Copper-Catalysed Synthesis of 5- and 6-Membered Nitrogen-Containing Heterocycles

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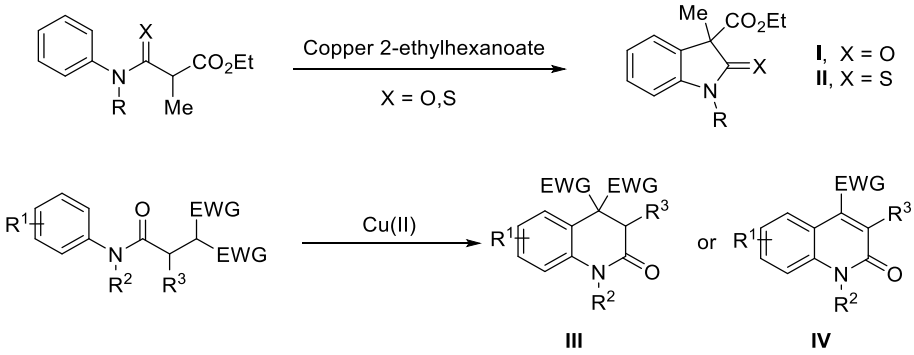
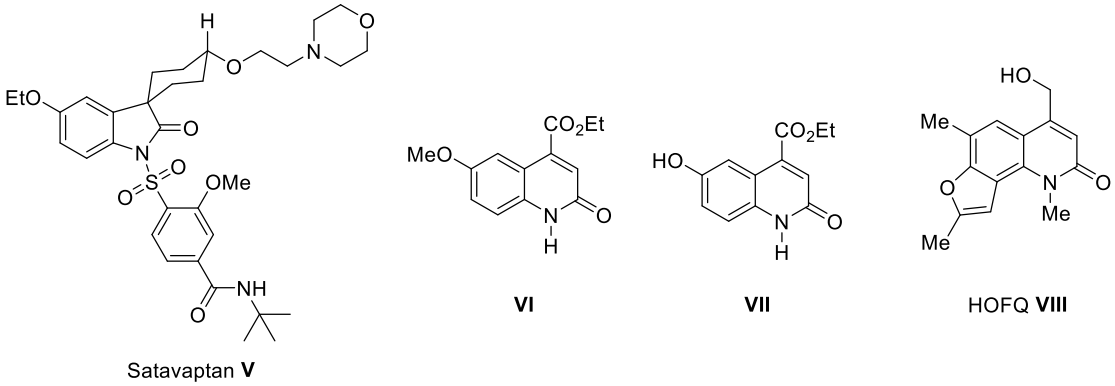
Abstract

Nitrogen-containing heterocycles are an important structural motif, prevalent in both nature and medicine. *N*-Heterocycles can be found at the core of numerous biologically active molecules resulting in a huge amount of attention focussed on the novel synthesis of these privileged motifs from both academic and industrial researchers alike. In recent years the importance of developing efficient, "green" and cost effective routes to medicinal agents has become increasingly at the forefront of modern research.

In 2009 the Taylor group reported the successful synthesis of oxindole heterocycles *via* a copper(II)-mediated approach. Following on from this research, the development of a high-yielding and green set of conditions is described for the synthesis of oxindoles (**I**). The successful application of these conditions to both 5-membered *N*-heterocycles (Chapter 2) and 6-membered *N*-heterocycles (Chapter 3) is described including thio-oxindoles (**II**), 3,4-dihydroquinolin-2(1*H*)-ones (**III**) and 2-quinolinones (**IV**).



Reported, is the application of this methodology to biologically active molecules, including formal synthesis of the oxindole-containing drug Satavaptan (**V**) (Chapter 2.2), the first reported total synthesis of two biologically active, 3,4-dihydroquinolin-2(1*H*)-one containing natural products (**VI** and **VII**) (Chapter 3.7) and efforts towards the total synthesis of the 2-quinolinone-containing drug candidate HOFQ (**VIII)** (Chapter 3.8).



Satavaptan **V** **VI** **VII** HOFQ **VIII**

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Acknowledgements

As I'm sure anyone who has undertaken a PhD will agree, one cannot achieve such a milestone achievement without the help of others. As I sat pondering over who I would like to acknowledge, the realisation of what an impossible task it was suddenly dawned upon me. To thank only the people I have been involved with over the past three years seems somewhat narrow minded given that without support prior to this I would never have been in a position to even to attempt such an undertaking.

During the last three years I have had an amazing time and can genuinely count these among the best and most enjoyable years of my life. I have met great people, had wonderful experiences and learned a lot along the way.

I would like to thank the entire Taylor research group, past and present, for making the working environment such an enjoyable place, as this helped me get through the tougher times. In particular I would like to thank Dr. Tim Hurst for being a great support within my research and Dr. Graeme McAllister for all his help with the preparation of my thesis.

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Though not directly involved in my research over the last three and a half years I would like to thank Prof. Colin Fishwick and Dr. Visuvanathar Sridharan from the University of Leeds. It was during a summer project within the Fishwick group in 2010 that I discovered how interesting research truly is. It is quite possible that should I have not been given that opportunity, I may have never ventured down the path of postgraduate research.

I owe a huge amount to Dr. Sridharan. He encouraged me during my undergraduate studies and it was under his supervision during the summer of 2012 that I learnt a huge amount about practical chemistry and research in general. I owe him a lot and truly appreciate all the time that he invested in me.

I have the best parents and grandparents anyone could ask for. They have always encouraged and supported every decision I have made in life and I am incredibly grateful for everything they have done.

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Whilst herself searching for jobs, working full-time and moving us down from York to London she still found time to bring my dinner up to the office during the many late night thesis writing sessions that took place before the move in addition to all her support since then.

Though this list is hardly exhaustive and there have been numerous other influences over me prior to and during my PhD studies, I am incredibly grateful to everyone who has been involved in my life as without you all, I would not be where I am today.

Declaration

The research presented in this thesis was carried out at the University of York between October 2012 and December 2015. The work is, to the best of my knowledge, original, except where due reference has been made to other workers. This work has not previously been presented for an award at this, or any other, University.

Chapter 1. Introduction: Nitrogen-containing heterocycles

This introduction will review the importance of nitrogen-containing heterocycles, including their use as medicinal agents. The basics of green chemistry and the increasing emphasis on elemental sustainability in synthesis will be highlighted. Finally, the importance of the oxindole motif and the various methods to synthesise it will also be discussed.

1.1 Nitrogen-containing heterocycles and sustainability

1.1.1 The importance of nitrogen-containing heterocycles

Nitrogen-containing heterocycles (*N*-heterocycles) are an incredibly important class of molecules. From the purines and pyrimidines that make up DNA base-pairs, to the plethora of medicines containing an *N*-heterocycle motif,[1] the sheer abundance of these scaffolds is astonishing. Given their abundance in nature it is unsurprising that many compounds containing *N*-heterocycles exhibit biological activity; studies recently showed that *N*-heterocycles are present in 59% of all small molecule drugs (for examples see Figure 1.1).[2]

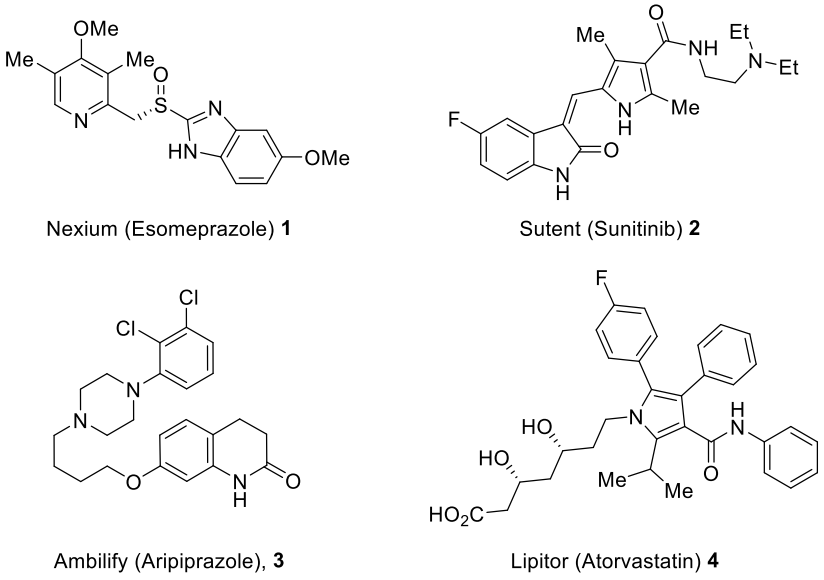


Figure 1.1 Examples of drug molecules containing *N*-heterocycles.

Given the importance of heterocyclic motifs, the field of heterocycle synthesis is a well-researched one, with entire journals dedicated solely to the publication of novel heterocycle syntheses[3] and classic reactions such as the Fischer indole,[4] Hantzsch pyridine[5] and Friedlander quinoline[6] syntheses still present in many undergraduate chemistry curriculums.

Baumann and Baxendale wrote a comprehensive review on the synthetic routes to the best-selling drugs containing 6-membered heterocycles.[7] Many steps in these syntheses utilise transition metals, operate under harsh conditions and give modest yields. Whilst developing novel methods for the

synthesis of heterocycles and drug compounds is still an important area of research, the development of 'greener' and more efficient syntheses of important heterocycles is receiving focus from academic and industrial researchers alike.

1.1.2 Green chemistry principles

The importance of efficient and safe synthesis is not a new consideration, but, it was only in 1998 that a concept called the '12 principles of green chemistry' was outlined by Anastas and Werner.[8] This concept defines what makes a process or product greener than an existing process or product, and is a philosophy that applies to all areas of chemistry. Below are the 12 principles of green chemistry and their relevance to the pharmaceutical industry.

1. Prevent waste

This can be achieved by developing methods where minimal purification of reagents or products is required. Tandem reactions or telescoped procedures can greatly reduce the amount of waste produced as do reactions carried out in minimal solvent. This is a crucial metric especially upon scale up of a reaction; all waste needs to be disposed of appropriately or recycled, meaning a process that produces a lot of waste creates increased cost.

2. Maximise atom economy

By developing procedures which incorporate as much of the starting materials into the product as possible, atom economy can be maximised. Atom economy[9] is calculated:

$$A + B \xrightarrow[\text{Conditions}]{\text{Reagents}} C \qquad \text{Atom economy (\%)} = \frac{MW(C)}{MW(A) + MW(B)} \times 100$$

Atom economy is a good measure of the efficiency of a reaction at the molecular level. By incorporating high amounts of the starting material into the product, the amount of waste produced is minimised. The reason this is favourable is the same as for metric 1.

3. Design less hazardous chemical syntheses

Design procedures that produce minimal amounts of toxic substances. This not only includes chemical products and by-products but also the choice of reagents during the work-up. This metric concerns the safety of the chemists performing the reactions. By minimising the amount of toxic substance produced, the risk of injury, illness or death are also reduced. Whilst this is an important consideration, there are times when the production of toxic substances is unavoidable.

4. Design safer chemicals and products

This can be achieved by designing chemical products which have little or no toxicity but are still fully effective. This metric is not considered a high priority as the synthesis carried out in the pharmaceutical industry and academia is often to create novel substances with unknown toxicity.

5. Use safer solvents and conditions

This can be achieved by using solvents which are non-toxic and carrying out reactions at temperatures that are below the solvent flash point. This is something that is now a huge focus within the pharmaceutical industry, with toxic solvents such as benzene and DMF now 'black-listed' and the discovery alternative solvents being researched. Solvent choice in synthesis is not only important from a safety perspective, but also in terms of cost; toxic solvents require precautions to be taken when disposing or recycling which often has a higher cost associated with it.

6. Increase energy efficiency

By running reactions as close to room temperature and pressure as possible, the energy efficiency can be increased. Efficient energy transfer is important as it can reduce the cost of a process and have a less negative environmental impact. Whilst this is a metric many people consider, it is not always practical as many reactions require very high or very low temperatures to achieve the desired outcome.

7. Use renewable feedstocks

The use of renewable starting materials such as agricultural products or by-products of other processes. This is a metric very few chemists consider, as the scope of renewable feedstocks is limited and not usually practical.

8. Reduce chemical derivatives

By minimising the number of protecting groups and temporary modifications used, waste can be reduced and overall efficiency improved. This is a consideration that most chemists will naturally attempt to adhere to where possible, as even at small scale, the additional work required to carry out reactions to add and remove protecting groups is impractical and costly.

9. Use catalysis, not stoichiometric reagents

Waste is minimised by using catalysts as opposed to stoichiometric reagents. Elementally sustainable, non-toxic and inexpensive catalysts are also preferred. This area is the subject of many research projects in both academia and the pharmaceutical industry. As many reagents and catalysts

are made from earth metals, investigating ways to better utilise these finite elements is important. The ability to use more abundant earth metals for catalysis is also preferable over metals in short supply.

10. Design chemicals and products to degrade after use

The design of chemicals that are able to degrade to harmless substances after use are favourable over those which accumulate in the environment. Very few reactions achieve this and few chemists place much importance on the ability to design chemicals that degrade after use.

11. Real-time analysis for pollution prevention

By monitoring reactions in real-time the formation of by-products can be minimised therefore reducing waste and improving efficiency. Monitoring reacting in real-time is mainly used to identify when a reaction is complete. Monitoring specifically for pollution prevention is not a metric that we will discuss further.

12. Minimise the potential for accidents

This can be achieved by considering potential incompatibilities, unsafe reaction conditions and toxic reagents.

It is important to note that there is no such thing as a wholly green process; these criteria are used as a measure of comparison between processes to define whether a method is 'greener' or not.

Another metric for measuring the overall efficiency of a reaction invented by GlaxoSmithKline (GSK)[9] is reaction mass efficiency (RME) which, unlike atom economy, takes into account the stoichiometry of reactants being used. RME is calculated:

$$A + B \xrightarrow[\text{Conditions}]{\text{Reagents}} C \qquad \text{RME} = \frac{\text{Mass of C}}{\text{Mass of A + Mass of B}}$$

Another metric called effective mass yield (EMY) takes into account the mass of desired product produced from the total mass of substances required to obtain it. This not only includes the masses of reactants, additives and solvents for the reaction but also any material required for purification including solvents, drying agents and chromatography. Effective mass yield is calculated:

$$A + B \xrightarrow[\text{Conditions}]{\text{Reagents}} C \qquad \text{EMY (\%)} = \frac{\text{Mass of product x 100}}{\text{Total mass input}}$$

Despite effective mass yield being a very effective measure of the overall efficiency of a reaction from a mass balance perspective, it is very difficult to compare results with literature information quantitatively, as vital information is often absent. This most commonly includes the volume of

solvent used during purification, the mass of drying agents being used, the mass of silica used in flash column chromatography etc. Many metrics have been identified however and as discussed, some are more significant than others. Metrics that will be discussed further during this report include waste prevention, atom economy, solvent choice, catalysis and RME.

Given that a common outcome of a highly 'green' and efficient synthesis is reduced cost, it is therefore of great interest to the pharmaceutical industry, with whole initiatives been funded to achieve greener processes for the synthesis of medicines.[10]

1.1.3 Elemental sustainability

The use of transition metals for C–C bond forming reactions is extremely common amongst academic researchers and the pharmaceutical industry alike. Whilst transition metals are extremely useful in synthesis, many reactions rely on the use of metal salts comprised of scarce elements such as the frequently used Suzuki cross-coupling reaction which requires a palladium-based catalyst and is used extensively by the pharmaceutical industry.[11] As there is a finite and limited amount of transition metals, it is important that research is carried out into the more efficient use of this resource.

It is estimated that the global reserves of the platinum group metals (Pd, Pt, Rh, Ru, Os and Ir) combined comes to a total of 66 million Kg.[12] To put this into perspective, the estimated global reserves of copper is 626 billion Kg.[12] It is therefore unsurprising that the cost of metal salts based on platinum group metals can be as high as twenty times more expensive than metal salts based on abundant transition metals such as copper and manganese.[13] As a result, the efforts of many research groups has been focussed on the use of more abundant transition metal salts in synthesis, or, the more efficient use of platinum group metal catalysts by means of lower catalyst loadings and re-use of catalysts.[14] It is worthy of note that the abundance of metals and the demand for them are not directly correlated. A study by the research group of James Clark[15] identified the expected lifetimes of the individual elements of the periodic table (Figure 1.2).

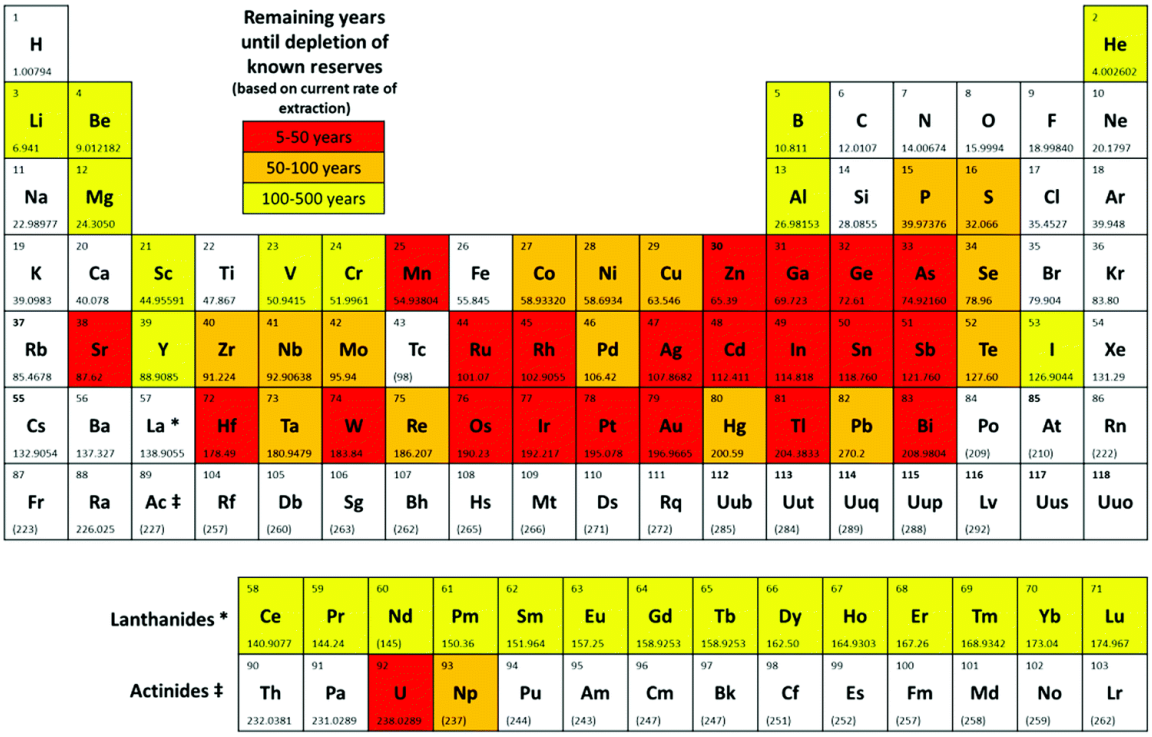


Figure 1.2 Predicted lifetimes of the periodic elements based on current rate of extraction.

What is noteworthy is that the abundance of elements is not directly related to their expected time of depletion. This is because abundant metals such as copper are used in high quantity for uses other than catalysis such as piping and wiring, whereas elements such as palladium is used in small quantities almost exclusively in catalysis.

1.2 Introduction to oxindoles

Oxindoles are of particular interest to the pharmaceutical industry and are a common ring system in many classes of biologically active natural products. Considered privileged structures,[16] oxindoles are also present in numerous pharmaceutical products and have shown a wide range of biological effects including analgesic, antibacterial, antiviral, antifungal, anticancer, anti-inflammatory, antiproliferative, antihypertensive and anticonvulsive properties.[17] Examples include the analgesic natural product Horsfiline (**5**), antihyponatremia drug Satavaptan (**6**) and the blockbuster anticancer drug Sutent® (**2**), which reached global sales of $1.19 billion in 2011 (Figure 1.3).[18]

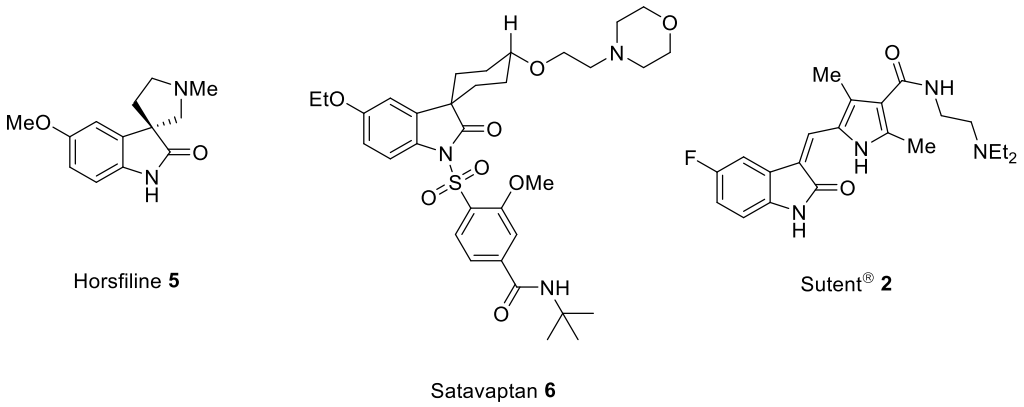


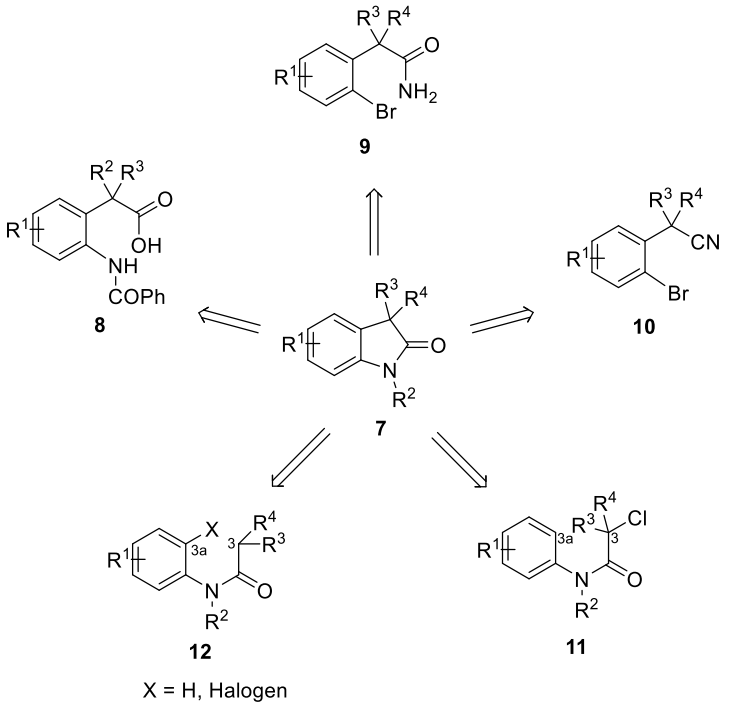
Figure 1.3 Oxindole natural product Horsfiline **5**, Satavaptan **6** (antihyponatremia drug) and Sutent **2** (RTK inhibitor).

It is therefore no surprise that the synthesis of oxindoles has received much interest from synthetic organic chemists. The Taylor group, and many others, have investigated the synthesis of this important heterocycle,[19] in particular 3,3-disubstituted oxindoles due to their abundance in related natural products and drug molecules.[20]

1.3 Synthetic approaches to oxindole formation

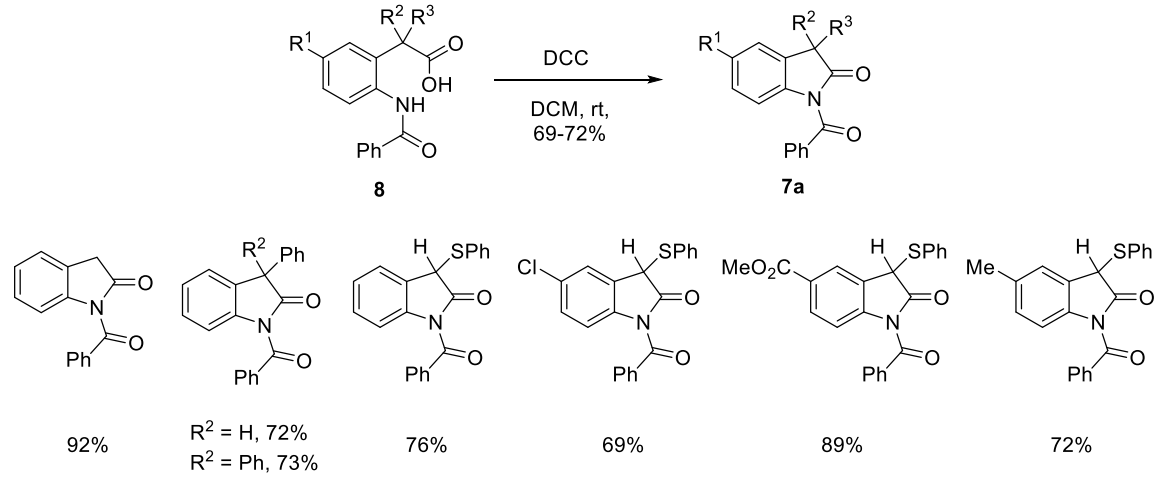
1.3.1 Overview

Several approaches to 3,3-disubstituted oxindoles **7** exist. A general summary of these approaches can be seen in scheme 1.1 and each approach will be discussed in further detail.



Scheme 1.1 Various disconnection approaches to oxindoles.

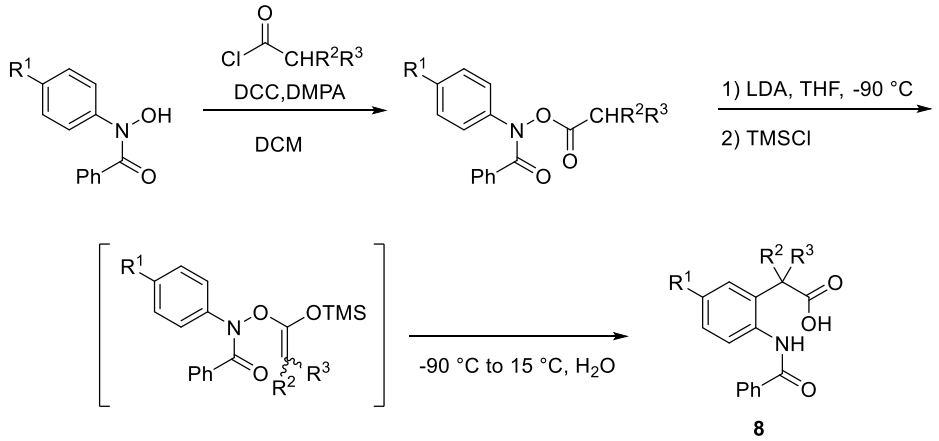
Prabhakar *et al.* synthesised 3,3-disubstituted oxindoles from carboxylic acids **8** by intramolecular formation of the amide bond using DCC (Scheme 1.2).[21] Despite this approach giving high yields, DCC is a very toxic coupling reagent and DCM is a solvent which is avoided by the pharmaceutical industry due to its carcinogenic properties.



Scheme 1.2 Prabhakar's approach to oxindole synthesis *via* amide bond formation.

Another shortfall of this approach is the approach to the synthesis of the amides **8** (Scheme 1.3). The scope of amides **8** is limited due to the 3-step synthetic route required to access them. Unfortunately yields are not provided in the literature but the general approach involves alkylation

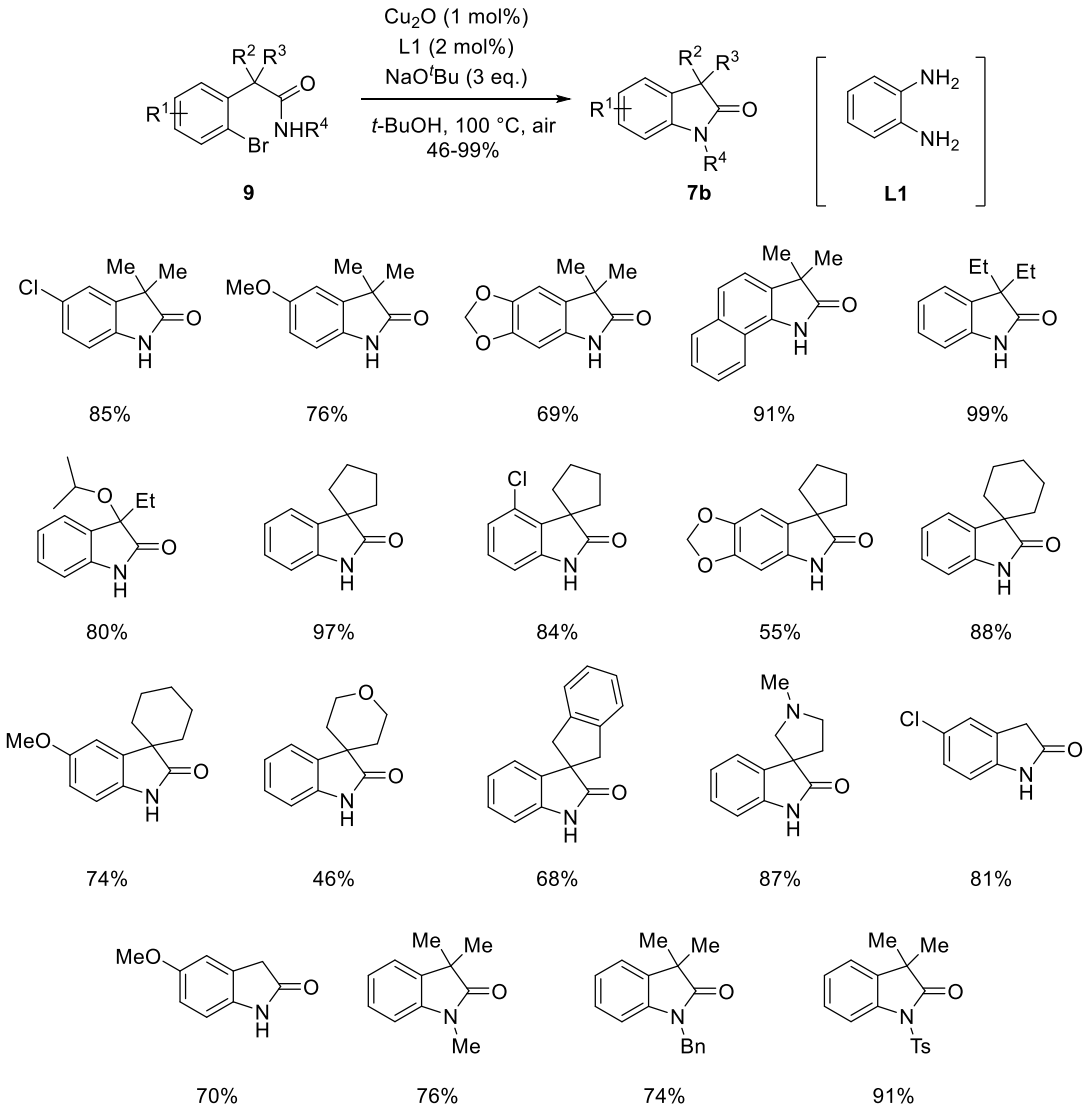
of hydroxamic acids using DCC in DCM solvent, followed by low temperature treatment with LDA in THF with subsequent treatment with TMSCl. Following thermal rearrangement the desired amide **8** is formed. This route required the use of toxic DCC in addition to the use of carcinogenic DCM solvent and several lo-temperature reaction steps. From a green metrics perspective this is unfavourable but additionally the R^2 and R^3 are limited to the scope of acid chlorides available.



Scheme 1.3 Prabhakar's synthesis of amides **8**.

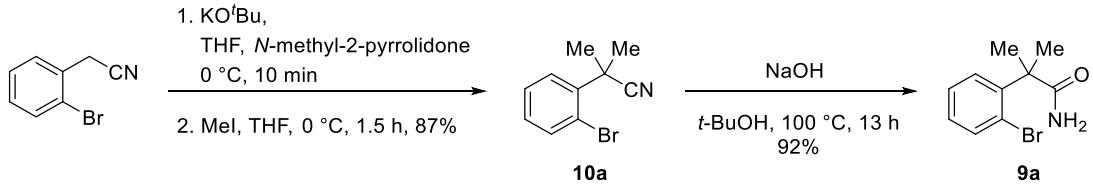
Two approaches to the formation of the aromatic C–*N* bond were achieved by Hsieh, one *via* intramolecular copper-catalysed *N*-arylation of amides **9**[22] and another *via* a copper-catalysed domino coupling reaction from nitriles **10**.[23]

Hsieh's copper catalysed *N*-arylation approach (Scheme 1.4) is a high yielding procedure with a wide substrate scope which utilises an inexpensive, elementally abundant copper oxide catalyst in low catalyst loadings. Whilst the choice of catalyst is favourable from a green metrics perspective there are several draw-backs to this method. Several additives are required for this reaction including 3 equivalents of NaO^{t}Bu, catalyst and ligand; the chosen ligand 2-amino aniline is also highly toxic. The reaction is also being carried out 89 °C above the flash point of *t*-BuOH (FP: 11 °C) in an atmosphere of air. This would present safety concerns upon scale up. Additionally, the loss of Bromine as a leaving group will inevitably produce hazardous halogenated waste and negatively impact upon the atom economy of the reaction.



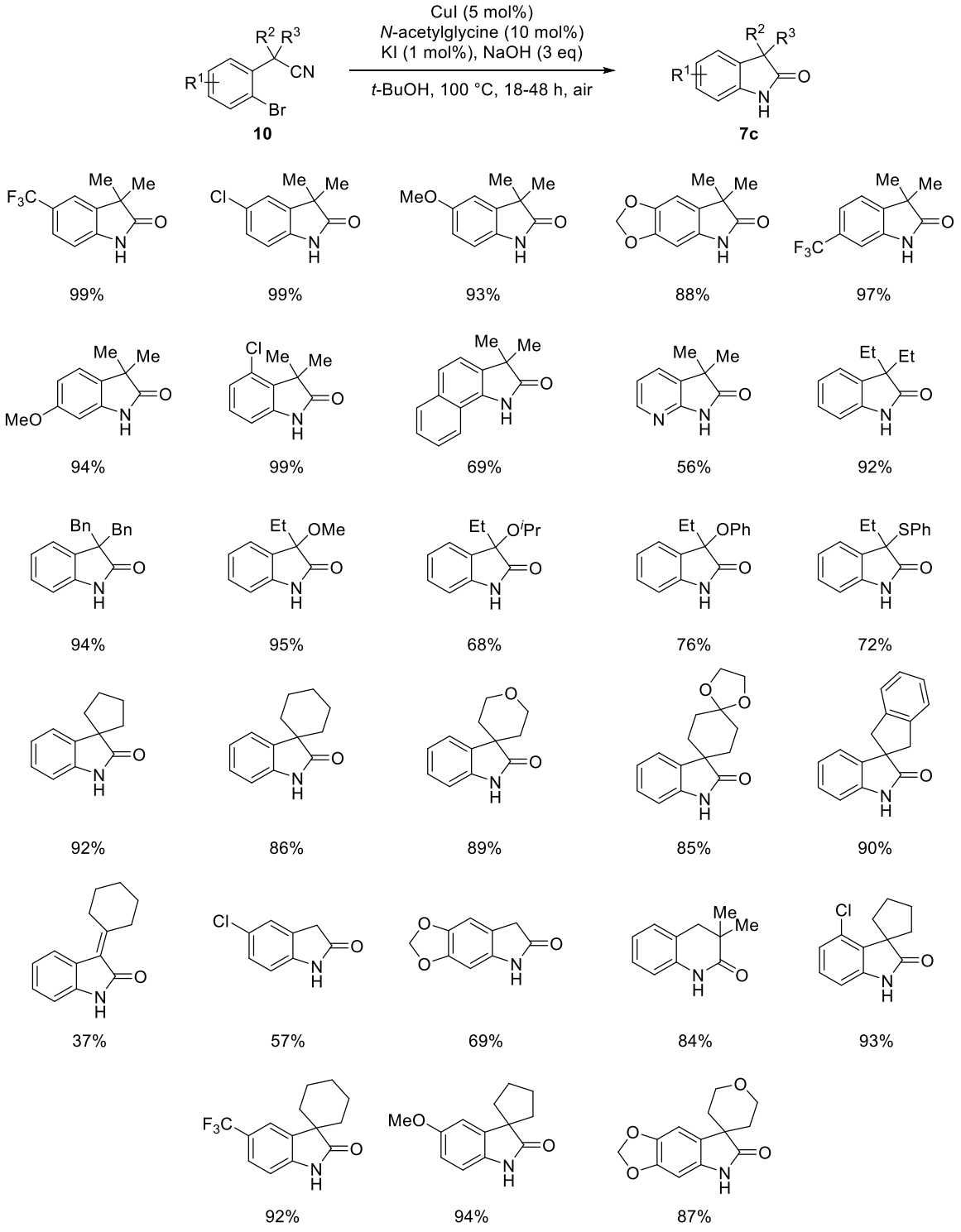
Scheme 1.4 Hsieh's intramolecular copper-catalysed *N*-arylation of amides approach to oxindole synthesis.

The general method for the synthesis of the amides required for Hsieh's method involve a 2-step procedure (Scheme 1.5). Step one requires the use of THF at 0 °C, a solvent considered to be 'un-green' as a result of its miscibility with water making its recovery from the environment problematic, in addition to its tendency to form peroxides posing a safety risk. The alkylation step also requires highly toxic alkylating agents such as methyl iodide. This dialkylation approach also limits the substrates on the carbon to being identical using this method.



Scheme 1.5 The synthetic route to forming amides **9** for Hsieh's method.

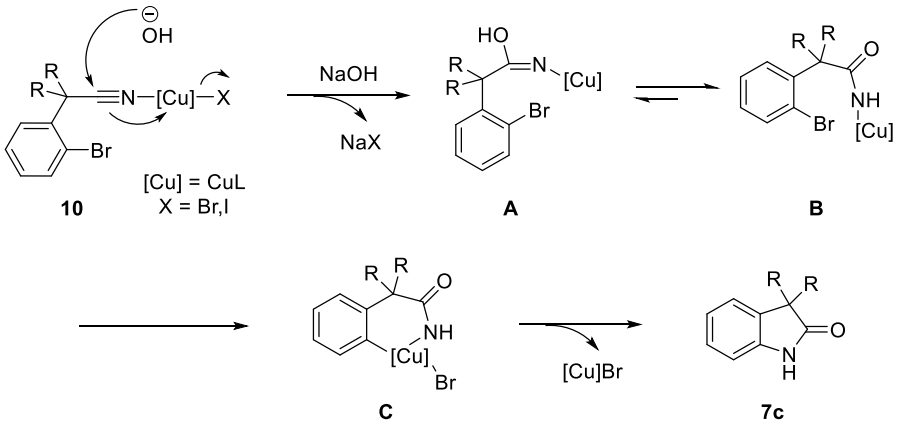
Hsieh also developed conditions to synthesise oxindoles directly from the nitrile intermediates **10** utilising copper-catalysis. Utilising similar conditions to the formation of oxindoles from amides it was possible to form a range of oxindole products in excellent yields using 5 mol% loading of CuI as catalyst (Scheme 1.6).



Scheme 1.6 Hsieh's copper-catalysed domino coupling approach to oxindoles.

This procedure as the same limitations as the Hsieh's previous method in that the substrate scope is limited to mainly oxindoles with identical substituents at the 3 position due to the method required to form the required nitrile compounds.

The mechanism for this procedure is expected to proceed as follows (Scheme 1.7): coordination of the nitrile functionality to the copper salt accelerates the rate of hydroxide addition resulting in intermediate **A**. Tautomerisation of **A** gives intermediate **B** which undergoes intramolecular oxidative addition to give complex **C**. Subsequent reductive elimination affords the desired oxindole **7c** and regenerates the copper complex.



Scheme 1.7 Suggested mechanism for Hsiesh's domino coupling approach to the synthesis of oxindoles.

It is worthy of note that the final two steps of the mechanism in scheme 1.7 (ie complex **B** to **7c**) is typical of most copper-mediated arylation of amides, most commonly known as the Goldberg reaction.[24]

The synthesis of 3,3-disubstituted oxindoles from anilides to generate a quaternary carbon centre *via* C(3)–C(3a) bond formation has seen significant advances in recent years.[25] A very early example is the Stollé procedure reported in 1914 utilising Friedel-Crafts chemistry to cyclise chloro-anilides **11**,[26] however the use of transition metal catalysis to achieve this feat, e.g. from anilide **12**, has now become common practice (Scheme 1.1).[20]

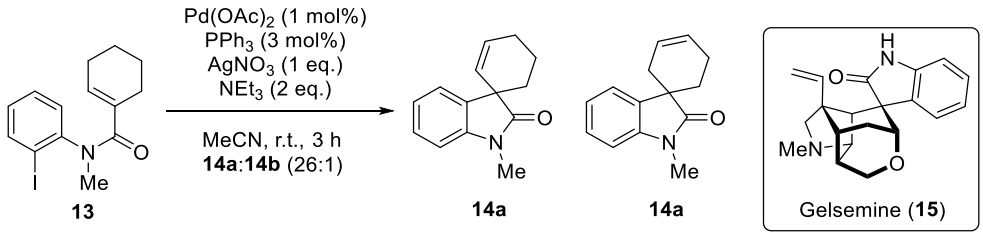
The value of creating quaternary carbon centres and the importance of C–C bond forming reactions make oxindole formation *via* the formation of a C(3)–C(3a) bond an interesting method. This method forms that basis of our research and shall therefore be reviewed in more detail.

1.3.2 Introduction to oxindole formation by C(3)–C(3a) bond formation

Although significant progress has been made in the field of oxindole synthesis *via* the formation of a C(3)–C(3a) bond, many methods suffer from limitations that restrict their general application, as outlined below.

1.3.3 Intramolecular Heck reaction

Access to 3,3-disubstituted oxindoles using the classical Heck reaction was first demonstrated by Overman whilst investigating the total synthesis of gelsemine (**15**)[27] (Scheme 1.8).

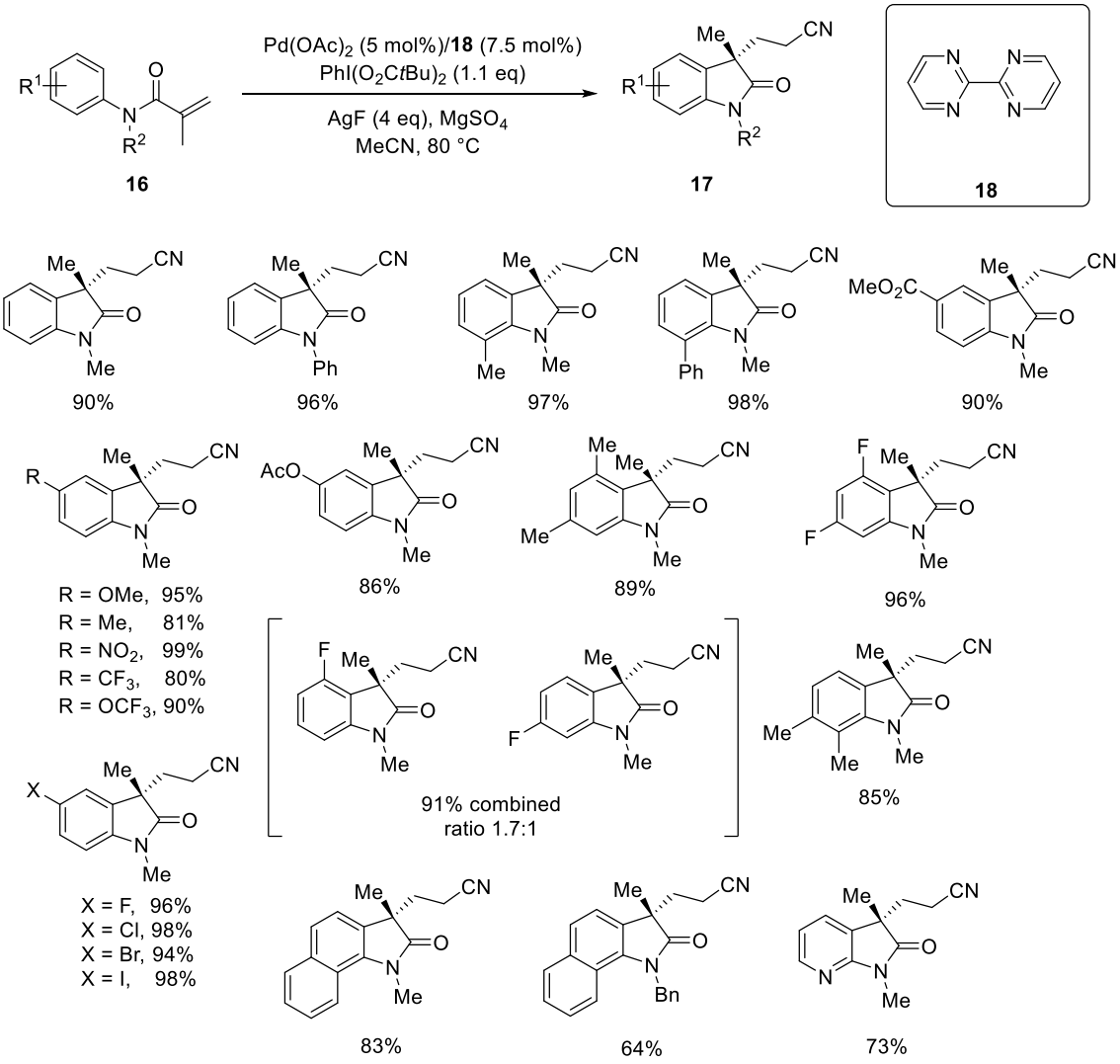


Scheme 1.8 The first reported Heck reaction for spiro-oxindole preparation.

Many research groups have since published variations on this method,[28,29] however most suffer from the same drawbacks, the requirement of a palladium catalyst and halogen leaving group in the starting material.

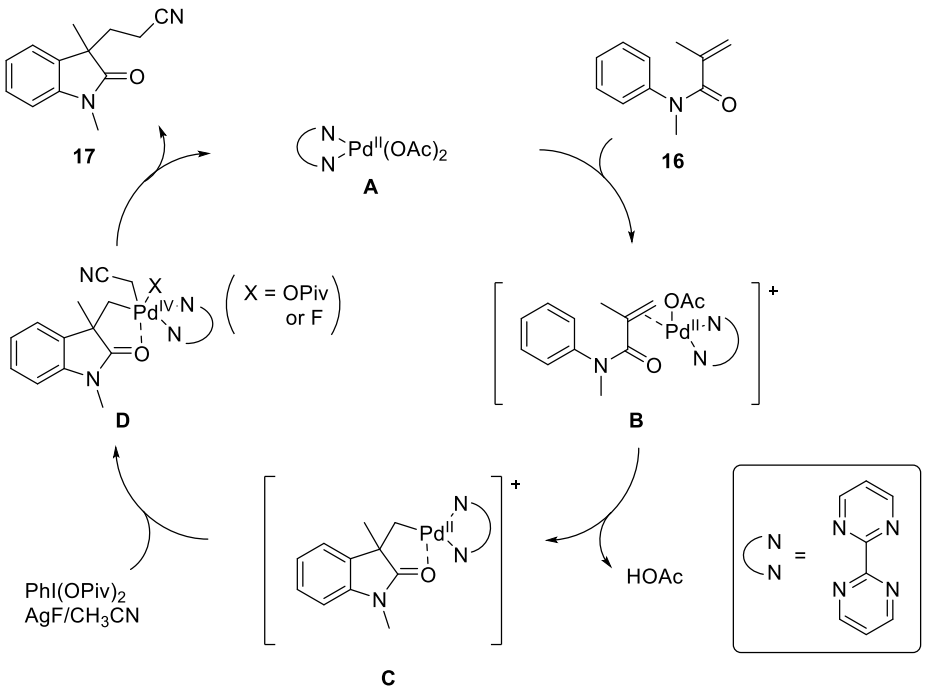
While using precious metals in synthesis is undesirable, the requirement of halogen functionality incorporated into the starting material poses other issues. From a synthetic perspective, requiring a carbon-halogen functionality can limit anilide scope and make anilide synthesis less trivial; from an industrial perspective, losing a halogen atom during cyclisation reduces atom economy and produces potentially toxic halogenated waste which is not only a health risk but also requires more costly disposal.

A noteworthy modification which avoids the requirement of a carbon-halogen bond by utilising C–H activation, is that reported by Liu and co-workers (Scheme 1.9).[30] Whilst they have avoided the carbon-halogen functionality and produces a range of substituents in high yields. Unfortunately, they require high catalyst loading of elementally unsustainable and expensive $Pd(OAc)_2$, along with several other additives which compromise the reaction mass efficiency.



Scheme 1.9 Liu's palladium-catalysed approach to oxindole synthesis.

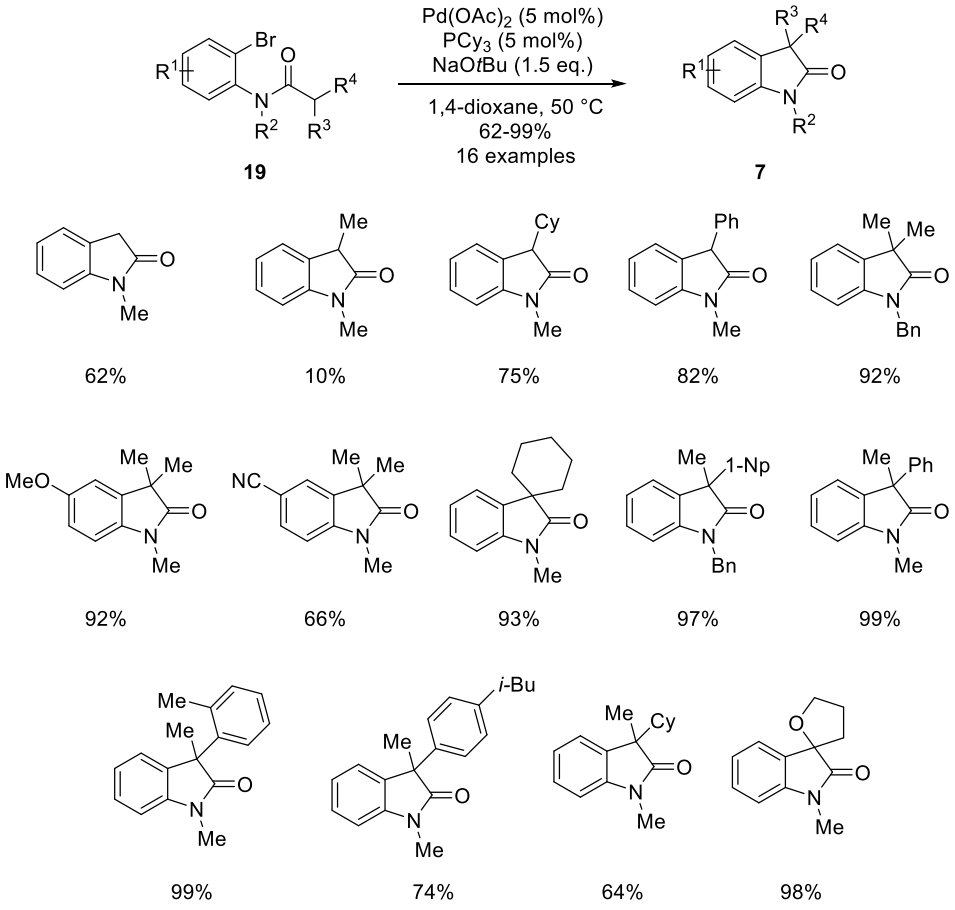
Whilst the exact mechanism of the reaction isn't known, Liu suggested a catalytic cycle shown in scheme 1.10. Coordination of the alkene moiety to Pd(II) (A) gives complex B, followed by nucleophilic attack of the alkene gives complex C. In the presence of $PhI(OPiv)_2$ and AgF, C–H activation of CH_3CN occurs generating Pd^{IV} complex D which undergoes reductive elimination to produce the oxindole product and regenerate palladium complex A.



Scheme 1.10 Proposed mechanism for Liu's palladium-catalysed approach to oxindole synthesis.

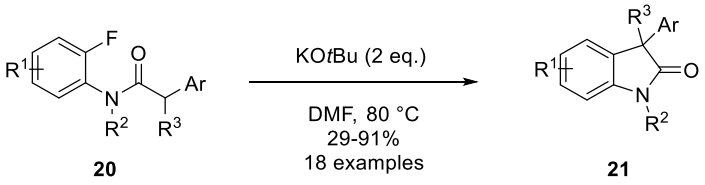
1.3.4 Intramolecular enolate arylation

A common approach to oxindole formation is *via* intramolecular enolate arylation using palladium catalysis. Although many groups have carried out work in this field,[31,32] the work of Hartwig illustrates this approach well (Scheme 1.11).[31b] Hartwig's method is high yielding and allows access to a variety of oxindoles. It does, however, rely on precious metal catalysis and the presence of a halogen leaving group on the aromatic ring.



Scheme 1.11 Hartwig's intramolecular enolate arylation approach to oxindole synthesis.

Advances in metal-free approaches to intramolecular enolate arylation include work by Bolm and coworkers.[33] In 2012, Bolm reported a transition metal-free variant of Hartwig's synthesis of oxindoles **21**, by KO*t*Bu promoted intramolecular α-arylation of 2-fluororanilides **20** (Scheme 1.12).



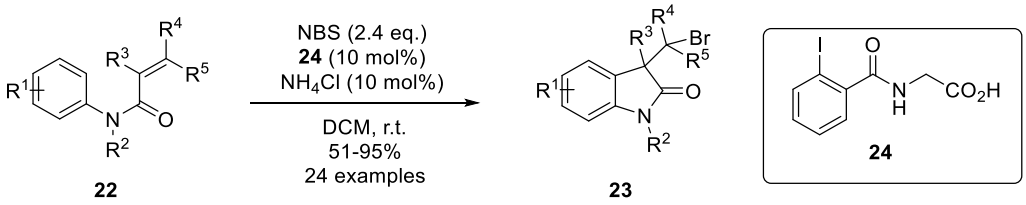
Scheme 1.12 Oxindole synthesis by KO*t*Bu promoted intramolecular α-arylation.

Despite avoiding the use of transition metals, however, there are several drawbacks to this approach. The reaction is effectively an S_NAr reaction with fluoride as the leaving group, thus producing halogenated waste. The C–F is bond is crucial for these reactions, and comes from pre-functionalised anilines. Due to the lack of availability and variety of commercial, fluoro anilides and fluoro aromatics, this somewhat limits the scope of the oxindoles that can be formed by this method; the substrate scope is more limited than Hartwig's process. The improvements to the green

metrics associated with avoiding precious metal catalysis are negated by the requirement for higher temperatures, longer reaction times and the use of the carcinogenic and teratogenic solvent DMF.

