H, CH_2), 4.89 (d, *J* = 14.7 Hz, 1H, CH_2), 4.63 (d, *J* = 14.7 Hz, 1H, CH_2), 4.51 (d, *J* = 15.9 Hz, 1H, CH_2), 4.20 (d, *J* = 15.9 Hz, 1H, CH_2), 3.72 (t, *J* = 6.4 Hz, 1H, C*H*), 2.69 – 2.63 (m, 2H, =CH_2). ^{13}C NMR (126 MHz, $CDCl_3$): δ 171.3, 136.9, 135.8, 134.4, 131.1, 128.8, 128.2, 127.7, 127.7, 127.5, 126.7, 125.3, 118.0, 50.3, 50.0, 47.5, 38.7 ppm. HRMS (ESI-Orbitrap) m/z: $[M + Na]^+$ calcd for $C_{19}H_{19}N_1O_1Na_1$, 300.1359; found, 300.1352. The spectral data were consistent with that reported in the literature[82]



2-Benzyl-4,4-di(prop-2-ynyl)-1,2-dihydroisoquinolin-3(4H)-one ***166***: Compound was synthesised according to general procedure C. RBr = propargyl bromide. Rf = 0.92 (4:1 CH_2Cl_2:EtOAc) Product was isolated as a yellow oil (29% yield). IR (thin film) cm^{-1}: 3449, 3293, 2925, 2855, 2119, 1644, 1495, 1451, 1430. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.44 (d, *J* = 8.0 Hz, 1H, H^{AR}), 7.39 – 7.25 (m, 7H, H^{AR}), 7.07 (d, *J* = 7.6 Hz, 1H, H^{AR}), 4.86 (s, 2H, CH_2), 4.47 (s, 2H, CH_2), 3.11 (dd, *J* = 16.4, 2.5 Hz, 2H, CH_2), 2.77 (dd, *J* = 16.4, 2.5 Hz, 2H, CH_2), 1.82 (t, *J* = 2.5 Hz, 2H, C*H*) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ 170.3, 136.6, 135.2, 131.1, 128.7, 128.3, 127.7, 127.3, 126.4, 125.4, 80.2, 71.1, 50.9, 49.8, 49.4, 29.4 ppm. HRMS (ESI-Orbitrap) m/z: $[M + Na]^+$ calcd for $C_{22}H_{19}N_1O_1Na_1$, 336.1359; found, 336.1358.

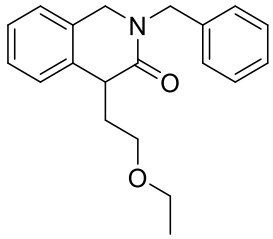


2-Benzyl-4-(prop-2-ynyl)-1,2-dihydroisoquinolin-3(4H)-one ***167***: **135** (20 mg) was dissolved in dry THF (0.4 mL), placed under an N_2 atmosphere and cooled to -78 °C with stirring. 1.1 equivalents of *n*-BuLi added and the reaction stirred for a further 10 minutes. 5 equivalents Propargyl bromide was then added and the solution immediately removed from the cooling bath and allowed to come up to room temperature. Quenched with the slow addition of distilled water (1 mL). Diluted with EtOAc (5 mL) and washed with distilled water (5 mL) and brine (5 mL). Organic layer dried over $MgSO_4$ and filtered. The solvent was removed via evaporation and the resulting product purified by column chromatography. RBr = propargyl bromide. Rf = 0.75 (4:1 CH_2Cl_2:EtOAc) Product was isolated as a yellow oil (83% yield). IR (thin film) cm^{-1}: 3289, 2920, 2850, 1638, 1496, 1454. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35 – 7.22 (m, 8H, H^{AR}), 7.09 (d, J = 7.5 Hz, 1H, H^{AR}), 4.90 (d, J = 14.8 Hz, 1H, CH_2), 4.68 (d, J = 14.8 Hz, 1H, CH_2), 4.58 (d, J = 15.8 Hz, 1H, CH_2), 4.26 (d, J = 15.8 Hz, 1H, CH_2), 3.79 – 3.73 (m, 1H, CH), 2.97 (ddd, J = 16.7, 5.8, 2.6 Hz, 1H, CH_2), 2.88 (ddd, J = 16.7, 5.8, 2.6 Hz, 1H, CH_2), 1.87 (t, J = 2.6 Hz, 1H, CH) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ 170.1, 136.7, 134.5, 131.5, 128.8 (2C), 128.3 (2C), 127.7, 127.5, 127.2, 125.4, 81.0, 70.9, 50.5, 50.2, 45.3, 29.9, 23.9 ppm. The spectral data were consistent with that reported in the literature.[82]

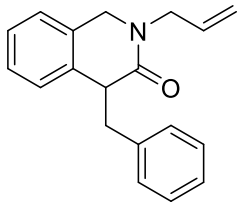


2-Benzyl-4-(3,3-dimethyl-2-oxobutyl)-1,2-dihydroisoquinolin-3(4H)-one ***168***: Compound was synthesised according to general procedure C. RBr = 1-bromopinacolone. Rf = 0.74 (4:1 CH_2Cl_2:EtOAc) Product was isolated as a yellow oil (81% yield). IR (thin film) cm^{-1}: 3466, 2970, 2870, 2037, 1702, 1645, 1495, 1478, 1453. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34 – 7.29 (m, J = 7.2 Hz, 2H, H^{AR}), 7.28 – 7.23 (m, 3H, H^{AR}), 7.22 (d, J = 7.5 Hz, 1H, H^{AR}), 7.17 (t, J = 7.5 Hz, 1H, H^{AR}), 7.08 (d, J = 7.5 Hz, 1H, H^{AR}), 7.05 (d, J = 7.5 Hz, 1H, H^{AR}), 4.84 (d, J = 15.0 Hz, 1H, CH_2), 4.68 (d, J = 15.0 Hz, 1H, CH_2), 4.47 (d, J = 15.5 Hz, 1H, CH_2), 4.39 (d, J = 15.5 Hz, 1H, CH_2), 4.08 (t, J = 5.5 Hz, 1H, CH), 3.43 (dd, J = 17.8, 5.5 Hz, 1H, CH_2), 3.27 (dd, J = 17.8, 5.5 Hz, 1H, CH_2), 1.15 (s, 9H, CH_3) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ 213.2, 171.2, 136.8, 135.5, 131.9, 128.8, 128.0,

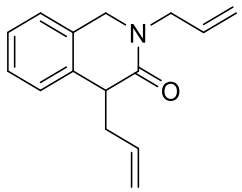
127.6, 127.5, 126.6, 125.7, 125.3, 50.5, 50.0, 44.2, 41.2, 38.0, 26.6 ppm. HRMS (ESI-Orbitrap) m/z: $[M + Na]^+$ calcd for $C_{22}H_{25}N_1O_2Na_1$, 358.1777; found, 358.1775.



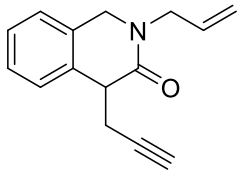
2-Benzyl-4-(2-ethoxyethyl)-1,2-dihydroisoquinolin-3(4H)-one ***169****:* Compound was synthesised according to general procedure C. RBr = 2-bromoethyl ethyl ether. Rf = 0.41 (4:1 CH_2Cl_2:EtOAc) Product was isolated as a yellow oil (58% yield). IR (thin film) cm^{-1}: 3500, 2079, 1642, 1485, 1453. ^1H NMR (500 MHz, $CDCl_3$): δ 7.34 – 7.30 (m, 2H), 7.29 – 7.24 (m, 4H), 7.22 – 7.16 (m, 2H), 7.07 (d, *J* = 7.4 Hz, 1H), 4.79 (d, *J* = 14.8 Hz, 1H, C*H*$_2$), 4.69 (d, *J* = 14.8 Hz, 1H, C*H*$_2$), 4.51 (d, *J* = 15.8 Hz, 1H, C*H*$_2$), 4.19 (d, *J* = 15.8 Hz, 1H, C*H*$_2$), 3.79 (t, *J* = 7.1 Hz, 1H, C*H*), 3.48 – 3.40 (m, 4H, C*H*$_2$), 2.23 – 2.13 (m, 1H, C*H*$_2$), 2.04 - 1.95 (m, 1H, C*H*$_2$), 1.17 (t, *J* = 7.0 Hz, 3H, C*H*$_3$) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ 171.9, 137.0, 136.2, 131.3, 128.8, 128.1, 127.6, 126.7, 125.5, 67.5, 66.2, 50.3, 49.8, 44.7, 33.2, 15.4 ppm. HRMS (ESI-Orbitrap) m/z: $[M + Na]^+$ calcd for $C_{20}H_{23}N_1O_2Na_1$, 332.1626; found, 332.1619.



2-Allyl-4-benzyl-1,2-dihydroisoquinolin-3(4H)-one ***170****:* Compound was synthesised according to general procedure C. RBr = Benzyl bromide. Rf = 0.75 (4:1 CH_2Cl_2:EtOAc) Product was isolated as a clear oil (42% yield). IR (thin film) cm^{-1}: 3029, 2925, 1634, 1487, 1454, 1417. ^1H NMR (500 MHz, $CDCl_3$): δ 7.24 – 7.14 (m, 3H, *H*^{AR}), 7.10 (dd, *J* = 10.1, 4.6 Hz, 2H, *H*^{AR}), 7.01 – 6.95 (m, 2H, *H*^{AR}), 6.77 – 6.74 (m, 2H, *H*^{AR}), 5.69 (ddt, *J* = 16.4, 10.2, 6.1 Hz, 1H, =C*H*), 5.16 – 5.09 (m, 2H, =C*H*$_2$), 4.16 (ddt, *J* = 15.0, 5.9, 1.3 Hz, 1H), 3.94 – 3.87 (m, 3H), 3.45 (d, *J* = 15.7 Hz, 1H), 3.30 (dd, *J* = 13.0, 5.5 Hz, 1H, C*H*$_2$), 3.10 (dd, *J* = 13.0, 5.5 Hz, 1H, C*H*$_2$) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ 170.7, 137.3, 135.3, 132.6, 131.7, 129.8, 128.0, 127.9, 127.5, 126.7 (d, *J* = 4.1 Hz), 124.9, 118.0, 49.4, 49.3, 48.8, 41.4 ppm. HRMS (ESI- Waters XEVO G2-XS QTof) m/z: $[M + H]^+$ calcd for $C_{19}H_{20}N_1O_1$, 278.1545; found, 278.1546.

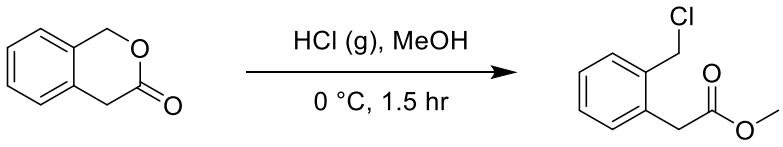


2,4-Diallyl-1,2-dihydroisoquinolin-3(4H)-one ***59***: Compound was synthesised according to general procedure C. RBr = Allyl bromide. Rf = 0.81 (4:1 CH_2Cl_2:EtOAc) Product was isolated as a yellow oil (98% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.29 – 7.20 (m, 2H, H^{AR}), 7.15 (d, *J* = 7.4 Hz, 2H, H^{AR}), 5.78 (m, 1H, C*H*), 5.73 – 5.65 (m, 1H, C*H*), 5.26 – 5.15 (m, 2H, CH_2), 5.01 – 4.93 (m, 2H, CH_2), 4.59 (d, *J* = 15.8 Hz, 1H, CH_2), 4.24 (d, *J* = 15.8 Hz, 1H, CH_2), 4.21 – 4.09 (m, 2H, CH_2), 3.64 (t, *J* = 6.3 Hz, 1H, C*H*), 2.62 (t, *J* = 7.1 Hz, 2H, CH_2) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ 171.0, 135.9, 134.4, 132.8, 131.3, 127.8, 127.5, 126.7, 125.3, 118.0, 117.9, 49.9, 49.4, 47.7, 38.5 ppm. The spectral data were consistent with that reported in the literature.[80]



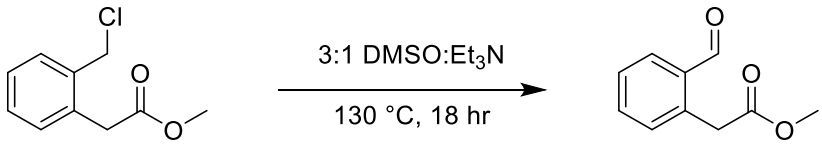
2-Allyl-4-(prop-2-ynyl)-1,2-dihydroisoquinolin-3(4H)-one ***171***: Compound was synthesised according to general procedure C. RBr = Propargyl bromide. Rf = 0.7 (4:1 CH_2Cl_2:EtOAc) Product was isolated as a clear oil (79% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33 – 7.26 (m, 3H, H^{AR}), 7.17 (d, *J* = 7.3 Hz, 1H, H^{AR}), 5.81 (m, 1H, =C*H*), 5.25 – 5.19 (m, 2H, =CH_2), 4.66 (d, *J* = 15.8 Hz, 1H, CH_2), 4.31 (d, *J* = 15.8 Hz, 1H, CH_2), 4.19 (m, 2H, CH_2), 3.71 – 3.67 (m, 1H), 2.94 – 2.83 (m, 2H, CH_2), 1.91 (t, *J* = 2.7 Hz, 1H, C*H*) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ 169.8, 134.6, 132.6, 131.6, 127.7, 127.5, 127.2, 125.3, 118.0, 81.1, 70.8, 50.1, 49.6, 45.3, 23.5 ppm. HRMS (ESI- Waters XEVO G2-XS QTof) m/z: $[M + H]^+$ calcd for $C_{15}H_{16}N_1O_1$, 226.1232; found, 226.1230.

*Methyl [2-(chloromethyl)phenyl]acetate (**151**)*



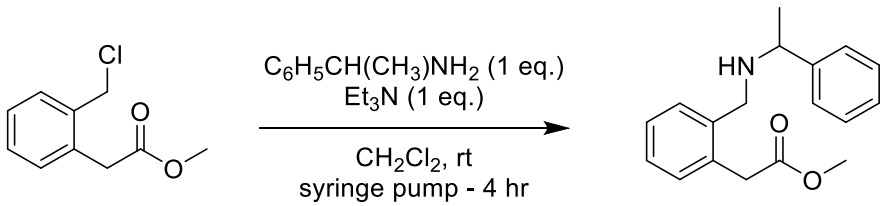
3-Isochromanone (50 mg, 0.34 mmol) was placed in a 5 mL oven-dried MW tube equipped with a stirrer bar under an Ar atmosphere and cooled to 0 °C. 1.5 mL 1.25M HCl in MeOH was added and the reaction stirred overnight. The reaction mixture was diluted with EtOAc (10 mL) and washed with satd. Bicarb solution (15 mL) and brine (15 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent removed in vacuo to yield a pale-orange oil. The spectral data were consistent with that reported in the literature.[125] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42-7.2 (m, 4H, H^{AR}), 4.67 (s, 2H, CH_2), 3.76 (s, 2H, CH_2), 3.70 (s, 3H, CH_3).

*Methyl [2-(formyl)phenyl]acetate (**122**)*



Methyl[2-(chloromethyl0phenyl]acetate (487 mg, 2.5 mmol) was placed in a 5 mL oven-dried MW tube equipped with a stirrer bar. The compound was dissolved in DMSO (1.5 mL) and Et_3N added (400 µL). The reaction vessel was sealed and heated to 130 °C for 18 hours with stirring. The reaction was allowed to cool to room temperature before being diluted with EtOAc (10 mL) and washed with distilled water (3 x 10 mL) and brine (10 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent removed in vacuo to yield an orange oil (420 mg, 98%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.12 (s, 1H, C*H*O), 7.85 (dd, *J* = 7.5, 1.4 Hz, 1H, H^{AR}), 7.57 (td, *J* = 7.5, 1.4 Hz, 1H, H^{AR}), 7.51 (td, *J* = 7.5, 1.4 Hz, 1H, H^{AR}), 7.31 (d, *J* = 7.5 Hz, 1H, H^{AR}), 4.06 (s, 2H, CH_2), 3.71 (s, 3H, CH_3). ^{1}H NMR consistent with commercial material.

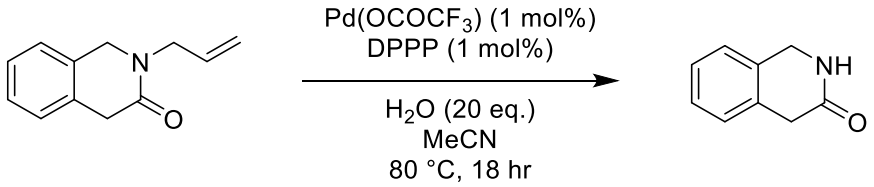
*Methyl (2-{[(1-phenylethyl)amino]methyl}phenyl)acetate (**152**)*



α-methyl benzylamine (65 µL, 0.5 mmol) and Et_3N (70 µL, 0.5 mmol) were placed in a 5 mL oven-dried MW tube equipped with a stirrer bar under an N_2 atmosphere and dissolved in dry CH_2Cl_2 (0.5 mL). **151** (100 mg, 0.5 mmol) was dissolved in dry CH_2Cl_2 (0.5 mL) and added to the mixture *via* syringe pump over a 4-hour period. The reaction was then diluted with EtOAc (10 mL) and washed with distilled water (10 mL) and brine (10 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent removed in vacuo to yield an oil. Purified by silica gel column chromatography (4:1 CH_2Cl_2:EtOAc, Rf = 0.78) to yield the product **152** as a pale yellow oil. (128 mg, 90%)

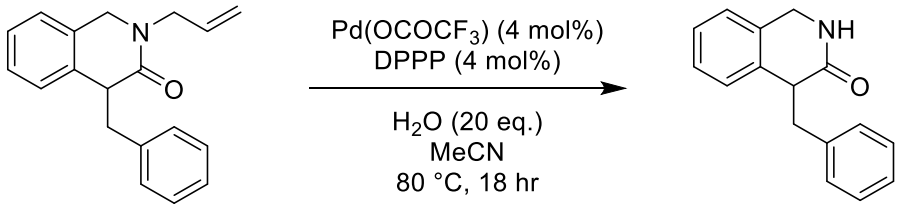
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.28 (m, 4H, H^{AR}), 7.26 (s, 5H, H^{AR}), 3.80 (q, *J* = 6.6 Hz, 1H, C*H*), 3.73 (d, *J* = 15.7 Hz, 1H, CH_2), 3.69 (d, *J* = 15.7 Hz, 1H, CH_2), 3.63 (s, 3H, CH_3), 3.60 (s, 2H, CH_2), 1.36 (d, *J* = 6.6 Hz, 3H, CH_3).