The requirement for pre-functionalised starting materials containing a (pseudo)halide leaving group and/or precious metal catalysis is common for oxindole synthesis.[31,32a, 32b]

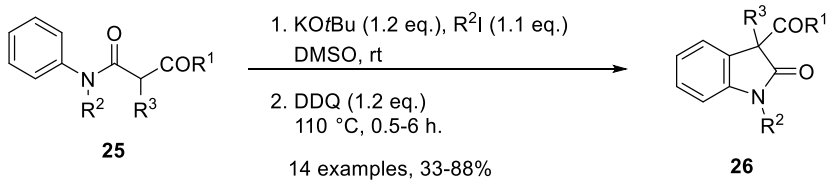
Several recent methods for forming the C(3)–C(3a) bond without the use of transition metals have been reported including the use of halogenating agents with α,β-unsaturated anilides[34] (Scheme 1.13).



Scheme 1.13 Bromo-cyclisation approach to oxindoles.

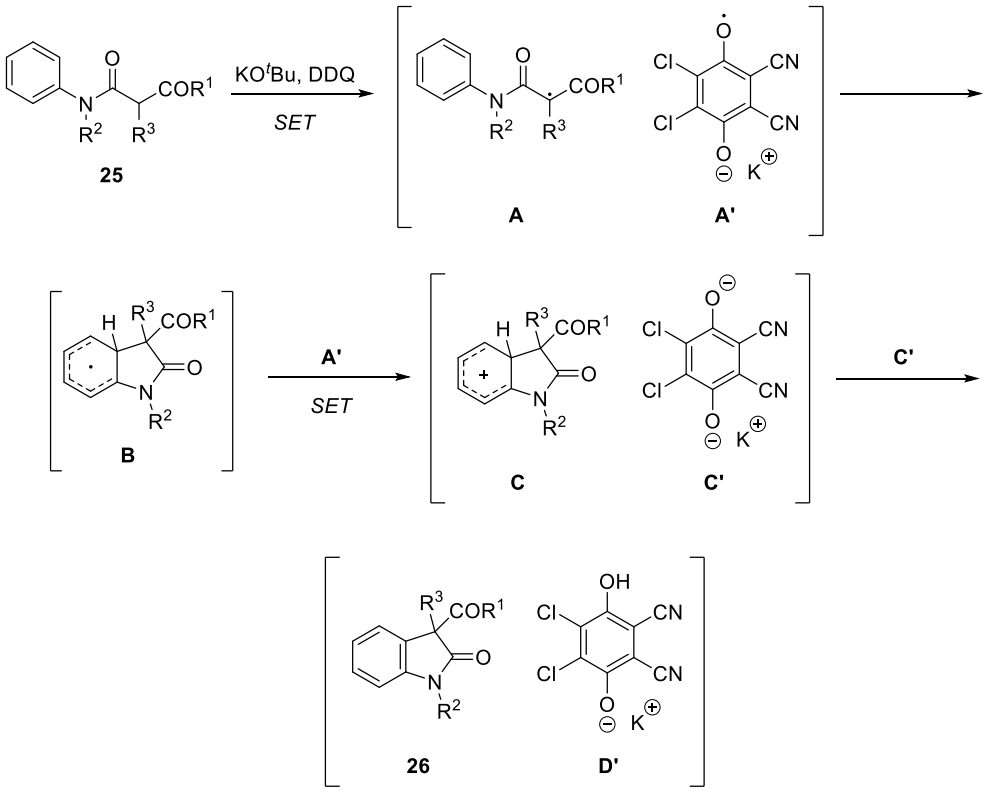
Unfortunately, a major drawback of this bromo-cyclisation approach is over-bromination of the aromatic ring which occurs with many of the substrates. This occurs as the reaction mechanism is believed to proceed *via* electrophilic aromatic substitution of the aromatic ring following reaction of "Br^{+}" with the alkene group. Over bromination occurs as a result of additional substitution on the aromatic ring. Another draw-back is that the reaction requires super-stoichiometric amounts of NBS which produces halogen-containing waste which is environmentally unfriendly.

Bisai *et al.* reported an approach to oxindoles **26** which utilised stoichiometric DDQ oxidant to induce cyclisation after methylation with an alkyl halide (Scheme 1.14).[35]



Scheme 1.14 DDQ mediated oxindole synthesis.

Following alkylation of the anilide, the reaction occurs *via* a formal homolytic aromatic substitution mechanism with DDQ being used as the oxidant (Scheme 1.15). Following deprotonation of anilide **25** and single electron transfer (SET) with DDQ, radical anilide **A** and radical species **A'** are formed. Formal homolytic aromatic substitution occurs giving radical species **B** with following an SET with species **A'** gives cationic species **C** and dianionic species **C'**. Rearomatisation of species **C** *via* deprotonation by **C'** gives the desired oxindole **26** and **D'**.

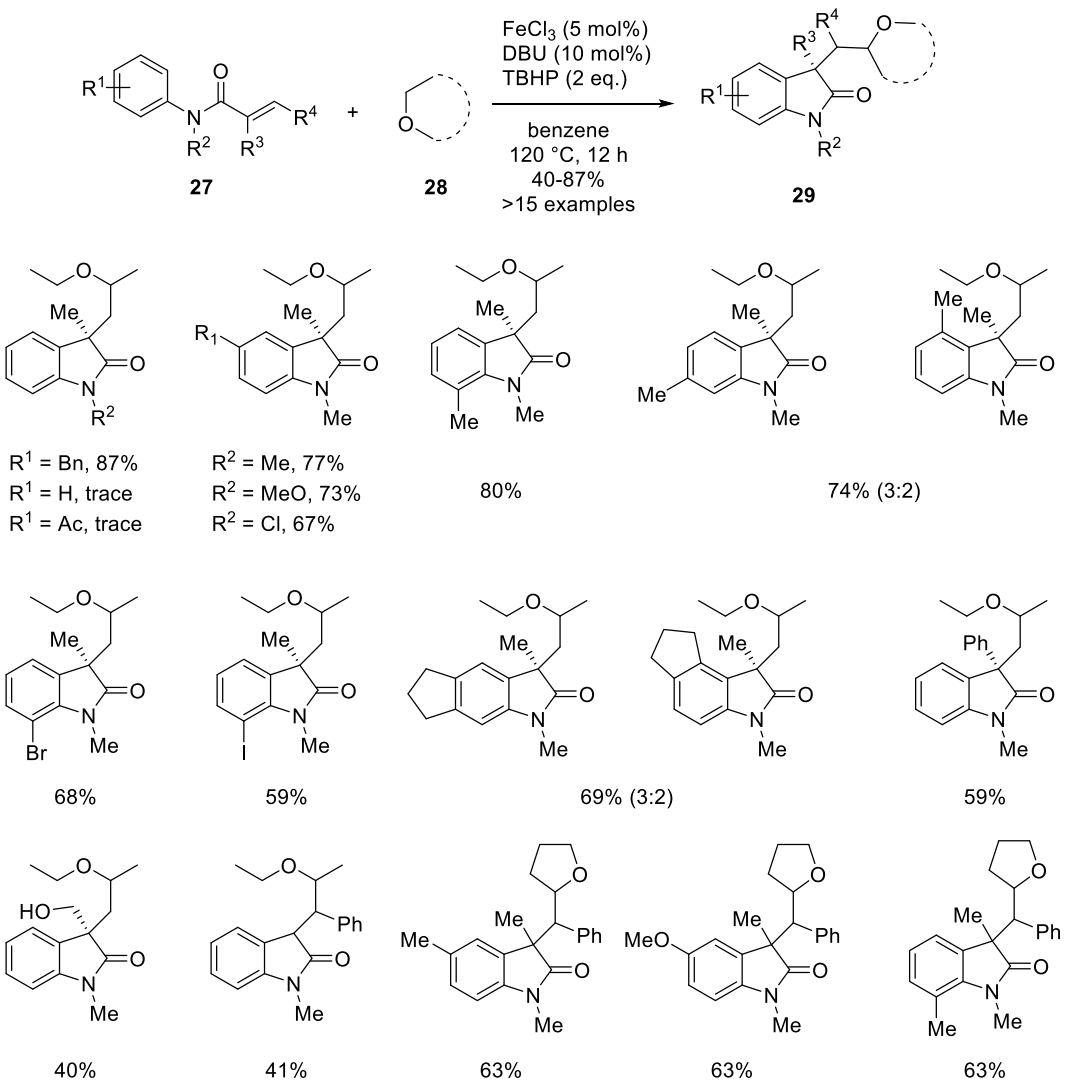


Scheme 1.15 Suggested mechanism for the DDQ mediated oxindole synthesis.

This approach avoids the use of precious metals and produces oxindoles in good yields, however, in place of using a metal catalyst this method uses stoichiometric amounts of DDQ which is a very toxic reagent and requires high temperatures.

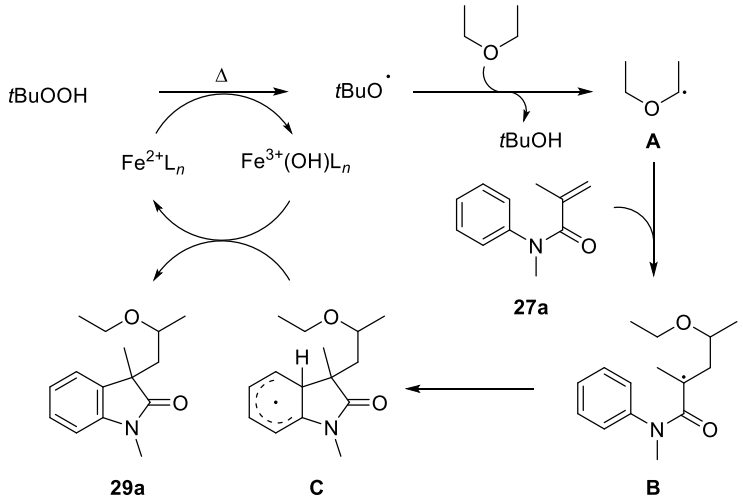
1.3.5 Radical mediated homolytic aromatic substitution

Homolytic aromatic substitution is defined as "replacement of a leaving group X by an attacking radical on an aromatic ring".[36] The key concepts and applications to heterocycle synthesis have been reviewed by Storey[36] and Kwong.[37] This method has been widely implemented in the synthesis of oxindoles.[38] An advantage of homolytic aromatic substitution is that a halogen leaving group is not required as the leaving group is usually H• or H^+. An excellent example of this approach is Li's method[39] which utilises inexpensive and elementally sustainable $FeCl_3$ as the catalyst (Scheme 1.16). This method offers high atom economy, utilises an inexpensive catalyst and gives high yields across a wich range of substrates.



Scheme 1.16 Iron-catalysed oxindole formation.

The mechanism for this reaction is typical of a formal homolytic aromatic substitution heterocycle formation. Tertiary butoxide radical is formed upon treatment of *t*BuOOH with heat in the presence of iron (II) metal salt (Scheme 1.17). The *t*-butoxide radical abstracts a proton from diethylether to form radical species **A** and *t*-butanol as the by product. Upon reaction of radical species **A** with anilide **27a**, radical species **B** is formed which undergoes a formal homolytic aromatic substitution to form heterocyclic radical species **C**. Upon reaction with iron (III) radical species **B** is converted into the desired oxindole **29a**.

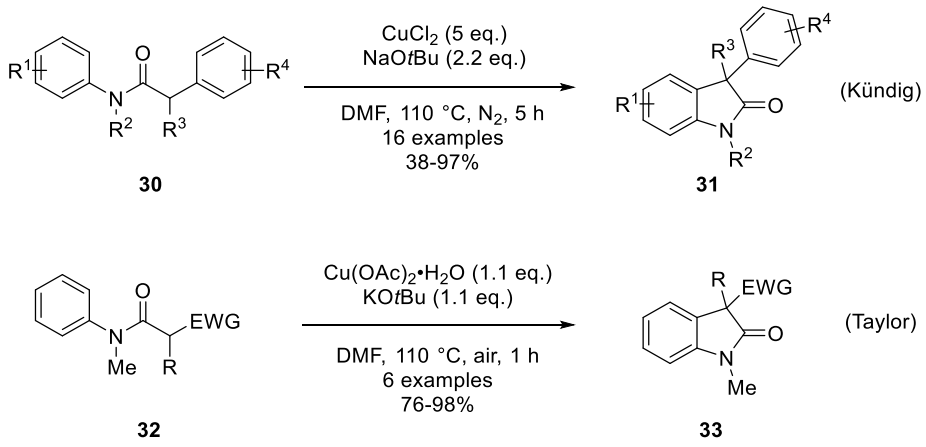


Scheme 1.17 Proposed mechanism for iron-catalysed oxindole formation.

Unfortunately, the reaction utilises benzene which is a black-listed solvent within the pharmaceutical industry due to its health risks, thus, limiting the applicability of this method.

1.3.5 Copper-catalysed approaches to oxindole formation

In 2009, both Kündig[40] and Taylor[19d] reported complementary copper-mediated approaches to 3,3-disubstituted oxindoles by a formal double C–H activation process *via* homolytic aromatic substitution (Scheme 1.18).

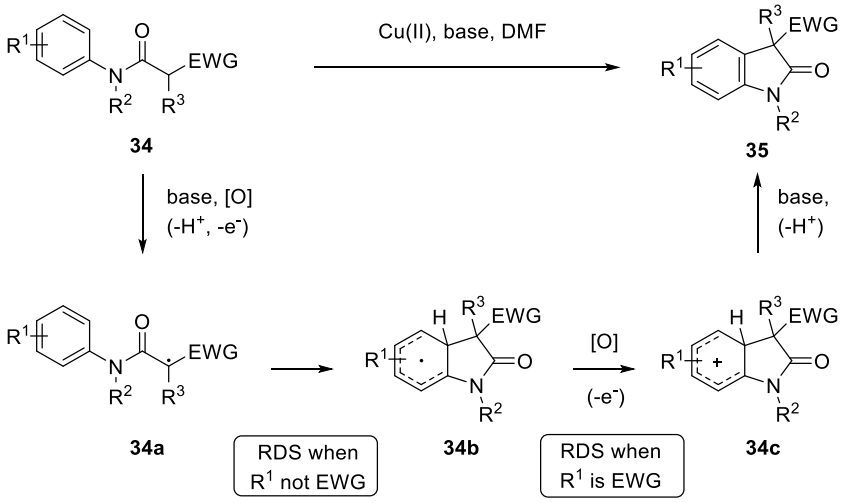


Scheme 1.18 Copper mediated formal double C–H activation.

This formal double C–H activation approach to oxindole formation negates the requirement for the previously discussed pre-functionalisation, as a direct C–H to Ar–H coupling was realised. This process also avoids the use of expensive 'precious metals' such as palladium, instead utilising the cheaper alternative of copper salts. The conditions developed by Taylor[19d] offer some advantage over those of Kündig.[40] Taylor's conditions offer an ease of operation, being carried out under an

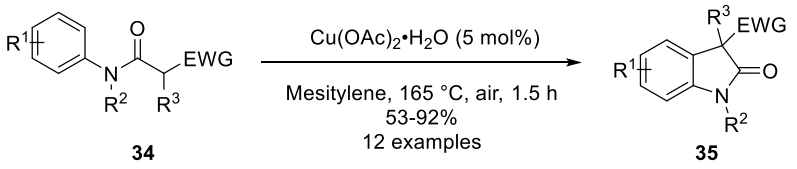
atmosphere of air without the need for rigorously anhydrous conditions; smaller amounts of copper salt and base are required and reactions proceed in shorter times.

The mechanism (Scheme 1.19) is believed to proceed initially by deprotonation of **34** followed by single electron oxidation by Cu(II) to give radical **34a** which undergoes formal homolytic aromatic substitution to give **34b**. Single electron oxidation by Cu(II) gives cationic species **34c** which following proton abstraction forms the oxindole product **35** (Scheme 1.10). Initial evidence for this mechanism included radical clock experiments which indicated that a radical was being formed[19d] and kinetic isotope effect studies[40] which suggested that the formation of the initial radical was not rate limiting. Further evidence was provided by a detailed DFT study by Kündig,[41] which suggests that the rate-determining step (RDS) is most commonly radical aromatic addition (**34a→34b**). In cases where the aromatic ring is electron-deficient (CF_3 substituted, aza-oxindoles) the second single electron oxidation by Cu(II) (**34b→34c**) can be rate-determining.



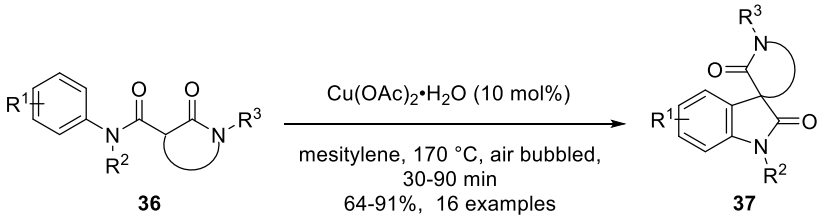
Scheme 1.19 Proposed mechanism for copper mediated oxindole formation.

An important further development of these conditions by Taylor *et al.* was a catalytic variant employing $Cu(OAc)_2 \cdot H_2O$ (5 mol%) in refluxing mesitylene without the requirement for base.[42] The reaction is carried out under aerobic conditions with oxygen likely re-oxidising the reduced copper species back to copper(II). It is worthy of note that when the reaction is carried out under argon no oxindole is formed. This procedure is an atom efficient process, utilising catalytic amounts of an inexpensive and commercially available catalyst, carried out under aerobic conditions and applicable to a broad range of substrates (Scheme 1.20), thus satisfying many of the green chemistry criteria previously mentioned. Areas for potential improvement include decreasing the reaction temperature and the use of a greener solvent.



Scheme 1.20 First formal C–H activation route to oxindoles using copper catalysis.

In addition, these conditions were successfully applied to the synthesis of spirocyclic oxindoles **37**,[43] again affording high yields of products across a range of ring sizes (4-, 5-, 6- and 7-membered rings) and aromatic substitution patterns (Scheme 1.21).



Scheme 1.21 Copper-catalysed synthesis of spiro-oxindoles.

1.4 Aims of this research

- Improvement on the Taylor group method for copper-catalysed synthesis of oxindoles
    - Reduced temperature
    - More efficient catalysis
    - Higher yield
- Application of the newly developed conditions to other *N*-heterocyclic motifs of medicinal interest
    - Synthesis of 5-membered nitrogen-containing heterocycles
    - Synthesis of 6-membered nitrogen-containing heterocycles
- Application of conditions to the synthesis of biologically active molecules based on *N*-heterocycles

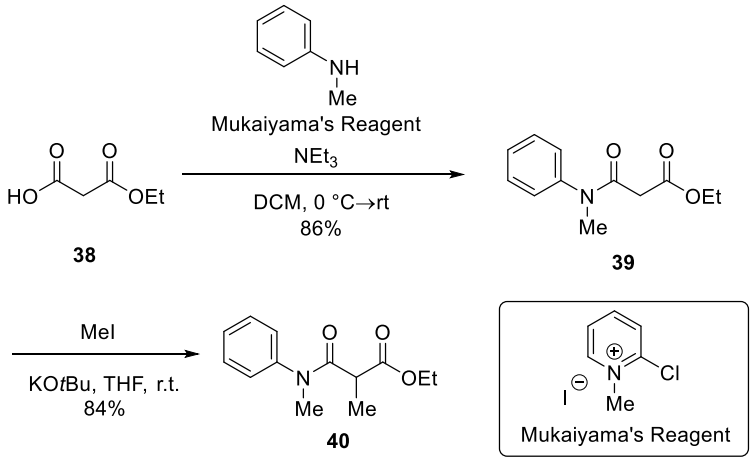
Chapter 2. Copper-catalysed synthesis of 5-membered nitrogen containing heterocycles

2.1 Oxindoles

2.1.1 Optimisation of reaction conditions for oxindole synthesis

Despite the copper-catalysed process reported by Taylor[42-43] being efficient and better than the original approaches in many aspects, there were still areas for improvement. The catalytic reaction was carried out at high temperature (165 °C) in mesitylene with significant drops in yield observed when lowering the temperature. Initial work therefore focussed on developing conditions which were lower in temperature.

Anilide **40** was synthesised in two steps from 3-ethoxy-3-oxopropanoic acid **38** by coupling with *N*-methylaniline using Mukaiyama's reagent to give anilide **39**. Subsequent treatment with base and MeI afforded anilide **40** in excellent yield (Scheme 2.1).



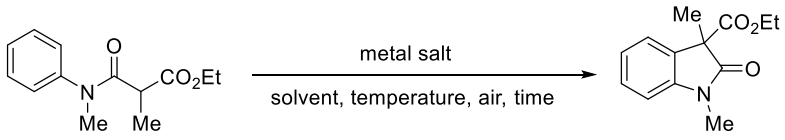
Scheme 2.1 Synthesis of anilide **40**.

Whilst this route is not atom economic and Mukaiyama's reagent is not a green coupling reagent, it is operationally simple to use, afforded excellent yield and has fewer health risks associated with it that other common amide coupling reagents such as DCC. Developing a green synthesis of starting material **40** was not an immediate goal, rather, a simple method that allowed access to large amounts of the substrate in good yields.

A number of metal salts were employed in an attempt to find a more efficient catalyst for the process of forming model oxindole **41** (Table 2.1). This initial screen was carried out using one equivalent of metal salt, with entries 1 and 2 being repeats of reported conditions.[42] Catalysts based on metals other than copper including $Fe(acac)_3$, $Ni(acac)_2$, $Cr(acac)_3$ and $Co(acac)_3$ were

investigated, but gave no desired product, with only anilide **40** recovered in each case. It was no surprise that $Mn(acac)_3$ (entry 3, Table 2.1) gave some conversion into the desired oxindole **41,** albeit in low yield, as manganese-mediated radical formation is known.[44] Neither copper(II) 2-pyrazinecarboxylate (entry 4, Table 2.1) or $Cu(NCCH_3)_4{\cdot}CF_3SO_3$ (entry 5, Table 2.1) showed any improvement over the originally reported conditions. However, the reaction proceeded smoothly when copper(II) 2-ethylhexanoate was employed giving **41** in 91% yield. Lowering the amount of copper salt to 10 mol% led to a further increase in yield (entry 6, Table 2.1). The rationale for the effectiveness of copper(II) 2-ethylhexanoate is its increased solubility relative to the other metal salts investigated. The solvent was also varied to assess whether comparable results could be achieved (entries 7-10, Table 2.1) but improved yields were not observed. Toluene was therefore identified as the most efficient solvent. Of the solvents trialed in Table 2.1, in addition to being the solvent that allows the highest yield, toluene also has the fewest health risks associated with it

Table 2.1 Investigation into the effect of differing metal salts and solvent on the formation of standard oxindole **41**.



40 **41**

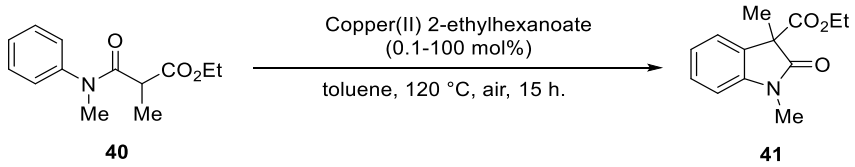
Entry	Metal Salt (1 eq. unless otherwise stated)	Solvent	Temperature (°C)	Time (hours)	Isolated yield (%)
1	$Cu(OAc)_2{\cdot}H_2O$	Mesitylene	165	3	85[a]
2	$Cu(OAc)_2{\cdot}H_2O$	Toluene	120	15	85, 83[a]
3	$Mn(acac)_3$	Toluene	120	15	56, 19[a]
4	Copper(II) 2-pyrazinecarboxylate	Toluene	120	15	46
5	$Cu(NCCH_3)_4{\cdot}CF_3SO_3$	Toluene	120	15	73
6	***Copper(II) 2-ethylhexanoate***	***Toluene***	***120***	***15***	***91, 100[a]***
7	Copper(II) 2-ethylhexanoate	DMF	120	15	37[a]
8	Copper(II) 2-	MeCN	120	15	trace[b]

	ethylhexanoate				
9	Copper(II) 2-ethylhexanoate	1,4-Dioxane	120	15	trace[b]
10	Copper(II) 2-ethylhexanoate	DMSO	120	15	< 5[b]

[a] 10 mol% metal salt used, [b] as observed by ^{1}H NMR spectroscopy. Metal salts that did not affect the transformation: $Fe(acac)_3$, $Ni(acac)_2$, $Cr(acac)_3$, $Co(acac)_3$, Cu(II)D-gluconate, EDTA copper(II) disodium salt, $Cu(OTf)_2$ EnCat, $CuPc_2$, $CuBr(PPh_3)_3$.

Having established that copper(II) 2-ethylhexanoate was the preferred catalyst for the desired transformation, the loading of copper(II) 2-ethylhexanoate was briefly investigated (Table 2.2). Copper(II) 2-ethylhexanoate proved to be an efficient catalyst showing good yield at 1 mol% loading (entry 3, Table 2.2) and even showed conversion to product (albeit slowly) at as low as 0.1 mol% catalyst loading (entry 4, Table 2.2). The optimum loading of catalyst was found to be 10 mol%.

Table 2.2 Investigation into the effect of decreased catalyst loading.



40 **41**

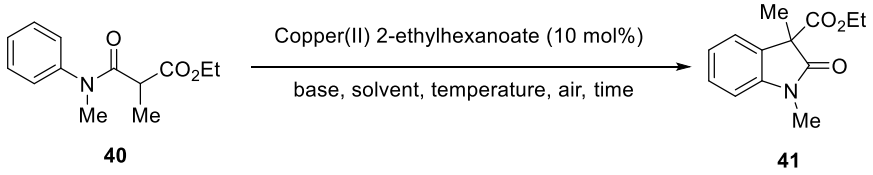
Entry	Metal Salt	Loading (mol%)	Isolated yield (%)
1	Copper(II) 2-ethylhexanoate	100	91
2	***Copper(II) 2-ethylhexanoate***	***10***	***100***
3	Copper(II) 2-ethylhexanoate	1	71[a]
4	Copper(II) 2-ethylhexanoate	0.1	16[a]

[a] Reactions not gone to completion. ^{1}H NMR spectroscopic analysis of the crude reaction mixture shows only starting material and product present.

Further optimisation was carried out with respect to the reaction temperature. When anilide **40** was subjected to catalytic copper(II) 2-ethylhexanoate in toluene at 100 °C (entry 1, Table 2.3) the yield was considerably lower than at 120 °C (entry 6, Table 2.1). Addition of inorganic bases KO*t*Bu and NaH (entries 2 and 3, Table 2.3) gave no improvement. On the other hand, organic bases piperidine, DBU and DIPEA (entries 4–6, Table 2.3) showed improved yields, with DIPEA affording the highest yield of oxindole **41** (89%). When the reaction was repeated with DIPEA as

the solvent the yield dropped to 43% (entry 7, Table 2.3). When the optimal conditions (entry 6, Table 2.3) were repeated at 80 °C (entry 8, Table 2.3) the yield dropped to 35%.

Table 2.3 Investigation into the effect of base on the formation of standard oxindole **41**.



40 **41**

Entry	Base (2 eq.)	Solvent	Temperature (C°)	Time (h)	Isolated Yield (%)
1	-	Toluene	100	40	34
2	KO*t*Bu	Toluene	100	40	0
3	NaH	Toluene	100	40	5[a]
4	Piperidine	Toluene	100	40	48
5	DBU	Toluene	100	40	22[a]
6	***DIPEA***	***Toluene***	***100***	***40***	***89***
7	-	DIPEA	100	40	43
8	DIPEA	Toluene	80	40	35

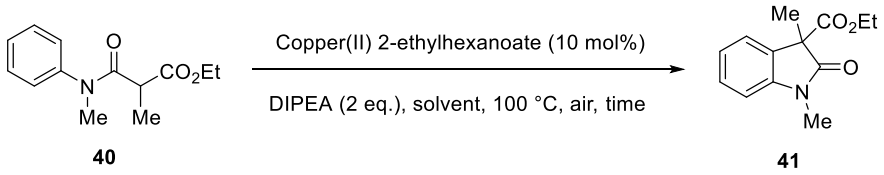
[a] Yield calculated by ^{1}H NMR spectroscopy using 1,1,2,2-tetrachloroethane as internal standard

It is worthy of note that reactions outlined in Tables 2.1, 2.2 and 2.3 proceeded smoothly from anilides **40** to oxindoles **41**, with no side reactions/products being formed.

From these optimisation studies, it was concluded that apolar, hydrocarbon solvents gave the best results and that organic bases were more effective than inorganic bases (which could be a result of their increased solubility). The yields of the transformation at 100 °C reflect the increasing boiling points of the bases employed, DIPEA (127 °C) > piperidine (106 °C) > DIPEA (80 °C).

As part of a collaboration with CatScI Ltd., more extensive solvent screens were carried out at 100 °C with DIPEA (2 eq.) to identify more effective and more environmentally friendly alternatives to toluene. Toluene is a solvent that the pharmaceutical industry uses frequently; however, efforts are being made to phase out its use in the coming years.

CatScI is a company which specialises in investigating transition metal catalysed processes using their specialist equipment to screen numerous conditions quickly. An initial study investigated the effect of various solvents on the synthesis of oxindole **41** at 100 °C using catalytic copper(II) 2-ethylhexanoate (Figure 2.1). Several solvents were identified by CatScI as potential improvements on toluene, showing very fast rates of product formation within the first 5 hours. These included $PhCF_3$, CPME and tetralin.



40 **41**

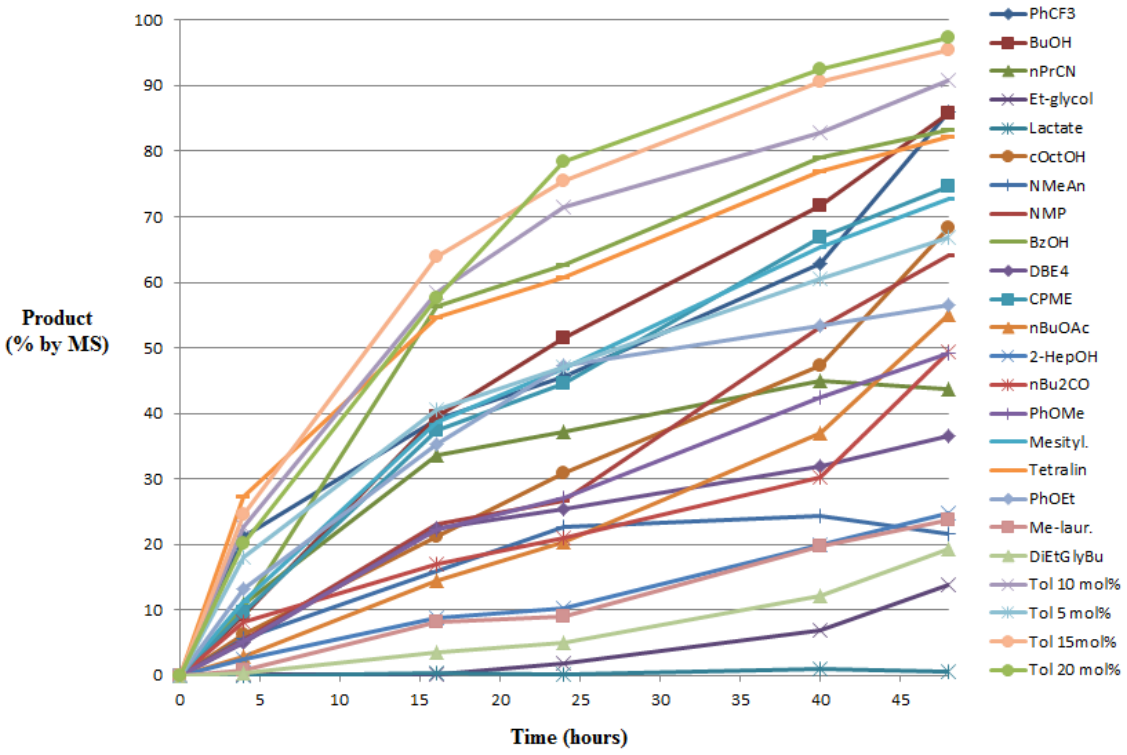
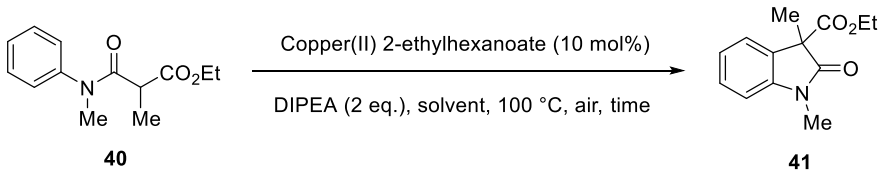


Figure 2.1 Investigation into the effect of solvent on oxindole **41** formation (CatScI).

Due to the differing apparatus and techniques used in the CatScI laboratories, the reactions using $PhCF_3$, CPME and tetralin were repeated in the Taylor lab (Table 2.4). CPME gave full conversion to product on a time scale similar to toluene although the yield was significantly lower (entry 2, Table 2.4). $PhCF_3$ gave full conversion in 28 hours, much quicker than toluene, in 73% yield. Tetralin showed full consumption of starting material to product by TLC analysis within 15 hours, less than half the time it took using toluene. Unfortunately it was found that the degradation of tetralin at 100 °C made isolation of oxindole **41** difficult and time-consuming.

Table 2.4 Investigation into the effect of solvent on oxindole **41** formation.



40 **41**

Entry	Solvent	Time (h)	Yield (%)
1	Toluene	40	89
2	CPME	40	46
3	$PhCF_3$	28	73
4	Tetralin	15	72

Despite the decreased reaction time required when using tetralin as the solvent, its decreased yield and decomposition at high temperature mean that isolation of the product is time consuming and requires several rounds of column chromatography. When using toluene the reaction is extremely efficient with no by-products being formed, and therefore column chromatography can be avoided entirely. The only form of purification required being a wash of the organics with 10% aqueous ammonium hydroxide solution to remove the copper-catalyst. Overall, toluene is the most effective solvent despite long reaction times.

2.1.2 Summary of optimisation studies

Following extensive investigation, the copper-catalysed synthesis of oxindole **41** can be performed at lower temperatures than previously reported[42] with improved yields; copper(II) ethylhexanoate in toluene at 120 °C for 15 hours gives quantitative yield of oxindole **41**, and the reaction temperature can be reduced to 100 °C with excellent yields still being observed although a longer reaction time (40 h) and the addition of DIPEA is required.

With these conditions in hand we now have a process which is:

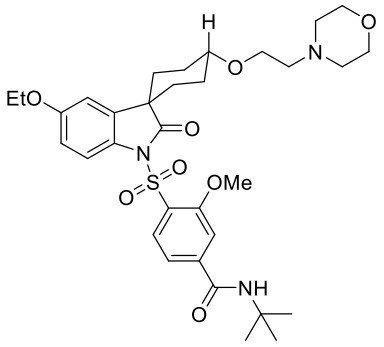
- High yielding
- >99% atom economy
- Uses a safer solvent
- Reacts at lower temperature
- Moisture and air insensitive
- Inexpensive catalyst

- Low waste production
- Operationally simple

2.2 Application to the formal synthesis of Satavaptan

2.2.1 Introduction to Satavaptan

Hyponatremia is a condition in which the sodium concentration of the blood is chronically low.[45] It can be caused by numerous factors including improper function of, or damaged kidneys, heart and liver. The consequence of low blood sodium levels can range from mild symptoms such as nausea and memory loss to more severe symptoms including the swelling of brain cells and increased pressure in the skull causing hyponatremic encephalopathy which often leads to death.[46] These symptoms result from the water-retention associated with increased secretion of anti-diuretic hormone (ADH) in response to the low sodium concentration in the blood. Unfortunately, combatting this condition with diet alone is not sufficient. A class of drugs names 'vaptans' are commonly used to treat it including Satavaptan **6** (Figure 2.2)



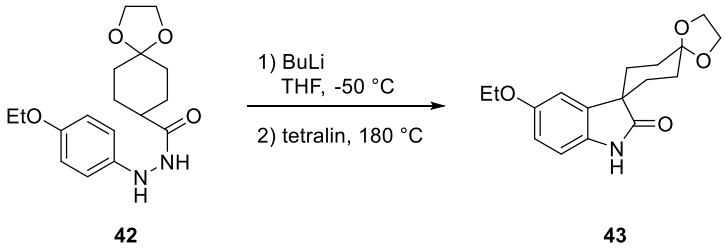
Satavaptan **6**

Figure 2.2 Vasopressin receptor antagonist Satavaptan **6**.

Satavaptan (SR121463) is a vasopressin receptor antagonist developed by Sanofi used to treat hyponatremia (Figure 2.2).[47] Importantly it contains a 3,3 disubstituted oxindole core, and we hoped that our copper-catalysed conditions developed for the synthesis of oxindoles could be applied to this molecule.

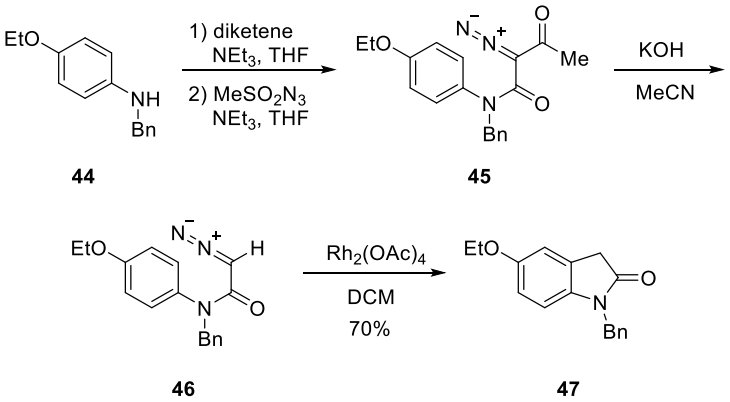
2.2.2 The synthesis of Satavaptan

The original synthesis of Satavaptan outlined in the patent from 1997 uses a Fischer indole synthesis to construct the oxindole core (Scheme 2.2).[48] There is, however, a lack of detail regarding the experimental procedure and yields obtained.



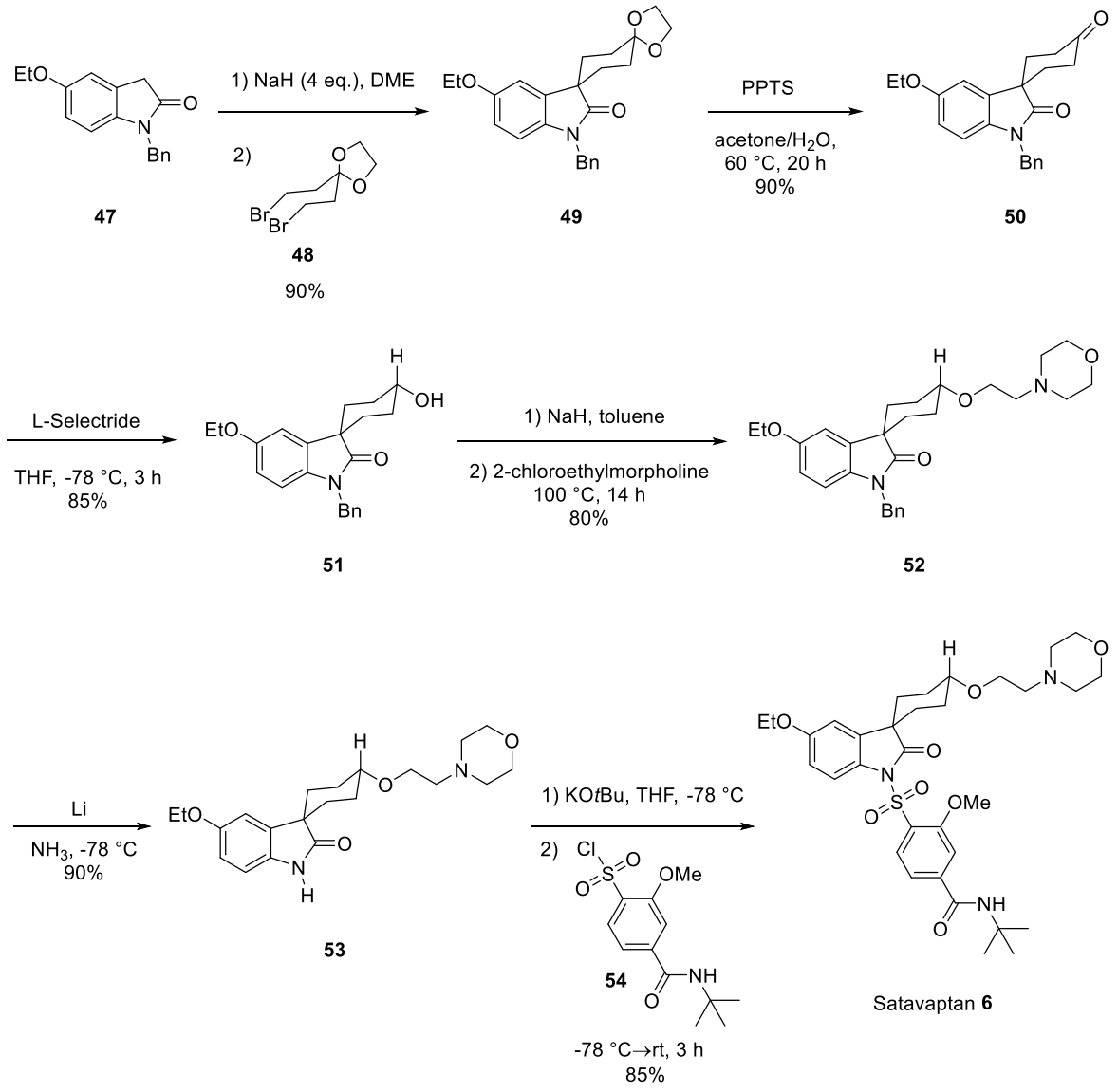
Scheme 2.2 Oxindole **43** formation in the patented synthesis of Satavaptan **6**.

There have been several other formal and total syntheses of Satavaptan since then;[49] the most relevant of which being the work by Liotta.[50] Liotta synthesised the oxindole core *via* a rhodium-catalysed cyclisation of diazo compound **46** which was prepared in 3 steps from *N*-benzyl-4-ethoxyaniline **44** following Doyle's procedure (Scheme 2.3).[51]



Scheme 2.3 Liotta's synthesis of the oxindole core in the total synthesis of Satavaptan **6**.

Spirocyclic oxindole **49** was obtained following treatment of oxindole **47** with NaH then subsequent exposure to dibromide **48**, which was itself synthesised in 3 steps (Scheme 2.4). The acetal functionality was deprotected with PPTS to afford ketone **50** which was selectively reduced using L-selectride to afford alcohol **51**. The alcohol was then alkylated with 2-chloroethylmorpholine, giving **52** in excellent yield. Removal of the benzyl protecting group proved to be difficult. Standard hydrogenation conditions using palladium on charcoal afforded only unreacted starting material, but deprotection was ultimately achieved by use of lithium in liquid ammonia affording **53** in excellent yield. The total synthesis was then completed upon treatment of **53** with KO*t*Bu followed by exposure to sulfonyl chloride **54** which had been previously synthesised in 4 steps.



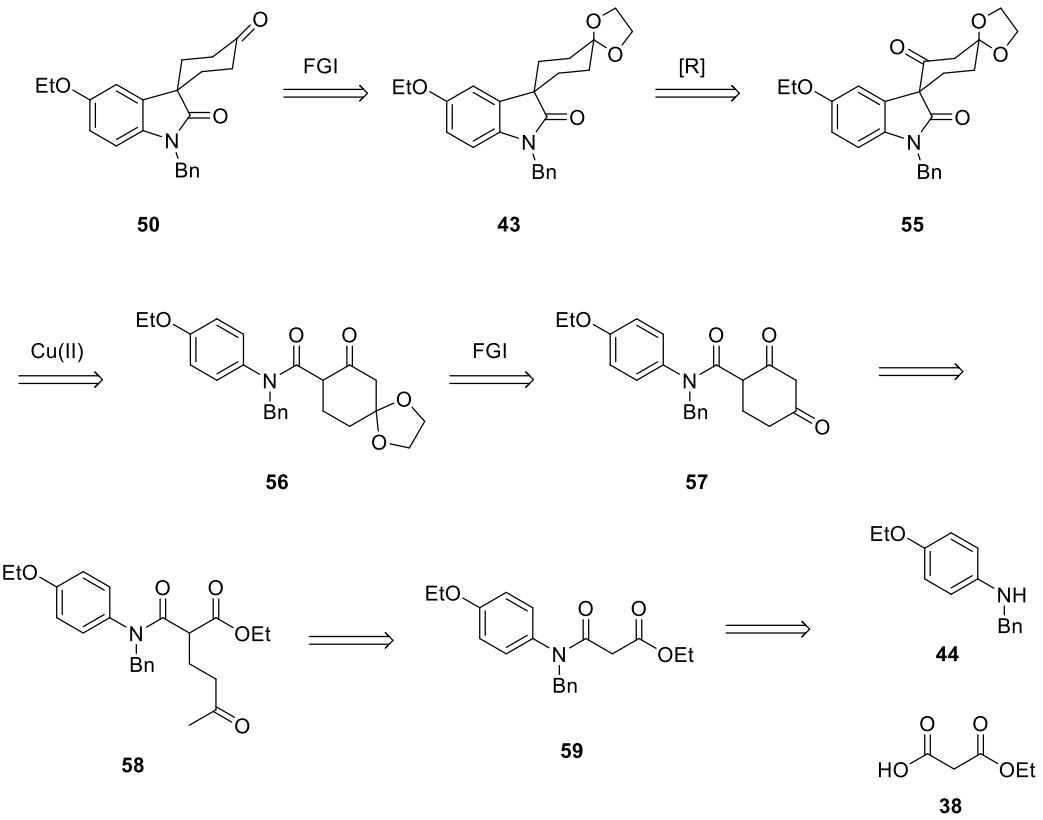
Scheme 2.4 Liotta's total synthesis of Satavaptan **6**.

2.2.3 Application of copper conditions to a formal synthesis of Satavaptan

Our synthesis of Satavaptain aimed to intercept Liotta's advanced intermediate **50**.[50]

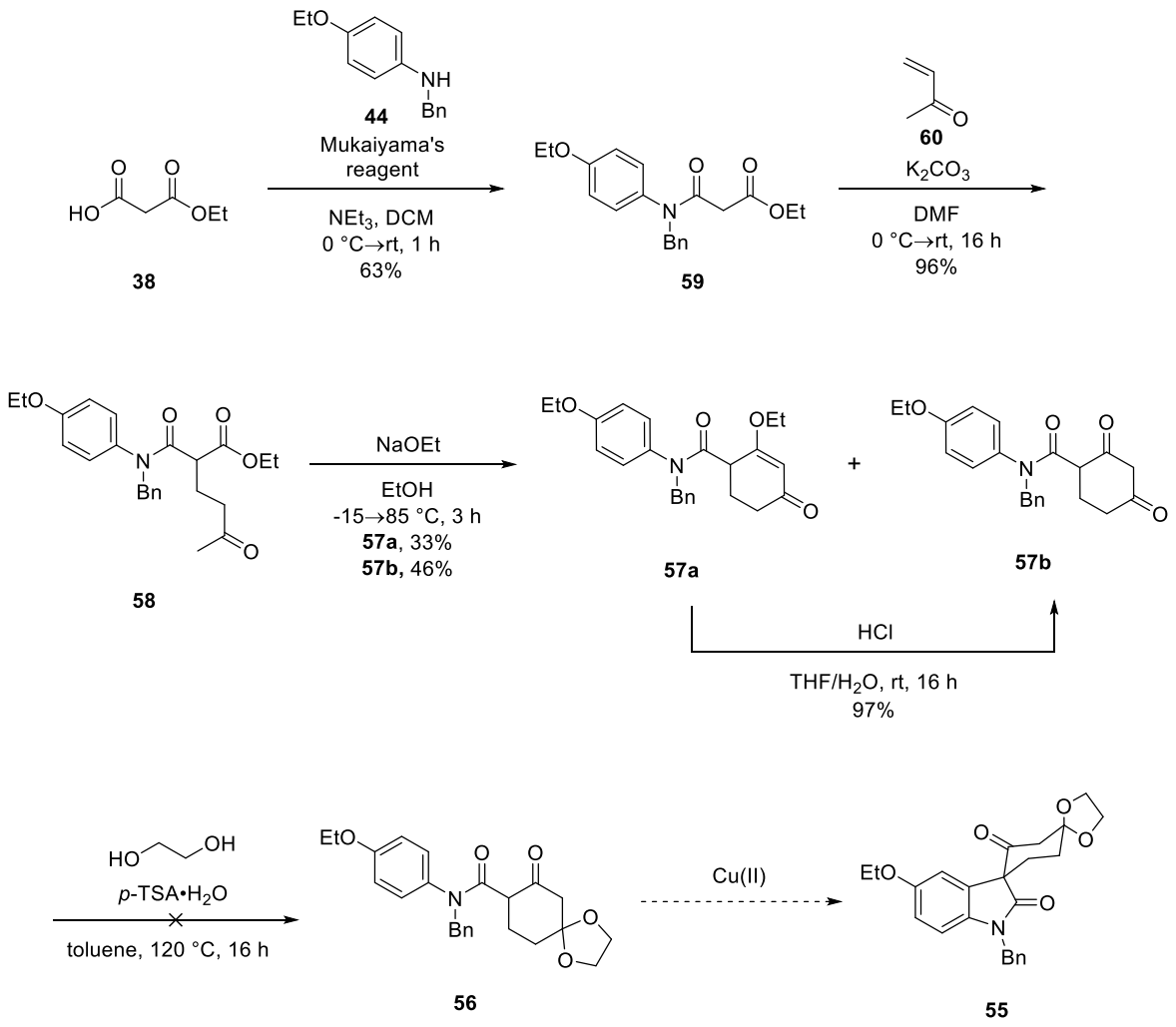
Route 1

We envisioned **55** to come from hydrolysis of acetal **43** which in turn could be obtained by reduction of the ketone in compound **55** (Scheme 2.5). This spirocyclic ketone oxindole could be synthesised using our copper methodology from anilide **56** which could be prepared by acetal formation on ketone **57**. This ketone could be synthesised by ethoxide-mediated Claisen condensation of **58**. Anilide **58** could be made from alkylation of anilide **59** which in turn could be synthesised by amide bond formation between *N*-benzyl-4-ethoxyaniline **44** and known carboxylic acid **38**.[19d]



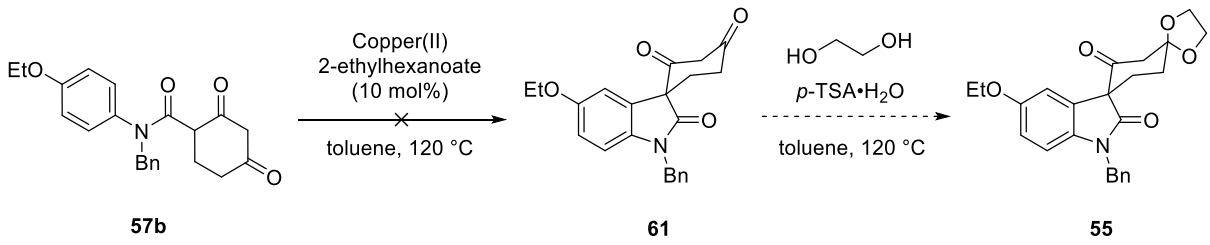
Scheme 2.5 Proposed retrosynthesis of advanced intermediate **55** in the synthesis of Satavaptan.

Coupling of carboxylic acid **38** with *N*-benzyl-4-ethoxyaniline **44** using Mukaiyama's reagent afforded anilide **59** in 63% yield which was alkylated with methyl vinyl ketone **60** giving anilide **58** in near quantitative yield (Scheme 2.6). Ethoxide-mediated cyclisation of **58** gave a mixture of enol ether **57a** and the desired ketone ketone **57b** in 33% and 46%, yield respectively. Enol ether **57a** could be converted into desired ketone **57b** in near quantitative yield upon exposure to aqueous HCl. Disappointingly the formation of acetal **56** was unsuccessful using ethylene glycol and p-TSA under a range of conditions.



Scheme 2.6 Initial efforts towards the synthesis of anilide **56**.

It was thought that, alternatively, the desired oxindole **61** could be synthesised by cyclisation of diketone **57b** with copper(II) followed by acetal formation (Scheme 2.7). Unfortunately however, cyclisation of **57b** using our copper catalysis conditions was unsuccessful with decomposition of the starting material being observed. Unfortunately, the decomposed material was unidentifiable by spectroscopic analysis.

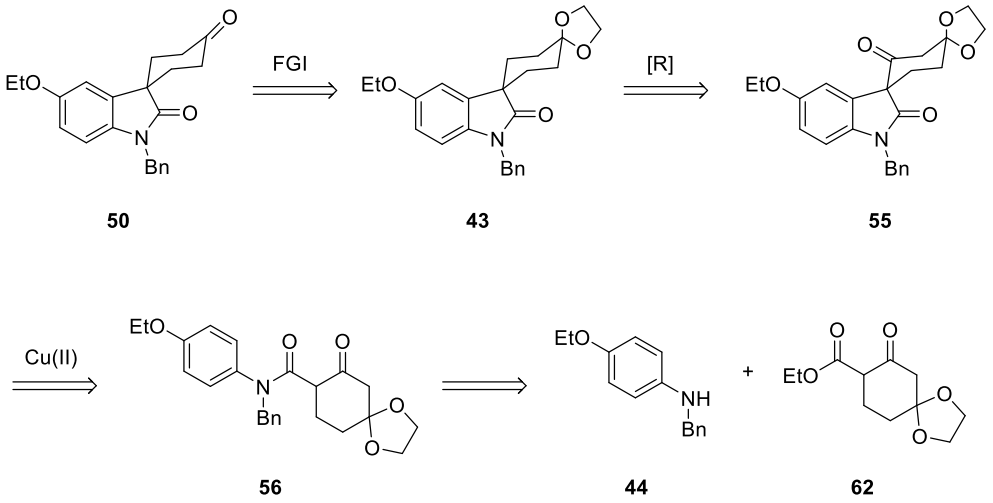


Scheme 2.7 Failed attempt to form oxindole **61** from diketone **57b**.

Due to the lack of success with this route, the retrosynthesis of anilide **56** was modified and an alternative synthesis implemented.