*1,4-Dihydro-3(2H)-isoquinolinone (**54**)*



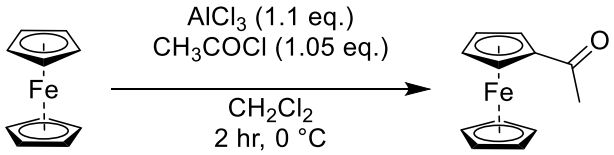
143 (50 mg, 0.27 mmol) was placed in a 5 mL Mw tube equipped with a stirrer bar and was dissolved in 0.5 mL MeCN. $Pd(OCOCF_3)$ (1 mg, 1 mol%) and DPPP (1 mg, 1 mol%) were added followed by H_2O (97 µL). The reaction vessel was sealed at heated to 80 °C for 18 hours. The reaction was removed from heat and allowed to cool to room temperature before being diluted with EtOAc (5 mL) and washed with satd. sodium bicarb. solution (2 x 5 mL) and brine (2 x 5 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent removed under vacuum. Crude ^{1}H NMR analysis showed that had formed. ^{1}H NMR analysis was consistent with literature.[106] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (s, 2H, H^{AR}), 7.20 – 7.14 (m, 2H, H^{AR}), 7.01 (s, br, 1H, N*H*), 4.50 (s, 2H, CH_2), 3.59 (s, 2H, CH_2).

*4-Benzyl-1,4-dihydroisoquinolin-3(2H)-one (**107**)*



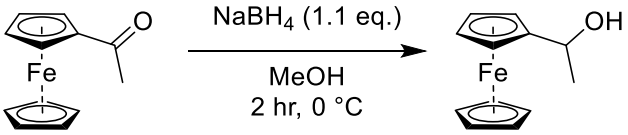
170 (98 mg, 0.353 mmol), $Pd(OCOCF_3)$ (4.70 mg, 0.014 mmol), DPPP (5.83 mg, 0.014 mmol) and H_2O (0.127 mL, 7.07 mmol) were suspended in MeCN (1 mL) in a microwave tube. The vessel was sealed with a stirrer bar and heated to 80 °C for 18 hours. Once cooled the reaction was diluted with EtOAc (~20 mL) and washed with saturated sodium bicarbonate solution (~20 mL) and brine (~20 mL). The organic layer was passed through an isolute phase separator and the solvent removed in vacuo to give an orange oil (88 mg). The sample was loaded in dichloromethane and purified on Companion 5 NP 6G silica (Si) 12g using 0-50% ethyl acetate-cyclohexane over 30 mins. The column was flushed with 3:1 EtOAc:EtOH and the solvent removed in vacuo to yield 62 mg of a yellow/white material. Recrystallised from MeOH:Pentane. A precipitate formed which was filtered off. Solvent removed in vacuo to leave yellow crystals. Crystals left to dry in a nitrogen blowdown. ^{1}H NMR showed compound present with an impurity in about ~33%. Purified on the arrays team MDAP (HpH Method B). Yielded **107** a yellow solid (34 mg, 35%). FT-IR (cm^{-1}): 3182, 3027, 2923, 1667, 1483, 1456, 1415. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 - 7.24 (m, 5H, H^{AR}), 7.01 - 7.05 (m, 1H, H^{AR}), 6.82 - 6.87 (m, 3H, H^{AR}), 4.08 (dd, *J* = 15.7, 4.2 Hz, 1H, CH_2), 3.84 (t, *J* = 6.3 Hz, 1H, C*H*), 3.71 (d, *J* = 15.7 Hz, 1H, CH_2), 3.28 (d, *J* = 6.3 Hz, 1H, CH_2), 3.17 (dd, *J* = 13.0, 4.2 Hz, 1H, CH_2). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.8, 137.2, 134.8, 131.4, 129.7, 128.2, 128.0, 127.2, 126.7, 126.6, 125.1, 48.4, 44.7, 40.8. HRMS (ESI- Waters XEVO G2-XS QTof) m/z: $[M + H]^+$ calcd for $C_{16}H_{16}N_1O_1$, 238.1232; found, 238.1232.

*Acetyl ferrocene (**184**)*



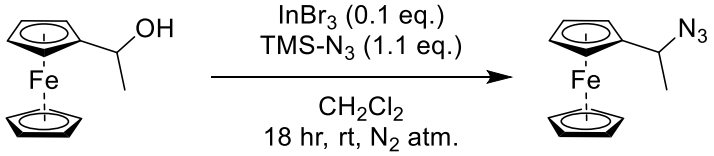
To an oven-dried 10 mL round-bottomed flask equipped with a stirrer bar under an Ar atmosphere was added Ferrocene (1g, 5.4 mmol). The reactants were suspended in dry CH_2Cl_2 (10 mL) and cooled to 0 °C. $AlCl_3$ (0.787 g, 5.9 mmol) was added and the reaction was stirred at 0 °C for 10 minutes. Acetyl chloride (0.447 g, 5.7 mmol) was then added dropwise and upon complete addition, the reaction was left to stir at 0 °C for 2 hours. After 2 hours, the reaction was allowed to warm to room temperature before quenching with distilled water (5 mL). The aqueous layer was extracted into CH_2Cl_2 (2 x 10 mL) and the organic layer was washed with distilled water (1 x 10 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent was removed under vacuum. Yielded a rust coloured solid (1.631 g). Compound purified by silica gel column chromatography (2:1 Hexane:EtOAc). Yielded **184** as an orange solid (1.013 g, 82% yield, Rf = 0.63). The spectral data were consistent with that reported in the literature.[173] ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.77 (s, 2H, CpC*H*), 4.50 (s, 2H, CpC*H*), 4.21 (s, 5H, CpC*H*), 2.40 (s, 3H, CH_3).

*(1-Hydroxyethyl)ferrocene (**185**)*



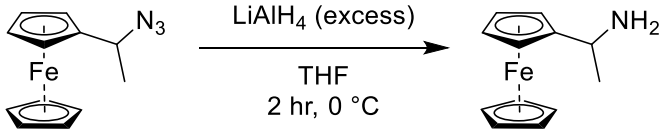
To an oven-dried 50 mL round-bottomed flask equipped with a stirrer bar was added **184** (1.013g, 4.43 mmol). The reactants were dissolved in MeOH (20 mL) and cooled to 0 °C. $NaBH_4$ (169 mg, 4.47 mmol) was added and the reaction was stirred at 0 °C for 2 hours. After 2 hours, the reaction was allowed to warm to room temperature before being poured onto brine (20 mL). The aqueous layer was extracted into Et_2O (2 x 10 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent was removed under vacuum to yield **185** as an orange solid (1.028 g, quant.). The spectral data were consistent with that reported in the literature.[174] ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.58 – 4.52 (m, 1H, O*H*), 4.24 – 4.16 (m, 9H, CpC*H*), 1.82 (d, *J* = 4.8 Hz, 1H, C*H*), 1.44 (d, *J* = 6.4 Hz, 3H, CH_3).

*(1-Azidoethyl)ferrocene (**186**)*



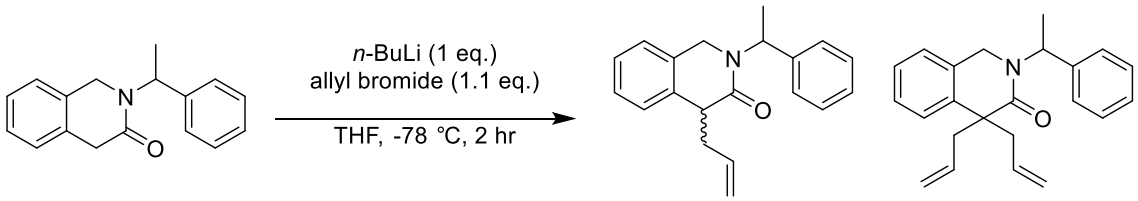
To an oven-dried 50 mL round-bottomed flask equipped with a stirrer bar under and N_2 atmosphere was added **185** (1.028g, 4.47 mmol). The reactants were dissolved in CH_2Cl_2 (15 mL). $TMSN_3$ (520 mg, 4.51 mmol) was added and the reaction was stirred at room temperature for 10 minutes. $InBr_3$ (158 mg, 0.447 mmol) was added and the reaction left stirring at room temperature for 18 hours. The reaction was quenched by the addition of distilled water (20 mL). The aqueous layer was extracted into CH_2Cl_2 (2 x 10 mL) and washed with brine (20 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent was removed under vacuum to yield **186** as an orange oil (1.077g, 94% yield). The spectral data were consistent with that reported in the literature.[149] ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.37 (q, *J* = 6.8 Hz, 1H, C*H*), 4.23 – 4.16 (m, 9H, CpC*H*), 1.55 (d, *J* = 6.8 Hz, 3H, CH_3).

*(1-Aminoethyl)ferrocene (**187**)*



To an oven-dried 50 mL round-bottomed flask equipped with a stirrer bar under and Ar atmosphere was added **186** (1.077g, 4.2 mmol). The reactants were dissolved in dry THF (15 mL) and cooled to 0 °C. An excess of $LiAlH_4$ (498 mg, 12.62 mmol) was added and the reaction was stirred at 0 °C for 2 hours. After 2 hours, the reaction was allowed to warm to room temperature before being poured slowly onto brine (20 mL). The aqueous layer was extracted into EtOAc (2 x 10 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent was removed under vacuum to yield **187** as an orange oil (1.05g, quant.). The spectral data were consistent with that reported in the literature.[175] ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.17 – 4.12 (m, 9H, CpC*H*), 3.79 (q, *J* = 6.6 Hz, 1H, C*H*), 1.53 (br, s, 2H, NH_2), 1.34 (d, *J* = 6.6 Hz, 3H, CH_3).

*2-(1-Phenylethyl)-4-(prop-2-en-1-yl)-1,4-dihydroisoquinolin-3(2H)-one (**188**) and 2-(1-Phenylethyl)-4,4-di(prop-2-en-1-yl)-1,4-dihydroisoquinolin-3(2H)-one (**189**)*

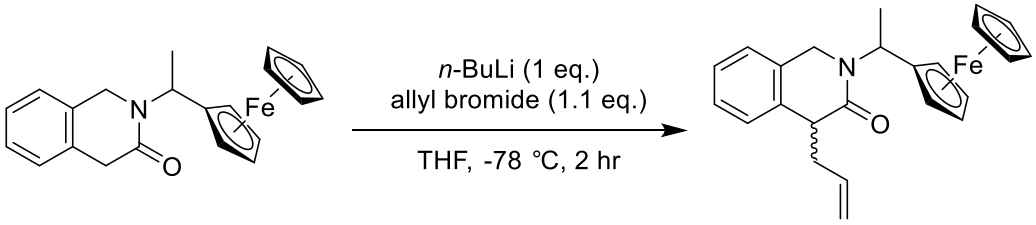


153 (100 mg, 0.398 mmol) was placed in an oven-dried Mw tube and dissolved in dry THF (0.6mL), placed under an N_2 atmosphere and cooled to -78 °C with stirring. *n*-BuLi (0.41 mmol) was added and the reaction was stirred for a further 10 minutes. Allyl bromide (48 mg, 0.398 mmol) was then added and the solution was stirred for a further 2 hours before being allowed to warm to 0 °C. The reaction was quenched with the slow addition of distilled water (5 mL), dilluted with EtOAc (10 mL) and washed with distilled water (10 mL) and brine (10 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent was removed via evaporation. Residue purified by silica-gel column chromatography (2:1 Hexane:EtOAc).

188 Rf = 0.25 (87 mg, 75% yield, yellow oil). ^{1}H NMR data contains both diastereomers of **188.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (s, 16H), 7.06 (d, *J* = 7.5 Hz, 1H), 6.96 (d, *J* = 7.4 Hz, 1H), 6.18 (q, *J* = 7.1 Hz, 2H), 5.79 – 5.66 (m, 2H), 5.05 – 4.96 (m, 4H), 4.41 (d, *J* = 15.6 Hz, 1H), 4.04 (d, *J* = 16.0 Hz, 1H), 3.95 (d, *J* = 16.0 Hz, 1H), 3.90 (d, *J* = 15.6 Hz, 1H), 3.74 – 3.67 (m, 2H), 2.69 – 2.62 (m, 3H), 2.62 – 2.55 (m, 1H), 1.60 (d, *J* = 7.1 Hz, 3H), 1.54 (d, *J* = 7.1 Hz, 3H). HRMS (ESI- Waters XEVO G2-XS QTof) m/z: $[M + H]^+$ calcd for $C_{20}H_{22}N_1O_1$, 292.1701; found, 292.1699.

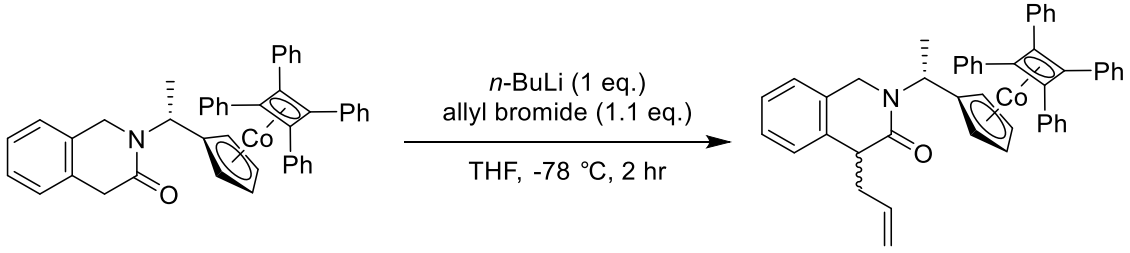
189 Rf = 0.41 (19 mg, 14% yield, yellow oil) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 – 7.27 (m, 7H), 7.17 – 7.13 (m, 1H), 6.95 (d, *J* = 7.5 Hz, 1H), 6.32 (q, *J* = 7.1 Hz, 1H), 5.42 (dddt, *J* = 17.2, 15.6, 10.2, 7.2 Hz, 2H), 5.00 (dddt, *J* = 17.0, 10.1, 2.3, 1.2 Hz, 2H), 4.92 – 4.86 (m, 2H), 4.26 (d, *J* = 16.1 Hz, 1H), 3.87 (d, *J* = 16.1 Hz, 1H), 3.08 (dd, *J* = 13.7, 7.3 Hz, 1H), 2.99 (dd, *J* = 13.5, 7.5 Hz, 1H), 2.57 (dd, *J* = 13.7, 6.9 Hz, 1H), 2.51 (dd, *J* = 13.5, 7.0 Hz, 1H), 1.57 (d, *J* = 7.1 Hz, 3H). HRMS (ESI- Waters XEVO G2-XS QTof) m/z: $[M + H]^+$ calcd for $C_{23}H_{26}N_1O_1$, 332.2014; found, 332.2013.

*2-(1-Ethyl)ferrocene-4-(prop-2-en-1-yl)-1,4-dihydroisoquinolin-3(2H)-one (**190**)*



161 (20 mg, 80 µmol) was dissolved in dry THF (0.6 mL) under an N_2 atmosphere and cooled to -78°C. Stirred for 15 minutes. nBuLi (30 µL, 2.7M in toluene) was added and the reaction stirred for a further 15 minutes. Allyl bromide (7 µL, 80 µmol) was added and the reaction stirred for a further 2 hours at -78°C. After 2 hours, the reaction was removed from cool bath and allowed to warm to room temperature before quenching with distilled water (2 mL). The reaction was diluted with EtOAc (5 mL) before being washed with distilled water (5 mL) and brine (5 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to yield a yellow oil. Purified by silica gel column chromatography (4:1 CH_2Cl_2:EtOAc) to yield **190** as a yellow solid (23 mg, 72% yield) Rf=0.85. ^{1}H NMR is crude and contains both diastereomers of **190**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 (t, *J* = 7.4 Hz, 2H), 7.19 – 7.09 (m, 4H), 7.05 (d, *J* = 7.4 Hz, 1H), 6.97 (d, *J* = 7.5 Hz, 1H), 5.94 (dq, *J* = 20.7, 7.0 Hz, 2H), 5.75 – 5.60 (m, 2H), 5.02 – 4.91 (m, 4H), 4.25 (d, *J* = 9.5 Hz, 3H), 4.21 – 4.06 (m, 18H), 4.01 – 3.95 (m, 2H), 3.91 (d, *J* = 16.1 Hz, 2H), 3.61 (t, *J* = 6.5 Hz, 2H), 2.63 – 2.58 (m, 2H), 2.53 (dd, *J* = 13.9, 6.7 Hz, 2H), 1.51 (d, *J* = 7.1 Hz, 3H), 1.48 (d, *J* = 7.0 Hz, 3H). HRMS (ESI- Waters XEVO G2-S) m/z: $[M + H]^+$ calcd for $C_{24}H_{25}N_1O_1Fe_1$, 397.1332; found, 397.1324.