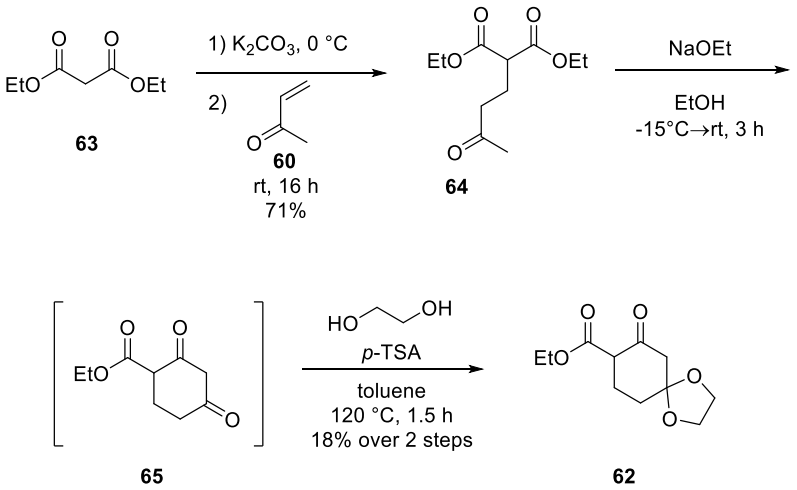
Route 2

Modificaton of the retrosynthesis produced an alternative route to the synthesis of anilide **50** (Scheme 2.8) from Brimble's acetal[52] **62** and *N*-benzyl-4-ethoxyaniline **44**.



Scheme 2.8 Modified retrosynthesis of advanced intermediate **50** in the synthesis of Satavaptan.

Acetal **62** was synthesised in 3 steps following the procedure of Brimble (Scheme 2.9).[52] Diethyl malonate was reacted with methyl vinyl ketone **60** to afford ketone **64** in good yield, which in turn underwent ethoxide-mediated cyclisation to afford diketone **65**. The acetal formation step was low-yielding due to the lack of regio-selectivity towards the desired ketone functionality. A mixture of acetal products were formed, but the desired acetal **62** was the only product that it was possible to isolate cleanly.

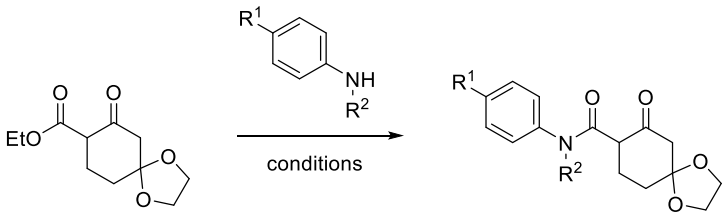


Scheme 2.9 Synthesis of acetal **62** following Brimble's procedure.

With acetal **62** in hand, efforts were made to directly convert it into anilide **56** (Table 2.5). *N*-Methylaniline was primarily used as a model aniline due to its availability, while *N*-benzyl-4-ethoxyaniline **44** was synthesised in 75% yield *via* reductive amination of 4-ethoxyaniline and benzaldehyde.

When using *N*-methylaniline as the coupling partner, a good yield of amide **66** was observed using catalytic DMAP in refluxing toluene (entry 1, Table 2.5). These conditions were then applied to *N*-benzyl-4-ethoxyaniline, however, only a trace amount of the desired anilide was observed (entry 2, Table 2.5). The same observation was made when the amount of DMAP used was increased to a full equivalent (entry 3, Table 2.5). The use of $AlMe_3$ with the aniline followed by subsequent addition of the ester gave no desired product (entry 4, Table 2.5); both ester **62** and aniline **44** were recovered.

Table 2.5 Attempted synthesis of anilide **66**/**56** directly from ethyl ester **62**.

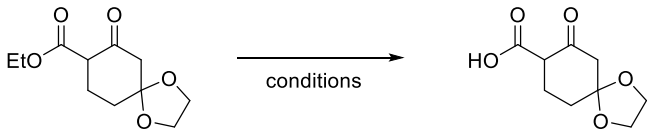


62 **66** or **56**

Entry	R^1	R^2	Reagent	Solvent	Temperature (°C)	Time (h)	Yield (%)
1	H	Me	DMAP (10 mol%)	Toluene	120	16	71
2	OEt	Bn	DMAP (10 mol%)	Toluene	120	16	trace
3	OEt	Bn	DMAP (1 eq.)	Toluene	120	16	trace
4	OEt	Bn	$AlMe_3$ (3 eq.)	Toluene	120	16	0

Attempts were then made to hydrolyse ethyl ester **62** to acid **67** with the intention of forming the anilide from the acid. Despite using a range of conditions (entries 1-3, Table 2.6), no formation of acid **67** was observed.

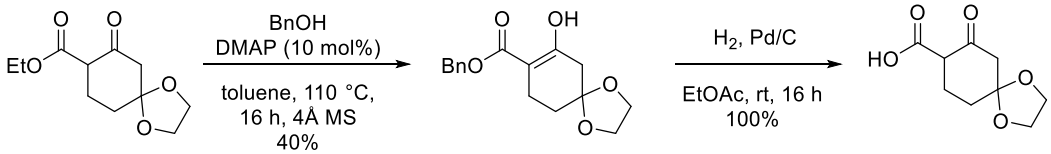
Table 2.6 Attempted hydrolysis of ethyl ester **62**.



62 **67**

Entry	Reagent	Solvent	Temperature (°C)	Time (h)	Yield (%)
1	LiOH	EtOH/H_2O	rt→70	24	0
2	KOH	EtOH/H_2O	rt	16	0
3	KOTMS	THF	rt	16	0

Given the apparent unreactivity of ethyl ester **62**, an alternative route to desired anilide **56** was devised (Scheme 2.10). Transesterification of ethyl ester **62** using BnOH with catalytic DMAP and 4Å molecular sieves under Dean-Stark conditions allowed access to benzyl ester **68**. Upon ^{1}H NMR spectroscopic analysis of **68**, it was found that it existed entirely as the enol tautomer. Hydrogenation of benzyl ester **68** afforded carboxylic acid **67** in quantitative yield. We found that carboxylic acid **67** was unstable and degraded over time (likely decarboxylation of the acid functionality); it was therefore used in subsequent steps immediately upon isolation.

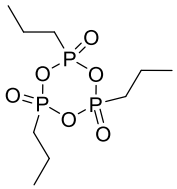


62 **68** **67**

Scheme 2.10 Two-step synthesis of carboxylic acid **67** from ethyl ester **62**.

With carboxylic acid **67** in hand, efforts were focussed on developing conditions to best synthesise anilide **57** (Table 2.7). We found that when using the carboxylic acid **67** as the limiting reagent and using Mukaiyama's coupling reagent, no product was observed, with only aniline **44** recovered (entry 1, Table 2.7). By making aniline **44** the limiting reagent and using DCC as the coupling reagent with catalytic DMAP, the desired anilide **56** was isolated in 40% yield (entry 2, Table 2.7). Both DCC and DMAP are toxic reagents which pose serious health risks. In the interest of keeping the synthesis as green as possible we chose to investigate the use of a greener coupling agent, commercially available propane phosphonic acid anhydride (T3P) (Figure 2.3). The green properties of T3P include the fact that it is non-toxic, non-allergenic/non-sensitising and the

solubility of its by-products in water enable ease of purification. The Taylor group have previously utilised T3P in a variety organic synthetic methodologies.[53]

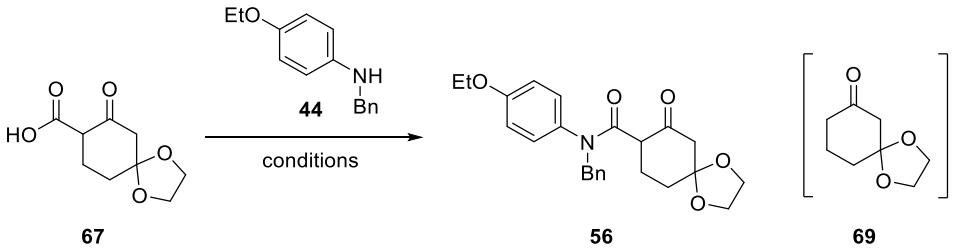


T3P **68**

Figure 2.3 Propylphosphonic acid anhydride (T3P)

Using T3P (in EtOAc) at room temperature in toluene gave the desired anilide **56** in an improved yield of 42% (entry 3, Table 2.7). Despite aniline **44** being the limiting reagent, it was still present at the end of the reaction suggesting that the reaction hadn't gone to completion. The reaction was repeated at the increased temperature of 60 °C but a decrease in yield was observed (entry 4, Table 2.7). We suspected that decarboxylation of the starting material was occurring during these reactions and that the increased temperature promoted this, thus decreasing the yield. The reaction was therefore carried at 0 °C with subsequent warming to room temperature (entry 5, Table 2.7). The yield obtained from this was comparable to the room temperature conditions (entry 3, Table 2.7). By removing base from the reaction we hoped that this would decrease the potential for decarboxylation occurring, however, we saw a decrease in yield indicating that the presence of base is important (entry 6, Table 2.7).

Table 2.7 Development of conditions for the synthesis of anilide **56**.



Entry	Eq. Acid	Eq. Aniline	Coupling Reagent	Base	Solvent	Temperature (°C)	Yield (%)
1	1	1.2	Mukaiyama's	NEt_3	DCM	rt	0
2	1.2	1.0	DCC	DMAP	DCM	rt	40
3	1.2	1.0	T3P (in EtOAc)	DIPEA	Toluene	rt	42
4	1.2	1.0	T3P (in EtOAc)	DIPEA	Toluene	60	12
5	1.2	1.0	T3P (in EtOAc)	DIPEA	Toluene	0→rt	38
6	1.2	1.0	T3P (in EtOAc)	-	Toluene	rt	16
7	1.2	1.0	T3P (in EtOAc) × 4	DIPEA × 4	Toluene	rt	6
8	1.2	1.0	T3P (in toluene)	DIPEA	Toluene	rt	46
9	1.2	1.0	T3P (in THF)	DIPEA	THF	rt	49
10	1.2	1.0	T3P (in EtOAc)	DIPEA	EtOAc	rt	58
11	***2.0***	***1.0***	***T3P (in EtOAc)***	***DIPEA***	***EtOAc***	***rt***	***75***

With the reaction still not consuming all the aniline **44**, T3P and DIPEA was added in sequential additions at 12 h intervals (entry 7, Table 2.7) in an attempt to overcome any stalling that may be occurring. Unfortunately, however, the yield dramatically decreased.

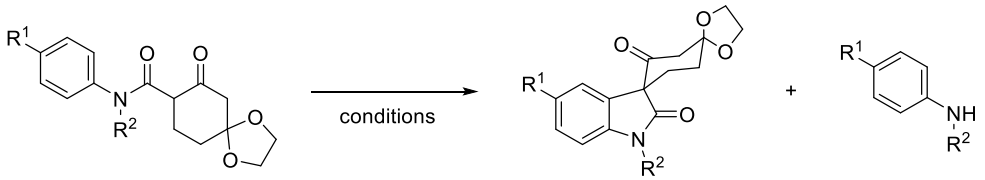
The reaction was repeated using a range of commercial T3P samples in different solvents with the reaction carried out in the matching solvent (entries 8-10, Table 2.7). Toluene, THF and EtOAc showed improved yields of 46%, 49% and 59%, respectively. When the EtOAc conditions (entry 10, Table 2.7) were repeated using 2 eq. of carboxylic acid **67** the yield improved dramatically to 75%. What was also interesting is that 1,4-dioxaspiro[4.5]decan-7-one **69** was also isolated, which proved that our assumption that decarboxylation of carboxylic acid **67** was occurring, was in fact

correct. This explains why the yield increases as the number of equivalents of carboxylic acid increases.

Conditions to convert anilide **66** into oxindole **70** using copper catalysis were then investigated. Upon treatment with our standard copper conditions, model anilide **66** was smoothly converted to oxindole product **70** in 83% yield (entry 1, Table 2.8). When these conditions were applied to the real system (anilide **56**) the yield was substantially lower, only 34% (entry 2, Table 2.8).

Elsewhere in the group, identical problems were encountered with a similar substrate, bearing *N*-PMB in place of *N*-Bn. Exposure of this PMB-anilide to catalytic $Cu(OAc)_2 \bullet H_2O$ in refluxing mesitylene with dried air bubbling through resulted in a significant improvement in yield. This was also observed by the Taylor group in their research into the cyclisation of spirocyclic lactam oxindoles.[43]

Table 2.8 Development of copper-catalysed conditions for the synthesis of oxindole **70** and **55**.



66 or **56** **70** or **55** **71** or **44**

Entry	R^1	R^2	Catalyst (10 mol%)	Solvent	Temperature (°C)	Time (h)	Yield (%)	Aniline isolated (%)
1	H	Me	Copper(II) 2-ethylhexanoate	Toluene	120	16	83	-
2	OEt	Bn	Copper(II) 2-ethylhexanoate	Toluene	120	16	34	-
3	***OEt***	***Bn***	***$Cu(OAc)_2 \bullet H_2O$***	***Mesitylene[a]***	***165***	***0.5***	***58[b]***	-
4	OEt	Bn	$Cu(OAc)_2 \bullet H_2O$	Mesitylene[a]	165	1	32[c]	33
5	OEt	Bn	$Cu(OAc)_2 \bullet H_2O$	Mesitylene[a]	165	1	40[d]	20

[a] dried compressed air bubbled through. [b] 169 µmol of anilide **56**. [c] 1.04 mmol of anilide **56**. [d] 1.54 mmol of anilide **56**.

These conditions were therefore applied to anilide **56** which afforded an increased yield of oxindole **55** (entry 3, Table 2.8). Despite these conditions affording the desired oxindole **55** in modest yield (58%), there were also other drawbacks. It was found that upon increasing the scale of the reaction,

the yield decreased to 32-40% and amide cleavage of anilide **56** occurred as demonstrated by the isolation of aniline **44** (entries 4 and 5, Table 2.8). In addition there is the associated danger of heating a solvent above its flash point in the presence of air. The flash point of a solvent is defined as "the temperature at which a particular organic compound gives off sufficient vapour to ignite in air".[12] Bubbling air through a reaction solvent increases the amount of solvent vapour and therefore decreases the flash point. This reaction is being carried out at 165 °C with the flash point of mesitylene being 53 °C. These safety issues would be of grave concern to industrial chemists making scale-up of this procedure unfavourable. It was with these safety concerns in mind that a brief investigation into the use of high flash point solvents for the synthesis of oxindoles was commenced.

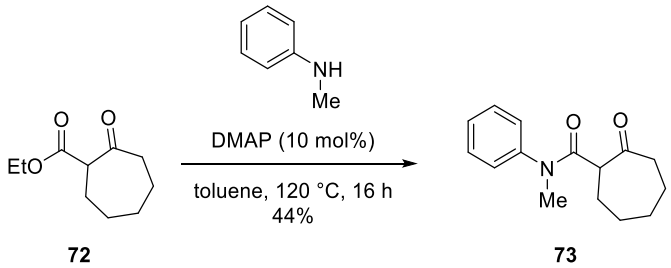
It is worthy of note that many high boiling point solvents have surprisingly low flash points (Table 2.9). Entries 1-5 have flash points below 100 °C which makes then unsuitable for large-scale applications of our copper-catalysed oxindole synthesis. Benzyl alcohol (entry 6, Table 2.9) has a flash point that is above 100 °C but is extremely difficult to remove after carrying out the reaction, often requiring several purifications by column chromatography. Propylene carbonate (PC) and ethylene carbonate (EC) (entries 7 and 8, Table 2.9) have high flash points, and can be removed after the reaction by washing with water and are commonly-used green solvents as substitutes for polar aprotics such as DMF due to their similar properties and lower toxicity.

Table 2.9 Boiling point and flash point of common high boiling solvents.

Entry	Solvent	Boiling Point (°C)	Flash Point (°C)
1	Toluene	111	6
2	Mesitylene	165	50
3	Cymene	177	47
4	NMP	202	90
5	Tetralin	206	77
6	Benzyl alcohol	205	101
7	Propylene carbonate (PC)	240	116
8	Ethylene carbonate (EC)	244	143

Efforts were then focussed on investigating whether PC and EC could be used as safer solvents for the synthesis of oxindoles, in particular, the formal synthesis of Satavaptan **6**.

The conditions were optimised on model substrate **73** which was prepared from ester **72** using catalytic DMAP in 44% yield (Scheme 2.11).

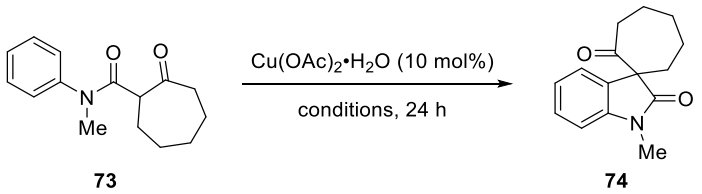


72 **73**

Scheme 2.11 Synthesis of anilide **73**.

Cyclisation of substrate **73** using copper-catalysis has been previously carried out in the group as its structure bears similarity to the natural product rankinidine.[54] Upon treatment with catalytic $Cu(OAc)_2 \bullet H_2O$ in toluene at 110 °C, oxindole **74** was isolated in 66% yield (entry 1, Table 2.10). Using PC as solvent at several temperatures (entries 2-4, Table 2.10) it was found that the best yield was observed at 100 °C affording oxindole **74** in 73% yield. This reaction is below the flash point of the solvent and gives higher yield than in toluene. The drawback of using PC is that it is tedious to remove after the reaction requiring a minimum of ten washes with H_2O. Clearly, this extensive purification has a hugely negative impact on the green metrics of the reaction, more specifically the waste produced and the EMY. The reaction was thus investigated with EC as solvent; it has a higher flash point and can be removed from the reaction mixture with considerably fewer washes. The reaction was carried out at a range of temperatures in EC (entries 5-7, Table 2.10) with the highest yield being observed at 100 °C affording the desired oxindole **74** in 81% isolated yield after purification. This reaction is higher yielding in EC than in PC and toluene, is being carried out below the flash point of the solvent and is considerably easier to remove than PC.

Table 2.10 Investigation into high flash point solvents in the synthesis of oxindole **74**.



73 **74**

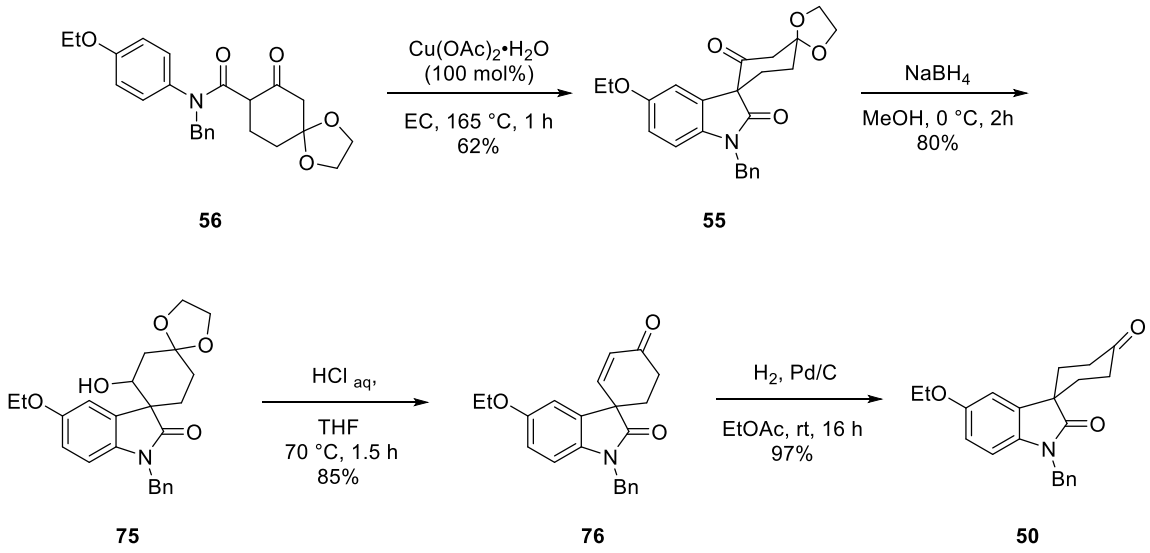
Entry	Solvent	Temperature (°C)	Yield (%)
1	Toluene	110	66[a]
2	PC	110	49
3	PC	100	73
4	PC	80	59[b]
5	EC	110	72
6	EC	100	81
7	EC	80	54

[a] Reaction carried out by a colleague. [b] Starting material still present

It is worthy of note that EC is a solid at room temperature and thus must be weighed out as a solid or melted and measured as a liquid to place in the reaction vessel. This adds slightly to the operational complexity of the procedure.

These optimised conditions were then applied to anilide **56** to complete the formal synthesis of Satavaptan (Scheme 2.12). Unfortunately the reaction would not proceed at low temperature and thus required the reaction to be carried out at 165 °C. With copper(II) 2-ethylhexanoate (100 mol%) as catalyst, 58% yield was observed and with $Cu(OAc)_2•H_2O$ (100 mol%) an improved yield of 62% was observed (Scheme 2.12).

Spirocyclic ketone oxindole **55** was next treated with $NaBH_4$ to afford alcohol **75** in excellent yield. By exposing alcohol **75** to aqueous HCl in THF it was possible to remove the acetal protecting group and eliminate the alcohol functionality in one pot to afford α,β-unsaturated ketone oxindole **76** in excellent yield. Upon hydrogenation, alkene **76** was converted into Liotta's advanced intermediate **54** in near quantitative yield, thus concluding the formal synthesis of Satavaptan **6**.



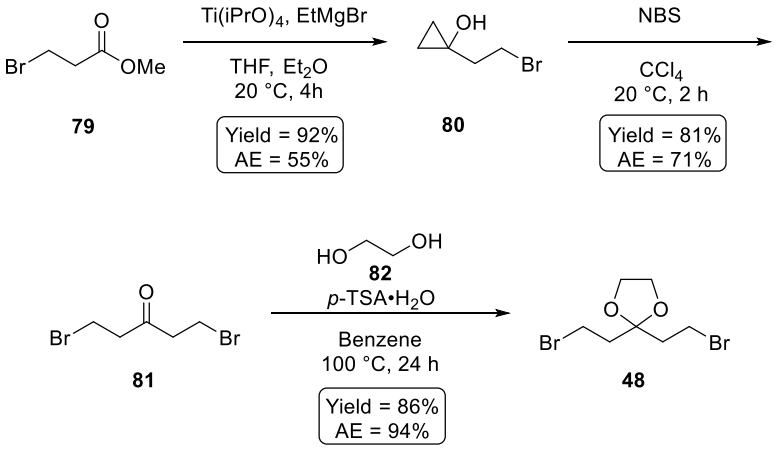
Scheme 2.12 4 Step synthesis of Liotta's advanced intermediate **50** from anilide **56**.

2.2.4 Green metrics comparison

Having successfully applied our copper-catalysis method in the formal synthesis of Satavaptan **6** by intercepting Liotta's advanced intermediate **50**, a comparison of some key green chemistry metrics are described. As some of the work carried out by Liotta lacks clarity around experimental information (e.g. repeats of literature procedures, volumes of solvents and masses of reagents used during purification), quanitiative comparison of metrics requiring this information, such as effective mass yield, cannot be calculated. Therefore, quantitative comparison of atom economy, yield and number of steps shall be described in addition to qualitative discussion around the conditions and reagents employed.

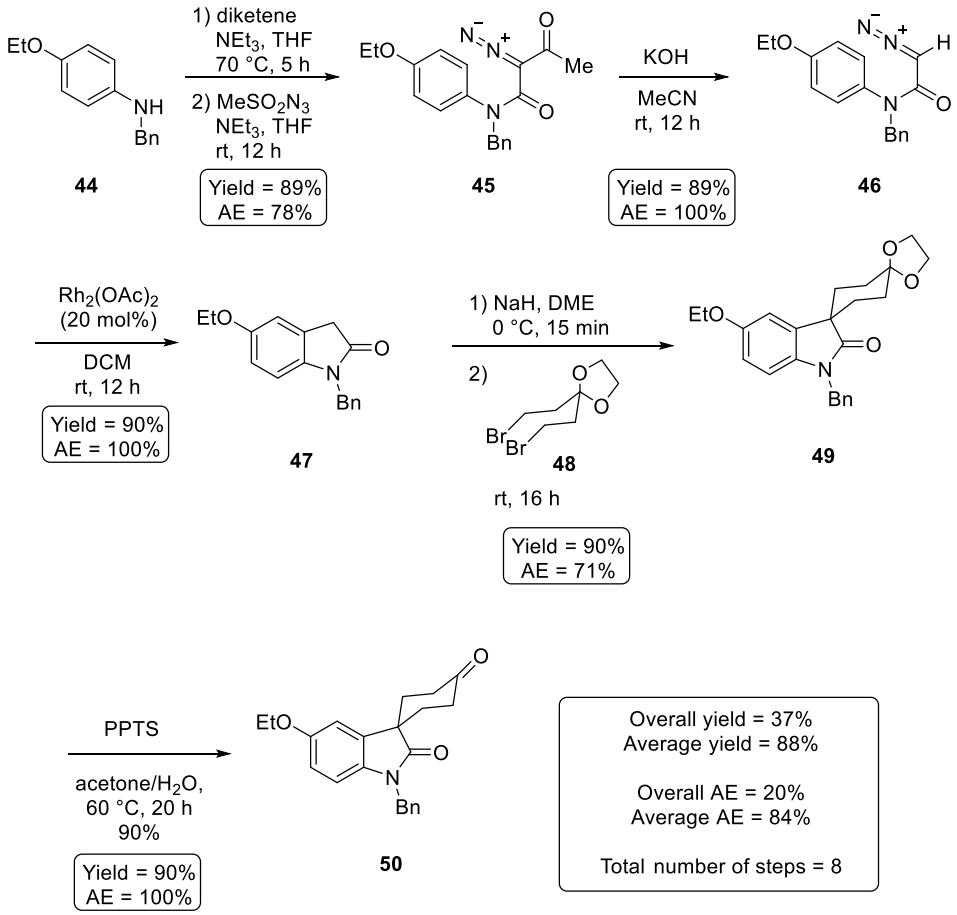
Liotta's approach includes a divergent synthesis, in which di-bromide **48** is synthesised in 3 steps from ester **79** (Scheme 2.13). Unfortunately, Liotta fails to report the specific conditions and yields observed for this process and only outlines the general approach used to obtain **48**. Unfortunately, the references given also fail to give experimental details. Therefore, the yields given in scheme 2.13 are the best yields observed by other research groups who carried out these reactions with the same reagents.[55]

The formation of cyclopropane **80** is high yielding, requires no heating, utilises an abundant metal salt and reacts in just 4 h. Unfortunately, the atom economy of the reaction is poor as a result of the Grignard alkylating reagent being used. From a safety perspective Et_2O is a solvent which has several safety concerns associated with it as do Grignard reagents due to their corrosive nature and violent reaction with water. Formation of ketone **81** is another high yielding step but requires the use of extremely toxic CCl_4 as solvent which is blacklisted in pharmaceutical synthesis. Again, the synthesis of di-bromide **48**, despite being high yielding and having a high AE, utilises the incredibly carcinogenic, blacklisted solvent benzene.



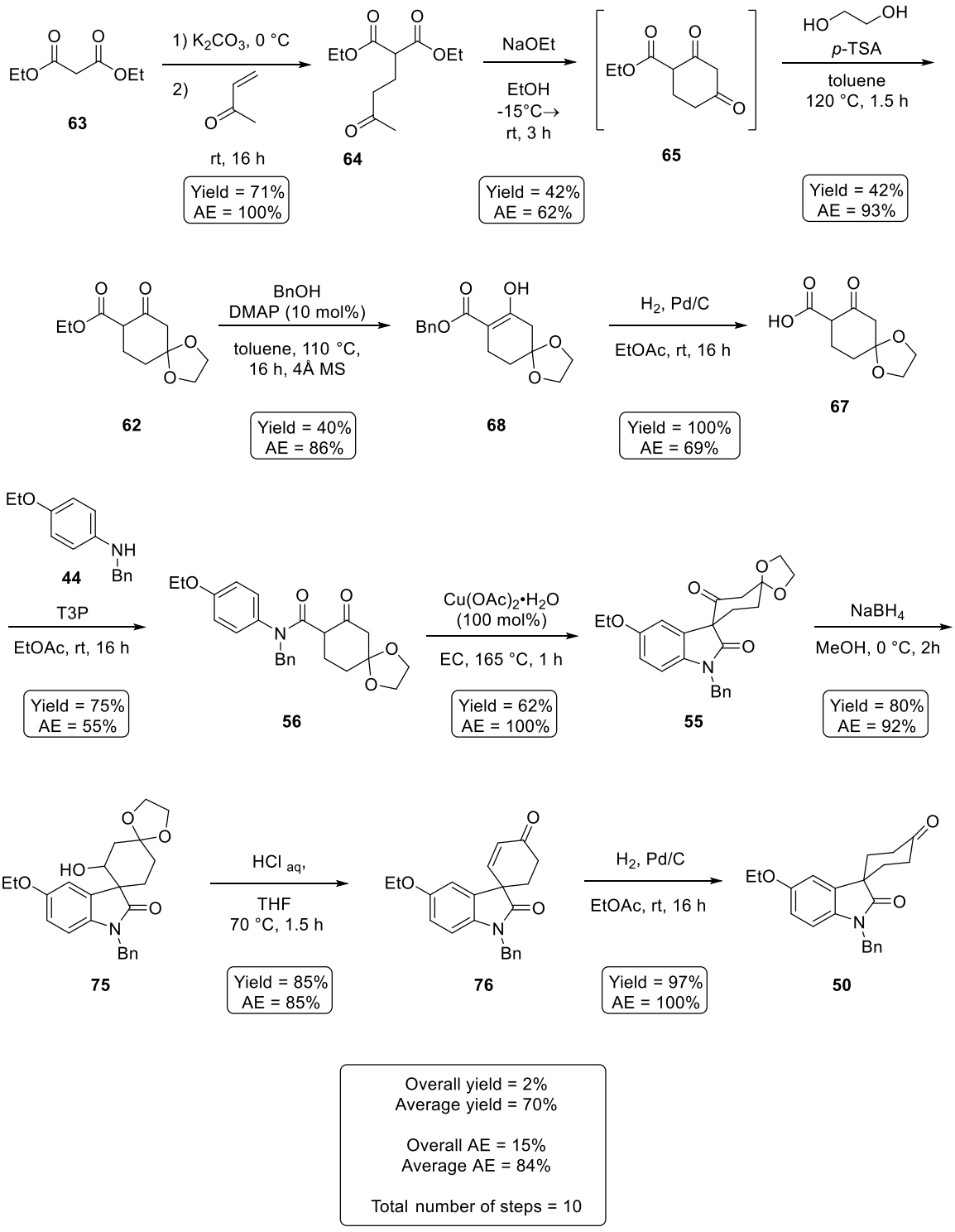
Scheme 2.13 Synthesis of dibromide **48** in 3 steps from **79**.

Synthesis of diazo compound **45** occurs in high yield and high atom economy, however, diazo compounds are known to be explosive which poses serious safety concerns (Scheme 2.14). **46** is formed in high yield and atom economy at room temperature. The rhodium-catalysed formation of oxindole **47** occurs in excellent yield and high atom economy, however, rhodium is a precious metal and is employed in high catalyst loading. Additionally, whilst it is carried out at room temperature which is favourable, carcinogenic DCM is used as the solvent. Spirocyclic oxindole **49** is formed in high yield and good atom economy, however, DCE is a carcinogenic solvent and blacklisted by the pharmaceutical industry. Acetal removal is high yielding and highly atom economical producing ketone **50**.



Scheme 2.14 Liotta's approach to oxindole **50**

Formation of malonate **64** occurs in high yield, high atom economy and is a solvent-free reaction. Ethoxide-mediated ring-closure of **64** to give **65** is poor yielding and has a poor atom economy (Scheme 2.15). It is however carried out in ethanol which is a reasonably green solvent due to its limited hazards. Formation of acetal **66** occurs in low yield but is highly atom economical. The reaction is required to be carried out in toluene at high temperature. A noteworthy step to draw attention to is the formation of anilide **56** which occurs in high yield. It utilises the green coupling agent T3P and is carried out in EtOAc which has limited health risks. Unfortunately due to the size of the T3P coupling agent the atom economy is negatively impacted however the overall reaction, which is carried out at room temperature, is a green process compared to typical amide bond-forming reactions. Another noteworthy step is the formation of α,β-unsaturated ketone **76** from alcohol **75**. This reaction combines the removal of the acetal functionality and elimination of the alcohol in one-pot, in high yield and atom economy in a short reaction time.



Scheme 2.15 Our approach to synthesis advanced intermediate **50**

Two metrics that have been directly compared quantitatively are yield and atom economy (AE). Average yield and AE are calculated as an average over the total number of steps in the reaction. Overall yield and AE are calculated cumulatively over the longest linear sequence. Our approach has a lower average and overall yield than Liotta's approach to advanced intermediate **50** (Figure 2.4). The lower overall yield is due to low yielding reactions early on in the synthetic route. Our approach is a longer sequence, however, AE values are comparable for both routes. What is

noticeable, is that our route utilises more mild conditions and less hazardous solvents. Half of the steps in Liotta's synthesis utilise carcinogenic reaction solvents whereas our approach doesn't utilise any.

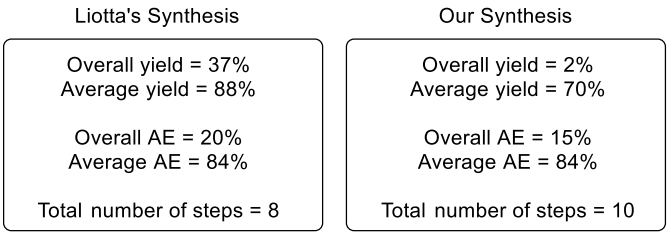
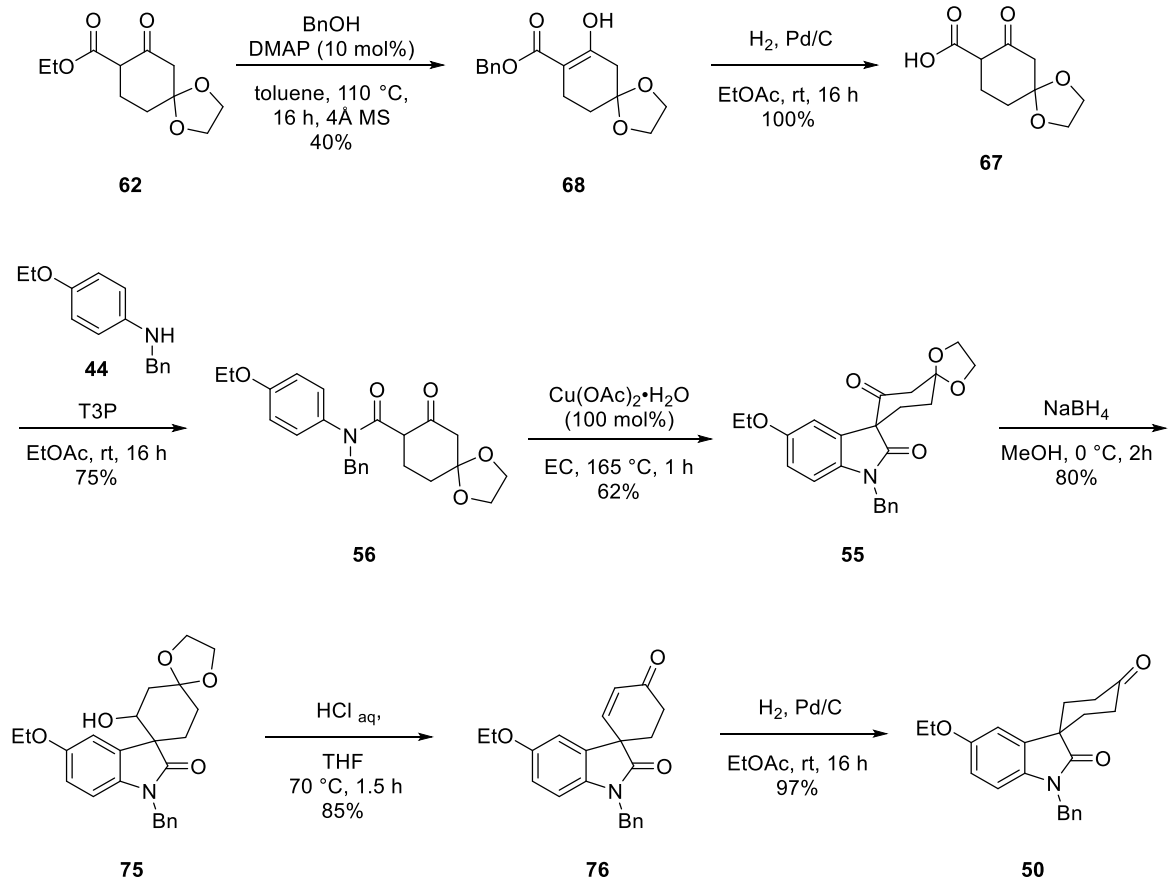


Figure 2.4 Metrics comparison for Liotta's and our approach to advanced intermediate **50**.

If early steps of our route were optimised, this would significantly improve our overall yield. That being the case, due to the use of safer conditions utilised in our approach, I believe our approach has the potential to be an entirely 'greener' process than Liotta's.

2.2.5 Application to the formal synthesis of Satavaptan summary

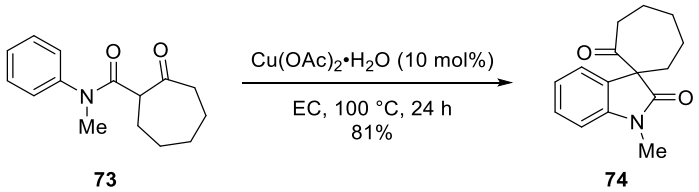
The formal synthesis of Satavaptan **6** was completed using copper-catalysed cyclisation of anilide **56** to form oxindole **55** which was subsequently transformed into Liotta's advanced intermediate **50**,[50] thus completing the formal synthesis (Scheme 2.16).



Scheme 2.16 Formal synthesis of Satavaptan **6**.

Despite being a longer linear synthesis that Liotta's approach to Satavaptan, it is only two steps longer when comparing the total number of steps. This new route avoids the use of the precious metal catalyst rhodium and also avoids having to generate an azide, which are known for being unsafe upon scale up.

Although the formation of the oxindole core of Satavaptan **6** could not be carried out below the flash point of the solvent, the development of copper-catalysed conditions for the formation of spirocyclic ketone oxindoles in ethylene carbonate (EC) shows promise (Scheme 2.17). These new 'green conditions' could have potential application in the formation of other spirocyclic ketone oxindoles and 3,3-disubstituted oxindoles.

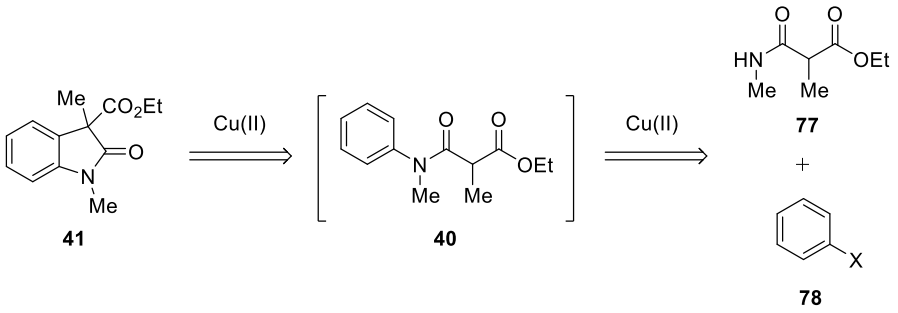


Scheme 2.17 Copper(II) catalysed cyclisation in ethylene carbonate as the solvent

These conditions could also have potential application for the scale-up of oxindole formation as it would allow reactions to be carried out in the presence of air with a lower risk of combustion.

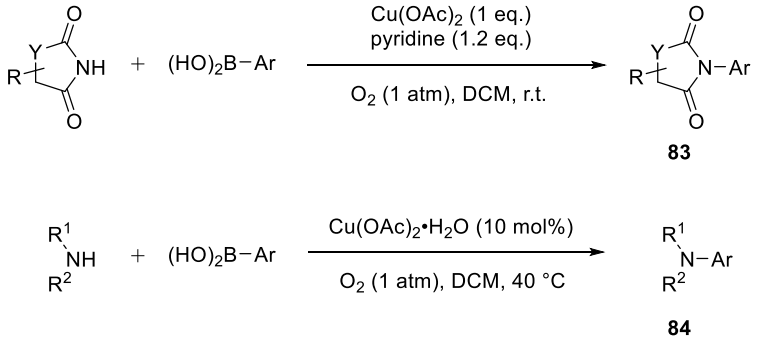
2.3 Copper-catalysed C–*N*/C–C approach to oxindole synthesis

Given that *N*-arylation of amides using copper-catalysis is well known,[56] we investigated whether it was possible to construct the anilide **40** using copper-catalysis, with the hope that cyclisation to oxindole **41** would occur afterwards in one-pot (Scheme 2.18). This would be an extremely powerful method given that one would be able to rapidly access the privileged oxindole motif from the simple commercial starting material **78** and anilide **77**. From a green chemistry perspective, being able to carry out a multi-step reaction in one pot would grealy reduce the amount of waste produced and time required by avoiding the physical manipulations associated with isolation and purification in multi-step synthesis.



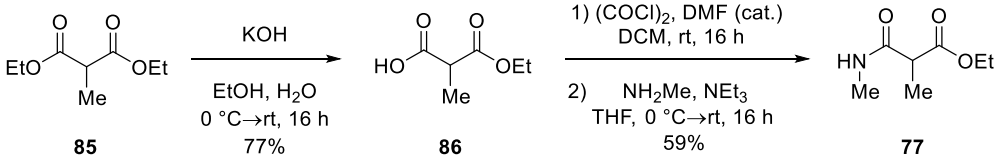
Scheme 2.18 Retrosynthesis of oxindole **41** *via* copper-catalysed C–*N*/C–C coupling approach.

The Chan-Lam reaction allows the construction of carbon-heteroatom bonds *via* an oxidative coupling between boronic acids and *N*–H containing compounds. The use of arylboronic acids for *N*-arylation of both amides and amines is extremely well reported.[57] These couplings are routinely carried out using catalytic $Cu(OAc)_2$ in the presence of air (Scheme 2.19),[57a, 57b] a catalyst system we have previously shown is competent in the formation of oxindoles from anilides.[19d, 42-43] There is, however, to the best of our knowledge, no precedent for Chan-Lam couplings on secondary amides. Whilst Chan-Lam reactions utilise toxic reagents such as pyridine and DCM, the overall improvement in green metrics that this approach could yield for our proposed synthesis of oxindoles justifies the use of this method.



Scheme 2.19 Examples of the Chan-Lam reaction.

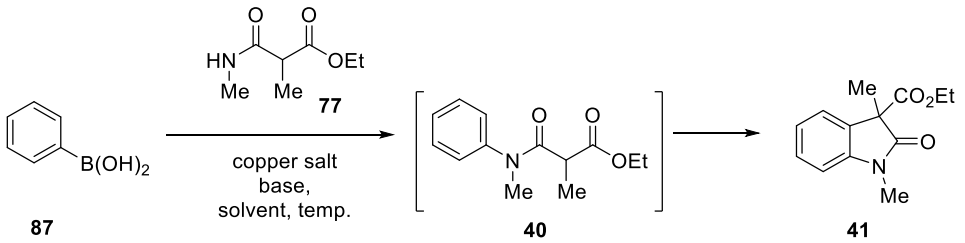
To synthesise amide **77**, diethyl methylmalonate **85** was converted into mono-acid **86** in high yield using KOH. Mono-acid **86** was then converted into amide **77** *via* oxalyl chloride mediated chlorination, followed by exposure to methylamine, yielding the desired amide **77** in 59% yield (Scheme 2.20). Oxalyl chloride, DMF and DCM are all toxic reagents and not considered to be 'green', however, when the amide formation was attempted using other greener methods incredibly poor yields were observed.



Scheme 2.20 Synthesis of amide **77** from diethylmethylmalonate **85**.

Phenylboronic acid **87** and amide **77** were treated with two equivalents of $Cu(OAc)_2 \cdot H_2O$ in DCM at room temperature under an atmosphere of argon but no reaction occurred in either case (entries 1 and 2, Table 2.11). Switching the catalyst to $Cu(OAc)_2$ gave no improvement (entries 3 and 4, Table 2.11) and changing the reaction solvent to methanol or toluene also showed no improvement (entries 5 and 6, Table 2.11). The reaction was repeated in DCM, methanol and toluene under an atmosphere of air, none of which gave any conversion into the desired product (entries 7-10, Table 2.11). The reaction was repeated in DCM at rt and 45 °C under an atmosphere of air with the addition of molecular sieves but again no reaction was observed (entries 11 and 12, Table 2.11). The reaction was repeated in DCM, methanol, toluene and dioxane with molecular sieves under an atmosphere of O_2 but still no reaction was observed (entries 13-16, Table 2.11).

Table 2.11 Investigation into cascade C–N/C–C coupling *via* a Chan-Lam process.



Entry	Copper Salt	Additive	Solvent	Temp (°C)	Atmosphere	Yield (%)
1	$Cu(OAc)_2 \cdot H_2O$ (200 mol%)	-	DCM	rt	Argon	0
2	$Cu(OAc)_2 \cdot H_2O$ (200 mol%)	-	DCM	45	Argon	0
3	$Cu(OAc)_2$ (200 mol%)	-	DCM	rt	Argon	0
4	$Cu(OAc)_2$ (200 mol%)	-	DCM	45	Argon	0
5	$Cu(OAc)_2$ (200 mol%)	-	MeOH	45	Argon	0
6	$Cu(OAc)_2$ (200 mol%)	-	Toluene	45	Argon	0
7	$Cu(OAc)_2$ (100 mol%)	-	DCM	rt	air	0
8	$Cu(OAc)_2$ (100 mol%)	-	DCM	45	air	0
9	$Cu(OAc)_2$ (100 mol%)	-	MeOH	45	air	0
10	$Cu(OAc)_2$ (100 mol%)	-	Toluene	120	air	0
11	$Cu(OAc)_2$ (100 mol%)	4Å MS	DCM	rt	air	0
12	$Cu(OAc)_2$ (100 mol%)	4Å MS	DCM	45	air	0
13	$Cu(OAc)_2$ (100 mol%)	4Å MS	DCM	rt	O_2	0
14	$Cu(OAc)_2$ (100 mol%)	4Å MS	MeOH	rt	O_2	0
15	$Cu(OAc)_2$ (100 mol%)	4Å MS	toluene	rt	O_2	0
16	$Cu(OAc)_2$ (100 mol%)	4Å MS	dioxane	rt	O_2	0

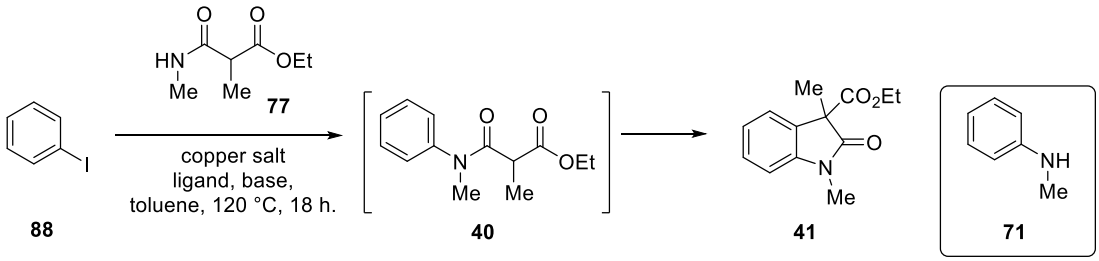
With the lack of success afforded by the Chan-Lam approach, we investigated an alternative method. We intended to couple aryl iodides with amide **77** *via* a Goldberg reaction[58] to form anilide **40** and investigate whether we could synthesise and isolate either anilde **40** or oxindole **41**.

In an initial experiment, iodobenzene **88** was exposed to amide **77** and catalytic copper(II) 2-ethylhexanoate in toluene. However, no reaction was observed under an atmosphere of air or argon (entries 1 and 2, Table 2.12). The addition of DIPEA to the reaction showed no improvement (entry 3, Table 2.12). Copper catalysed C–N couplings are typically carried out under an atmosphere of argon whereas the copper-catalysed cyclisation of anilides to give oxindoles requires air to re-oxidise the reduced copper catalyst; the reaction mechanism involves two single electron oxidations. Therefore anilide cyclisation should work under an atmosphere of argon if two equivalents of copper(II) salt are employed. The use of stoichiometric copper(II) 2-ethylhexanoate under an argon atmosphere (entry 4, Table 2.12), however, gave no reaction.

Conditions reported by Taillefer[59] for *N*-arylation of amides were employed using catalytic CuI and 2,2,6,6-tetramethylheptane-3,5-dione as ligand and K_3PO_4 (entry 5, Table 2.12) and phosphazene bases (entry 6, Table 2.12), neither of which gave any reaction. Conditions developed by Buchwald[58] for *N*-arylation of amides were next employed utilising diamine ligands. However, both K_3PO_4 (entry 7, Table 2.12) and phosphazene base (entry 8, Table 2.12) gave no reaction. Buchwald identified KHMDS as an effective base. It is reported that the pK_{aH} of the base is crucial to the success of the *N*-arylations. If the base is too strong large amounts of the nitrogen anion are present in solution and are able to coordinate copper and slow down the rate of reaction. This is given as justification as to why Buchwald observed improved yields when adding KHMDS to the reaction mixture slowly.[58]

Slow addition of KHMDS to the reaction (entry 9, Table 2.12) showed a trace of the desired oxindole by ^{1}H NMR spectroscopy with and *N*-methylaniline **71** as a major by-product. This indicated that C–*N* coupling to give **40** was successful, but amide cleavage was occurring to give the by-product. When the copper loading was increased (entry 10, Table 2.12) similar amide cleavage was observed. When KHMDS was added in one portion to the refluxing reaction mixture (entry 11, Table 2.12) a ratio of 1:4 oxindole **41** to *N*-methylaniline **71** was observed and the oxindole **71** was isolated in 6% yield.

Table 2.12 Investigation into cascade C–N/C–C coupling.



Entry	Copper Salt	Ligand	Base (2 eq.)	Atmosphere	Yield (%)
1	Copper(II) 2-ethylhexanoate (10 mol%)	-	-	Air	0
2	Copper(II) 2-ethylhexanoate (10 mol%)	-	-	Argon	0
3	Copper(II) 2-ethylhexanoate (10 mol%)	-	DIPEA	Air	0
4	Copper(II) 2-ethylhexanoate (200 mol%)	-	DIPEA	Argon	0
5	CuI (5 mol%)	(tBuCO)$_2$CH$_2$ (20 mol%)	K_3PO_4	Argon	0
6	CuI (5 mol%)	(tBuCO)$_2$CH$_2$ (20 mol%)	Phosphazene[a]	Argon	0
7	CuI (5 mol%)	MeNH(CH$_2$)$_2$NHMe (20 mol%)	K_3PO_4	Argon	0
8	CuI (5 mol%)	MeNH(CH$_2$)$_2$NHMe (20 mol%)	Phosphazene[a]	Argon	0
9	CuI (5 mol%)	MeNH(CH$_2$)$_2$NHMe (20 mol%)	KHMDS[b]	Argon	Trace[c]
10	CuI (50 mol%)	MeNH(CH$_2$)$_2$NHMe (200 mol%)	KHMDS[b]	Argon	Trace[d]

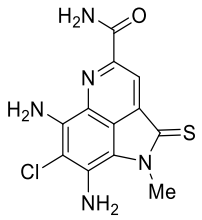
11	CuI (50 mol%)	$MeNH(CH_2)_2NHMe$ (200 mol%)	KHMDS[c]	Argon	6[d]

[a] phosphazene base is *tert*-butylimino-tris(dimethylamino)phosphorane, [b] 2.2 equiv in toluene added by syringe punp over 4 hours [c] 2.2 eq. KHMDS used [d] *N*-methylaniline **71** observed as major product in crude reaction mixture by ^{1}H NMR

This result was encouraging as it shows that a copper-catalysed tandem C–*N*/C–C approach to oxindoles is possible. Due to time constraints, however, efforts were shifted towards other applications of copper-catalysis to other heterocycles and target molecules.

2.4 Application of copper conditions to the synthesis of thio-oxindoles

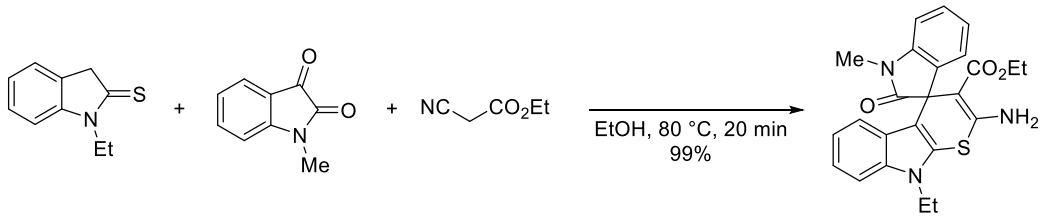
Thio-oxindoles can be found in natural products **89** (Figure 2.5),[60] but are more commonly employed as useful synthetic intermediates[61] such as in drug synthesis and other applications.[62] A comprehensive review of the thio-amide functionality and its synthetic applications has been published by Jagodinski.[63]



89

Figure 2.5 Thio-oxindole natural product ammosamide A **89** isolated from a marine-derived *Streptomyces* strain.

A noteworthy use of thio-oxindoles in synthesis is that of Majumdar and co-workers[64] in which they illustrate a one-pot green synthesis of spirooxindole-annulated thiopyran derivatives such as **93** (Scheme 2.21). This occurs *via* a Knovenagel condensation followed by Michael addition. Tetrahydrothiopyrano[2,3-*b*] indoles are known to have pain-killing activity.[65] This example is of particular interest as it functionalises an oxindole with a thio-oxindole but does so by employing a green approach. This procedure utilises ethanol as the solvent, is metal-free, has an excellent atom economy, is a tandem reaction carried out in short times and most importantly gives excellent yield.

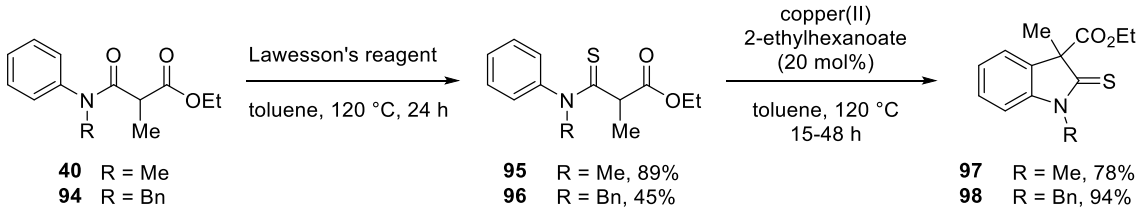


90 **91** **92** **93**

Scheme 2.21 Synthesis of tetrahydrothiopyrano[2,3-*b*] indole **93** *via* one-pot reaction.