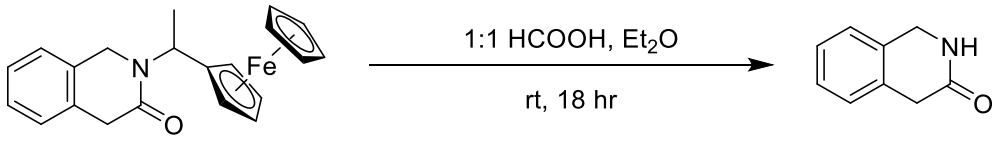
*2-(Ethylcyclopentadienyltetraphenylcyclobutadienecobalt)-4-(prop-2-en-1-yl)-1,4-dihydroisoquinolin-3(2H)-one (**193**)*



162 (33 mg, 51 µmol) was placed in an oven-dried Mw tube and dissolved in dry THF (0.6mL), placed under an N_2 atmosphere and cooled to -78 °C with stirring. *n*-BuLi (51 µmol) added and the

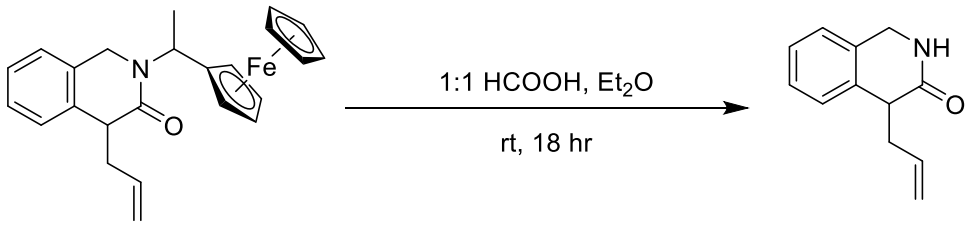
reaction stirred for a further 10 minutes. Allyl bromide (6 mg, 51 µmol) was then added and the solution stirred for a further 2 hours before being allowed to warm to 0 °C. The reaction was quenched with the slow addition of distilled water (5 mL), diluted with EtOAc (10 mL) and washed with distilled water (10 mL) and brine (10 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent was removed via evaporation. The residue was purified by silica-gel column chromatography (2:1 Hexane:EtOAc) to yield **193** as an orange solid (11 mg, 31% yield). ^{1}H NMR is crude and contains both diastereomers of **193**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 – 7.37 (m, 16H), 7.26 (s, 40H), 5.69 – 5.44 (m, 1H), 4.90 (dt, *J* = 22.6, 14.7 Hz, 4H), 4.77 – 4.60 (m, 8H), 4.59 – 4.52 (m, 4H), 4.49 – 4.42 (m, 2H), 4.39 – 4.34 (m, 2H), 4.18 (dd, *J* = 14.1, 7.6 Hz, 1H), 3.91 (t, *J* = 9.7 Hz, 2H), 3.83 (d, *J* = 15.7 Hz, 1H), 3.75 (t, *J* = 7.9 Hz, 1H), 3.56 – 3.52 (m, 1H), 2.60 – 2.44 (m, 4H), 1.04 (dd, *J* = 13.7, 6.9 Hz, 1H), 0.89 (dd, *J* = 11.6, 4.4 Hz, 1H), 0.85 (d, *J* = 7.0 Hz, 3H), 0.79 (d, *J* = 6.9 Hz, 3H).

*1,4-Dihydro-3(2H)-isoquinolinone (**54**)*



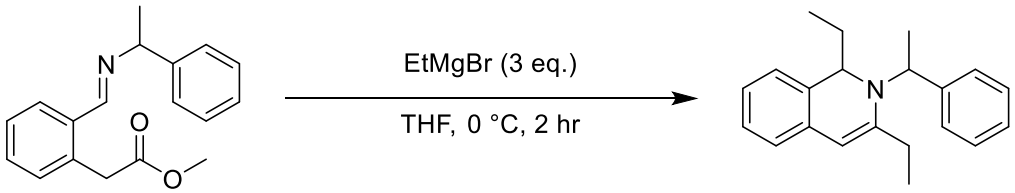
161 (11 mg) was placed in a 5 mL Mw tube and dissolved in 0.9 mL of a 2:1 mix of formic acid to diethyl ether and left stirring at room temperature for 24 hours. The solvent was removed under a nitrogen blowdown. Residue was purified by silica gel column chromatography (4:1 CH_2Cl_2:EtOAc to remove impurities before flushing with 10% MeOH in 4:1 CH_2Cl_2:EtOAc. (Product **54** elutes with the flush as a brown solid (4 mg, 86%). ^{1}H NMR analysis consistent with literature.[106] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.22 (m, 2H, H^{AR}), 7.18 (d, *J* = 7.2 Hz, 2H, H^{AR}), 6.49 (br, s, 1H, NH_2), 4.52 (s, 2H, CH_2), 3.60 (s, 2H, CH_2).

*4-Allyl-1,2-dihydroisoquinolin-3(4H)-one (**194**)*



190 (23 mg, 58 µmol) was placed in a 5 mL Mw tube and dissolved in 0.9 mL of a 2:1 mix of formic acid to diethyl ether and left stirring at room temperature for 24 hours. The solvent was removed under a nitrogen blowdown. Residue was purified by silica gel column chromatography (4:1 CH_2Cl_2:EtOAc to remove impurities before flushing with 10% MeOH. Product **194** elutes with the flush as a brown solid (6 mg, 55%).^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.22 (m, 2H, H^{AR}), 7.16 (t, J = 8.0 Hz, 2H, H^{AR}), 6.41 (br, s, 1H, N*H*), 5.73 (ddt, J = 16.1, 10.9, 7.2 Hz, 1H, C*H*), 5.03 – 4.97 (m, 2H, CH_2), 4.63 (d, J = 15.6 Hz, 1H, CH_2), 4.36 (dd, J = 15.6, 3.8 Hz, 1H, CH_2), 3.58 (t, J = 6.5 Hz, 1H, C*H*), 2.65 (t, J = 6.5 Hz, 2H, CH_2). ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.5, 134.2, 131.0, 128.2, 127.6, 126.9, 125.6, 118.2, 46.8, 45.2, 38.4, 29.9. HRMS (ESI- Waters XEVO G2-XS QTof) m/z: $[M + H]^+$ calcd for $C_{12}H_{14}N_1O_1$, 188.1075; found, 188.1069.

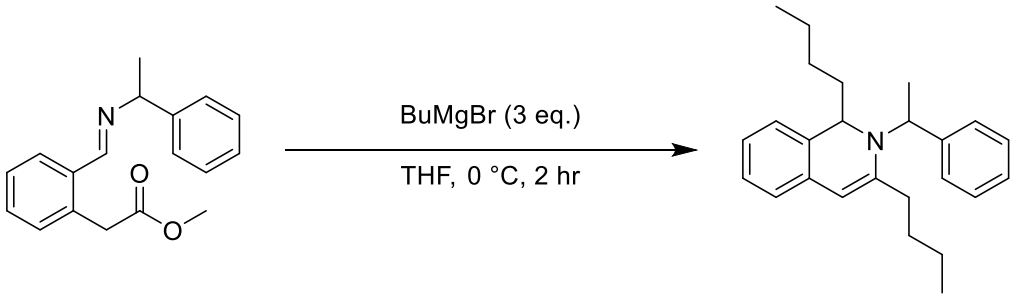
*1,3-Diethyl-2-(1-phenylethyl)-1,2-dihydroisoquinoline (**195**)*



147 (50 mg, 0.18 mmol) was added to an oven-dried Mw tube under an N_2 atmosphere. Dissolved in dry THF (0.5 mL) and cooled to 0 °C. EtMgBr (0.54 mmol) was added and the reaction stirred at 0 °C for 2 hours before being allowed to warm to room temperature. The reaction was quenched by pouring onto 1M HCl (10 mL). Diluted with EtOAc (10 mL) and the organic layer was washed with brine (10 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent removed in vacuo. Residue purified by silica-gel column chromatography (4:1 Hexane:EtOAc) Yielded **195** as a yellow oil, Rf = 0.6 (24 mg, 46% yield). IR (thin film) cm^{-1}: 2921, 1603, 1450. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.09 – 7.00 (m, 6H, H^{AR}), 6.88 – 6.82 (m, 2H, H^{AR}), 6.53 (d, J = 7.3 Hz, 1H, H^{AR}), 5.55 (s, 1H, C*H*), 4.85 (q, J = 7.1 Hz, 1H, C*H*), 4.02 (dd, J = 8.1, 6.1 Hz, 1H, C*H*), 2.51 (dt, J = 14.9, 7.5 Hz, 1H, CH_2), 2.33 – 2.24 (m, 1H, CH_2), 1.66 (t, J = 5.9 Hz, 3H, CH_3), 1.65 – 1.59 (m, 1H, CH_2), 1.48 – 1.41 (m, 1H, CH_2), 1.21 (t, J = 7.5 Hz, 3H, CH_3), 0.76 (t, J = 7.5 Hz, 3H, CH_3). ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.2, 128.6, 128.0, 126.7, 126.4, 125.4, 123.8, 122.1, 101.3, 57.8, 55.3, 29.9 (2C, s), 27.8,

26.7, 20.3, 13.7, 10.3. HRMS (ESI- Waters XEVO G2-S) m/z: $[M + H]^+$ calcd for $C_{21}H_{26}N_1$, 292.2065; found, 292.2066.

*1,3-Dibutyl-2-(1-phenylethyl)-1,2-dihydroisoquinoline (**196**)*



147 (50 mg, 0.18 mmol) was added to an oven-dried Mw tube under an N_2 atmosphere. Dissolved in dry THF (0.5 mL) and cooled to 0 °C. BuMgBr (0.54 mmol) was added and the reaction stirred at 0 °C for 2 hours before being allowed to warm to room temperature. The reaction was quenched by pouring onto 1M HCl (10 mL). Diluted with EtOAc (10 mL) and the organic layer was washed with brine (10 mL), dried over $MgSO_4$, filtered and the solvent removed in vacuo. The residue was purified by silica-gel column chromatography (4:1 Hexane:Et_2O) Yielded **197** as a yellow oil, Rf = 0.6 (11mg, 17% yield). IR (thin film) cm^{-1}: 2928, 1713, 1452. ^1H NMR (500 MHz, $CDCl_3$) δ 7.08 – 6.97 (m, 6H H^{AR}), 6.86 – 6.80 (m, 2H, H^{AR}), 6.51 (d, J = 7.4 Hz, 1H, H^{AR}), 5.55 (s, 1H, C*H*), 4.84 (q, J = 7.1 Hz, 1H, C*H*), 4.11 (dd, J = 8.1, 6.3 Hz, 1H, C*H*), 2.59 – 2.50 (m, 1H, CH_2), 2.18 (dt, J = 12.9, 8.1 Hz, 1H, CH_2), 1.65 (t, J = 6.8 Hz, 3H, CH_3), 1.63 – 1.53 (m, 6H, CH_2), 1.48 – 1.34 (m, 4H, CH_2), 0.96 (t, J = 7.3 Hz, 3H, CH_3), 0.84 (t, J = 7.2 Hz, 3H, CH_3). ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.7, 144.5, 133.2, 130.8, 128.0, 126.7, 126.4, 125.2, 123.9, 122.0, 102.6, 56.3, 55.4, 34.8, 33.4, 31.1, 29.9, 28.0, 22.9, 22.5, 20.2, 14.3, 14.2. HRMS (ESI- Waters XEVO G2-S) m/z: $[M + H]^+$ calcd for $C_{25}H_{34}N_1$, 348.2691; found, 348.2692.

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Appendix

2018ncs0037

UK National Crystallography Service

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Submitted by: **Dr Bew**

Solved by: **Wim T. Klooster**

Sample ID: **B3-EX53**

Crystal Data and Experimental

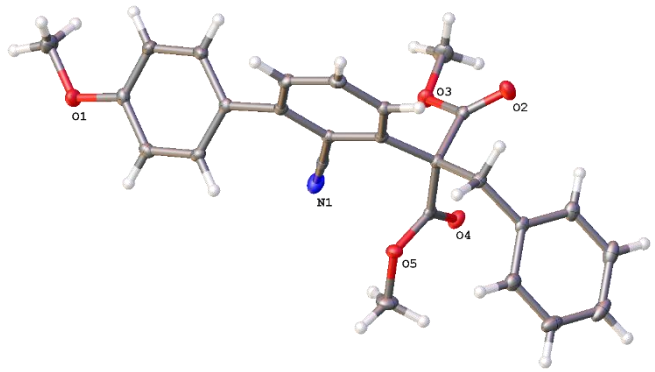

Figure 1: Thermal ellipsoids drawn at the 50% probability level.

Experimental. Single colourless irregular-shaped crystals of (**2018ncs0037**) were recrystallised from methanol. A suitable crystal (0.200×0.080×0.050) mm^3 was selected and mounted on a MITIGEN holder in perfluoroether oil on a Rigaku FRE+ diffractometer equipped with HF Varimax confocal mirrors and an AFC12 goniometer and HG Saturn 724+ detector. The crystal was kept at T = 99.99(10) K during data collection. Using **Olex2** (Dolomanov et al., 2009), the structure was solved with the **ShelXT** (Sheldrick, 2015) structure solution program, using the Intrinsic Phasing solution method. The model was refined with version 2014/7 of **ShelXL** (Sheldrick, 2015) using Least Squares minimisation.

Crystal Data. $C_{26}H_{23}NO_5$, M_r = 429.45, monoclinic, $P2_1/c$ (No. 14), a = 14.3512(2) Å, b = 9.48460(10) Å, c = 15.8435(2) Å, β = 96.3120(10)°, α = γ = 90°, V = 2143.47(5) Å^3, T = 99.99(10) K, Z = 4, Z' = 1, μ(MoK$_\alpha$) = 0.092 mm^{-1}, 47859 reflections measured, 4915 unique (R_{int} = 0.0474) which were used in all calculations. The final wR_2 was 0.0985 (all data) and R_1 was 0.0484 (I > 2(I)).

Compound	**2018ncs0037**
Formula	$C_{26}H_{23}NO_5$
$D_{calc.}$/ g cm^{-3}	1.331
μ/mm^{-1}	0.092
Formula Weight	429.45
Colour	colourless
Shape	irregular
Size/mm^3	0.200×0.080×0.050
T/K	99.99(10)
Crystal System	monoclinic
Space Group	$P2_1/c$
a/Å	14.3512(2)
b/Å	9.48460(10)
c/Å	15.8435(2)
α/°	90
β/°	96.3120(10)
γ/°	90
V/Å^3	2143.47(5)
Z	4
Z'	1
Wavelength/Å	0.71075
Radiation type	MoK_α
Θ_{min}/°	2.507
Θ_{max}/°	27.484
Measured Refl.	47859
Independent Refl.	4915
Reflections Used	4806
R_{int}	0.0474
Parameters	292
Restraints	0
Largest Peak	0.299
Deepest Hole	-0.201
GooF	1.199
wR_2 (all data)	0.0985
wR_2	0.0977
R_1 (all data)	0.0500
R_1	0.0484

Structure Quality Indicators

Reflections:	d min (Mo) 0.77	I/σ 27.0	Rint 4.74%	complete at 2θ=55° 100%
Refinement:	Shift 0.000	Max Peak 0.3	Min Peak -0.2	GooF 1.199

A colourless irregular-shaped crystal with dimensions 0.200×0.080×0.050 mm^3 was mounted on a MITIGEN holder in perfluoroether oil. X-ray diffraction data were collected using a Rigaku FRE+ diffractometer equipped with HF Varimax confocal mirrors and an AFC12 goniometer and HG Saturn 724+ detector, and equipped with an Oxford Cryosystems low-temperature device, operating at T = 99.99(10) K.

Data were measured using ω scans of 1.0 ° per frame for 2.0 s using MoK_α radiation (Rotating-anode X-ray tube, 45 kV, 55 mA). The total number of runs and images was based on the strategy calculation from the program **CrysAlisPro** (Rigaku, V1.171.39.34b, 2017). The maximum resolution achieved was Θ = 27.484°.

Cell parameters were retrieved using the **CrysAlisPro** (Rigaku, V1.171.39.34b, 2017) software and refined using **CrysAlisPro** (Rigaku, V1.171.39.34b, 2017) on 16142 reflections, 34 % of the observed reflections.

Data reduction was performed using the **CrysAlisPro** (Rigaku, V1.171.39.34b, 2017) software which corrects for Lorentz polarisation. The final completeness is 100.00 % out to 27.484° in Θ.

A multi-scan absorption correction was performed using CrysAlisPro 1.171.39.34b (Rigaku Oxford Diffraction, 2017) Empirical absorption correction using spherical harmonics, implemented in SCALE3 ABSPACK scaling algorithm. The absorption coefficient μ of this material is 0.092 mm^{-1} at this wavelength (λ = 0.71075Å) and the minimum and maximum transmissions are 0.72171 and 1.00000.

The structure was solved in the space group $P2_1/c$ (# 14) by Intrinsic Phasing using the **ShelXT** (Sheldrick, 2015) structure solution program and refined by Least Squares using version 2014/7 of **ShelXL** (Sheldrick, 2015). All non-hydrogen atoms were refined anisotropically. Hydrogen atom positions were calculated geometrically and refined using the riding model.

There is a single molecule in the asymmetric unit, which is represented by the reported sum formula. In other words: Z is 4 and Z' is 1.