Despite their utility, *de novo* synthesis of the thio-oxindole core is scarcely reported and generally relies on the sulfonication of preformed oxindole.[62] Functionalisation of thio-oxindoles at the 3-position is usually achieved by deprotonation of thiooxindole by strong base followed by treatment with an electrophile.[62] The formation of thio-oxindoles from thioanilides *via* formation of the C(3)–C(3a) bond has not been reported.

Our conditions developed for the copper-catalysed synthesis of oxindoles was therefore applied to the synthesis of thio-oxindoles (Scheme 2.22). Upon treatment with Lawesson's reagent, anilides **40** and **94** afforded thio-anilide **95** in excellent yield and thio-anilide **96** in modest yield. Cyclisation of **95** stalled when using 10 mol% of the copper catalyst. This problem was alleviated upon the addition of a second portion of 10 mol% catalyst after 24 h affording **97** in 78% yield. Cyclisation of thio-anilide **96** proceeded smoothly to thio-oxindole **98** without the requirement of a second addition of catalyst. It is noteworthy that the synthesis of **97** has been carried out successfully on a multi-gram scale (3.5 g of **95**).



40 R = Me
94 R = Bn

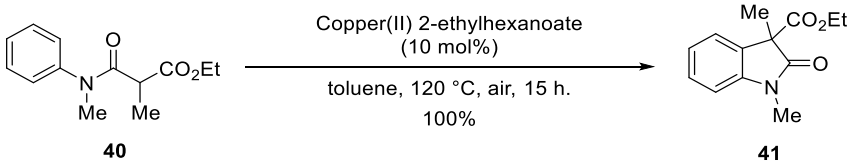
95 R = Me, 89%
96 R = Bn, 45%

97 R = Me, 78%
98 R = Bn, 94%

Scheme 2.22 Synthesis of thio-oxindoles using copper-catalysis.

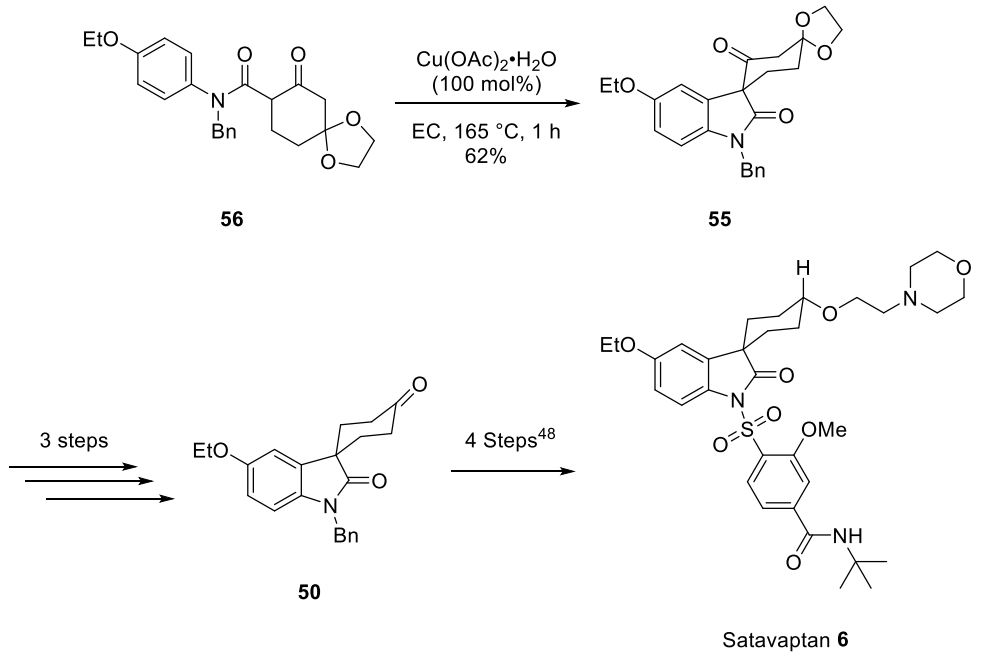
2.5 Summary of copper-catalysed synthesis of oxindoles and thio-oxindoles

Following on from the reported method of oxindole synthesis by copper catalysis, an optimised procedure offering higher yield, lower temperature and greener conditions has been demonstrated.



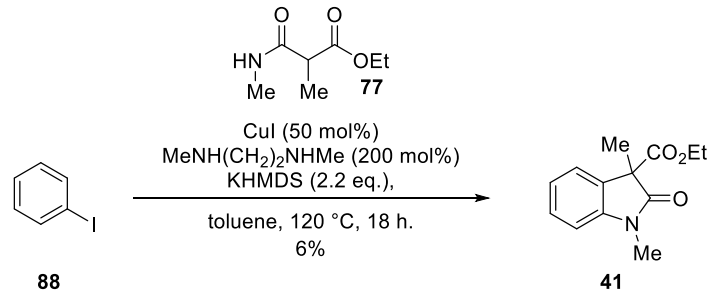
40 **41**

This optimised set of conditions has been successfully applied to the formal synthesis of oxindole-containing drug molecule Satavaptan **6**.

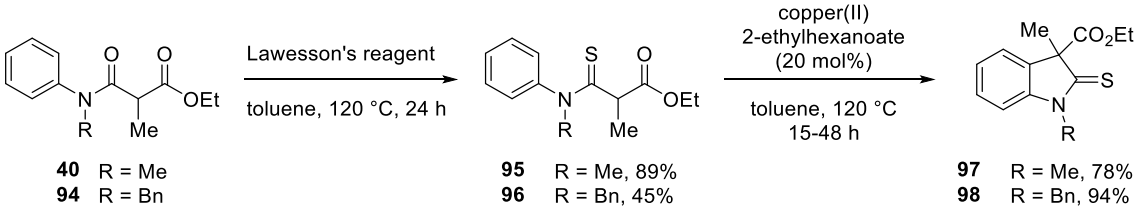


Copper-catalysed oxindole formation can be performed below the flash point of the solvent when ethylene carbonate is used as reaction solvent offering a safer alternative for scale up of reaction.

It is possible to form oxindole **41** *via* a one-pot C–N/C–C coupling albeit in modest yield; further optimisation is required, however, it has been demonstrated that the concept is feasible.



Finally it has been demonstrated that the conditions developed for the copper-catalysed synthesis of oxindoles can be successfully applied to thio-oxindoles.



40 R = Me
94 R = Bn

95 R = Me, 89%
96 R = Bn, 45%

97 R = Me, 78%
98 R = Bn, 94%

Chapter 3. Copper-catalysed synthesis of 6-membered nitrogen containing heterocycles

3.1 Introduction to 3,4-dihydroquinolin-2(1*H*)-ones

The 3,4-dihydroquinolin-2(1*H*)-one scaffold is present in numerous natural products and is often associated with anti-tumour properties. Natural products include compound **99** isolated from *Isatis indigota*[66] and **100a** and **100b** isolated from *Trigonostemon lutescens*. Melicodenine C **101** isolated from *Melicope denhamii* exhibits anti-tumour like properties showing cell growth suppression of DLD-1 human colon cancer cells (Figure 3.1).[67]

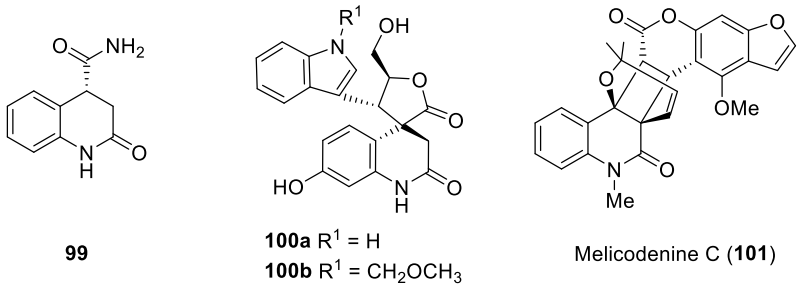


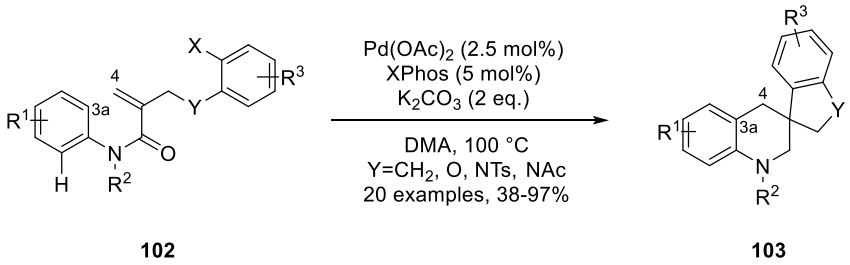
Figure 3.1 Natural products **99**, **100a**, **100b** and **101**.

Derivatives of the 3,4-dihydroquinolin-2(1*H*)-one motif have also demonstrated cytotoxic,[68] antibacterial,[69] inotropic,[70] antihypertensive[71] and antiviral[72] properties. Therefore the development of novel routes to this medicinally relevant scaffold is important.

3.2 Synthetic approaches to 3,4-dihydroquinolin-2(1*H*)-ones by C(4)–C(4a) bond formation

3.2.1 Various transition metal catalysed approaches to 3,4-dihydroquinolin-2(1*H*)-ones

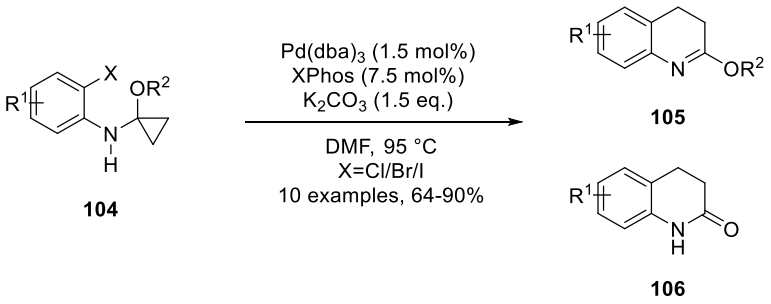
3,4-Dihydroquinolin-2(1*H*)-ones have been synthesised in a multitude of fashions. In a similar approach to oxindole synthesis, 3,4-dihydroquinolin-2(1*H*)-ones can be prepared by palladium-catalysed intramolecular Heck reactions as shown by Piou *et al.*[73] This is an effective method as two C–C bonds are being formed in one-pot. It does however rely on precious metal catalysis and utilises teratogenic DMA as the reaction solvent (Scheme 3.1).



102 **103**

Scheme 3.1 Piou's approach to the synthesis of 3,4-dihydroquinolin-2(1*H*)-ones.

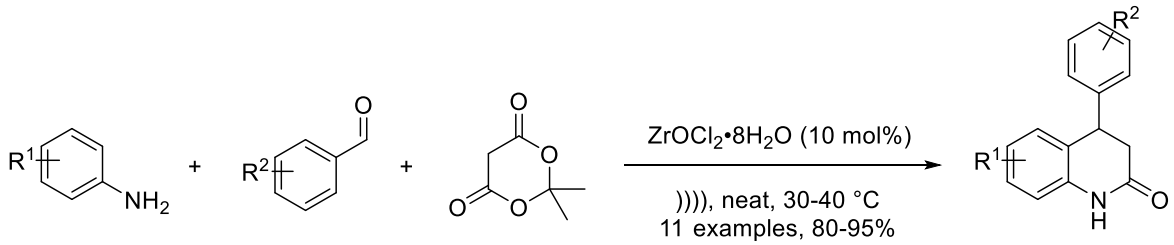
An interesting route to this heterocycle is a palladium-catalysed cyclopropane ring expansion which was reported by Tsuritani and coworkers (Scheme 3.2).[74] Despite yields being mostly excellent they observe both carboximidates **105** and the desired 3,4-dihydroquinolin-2(1*H*)-ones **106** whilst again relying on palladium-catalysis and a teratogenic solvent, in this case DMF. This method also produces halogen-containing waste.



104 **105** **106**

Scheme 3.2 Palladium-catalysed cyclopropane ring expansion approach to 3,4-dihydroquinolin-2(1*H*)-ones.

Azarifar and co-workers developed an ultrasound-accelerated multi-component reaction for the synthesis of 3,4-dihydroquinolin-2(1*H*)-ones (Scheme 3.3).[75] This process is extremely efficient offering high yields, utilising an inexpensive zirconium catalyst at low temperatures and does not require a reaction solvent.



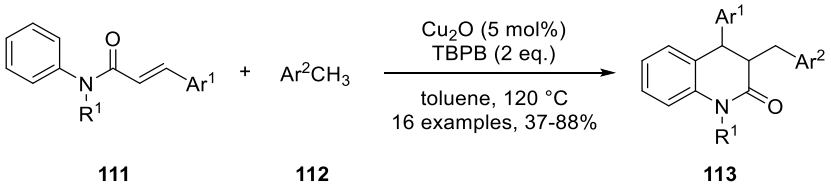
107 **108** **109** **110**

Scheme 3.3 Zirconium-catalysed multi-component approach to 3,4-dihydroquinolin-2(1*H*)-ones.

3.2.2 3,4-Dihydroquinolin-2(1*H*)-ones by free radical cyclisation

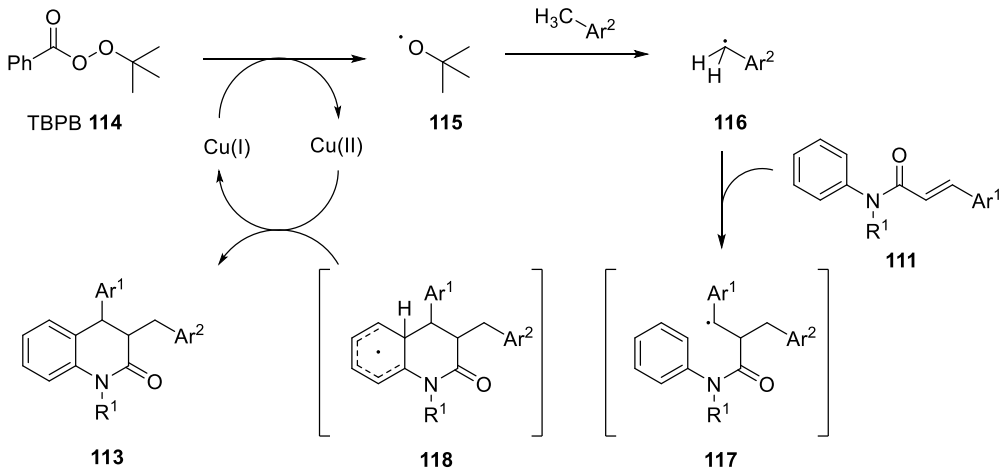
The use of radicals to form 3,4-dihydroquinolin-2(1*H*)-ones offers the same benefits as using a radical approach to forming oxindoles. The need for pre-functionalisation of the starting materials to contain a (pseudo)halogen leaving group can be avoided, increasing atom efficiency and simplifying starting material synthesis.

Much research has been carried out in the field of 3,4-dihydroquinolin-2(1*H*)-one synthesis to form the C(4)–C(4a) bond *via* free radical cyclisation. Many examples use *in situ* generated radical sources to react with/abstract a proton from a linear anilide which is then able to cyclise *via* homolytic aromatic substitution.[76] An example that illustrates this well is Zhou's copper-catalysed approach (Scheme 3.4).[77] The scope is good, the yields are generally excellent and inexpensive Cu_2O is used as the catalyst.



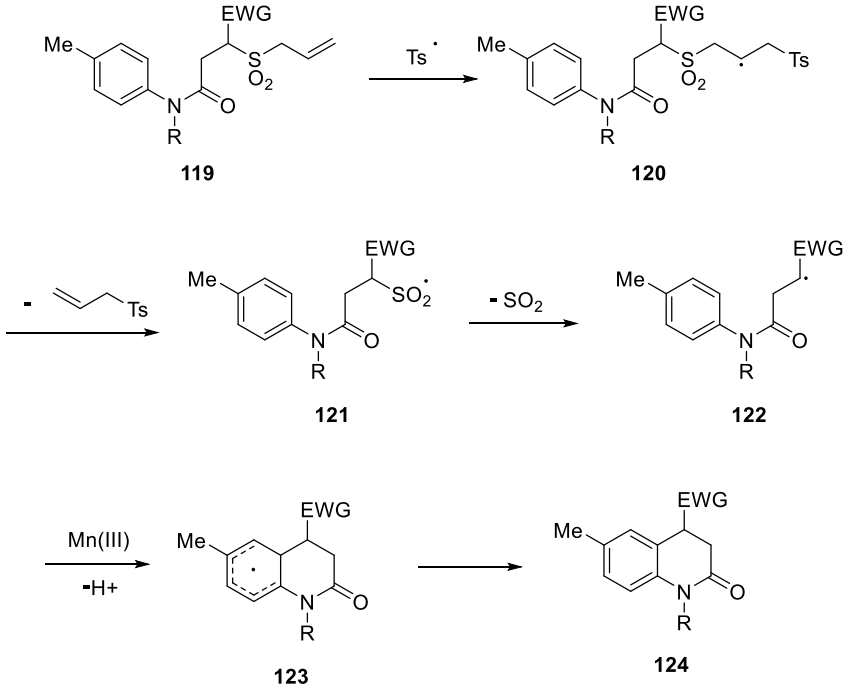
Scheme 3.4 Zhou's copper-catalysed approach to 3,4-dihydroquinolin-2(1*H*)-ones.

The likely mechanism for Zhou's approach is as follows (Scheme 3.5): TBPB is converted into the *tert*-butoxide radical **115** by Cu(I), which is oxidised to Cu(II). Radical **115** is then able to abstract a proton from toluene to give radical **116** which in turn reacts with the alkene group of **111** giving radical species **117**. This is then able to cyclise *via* homolytic aromatic substitution to species **118** which upon single electron oxidation by Cu(II) gives the desired 3,4-dihydroquinolin-2(1*H*)one **113** and Cu(I) thus completing the catalytic cycle of copper.



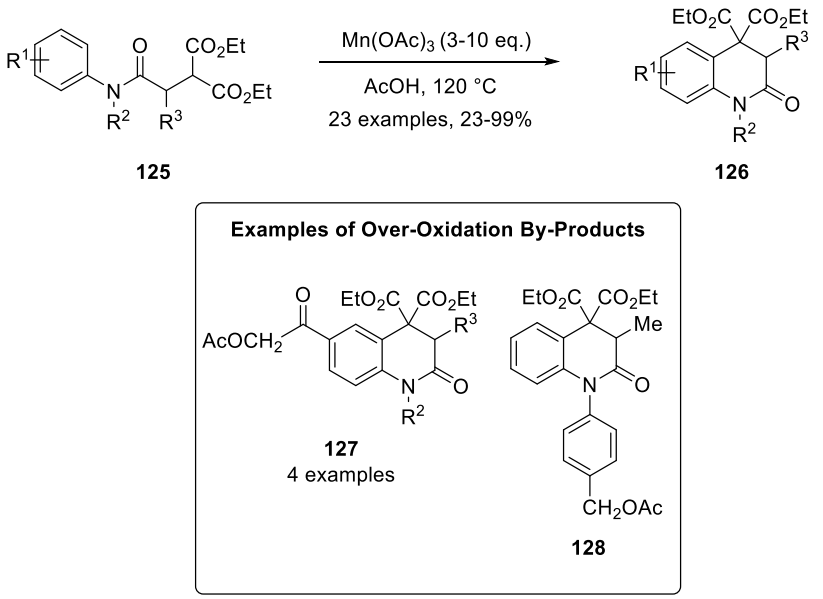
Scheme 3.5 Proposed mechanism for Zhou's copper-catalysed approach to 3,4-dihydroquinolin-2(1*H*)ones.

A similar method was developed by Chuang utilising Mn(III) to form 3,4-dihydroquinolin-2(1*H*)-ones (Scheme 3.6).[76a] In this example a tosyl radical reacts with the allyl functionality of anilide **119** to form radical **120** which upon fragmentation gives sulfone-centred radical **121**. Upon loss of SO_2, radical **122** is formed which undergoes homolytic aromatic substitution to form radical **123**. Upon single electron oxidation by Mn(III) and loss of a proton, 3,4-dihydroquinolin-2(1*H*)-one **124** is formed.



Scheme 3.6 Proposed mechanism for Chuang's manganese-mediated approach to the synthesis of 3,4-dihydroquinolin-2(1*H*)ones.

Nishino and co-workers reported a manganese-mediated approach to the synthesis of 3,4-dihydroquinolin-2(1*H*)ones which generates radicals and cyclises anilides in a similar fashion to our copper-catalysed approach to oxindoles (Scheme 3.7).[44a] This method is high-yielding across a range of substrates but the harsh conditions employed (>3 eq. $Mn(OAc)_3$ in refluxing AcOH) gave over-oxidation by-products in some cases (methyl groups oxidised to acetoxy groups).



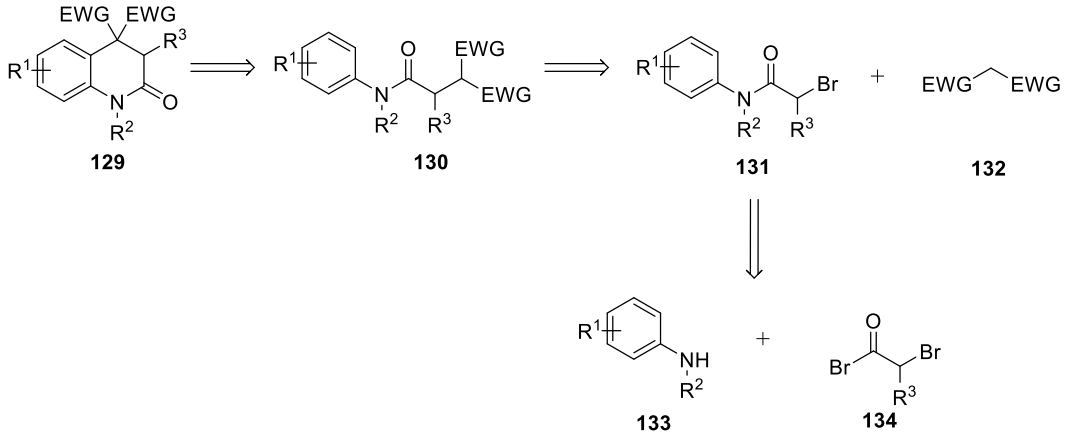
Scheme 3.7 Nishino's manganese-mediated approach to 3,4-dihydroquinolin-2(1*H*)ones.

In light of Nishino's findings, our efforts were focussed on the application of our copper-conditions to the synthesis of 3,4-dihydroquinolin-2(1*H*)-ones. We wished to directly compare our methods to those of Nishino with the hope that the copper(II) method would provide milder conditions, improved yields and no unwanted side-products.

3.3 Application of copper conditions to the synthesis of 3,4-dihydroquinolin-2(1*H*)-ones

3.3.1 Synthesis and substrate scope

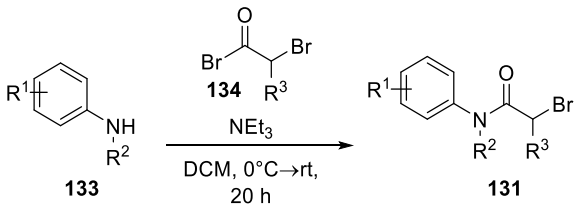
The mild conditions developed for the copper-catalysed synthesis of oxindoles were applied to the synthesis of 3,4-dihydroquinolin-2(1*H*)-ones with the envisaged route outlined in Scheme 3.8. The required cyclisation precursors **130** were expected to arise from alkylation of α-bromo anilides **131** which themselves can be readily prepared from commercially available anilines **133** and bromoacetyl bromides **134**.

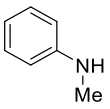
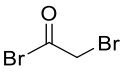
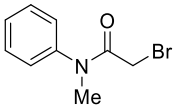
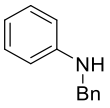
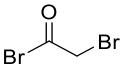
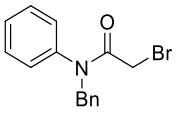
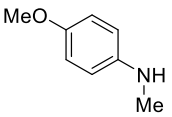
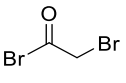
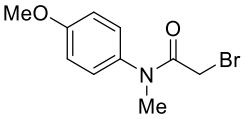
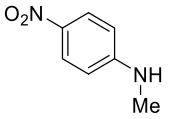
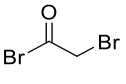
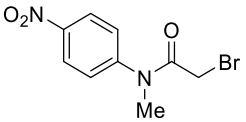
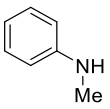
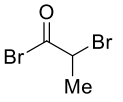
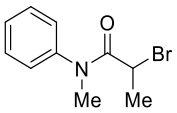
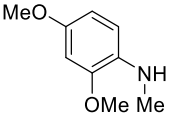
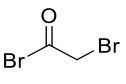
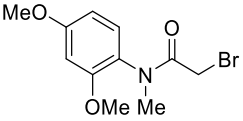


Scheme 3.8 Retrosynthesis of 3,4-dihydroquinolin-2(1*H*)-ones **129**.

Anilines **133a-d** were commercially available but aniline **133e** was synthesised in 3 steps from 2,4-dimethoxyaniline by Boc protection, methylation then de-protection in 92% yield over the three steps.[78] Thus, coupling of anilines **133a-e** to bromoacetyl bromides **134a-b** proceeded smoothly to give α-bromo anilides **131a-f** in 48-99% yield (Table 3.1). As the reaction is a nucleophilic substitution, it is not surprising that the yields observed directly relate to the nucleophilicity of the aniline substrates, with the electron-rich aniline **133c** giving the highest yield.

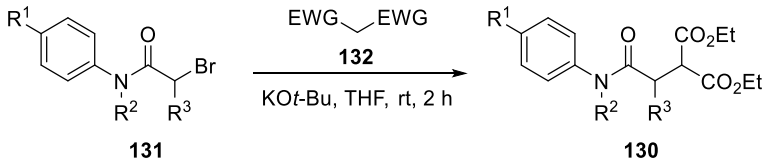
Table 3.1 Synthesis of α-bromo anilides **131a-f**.

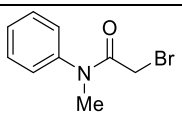
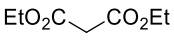
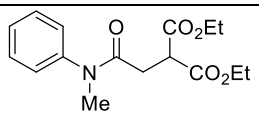
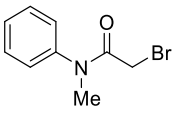
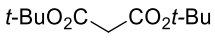
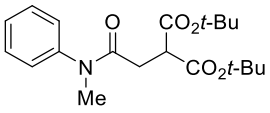
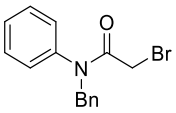
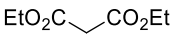
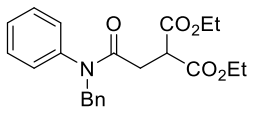
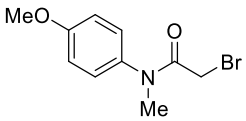
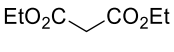
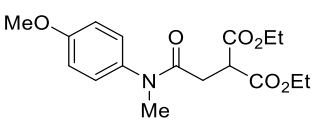
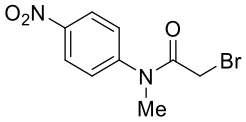
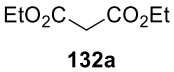
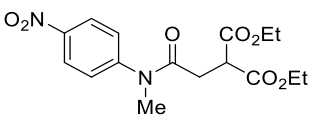
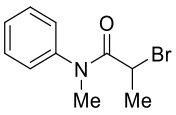
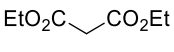
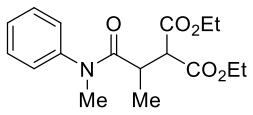
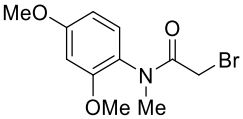
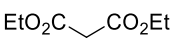
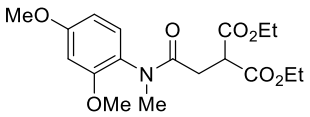


Entry	Aniline	Acyl Bromide	Product	Yield (%)
1	 **133a**	 **134a**	 **131a**	78
2	 **133b**	 **134a**	 **131b**	68
3	 **133c**	 **134a**	 **131c**	87
4	 **133d**	 **134a**	 **131d**	48
5	 **133a**	 **134b**	 **131e**	99
6	 **133e**	 **134a**	 **131f**	81

α-Bromo anilides **131a-f** were subsequently alkylated upon treatment with the potassium salt of activated methylene compounds **132a** and **132b** to yield malonates **130a-g** in excellent yields (Table 3.2). Yields were high across all substrates with no observable trend between substrate structure and yield obtained.

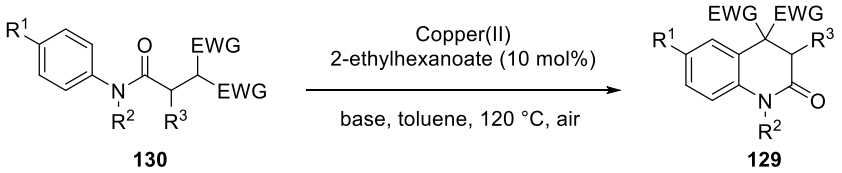
Table 3.2 Synthesis of malonates **130a-g**.



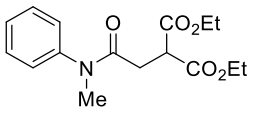
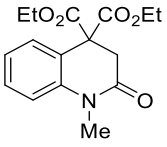
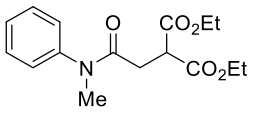
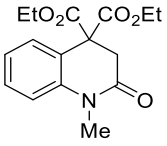
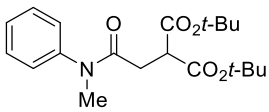
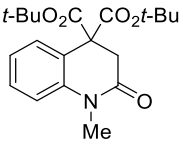
Entry	Anilide	Malonate	Product	Yield (%)
1	 **131a**	 **132a**	 **130a**	90
2	 **131a**	 **132b**	 **130b**	71
3	 **131b**	 **132a**	 **130c**	84
4	 **131c**	 **132a**	 **130d**	83
5	 **131d**	 **132a**	 **130e**	74
6	 **131e**	 **132a**	 **130f**	82
7	 **131f**	 **132a**	 **130g**	84

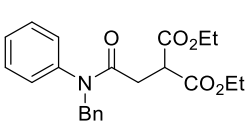
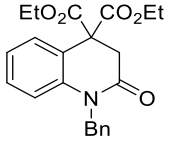
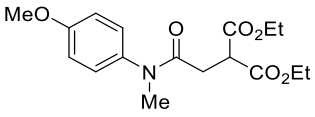
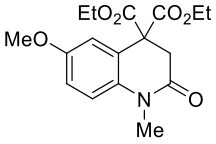
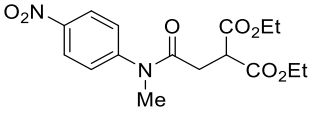
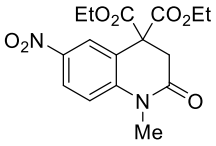
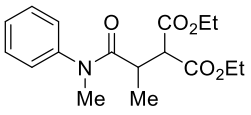
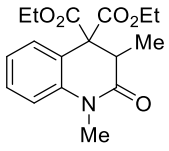
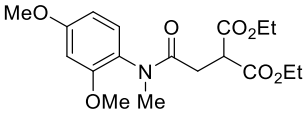
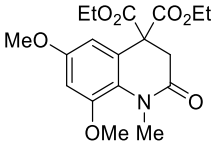
Cyclisation precursor **130a** was subjected to the optimised conditions developed for the copper-catalysed synthesis of oxindoles at 120 °C (entry 1, Table 3.3). However, incomplete conversion into 3,4-dihydroquinolin-2(1*H*)-one **129a** was observed. The addition of DIPEA to the reaction gave **129a** in quantitative yield, however (entry 2, Table 3.3). These conditions were then applied to malonates **130b-f** giving excellent yields of products in all cases (entries 3-7, Table 3.3). It is interesting to observe that the yield was equally high for both anilides with an electron-rich aromatic ring (entry 5, Table 3.3) and an electron-poor aromatic ring (entry 6, Table 3.3); Nishino observed lower yield of **129e** than **129d** and this is also a trend observed by the Taylor group in the synthesis of oxindoles by copper catalysis.[42] It was very pleasing to observe a higher yield than Nishino for the synthesis of compound **129f** containing a methyl group at the 3 position as Nishino was required increase his metal salt loading from 3 equivalents to 10 equivalents of catalyst to synthesise this substrate.

Table 3.3 Synthesis of 3,4-dihydroquinolin-2(1*H*)-ones **129a-f** by copper catalysis, and yields reported by Nishino by a manganese-mediated process.



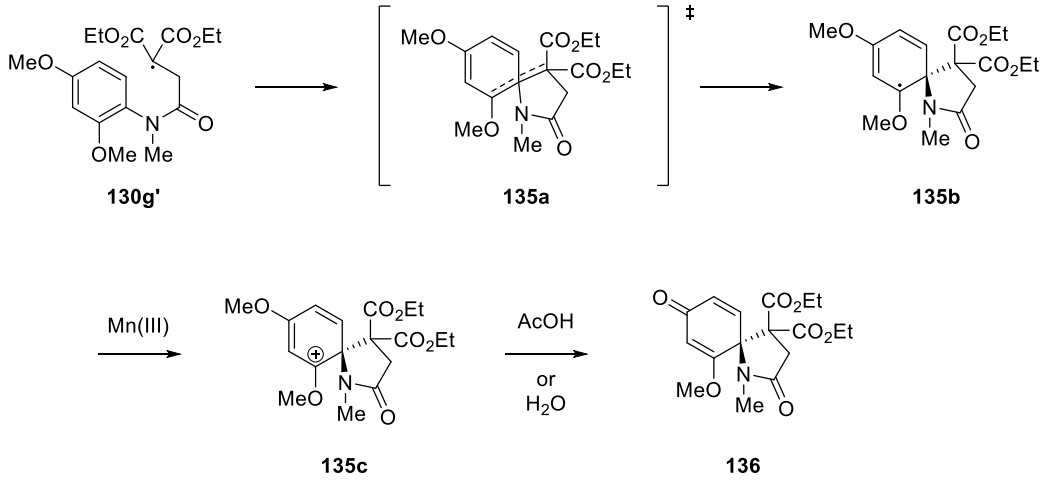
130 **129**

Entry	Malonate	Base (2.4 eq.)	Time (h)	Product	Cu(II) Yield	Mn(III) Yield[a]
1	 **130a**	-	24	 **129a**	(46)[b]	-
2	 **130a**	DIPEA	15	 **129a**	100	97
3	 **130b**	DIPEA	2	 **129b**	74	-

4	 **130c**	DIPEA	15	 **129c**	100	93
5	 **130d**	DIPEA	15	 **129d**	100	97
6	 **130e**	DIPEA	15	 **129e**	100	92
7	 **130f**	DIPEA	24	 **129f**	93	61[d,e]
8	 **130g**	DIPEA	15	 **129g**	0	0[f]

[a] Yields reported by Nishino[44a] employing 3 equivalents of $Mn(OAc)_3$ in refluxing AcOH for 30 min, [b] Conversion based on ratio of anilide to product inthe ^{1}H NMR spectrum of the crude reaction mixture, [c] 165 °C in mesitylene, [d] 10 equivalents of $Mn(OAc)_3$ were used in AcOH for 5 h, [e] Oxidation product **129f'** was also isolated in 28% yield, [f] Spirolactoam **136** was isolated in 85% yield.

When malonate **130g** was exposed to the Mn(III) conditions, Nishino observed only formation of spirolactam **136**, isolated in 85% yield. This occurs due to radical aromatic addition occurring at the *ipso*-position giving intermediate **135b** *via* transition state **135a** (Scheme 3.9). This is thought to be more favourable due to the steric clash between the methoxy substituent at the 2-position of the aromatic ring and the *N*-Me group when *ortho* homolytic aromatic substitution occurs. Radical **135b** is then oxidised by Mn(III) to give cationic species **135c** which upon demethylation of the enol ether either by the AcOH or H_2O gives spirolactam **136**.



Scheme 3.9 Proposed mechanism for the formation of spirolactam **136**.

When malonate **130g** was treated with catalytic copper(II) 2-ethylhexanoate none of the starting material was consumed (entry 8, Table 3.3). This could suggest that radical addition into the aromatic ring is reversible in this case, with the absence of acetic acid preventing irreversible demethylation to spirolactam **135c** from occurring.

The yields observed by employing copper catalysis for the synthesis of 3,4-dihydroquinolin-2(1*H*)-ones **129a-f** are higher than those observed by Nishino,[44a] in particular for substrate **129f** which required 10 equivalents of $Mn(OAc)_3$. The oxidation by-product **129f'** (Figure 3.2) observed in 28% yield with the manganese mediated approach (entry 7, Table 3.3) was avoided completely using copper catalysis.

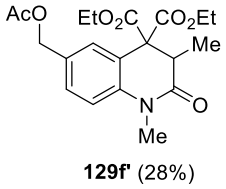
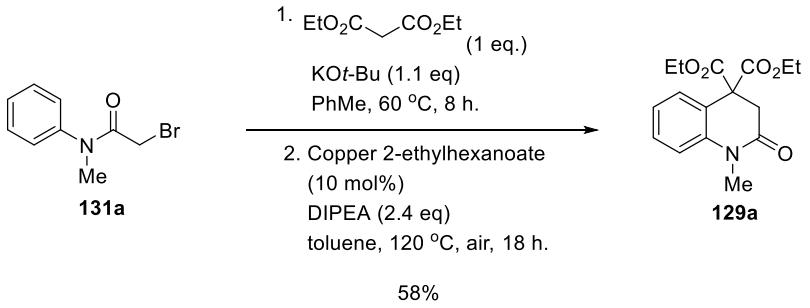


Figure 3.2 Oxidation by-product **129f'** observed by Nishino.

3.3.2 One-pot synthesis of 3,4-dihydroquinolin-2(1*H*)-one

The synthesis of 3,4-dihydroquinolin-2(1*H*)-one **129a** can be achieved from α-bromo-anilide **131a** in a one-pot fashion by sequential addition of diethyl malonate and KO*t*Bu, followed by catalytic copper(II) 2-ethylhexanoate and DIPEA in 58% overall yield (Scheme 3.10). Since publishing this reaction we have found that the malonate addition step can occur in as little as 10 minutes when heated to 100 °C.

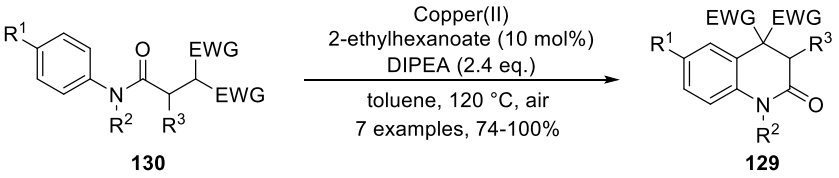


Scheme 3.10 One-pot synthesis of 3,4-dihydroquinolin-2(1*H*)-one **129a**.

This one-pot alkylation/cyclisation procedure is extremely convenient but further work is needed to optimise the yield; the sequential method gives an overall 90% yield as compared to 58% *via* this one-pot procedure. It is still however an impressive achievement from a green chemistry perspective, as the volume of waste produced, the number of physical manipulations and the time taken to obtain desired 3,4-dihydroquinolin-2(1*H*)-one **129a** from bromo-anilide **131a** are significantly reduced compared with the 2-step process.

3.3.3 Summary of copper-catalysed 3,4-dihydroquinolin-2(1*H*)-one synthesis

Unlike many other procedures, by utilising a homolytic aromatic substitution approach to synthesise 3,4-dihydroquinolin-2(1*H*)-ones, pre-functionalisation of the starting materials to contain a halogen leaving group has been avoided. This made the synthesis of the starting materials trivial and the atom efficiency of our reactions >99% in all cases.



Copper-catalysis offers a milder and more efficient approach to 3,4-dihydroquinolin-2(1*H*)-one synthesis compared to Nishino's manganese-mediated method,[44a] showing excellent yields across a range of substrates. Utilisation of 10 mol% copper(II) 2-ethylhexanoate versus 300-1000 mol% $Mn(OAc)_3$ demonstrates more efficient use of transition metals in synthesis, and the use of toluene rather than refluxing acetic acid carries far fewer hazards and health risks. Preliminary studies to develop a one-pot alkylation-cyclisation variant are encouraging.

3.4 Introduction to 2-quinolinones

2-Quinolinones are an important class of heterocycle exhibiting a wide range of biological activities including antiviral, anticancer, antibiotic and antihypersensitivity.[79] They are also found at the core of numerous natural products (Figure 3.3),[80] and are key synthetic intermediates in the synthesis of 2-amino, 2-alkoxy and 2-amino substituted quinolinones.[81]

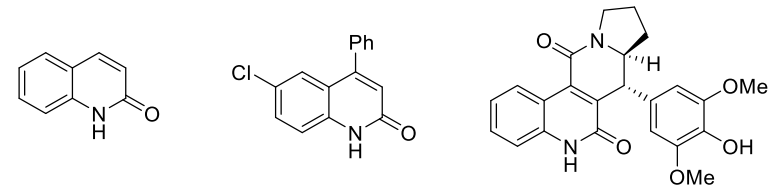


Figure 3.3 Examples of biologically active 2-quinolinones **137**-**139**.

Furoquinolinones are synthetic derivatives of 2-quinolinones which have antitumour properties and are also used to treat skin conditions, e.g. FQ and HOFQ (Figure 3.4).[82] The properties of HOFQ will be discussed in further detail in Chapter 3.8.

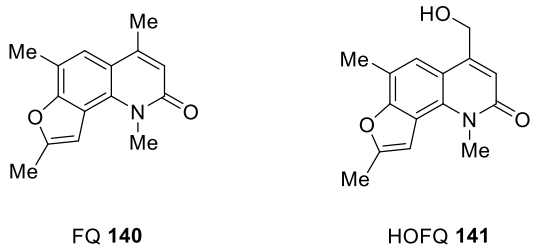


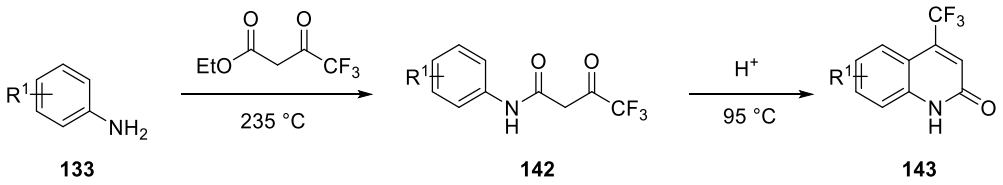
Figure 3.4 Examples of biologically active synthetic furoquinolinones **140** and **141**.

It is therefore important to develop novel synthetic routes to this class of medicinally important heterocycle.

3.5 Synthetic approaches to 2-quinolinones

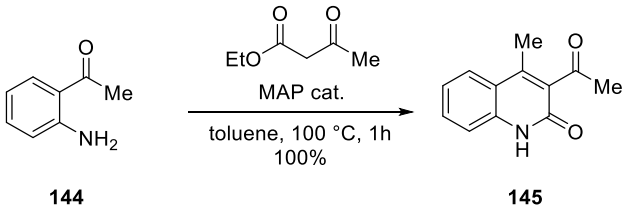
3.5.1 Classical approaches to 2-quinolinones

A traditional approach to the synthesis of 2-quinolinone derivatives is by intramolecular cyclisation of β-keto anilides (Knorr synthesis).[83] This is often achieved by heating the substrate in concentrated sulfuric acid (Scheme 3.11).



Scheme 3.11 Knorr approach to 2-quinolinone synthesis.

Another classical approach is the Friedlander synthesis, which was recently utilised by Cejka and co-workers to synthesise 2-quinolinone **145** (Scheme 3.12), in which they utilise a methylaminopropyl (MAP)/ molecular sieves as a solid-supported catalyst.[84]

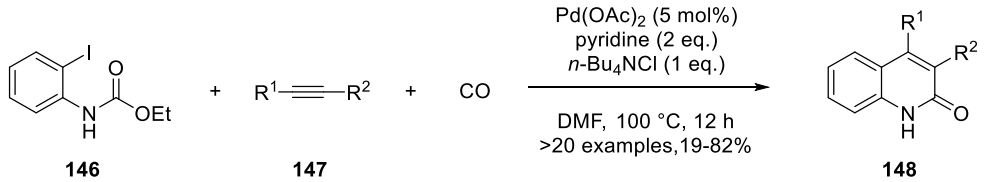


Scheme 3.12 Friedlander approach to 2-quinolinone synthesis.

More recently transition metal catalysed approaches have been extensively investigated.[85]

3.5.2 Palladium-catalysed approaches to 2-quinolinones

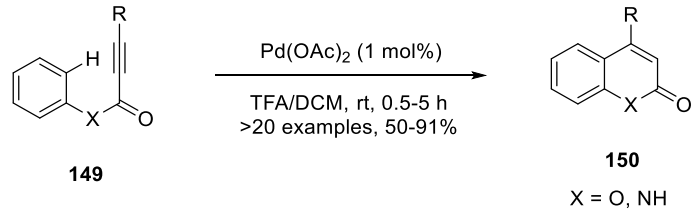
There are numerous palladium-catalysed approaches to the synthesis of 2-quinolinones. Many require a halogen heaving group in the starting material.[85b] A sophisticated example of this from the Larock group, is the carbonylative annulation of 2-iodoanilides with alkynes and CO, catalysed by palladium (Scheme 3.13).[85a] One drawback of this method from a synthetic perspective is the lack of regio-selectivity over the substituents at the 3- and 4- positions which come from the groups on the alkyne moity, as mixtures are often observed. Another short-coming is that it utilises precious metal catalysis in 5 mol% loading which is very high for a palladium-catalysed reaction, and is carried out in the incredibly toxic and teratogenic solvent DMF.



Scheme 3.13 Larock's palladium-catalysed approach to the synthesis of 2-quinolinones.

Fujiwara developed a palladium-catalysed method that utilises C–H insertion, thus avoiding the requirement of a halogen leaving group (Scheme 3.14).[85c] This method is carried out at room temperature, has a wide substrate scope and is atom efficient. This approach, however, is unable to tolerate electron-deficient aromatics and works most efficiently when the aromatic rings contain

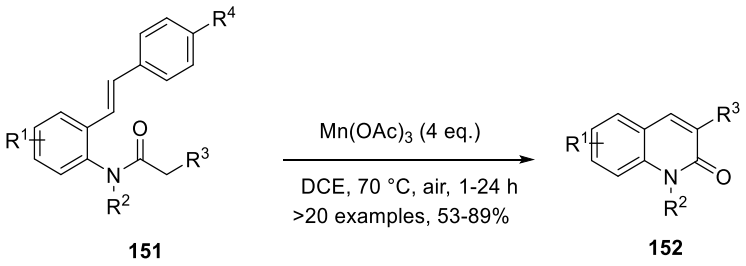
electron-donating groups. It is also carried out in the carcinogenic solvent DCM and requires precious metal catalysis.



Scheme 3.14 Fujiwara's palladium-catalysed approach to the synthesis of 2-quinolinones.

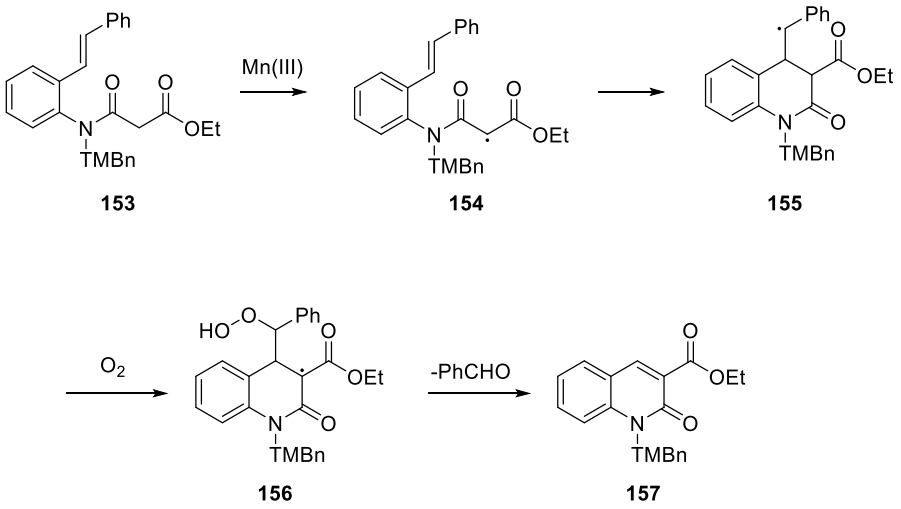
3.5.2 Free radical approaches to 2-quinolinones

Examples of free radical-mediated cyclisations to form the 2-quinolinone core are scarce. One method by Chuang utilises $Mn(OAc)_3$-mediated radical cyclisations of substituted *N*-[(*E*)-stilben-2-yl]acetamides to form 2-quinolinones (Scheme 3.15).[86] This method offers excellent yields, a broad functional group tolerance and avoids precious metal catalysis, however it uses DCE as solvent, super-stoichiometric amounts of $Mn(OAc)_3$ and has a poor atom economy.



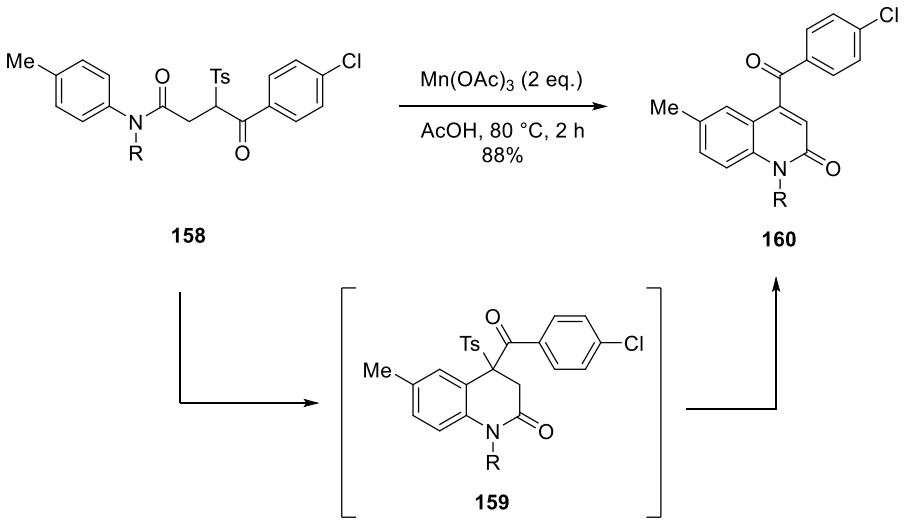
Scheme 3.15 Chuang's manganese-mediated approach to the synthesis of 2-quinolinones.

The mechanism for the reaction is probably as follows (Scheme 3.16): Once radical species **154** is formed by oxidation of anilide **153**, it undergoes a 6-*exo*-*trig* cyclisation to form radical **155**. Upon reaction of **155** with molecular oxygen, **156** undergoes fragmentation to give 2-quinolinone **157** and benzaldehyde.



Scheme 3.16 Proposed mechanism for Chuang's manganese-mediated approach to the synthesis of 2-quinolinones from *N*-[(*E*)-stilben-2-yl]acetamides.

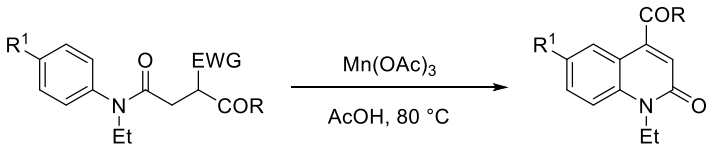
Chuang made an interesting observation during his Mn-mediated synthesis of 3,4-dihydroquinolin-2(1*H*)-ones[76a] (Chapter 3.22). It was observed that when the electron withdrawing group is SO_2Allyl, the sulfone group is lost and a 2-quinolinone heterocycle is formed (Scheme 3.17).



Scheme 3.17 Sulfone elimination to form 2-quinolinone **160**.

Chuang then investigated forming 4-substituted 2-quinolinones using tosyl and mesyl electron withdrawing groups. The yields range from modest to good and the demonstrated substrate scope is of limited variety (Table 3.4).

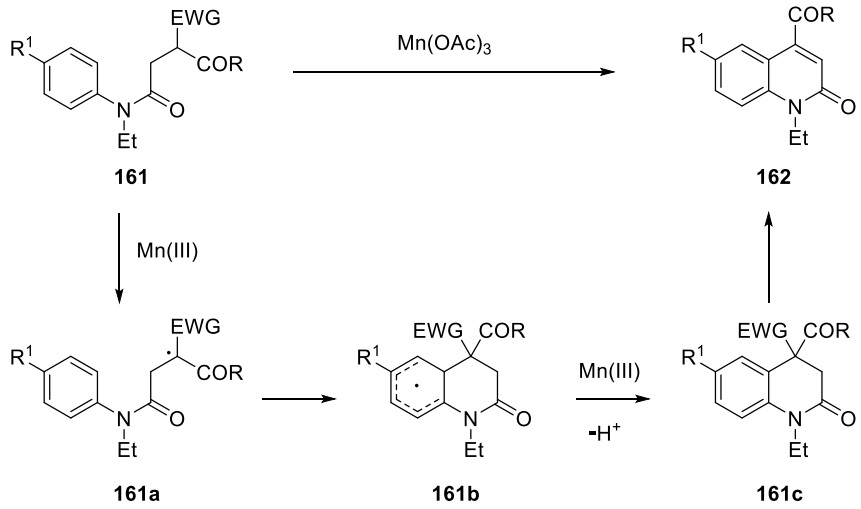
Table 3.4 Chuang's manganese mediated synthesis of 2-quinolinones *via* cyclisation/sulfone elimination.



161 **162**

Entry	R^1	EWG	R	Yield (%)
1	Me	Ts	4-Cl(C_6H_4)	88
2	Me	Ts	2,4-Cl_2(C_6H_3)	85
3	Br	Ms	C_6H_5	65
4	Me	Ts	Me	62
5	Me	Ms	OEt	53
6	H	Ms	OEt	51
7	Br	Ms	OEt	44
8	CO_2Et	Ms	OEt	42
9	Cl	Ms	OEt	41

It was postulated that the mechanism for this reaction was as follows (Scheme 3.18): Mn(III)-mediated oxidation of anilide **161** to radical **161a** occurs followed by homolytic aromatic substitution to form **161b**. Following oxidation by Mn(III) and proton loss, 3,4-dihydroquinolin-2(1*H*)-one **161c** forms. It is thought β-elimination of *p*-toluenesulfinic acid or methanesulfinic acid then occurs to afford the 2-quinolinone **161**.