Reflection Statistics

Total reflections (after filtering)	49502	Unique reflections	4915
Completeness	1.0	Mean I/σ	26.98
hkl_{max} collected	(17, 12, 20)	hkl_{min} collected	(-18, -12, -20)
hkl_{max} used	(18, 12, 20)	hkl_{min} used	(-18, 0, 0)
Lim d_{max} collected	100.0	Lim d_{min} collected	0.36
d_{max} used	8.12	d_{min} used	0.77
Friedel pairs	9131	Friedel pairs merged	1
Inconsistent equivalents	0	R_{int}	0.0474
R_{sigma}	0.0229	Intensity transformed	0
Omitted reflections	0	Omitted by user (OMIT hkl)	0
Multiplicity	(3574, 5670, 5345, 3465, 736, 145, 17, 3)	Maximum multiplicity	16
Removed systematic absences	1643	Filtered off (Shel/OMIT)	0

Table 1: Fractional Atomic Coordinates (×10⁴) and Equivalent Isotropic Displacement Parameters (Å²×10³) for **2018ncs0037**. U_{eq} is defined as 1/3 of the trace of the orthogonalised U_{ij}.

Atom	x	y	z	U_{eq}
O1	1491.3(7)	8144.4(11)	3884.6(7)	20.1(2)
O2	8711.9(7)	8487.8(12)	3971.0(7)	23.1(2)
O3	7198.4(7)	8549.3(11)	3436.8(7)	17.7(2)
O4	7623.8(7)	5818.2(11)	2707.4(6)	16.7(2)
O5	6914.8(7)	4441.2(10)	3603.0(6)	15.1(2)
N1	5310.2(9)	6591.2(14)	2910.6(8)	20.0(3)
C1	1054.4(11)	9481.4(17)	3982.6(11)	24.5(3)
C2	2412.5(9)	8010.8(15)	4195.1(9)	14.7(3)
C3	2936.9(10)	9047.5(15)	4650.3(9)	16.7(3)
C4	3875.7(10)	8782.2(15)	4931.5(9)	16.0(3)
C5	4302.7(9)	7514.0(14)	4757.3(8)	12.7(3)
C6	3759.2(9)	6477.1(14)	4307.4(8)	13.3(3)
C7	2825.2(10)	6723.6(15)	4037.1(8)	14.5(3)
C8	5312.1(9)	7287.9(14)	5054.7(8)	12.3(3)
C9	5635.5(10)	7525.6(15)	5906.1(9)	14.8(3)
C10	6575.3(10)	7382.4(15)	6192.7(8)	15.3(3)
C11	7214.6(9)	7008.8(14)	5632.8(8)	13.2(3)
C12	6930.3(9)	6753.2(14)	4777.3(8)	11.1(3)
C13	5965.6(9)	6900.1(14)	4493.0(8)	11.5(3)
C14	5614.6(9)	6725.9(15)	3608.1(9)	13.5(3)
C15	7689.7(9)	6483.6(14)	4180.7(8)	11.4(3)
C16	7955.6(9)	7942.3(15)	3852.3(8)	13.4(3)
C17	7322.7(11)	9933.4(16)	3094.5(10)	23.2(3)
C18	7391.3(9)	5576.8(14)	3399.2(8)	12.6(3)
C19	6636.0(12)	3510.5(17)	2893.6(10)	24.1(3)
C20	8564.5(9)	5729.4(15)	4662.8(8)	13.5(3)
C21	9162.8(9)	4889.3(15)	4114.9(8)	13.6(3)
C22	9833.6(10)	5531.4(17)	3672.0(9)	17.7(3)
C23	10371.7(10)	4730.8(19)	3173.0(9)	23.1(3)
C24	10258.1(11)	3281.0(19)	3116(1)	25.5(4)
C25	9604.3(11)	2629.8(18)	3567.4(10)	24.1(3)
C26	9059.3(10)	3429.8(16)	4061.5(9)	18.3(3)

Table 2: Anisotropic Displacement Parameters (×10⁴) **2018ncs0037**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2} \times U_{11} + \ldots + 2hka^* \times b^* \times U_{12}]$

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O1	12.9(5)	18.0(5)	28.2(6)	-0.2(4)	-2.5(4)	1.9(4)
O2	15.9(5)	18.8(5)	34.4(6)	4.3(5)	1.6(4)	-3.2(4)
O3	16.6(5)	14.0(5)	22.4(5)	7.5(4)	2.1(4)	1.5(4)
O4	17.6(5)	21.5(5)	11.0(5)	1.2(4)	2.3(4)	5.5(4)
O5	16.8(5)	13.0(5)	15.3(5)	-2.6(4)	0.6(4)	-0.2(4)
N1	17.6(6)	28.5(7)	13.8(6)	0.7(5)	1.4(5)	5.1(5)
C1	16.7(7)	21.0(8)	34.7(9)	-1.1(7)	-2.0(6)	5.3(6)
C2	12.1(6)	16.9(7)	15.5(6)	3.5(5)	2.5(5)	-0.2(5)
C3	15.6(7)	12.5(7)	22.6(7)	-1.8(5)	4.9(5)	2.2(5)
C4	14.9(7)	14.1(7)	19.1(7)	-3.9(5)	3.1(5)	-2.2(5)
C5	13.6(6)	13.2(6)	11.8(6)	1.2(5)	3.5(5)	-0.4(5)
C6	16.6(6)	10.7(6)	13.2(6)	0.7(5)	4.5(5)	1.3(5)
C7	16.7(7)	14.2(7)	12.6(6)	0.2(5)	1.5(5)	-3.4(5)
C8	13.9(6)	9.3(6)	13.8(6)	0.6(5)	2.2(5)	0.3(5)
C9	17.8(7)	14.2(7)	13.2(6)	-2.6(5)	5.1(5)	0.9(5)
C10	20.2(7)	14.6(7)	10.8(6)	-2.0(5)	0.3(5)	-1.0(5)
C11	13.1(6)	12.6(6)	13.4(6)	-0.2(5)	-0.8(5)	0.5(5)
C12	12.8(6)	8.4(6)	12.4(6)	0.5(5)	2.1(5)	0.7(5)
C13	14.2(6)	9.5(6)	10.9(6)	1.1(5)	1.5(5)	0.1(5)
C14	10.2(6)	16.0(7)	14.9(6)	1.5(5)	3.9(5)	2.7(5)
C15	10.7(6)	12.5(6)	10.9(6)	0.1(5)	1.1(5)	1.8(5)
C16	14.1(6)	13.8(6)	12.7(6)	-0.2(5)	3.3(5)	1.7(5)
C17	27.4(8)	15.9(7)	27.3(8)	10.8(6)	7.0(6)	2.2(6)
C18	10.2(6)	13.7(6)	13.6(6)	1.0(5)	-0.5(5)	4.7(5)
C19	27.4(8)	19.0(8)	24.6(8)	-9.1(6)	-2.8(6)	-1.2(6)
C20	13.7(6)	15.3(7)	11.3(6)	0.8(5)	-0.1(5)	2.1(5)
C21	11.2(6)	18.3(7)	10.6(6)	1.0(5)	-1.9(5)	4.0(5)
C22	14.0(6)	22.7(8)	15.9(6)	3.7(6)	-0.9(5)	2.8(6)
C23	15.8(7)	38.9(9)	14.7(7)	4.1(6)	2.6(5)	6.6(6)
C24	20.4(7)	39.5(10)	15.9(7)	-8.1(7)	-0.5(6)	13.1(7)
C25	23.4(8)	21.5(8)	25.7(8)	-8.0(6)	-5.1(6)	8.8(6)
C26	15.3(7)	20.2(7)	18.9(7)	0.1(6)	-0.4(5)	2.5(6)

Table 3: Bond Lengths in Å for **2018ncs0037**.

Atom	Atom	Length/Å
O1	C1	1.4306(18)
O1	C2	1.3648(16)
O2	C16	1.1985(17)
O3	C16	1.3372(17)
O3	C17	1.4390(17)
O4	C18	1.2023(16)
O5	C18	1.3343(17)
O5	C19	1.4504(17)
N1	C14	1.1500(18)
C2	C3	1.391(2)
C2	C7	1.392(2)
C3	C4	1.395(2)
C4	C5	1.3913(19)
C5	C6	1.4004(19)
C5	C8	1.4887(19)
C6	C7	1.3815(19)

Atom	Atom	Length/Å
C8	C9	1.3957(19)
C8	C13	1.4108(18)
C9	C10	1.382(2)
C10	C11	1.3905(19)
C11	C12	1.3931(18)
C12	C13	1.4150(18)
C12	C15	1.5405(18)
C13	C14	1.4461(18)
C15	C16	1.5409(19)
C15	C18	1.5295(18)
C15	C20	1.5686(18)
C20	C21	1.5131(18)
C21	C22	1.392(2)
C21	C26	1.394(2)
C22	C23	1.390(2)
C23	C24	1.387(3)

Atom	Atom	Length/Å
C24	C25	1.386(2)

Atom	Atom	Length/Å
C25	C26	1.391(2)

Table 4: Bond Angles in ° for **2018ncs0037**.