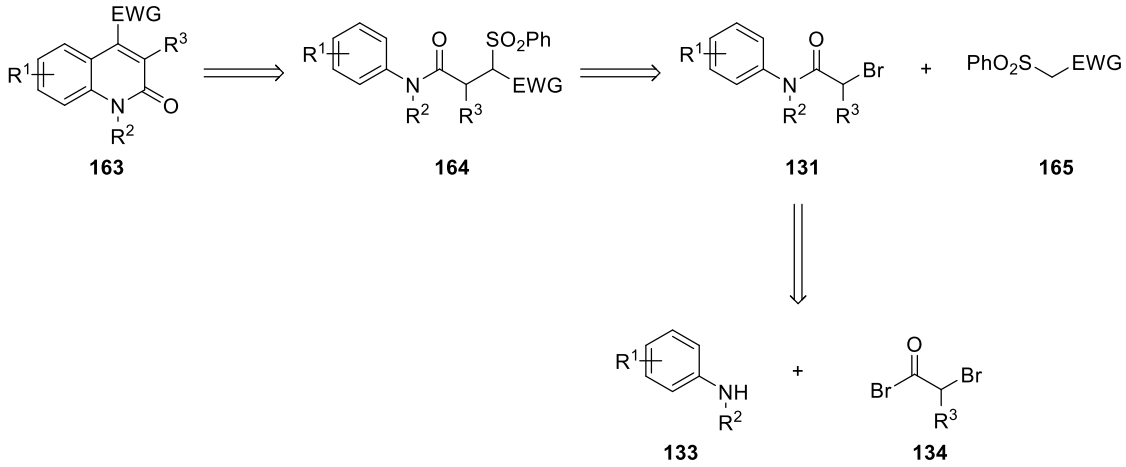
Scheme 3.18 Suggested mechanism for the formation of 2-quinolinones *via* cyclisation/sulfone elimination.

In light of Chuang's findings, efforts were focussed on the application of our copper conditions to the synthesis of 2-quinolinones. We planned to demonstrate that the milder Cu(II) conditions would be effective at performing similar transformations. We also planned to expand the substrate scope and apply the chemistry to some medicinally relevant target molecules.

3.6 Copper-catalysed cyclisation/sulfone elimination approach to 2-quinolinones

3.6.1 Synthesis and substrate scope

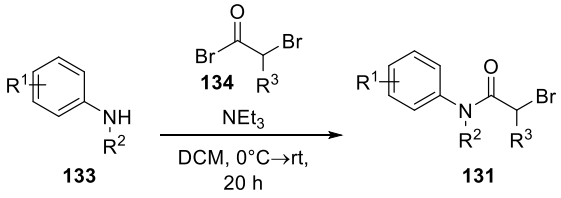
Our previously developed copper(II) 2-ethylhexanoate conditions for the synthesis of 3,4-dihydroquinolin-2(1*H*)-ones were applied to the synthesis of 2-quinolinones with the envisaged route outlined in Scheme 3.19. The required cyclisation precursors **164** were expected to arise from alkylation of α-bromo anilides **131** which themselves can be readily prepared from anilines **133** and bromoacetyl bromides **134** (Scheme 3.19).

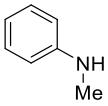
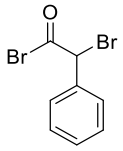
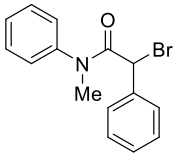
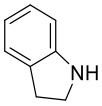
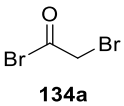
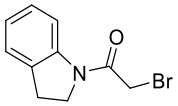
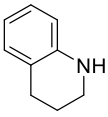
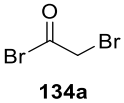
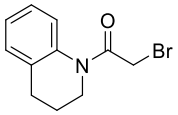
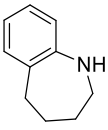
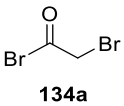
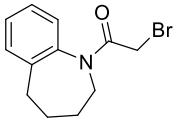


Scheme 3.19 Retrosynthesis of 2-quinolinones **163**.

Several α-bromo anilides previously synthesised for the synthesis of 3,4-quinolin-2(1*H*)-ones could be used in this sequence but some additional examples were also prepared. Thus, coupling of anilines **133a** and **133f-h** with bromoacetyl bromides **134a** and **134b** proceeded smoothly to give α-bromo anilides **131g-j** in 62-89% yield (Table 3.5). Interestingly, as ring size on the aniline increased from 5-membered ring, to 6-membered ring, to 7-membered ring, the yield observed decreased. The increased ring-size is likely decreasing the nucleophilicity of the anilines.

Table 3.5 Synthesis of α-bromo anilides **131g-j**.



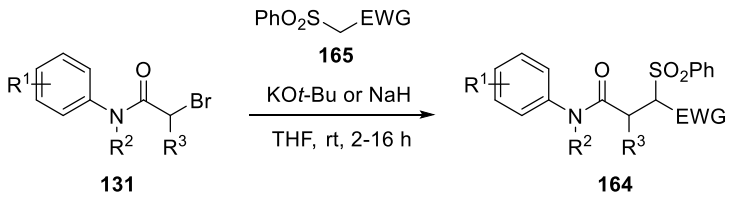
Entry	Aniline	Acyl Bromide	Product	Yield (%)
1	 **133a**	 **134c**	 **131g**	62
2	 **133f**	 **134a**	 **131h**	89
3	 **133g**	 **134a**	 **131i**	88
4	 **133h**	 **134a**	 **131j**	71

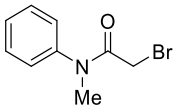
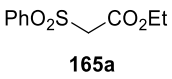
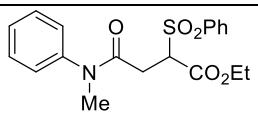
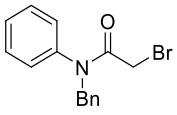
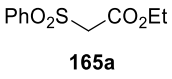
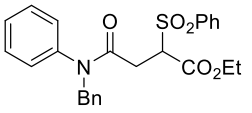
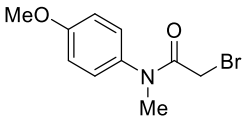
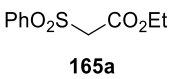
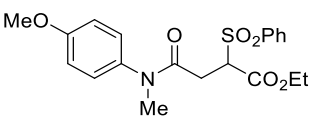
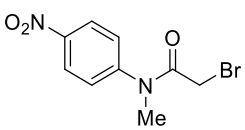
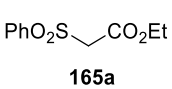
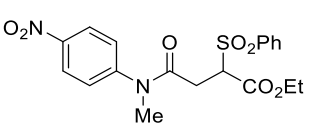
α-Bromo anilides **131a-k** were subsequently alkylated upon treatment with the potassium salt of the activated methylene compounds **165a-e** to afford the sulfone-containing anilides **164a-m** in generally good to excellent yields (entries 1-11, Table 3.6). When the coupling of α-bromo anilide **131a** with the methylene disulfone compound **165d** was conducted (entry 12, Table 3.6), the

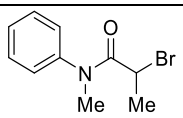
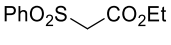
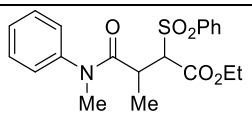
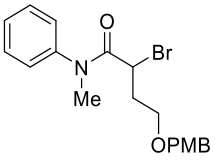
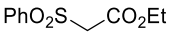
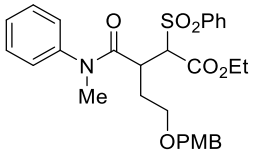
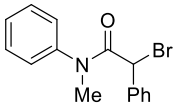
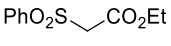
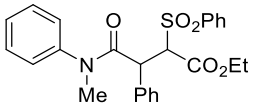
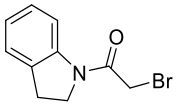
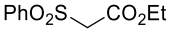
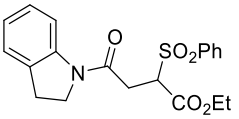
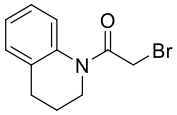
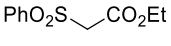
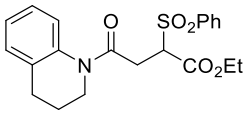
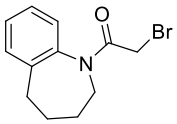
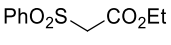
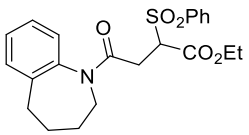
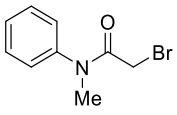
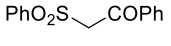
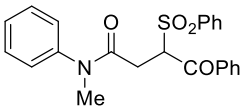
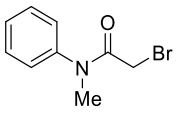
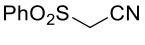
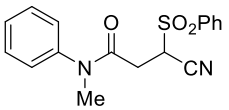
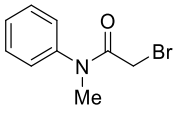
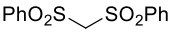
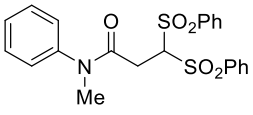
desired sulfone-containing anilide **164m** was observed as well as alkene **164m'** which is the result of sulfone elimination. A similar observation was made when α-bromo anilide **131a** was treated with the potassium salt of **165e** (entry 13, Table 3.6), with the alkene **164n'** being the sole product observed.

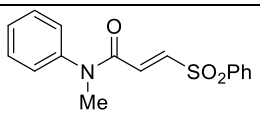
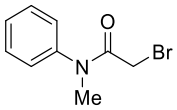
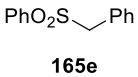
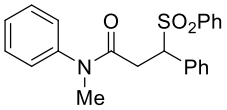
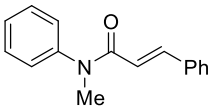
It is noteworthy that α-bromo anilide **131** or activated methylene compound **165** often have a retention factor on silica identical to that of the sulfone-containing anilide product **164**, thus making separation by flash column chromatography challenging. As all of these reactions go to completion this problem can be avoided by making either α-bromo anilide **131** or activated methylene compound **165** the limiting reagent on a case by case basis. Unfortunately this could only be implemented by trial and error.

Table 3.6 Synthesis of sulfone-containing anilides **164a-m**.



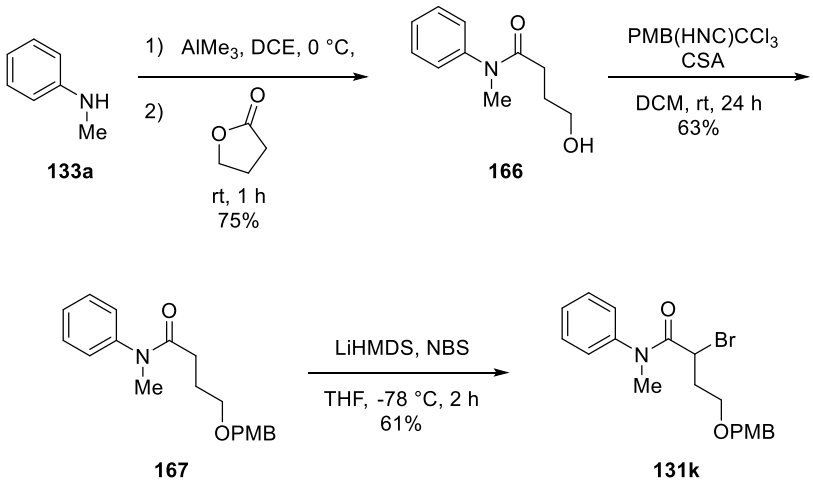
Entry	Anilide	Activated Methylene	Product	Yield (%)
1	 **131a**	 **165a**	 **164a**	93
2	 **131b**	 **165a**	 **164b**	99
3	 **131c**	 **165a**	 **164c**	71
4	 **131d**	 **165a**	 **164d**	66

5	 **131e**	 **165a**	 **164e**	22
6	 **131k**	 **165a**	 **164f**	79
7	 **131g**	 **165a**	 **164g**	46
8	 **131h**	 **165a**	 **164h**	81
9	 **131i**	 **165a**	 **164i**	68
10	 **131j**	 **165a**	 **164j**	64
11	 **131a**	 **165b**	 **164k**	99
12	 **131a**	 **165c**	 **164l**	57
13	 **131a**	 **165d**	 **164m**	43

			 **164m'**	26
14	 **131a**	 **165e**	 **164n**	0
			 **164n'**	(100)[a]

[a] Conversion based on ^{1}H NMR spectroscopic analysis of the crude reaction mixture relative to the amount of starting material present.

α-Bromo anilide **131k** was synthesised in 3 steps (Scheme 3.20). γ-Butyrolactone was opened by *N*-methylaniline **133a** after treatment with $AMeI_3$ to afford anilide **166**. The alcohol functionality was protected with a PMB group using PMB-TCA and CSA in good yield to afford **167** which was successfully brominated using NBS giving α-bromo anilide **131k** in good yield.



Scheme 3.20 Synthesis of α-bromo anilide **131k**

Cyclisation of sulfone-containing anilides **164a-m** was then attempted with the aim of forming 2-quinolinones *via* a cyclisation/sulfone elimination approach. Upon treatment of sulfone-containing anilide **164a** with our conditions developed for the copper-catalysed synthesis of 3,4-dihydroquinolinones **129a-f,** i.e. copper(II) 2-ethylhexanoate (10 mol%), DIPEA (2.4 eq.) in toluene at 120 °C under an atmosphere of air, only unreacted starting material was isolated. Upon changing the solvent to mesitylene and heating to 165 °C with 10 mol% , 100 mol% and 200 mol% of copper(II) 2-ethylhexanoate (entry 1, Table 3.7) the reaction proceeded to give 2-quinolinone **163a** in excellent yields. The best yield was observed using 100 mol% Cu(II) loading therefore the

remaining substrates were exposed to 1 equivalent of copper(II) 2-ethylhexanoate. Under these conditions anilide **164b** gave a mixture of 2-quinolinone **163b** and alkene **163b'** in 54% and 11% respectively (entry 2, Table 3.7).

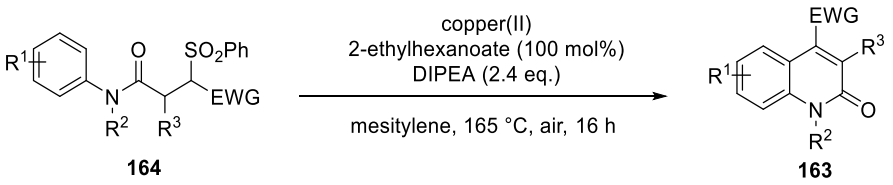
The electronics of the aromatic ring was then explored. 4-Methoxy-anilide **164c** gave 2-quinolinone **163c** in good yield (entry 3, Table 3.7) however 4-nitro-containing anilide **164d** gave 2-quinolinone **163d** in 23% yield and alkene **163d'** as the major product in 34% yield (entry 4, Table 3.7).

We then investigated tolerance of functional groups at the 3-position of the 2-quinolinone. We found that our method gave 2-quinolinone **163e** in excellent yield (86%) thus tolerating a methyl group at the 3-position (entry 5, Table 3.7). This was extended to substrate **164f** which contained an alkyl tethered PMB protected alcohol. This substrate successfully afforded 2-quinolinone **163f** in 71% yield (entry 6, Table 3.7); one could envisage the removal of the PMB protecting group to reveal the reactive alcohol functionality. Unfortunately we found that anilide **164g** did not undergo cyclisation, therefore, aromatics at the 3-position of the 2-quinolinone cannot be tolerated (entry 7, Table 3.7). It is thought that elimination of the sulfone functional group occurred giving alkene **164g'**, however, this was merely speculation as it was never isolated.

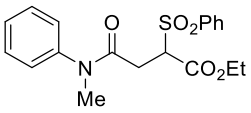
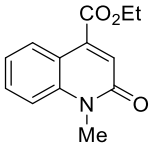
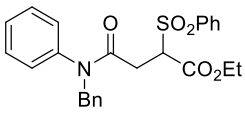
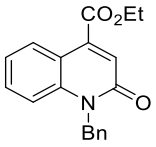
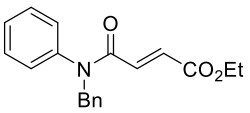
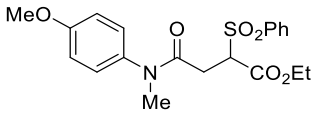
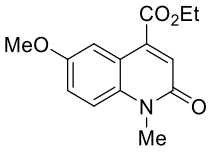
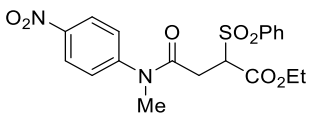
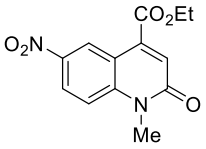
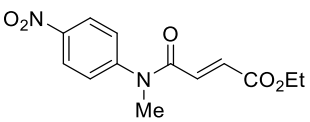
It was then investigated whether tricyclic systems fused though the 2-position of the aromatic ring and nitrogen of the heterocycle could be synthesised. Anilides **164h-j** were exposed to the reaction conditions: anilide **164h** gave the desired 2–quinolinone **163h** in poor yield (17%) along with alkene **163h'** as the major product (46%) (entry 8, Table 3.7). The 6-membered anilide **164i** afforded the desired 2-quinolinone **163i** in 54% yield (entry 9, Table 3.7) and the 7-membered anilide **164j** gave the desired 2-quinolinone **163j** in 77% yield (entry 10, Table 3.7). The yields directly correlate with the ring size fused through the amide, with 7-membered ring being the highest yielding and 5-membered ring being the lowest yielding.

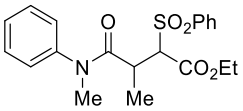
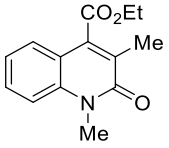
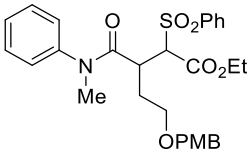
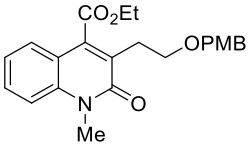
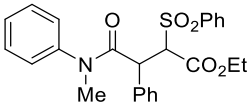
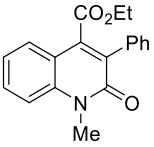
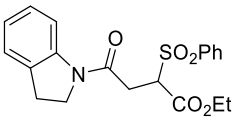
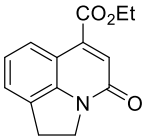
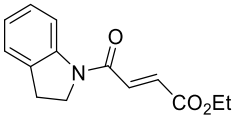
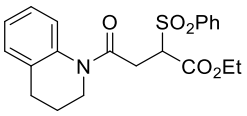
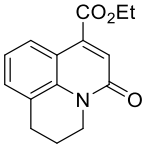
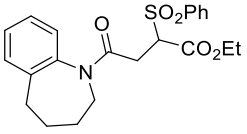
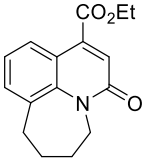
We finally investigated whether changing the electron-withdrawing-group could be tolerated. Thus anilide **164k** bearing CHO as its electron-withdrawing-group was exposed to the reaction conditions, affording 2-quinolinone **163k** as the major product in 76% and alkene **163k'** as the minor product in 22% yield (entry 11, Table 3.7). Nitrile-containing anilide **164l** successfully afforded the desired 2-quinolinone **163l** in 56% yield (entry 12, Table 3.7). Unfortunately the SO_2Ph electron-withdrawing-group could not be tolerated; when anilide **164m** was exposed to the reaction conditions, alkene **163m'** was the sole product observed in 43% yield (entry 13, Table 3.7).

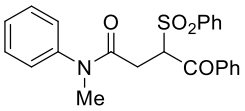
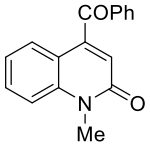
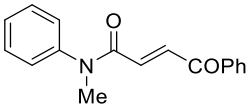
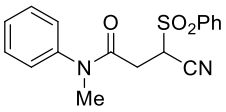
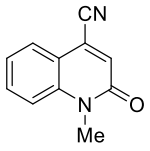
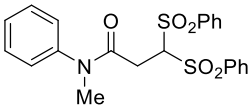
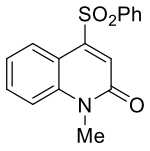
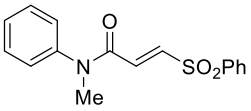
Table 3.7 Synthesis of 2-quinolinones **163a-l**.



164 **163**

Entry	Sulfone-containing anilide	Product	Yield (%)
1	 **164a**	 **163a**	84[a], 96[b], 95[c]
2	 **164b**	 **163b**	54
		 **163b'**	11
3	 **164c**	 **163c**	71
4	 **164d**	 **163d**	23
		 **163d'**	34

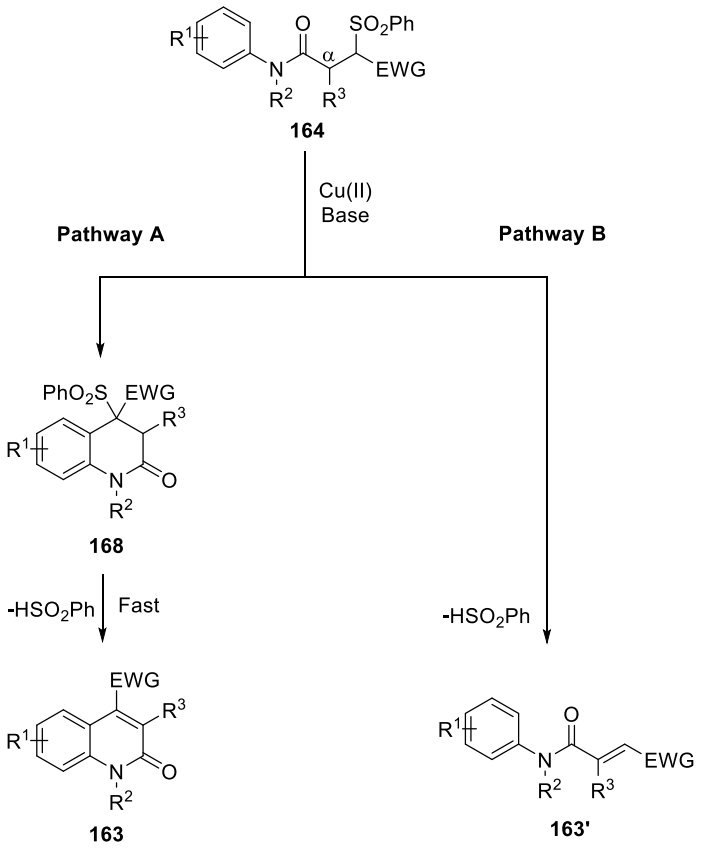
5	 **164e**	 **163e**	86
6	 **164f**	 **163f**	71
7	 **164g**	 **163g**	0
8	 **164h**	 **163h**	17
		 **163h'**	46
9	 **164i**	 **163i**	54
10	 **164j**	 **163j**	77

11	 **164k**	 **163k**	76
		 **163k'**	22
12	 **164l**	 **163l**	56
13	 **164m**	 **163m**	0
		 **163m'**	43

[a] 10 mol% copper(II) 2-ethylhexanoate used. [b] 100 mol% copper(II) 2-ethylhexanoate used. [c] 200 mol% copper(II) 2-ethylhexanoate used.

^{1}H NMR spectroscopic analysis of the alkene by-products **163'** suggests that they are all *E*-isomers with coupling constant values of ~16 Hz. To understand why alkene by-products **163'** are being formed, the mechanism of the reaction was considered. It can be rationalised that there are two competing reactions occurring during this procedure. Pathway A proceeds *via* a tandem cyclisation/sulfone elimination to give the desired 2-quinolinones **163** whereas pathway B proceeds with elimination of the sulfone prior to cyclisation and thus yielding alkenes **163'** (Scheme 3.21). Alkene **163m'** was subjected to the cyclisation reaction conditions; no reaction occurred suggesting that pathway B is irreversible. It also rules out the possibility that alkenes **163'** cyclise to give the desired 2-quinolinones **163**. Given the stability of our previously synthesised quinolin-2(1*H*)-ones **168** it is reasonable to assume that the formation of quinolin-2(1*H*)-ones **168** from **164** is irreversible. Given that we never observe sulfone-containing quinolinone **168** it suggests that the sulfone elimination step is extremely fast and irreversible.

The ratio of 2-quinolinone **163** to alkene **163'** formed during the reaction would therefore be related to the relative rates of pathway A and pathway B. If pathway A is fast, then it is likely that little to no alkene **163'** will be formed. If pathway A is slow it can be expected that alkene **163'** will be formed to some extent. It is also worth considering the change in acidity of the proton at the α-position; sulfone elimination is expected to proceed *via* β-elimination[76a] therefore increased acidity of the proton at the α-position should increase the rate of sulfone elimination, thus increasing the likelihood of the reaction proceeding *via* pathway B. It is likely that the extent of hyperconjugation with a phenyl ketone or a sulfone as the electron-withdrawing group is greater than with an ethyl ester thus increasing the leaving group ability of the sulfone resulting in formation of alkenes **163k'** and **163m'**.

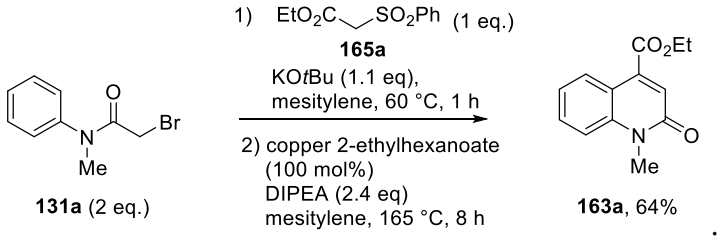


Scheme 3.21 Proposed mechanism for the formation of 2-quinolinones **163** and alkenes **163'**.

The formation of alkene **163b'** could be attributed to the steric bulk of the associated benzyl group slowing down the cyclisation step. Alkene **163d'** could arise due to the electron-withdrawing nature of the nitro-aromatic acidifying the proton at the α-position thus improving the likelihood of sulfone elimination. 5-Membered ring containing alkene **163h'** is likely to occur as a result of slow cyclisation, thus resulting in an increased proportion of the anilide proceeding *via* pathway B.

3.6.2 One-pot synthesis of 2-quinolinones

The synthesis of 2-quinolinone **163a** can be achieved in a one-pot fashion from α-bromo anilide **131a** (Scheme 3.22). To the potassium salt of **165a** in mesitylene was added α-bromo-anilide **131a** and after stirring for 1 hour at 60 °C was added the catalyst, base and more solvent were added. The reaction was complete after 8 hours giving a yield of 64%.



Scheme 3.22 One-pot synthesis of 2-quinolinone **163a** from α-bromo-anilide **131a**.

This alkylation/cyclisation/sulfone elimination approach gives the desired 2-quinolinone **163a** in 64% yield versus 89% yield over the two steps separately. However, this is still an impressive feat as this approach forms 3 new C–C bond in one-pot with significantly fewer manipulations.

3.6.3 Summary of copper-catalysed 2-quinolinone synthesis

The application of copper-catalysis to the synthesis of 2-quinolinones *via* a cyclisation/sulfone elimination approach was successful. A varied and extensive substrate scope has been demonstrated using our copper-catalysed method in comparable yields to those obtained by Chuang using manganese. Our copper-catalysed approach affords 2-quinolinone **163a** with as little as 10 mol% catalyst loading; even the use of 100 mol% copper(II) 2-ethylhexanoate is preferable to > 3 eq. of $Mn(OAc)_3$ utilised by Chuang. This Cu(II) method also uses less hazardous solvent and a one-pot alkylation/cyclisation/sulfone elimination has been demonstrated.

3.7 The first reported total synthesis of the biologically active 2-quinolinones 169 and 170

In 2010, Chung and co-workers reported the isolation of 2-quinolinones **169** and **170** from *Oryza sativa* (commonly known as Asian rice) and showed that it possessed immune-stimulating properties (Figure 3.5).[80c]

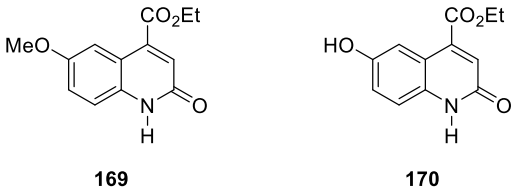
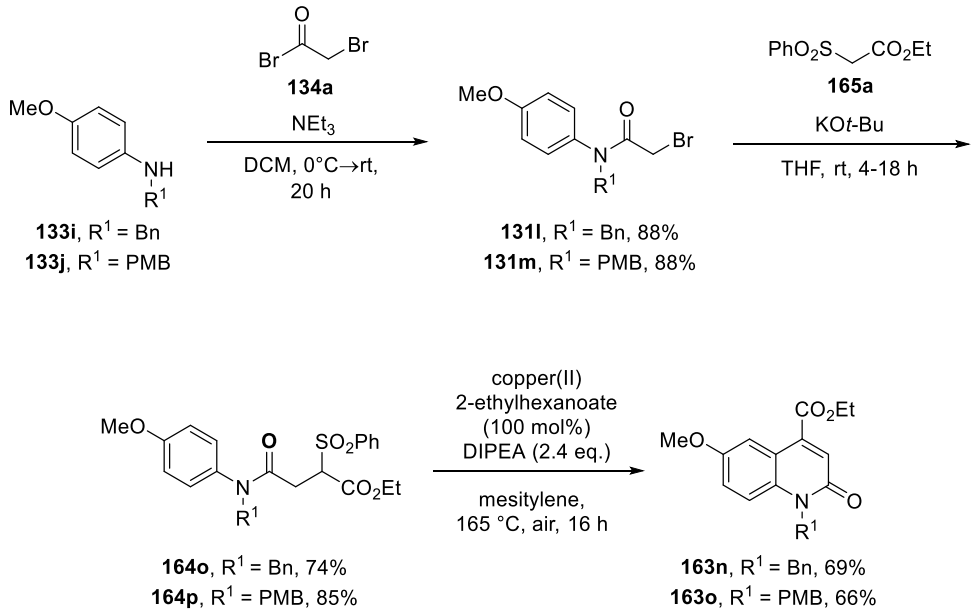


Figure 3.5 Biologically active 2-quinolinone natural products **169** and **170** isolated from *oryza sativa.*

To the best of our knowledge there have been no reported methods for the synthesis of these naturally occurring 2-quinolinones. We therefore decided to apply the conditions developed for the copper-catalysed synthesis of 2-quinolinones to the synthesis of these natural products.

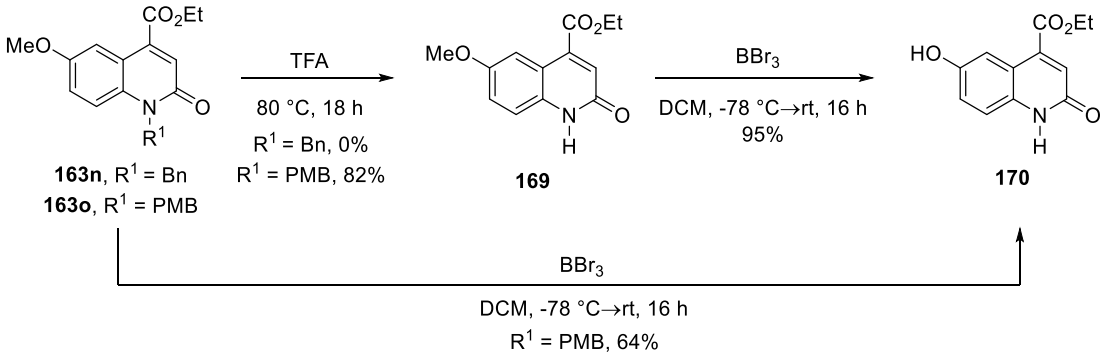
Anilines **133i** and **133j** were synthesised in 75% and 79% yield by reductive amination using the same method as previously described for aniline **44**. These anilines were exposed to bromoacetylbromide **134a** to afford α-bromo-anilides **131l** and **131m** in excellent yield (Scheme 3.23). These were then treated with the potassium salt of sulfone-containing, activated methylene compound **165a** to afford the sulfone-containing malonates **164o** and **164p** in good yield. 2-Quinolinones **163n** and **163o** were isolated in good yield upon treatment of malonates **164o** and **164p** with the copper conditions developed for the synthesis of the earlier 2-quinolinones.



Scheme 3.23 Synthesis of 2-quinolinones **163n** and **163o** in 3 steps from anilines **133i** and **133j**.

With 2-quinolinones **163n** and **163o** in hand, attempts were made to remove the benzyl and PMB protecting groups to afford natural product **169** (Scheme 3.24). Upon heating in neat TFA, the *N*-benzyl group of **163n** remained intact with only unreacted starting material recovered, but the *N*-PMB protected **163o** was smoothly converted into the natural product **169** in 82% yield. Natural product **169** could be converted into natural product **170** in near quantitative yield upon treatment with BBr_3 in DCM. The spectroscopic data for **169** and **170** were identified as those reported (see experimental section).

It was possible to remove both the O-Me and *N*-PMB protecting groups of upon treatment with BBr_3 in DCM thus allowing direct conversion of 2-quinolinone **163o** to natural product **170** in 64% yield, versus 78% yield of the two individual de-protections combined.



Scheme 3.24 Synthesis of the 2-quinolinone natural products **169** and **170**.

3.8 Efforts towards the total synthesis of HOFQ

3.8.1 Introduction to HOFQ

Furocumarins (psoralens) are a class of heterocycle used in a range of therapies. Examples include psoralen plus UVA (PUVA) therapy for treatment of skin diseases,[87] photopheresis for the treatment of autoimmune diseases and T-cell lymphoma, and in the prevention of organ transplant rejection.[88] Unfortunately many of the furocumarin compounds used in such treatments suffer from toxic side-effects such as genotoxicity,[89] skin erythemas[87] and carcinogenicity.[90]

To reduce furocumarin genotoxicity, derivatives were investigated; among the tested compounds the most active derivative was found to be FQ **140**.[91] Further derivatisation of FQ **140** afforded HOFQ **141** which showed similar photobiological behaviour to HQ but with lower genotoxicity and no skin phototoxicity (Figure 3.6).[82]

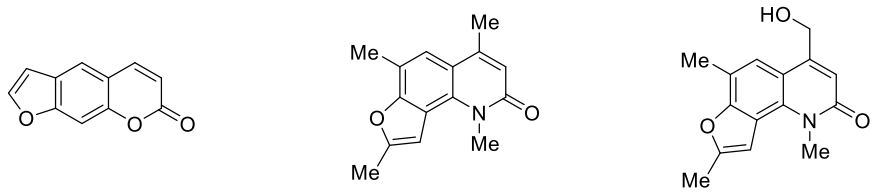
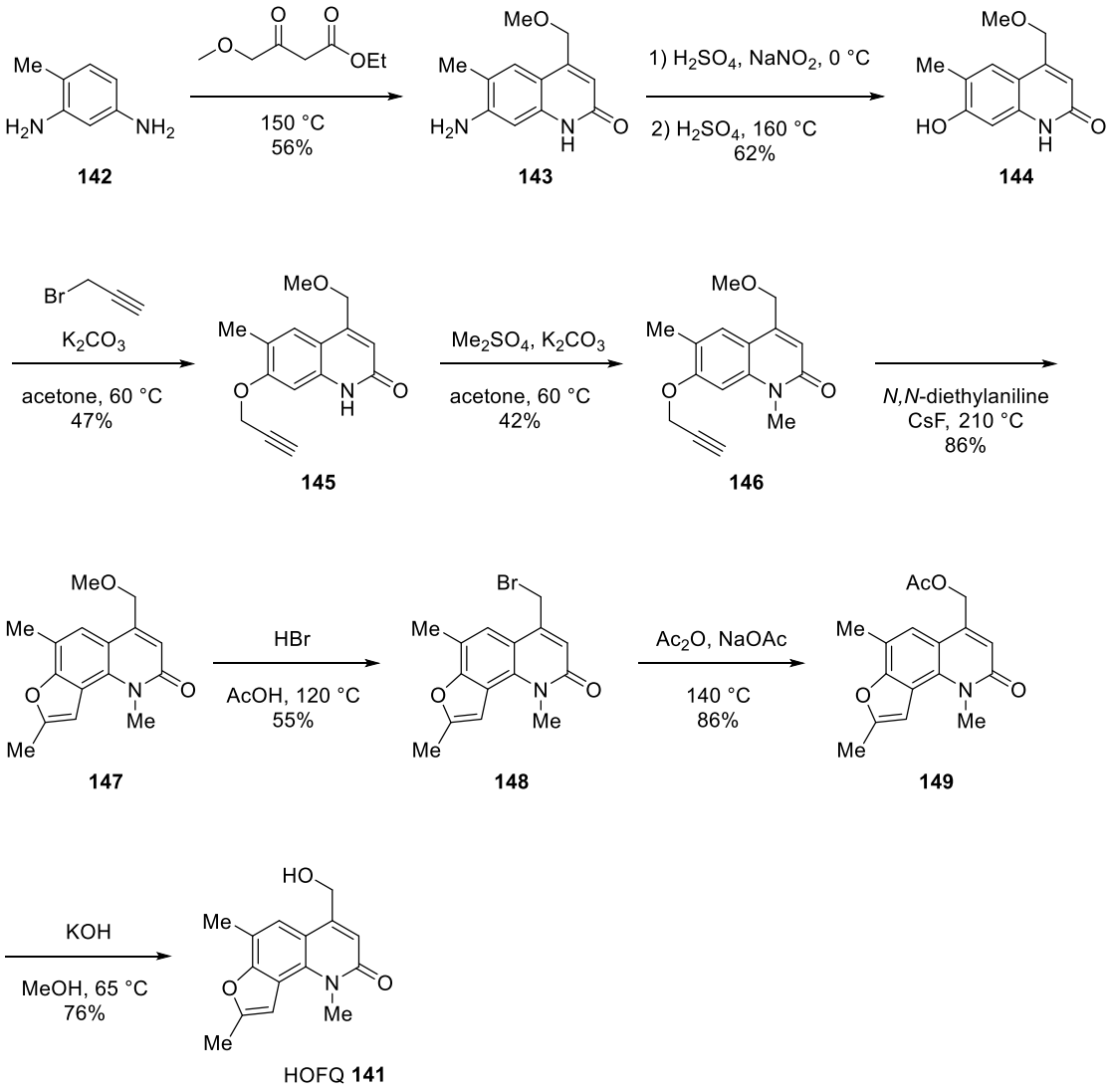


Figure 3.6 Biologically active heterocycles furocoumarin **171**, FQ **140** and HOFQ **141**.

3.8.2 Synthetic approaches to HOFQ

To the best of our knowledge HOFQ **141** has only been synthesised by the Chilin research group who have carried out extensive investigations into its biological activity.[82, 91-92] Chilin's synthesis of HOFQ is 8 linear steps, 5 of which are carried out at high temperature with yields being generally modest (Scheme 3.25).

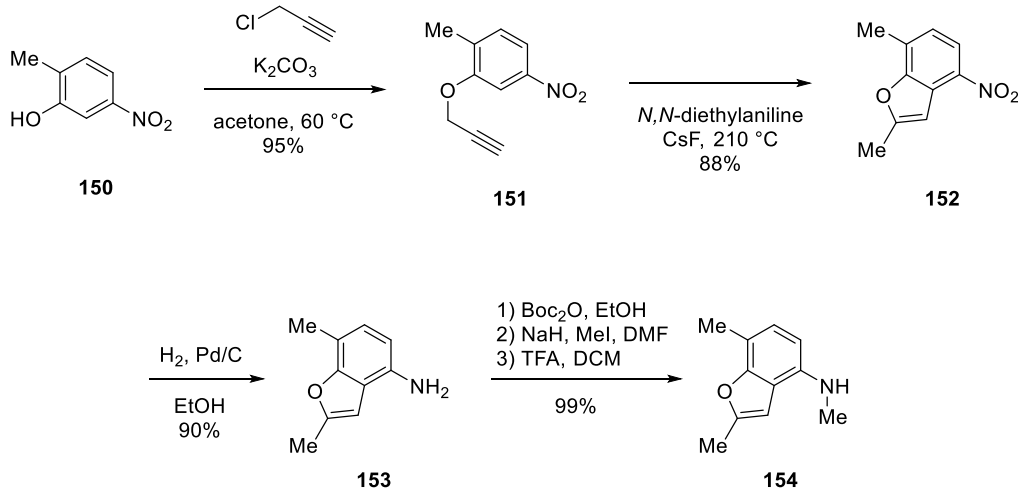


Scheme 3.25 Chilin's synthesis of HOFQ **141**.

We saw the opportunity to synthesise the HOFQ core *via* a copper-catalysed cyclisation/sulfone elimination approach.

3.8.3 Application of copper conditions to the total synthesis of HOFQ

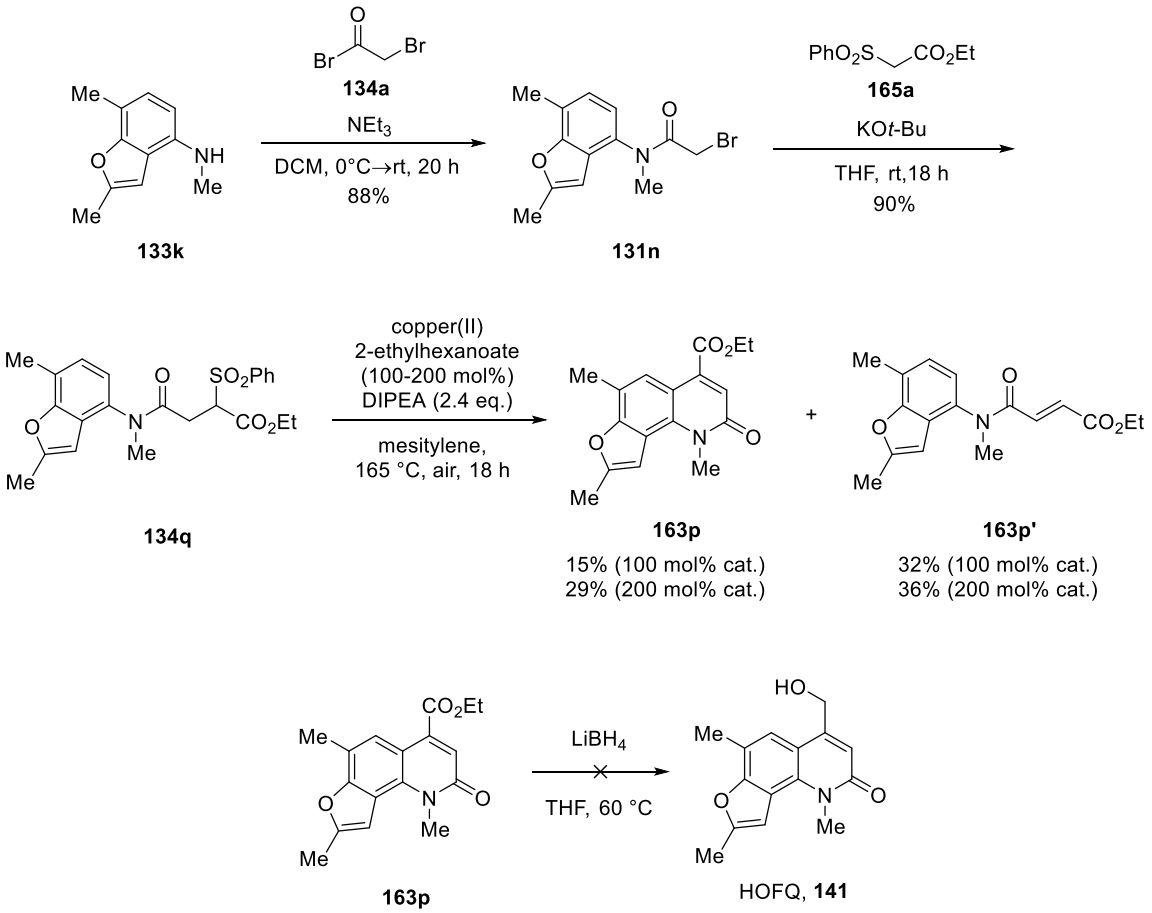
Elsewhere in the group aniline **150** was synthesised according to the procedure of Rodighiero and subsequently methylated to afford aniline **154** (Scheme 3.26).[93]



Scheme 3.26 Synthesis of aniline **154**.

Aniline **154** was treated with bromoacetyl bromide **134a** which afforded α-bromo-anilide **131n** in excellent yield (Scheme 3.27). Upon treatment with the potassium salt of methylene compound **165a**, sulfone-containing anilide **134q** was obtained in excellent yield. Disappointingly, the copper-catalysed cyclisation/sulfone elimination procedure afforded a mixture of both desired furoquinolinone **163p** and alkene **163p'**. When 100 mol% catalyst loading was used 15% of furoquinolinone **163p** was isolated along with 32% alkene **163p'**. When 200 mol% catalyst loading was used an improved yield of furoquinolinone **163p** was isolated 29%, and alkene **163p'** in 36% yield.

To our disappointment, reduction of furoquinolinone **163p** to HOFQ **141** using lithium borohydride was unsuccessful, with full decomposition of the starting material observed; the decomposed material was not able to be identified. Due to time constraints and limited quantities of furoquinolinone **163p** alternative conditions were not attempted for the conversion of furoquinolinone **163p** into HOFQ **141**.

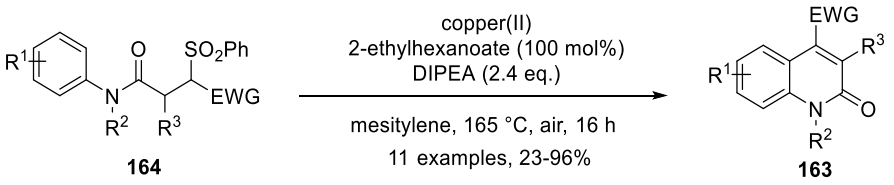


Scheme 3.27 Attempted synthesis of HOFQ **141**.

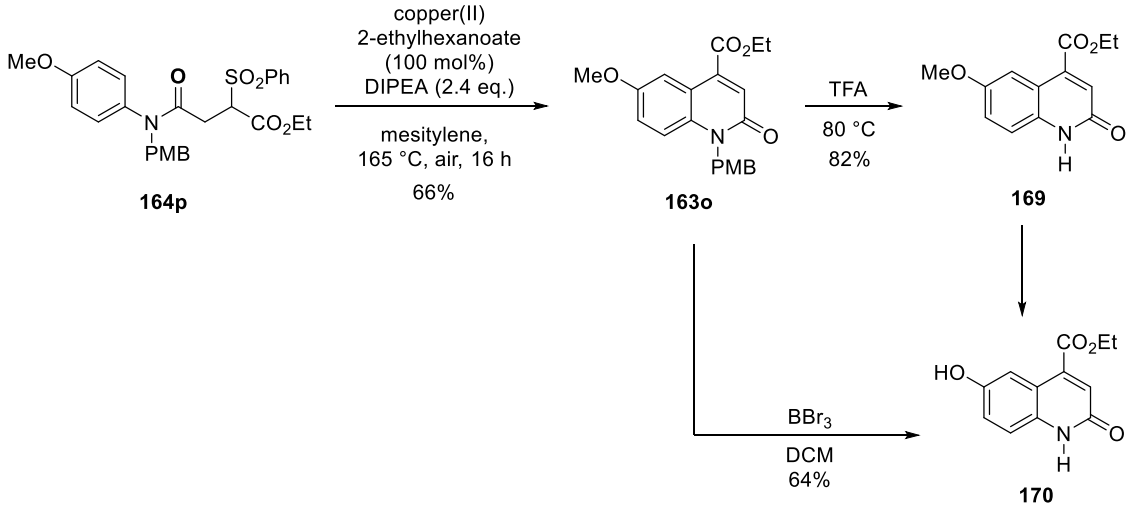
It was therefore concluded that copper-catalysed cyclisation/sulfone elimination does not appear to be a viable method for the synthesis of HOFQ due to the low yield of furoquinolinone **163p** observed and the elimination product alkene **163p'** as the major product. However, this study does provide a new route to FQ-type structures and further work is being carried out within the research group to utilise and improve upon this method for the synthesis of HOFQ.

3.9 Summary of copper-catalysed 2-quinolinone synthesis

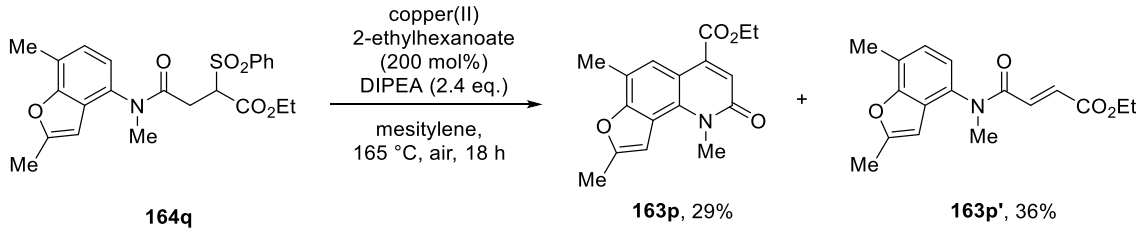
Copper-catalysed cyclisation/sulfone elimination has been applied to a range of substrates with varying functionality in modest to excellent yields with catalyst loading as low as 10 mol% (Scheme 3.7). Despite being at higher temperature, our copper-catalysed method offers a milder and safer alternative to Chuang's manganese-mediated approach with a much wider substrate scope. Unfortunately alkene by-products can arise as a result of slow cyclisation relative to the speed of sulfone elimination. It has been demonstrated that a one-pot alkylation/cyclisation/sulfone elimination approach can be achieved to synthesise 2-quinolinone **163a** forming three new C–C bonds in one procedure.



Copper-catalysed cyclisation/sulfone elimination has been successfully utilised to complete the first reported total synthesis of biologically active natural products **169** and **170**.



Unfortunately this method is not suitable for the synthesis of HOFQ **141** as the yield of the desired furoquinolinone intermediate **163p** is low with alkene **163p'** being the major by-product resulting from elimination of the sulfone group prior to cyclisation (Scheme 3.27).



Chapter 4 Final conclusions and future work

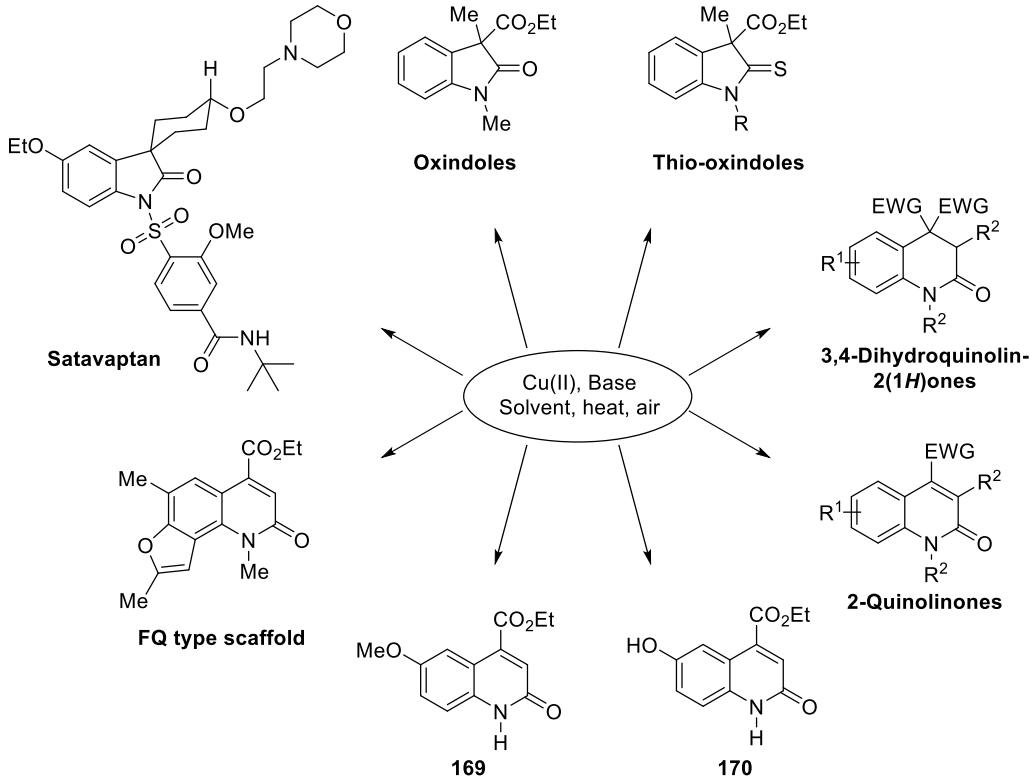
4.1 Final conclusions

The original aims of this research were:

- Improvement on the Taylor group method for copper-catalysed synthesis of oxindoles
    - Reduced temperature
    - More efficient catalysis
    - Higher yield
- Application of the newly developed conditions to other *N*-heterocyclic motifs of medicinal interest
    - Synthesis of 5-membered nitrogen-containing heterocycles
    - Synthesis of 6-membered nitrogen-containing heterocycles
- Application of conditions to the synthesis of biologically active molecules based on *N*-heterocycles

This report outlines the development of an improved set of conditions for the synthesis of oxindoles using copper catalysis. These conditions are effective at lower temperature and offer high yields, with smooth conversion of anilide **40** into oxindole **41** with no observed by-products. This approach to heterocycles formation is highly atom efficient, uses an inexpensive copper-salt as catalyst and is moisture and air insensitive.

Furthermore, it has been demonstrated that copper-catalysis is an effective method not only for the synthesis of oxindoles, but also thio-oxindoles, 3,4-dihydroquinolin-2(1*H*)ones and 2-quinolinones. Additionally, copper-catalysis has been successfully applied to the formal synthesis of oxindole-containing drug molecule Satavaptan **6**, the first reported synthesis of biologically active, 2-quinolinone containing natural products **169** and **170**, and the synthesis of FQ type structures.



The ability to apply a single method to a range of medicinally interesting heterocycles makes this copper-catalysed approach incredibly powerful.

4.2 Future work

Future work would be valuable to further modify the copper-catalysed cyclisation conditions to carry out the processes at even lower temperatures. Additional research into the formation of oxindoles by a one-pot copper-catalysed C–*N*/C–C procedure would also be worthy of investigation following the promising preliminary results (Table 2.12). Additional studies to optimise the formation of **163p** and then complete the synthesis of HOFQ **141** would also be of interest. Finally applications in complex natural product synthesis could be explored.

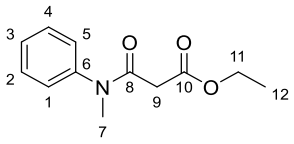
Chapter 5 Experimental

5.1 Instrumentation

Anhydrous toluene, DMF and DCM were collected from a PureSolv® solvent purification system. Anhydrous THF was obtained by distillation over sodium benzophenone ketyl immediately before use. ^{1}H NMR and ^{13}C NMR spectra were recorded on a JEOL ECX400 or JEOL ECS400 spectrometer, operating at 400 MHz and 100 MHz for ^{1}H and ^{13}C nuclei respectively, or a Bruker DRX500 spectrometer, operating at 500 MHz and 125 MHz, respectively. All spectral data was acquired at 295 K. Chemical shifts (δ) are quoted in parts per million (ppm). The residual solvent peak, δ_H 7.26 for $CHCl_3$ and δ_H 2.50 for DMSO were used as a reference for ^{1}H NMR and δ_C 77.0 for $CDCl_3$ and δ_C 39.5 for *d6*-DMSO were used as a reference for ^{13}C NMR. Coupling constants (*J*) are reported in Hertz (Hz) to the nearest 0.1 Hz. The multiplicity abbreviations used are: s singlet, d doublet, t triplet, q quartet, m multiplet, dd doublet of doublets, dt doublet of triplets, td triplet of doublets. Signal assignment was achieved by analysis of DEPT, COSY, HMBC and HSQC experiments where required. Infrared (IR) spectra were recorded on either a ThermoNicolet IR-100 spectrometer with NaCl plates as a thin film dispersed from either CH_2Cl_2 or $CDCl_3$, or a PerkinElmer UATR Two spectrometer. Mass-spectra (low and high-resolution) were obtained by the University of York Mass Spectrometry Service, using electrospray ionisation (ESI) on a Bruker Daltonics, micrOTOF spectrometer. Melting points were determined using Gallenkamp apparatus and are uncorrected. Thin layer chromatography was carried out on Merck silica gel $60F_{254}$ pre-coated aluminium foil sheets and were visualised using UV light (254 nm) and stained with basic aqueous potassium permanganate as visualizing agent. Flash column chromatography was carried out using slurry packed Fluka silica gel (SiO_2), 35–70 μm, 60 Å, under a light positive pressure, eluting with the specified solvent system. Petrol refers to petroleum ether 40–60 °C. Atom numbering of compounds are not related to IUPAC and are merely used as an aid for assignment of atoms.

5.2 Optimisation of Reaction conditions

Ethyl 3-[methyl(phenyl)amino]-3-oxopropanoate (**39**)



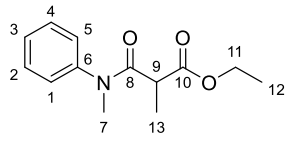
To a stirred solution of 3-ethoxy-3-oxopropanoic acid **38** (6.60 g, 50.0 mmol) in DCM (160 mL) at 0 °C were added *N*-methylaniline (5.90 mL, 55.0 mmol), Mukaiyama's reagent (chloro-*N*-methyl pyridinium iodide) (19.1 g, 75.0 mmol) and NEt_3 (34.4 mL, 250 mmol). The reaction mixture was allowed to warm to rt and stirred for 1 h. The solution was quenched with 10% HCl (150 ml), the organics separated and washed with $NaHCO_3$ (100 mL) then brine (100 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification by flash column chromatography (1:1 petrol/EtOAc) afforded the title compound **39** (8.52 g, 38.5 mmol, 77%) as a yellow oil.

R_f: 0.29 (1:1 petrol/EtOAc); ν_{max}/cm^{-1} (neat): 2983, 1736 (C=O), 1659 (C=O), 1595, 1496, 1381; δ_H (400 MHz, $CDCl_3$): 7.44-7.37 (2 H, m, H-2 and H-4), 7.37-7.31 (1 H, m, H-3), 7.24-7.19 (2 H, m, H-1 and H-5), 4.14-4.06 (2 H, m, H-11), 3.29 (3 H, s, H-7), 3.19 (2 H, s, H-9), 1.21 (3 H, t, J = 7.2 Hz, H-12); δ_C (100 MHz, $CDCl_3$): 167.8 (C-8), 166.1 (C-10), 143.6 (C-6), 130.0 (C-2 and C-4), 128.4 (C-3), 127.4 (C-1 and C-5), 61.3 (C-11), 41.7 (C-9), 37.5 (C-7), 14.2 (C-12); HRMS [ES^+] found MH^+, 222.1130. $C_{12}H_{16}NO_3$ requires 222.1125.

Lab book ref. RG001

Data consistent with literature values.[54]

Ethyl 2-methyl-3-[methyl(phenyl)amino]-3-oxopropanoate (**40**)



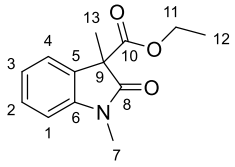
To a stirred solution of ethyl 3-[methyl(phenyl)amino]-3-oxopropanoate **39** (7.95 g, 36.0 mmol) in THF (440 mL) at room temperature was added KO*t*-Bu (4.51 g, 40.2 mmol) giving a yellow solution. Once dissolution was complete, MeI (2.50 mL, 40.2 mmol) was added dropwise, giving a colourless suspension which was stirred for 1 h. Saturated NH_4Cl (200 mL) was added and the aqueous layer extracted with EtOAc (3 × 200 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (10:3 petrol/EtOAc) afforded the title compound **40** (7.13 g, 30.3 mmol, 84%) as a yellow oil.

R_f: 0.47 (1:1 petrol/EtOAc); ν_{max}/cm^{-1} (neat): 2938, 1715 (C=O), 1635 (C=O), 1571, 1473; δ_H (400 MHz, $CDCl_3$): 7.42 (2 H, t, *J* = 6.8 Hz, H-2 and H-4), 7.35 (1 H, tt, *J* = 7.6, 2.0 Hz, H-3), 7.25-7.23 (2 H, m, H-1 and H-5), 4.14-4.03 (2 H, m, H-11), 3.38 (1 H, q, *J* = 7.0 Hz, H-9), 3.29 (3 H, s, H-7), 1.28 (3 H, d, *J* = 7.0 Hz, H-13), 1.21 (3 H, t, *J* = 7.2 Hz, H-12); δ_C (100 MHz, $CDCl_3$): 170.8 (C-8), 170.2 (C-10), 143.7 (C-6), 130.0 (C-2 and C-4), 128.3 (C-3), 127.6 (C-1 and C-5), 61.2 (C-11), 43.6 (C-9), 37.7 (C-7), 14.24 (C-12 or C-13), 14.16 (C-12 or C-13); HRMS [ES^+] found MH^+, 236.1284. $C_{13}H_{18}NO_3$ requires 236.1281.

Lab book ref. RG002

Data consistent with literature values.[42]

Ethyl 1,3-dimethyl-2-oxoindoline-3-carboxylate (**41**)



Ethyl 2-methyl-3-[methyl(phenyl)amino]-3-oxopropanoate **40** (94.0 mg, 0.40 mmol) and copper(II) 2-ethylhexanoate (14.0 mg, 10 mol%) in toluene (8 mL) was stirred at 120 °C under an atmosphere of air for 15 h. Upon completion of the reaction, toluene was removed under reduced pressure and EtOAc (10 mL) was added. The solution was washed with 10% HCl solution (3 × 8 mL), 10% NH_4OH solution (3 × 8 mL), brine (10 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (4:1 petrol/EtOAc) afforded the title compound **41** (93.2 mg, 0.40 mmol, 100%) as a yellow oil.

R_f: 0.21 (4:1 petrol/EtOAc); ν_{max}/cm^{-1} (neat): 3011, 1729 (C=O), 1689 (C=O), 1567, 1471; δ_H (400 MHz, $CDCl_3$): 7.30 (1 H, td, *J* = 7.6, 1.2 Hz, H-2), 7.23 (1 H, dd, *J* = 7.6, 1.2 Hz, H-1), 7.04 (1 H, td, *J* = 7.6, 1.2 Hz, H-3), 6.85 (1 H, d, *J* = 7.6 Hz, H-4), 4.12 (1 H, dq, *J* = 11.0, 7.1 Hz, H-11), 4.07 (1 H, qd, *J* = 11.0, 7.1 Hz, H-11), 3.23 (3 H, s, H-7), 1.64 (3 H, s, H-13), 1.13 (3 H, t, *J* = 7.1 Hz, H-12); δ_C (100 MHz, $CDCl_3$): 175.1 (C-8), 169.6 (C-10), 143.5 (C-6), 130.1 (C-5), 128.9 (C-3), 122.8 (C-4), 122.7 (C-2), 108.3 (C-1), 61.8 (C-11), 54.9 (C-9), 26.4 (C-7), 20.0 (C-13), 13.8 (C-12); HRMS [ES^+] found MH^+, 234.1126. $C_{13}H_{16}NO_3$ requires 234.1125.

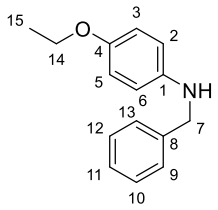
Lab book ref. RG007

Data consistent with literature values.[42]

5.3 Application of copper conditions to the formal synthesis of Satavaptan

5.3.1 *Route 1*

_N_-Benzyl-4-ethoxyaniline (44)[50]



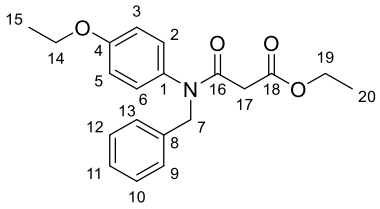
To a stirred solution of 4-ethoxyaniline (7.46 mL, 58 mmol) in methanol (100 mL) at room temperature was added benzaldehyde (5.72 mL, 58 mmol) over 30 min by syringe-pump. The reaction mixture was heated to reflux and held for 2 min then allowed to cool to room temperature. $NaBH_4$ (2.40 g, 63.5 mmol) was added portion-wise over 1 h then the reaction mixture was stirred at room temperature for 2 h. The reaction was quenched with water (100 mL) then the MeOH removed under reduced pressure. The remaining aqueous solution was extracted with EtOAc (3 × 75 mL) and the combined organic fractions concentrated *in vacuo*. Purification by flash column chromatography (19:1 → 9:1 petrol/EtOAc) afforded the title compound **44** (9.88 g, 43.5 mmol, 75%) as an orange powder.

R_f: 0.35 (9:1 petrol/EtOAc); m.p: 45-47 °C (Lit.[50] 44–46 °C); ν_{max}/cm^{-1} (solid): 3412, 2977, 1511, 1478, 1232, 1049; δ_H (400 MHz, $CDCl_3$): 7.31-7.15 (5 H, m, ArH), 6.70 (2 H, d, *J* = 9.0 Hz, H-2 and H-6), 6.52 (2 H, d, *J* = 9.0 Hz, H-3 and H-5), 4.20 (2 H, s, H-7), 3.86 (2 H, q, *J* = 7.0 Hz, H-14), 1.29 (3 H, t, *J* = 7.0 Hz, H-15); HRMS [ES^+] found MH^+, 228.1375. $C_{15}H_{18}NO$ requires 228.1383.

Lab Book ref. RG155

Data is consistent with literature values.[50]

Ethyl 3-[benzyl(4-ethoxyphenyl)amino]-3-oxopropanoate (**59**)

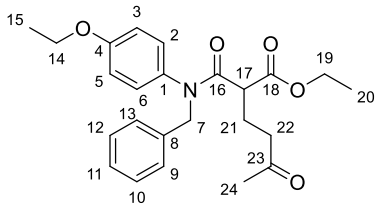


To a stirred solution of 3-ethoxy-3-oxopropanoic acid **38** (2.15 g, 16.3 mmol) in DCM (55 mL) at 0 °C were added *N*-benzyl-4-ethoxyaniline **44** (4.07 g, 17.9 mmol), 2-chloro-*N*-methyl pyridinium iodide (6.22 g, 24.4 mmol) and triethylamine (11.3 mL, 81.4 mmol). The reaction mixture was allowed to warm to rt and stirred for 1 h. The solution was quenched with 10% HCl (60 mL), the organics separated and washed with $NaHCO_3$ (50 mL) then brine (50 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification by flash column chromatography (7:3 petrol/EtOAc) afforded the title compound **59** (3.50 g, 10.3 mmol, 63%) as a colourless oil.

R_f: 0.18 (7:3 petrol/EtOAc); ν_{max}/cm^{-1} (neat): 2981, 1736 (C=O), 1656 (C=O), 1509, 1396, 1326, 1292, 1244, 1151; δ_H (400 MHz, $CDCl_3$): 7.26-7.16 (5 H, m, ArH), 6.88 (2 H, d, *J* = 9.0 Hz, H-2 and H-6), 6.78 (2 H, d, *J* = 9.0 Hz, H-3 and H-5), 4.86 (2 H, s, H-7), 4.12 (2 H, q, *J* = 7.2 Hz, H-19), 3.97 (2 H, q, *J* = 7.0 Hz, H-14), 3.20 (2 H, s, H-17), 1.39 (3 H, t, *J* = 7.0 Hz, H-15), 1.23 (3 H, t, *J* = 7.2 Hz, H-20); δ_C (100 MHz, $CDCl_3$): 167.8 (C-18), 166.4 (C-16), 158.6 (C-4), 137.0 (C-8), 134.2 (C-1), 129.4 (C-2 and C-6), 128.9 (Ar-CH), 128.3 (Ar-CH), 127.4 (Ar-CH), 115.1 (C-3 and C-5), 63.6 (C-14), 61.2 (C-19), 53.1 (C-7), 41.8 (C-17), 14.7 (C-15), 14.1 (C-20); HRMS [ES^+] found MNa^+, 364.1510. $C_{20}H_{23}NNaO_4$ requires 364.1519.

Lab book ref. RG176

Ethyl 2-[benzyl(4-ethoxyphenyl)carbamoyl]-5-oxohexanoate (**58**)



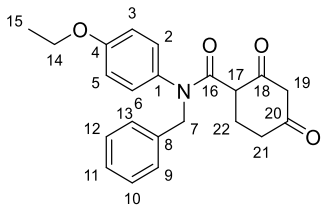
To a stirred solution of ethyl 3-[benzyl(4-ethoxyphenyl)amino]-3-oxopropanoate **59** (2.87 g, 8.42 mmol) and K_2CO_3 (116 mg, 10 mol%) in DMF (8.5 mL) was added dropwise methyl vinyl ketone (841 µL, 10.1 mmol) at 0 °C. The mixture was allowed to warm to room temperature and stirred for 16 h. The mixture was quenched with 2M H_2SO_4 (10 mL) then diluted with ether (12 mL). The organic layer was separated and the aqueous layer extracted with ether (12 mL). The ethereal layers

were combined, washed with brine (15 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the title compound **58** (3.33 g, 8.09 mmol, 96%) as a pale yellow oil.

R_f: 0.50 (1:1 hexane/EtOAc); ν_{max}/cm^{-1} (neat): 2981, 1737 (C=O), 1715 (C=O), 1657 (C=O), 1510, 1399, 1292, 1248, 1171; δ_H (400 MHz, $CDCl_3$): 7.29-7.15 (5 H, m, ArH), 6.87 (2 H, d, *J* = 9.2 Hz, H-2 and H-6), 6.76 (2 H, d, *J* = 9.2 Hz, H-3 and H-5), 5.04 (1 H, d, *J* = 14.3 Hz, H-7), 4.64 (1 H, d, *J* = 14.3 Hz, H-7), 4.12-4.01 (2 H, m, H-19), 3.97 (2 H, q, *J* = 8.0 Hz, H-14), 3.35 (1 H, t, *J* = 7.0 Hz, H-17), 2.51-2.42 (2 H, m, H-22), 2.16-2.03 (2 H, m, H-21), 2.08 (3 H, s, H-24), 1.39 (3 H, t, *J* = 8.0 Hz, H-15), 1.24-1.17 (3 H, m, H-20); HRMS [ES^+] found MH^+, 412.2104. $C_{24}H_{30}NO_5$ requires 412.2118.

Lab book ref. RG178

***N*-Benzyl-*N*-(4-ethoxyphenyl)-2,4-dioxocyclohexanecarboxamide** (**57b**)



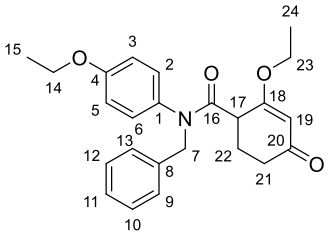
To EtOH (17 mL) at room temperature, sodium metal (162 mg, 7.06 mmol) was added and stirred until dissolution was complete. The solution was cooled to -15 °C and ethyl 2-[benzyl(4-ethoxyphenyl)carbamoyl]-5-oxohexanoate **58** (2.90 g, 7.06 mmol) in EtOH (12 mL) was added dropwise. The reaction mixture was allowed to warm to room temperature with stirring continued. The mixture was then heated at 85 °C for 3 h. The reaction mixture was quenched with 10% HCl solution (25 mL) and extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine (70 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (1:1 hexane/EtOAc → 9:1 DCM/MeOH) afforded the title compound **57b** (1.18 g, 3.24 mmol, 46%) as a colourless solid and **57a** (904 mg, 2.30 mmol, 33%) as a yellow powder.

R_f: 0.10 (1:1 petrol/EtOAc); m.p. 61–64 °C; ν_{max}/cm^{-1} (neat): 2979, 1716 (C=O), 1653-1603 (C=O), 1508, 1396, 1298, 1244, 1187; δ_H (400 MHz, $CDCl_3$): 7.29-7.10 (5 H, m, H-9 to H-13), 7.01-6.72 (4 H, m, H-2, H-3, H-5 and H-6), 4.97-4.72 (2 H, m, H-7), 4.00-3.91 (2 H, m, H-14), 3.70-2.19 (3 H, m, H-17 and H-19), 2.59-1.90 (4 H, m, H-21 and H-22), 1.38-1.27 (3 H, m, H-15); δ_C (100 MHz, $CDCl_3$): 207.3 (C-18 or C-20), 200.5 (C-18 or C-20), 171.7 (C-16), 158.5 (C-4), 136.9 (C-1 or C-8), 134.2 (C-1 or C-8), 129.3 (Ar-CH or ArC), 128.8 (Ar-CH or ArC), 128.6 (Ar-CH or ArC), 128.3 (Ar-CH or ArC), 127.3 (Ar-CH or ArC), 63.6 (C-14), 53.3 (C-7), 47.2 (C-17 or C-19), 46.7

(C-17 or C-19), 29.4 (C-21 or C-22), 24.7 (C-21 or C-22), 14.7 (C-15); HRMS [ES^+] found MNa^+, 388.1519. $C_{22}H_{23}NNaO_4$ requires 388.1519.

Lab book ref. RG180-F2 and RG182

***N*-Benzyl-2-ethoxy-*N*-(4-ethoxyphenyl)-4-oxocyclohex-2-enecarboxamide (57a)**

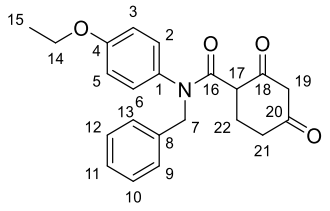


Isolated as a colourless oil. R_f: 0.24 (1:1 petrol/EtOAc); ν_{max}/cm^{-1} (neat): 2981, 2937, 1716 (C=O), 1644 (C=O), 1601, 1509, 1397, 1245, 1188; δ_H (400 MHz, $CDCl_3$): 7.27-7.14 (5 H, m, ArH), 6.91-6.76 (2 H, m, ArH), 6.73 (2 H, d, *J* = 9.1 Hz, ArH), 5.30 (1 H, s, H-19), 5.01-4.72 (2 H, m, H-7), 3.99-3.89 (2 H, m, H-14 or H-23), 3.88-3.74 (2 H, m, H-14 or H-23), 3.34-3.22 (1 H, m, H-17), 2.54-2.34 (2 H, m, H-21 or H-22), 2.11-2.00 (2 H, m, H-21 or H-22), 1.35 (3 H, t, *J* = 7.0 Hz, H-15 or H-24), 1.29 (3 H, t, *J* = 7.1 Hz, H-15 or H-24); δ_C (100 MHz, $CDCl_3$): 207.2 (C-20), 195.6 (C-16), 177.4 (C-18), 158.3 (C-4), 137.2 (C-1 or C-8), 134.5 (C-1 or C-8), 128.8 (Ar-CH), 128.5 (Ar-CH), 128.2 (Ar-CH), 127.0 (Ar-CH), 114.8 (Ar-CH), 102.3 (C-19), 64.2 (C-14 or C-23), 63.4 (C-14 or C-23), 53,1 (C-7), 49.7 (C-17), 27.8 (C-21 or C-22), 24.5 (C-21 or C-22), 14.6 (C-15), 13.9 (C-24); HRMS [ES^+] found MH^+, 394.2010. $C_{24}H_{28}NO_4$ requires 394.2013.

Lab book ref. RG180-F1

***N*-Benzyl-*N*-(4-ethoxyphenyl)-2,4-dioxocyclohexanecarboxamide (57b)**

*From N-benzyl-2-ethoxy-N-(4-ethoxyphenyl)-4-oxocyclohex-2-enecarboxamide (**57a**)*



To a stirred solution of *N*-benzyl-2-ethoxy-*N*-(4-ethoxyphenyl)-4-oxocyclohex-2-enecarboxamide **57a** (170 mg, 433 µmol) in THF/water (10:1, 3.5 mL) was added 1 M HCl (350 µL) and stirred at room temperature overnight. Upon completion of the reaction the rection mixture was diluted with

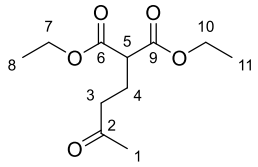
EtOAc/water (2:1, 10 mL) and the organic phase separated. The aqueous phase was extracted with EtOAc (2 × 8 mL) and the combined organics washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford the title compound **57b** (153 mg, 419 µmol, 97%) as a colourless solid.

Lab book ref. RG182

Data as above.

5.3.2 *Route 2*

Diethyl 2-(3-oxobutyl)malonate (**64**)[52]



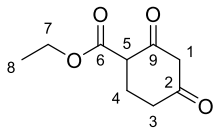
To a stirred solution of diethyl malonate **63** (7.63 mL, 50.0 mmol) and K_2CO_3 (691 mg, 10 mol%) was added dropwise 3-buten-2-one **60** (5.00 mL, 60.1 mmol) at 0 °C. The mixture was allowed to warm to room temperature and stirred for 16 h. The mixture was quenched with 2M H_2SO_4 (3 mL) then diluted with ether (4 mL). The organic layer was separated and the aqueous layer extracted with ether (6 mL). The ethereal layers were combined, washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (4:1 petrol/EtOAc) afforded the title compound **64** (8.22 g, 35.7 mmol, 71%) as a colourless oil.

R_f: 0.24 (4:1 petrol/EtOAc); ν_{max}/cm^{-1} (neat): 2984, 1748 (C=O), 1730 (C=O), 1447, 1370, 1229, 1155, 1028; δ_H (400 MHz, $CDCl_3$): 4.17 (4 H, dq, *J* = 7.2, 1.0 Hz, H-7 and H-10), 3.35 (1 H, t, *J* = 7.6 Hz, H-5), 2.50 (2 H, t, *J* = 7.3 Hz, H-3), 2.17-2.06 (2 H, m, H-4), 2.15 (3 H, s, H-1), 1.23 (6 H, t, *J* = 7.2 Hz, H-8 and H-11); δ_C (100 MHz, $CDCl_3$): 207.0 (C-2), 169.1 (C-6 and C-9), 61.4 (C-7 and C-10), 50.6 (C-5), 40.4 (C-3), 29.9 (C-1), 22.4 (C-4), 14.0 (C-8 and C-11); HRMS [ES^+] found MNa^+, 253.1043. $C_{11}H_{18}NaO_5$ requires 253.1046.

Lab Book ref. RG145

Data consistent with literature values.[52]

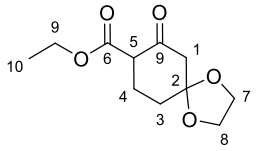
Ethyl 2,4-dioxocyclohexanecarboxylate (**65**)[52]



To EtOH (15 mL) at room temperature, sodium metal (821 mg, 35.7 mmol) was added and stirred until dissolution was complete. The solution was cooled to -15 °C and diethyl 2-(3-oxobutyl)malonate **64** (8.22 g, 35.7 mmol) in EtOH (3 mL) was added dropwise. The reaction mixture was allowed to warm to room temperature with stirring continued. The mixture was then heated at 85 °C for 3 h. The crude material was dissolved in brine (125 mL) and washed with ether (2 × 35 mL). The aqueous layer was cooled to 0 °C and acidified with 2 M H_2SO_4. The mixture was extracted with ether (3 × 70 mL), the combined organic extracts were washed with brine (70 mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford the title compound **65** as a colourless oil (7.06 g) which was used in the next step without further purification.

Lab Book ref. RG146

Ethyl 7-oxo-1,4-dioxaspiro[4.5]decane-8-carboxylate (**62**)[52]



Ethyl 2,4-dioxocyclohexanecarboxylate **65** (7.06 g, 38.4 mmol), ethylene glycol (2.15 mL, 38.6 mmol), *p*-TSA·H_2O (88 mg, 1.2 mol%) and toluene (80 mL) were combined and heated under reflux in a Dean-Stark apparatus for 1.5 h. The crude mixture was concentrated *in vacuo*. Purification by flash column chromatography (9:1 petrol/EtOAc) afforded the title compound **62** (1.49 g, 6.55 mmol, 17% over the two steps) as a colourless oil.

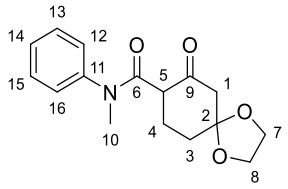
A mixture of keto/enol tautomers.

R_f: 0.57 (1:1 petrol/EtOAc); ν_{max}/cm^{-1} (neat): 3389, 2942, 1727 (C=O), 1650, 1598, 1372, 1222, 1181; δ_H (400 MHz, $CDCl_3$): 4.24-4.13 (2 H, m, H-9), 4.01-3.89 (4 H, m, H-7 and H-8), 3.33 (0.3 H, dd, *J* = 8.1, 5.6 Hz, H-5), 2.76 (0.3 H, d, *J* = 13.9 Hz, H-1), 2.62 (0.3 H, d, *J* = 13.9 Hz, H-1), 2.50 (1.3 H, s), 2.40-2.35 (1.4 H, m), 2.26-2.16 (0.4 H, m), 2.09-1.93 (0.7 H, m), 1.91-1.83 (0.3 H, m), 1.78-1.72 (1.6 H, m), 1.56 (0.4 H, s), 1.30-1.22 (3 H, m, H-10); HRMS [ES^+] found MNa^+, 251.0884. $C_{11}H_{16}NaO_5$ requires 251.0890.

Lab Book ref. RG148a

Data consistent with literature values.[52]

***N*-Methyl-7-oxo-*N*-phenyl-1,4-dioxaspiro[4.5]decane-8-carboxamide (66)**[94]

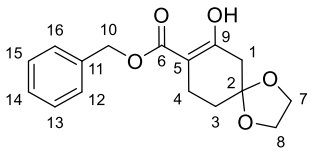


Ethyl 7-oxo-1,4-dioxaspiro[4.5]decane-8-carboxylate **62** (100 mg, 438 µmol), *N*-methylaniline (47 µL, 438 µmol), DMAP (5.3 mg, 10 mol%) and toluene (3 mL) were combined and stirred at 120 °C for 16 h. The crude mixture was concentrated *in vacuo*. Purification by flash column chromatography (1:1 petrol/EtOAc) afforded the title compound **66** (90 mg, 312 µmol, 71%) as a colourless solid.

R_f: 0.19 (1:1 petrol/EtOAc); m.p. 112–114 °C; ν_{max}/cm^{-1} (solid): 2959, 2887, 1716 (C=O), 1655 (C=O), 1595, 1496, 1387, 1308; δ_H (400 MHz, $CDCl_3$): 7.31-7.42 (3 H, m, H-13, H-14 and H-15), 7.20-7.15 (2 H, m, H-12 and H-16), 3.92-3.79 (4 H, m, H-7 and H-8), 3.23 (3 H, s, H-10), 3.16 (1 H, dd, *J* = 8.1, 5.6 Hz, H-5), 2.65 (1 H, d, *J* = 13.9 Hz, H-1), 2.26 (1 H, d, *J* = 13.9 Hz, H-1), 2.22-2.11 (1 H, m, CH_2), 2.05-2.95 (1 H, m, CH_2), 1.88-1.79 (1 H, m, CH_2), 1.71-1.61 (1 H, m, CH_2); δ_C (100 MHz, $CDCl_3$): 203.2 (C-9), 168.9 (C-6), 143.5 (C-11), 129.9 (C-13 and C-15), 128.2 (C-14), 127.2 (C-12 and C-16), 109.5 (C-2), 64.7 (C-7 and C-8), 53.3 (C-5), 51.2 (C-1), 37.5 (C-10), 32.8 (CH_2), 24.0 (CH_2); HRMS [ES^+] found MNa^+, 312.1202. $C_{16}H_{19}NNaO_4$ requires 312.1206.

Lab Book ref. RG149

Benzyl 7-oxo-1,4-dioxaspiro[4.5]decane-8-carboxylate (68)

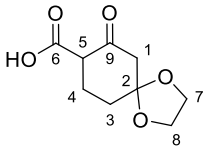


To a B14 necked round bottomed flask containing a stirred solution of ethyl 7-oxo-1,4-dioxaspiro[4.5]decane-8-carboxylate **62** (734 mg, 3.22 mmol), benzyl alcohol (1.20 mL, 11.59 mmol) and DMAP (39.3 mg, 10 mol%) in toluene (32 mL) was fitted a B24-B19 reduction adapter containing 4Å molecular sieves held within the adapter by cotton wool. The reaction flask and adapter were covered with aluminium foil and stirred at 110 °C for 16 h. The reaction was allowed to cool to room temperature and EtOAc (35 mL) was added. The organic mixture was washed with 2% aqueous HCl solution (3 × 30 mL), H_2O (3 × 30 mL), Brine (30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (19:1 Hexane/EtOAc) afforded the title compound **68** (377 mg, 1.30 mmol, 40%) as a colourless oil.

R_f: 0.15 (19:1 hexane/EtOAc); ν_{max}/cm^{-1} (neat): 2954, 1719 (C=O), 1655 (C=O), 1617 1399, 1297, 1262, 1216; δ_H (400 MHz, $CDCl_3$): 12.10 (1 H, s, O–H), 7.37-7.27 (5 H, m, H-12 to H-16), 5.19 (2 H, s, H-10), 4.00-3.92 (4 H, m, H-7 and H-8), 2.52 (2 H, s, H-1), 2.44 (2 H, t, *J* = 6.6 Hz, H-3 or H-4), 1.75 (2 H, t, *J* = 6.6 Hz, H-3 or H-4); δ_C (100 MHz, $CDCl_3$): 172.0 (C-6 or C-9), 169.1 (C-6 or C-9), 135.9 (C-10), 128.6 (Ar-CH), 128.3 (Ar-CH), 128.1 (Ar-CH), 107.2 (C-2 or C-5), 96.9 (C-2 or C-5), 66.0 (C-10), 64.7 (C-7 and C-8), 39.4 (C-1) 31.2 (C-3 or C-4), 20.4 (C-3 or C-4); HRMS [ES^+] found MH^+, 291.1226. $C_{16}H_{19}O_5$ requires 291.1227.

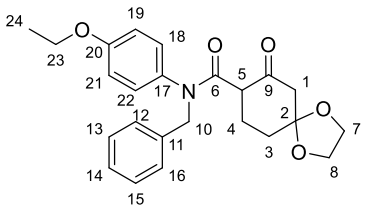
Lab Book Ref. RG287 and RG215

7-Oxo-1,4-dioxaspiro[4.5]decane-8-carboxylic acid (**67**)



To stirred solution of benzyl 7-oxo-1,4-dioxaspiro[4.5]decane-8-carboxylate **68** (340 mg, 1.17 mmol) in EtOAc (12.2 mL) was added palladium on carbon (68 mg, 10 wt. %). The vessel was placed under vacuum and back-filled with hydrogen three times before being and stirred at room temperature for 16 h under an atmosphere of hydrogen. The reaction mixture was filtered through celite. The celite was washed with EtOAc (3 × 7 mL) then the combined organics concentrated *in vacuo* to afford the title compound **67** (234 mg, 1.17 mmol, 100%) as a colourless oil. 7-Oxo-1,4-dioxaspiro[4.5]decane-8-carboxylic acid **67** was used in the next step without further purification. *N.B. This compound is unstable so must be reacted in the next step immediately after isolating.*

***N*-Benzyl-*N*-(4-ethoxyphenyl)-7-oxo-1,4-dioxaspiro[4.5]decane-8-carboxamide** (**56**)



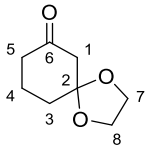
To a stirred solution of ethyl 7-oxo-1,4-dioxaspiro[4.5]decane-8-carboxylate **67** (577 mg, 1.41 mmol), *N*-benzyl-4-ethoxyaniline (141 mg, 705 µmol) and DIPEA (311 µL, 1.83 mmol) in EtOAc (9 mL) at room temperature was added T3P (897 mg, 1.41 mmol, 50% w/w solution in EtOAc). The reaction mixture was stirred at room temperature for 16 h. Saturated $NaHCO_3$ solution (10 mL) was added and the aqueous phase extracted with EtOAc (10 × 5 mL). The combined organic

extracts were washed with saturated $NaHCO_3$ solution (10 mL), brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (1:1 hexane/EtOAc) afforded the title compound **56** (220 mg, 538 µmol, 76%) as a colourless oil.

R_f: 0.26 (1:1 hexane/EtOAc); ν_{max}/cm^{-1} (neat): 2978, 1718 (C=O), 1657 (C=O), 1511, 1401, 1301, 1247; δ_H (400 MHz, $CDCl_3$): 7.28-7.16 (5 H, m, H-12 to H-16), 6.83 (2 H, d, *J* = 8.9 Hz, H-22 and H-18), 6.73 (2 H, d, *J* = 8.9 Hz, H-19 and H-21), 5.00 (1 H, d, *J* = 14.4 Hz, H-10), 4.73 (1 H, d, *J* = 14.4 Hz, H-10), 3.98-3.85 (6 H, m, H-7, H-8 and H-23), 3.21 (1 H, dd, *J* = 5.95, 4.12 Hz, H-5), 2.66 (1 H, d, *J* = 14.0 Hz, H-1), 2.31 (1 H, d, *J* = 14.0 Hz, H-1), 2.34-2.20 (1 H, m, H-3), 2.07-2.20 (1 H, m, H-4), 1.96-1.87 (1 H, m, H-3), 1.72 (1 H, td, *J* = 12.8, 4.12 Hz, H-4), 1.37 (3 H, t, *J* = 6.9 Hz, H-24); δ_C (100 MHz, $CDCl_3$): 203.3 (C-9), 169.4 (C-6), 158.7 (C-20), 137.4 (C-11), 134.3 (C-17), 129.5 (Ar-CH), 128.9 (Ar-CH), 128.4 (Ar-CH), 127.4 (Ar-CH), 115.1 (C-19 and C-21), 109.7 (C-2), 64.9 (C-7/8 or C-23), 63.7 (C-7/8 or C-23), 53.7 (C-5), 53.3 (C-10), 51.4 (C-1), 33.1 (C-3 or C-4), 24.1 (C-3 or C-4), 14.8 (C-24); HRMS [ES^+] found MNa^+, 432.1776. $C_{24}H_{27}NNaO_5$ requires 432.1781.

Lab Book Ref. RG220-F3 and RG288

1,4-Dioxaspiro[4.5]decan-7-one (69)

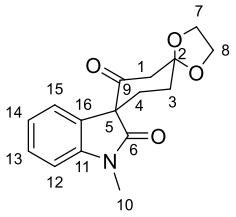


Isolated as a yellow oil. R_f: 0.46 (1:1 hexane/EtOAc); ν_{max}/cm^{-1}: 2957, 2884, 1716 (C=O), 1121, 1087; δ_H (400 MHz, $CDCl_3$): 3.96-3.66 (4 H, m, H-7 and H-8), 2.56 (2 H, s, H-1), 2.30 (2 H, t, *J* = 6.3 Hz, H-5), 1.91-1.81 (4 H, m, H-3 and H-4);

Lab book ref. RG245-decarbox

Data consistent with literature values.[95]

1’’-Methyl-1’’,2’’-dihydrodispiro[1,3-dioxolane-2,1’-cyclohexane-4’,3’’-indole]-2’’,3’-dione (**70**)

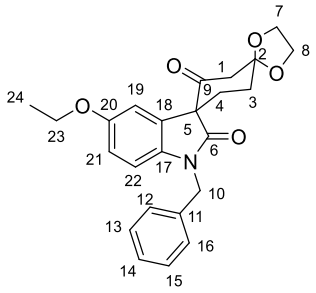


N-Methyl-7-oxo-*N*-phenyl-1,4-dioxaspiro[4.5]decane-8-carboxamide **66** (26.0 mg, 90 µmol) and copper(II) 2-ethylhexanoate (3.1 mg, 10 mol%) in toluene (2.5 mL) was stirred at 120 °C under an atmosphere of air for 15 h. Upon completion of the reaction, toluene was removed under reduced pressure and EtOAc (3 mL) was added. The solution was washed with 10% HCl solution (2 × 2 mL), 10% NH_4OH solution (2 × 2 mL), brine (2 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (4:1 petrol/EtOAc) afforded the title compound **70** (21.4 mg, 75 µmol, 83%) as a yellow oil.

R_f: 0.37 (1:1 petrol/EtOAc); ν_{max}/cm^{-1} (neat): 2928, 1701 (C=O), 1613 (C=O), 1496, 1472, 1350, 1135, 1100; δ_H (400 MHz, $CDCl_3$): 7.26 (1 H, t, *J* = 7.6 Hz, H-13), 7.19 (1H, t, *J* = 7.6 Hz, H-12), 7.06 (1 H, t, *J* = 7.6 Hz, H-14), 6.79 (1 H, d, *J* = 7.6 Hz, H-15), 4.10-3.91 (4 H, m, H-7 and H-8), 3.43 (1 H, d, *J* = 13.9 Hz, H-1), 3.12 (3 H, s, H-10), 2.74 (1 H, td, *J* = 13.1, 4.8 Hz, CH_2), 2.70 (1 H, d, *J* = 13.9 Hz, H-1), 2.24-2.15 (1 H, m, CH_2), 2.03 (1 H, m, CH_2), 1.92-1.84 (1 H, m, CH_2); δ_C (100 MHz, $CDCl_3$): 200.8 (C-9), 173.4 (C-6), 143.3 (C-11), 128.9 (Ar-CH), 128.8 (Ar-C), 125.0 (Ar-CH), 123.1 (Ar-CH), 109.9 (C-2), 108.5 (Ar-CH), 65.1 (CH_2), 64.8 (CH_2), 62.3 (C-5), 49.8 (CH_2), 31.6 (CH_2), 30.4 (CH_2), 22.6 (C-10); HRMS [ES^+] found MNa^+, 310.1045. $C_{16}H_{17}NNaO_4$ requires 310.1050.

Lab Book ref. RG151

1''-Benzyl-5''-ethoxy-2'*H*-dispiro[1,3-dioxolane-2,4'-cyclohexane-1',3''-indole]-2',2''(1''*H*)-dione (**55**)



In Ethylene Carbonate:

N-Benzyl-*N*-(4-ethoxyphenyl)-7-oxo-1,4-dioxaspiro[4.5]decane-8-carboxamide **56** (55.0 mg, 134 µmol) and $Cu(OAc)_2 \cdot H_2O$ (26.8 mg, 134 µmol) in ethylene carbonate (3.3 mL) was stirred at 165 °C under an atmosphere of air for 1 h. The reaction mixture was removed from heat and allowed to cool for 10 min then H_2O (8 mL) and EtOAc (8 mL) were added and the reaction mixture allowed to cool to room temperature. The reaction mixture was transferred to a separating funnel to which EtOAc (15 mL) was added and the organic phase washed with H_2O (5 × 10 mL), 10% aqueous NH_4OH solution (3 × 5 mL), brine (5 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (7:3 hexane/EtOAc) afforded the title compound **55** (34.0 mg, 83.5 µmol, 62%) as a yellow oil.

Lab book ref. RG289a

In Mesitylene:

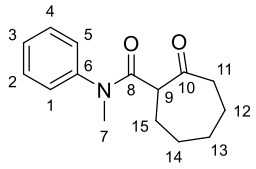
N-Benzyl-*N*-(4-ethoxyphenyl)-7-oxo-1,4-dioxaspiro[4.5]decane-8-carboxamide **56** (80.0 mg, 196 µmol) and $Cu(OAc)_2 \cdot H_2O$ (3.9 mg, 10 mol%) in mesitylene (4 mL) was stirred at 165 °C with compressed air bubbled through for 0.5 h. Upon completion of the reaction, mesitylene was removed under reduced pressure and EtOAc (5 mL) was added. The solution was washed with 10% HCl solution (2 × 5 mL), 10% NH_4OH solution (2 × 5 mL), brine (5 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (7:3 petrol/EtOAc) afforded the title compound **55** (46.0 mg, 113 µmol, 58%) as a yellow oil.

R_f: 0.21 (7:3 hexane/EtOAc); ν_{max}/cm^{-1} (neat): 2978, 1718 (C=O), 1698 (C=O), 1496, 1455, 1352, 1300; δ_H (400 MHz, $CDCl_3$): 7.25-7.12 (5 H, m, H-12 to H16), 6.77 (1 H, d, *J* = 2.3 Hz, H-19), 6.63 (1 H, dd, *J* = 8.4, 2.3 Hz, H-21), 6.51 (1 H, d, *J* = 8.4 Hz, H-22), 4.79 (2 H, s, H-10), 4.01-3.83 (6 H, m, H-7, H-8 and H-23), 3.46 (1 H, d, *J* = 13.7 Hz, H-1), 2.77 (1 H, td, *J* = 12.9, 4.9 Hz, H-3 or H-4), 2.72 (1 H, d, *J* = 13.7 Hz, H-1), 2.29-2.16 (1 H, m, H-3 or H-4), 2.09 (1 H, dt, *J* = 14.1, 4.6 Hz, H-3 or H-4), 1.93-1.86 (1 H, m, H-3 or H-4), 1.30 (3 H, t, *J* = 6.9 Hz, H-24); δ_C (100 MHz,

$CDCl_3$): 200.8 (C-9), 173.2 (C-6), 155.5 (C-20), 135.54 (C-11, C-17 or C-18), 135.47 (C-11, C-17 or C-18), 129.9 (C-17 or C-18), 128.8 (Ar-CH), 127.6 (Ar-CH), 127.0 (Ar-CH), 114.1 (C-22), 113.9 (C-21), 112.6 (C-19), 109.8 (C-2), 65.0 (C-7, C-8 or C-23), 64.7 (C-7, C-8 or C-23), 64.0 (C-7, C-8 or C-23), 62.6 (C-5), 49.8 (C-1), 43.9 (C-10), 31.8 (C-3 or C-4), 30.4 (C-3 or C-4), 14.8 (C-24); HRMS [ES^+] found MNa^+, 430.1620. $C_{24}H_{25}NNaO_5$ requires 430.1625.

Lab book ref. RG246, RG231 and RG222.

***N*-Methyl-2-oxo-*N*-phenylcycloheptanecarboxamide (73)**

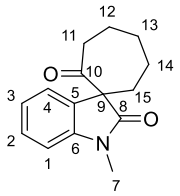


A stirred solution of ethyl 2-oxocycloheptanecarboxylate **72** (170 mg, 1.0 mmol), *N*-methylaniline (108 µL, 1.0 mmol) and DMAP (12.2 mg, 10 mol%) in toluene (7 mL) was heated at 120 °C for 16 h. The reaction mixture was allowed to cool to room temperature then EtOAc (18 mL) was added. The mixture was washed with 10% aqueous HCl solution (15 mL), brine (15 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography afforded the title compound **73** (108 mg, 440 µmol, 44%) as an orange oil.

R_f: 0.27 (13:7 petrol/EtOAc); ν_{max}/cm^{-1} (neat): 2930, 1705 (C=O), 1649 (C=O), 1595, 1496, 1381; δ_H (400 MHz, $CDCl_3$): 7.42 (2 H, t, *J* = 7.3 Hz, H-2 and H-4), 7.36 (1 H, t, *J* = 7.3 Hz, H-3), 7.21 (2 H, d, *J* = 7.3 Hz, H-1 and H-5), 3.47 (1 H, dd, *J* = 10.7, 3.8 Hz, H-9), 3.27 (3 H, s, H-7), 2.61-2.53 (1 H, m, CH_2), 2.15-2.06 (1 H, m, CH_2), 2.02-1.73 (5 H, m, CH_2), 1.37-1.10 (3 H, m, CH_2); δ_C (100 MHz, $CDCl_3$): 210.7 (C-10), 170.4 (C-8), 143.4 (C-6), 129.7 (C-2 and C-4), 128.0 (C-3), 127.9 (C-5), 56.4 (C-9), 43.1 (CH_2), 37.4 (C-7), 29.4 (CH_2), 28.4 (CH_2), 28.5 (CH_2), 24.4 (CH_2); HRMS [ES^+] found MNa^+, 268.1308. $C_{15}H_{19}NNaO_2$ requires 268.1308.

Lab book ref. RG252

1'-Methylspiro[cycloheptane-1,3'-indoline]-2,2'-dione (**74**)

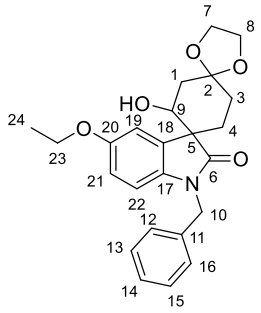


N-Methyl-2-oxo-*N*-phenylcycloheptanecarboxamide **73** (77.0 mg, 314 µmol) and $Cu(OAc)_2 \cdot H_2O$ (6.3 mg, 100 mol%) in ethylene carbonate (6.5 mL) was stirred at 100 °C under an atmosphere of air for 24 h. The reaction mixture was removed from heat and allowed to cool for 10 min then H_2O (8 mL) and EtOAc (8 mL) were added and the reaction mixture allowed to cool to room temperature. The reaction mixture was transferred to a separating funnel to which EtOAc (15 mL) was added and the organic phase washed with H_2O (5 × 10 mL), 10% aqueous NH_4OH solution (3 × 5 mL), brine (5 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (3:1 hexane/EtOAc) afforded the title compound **74** (62 mg, 255 µmol, 81%) as a colourless solid.

R_f: 0.22 (3:1 petrol/EtOAc); m.p. 104–107 °C; ν_{max}/cm^{-1} (solid): 2932, 1719 (C=O), 1693 (C=O), 1608, 1493, 1470, 1346; δ_H (400 MHz, $CDCl_3$): 7.29 (1 H, t, *J* = 7.6 Hz, H-2), 7.25 (1 H, d, *J* = 7.6 Hz, H-4), 7.06 (1 H, t, *J* = 7.6 Hz, H-3), 6.83 (1 H, d, *J* = 7.6 Hz, H-1), 3.16 (3 H, s, H-7), 3.08-3.01 (1 H, m, CH_2), 2.75-2.67 (1 H, m, CH_2), 2.35-2.26 (1 H, m, CH_2), 2.16-2.07 (1 H, m, CH_2), 2.05-1.96 (1 H, m, CH_2), 1.93-1.72 (5 H, m, CH_2); δ_C (100 MHz, $CDCl_3$): 207.4 (C-10), 175.1 (C-8), 143.3 (C-6), 130.6 (C-5), 128.6 (C-2), 123.4 (C-4), 122.6 (C-3), 108.4 (C-1), 65.4 (C-9), 42.2 (CH_2), 34.7 (CH_2), 30.7 (CH_2), 26.6 (CH_2), 26.3 (C-7), 25.3 (CH_2); HRMS [ES^+] found MNa^+, 266.1147. $C_{15}H_{17}NNaO_2$ requires 266.1151.

Lab book ref. RG254a

1''-Benzyl-5''-ethoxy-3'-hydroxydispiro[1,3-dioxolane-2,1'-cyclohexane-4',3''-indol]-2''(1''H)-one (**75**)

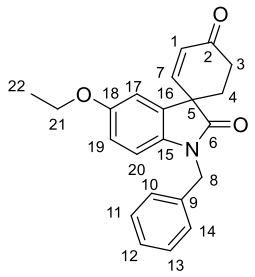


To a stirred solution of 1’’-benzyl-5’’-ethoxy-1’’,2’’-dihydrodispiro[1,3-dioxolane-2,1’-cyclohexane-4’,3’’-indole]-2’’,3’-dione **55** (355 mg, 872 µmol) in MeOH (10.5 mL) at 0 °C was added $NaBH_4$ (49.5 mg, 1.31 mmol) and stirred for 2 h. The reaction mixture was quenched with NH_4Cl (10 mL) then the aqueous phase was extracted with EtOAc (2 × 10 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (1:1 hexane/EtOAc) afforded a single diastereoisomer of the title compound **75** (284 mg, 694 µmol, 80%) as a colourless powder.

Rf: 0.23 (1:1 hexane/EtOAc); m.p. 174–175 °C; ν_{max}/cm^{-1} (solid): 3452 (O–H), 2933, 1698 (C=O), 1597, 1496, 1455, 1442, 1351; δ_H (400 MHz, $CDCl_3$): 7.31-7.19 (5 H, m, H-12 to H-16), 7.16 (1 H, d, *J* = 2.5 Hz, H-19), 6.68 (1 H, dd, *J* = 8.5, 2.5 Hz, H-21), 6.57 (1 H, d, *J* = 8.5 Hz, H-22), 4.98 (1 H, d, *J* = 16.0 Hz, H-10), 4.81 (1 H, d, *J* = 16.0 Hz, H-10), 4.20-3.91 (7 H, m, H-7, H-8, H-23 and H-9), 2.60-2.46 (1 H, m, H-1, H-3 or H-4), 2.25-2.13 (1 H, m, H-1, H-3 or H-4), 2.09-1.96 (3 H, m, H-1, H-3 or H-4), 1.94-1.86 (1 H, m, H-1, H-3 or H-4), 1.37 (3 H, t, *J* = 7.0 Hz, H-24); δ_C (100 MHz, $CDCl_3$): 178.3 (C-6), 154.9 (C-20), 136.3 (C-11, C-17 or C-18), 136.0 (C-11, C-17 or C-18), 128.8 (Ar-CH), 127.5 (Ar-CH), 127.1 (C-17 or C-18), 127.0 (Ar-CH), 114.5 (C-19), 112.7 (C-21), 109.3 (C-22), 108.9 (C-2), 73.4 (C-9), 71.3 (C-5), 64.6 (C-7, C-8 or C-23), 64.5 (C-7, C-8 or C-23), 64.1 (C-7, C-8 or C-23), 43.7 (C-10), 38.1 (C-1, C-3 or C-4), 30.1 (C-1, C-3 or C-4), 28.4 (C-1, C-3 or C-4), 15.0 (C-24); HRMS [ES^+] found MH^+, 410.1957. $C_{24}H_{28}NO_5$ requires 410.1962.

Lab book ref. RG248

1'-Benzyl-5'-ethoxyspiro[cyclohex[2]ene-1,3'-indoline]-2',4-dione (**76**)

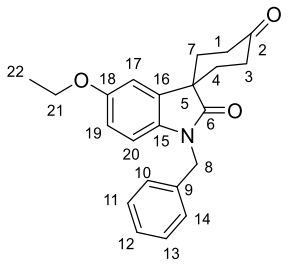


To 1''-benzyl-5''-ethoxy-3'-hydroxydispiro[1,3-dioxolane-2,1'-cyclohexane-4',3''-indol]-2''(1''*H*)-one **75** (261 mg, 638 µmol) was added THF (3 mL) and 10% aqueous HCl solution (1.2 mL) and the mixture stirred at 70 °C for 90 min. The reaction mixture was allowed to cool to room temperature then quenched with sat. $NaHCO_3$ (6mL). The aqueous phase was extracted with EtOAc (2 × 5 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (7:3 hexane/EtOAc) afforded the title compound **76** (188 mg, 542 µmol, 85%) as a colourless oil.

Rf: 0.24 (7:3 hexane/EtOAc); ν_{max}/cm^{-1} (neat): 2979, 1705 (C=O), 1675 (C=O), 1560, 1495, 1453, 1384, 1341; δ_H (400 MHz, $CDCl_3$): 7.34-7.23 (5 H, m, H-10 to H-14), 6.80 (1 H, d, *J* = 2.4 Hz, H-17), 6.73 (1 H, dd, *J* = 8.4, 2.4 Hz, H-19), 6.67 (1 H, d, *J* = 8.4 Hz, H-20), 6.57 (1 H, d, *J* = 10.0 Hz, H-7), 6.27 (1 H, d, *J* = 10.0 Hz, H-1), 4.95 (1 H, d, *J* = 15.7 Hz, H-8), 4.85 (1 H, d, *J* = 15.7 Hz, H-8), 3.94 (2 H, q, *J* = 7.0 Hz, H-21), 3.16 (1 H, ddd, *J* = 17.2, 10.0, 5.3, H-3), 2.63 (1 H, ddd, *J* = 17.2, 6.9, 5.0 Hz, H-3), 2.51-2.42 (1 H, m, H-4), 2.31 (1 H, ddd, *J* = 13.8, 10.0, 5.0 Hz, H-4), 1.36 (3 H, t, *J* = 7.0 Hz, H-22); δ_C (100 MHz, $CDCl_3$): 198.0 (C-2), 176.0 (C-6), 155.6 (C-18), 146.2 (C-7), 135.5 (C-9, C-15 or C-16), 135.4 (C-9, C-15 or C-16), 132.5 (C-15 or C-16), 131.6 (C-1), 128.9 (Ar-CH), 127.8 (Ar-CH), 127.2 (Ar-CH), 113.8 (C-19), 111.8 (C-17), 110.1 (C-20), 64.1 (C-21), 50.1 (C-5), 44.1 (C-8), 33.2 (C-3 or C-4), 32.3 (C-3 or C-4), 14.9 (C-22); HRMS [ES^+] found MH^+, 348.1588. $C_{22}H_{22}NO_3$ requires 348.1594.

Lab book ref. RG249

1'-Benzyl-5'-ethoxyspiro[cyclohexane-1,3'-indoline]-2',4-dione (**50**)



To stirred solution of 1'-benzyl-5'-ethoxyspiro[cyclohex[2]ene-1,3'-indoline]-2',4-dione **76** (166 mg, 478 µmol) in EtOAc (6.5 mL) was added palladium on carbon (21.7 mg, 10 wt. %). The vessel was placed under vacuum and back-filled with hydrogen three times before being stirred at room temperature for 16 h under an atmosphere of hydrogen. The reaction mixture was filtered through celite. The celite was washed with EtOAc (3 × 5 mL) then the combined organics concentrated *in vacuo*. Purification by flash column chromatography (7:3 hexane/EtOAc) afforded the title compound **50** (162 mg, 464 µmol, 97%) as a colourless powder.