Atom	Atom	Atom	Angle/°
C2	O1	C1	117.51(11)
C16	O3	C17	116.78(11)
C18	O5	C19	114.14(11)
O1	C2	C3	124.66(13)
O1	C2	C7	115.55(12)
C3	C2	C7	119.79(13)
C2	C3	C4	119.13(13)
C5	C4	C3	121.58(13)
C4	C5	C6	118.38(13)
C4	C5	C8	119.75(12)
C6	C5	C8	121.87(12)
C7	C6	C5	120.40(13)
C6	C7	C2	120.69(13)
C9	C8	C5	119.42(12)
C9	C8	C13	118.57(12)
C13	C8	C5	121.94(12)
C10	C9	C8	120.71(12)
C9	C10	C11	120.27(12)
C10	C11	C12	121.46(12)
C11	C12	C13	117.66(12)
C11	C12	C15	118.33(11)
C13	C12	C15	123.68(11)
C8	C13	C12	121.33(12)
C8	C13	C14	117.16(12)

Atom	Atom	Atom	Angle/°
C12	C13	C14	121.45(12)
N1	C14	C13	178.06(14)
C12	C15	C16	106.04(10)
C12	C15	C20	111.05(10)
C16	C15	C20	111.05(11)
C18	C15	C12	115.85(11)
C18	C15	C16	106.81(10)
C18	C15	C20	106.00(10)
O2	C16	O3	124.36(13)
O2	C16	C15	126.03(13)
O3	C16	C15	109.56(11)
O4	C18	O5	125.11(13)
O4	C18	C15	123.35(13)
O5	C18	C15	111.31(11)
C21	C20	C15	115.78(11)
C22	C21	C20	121.75(13)
C22	C21	C26	118.61(13)
C26	C21	C20	119.63(13)
C23	C22	C21	120.39(15)
C24	C23	C22	120.66(15)
C25	C24	C23	119.33(14)
C24	C25	C26	120.12(15)
C25	C26	C21	120.87(15)

Table 5: Torsion Angles in ° for **2018ncs0037**.

Atom	Atom	Atom	Atom	Angle/°
O1	C2	C3	C4	-179.80(13)
O1	C2	C7	C6	178.80(12)
C1	O1	C2	C3	4.7(2)
C1	O1	C2	C7	-175.97(13)
C2	C3	C4	C5	0.9(2)
C3	C2	C7	C6	-1.8(2)
C3	C4	C5	C6	-1.7(2)
C3	C4	C5	C8	178.73(13)
C4	C5	C6	C7	0.75(19)
C4	C5	C8	C9	51.75(18)
C4	C5	C8	C13	-125.31(14)
C5	C6	C7	C2	1.0(2)
C5	C8	C9	C10	-177.24(13)
C5	C8	C13	C12	176.99(12)
C5	C8	C13	C14	-0.10(19)
C6	C5	C8	C9	-127.80(14)
C6	C5	C8	C13	55.14(19)
C7	C2	C3	C4	0.9(2)
C8	C5	C6	C7	-179.70(12)
C8	C9	C10	C11	0.5(2)
C9	C8	C13	C12	-0.1(2)
C9	C8	C13	C14	-177.19(12)
C9	C10	C11	C12	-0.8(2)
C10	C11	C12	C13	0.6(2)
C10	C11	C12	C15	174.26(12)
C11	C12	C13	C8	-0.16(19)
C11	C12	C13	C14	176.81(12)
C11	C12	C15	C16	-88.94(14)
C11	C12	C15	C18	152.79(12)
C11	C12	C15	C20	31.81(16)
C12	C15	C16	O2	117.52(15)
C12	C15	C16	O3	-59.96(13)
C12	C15	C18	O4	139.79(13)
C12	C15	C18	O5	-45.39(15)
C12	C15	C20	C21	155.98(12)
C13	C8	C9	C10	-0.1(2)
C13	C12	C15	C16	84.33(15)
C13	C12	C15	C18	-33.95(18)
C13	C12	C15	C20	-154.93(12)
C15	C12	C13	C8	-173.46(12)
C15	C12	C13	C14	3.5(2)
C15	C20	C21	C22	81.51(16)
C15	C20	C21	C26	-99.86(15)
C16	C15	C18	O4	21.94(17)
C16	C15	C18	O5	-163.24(10)
C16	C15	C20	C21	-86.29(14)
C17	O3	C16	O2	1.8(2)
C17	O3	C16	C15	179.35(11)
C18	C15	C16	O2	-

Atom	Atom	Atom	Atom	Angle/°
				118.37(15)
C18	C15	C16	O3	64.15(13)
C18	C15	C20	C21	29.36(15)
C19	O5	C18	O4	-3.43(19)
C19	O5	C18	C15	-178.14(11)
C20	C15	C16	O2	-3.23(19)
C20	C15	C16	O3	179.29(11)
C20	C15	C18	O4	-96.55(15)
C20	C15	C18	O5	78.27(13)
C20	C21	C22	C23	-179.93(12)
C20	C21	C26	C25	-179.56(13)
C21	C22	C23	C24	-0.8(2)
C22	C21	C26	C25	-0.9(2)
C22	C23	C24	C25	-0.4(2)
C23	C24	C25	C26	1.0(2)
C24	C25	C26	C21	-0.3(2)
C26	C21	C22	C23	1.4(2)

Table 6: Hydrogen Fractional Atomic Coordinates (×10⁴) and Equivalent Isotropic Displacement Parameters (Å²×10³) for **2018ncs0037**. U_{eq} is defined as 1/3 of the trace of the orthogonalised U_{ij}.

Atom	x	y	z	U_{eq}
H1A	1375	10193	3694	37
H1B	1085	9710	4575	37
H1C	411	9438	3744	37
H3	2665	9906	4766	20
H4	4225	9470	5243	19
H6	4029	5617	4190	16
H7	2469	6022	3747	17
H9	5214	7783	6284	18
H10	6781	7536	6763	18
H11	7846	6928	5834	16
H17A	7794	9898	2709	35
H17B	7516	10575	3549	35
H17C	6741	10250	2797	35
H19A	6251	4019	2463	36
H19B	6288	2730	3085	36
H19C	7184	3166	2664	36
H20A	8957	6439	4966	16
H20B	8348	5100	5083	16
H22	9922	6502	3710	21
H23	10812	5172	2874	28
H24	10617	2751	2778	31
H25	9530	1656	3540	29
H26	8620	2985	4360	22

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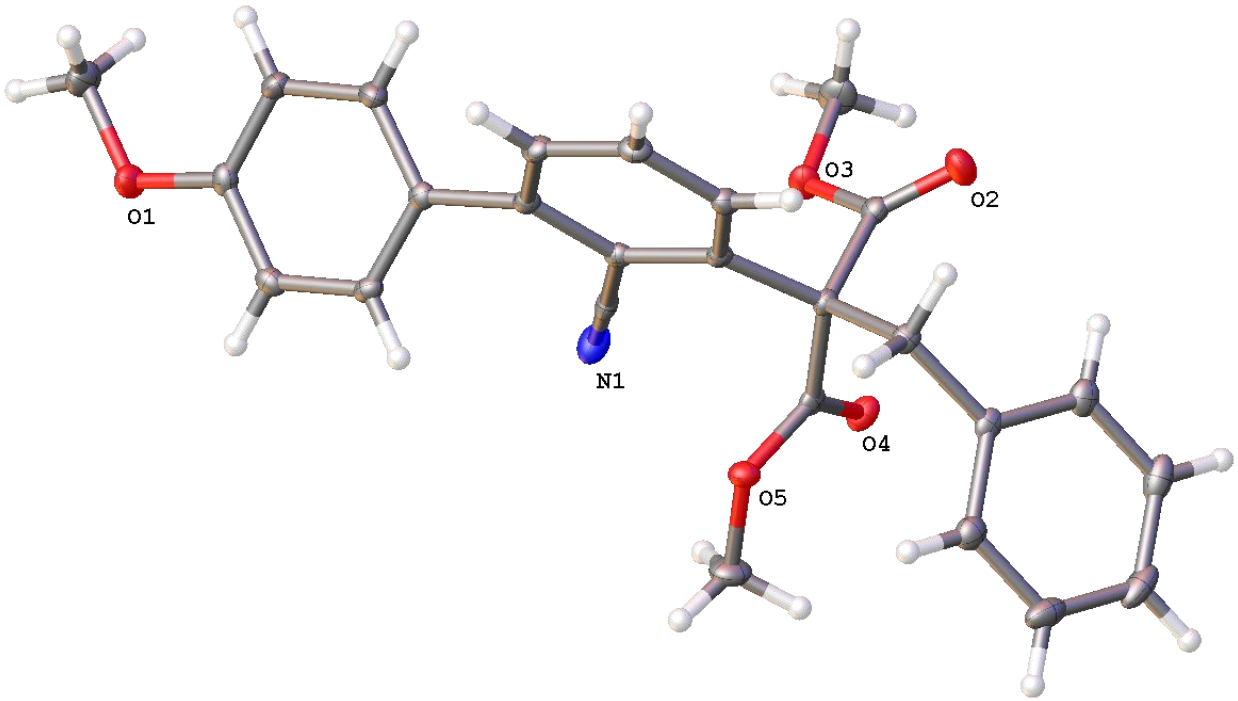
O1
N1
O3
O2
O4
O5