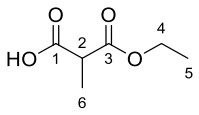
Rf: 0.23 (7:3 hexane/EtOAc); m.p. 140–143 °C (Lit.[50] 125–128 °C); ν_{max}/cm^{-1}: 3033, 2977, 2928, 1710 (C=O), 1692 (C=O), 1600, 1495, 1477, 1449, 1369, 1345; δ_H (400 MHz, $CDCl_3$): 7.32-7.21 (5 H, m, H-10 to H-14), 6.84 (1 H, d, *J* = 2.5 Hz, H-17), 6.68 (1 H, d, *J* = 8.6 Hz, H-19), 6.62 (1 H, d, *J* = 8.6 Hz, H-20), 4.90 (2 H, s, H-8), 3.94 (2 H, q, *J* = 6.9 Hz, H-21), 3.25-3.14 (2 H, m, H-4 or H-7), 2.58-2.44 (2 H, m, H-4 or H-7), 2.25-2.09 (4 H, m, H-1 and H-3), 1.36 (3 H, t, *J* = 6.9 Hz, H-22); δ_C (100 MHz, $CDCl_3$): 210.6 (C-2), 179.1 (C-6), 155.3 (C-18), 135.8 (C-9, C-15 or C-16), 135.1 (C-9, C-15 or C-16), 134.4 (C-9, C-15 or C-16), 128.7 (Ar-CH), 127.6 (Ar-CH), 127.0 (Ar-CH), 112.5 (C-19), 111.1 (C-17), 109.6 (C-20), 64.0 (C-21), 45.8 (C-5), 43.5 (C-8), 36.8 (C-4 and C-7), 33.7 (C-C-1 and C-3), 14.8 (C-22); HRMS [ES^+] found MH^+, 350.1741. $C_{22}H_{24}NO_3$ requires 350.1751.

Lab book ref. RG250

Data consistent with literature values.[50]

5.4 Copper-catalysed C–*N*/C–C approach to oxindole synthesis

3-Ethoxy-2-methyl-3-oxopropanoic acid (86)

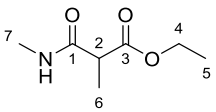


To a stirred solution of diethylmethylmalonate **85** (10.2 mL, 60.0 mmol) in EtOH (30 mL) at 0 °C was added KOH (3.36 g, 60.0 mmol) in EtOH (20 mL). The solution was warmed to room temperature, H_2O (100 ml) added, and the reaction mixture stirred at room temperature for 16 h. The ethanol was removed in *vacuo* and the residue washed with ether (3 × 40 mL). The ethereal layer was discarded and the aqueous phase acidified with 10% aqueous HCl (30 mL), extracted with EtOAc (3 × 20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the title compound **86** (6.79 g, 46.5 mmol, 77%) as a colourless oil.

R_f: 0.51 (1:1 petrol/EtOAc); ν_{max}/cm^{-1} (neat): 3256 (O–H), 1718 (C=O), 1459, 1380, 1181; δ_H (400 MHz, $CDCl_3$): 9.26 (1 H, br s, –O*H*), 4.26-4.17 (2 H, m, H-4), 3.47 (1 H, q *J* = 7.3 Hz, H-2), 1.45 (3 H, d, *J* = 7.3 Hz, H-6), 1.28 (3 H, t, *J* = 7.1 Hz, H-5); δ_C (100 MHz, $CDCl_3$): 175.5 (C-1), 169.9 (C-3), 61.8 (C-4), 45.9 (C-2), 14.0 (C-5), 13.5 (C-6); HRMS [ES^+] found MNa^+, 169.0464. $C_6H_{10}NaO_4$ requires 169.0471.

Lab book ref. RG120

Ethyl 2-methyl-3-(methylamino)-3-oxopropanoate (77)



To a stirred solution of 3-ethoxy-3-oxopropanoic acid **86** (5.94 g, 40.7 mmol), in DCM (120 mL) was added DMF (2 drops) and oxalyl chloride (4.37 mL, 50.8 mmol) and the reaction held at room temperature for 16 h. The solvent was removed under reduced pressure, THF added (40 mL), then the solution added to 2M NH_2Me in THF (81.3 mL, 162 mmol) at 0 °C *via* cannula and stirring continued for 3 h. Triethylamine (14.1 mL, 163 mmol) was added and the solution allowed to warm to room temperature and stirred overnight. The reaction mixture was quenched by the addition of H_2O (80 mL), extracted with EtOAc (3 × 60 mL), and the combined organics washed with saturated aqueous $NaHCO_3$ (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo.*

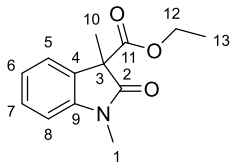
Purification by flash column chromatography (EtOAc) afforded the title compound **77** (3.82 g, 24.0 mmol, 59%) as a colourless powder.

R_f: 0.40 (EtOAc); m.p. 69–71 °C; ν_{max}/cm^{-1} (solid): 3289 (N–H), 2989, 1731 (C=O), 1642 (C=O), 1571, 1369, 1325; δ_H (400 MHz, $CDCl_3$): 6.62 (1 H, br s, N*H*), 4.17 (2 H, q, *J* = 7.1 Hz, H-4), 3.27 (1 H, q, *J* = 7.3 Hz, H-2), 2.81 (3 H, d, *J* = 4.8 Hz, H-7), 1.42 (3 H, d, *J* = 7.3 Hz, H-6), 1.26 (3 H, t, *J* = 7.1 Hz, H-5); δ_C (100 MHz, $CDCl_3$): 172.6 (C-3), 169.7 (C-1), 61.4 (H-4), 46.7 (C-2), 26.4 (C-7), 15.2 (C-6), 14.0 (C-5); HRMS [ES^+] found MH^+, 160.0968. $C_7H_{14}NO_3$ requires 160.0968.

Lab book ref. RG121

Ethyl 1,3-dimethyl-2-oxoindoline-3-carboxylate (41)

*From Ethyl 2-methyl-3-(methylamino)-3-oxopropanoate (**77**)*



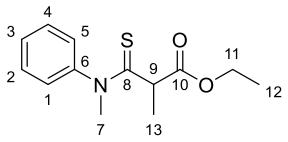
To ethyl 2-methyl-3-(methylamino)-3-oxopropanoate **77** (191 mg, 1.20 mmol), and CuI (95.2 mg, 50 mol%) in toluene (4.5 mL) was added *N*,*N*-dimethylethylenediamine (222 µL, 200 mol%) followed by iodobenzene **88** (111 µL, 1.00 mmol) at room temperature. The stirred solution was heated to 100 °C then KHMDS (0.7 M in toluene, 626 µL, 2.2 mmol) was added in one portion. The solution was heated to 120 °C and stirred overnight. The reaction mixture unintentionally ran to dryness. The crude reaction mixture was partitioned between EtOAc (10 mL) and water (10 mL), the aqueous discarded, the organic layer washed with brine (8 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by preparative TLC (1:1 petrol/EtOAc) afforded the title compound **41** (13.0 mg, 60 µmol, 6%) as a yellow oil.

Lab book ref. RG134(b)

Data as above.

5.5 Application to the synthesis of thio-oxindoles

Ethyl 2-methyl-3-[methyl(phenyl)amino]-3-thioxopropanoate (**95**)

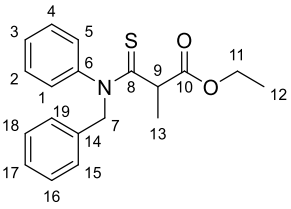


Ethyl 2-methyl-3-[methyl(phenyl)amino]-3-oxopropanoate **40** (4.00 g, 17.0 mmol) and Lawessons reagent (4.13 g, 10.2 mmol) were dissolved in toluene (200 mL) and stirred at 120 °C for 24 h. The solvent was removed under reduced pressure to give a yellow oil. Et_2O (150 mL) was added and the precipitate filtered. The filtrate was concentrated *in vacuo.* Purification by flash column chromatography (9:1 petrol/EtOAc) afforded the title compound **95** (3.81 g, 15.2 mmol, 89%) as an orange powder.

R_f: 0.78 (1:1 petrol/EtOAc); m.p. 34–36 °C; ν_{max}/cm^{-1} (solid): 2936, 2890, 1715 (C=O), 1470, 1362, 1095 (C=S); δ_H (400 MHz, d-6 DMSO, 75 °C): 7.55 (2 H, t, *J* = 7.5 Hz, H-2 and H-4), 7.47 (1 H, t, *J* = 7.5 Hz, H-3), 7.56 (2 H, d, *J* = 7.5 Hz, H-1 and H-5), 4.02 (2 H, q, *J* = 7.1 Hz, H-11), 3.72-3.63 (4 H, m, H-7 and H-9), 1.27 (3 H, d, *J* = 6.6 Hz, H-13), 1.15 (3 H, t, *J* = 7.0 Hz, H-12); δ_C (100 MHz, d-6 DMSO, 75 °C): 201.5 (C-8), 169.0 (C-10), 144.6 (C-6), 129.6 (C-2 and C-4), 128.3 (C-3), 125.3 (C-1 and C-5), 60.0 (C-11), 49.2 (C-9), 44.7 (C-7), 17.2 (C-13), 13.3 (C-12); HRMS [ES^+] found MNa^+, 274.0871. $C_{13}H_{17}NNaO_2S$ requires 274.0872.

Lab book ref. RG066 and RG106

Ethyl 2-methyl-3-[benzyl(phenyl)amino]-3-thioxopropanoate (**96**)

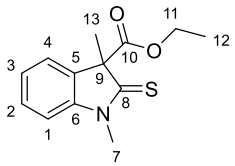


Ethyl 2-methyl-3-[benzyl(phenyl)amino]-3-oxopropanoate **94** (1.00 g, 3.22 mmol) and Lawessons reagent (781 mg, 1.93 mmol) were dissolved in toluene (40 mL) and stirred at 120 °C for 24 h. The solvent was removed under reduced pressure to give a yellow oil. Et_2O (100 mL) was added and the precipitate filtered. The filtrate was concentrated *in vacuo.* Purification by flash column chromatography (9:1→1:1 petrol/EtOAc) afforded the title compound **96** (470 g, 1.45 mmol, 45%) as a yellow oil.

R_f: 0.20 (9:1 petrol/EtOAc); ν_{max}/cm^{-1} (neat): 2981, 1742 (C=O), 1492, 1445, 1416, 1074 (C=S); δ_H (400 MHz, $CDCl_3$): 7.38–7.32 (3 H, m, ArH), 7.32–7.26 (5 H, m, ArH), 7.07 (1 H, br s, ArH), 7.00 (1 H, br s, ArH), 5.87 (1 H, d, *J* = 14.2 Hz, H-7), 5.33 (1 H, d, *J* = 14.2 Hz, H-7), 4.23–4.08 (2 H, m, H-11), 3.71 (1 H, q, *J* = 6.8 Hz, H-9), 1.42 (3 H, d, *J* = 6.8 Hz, H-13), 1.27 (3 H, t, J = 7.1 Hz, H-12); δ_C (100 MHz, $CDCl_3$): 204.0 (C-8), 170.3 (C-10), 143.4 (C-6), 135.3 (C-14), 129.8 (C-2 and C-4), 128.9 (Ar-CH), 128.6 (Ar-CH), 128.4 (Ar-CH), 128.1 (Ar-CH), 127.8 (Ar-CH), 61.3 (C-11), 59.5 (C-7) 50.6 (C-9), 17.8 (C-13), 14.0 (C-12); HRMS [ES^+] found MH^+, 328.1368. $C_{19}H_{22}NO_2S$ requires 328.1366.

Lab book ref. RG162

Ethyl 1,3-dimethyl-2-thioxoindoline-3-carboxylate (**97**)

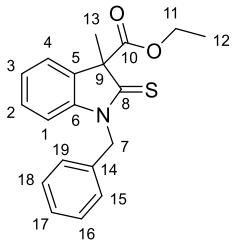


Ethyl 2-methyl-3-[methyl(phenyl)amino]-3-thioxopropanoate **95** (3.50 g, 13.9 mmol), copper(II) 2-ethylhexanoate (486 mg, 10 mol%) and DIPEA (5.82 mL, 33.4 mmol) in toluene (360 mL) were heated at 120 °C for 48 h, under an atmosphere of air with further copper(II) 2-ethylhexanoate (486 mg, 10 mol%) added after 24 h. The solvent was removed under reduced pressure and EtOAc (100 mL) was added. The solution was washed with 10% HCl solution (60 mL), 10% NH_4OH solution (60 mL), brine (60 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (17:3 petrol/EtOAc) afforded the title compound **97** (2.69 g, 10.8 mmol, 78%) as an off-white powder.

R_f: 0.23 (5:2 petrol/EtOAc); m.p. 66–67 °C; ν_{max}/cm^{-1} (solid): 2989, 1736 (C=O), 1466, 1433, 1369, 1101 (C=S); δ_H (400 MHz, $CDCl_3$): 7.38 (1 H, td, *J* = 7.6, 1.2 Hz, H-2), 7.28 (1 H, dd, *J* = 7.6, 1.2 Hz, H-1), 7.18 (1 H, td, *J* = 7.6, 1.2 Hz, H-3), 7.04 (1 H, d, *J* = 7.6 Hz, H-4), 4.14 (1 H, dq, *J* = 10.8, 7.1 Hz, H-11), 4.03 (1 H, td, *J* = 10.8, 7.1 Hz, H-11), 3.66 (3 H, s, H-7), 1.74 (3 H, s, H-13), 1.10 (3 H, t, *J* = 7.1 Hz, H-12); δ_C (100 MHz, $CDCl_3$): 203.9 (C-8), 169.2 (C-10), 145.1 (C-6), 134.7 (C-5), 128.9 (C-2), 124.5 (C-3), 122.9 (C-1), 109.7 (C-4), 65.2 (C-9), 61.9 (C-11), 31.5 (C-7), 23.9 (C-13), 13.8 (C-12); HRMS [ES^+] found MNa^+, 272.0905. $C_{13}H_{15}NNaO_2S$ requires 272.0896.

Lab book ref. RG108 and RG074

Ethyl 1-benzyl-3-methyl-2-thioxoindoline-3-carboxylate (**98**)



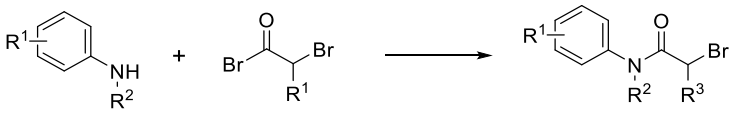
Ethyl 2-methyl-3-[benzyl(phenyl)amino]-3-thioxopropanoate **96** (107 mg, 326 µmol), copper(II) 2-ethylhexanoate (11.4 mg, 10 mol%) and DIPEA (136 µL, 782 µmol) in toluene (8 mL) were heated at 120 °C under an atmosphere of air for 48 h. The solvent was removed under reduced pressure and EtOAc (15 mL) was added. The solution was washed with 10% HCl solution (2 × 15 mL), 10% NH_4OH solution (2 × 15 mL), brine (15 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (9:1 petrol/EtOAc) afforded the title compound **98** (93 mg, 286 µmol, 94%) as a colourless powder.

R_f: 0.21 (9:1 petrol/EtOAc); m.p. 76–78 °C; ν_{max}/cm^{-1} (solid); 2985, 1738 (C=O), 1465, 1386, 1214, 1108 (C=S); δ_H (400 MHz, $CDCl_3$): 7.35-7.22 (7 H, m, ArH), 7.14 (1 H, t, *J* = 7.5 Hz, ArH), 6.87 (1 H, d, *J* = 7.5 Hz, ArH), 5.79 (1 H, d, *J* = 15.5 Hz, H-7), 5.17 (1 H, d, *J* = 15.5 Hz, H-7), 4.24-4.16 (1 H, m, H-11), 4.06-3.98 (1 H, m, H-11), 1.81 (3 H, s, H-13), 1.13 (3 H, t, *J* = 7.1 Hz, H-12); δ_C (100 MHz, $CDCl_3$): 204.7 (C-8), 169.2 (C-10), 144.3 (C-6), 134.6 (C-5), 134.3 (C-14), 128.9 (Ar-CH), 128.7 (Ar-CH), 127.7 (Ar-CH), 126.9 (Ar-CH), 124.4 (Ar-CH), 122.9 (Ar-CH), 110.6 (C-4), 65.3 (C-9), 62.0 (C-11), 47.8 (C-7), 23.8 (C-13), 13.7 (C-12); HRMS [ES^+] found MH^+, 326.1216. $C_{19}H_{20}NO_2S$ requires 326.1209.

Lab book ref. RG163c

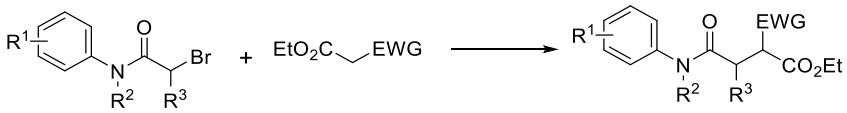
5.6 General Procedures

General Procedure A



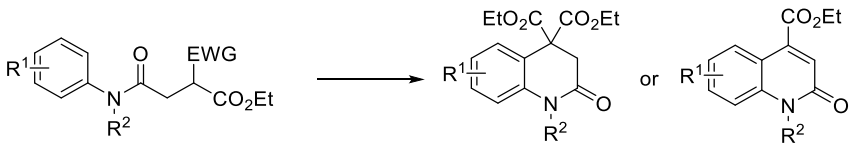
To a stirred solution of the aniline (1 eq.) and triethylamine (1 eq.) in DCM (~0.86 mM) at 0 °C was added acid bromide (1 eq.) in DCM (~0.60 M) *via* cannula. The solution was allowed to warm to room temperature and stirred for 20 h. DCM was added and the organics washed with 10% HCl solution, brine, dried ($MgSO_4$) and concentrated *in vacuo* to afford the title compounds.

General Procedure B[44a]



To a stirred solution of activated methylene compound (1–2 eq.) in THF (~0.26 M) was added KO*t*-Bu (1–2 eq.) or NaH (60% dispersion in mineral oil, 1.1–2 eq.) and held for 5 min. The anilide (1–2 eq.) in THF (~0.94 M) was added *via* cannula and stirring continued for 2 h at room temperature. The reaction mixture was quenched (sat. NH_4Cl solution), the aqueous extracted (EtOAc), and the combined organics washed (brine), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography afforded the title compounds.

General Procedure C

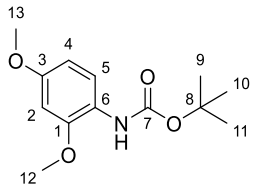


To a stirred solution of the anilide and copper(II) 2-ethylhexanoate (10 mol% to 200 mol%) in toluene or mesitylene (~0.1 M) was added DIPEA (2.4 eq). The reaction was stirred at reflux under an atmosphere of air. Upon completion of the reaction, the solvent was removed under reduced pressure and EtOAc was added. The solution was washed with 10% HCl solution, 10% aqueous NH_4OH solution, brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography afforded the title compounds.

5.7 Application of copper conditions to the synthesis of 3,4-dihydroquinolin-2(1*H*)-ones

5.7.1 Anilines

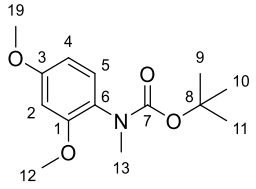
tert-Butyl 2,4-dimethoxyphenylcarbamate[96]



To a stirred solution of Boc_2O (288 mg, 1.31 mmol) and A-21 amberlyst resin (20.0 mg) in EtOH (2 mL) was added 2,4-dimethoxyaniline (200 mg, 1.31 mmol) and the reaction mixture held at room temperature for 1.5 h. The solution was filtered and concentrated *in vacuo*. Partial purification by flash column chromatography (9:1 petrol/EtOAc) afforded title compound (326 mg) as a colourless oil which was used in the next step without further purification.

Lab book ref. RG087

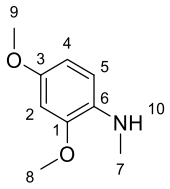
tert-Butyl 2,4-dimethoxyphenyl(methyl)carbamate[97]



To a stirred solution of NaH (60% dispersion in mineral oil, 442 mg, 11.1 mmol) in DMF (25 ml) at 0 °C was added dropwise *tert*-butyl 2,4-dimethoxyphenylcarbamate (2.00 g, 8.51 mmol) in DMF (7 ml) and the reaction mixture stirred for 10 min at 0 °C then at room temperature for 20 min. The solution was cooled to 0 °C and MeI (1.06 ml, 17.0 mmol) was added and the solution stirred at 0 °C for 1 h. The reaction was quenched by the addition of H_2O (20 mL) and the aqueous phase extracted with Et_2O (3 × 30 mL). The ethereal extracts were combined and washed with brine (40 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield the title compound (2.19 g) as a colourless oil which was used in the next step without further purification.

Lab book ref. RG089

2,4-Dimethoxy-*N*-methylaniline (133e)[98]



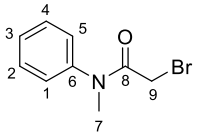
To a stirred solution of *tert*-butyl 2,4-dimethoxyphenyl(methyl)carbamate (1.50 g, 6.02 mmol) in DCM (100 mL) at 0 °C was added TFA (10 mL) and the reaction mixture stirred for 1 h. The colour of the solution changed from pale green to yellow upon addition of TFA. The solution was allowed to warm to room temperature then stirred for 2 h. The reaction mixture was concentrated in *vacuo* and the residue taken up in DCM (100 mL) and washed with saturated K_2CO_3 solution (80 mL) and brine (80 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (17:3 petrol/EtOAc) afforded the title compound **133e** (704 mg, 4.22 mmol, 70%) as a dark purple oil.

R_f: 0.35 (4:1 petrol/EtOAc); ν_{max}/cm^{-1} (neat): 3418 (N–H); δ_H (400 MHz, $CDCl_3$): 6.54-6.49 (1 H, m, ArH), 6.47-6.42 (2 H, m, ArH), 3.83 (3 H, s, H-8 or H-9), 3.77 (3 H, s, H-8 or H-9), 2.84 (3 H, s, H-7); δ_C (100 MHz, $CDCl_3$): 151.8 (C-Ar), 147.9 (C-Ar), 133.8 (C-Ar), 109.5 (CH-Ar), 103.6 (CH-Ar), 99.0 (CH-Ar), 55.8 (C-8 or C-9), 55.4 (C-8 or C-9), 31.0 (C-7); HRMS [ES^+] found MH^+, 168.1013. $C_9H_{14}NO_2$ requires 168.1019.

Lab book ref. RG090

5.7.2 Anilides

2-Bromo-*N*-methyl-*N*-phenylacetamide (131a)



N-Methylaniline **133a** (1.30 mL, 12.0 mmol), triethylamine (1.67 mL, 12.0 mmol), DCM (14 mL) and bromoacetyl bromide (1.04 mL, 12.0 mmol) in DCM (20 mL) were subjected to general procedure A to afford the title compound **131a** (2.15 g, 9.43 mmol, 78%) as a brown solid.

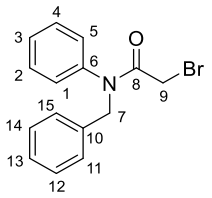
R_f: 0.72 (1:1 Petrol/EtOAc); m.p. 45–46 °C (Lit.[99] 47 °C); ν_{max}/cm^{-1} (solid): 2997, 2926, 2328, 1622 (C=O), 1570, 1474; δ_H (400 MHz, $CDCl_3$): 7.44 (2 H, tt, *J* = 7.2, 1.6 Hz, H-1 and H-5), 7.38 (1 H, tt, *J* = 7.2, 1.6 Hz, H-3), 7.27 (2 H, dt, *J* = 7.2, 1.6 Hz, H-2 and H-4), 3.65 (2 H, s, H-9), 3.29 (3 H, s, H-7); δ_C (100 MHz, $CDCl_3$): 166.4 (C-8), 143.0 (C-6), 130.0 (C-1 and C-5), 128.5 (C-3),

126.9 (C-2 and C-4), 38.0 (C-7), 26.8 (C-9); HRMS [ES^+] found MH^+, 228.0019. $C_9H_{11}{}^{79}BrNO$ requires 228.0019.

Lab book ref. RG046

Data is consitent with literature values.[100]

_N_-Benzyl-2-bromo-_N_-phenylacetamide (131b)



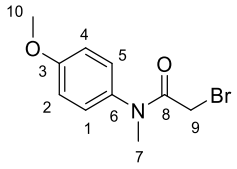
_N_-Benzylaniline **133b** (2.07 mL, 12.0 mmol), triethylamine (1.67 mL, 12.0 mmol), DCM (14 mL) and bromoacetyl bromide (1.04 mL, 12.0 mmol) in DCM (20 mL) were subjected to general procedure A to afford the title compound **131b** (2.49 g, 8.18 mmol, 68%) as a brown/yellow crystalline solid.

R_f: 0.25 (4:1 Petrol/EtOAc); m.p. 64–65 °C (Lit.[101] 70 °C); ν_{max}/cm^{-1} (solid): 2325, 1634 (C=O), 1567, 1470, 1366, 1176; δ_H (400 MHz, $CDCl_3$): 7.35-7.32 (3 H, m, ArH), 7.28-7.24 (3 H, m, ArH), 7.20-7.17 (2 H, m, ArH), 7.07-7.03 (2 H, m, ArH), 4.89 (2 H, s, H-7), 3.66 (2 H, s, H-9); δ_C (100 MHz, $CDCl_3$): 166.5 (C-8), 141.3 (C-Ar), 136.7 (C-Ar), 129.9 (CH-Ar), 129.0 (CH-Ar), 128.8 (CH-Ar), 128.6 (CH-Ar), 128.3 (CH-Ar), 127.8 (CH-Ar), 53.8 (C-7), 27.5 (C-9); HRMS [ES^+] found MH^+, 304.0321. $C_{15}H_{15}{}^{79}BrNO$ requires 304.0332.

Lab book ref. RG052

Data is consistent with literature values.[101]

2-Bromo-_N_-(4-methoxyphenyl)-_N_-methylacetamide (131c)



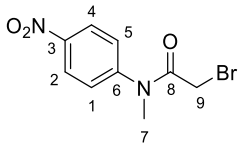
4-Methoxy-_N_-methylaniline **133c** (927 mg, 6.76 mmol), triethylamine (0.95 mL, 6.76 mmol), DCM (8 mL) and bromoacetyl bromide (589 µL, 6.76 mmol) in DCM (12 mL) were subjected to general procedure A to afford the title compound **131c** (1.53 g, 5.93 mmol, 87%) as a brown oil.

R_f: 0.38 (1:1 petrol/EtOAc); ν_{max}/cm^{-1} (neat): 2914, 1638 (C=O), 1489, 1419, 1359, 1281, 1230; δ_H (400 MHz, $CDCl_3$): 7.20 (2 H, d, *J* = 8.8 Hz, H-1 and H-5), 6.94 (2 H, d, *J* = 8.8 Hz, H-2 and H-4), 3.84 (3 H, s, H-10), 3.66 (2 H, s, H-9), 3.27 (3 H, s, H-7); δ_C (100 MHz, $CDCl_3$): 166.9 (C-8), 159.3 (C-3), 135.7 (C-6), 128.1 (C-1 and C-5), 115.0 (C-2 and C-4), 55.5 (C-10), 38.2 (C-7), 26.8 (C-9); HRMS [ES^+] found MH^+ 258.0132. $C_{10}H_{13}{}^{79}BrNO_2$ requires 258.0124.

Lab book ref. RG067

Data is consistent with literature values.[102]

2-Bromo-*N*-methyl-*N*-(4-nitrophenyl)acetamide (131d)



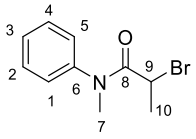
4-Nitro-*N*-methylaniline **133d** (1.82 g, 12.0 mmol), triethylamine (1.67 mL, 12.0 mmol), DCM (14 mL) and bromoacetyl bromide (1.04 mL, 12.0 mmol) in DCM (20 mL) were subjected to general procedure A. Purification by flash column chromatography (13:7 Petrol/EtOAc) afforded the title compound **131d** (1.59 g, 5.82 mmol, 48%) as a colourless powder.

R_f: 0.34 (1:1 petrol/EtOAc); m.p. 84–85 °C (Lit.[103] 88–89 °C); ν_{max}/cm^{-1} (solid): 1654 (C=O), 1587, 1518, 1341, 1104, 866; δ_H (400 MHz, $CDCl_3$): 8.33 (2 H, d, *J* = 8.8 Hz, H-2 and H-4), 7.51 (2 H, d, *J* = 9.2 Hz, H-1 and H-5), 3.74 (2 H, s, H-9), 3.39 (3 H, s, H-7); δ_C (100 MHz, $CDCl_3$): 166.1 (C-8), 148.5 (C-6), 146.3 (C-3), 127.5 (C-1 and C-5), 125.2 (C-2 and C-4), 38.1 (C-7), 26.2 (C-9); HRMS [ES^+] found MH^+ 272.9873. $C_9H_{10}{}^{79}BrN_2O_3$ requires 272.9869.

Lab book ref. RG068

Data consistent with literature values.[103]

2-Bromo-*N*-methyl-*N*-phenylpropanamide (131e)



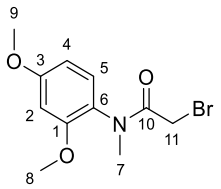
N-Methylaniline **133a** (1.30 mL, 12.0 mmol), triethylamine (1.67 mL, 12.0 mmol), DCM (14 mL) and 2-bromopropionyl bromide (1.26 mL, 12.0 mmol) in DCM (20 mL) were subjected to general procedure A to afford the title compound **131e** (2.87 g, 11.8 mmol, 99%) as an orange oil.

R_f: 0.60 (1:1 petrol/EtOAc); ν_{max}/cm^{-1} (neat): 1641 (C=O), 1571, 1472, 1368, 1250, 1104; δ_H (400 MHz, $CDCl_3$): 7.48-7.47 (2 H, m, H-1 and H-5), 7.40 (1 H, tt, *J* = 7.2, 1.2 Hz, H-3), 7.29 (2 H, d, *J* = 7.2 Hz, H-2 and H-4), 4.26 (1 H, q, *J* = 6.8 Hz, H-9), 3.29 (3 H, s, H-7), 1.73 (3 H, d, *J* = 6.8 Hz, H-10); δ_C (100 MHz, $CDCl_3$): 169.6 (C-8), 142.8 (C-6), 129.9 (C-1 and C-5), 128.4 (C-3), 127.1 (C-2 and C-4), 39.0 (C-9), 38.1 (C-7), 21.8 (C-10); HRMS [ES^+] found MH^+ 242.0172. $C_{10}H_{13}{}^{79}BrNO$ requires 242.0175.

Lab book ref. RG059

Data is consistent with literature values.[104]

2-Bromo-*N*-(2,4-dimethoxyphenyl)-*N*-methylacetamide (133e)



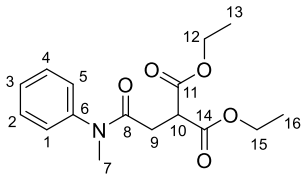
2,4-Dimethoxy-*N*-methylaniline **133e** (726 mg, 4.35 mmol), triethylamine (604 µL, 4.35 mmol), DCM (5 mL) and bromoacetyl bromide (377 µL, 4.35 mmol) in DCM (7 ml) were subjected to general procedure A. Purification by flash column chromatography (7:3 Petrol/EtOAc) afforded the title compound **133e** (1.02 g, 3.53 mmol, 81%) as a colourless oil.

R_f: 0.42 (1:1 petrol/EtOAc); ν_{max}/cm^{-1} (neat): 1664 (C=O); δ_H (400 MHz, $CDCl_3$): 7.17-7.13 (1 H, dd, *J* = 8.3, 0.5 Hz, H-5), 6.52-6.47 (2 H, m, H-2 and H-4), 3.82 (3 H, s, H-8 or H-9), 3.81 (3 H, s, H-8 or H-9), 3.65 (1 H, d, *J* = 11.2, H-11), 3.61 (1 H, d, *J* = 11.2, H-11), 3.17 (3 H, s, H-7); δ_C (100 MHz, $CDCl_3$): 167.5 (C-10), 160.9 (C-1 or C-3), 155.7 (C-1 or C-3), 129.3 (C-5), 124.5 (C-6), 104.5 (C-2 or C-4), 100.0 (C-2 or C-4), 55.6 (C-8 and C-9), 37.0 (C-7), 27.3 (C-11); HRMS [ES^+] found MH^+, 288.0225. $C_{11}H_{15}{}^{79}BrNO_3$ requires 288.0230.

Lab book ref. RG094

5.7.3 Malonates

Diethyl 2-(2-(methyl(phenyl)amino)-2-oxoethyl)malonate (130a)



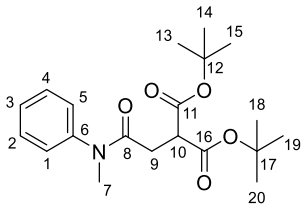
Diethyl malonate **132a** (2.00 mL, 13.2 mmol) and KO*t*-Bu (1.61g, 13.2 mmol) in THF (50 mL) and 2-bromo-*N*-methyl-*N*-phenylacetamide **131a** (1.50 g, 6.58 mmol) in THF (7 mL) were subjected to general procedure B. Purification by flash column chromatography (3:2 Petrol/EtOAc) afforded the title compound **130a** (1.82 g, 5.93 mmol, 90%) as a colourless oil.

R_f: 0.46 (1:1 Petrol/EtOAc); ν_{max}/cm^{-1} (neat): 2989, 1745 (C=O), 1729 (C=O), 1656 (C=O), 1496, 1391; δ_H (400 MHz, $CDCl_3$): 7.44 (2 H, t, *J* = 7.6 Hz, H-2 and H-4), 7.35 (1 H, t, *J* = 7.6 Hz, H-3), 7.23 (2 H, d, *J* = 7.6 Hz, H-1 and H-5), 4.22-4.09 (4 H, m, H-12 and H-15), 3.94 (1 H, t, *J* = 7.2 Hz, H-10), 3.24 (3 H, s, H-7), 2.64 (2 H, d, *J* = 7.2 Hz, H-9), 1.23 (6 H, t, *J* = 7.2 Hz, H-13 and H-16); δ_C (100 MHz, $CDCl_3$): 169.5 (C-8), 168.5 (C-11 and C-14), 143.2 (C-6), 129.8 (C-2 and C-4), 127.9 (C-3), 127.2 (C-1 and C-5), 61.3 (C-12 and C-15), 48.0 (C-10), 37.2 (C-7), 33.3 (C-9), 13.8 (C-13 and C-16); HRMS [ES^+] found MH^+, 308.1486. $C_{16}H_{22}NO_5$ requires 308.1492.

Lab book ref. RG041 and RG049

Data is consistent with literature values.[44a]

Di-*tert*-butyl 2-(2-(methyl(phenyl)amino)-2-oxoethyl)malonate (130b)



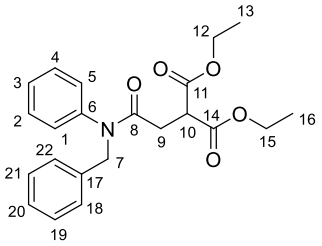
Di-*tert*-butyl malonate **132b** (979 µL, 4.38 mmol) and KO*t*-Bu (491 mg, 4.38 mmol) in THF (16.5 mL) and 2-bromo-*N*-methyl-*N*-phenylacetamide **131a** (500 mg, 2.19 mmol) in THF (2.5 mL) were subjected to general procedure B. Purification by flash column chromatography (1:1 Petrol/EtOAc) afforded the title compound **130b** (564 mg, 1.55 mmol, 71%) as a colourless oil.

R_f: 0.22 (1:1 Petrol/EtOAc); ν_{max}/cm^{-1} (neat): 1978, 1742 (C=O), 1724 (C=O), 1660 (C=O), 1597, 1497; δ_H (400 MHz, $CDCl_3$): 7.41 (2 H, t, *J* = 7.4 Hz, H-2 and H-4), 7.33 (1 H, t, *J* =7.4 Hz, H-3),

7.23 (2 H, d, *J* = 7.4 Hz, H-1 and H-5), 3.76 (1 H, t, *J* = 7.3 Hz, H-10), 3.24 (3 H, s, H-7), 2.55 (2 H, d, *J* =7.3 Hz, H-9), 1.42 (18 H, s, H-13, H-14, H-15, H-18, H-19 and H-20); δ_C (100 MHz, $CDCl_3$): 170.0 (C-8), 168.4 (C-11 and C-16), 143.5 (C-6), 129.8 (C-2 and C-4) 127.9 (C-3), 127.4 (C-1 and C-5), 81.4 (C-12 and C-17), 50.1 (C-10), 37.4 (C-7), 33.3 (C-9), 27.8 (C-13, C-14, C-15, C-18, C-19 and C-20); HRMS [ES^+] found MH^+, 364.2117. $C_{20}H_{30}NO_5$ requires 364.2118.

Lab book ref. RG158

Diethyl 2-(2-(benzyl(phenyl)amino)-2-oxoethyl)malonate (130c)



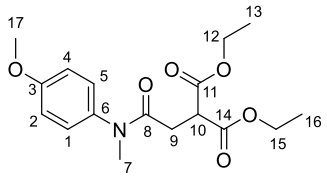
Diethyl malonate **132a** (1.00 mL, 6.57 mmol) and KO*t*Bu (73 mg, 6.57 mmol) in THF (25 mL) and *N*-Benzyl-2-bromo-*N*-phenylacetamide **131b** (1.00 g, 3.33 mmol) in THF (10 mL) were subjected to general procedure B. Purification by flash column chromatography (7:3 Petrol/EtOAc) afforded the title compound **130c** (1.06 g, 2.78 mmol, 84%) as a yellow oil.

R_f: 0.41 (3:2 Petrol/EtOAc); ν_{max}/cm^{-1} (neat): 2988, 1746 (C=O), 1727 (C=O), 1654 (C=O), 1397, 1366; δ_H (400 MHz, $CDCl_3$): 7.35-7.29 (3 H, m, ArH), 7.26-7.21 (3 H, m, ArH), 7.19-7.14 (2 H, m, ArH), 7.05-7.01 (2 H, m, ArH), 4.83 (2 H, s, H-7), 4.24-4.08 (4 H, m, H-12 and H-15), 4.01 (1 H, t *J* = 7.4 Hz, H-10), 2.65 (2 H, d, *J* = 7.4 Hz, H-9), 1.24 (6 H, t, *J* = 7.2 Hz, H-13 and H-16); δ_C (100 MHz, $CDCl_3$): 169.6 (C-8), 169.1 (C-11 and C-14), 141.6 (Ar-C), 137.2 (Ar-C) 129.7 (Ar-CH), 128.7 (Ar-CH), 128.4 (Ar-CH), 128.3 (Ar-CH) 128.2 (Ar-CH), 127.3 (Ar-CH), 61.5 (C-12 and C-15), 53.2 (C-7), 48.3 (C-10), 33.7 (C-9), 14.0 (C-13 and C-16); HRMS [ES^+] found MH^+, 384.1791. $C_{22}H_{26}NO_5$ requires 384.1805.

Lab book ref. RG053

Data is consistent with literature values.[44a]

Diethyl 2-(2-((4-methoxyphenyl)(methyl)amino)-2-oxoethyl)malonate (130d)



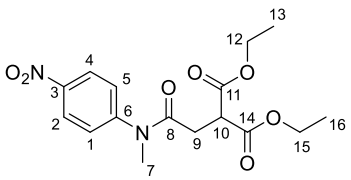
Diethyl malonate **132a** (1.18 mL, 7.75 mmol) and KO*t*Bu (867 mg, 7.75 mmol) in THF (35 mL) and 2-bromo-*N*-(4-methoxyphenyl)-*N*-methylacetamide **131d** (1.00 g, 3.88 mmol) in THF (15 mL) were subjected to general procedure B. Purification by flash column chromatography (2:1 Petrol/EtOAc) afforded the title compound **130d** (1.09 g, 3.23 mmol, 83%) as an orange oil.

R_f: 0.39 (1:1 petrol/EtOAc); ν_{max}/cm^{-1} (neat): 2989, 1739 (C=O), 1728 (C=O), 1655 (C=O), 1510, 1245; δ_H (400 MHz, $CDCl_3$): 7.17-7.13 (2 H, m, H-1 and H-5), 6.94-6.90 (2 H, m, H-2 and H-4), 4.22-4.09 (4 H, m, H-12 and H-15), 3.93 (1 H, t, *J* = 7.6 Hz, H-10), 3.83 (3 H, s, H-17), 3.21 (3 H, s, H-7), 2.63 (2 H, d, *J* = 7.6 Hz, H-9), 1.24 (6 H, t, *J* = 7.2 Hz, H-13 and H-16); δ_C (100 MHz, $CDCl_3$): 170.0 (C-8), 169.2 (C-11 and C-14), 159.0 (C-3), 136.1 (C-6), 128.4 (C-1 and C-5), 115.0 (C-2 and C-4), 61.5 (C-12 and C-15), 55.5 (C-17), 48.2 (C-10), 37.5 (C-7), 33.4 (C-9), 14.0 (C-13 and C-16); HRMS [ES^+] found MH^+, 338.1596. $C_{17}H_{24}NO_6$ requires 338.1598.

Lab ref. RG069

Data is consistent with literature values.[44a]

Diethyl 2-(2-(methyl(4-nitrophenyl)amino)-2-oxoethyl)malonate (130e)



Diethyl malonate **132a** (1.11 mL, 7.32 mmol) and KO*t*Bu (819 mg, 7.32 mmol) in THF (35 mL) and 2-bromo-*N*-methyl-*N*-(4-nitrophenyl)acetamide **131d** (1.00 g, 3.66 mmol) in THF (15 mL) were subjected to general procedure B. Purification by flash column chromatography (3:2 Petrol/EtOAc) afforded the title compound **130e** (950 mg, 2.70 mmol, 74%) as a yellow oil.

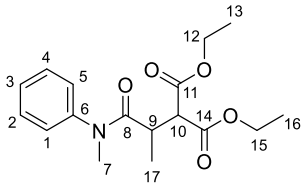
R_f: 0.39 (1:1 petrol/EtOAc); ν_{max}/cm^{-1} (neat): 2983, 1740 (C=O), 1727 (C=O), 1656 (C=O), 1592, 1520, 1343; δ_H (400 MHz, $CDCl_3$): 8.33-8.28 (2 H, m, H-2 and H-4), 7.49-7.44 (2 H, m, H-1 and H-5), 4.26-4.11 (4 H, m, H-12 and H-15), 3.98 (1 H, t, *J* = 7.6 Hz, H-10), 3.33 (3 H, s, H-7), 2.75 (2 H, br s, H-9), 1.21 (6 H, t, *J* = 7.2 Hz, H-13 and H-16); δ_C (100 MHz, $CDCl_3$): 169.3 (C-8),

168.7 (C-11 and C-14), 148.9 (C-6), 146.3 (C-3), 127.7 (C-1 and C-5), 125.0 (C-2 and C-4), 61.6 (C-12), 48.0 (C-10), 37.3 (C-7), 33.4 (C-9), 13.8 (C-13 and C-16); HRMS [ES^+] found MNa^+, 375.1151. $C_{16}H_{20}N_2NaO_7$ requires 375.1163.

Lab book ref. RG071

Data is consistent with literature values.[44a]

Diethyl 2-(1-(methyl(phenyl)amino)-1-oxopropan-2-yl)malonate (130f)



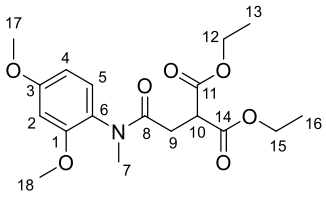
Diethyl malonate **132a** (1.26 mL, 8.26 mmol) and KO*t*Bu (926 mg, 8.26 mmol) in THF (25 mL) and 2-bromo-*N*-methyl-*N*-phenylpropanamide **131e** (1.00 g, 4.13 mmol) in THF (10 mL) were subjected to general procedure B at 70 °C for 18 h. Purification by flash column chromatography (3:1 Petrol/EtOAc) afforded the title compound **130f** (1.10 g, 3.44 mmol, 82%) as a colourless oil.

R_f: 0.60 (1:1 Petrol/EtOAc); ν_{max}/cm^{-1} (neat): 2983, 1747 (C=O), 1729 (C=O), 1652 (C=O), 1595, 1496, 1391, 1367; δ_H (400 MHz, $CDCl_3$): 7.46-7.30 (5 H, m, H-1 to H-5), 4.23-4.04 (4 H, m, H-12 and H-15), 3.86 (1 H, d, *J* = 11.0 Hz, H-10), 3.24 (3 H, s, H-7), 3.15-3.05 (1 H, m, H-9), 1.24 (3 H, t, *J* = 7.1 Hz, H-13 or H-16), 1.19 (3 H, t, *J* = 7.1 Hz, H-13 or H-16), 1.95 (3 H, d, *J* = 7.0 Hz, H-17); δ_C (100 MHz, $CDCl_3$): 174.1 (C-8), 168.7 (C-11 or C-14), 168.6 (C-11 or C-14), 143.5 (C-6), 129.72 (C-1 and C-5 or C-2 and C-4), 127.9 (C-3), 127.6 (C-1 and C-5 or C-2 and C-4), 61.4 (C-12 and C-15), 55.3 (C-10), 37.7 (C-7), 36.5 (C-9), 15.7 (C-17), 14.0 (C-13 and C-16); HRMS [ES^+] found MH^+, 322.1647. $C_{17}H_{24}NO_5$ requires 322.1649.

Lab book ref. RG061

Data is consistent with literature values.[44a]

Diethyl 2-(2-((2,4-dimethoxyphenyl)(methyl)amino)-2-oxoethyl)malonate (130g)



Diethyl malonate **132a** (1.05 mL, 6.94 mmol) and KO*t*Bu (777 mg, 6.94 mmol) in THF (25 mL) and 2-bromo-*N*-(2,4-dimethoxyphenyl)-*N*-methylacetamide **131f** (1.00 g, 3.47 mmol) in THF (5 mL) were subjected to general procedure B. Purification by flash column chromatography (2:1 Petrol/EtOAc) afforded the title compound **130g** (1.07 g, 2.91 mmol, 84%) as a colourless oil.

R_f: 0.38 (1:1 Petrol/EtOAc); ν_{max}/cm^{-1} (neat): 1982, 1742 (C=O), 1730 (C=O), 1658 (C=O), 1512; δ_H (400 MHz, $CDCl_3$): 7.11 (1 H, d, *J* = 8.4 Hz, H-5), 6.52-6.46 (2 H, m, H-2 and H-4), 4.25-4.10 (4 H, m, H-12 and H-15), 3.91 (1 H, dd, *J* = 8.5, 6.2 Hz, H-10), 3.83 (3 H, s, H-17 or H-18), 3.81 (3 H, s, H-17 or H-18), 3.12 (3 H, s, H-7), 2.73 (1 H, dd, *J* = 16.8, 8.5 Hz, H-9), 2.46 (1 H, dd, *J* = 16.8, 6.2 Hz, H-9), 1.27-1.20 (6 H, m, H-13 and H-16); δ_C (100 MHz, $CDCl_3$): 170.8 (C-8), 169.33 (C-11 or C-14), 169.30 (C-11 or C-14), 160.6 (C1 or C-3), 155.9 (C-1 or C-3), 129.5 (C-5), 124.8 (C-6), 104.7 (C-2 or C-4), 99.6 (C-2 or C-4), 61.4 (C-12 or C-15), 61.4 (C-12 or C-15), 55.5 (C-17 and C-18), 48.2 (C-10), 36.3 (C-7), 32.8 (C-9), 14.01 (C-13 or C-16), 14.00 (C-13 or C-16); HRMS [ES^+] found MH^+, 368.1691. $C_{18}H_{26}N_2O_7$ requires 368.1704.

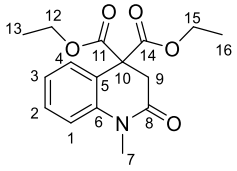
Lab book ref. RG097

Data is consistent with literature values.[44a]

5.7.4 3,4-Dihydroquinolin-2(1H)-ones

Diethyl 1-methyl-2-oxo-2,3-dihydroquinoline-4,4(1*H*)-dicarboxylate (129a)

From diethyl 2-(2-(methyl(phenyl)amino)-2-oxoethyl)malonate 130a:



Diethyl 2-(2-(methyl(phenyl)amino)-2-oxoethyl)malonate **130a** (51 mg, 165 µmol), copper(II) 2-ethylhexanoate (5.5 mg, 10 mol%) and DIPEA (69 µL, 0.396 mmol) in toluene (4 mL) were subjected to standard procedure C at 120 °C for 15 h. Purification by flash column chromatography

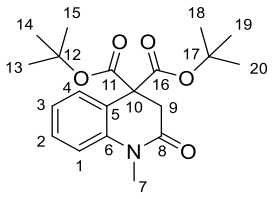
(3:2 petrol/EtOAc) afforded the title compound **129a** (50 mg, 165 µmol, 100%) as a colourless powder.

R_f: 0.23 (10:3 Petrol/EtOAc); m.p. 80–81 °C (Lit.[44a] 86–87 °C); ν_{max}/cm^{-1} (solid): 2983, 2934, 1729 (C=O), 1658 (C=O), 1367, 1224; δ_H (400 MHz, $CDCl_3$): 7.35 (1 H, ddd, *J* = 8.0, 7.2, 1.6 Hz, H-2), 7.28 (1 H, dd, *J* = 8.0, 1.6 Hz, H-4), 7.09 (1 H, td, *J* = 7.6, 1.2 Hz, H-3), 7.01 (1 H, dd, *J* = 8.0, 1.2 Hz, H-1), 4.28-4.21 (4 H, m, H-12 and H-15), 3.32 (3 H, s, H-7), 3.22 (2 H, s, H-9), 1.25 (6 H, t, *J* = 7.2, H-13 and H-16); δ_C (100 MHz, $CDCl_3$): 169.1 (C-11 and C-14), 166.8 (C-8), 140.0 (C-6), 129.5 (C-2), 127.9 (C-4), 123.3 (C-3), 122.7 (C-5), 115.4 (C-1), 62.5 (C-12 and C-15), 57.0 (C-10), 38.1 (C-9), 29.7 (C-7), 14.0 (C-13 and C-16); HRMS [ES^+] found MH^+, 306.1336. $C_{16}H_{20}NO_5$ requires 306.1336.

Lab book ref. RG043/RG047

Data is consistent with literature values.[44a]

Di-*tert*-butyl 1-methyl-2-oxo-2,3-dihydroquinoline-4,4(1*H*)-dicarboxylate (129b)

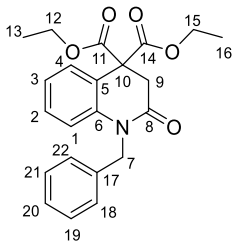


Di-*tert*-butyl 2-(2-(methyl(phenyl)amino)-2-oxoethyl)malonate **130b** (59.9 mg, 165 µmol), copper(II) 2-ethylhexanoate (5.5 mg, 10 mol%) and DIPEA (69 µL, 396 µmol) in mesitylene (4 mL) were subjected to standard procedure C at 165 °C for 2 h. Purification by flash column chromatography (17:3 → 3:2 petrol/EtOAc) afforded the title compound **129b** (44 mg, 121 µmol, 74%) as colourless solid.

R_f: 0.58 (1:1 petrol/EtOAc); m.p. 69–71 °C; ν_{max}/cm^{-1} (solid): 2978, 1728 (C=O), 1686 (C=O), 1448, 1368, 1285, 1248, 1146; δ_H (400 MHz, $CDCl_3$): 7.39 (1 H, dd, *J* = 7.7, 1.5 Hz, H-4), 7.34 (1 H, ddd, *J* = 8.1, 7.5, 1.5 Hz, H-2), 7.10 (1 H, td, *J* = 7.6, 1.2 Hz, H-3), 7.01 (1 H, dd, *J* = 8.2, 1.0 Hz, H-1), 3.33 (3 H, s, H-7), 3.10 (2 H, s, H-9), 1.47 (18 H, s, H-13 to H-15 and H-18 to H-20); δ_C (100 MHz, $CDCl_3$): 168.1 (C-11 and C-16), 167.2 (C-8), 139.9 (C-6), 129.0 (C-2), 127.5 (C-4), 123.6 (C-3), 123.0 (C-5), 115.2 (C-1), 82.9 (C-12 and C-17), 57.8 (C-10), 38.4 (C-9), 29.6 (C-7), 27.7 (C-13 to C-15 and C-18 to C-20); HRMS [ES^+] found MNa^+, 384.1788. $C_{20}H_{27}NNaO_5$ requires 384.1781.

Lab book ref. RG160e

Diethyl 1-benzyl-2-oxo-2,3-dihydroquinoline-4,4(1*H*)-dicarboxylate (129c)



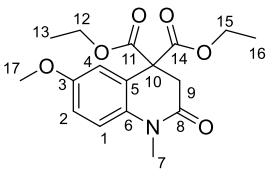
Diethyl 2-(2-(benzyl(phenyl)amino)-2-oxoethyl)malonate **130c** (63 mg, 165 µmol), copper(II) 2-ethylhexanoate (5.5 mg, 10 mol%) and DIPEA (69 µL, 396 µmol) in toluene (4 mL) were subjected to standard procedure C at 120 °C for 15 h. Purification by flash column chromatography (3:1 petrol/EtOAc) afforded the title compound **129c** (63 mg, 165 µmol, 100%) as colourless crystals.

R_f: 0.50 (1:1 petrol/EtOAc); m.p. 80–81 °C (Lit.[44a] 96–97 °C); ν_{max}/cm^{-1} (solid): 2977, 1757 (C=O), 1724 (C=O), 1678 (C=O), 1381, 1268; δ_H (400 MHz, $CDCl_3$): 7.34-7.14 (7 H, m, ArH), 7.05 (1 H, td, *J* = 7.6, 1.2 Hz, ArH), 6.92 (1 H, dd, *J* = 8.2, 1.0 Hz, ArH), 5.17 (2 H, s, H-7), 4.32-4.21 (4 H, m, H-12 and H-15), 3.36 (2 H, s, H-9), 1.27 (6 H, t, *J* = 7.2 Hz, H-13 and H-16); δ_C (100 MHz, $CDCl_3$): 169.0 (C-11 and C-14), 166.8 (C-8), 138.9 (C-Ar), 136.4 (C-Ar), 129.3 (CH-Ar), 128.7 (CH-Ar), 128.1 (CH-Ar), 127.1 (CH-Ar), 126.4 (CH-Ar), 123.3 (CH-Ar), 122.7 (C-Ar), 116.2 (CH-Ar), 62.5 (C-12 and C-15), 57.0 (C-10), 45.9 (C-7), 38.1 (C-9), 13.9 (C-13 and C-16); HRMS [ES^+] found MNa^+, 404.1465. $C_{22}H_{23}NNaO_5$ requires 404.1468.

Lab book ref. RG057

Data is consistent with literature values.[44a]

Diethyl 6-methoxy-1-methyl-2-oxo-2,3-dihydroquinoline-4,4(1*H*)-dicarboxylate (129d)



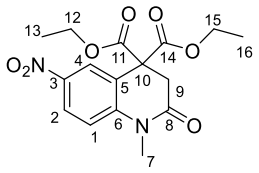
Diethyl 2-(2-((4-methoxyphenyl)(methyl)amino)-2-oxoethyl)malonate **130d** (56 mg, 165 µmol) copper(II) 2-ethylhexanoate (5.5 mg, 10 mol%) and DIPEA (69 µL, 396 µmol) in toluene (4 mL) were subjected to standard procedure C at 120 °C for 15 h. Purification by flash column chromatography (3:2 petrol/EtOAc) afforded the title compound **129d** (55 mg, 165 µmol, 100%) as a yellow oil.

R_f: 0.38 (1:1 petrol/EtOAc); ν_{max}/cm^{-1}: 2989, 1730 (C=O), 1675 (C=O), 1506, 1432, 1367, 1268, 1231; δ_H (400 MHz, $CDCl_3$): 6.95-6.91 (1 H, m, H-1), 6.89-6.84 (2 H, m, H-2 and H-4), 4.31-4.19 (4 H, m, H-12 and H-15), 3.77 (3 H, s, H-17), 3.28 (3 H, s, H-7), 3.18 (2 H, s, H-9), 2.25 (6 H, t, *J* = 7.2 Hz, H-13 and H-16); δ_C (100 MHz, $CDCl_3$): 168.8 (C-11 and C-14), 166.3 (C-8), 155.3 (C-3), 133.4 (C-6), 123.8 (C-5), 116.2 (C-1), 114.1 (C-2 or C-4), 113.7 (C-2 or C-4), 62.4 (C-12 and C-15), 56.9 (C-10), 55.5 (C-17), 38.0 (C-9), 29.7 (C-7), 13.9 (C-13 and C-16); HRMS [ES^+] found MH^+, 358.1258. $C_{17}H_{21}NNaO_6$ requires 358.1261.

Lab book ref. RG072

Data is consistent with literature values.[44a]

Diethyl 1-methyl-6-nitro-2-oxo-2,3-dihydroquinoline-4,4(1*H*)-dicarboxylate (129e)



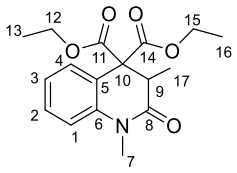
Diethyl 2-(2-(methyl(4-nitrophenyl)amino)-2-oxoethyl)malonate **130e** (58 mg, 165 µmol) copper(II) 2-ethylhexanoate (5.5 mg, 10 mol%) and DIPEA (69 µL, 0.396 mmol) in toluene (4 mL) were subjected to standard procedure C at 120 °C for 15 h. Purification by flash column chromatography (3:2 petrol/EtOAc) afforded the title compound **129e** (55 mg, 165 µmol, 100%) as a yellow solid.

R_f: 0.23 (3:2 petrol/EtOAc); m.p. 82–84 °C (Lit[44a] 89 °C); ν_{max}/cm^{-1}: 2989, 2940, 1731 (C=O), 1696 (C=O), 1594, 1521, 1334; δ_H (400 MHz, $CDCl_3$): 8.30-8.23 (2 H, m, H-2 and H-4), 7.13 (1 H, d, *J* = 8.9 Hz, H-1), 4.32-4.22 (4 H, m, H-12 and H-15), 3.39 (3 H, s, H-7), 3.27 (2 H, s, H-9), 1.31-1.27 (6 H, m, H-13 and H-16); δ_C (100 MHz, $CDCl_3$): 167.9 (C-11 and C-14), 166.3 (C-8), 145.2 (C-6), 142.8 (C-3), 125.2 (C-2 or C-4), 124.0 (C-2 or C-4), 123.0 (C-5), 115.4 (C-1), 63.0 (C-12 and C-15), 56.3 (C-10), 37.3 (C-9), 30.0 (C-7), 13.9 (C-13 and C-16); HRMS [ES^+] found MH^+, 373.1000. $C_{16}H_{18}N_2NaO_7$ requires 373.1006.

Lab book ref. RG073

Data is consistent with literature values.[44a]

Diethyl 1,3-dimethyl-2-oxo-2,3-dihydroquinoline-4,4(1*H*)-dicarboxylate (129f)



Diethyl 2-(1-(methyl(phenyl)amino)-1-oxopropan-2-yl)malonate **130f** (53 mg, 165 µmol), copper(II) 2-ethylhexanoate (5.5 mg, 10 mol%) and DIPEA (69 µL, 396 µmol) in toluene (4 mL) were subjected to standard procedure C at 120 °C for 24 h. Purification by flash column chromatography (3:1 petrol/EtOAc) afforded the title compound **129f** (63 mg, 165 µmol, 100%) a colourless solid.

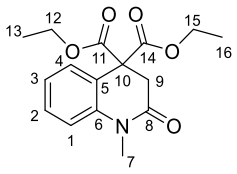
R_f: 0.45 (1:1 petrol/EtOAc); m.p. 59–61 °C (Lit[44a] 60-61 °C); ν_{max}/cm^{-1}: 2936, 1706 (C=O), 1659 (C=O), 1437, 1341, 1229; δ_H (400 MHz, $CDCl_3$): 7.53 (1 H, dd, *J* = 7.6, 1.2 Hz, H-4), 7.36-7.31 (1 H, m, H-2), 7.10 (1 H, td, *J* = 7.6, 1.2 Hz, H-3), 6.98 (1 H, dd, *J* = 7.6, 1.2 Hz, H-1), 4.30-4.07 (4 H, m, H-12 and H-15), 3.33 (3H, s, H-7), 3.30 (1 H, q, *J* = 7.2 Hz, H-9), 1.23 (3 H, t, *J* = 7.1 Hz, H-13 or H-16), 1.21 (3 H, t, *J* = 7.2, H-13 or H-16), 1.21 (3 H, d, *J* = 7.2 Hz, H-17); δ_C (100 MHz, $CDCl_3$): 169.9 (C-8), 169.1 (C-11 or C-14), 167.7 (C-11 or C-14), 139.6 (C-6), 129.5 (C-4), 129.2 (C-2), 123.0 (C-3), 121.5 (C-5), 114.9 (C-1), 62.1 (C-12 or C-15), 61.7 (C-12 or C-15), 60.6 (C-10), 41.3 (C-9), 29.8 (C-7), 13.9 (C-13 or C-16), 13.8 (C-13 or C-16), 12.5 (C-17); HRMS [ES^+] found MNa^+, 342.1309. $C_{17}H_{21}NNaO_5$ requires 342.1312.

Lab book ref. RG064

Data is consistent with literature values.[44a]

5.7.5 One-pot synthesis of 3,4-dihydroquinolin-2(1H)-one

Diethyl 1-methyl-2-oxo-2,3-dihydroquinoline-4,4(1*H*)-dicarboxylate (129a)



From 2-bromo-N-methyl-N-phenylacetamide:

To a stirred solution of diethyl malonate **132a** (66 µL, 432 µmol) in toluene (4 mL) was added KO*t*Bu (54 mg, 482 µmol) and the reaction mixture stirred at room temperature for 10 min. To the stirred solution was added 2-bromo-*N*-methyl-*N*-phenylacetamide **131a** (100 mg, 438 µmol) in

toluene (2 ml) *via* cannula and stirring maintained at 60 °C for 6 h under an atmosphere of air. Copper(II) 2-ethylhexanoate (15.3 mg, 10 mol%) and DIPEA (182µL, 1.05 mmol) were added and the solution stirred at reflux (120 °C) for 18 h. The reaction mixture was worked up as outlined in general procedure A. Purification by flash column chromatography (3:2 petrol/EtOAc) afforded the title compound **129a** (77 mg, 254 µmol, 58%) as a colourless powder.

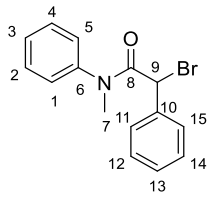
Lab book ref. RG105

Data as above

5.8 Copper-catalysed cyclisation/sulfone elimination approach to 2-quinolinones

5.8.1 Anilides

2-Bromo-*N*-methyl-*N*,2-diphenylacetamide (131g)



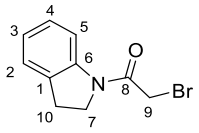
To a stirred solution of bromo-phenyl acetic acid **134c** (2.50 g, 11.6 mmol) in DCM (38 mL) at 0 °C were added *N*-methylaniline **133a** (1.38 mL, 12.8 mmol), chloro-*N*-methyl pyridinium iodide (4.45 g, 17.4 mmol) and NEt_3 (8.09 mL, 58.1 mmol). The reaction mixture was allowed to warm to rt and stirred for 1 h. The solution was quenched with 10% HCl (40 ml), the organics separated and washed with $NaHCO_3$ (40 mL), brine (40 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification by flash column chromatography (17:3 hexane/EtOAc) afforded the title compound **131g** (2.19 g, 7.23 mmol, 62%) as a green oil.

R_f: 0.21 (17:3 petrol/EtOAc); ν_{max}/cm^{-1} (neat): 1650 (C=O), 1593, 1494, 1377, 1118; δ_H (400 MHz, $CDCl_3$): 7.45-7.33 (3 H, m, ArH), 7.33-7.21 (5 H, m, ArH), 7.19-7.02 (1 H, m, ArH), 6.83-6.72 (1 H, m, ArH), 5.30 (1 H, s, H-9), 3.28 (3 H, s, H-7); δ_C (100 MHz, $CDCl_3$): 167.6 (C-8), 142.7 (C-6 or C-10), 136.5 (C-6 or C-10), 130.1 (Ar-CH), 129.0 (Ar-CH), 128.70 (Ar-CH), 12.69 (Ar-CH), 128.3 (Ar-CH), 127.6 (Ar-CH), 56.9 (C-9), 38.4 (C-7); HRMS [ES^+] found MNa^+ 326.0173. $C_{15}H_{14}{}^{79}BrNNaO$ requires 326.0151.

Lab book ref. RG214

Data is consistent with literature values.[105]

2-Bromo-1-(indolin-1-yl)ethanone (131h)



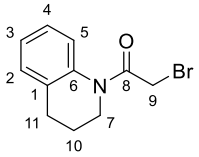
Indoline **133f** (1.12 mL, 10 mmol), triethylamine (1.39 mL, 10 mmol), DCM (16 mL) and bromoacetyl bromide **134a** (869 µL, 10 mmol) in DCM (12 mL) were subjected to general procedure A to afford the title compound **131h** (2.13 g, 8.89 mmol, 89%) as an off-white powder

R_f: 0.52 (1:1 Petrol/EtOAc); m.p. 96–98 °C; ν_{max}/cm^{-1} (neat): 2949, 1664 (C=O), 1598, 1481, 1461, 1410, 1347; δ_H (400 MHz, $CDCl_3$): 8.18 (1 H, d, *J* = 8.1 Hz, H-2), 7.25-7.16 (2 H, m, H-5 and H-3 or H-4), 7.04 (1 H, t, *J* = 7.4 Hz, H-3 or H-4), 4.16 (2 H, t, *J* = 8.2 Hz, H-7), 3.92 (2 H, s, H-9), 3.22 (2 H, t, *J* = 8.2 Hz, H-10); δ_C (100 MHz, $CDCl_3$): 164.1 (C-8), 142.5 (Ar-CH), 131.3 (C-1 or C-6), 127.6 (C-1 or C-6), 124.6 (Ar-CH), 124.5 (Ar-CH), 116.4 (Ar-CH), 48.3 (C-7), 28.4 (C-9), 28.1 (C-10); HRMS [ES^+] found MNa^+ 261.9829. $C_{10}H_{10}{}^{79}BrNNaO$ requires 261.9838.

Lab book ref. RG237

Data is consistent with literature values.[78a]

2-Bromo-1-(3,4-dihydroquinolin-1(2*H*)-yl)ethanone (131g)



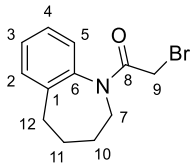
1,2,3,4-Tetrahydroquinoline **133g** (1.25 mL, 10 mmol), triethylamine (1.39 mL, 6.0 mmol), DCM (12 mL) and bromoacetyl bromide **134a** (869 µL, 10 mmol) in DCM (16 mL) were subjected to general procedure A to afford the title compound **131g** (2.25 g, 8.91 mmol, 88%) as a brown oil.

R_f: 0.52 (1:1 hexane/EtOAc); ν_{max}/cm^{-1} (neat): 2948, 1654 (C=O), 1581, 1491, 1458, 1428, 1389; δ_H (400 MHz, $CDCl_3$): 7.23-7.08 (4 H, m, H-2 to H-5), 4.03 (2 H, s, H-9), 3.80 (2 H, t, *J* = 6.5 Hz, H-7), 2.76-2.65 (2 H, m, H-11), 2.02-1.90 (2 H, m, H-10); δ_C (100 MHz, $CDCl_3$): 166.3 (C-8), 138.5 (C-1 or C-6), 134.3 (C-1 or C-6), 128.6 (Ar-CH), 126.5 (Ar-CH), 126.1 (Ar-CH), 123.4 (Ar-CH), 43.4 (C-7), 27.5 (C-9), 26.5 (C-11), 23.7 (C-10); HRMS [ES^+] found MNa^+ 275.9984. $C_{11}H_{12}{}^{79}BrNNaO$ requires 275.9994.

Lab book ref. RG238

Data consistent with literature values.[78b]

2-Bromo-1-(2,3,4,5-tetrahydro-1*H*-benzo[b]azepin-1-yl)ethanone (131j)



2,3,4,5-Tetrahydro-1*H*-benzo[b]azepine **133h** (525 mg, 3.57 mmol), triethylamine (480 µL, 3.57 mmol), DCM (5 mL) and bromoacetyl bromide **134a** (310 µL, 3.57 mmol) in DCM (6.5 mL) were subjected to general procedure A. Purification by flash column chromatography (4:1 Hexane/EtOAc) afforded the title compound **131j** (679 mg, 2.53 mmol, 71%) as a colourless solid.

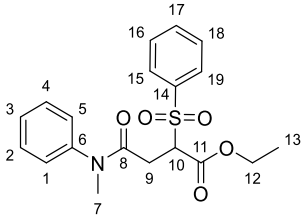
R_f: 0.21 (4:1 hexane/EtOAc); m.p. 93-95 °C; ν_{max}/cm^{-1} (neat): 2938, 1654 (C=O), 1492, 1440, 1399, 1311; δ_H (400 MHz, $CDCl_3$): 7.27-7.18 (4 H, m, ArH), 4.69-4.62 (1 H, m, CH_2), 3.73 (1 H, d, *J* = 10.8 Hz, H-9), 3.65 (1 H, d, *J* = 10.8 Hz, H-9), 2.94-2.85 (1 H, m, CH_2), 2.73-2.61 (2 H, m, CH_2), 2.03-1.87 (2 H, m, CH_2), 1.82-1.73 (1 H, m, CH_2), 1.43-1.31 (1 H, m, CH_2); δ_C (100 MHz, $CDCl_3$): 165.3 (C-8), 142.3 (C-1 or C-5), 140.7 (C-1 or C-5), 130.5 (Ar-CH), 128.6 (Ar-CH), 127.4 (Ar-CH), 126.8 (Ar-CH), 48.0 (CH_2), 34.4 (CH_2), 28.7 (CH_2), 26.9 (CH_2), 26.3 (CH_2); HRMS [ES^+] found MH^+ 268.0329. $C_{12}H_{15}{}^{79}BrNO$ requires 268.0332.

Lab book ref. RG277

Data consistent with literature values.[78c]

5.8.2 Malonates

Ethyl 4-(methyl(phenyl)amino)-4-oxo-2-(phenylsulfonyl)butanoate (164a)



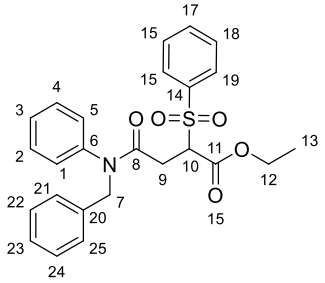
Ethyl 2-(phenylsulfonyl)acetate **165a** (2.00 g, 8.76 mmol) and KO*t*Bu (982 mg, 8.76 mmol) in THF (32 mL) and 2-bromo-*N*-methyl-*N*-phenylacetamide **131a** (1.00 g, 4.38 mmol) in THF (6 mL) were subjected to general procedure B for 18 h. Purification by flash column chromatography (3:2 hexane/EtOAc) afforded the title compound **164a** (1.53 g, 4.07 mmol, 93%) as a colourless solid.

R_f: 0.25 (1:1 hexane/EtOAc); m.p. 120–123 °C; ν_{max}/cm^{-1} (neat): 2936, 1736 (C=O), 1649 (C=O), 1595, 1497, 1449, 1309 (S=O), 1226, 1145 (S=O); δ_H (400 MHz, $CDCl_3$): 7.79 (2 H, dd, *J* = 8.2,

1.0 Hz, ArH), 7.66 (1 H, tt, *J* = 7.5, 1.2 Hz, ArH), 7.55-7.49 (2 H, m, ArH), 7.48-7.37 (3 H, m, ArH), 7.24-7.21 (2 H, m, ArH), 4.56 (1 H, dd, *J* = 6.7, 3.9 Hz, H-10), 4.10-3.98 (2 H, m, H-12), 3.24 (3 H, s, H-7), 2.97 (1 H, dd, *J* = 16.8, 10.7 Hz, H-9), 2.84 (1 H, dd, *J* = 10.7, 3.9 Hz, H-9), 1.06 (3 H, t, *J* = 7.1 Hz, H-13); δ_C (100 MHz, $CDCl_3$): 168.4 (C-8), 165.3 (C-11), 142.8 (C-6), 137.8 (C-14), 134.2 (CH-Ar), 130.1 (CH-Ar), 129.0 (CH-Ar), 128.9 (CH-Ar), 128.4 (CH-Ar), 127.2 (CH-Ar), 66.9 (C-10), 62.2 (C-12), 37.5 (C-7), 30.8 (C-9), 13.6 (C-13); HRMS [ES^+] found MNa^+, 398.1030. $C_{19}H_{21}N_2NaO_5S$ requires 398.1033.

Lab book ref. RG142 and RG183

Ethyl 4-(benzyl(phenyl)amino)-4-oxo-2-(phenylsulfonyl)butanoate (164b)

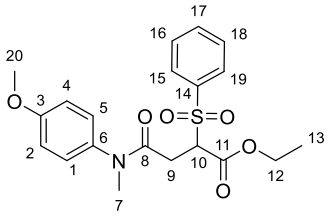


Ethyl 2-(phenylsulfonyl)acetate **165a** (422 mg, 1.85 mmol) and KO*t*Bu (227 mg, 2.03 mmol) in THF (20 mL) and 2-bromo-*N*-benzyl-*N*-phenylacetamide **131b** (727 mg, 2.40 mmol) in THF (4 mL) were subjected to general procedure B for 18 h. Purification by flash column chromatography (7:3 hexane/EtOAc) afforded the title compound **164b** (830 mg, 1.84 mmol, 99%) as a colourless oil.

R_f: 0.18 (7:3 hexane/EtOAc); ν_{max}/cm^{-1} (neat): 1736 (C=O), 1651 (C=O), 1595, 1494, 1407, 1322 (S=O), 1146 (S=O); δ_H (400 MHz, $CDCl_3$): 7.78 (2 H, dd, *J* = 7.2, 1.4 Hz, H-15 and H-19), 7.65 (1 H, tt, *J* = 7.4, 1.1 Hz, H-17), 7.51 (2 H, t, *J* = 7.9 Hz, H-16 and H-18), 7.36-7.29 (3 H, m, ArH), 7.26-7.19 (3 H, m, ArH), 7.15-7.11 (2 H, m, ArH), 7.03-6.99 (2H, m, ArH), 4.83 (2 H, dd, *J* = 18.9, 14.4 Hz, H-7), 4.62 (1 H, dd, *J* = 10.4, 4.1 Hz, H-10), 4.14-4.00 (2 H, m, H-12), 2.94 (1 H, dd, *J* = 16.9, 10.4 Hz, H-9), 2.85 (1 H, dd, *J* = 16.9, 4.1 Hz, H-9), 1.07 (3 H, t, *J* = 7.1 Hz, H-13); δ_C (100 MHz, $CDCl_3$): 168.4 (C-8), 165.2 (C-11), 141.1 (C-6), 137.8 (C-14 or C-20), 136.8 (C-14 or C-20), 134.1 (CH-Ar), 129.8 (CH-Ar), 128.9 (CH-Ar), 128.8 (CH-Ar), 128.6 (CH-Ar), 128.5 (CH-Ar), 128.3 (CH-Ar), 128.2 (CH-Ar), 127.4 (CH-Ar), 66.9 (C-10), 62.2 (C-12), 53.3 (C-7), 31.1 (C-9), 13.6 (C-13); HRMS [ES^+] found MNa^+, 474.1337. $C_{25}H_{25}NNaO_5S$ requires 474.1346.

Lab book ref. RG191b

Ethyl 4-((4-methoxyphenyl)(methyl)amino)-4-oxo-2-(phenylsulfonyl)butanoate (164c)

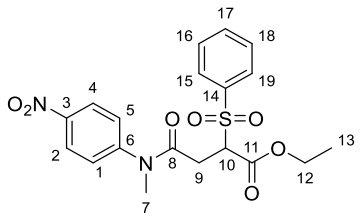


Ethyl 2-(phenylsulfonyl)acetate **165a** (575 mg, 2.52 mmol) and KO*t*Bu (282 mg, 2.52 mmol) in THF (11 mL) and 2-bromo-*N*-(4-methoxyphenyl)-*N*-methylacetamide **131c** (325 mg, 1.26 mmol) in THF (2 mL) were subjected to general procedure B for 18 h. Purification by flash column chromatography (55:45 hexane/EtOAc) afforded the title compound **164c** (361 mg, 891 µmol, 71%) as a brown semi-solid.

R_f: 0.12 (55:45 hexane/EtOAc); ν_{max}/cm^{-1} (neat): 1738 (C=O), 1655 (C=O), 1512, 1448, 1392, 1323 (S=O), 1249, 1148 (S=O); δ_H (400 MHz, $CDCl_3$): 7.80 (2 H, dd, *J* = 7.2, 1.3 Hz, H-15 and H-19), 7.66 (1 H, tt, *J* = 7.5, 1.2 Hz, H-17), 7.53 (2 H, t, *J* = 7.5 Hz, H-16 and H-18), 7.13 (2 H, tt, *J* = 8.9, 2.2 Hz, H-1 and H-5), 6.94 (2 H, tt, *J* = 8.9, 2.2 Hz, H-2 and H-4), 4.54 (1 H, dd, *J* = 10.7, 3.9 Hz, H-10), 4.15-3.97 (2 H, m, H-12), 3.86 (3 H, s, H-20), 3.20 (3 H, s, H-7), 2.97 (1 H, dd, *J* = 16.8, 10.7 Hz, H-9), 2.83 (1 H, dd, *J* = 16.8, 3.8 Hz, H-9), 1.05 (3 H, t, *J* = 7.2 Hz, H-13); δ_C (100 MHz, $CDCl_3$): 168.8 (C-8), 165.3 (C-11), 159.3 (C-3), 137.9 (C-14), 135.5 (C-6), 134.1 (C-17), 129.0 (C-15 and C-19), 128.8 (C-16 and C-18), 128.3 (C-1 and C-5), 115.2 (C-2 and C-4), 66.9 (C-10), 62.2 (C-12), 55.5 (C-20), 37.6 (C-7), 30.7 (C-9), 13.6 (C-13); HRMS [ES^+] found MNa^+, 428.1139. $C_{20}H_{23}NNaO_6S$ requires 428.1138.

Lab book ref. RG195

Ethyl 4-(methyl(4-nitrophenyl)amino)-4-oxo-2-(phenylsulfonyl)butanoate (164d)

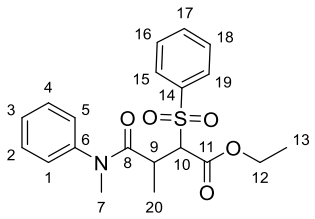


Ethyl 2-(phenylsulfonyl)acetate **165a** (399 mg, 1.75 mmol) and KO*t*Bu (196 mg, 1.75 mmol) in THF (8 mL) and 2-bromo-*N*-(4-nitrophenyl)-*N*-methylacetamide **131d** (361 mg, 1.26 mmol) in THF (1.5 mL) were subjected to general procedure B for 18 h. Purification by flash column chromatography (1:1 Petrol/EtOAc) afforded the title compound **164d** (364 mg, 867 µmol, 66%) as a colourless oil.

R_f: 0.19 (1:1 Petrol/EtOAc); ν_{max}/cm^{-1} (neat): 1737 (C=O), 1663 (C=O), 1593, 1522, 1496 1448, 1342 (S=O), 1148 (S=O); δ_H (400 MHz, $CDCl_3$): 8.31 (2 H, d, *J* = 8.3 Hz, H-2 and H-4), 7.83 (2H, d, *J* = 7.8 Hz, H-15 and H-19), 7.69 (1 H, t, *J* = 7.8 Hz, H-17), 7.59 (2 H, t, *J* = 7.8 Hz, H-16 and H-18), 7.45 (2 H, d, *J* = 8.3 Hz, H-1 and H-5), 4.59 (1 H, dd, *J* = 10.2, 4.2 Hz, H-10), 4.14-3.96 (2 H, m, H-12), 3.30 (3 H, s, H-7), 3.02 (2 H, br s, H-9), 1.03 (3 H, t, *J* = 7.2 Hz, H-13); δ_C (100 MHz, $CDCl_3$): 168.4 (C-8), 165.3 (C-11), 148.6 (C-6), 146.9 (C-3), 137.9 (C-14), 134.5 (C-17), 129.3 (C-16 and C-18), 129.0 (C-15 and C-19), 128.0 (C-1 and C-5), 125.5 (C-2 and C-4), 66.8 (C-10), 62.6 (C-12), 37.8 (C-7), 30.9 (C-9), 13.7 (C-13); HRMS [ES^+] found MNa^+, 443.0890. $C_{19}H_{20}N_2NaO_7S$ requires 443.0883.

Lab book ref. RG196

Ethyl 3-methyl-4-(methyl(phenyl)amino)-4-oxo-2-(phenylsulfonyl)butanoate (164e)



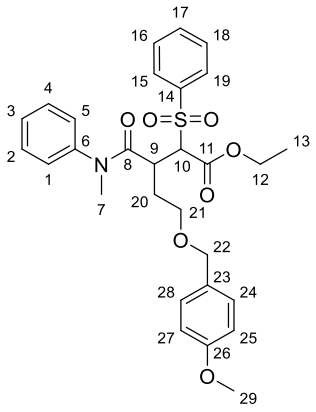
Ethyl 2-(phenylsulfonyl)acetate **165a** (839 mg, 3.68 mmol) and KO*t*Bu (448 mg, 3.68 mmol) in THF (14 mL) and 2-bromo-*N*-methyl-*N*-phenylpropanamide **131e** (594 mg, 2.45 mmol) in THF (4 mL) were subjected to general procedure B for 16 h. Purification by flash column chromatography (17:3 → 3:1 hexane/EtOAc) afforded the title compound **164e** (208 mg, 535 µmol, 22%) as an orange oil which was an inseparable (1:1.6) mixture of diastereoisomers. The diastereotopicity is lost in the next synthetic step therefore the dr is not important.

R_f: 0.23 (1:1 Petrol/EtOAc); ν_{max}/cm^{-1} (neat): 2983, 1732 (C=O), 1651 (C=O), 1595, 1495, 1448, 1392, 1323 (S=O), 1144 (S=O); δ_H (400 MHz, $CDCl_3$): *Major diastereoisomer:* 7.68 (2 H, d, *J* = 7.6 Hz, H-15 and H-19), 7.57 (2 H, t, *J* = 7.6 Hz, H-16 and H-18), 7.44-7.25 (4 H, m, H-2 to H-4 and H-17), 7.18 (2 H, d, *J* = 7.6 Hz, H-1 and H-5), 4.25 (1 H, d, *J* = 10.7 Hz, H-10), 3.98-3.90 (2 H, m, H-12), 3.37-3.24 (1 H, m, H-9), 3.09 (3 H, s, H-7), 1.29-1.25 (3 H, m, H-20), 1.05-0.94 (3 H, m, H-13); *Minor diastereoisomer:* 7.82 (2 H, d, *J* = 6.8 Hz, H-15 and H-19), 7.47 (2 H, t, *J* = 6.8 Hz, H-16 and H-18), 7.44-7.25 (6 H, m, H-1 to H-5 and H-17), 4.72 (1 H, d, *J* = 10.7 Hz, H-10), 3.85-3.75 (2 H, m, H-12), 3.37-3.24 (1 H, m, H-9), 3.23 (3 H, s, H-7), 1.29-1.25 (3 H, m, H-20), 1.05-0.94 (3 H, m, H-13); δ_C (100 MHz, $CDCl_3$): *Major diastereoisomer*; 173.2 (C-8), 166.3 (C-11), 142.8 (C-6), 137.5 (C-14), 133.9 , 129.66, 128.73, 128.70 127.8, 127.0, 73.5 (C-10), 61.9 (C-12), 37.3 (C-7), 36.3 (C-9), 16.5 (C-20), 13.3 (C-13); *Minor diastereoisomer*: 172.3 (C-8), 164.5 (C-11), 143.0 (C-6), 139.0 (C-14), 133.8, 129.73, 128.8, 128.3, 128.1, 127.3, 72.7 (C-10), 61.7 (C-

12), 37.8 (C-7), 34.6 (C-9), 16.4 (C-20), 13.5 (C-13); HRMS [ES^+] found MNa^+, 412.1179. $C_{20}H_{23}N_2NaO_3S$ requires 412.1189.

Lab book ref. RG208c

Ethyl 5-(4-methoxybenzyloxy)-3-(methyl(phenyl)carbamoyl)-2-(phenylsulfonyl)pentanoate (164f)

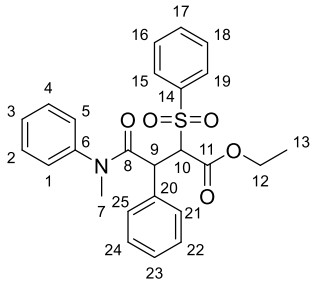


Ethyl 2-(phenylsulfonyl)acetate **165a** (140 mg, 306 µmol) and NaH (60% w/w dispersion in mineral oil, 24.5 mg, 612 µmol) in DMF (4 mL) and 2-bromo-4-(4-methoxybenzyloxy)-*N*-methyl-*N*-phenylbutanamide **131k** (120 mg, 306 µmol) in DMF (1.5 mL) were subjected to general procedure B for 18 h at 80 °C. Purification by flash column chromatography (3:2 hexane/EtOAc) afforded the title compound **164f** (131 mg, 243 µmol, 79%) as a yellow oil.

R_f: 0.22 (3:2 hexane/EtOAc); ν_{max}/cm^{-1} (neat): 2935, 1736 (C=O), 1655 (C=O), 1595, 1513, 1496, 1447, 1323 (S=O), 1248, 1148 (S=O); δ_H (400 MHz, $CDCl_3$): An inseparable mixture of diastereoisomers; 7.91-7.86 (2 H, m, Ar H), 7.77-7.74 (2 H, m, ArH), 7.72-7.68 (2 H, m, ArH), 7.67-7.56 (3 H, m, ArH), 7.54-7.48 (4 H, m, ArH), 7.40-7.34 (5 H, m, ArH), 7.30-2.26 (5 H, m, ArH), 7.22-7.19 (3 H, m, ArH), 7.13-7.10 (4 H, m, ArH), 6.87-6.77 (5 H, m, ArH), 5.29 (2 H, s), 4.81 (1 H, d, *J* = 10.5), 4.52 (1 H, d, *J* = 10.0 Hz), 4.34-4.22 (6 H, m), 4.12-3.82 (5 H, m), 3.80 (3 H, s), 3.79 (3 H, m), 3.77 (2 H, s), 3.59-3.31 (8 H, m), 3.27 (2 H, s), 3.24 (2 H, s), 3.11 (2 H, s), 2.26-2.14 (2 H, m), 2.10-1.93 (2 H, m), 1.08 (3 H, t, *J* = 7.0 Hz, H-13), 0.96 (3 H, t, *J* = 7.0 Hz, H-13); δ_C (100 MHz, $CDCl_3$): 159.0 (C), 150.0 (C), 143.1 (C), 133.9, 129.9, 129.8, 129.7, 129.6, 129.4, 129.3, 129.21, 129.16, 129.1, 128.9, 128.8, 128.7, 128.2, 127.73, 127.66, 127.3, 113.65, 113.6, 72.5, 72.4, 72.3, 72.2, 72.0, 71.7, 66.7, 66.5, 64.4, 62.2, 61.8, 55.3, 38.8, 38.1, 37.9, 37.3, 29.9, 28.6, 13.6; HRMS [ES^+] found MH^+, 540.2037. $C_{29}H_{34}NO_7S$ requires 540.2050.

Lab book ref. RG279

Ethyl 4-(methyl(phenyl)amino)-4-oxo-3-phenyl-2-(phenylsulfonyl)butanoate (164g)

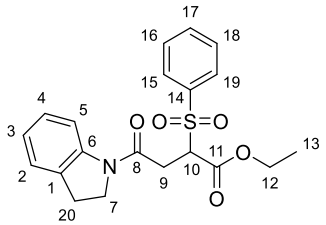


Ethyl 2-(phenylsulfonyl)acetate **165a** (225 mg, 987 µmol) and KO*t*Bu (120 mg, 987 µmol) in THF (5 mL) and 2-bromo-*N*-methyl-*N*,2-diphenylacetamide **131g** (200 mg, 658 mmol) in THF (2 mL) were subjected to general procedure B at rt for 48 h followed by 18 h at 75 °C. Purification by flash column chromatography (4:1 → 3:2 hexane/EtOAc) afforded the title compound **164g** (137 mg, 303 µmol, 46%) as a colourless oil which was an inseparable (1:2.8) mixture of diastereoisomers. The diastereotopicity is lost in the next synthetic step therefore the dr is not important.

R_f: 0.15 (9:1 hexane/EtOAc); ν_{max}/cm^{-1} (neat): 1741 (C=O), 1655 (C=O), 1496, 1448, 1325 (S=O), 1309, 1151 (S=O); δ_H (400 MHz, $CDCl_3$): *major diastereoisomer*: 7.98-6.75 (15 H, m, ArH), 5.29 (1 H, d, *J* = 11.5 Hz, H-10), 4.46 (1 H, d, *J* = 11.5 Hz, H-9), 4.13 (2 H, q, *J* = 7.1 Hz, H-12), 3.04 (3 H, s, H-7), 1.18 (3 H, t, *J* = 7.1 Hz, H-13); *minor diastereoisomer*: 7.98-6.75 (15 H, m, ArH), 4.99 (1 H, d, *J* = 6.9 Hz, H-10), 4.49 (1 H, d, *J* = 6.9 Hz, H-9), 3.67 (2 H, q, *J* = 7.1 Hz, H-12), 3.25 (3 H, s, H-7), 0.74 (3 H, t, *J* = 7.1 Hz, H-13); δ_C (100 MHz, $CDCl_3$): 169.6 (C-8 *minor*), 169.2 (C-8 *major*), 163.8 (C-11 *minor*), 162.3 (C-11 *major*), 142.7 (C-6 *major*), 142.5 (C-6 *minor*), 134.5 (Ar-C), 134.3 (Ar-C), 134.1 (Ar-C), 133.7 (Ar-C), 130.4 (Ar-CH), 130.2 (Ar-CH), 129.5 (Ar-CH), 129.3 (Ar-CH), 129.2 (Ar-CH), 129.1 (Ar-CH), 129.0 (Ar-CH), 128.7 (Ar-CH), 128.6 (Ar-CH), 128.5 (Ar-CH), 128.38 (Ar-CH), 128.35 (Ar-CH), 128.3 (Ar-CH), 128.2 (Ar-CH), 128.1 (Ar-CH), 127.6 (Ar-CH), 127.3 (Ar-CH), 127.2 (Ar-CH), 73.6 (C-10 *major*), 72.6 (C-10 *minor*), 61.7 (C-12 *minor*), 61.0 (C-12 *major*), 46.4 (C-9 *minor*), 44.5 (C-9 *major*), 41.1 (C-7 *major*), 38.1 (C-7 *minor*), 13.8 (C-13 *major*), 13.3 (C-13 *minor*); HRMS [ES^+] found MH^+, 452.1529. $C_{25}H_{26}NO_5S$ requires 474.1526.

Lab book ref. RG216-c

Ethyl 4-(indolin-1-yl)-4-oxo-2-(phenylsulfonyl)butanoate (164h)

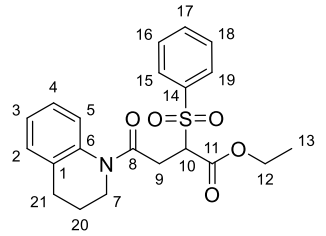


Ethyl 2-(phenylsulfonyl)acetate **165a** (285 mg, 1.25 mmol) and KO*t*Bu (154 mg, 1.38 mmol) in THF (9 mL) and 2-bromo-1-(indolin-1-yl)ethanone **131h** (399 mg, 1.67 mmol) in THF (2 mL) were subjected to general procedure B for 16 h. Purification by flash column chromatography (7:3 hexane/EtOAc) afforded the title compound **164h** (394 mg, 1.02 mmol, 81%) as a colourless solid.

R_f: 0.21 (7:3 hexane/EtOAc); m.p. 126–128 °C; ν_{max}/cm^{-1} (neat): 2980, 1738 (C=O), 1654 (C=O), 1483, 1421, 1324 (S=O), 1148 (S=O); δ_H (400 MHz, $CDCl_3$): 8.07 (1 H, d, *J* = 7.9 Hz, H-2), 7.90 (2 H, d, *J* = 7.6 Hz, H-15 and H-19), 7.72-7.66 (1 H, m, H-17), 7.58 (2 H, t, *J* = 7.3 Hz, H-16 and H-18), 7.18-7.11 (2 H, m, H-5 and H-3 or H-4), 7.00 (1 H, t, *J* = 7.1 Hz, H-3 or H-4), 4.67-4.61 (1 H, m, H-10), 4.17-3.98 (4 H, m, H-7 and H-12), 3.41-3.17 (4 H, H-9 and H-20), 1.03 (3 H, t, *J* = 7.1 Hz, H-13); δ_C (100 MHz, $CDCl_3$): 166.3 (C-8), 165.2 (C-11), 142.4 (C-1 or C-6), 137.8 (C-14), 134.3 (Ar-CH), 131.1 (C-1, C-6 or C-14), 129.1 (Ar-CH), 128.9 (Ar-CH), 127.5 (C-Ar-CH), 124.6 (Ar-CH), 124.1 (C-3 or C-4), 116.9 (C-2), 66.3 (C-10), 62.4 (C-7 or C-12), 47.9 (C-7 or C-12), 32.0 (C-9 or C-20), 27.9 (C-9 or C-20), 13.6 (C-13); HRMS [ES^+] found MH^+, 388.1219. $C_{20}H_{22}NO_5S$ requires 388.1213.

Lab book ref. RG240

Ethyl 4-(3,4-dihydroquinolin-1(2*H*)-yl)-4-oxo-2-(phenylsulfonyl)butanoate (164i)

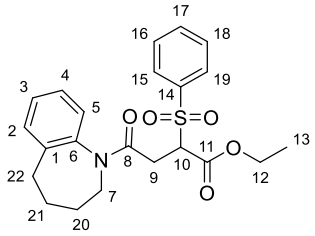


Ethyl 2-(phenylsulfonyl)acetate **165a** (381 mg, 1.67 mmol) and KO*t*Bu (187 mg, 1.67 mmol) in THF (9 mL) and 2-bromo-1-(3,4-dihydroquinolin-1(2H)-yl)ethanone **131i** (316 g, 1.25 mmol) in THF (2 mL) were subjected to general procedure B for 18 h. Purification by flash column chromatography (13:7 hexane/EtOAc) afforded the title compound **164i** (339 g, 845 µmol, 68%) a yellow oil.

R_f: 0.23 (13:7 hexane/EtOAc); ν_{max}/cm^{-1} (neat): 2942, 1737 (C=O), 1650 (C=O), 1492, 1400, 1323 (S=O), 1240, 1147 (S=O); δ_H (400 MHz, $CDCl_3$): 7.87-7.75 (2 H, m, ArH), 7.68-7.61 (1 H, m, ArH), 7.56-7.49 (2 H, m, ArH), 7.22-7.03 (4 H, m, ArH), 4.64-4.56 (1 H, m, H-10), 4.08-3.96 (2 H, m, H-12), 3.83-3.64 (2 H, m, H-7), 3.45-3.16 (2 H, m, H-9), 2.75-2.63 (2 H, m, H-21), 2.01-1.79 (2 H, m, H-20), 1.07-0.99 (3 H, m, H-13); δ_C (100 MHz, $CDCl_3$): 168.1 (C-8), 165.2 (C-11), 137.6 (Ar-CH), 134.2 (Ar-CH), 129.0 (Ar-CH), 128.8 (Ar-CH), 128.6 (Ar-CH), 126.3 (Ar-CH), 126.0 (Ar-CH) 124.4 (Ar-C), 67.1 (C-10), 62.2 (C-12), 43.0 (C-7), 31.3 (C-9), 26.5 (C-21), 23.7 (C-20), 13.5 (C-13); HRMS [ES^+] found MH^+, 402.1369. $C_{21}H_{24}NO_5S$ requires 402.1370.

Lab book ref. RG241

Ethyl 4-oxo-2-(phenylsulfonyl)-4-(2,3,4,5-tetrahydro-1*H*-benzo[b]azepin-1-yl)butanoate (164j)

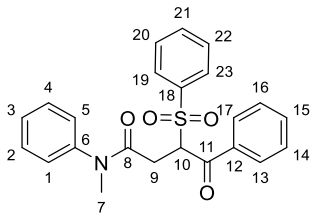


Ethyl 2-(phenylsulfonyl)acetate **165a** (204 mg, 896 µmol) and KO*t*Bu (100 mg, 896 µmol) in THF (5 mL) and 2-bromo-1-(2,3,4,5-tetrahydro-1*H*-benzo[b]azepin-1-yl)ethanone **131j** (120 mg, 448 µmol) in THF (2 mL) were subjected to general procedure B for 16 h. Purification by flash column chromatography (3:2 hexane/EtOAc) afforded the title compound **164j** (119 g, 286 µmol, 64%) as an colourless oil.

R_f: 0.22 (3:2 hexane/EtOAc); ν_{max}/cm^{-1} (neat): 2938, 1737 (C=O), 1650 (C=O), 1408, 1400, 1322 (S=O), 1145 (S=O); δ_H (400 MHz, $CDCl_3$): 7.81-7.77 (2 H, m, ArH), 7.68-7.62 (1 H, m, ArH), 7.52 (2 H, t, *J* = 7.8 Hz, ArH), 7.26-7.12 (4 H, m, ArH), 4.63-4.56 (2 H, m, H-10 and CH_2), 4.13-3.96 (2 H, m, H-12), 3.24-3.02 (1 H, m, CH_2), 2.89-2.76 (1 H, m, CH_2), 2.73 (3 H, m, CH_2 and CH_2), 2.01-1.69 (3 H, m, CH_2 and CH_2), 1.41-1.27 (1 H, m, CH_2), 1.08-1.02 (3 H, m, H-13); δ_C (100 MHz, $CDCl_3$): 167.5 (C-8), 167.4 (C-8), 165.5 (C-11), 165.2 (C-11), 142.0 (Ar-C), 141.9 (Ar-C), 140.9 (Ar-C), 140.7 (Ar-C), 138.0 (Ar-C), 137.9 (Ar-C), 134.2 (Ar-CH), 130.6 (Ar-CH), 129.0 (Ar-CH), 128.9 (Ar-CH), 128.8 (Ar-CH), 128.6 (Ar-CH), 128.5 (Ar-CH), 127.7 (Ar-CH), 127.6 (Ar-CH), 127.5 (Ar-CH), 127.3 (Ar-CH), 66.9 (C-10), 62.28 (C-12), 62.25 (C-12), 47.70 (CH_2), 47.65 (CH_2), 34.4 (CH_2), 34.2 (CH_2), 31.1 (CH_2), 31.0 (CH_2), 29.0 (CH_2), 28.96 (CH_2), 26.4 (CH_2), 13.7 (C-13) (nb. ^{13}C spectra contains mixture of rotamers so assignment was problematic); HRMS [ES^+] found MH^+, 438.1349. $C_{22}H_{25}NNaO_5S$ requires 438.1346.

Lab book ref. RG283

***N*-Methyl-4-oxo-*N*,4-diphenyl-3-(phenylsulfonyl)butanamide (164k)**

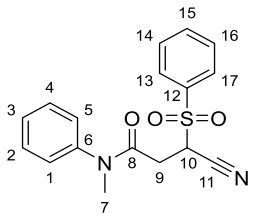


1-Phenyl-2-(phenylsulfonyl)ethanone **165b** (274 mg, 1.05 mmol) and KO*t*Bu (118 mg, 1.05 mmol) in THF (4 mL) and 2-bromo-*N*-methyl-*N*-phenylacetamide **131a** (120 mg, 0.526 mmol) in THF (1.5 mL) were subjected to general procedure B for 18 h. Purification by flash column chromatography (4:1 hexane/EtOAc) afforded the title compound **164k** (213 mg, 523 µmol, 99%) as a colourless solid.

R_f: 0.22 (4:1 hexane/EtOAc); ν_{max}/cm^{-1} (neat): 3061, 1681 (C=O), 1654 (C=O), 1596, 1496, 1448, 1377, 1310 (S=O), 1150 (S=O); δ_H (400 MHz, $CDCl_3$): 7.90 (2 H, d, *J* = 7.3 Hz, ArH), 7.54-7.30 (11 H, m, ArH), 7.21 (2 H, d, *J* = 7.3 Hz, ArH), 5.61 (1 H, dd, *J* = 10.9, 3.1 Hz, H-10), 3.17-3.09 (1 H, m, H-9), 3.16 (3 H, s, H-7), 2.89 (1 H, dd, *J* = 16.7, 3.1 Hz, H-9); δ_C (100 MHz, $CDCl_3$): 191.8 (C-11), 168.6 (C-8), 142.7 (C-6), 136.7 (Ar-C), 134.1 (Ar-CH), 133.5 (Ar-CH), 130.1 (Ar-CH), 129.2 (Ar-CH), 129.1 (Ar-CH), 128.8 (Ar-CH), 128.5 (Ar-CH), 128.4 (Ar-CH), 127.2 (Ar-CH), 66.4 (C-10), 37.4 (C-7), 33.3 (C-9); HRMS [ES^+] found MNa^+, 430.1070. $C_{23}H_{21}NNaO_4S$ requires 430.1083.

Lab book ref. RG280b

***N*-Methyl-4-oxo-*N*,4-diphenyl-3-(phenylsulfonyl)butanamide (164l)**



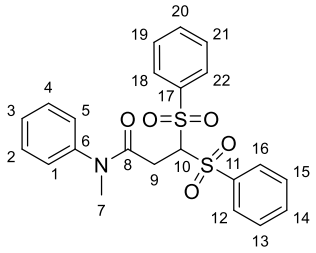
2-(Phenylsulfonyl)acetonitrile **165c** (191 mg, 1.05 mmol) and KO*t*Bu (118 mg, 1.05 mmol) in THF (4 mL) and 2-bromo-*N*-methyl-*N*-phenylacetamide **131a** (120 mg, 0.526 mmol) in THF (1.5 mL) were subjected to general procedure B for 18 h. Purification by flash column chromatography (4:1 hexane/EtOAc) afforded the title compound **164l** (123 mg, 302 µmol, 57%) as a colourless solid.

R_f: 0.24 (4:1 hexane/EtOAc); ν_{max}/cm^{-1} (neat): 2925, 1656 (C=O), 1596, 1496, 1333 (S=O), 1157 (S=O); δ_H (400 MHz, $CDCl_3$): 7.97-7.93 (2 H, m, H-13 and H-17), 7.83-7.73 (1 H, m, H-3), 7.68-

7.59 (2 H, m, ArH), 7.54-7.40 (3 H, m, ArH), 7.23 (2 H, d, *J* = 7.6 Hz, H-1 and H-5), 4.73-4.65 (1 H, m, H-10), 3.31 (3 H, s, H-7), 3.06 (1 H, dd, *J* = 16.4, 4.6 Hz, H-9), 2.73 (1 H, dd, *J* = 16.4, 9.2 Hz, H-9); δ_C (100 MHz, $CDCl_3$): 166.0 (C-8), 142.2 (C-6), 135.6 (C-12), 135.4 (Ar-CH), 130.4 (Ar-CH), 129.6 (Ar-CH), 129.4 (Ar-CH), 127.8 (Ar-CH), 127.2 (Ar-CH), 114.0 (C-11), 53.8 (C-10), 37.8 (C-7), 31.5 (C-9); HRMS [ES^+] found MH^+, 329.0947. $C_{17}H_{17}N_2O_3S$ requires 329.0954.

Lab book ref. RG280a-F1

_N_-Methyl-_N_-phenyl-3,3-bis(phenylsulfonyl)propanamide (164m)

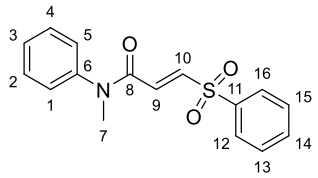


Bis(phenylsulfonyl)methane **165d** (1.30 g, 4.39 mmol) and KO*t*Bu (491 mg, 4.39 mmol) in THF (17 mL) and 2-bromo-*N*-methyl-*N*-phenylacetamide **131a** (500 mg, 2.19 mmol) in THF (5 mL) were subjected to general procedure B for 18 h at 70 °C. Purification by flash column chromatography (7:3 → 3:2 hexane/EtOAc) afforded the title compound **164m** (414 mg, 934 µmol, 43%) as a colourless solid and the by-product (*E*)-*N*-methyl-*N*-phenyl-3-(phenylsulfonyl)acrylamide **164m'** (173 mg, 574 µmol, 26%) as a colourless solid.

R_f: 0.23 (7:3 hexane/EtOAc); m.p. 112–114 °C; ν_{max}/cm^{-1} (neat): 1655 (C=O), 1596, 1497, 1448, 1392, 1331 (S=O), 1156 (S=O), 1079; δ_H (400 MHz, $CDCl_3$): 7.78 (4 H, dd, *J* = 8.4, 1.1 Hz, ArH), 7.62 (2 H, tt, *J* = 7.5, 1.7 Hz, ArH), 7.48-7.43 (6 H, m, ArH), 7.40 (1 H, tt, *J* = 7.3, 2.3 Hz, ArH), 7.27- 7.22 (2 H, m, ArH), 5.63 (1 H, t, *J* = 5.8 Hz, H-10), 3.25 (3 H, s, H-7), 2.97 (2 H, d, *J* = 5.8 Hz, H-9); δ_C (100 MHz, $CDCl_3$): 166.8 (C-8), 142.5 (C-9), 138.1 (C-11 and C-17), 134.4 (CH-Ar), 130.2 (CH-Ar), 129.2 (CH-Ar), 129.0 (CH-Ar), 128.6 (CH-Ar), 127.2 (CH-Ar), 79.8 (C-10), 37.9 (C-7), 29.9 (C-9); HRMS [ES^+] found MNa^+, 466.0755. $C_{22}H_{21}NNaO_5S_2$ requires 466.0753.

Lab book ref. RG172-F3

(*E*)-*N*-Methyl-*N*-phenyl-3-(phenylsulfonyl)acrylamide (164m')

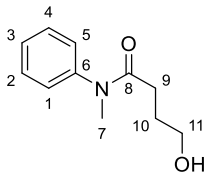


R_f: 0.21 (3:2 hexane/EtOAc); m.p. 85–87 °C; ν_{max}/cm^{-1} (neat): 3032, 1701 (C=O), 1650, 1612, 1493, 1466, 1447, 1377, 1310 (S=O), 1146 (S=O); δ_H (400 MHz, $CDCl_3$): 7.78 (2 H, dd, *J* = 7.2, 1.4 Hz, ArH), 7.62 (1 H, tt, *J* = 7.5, 1.9 Hz, ArH), 7.54-7.48 (2 H, m, ArH), 7.47-7.36 (3 H, m, ArH), 7.28 (1 H, d, *J* = 14.7 Hz, H-9 or H-10) 7.15-7.11 (2 H, m, ArH), 6.82 (1 H, d, *J* = 14.7 Hz, H-9 or H-10), 3.35 (3 H, s, H-7); δ_C (100 MHz, $CDCl_3$): 162.3 (C-8), 141.9 (C-6), 140.4 (C-9 or C-10), 138.9 (C-11), 134.0, 131.6 (Ar-CH or C-9 or C-10), 130.0 (Ar-CH), 129.4 (Ar-CH), 128.5 (Ar-CH or C-9 or C-10), 128.0 (Ar-CH), 126.8 (Ar-CH), 37.8 (C-7); HRMS [ES^+] found MNa^+, 324.0654. $C_{16}H_{15}NNaO_3S$ requires 324.0665.

Lab book ref. RG172-F2

5.8.3 Intermediates

4-(4-Hydroxybenzyloxy)-*N*-methyl-*N*-phenylbutanamide (166)[106]



To a stirred solution of $AlCl_3$ (866 mg, 6.60 mmol) in DCE (2.0 mL) at 0 °C was added a solution of *N*-methylaniline **133a** (1.35 mL, 12.50 mmol) in DCE (1.2 mL). The reaction was allowed to warm to room temperature before γ-butyrolactone (384 µL, 5.00 mmol) was added in one portion. The reaction mixture was stirred at rt for 1 h before being quenched with H_2O (10 mL). The aqueous phase was extracted with DCE (2 × 10 mL) and the combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (EtOAc) afforded the title compound **166** (582 mg, 3.01 mmol, 60%) as a colourless oil.

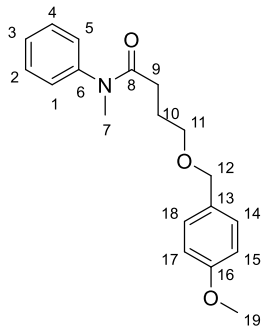
R_f: 0.21 (EtOAc); ν_{max}/cm^{-1} (neat); 3418 (O–H), 2934, 1635 (C=O), 1595, 1422, 1390; δ_H (400 MHz, $CDCl_3$): 7.42 (2 H, t, *J* = 7.5 Hz, H-2 and H-4), 7.34 (1 H, t, *J* = 7.5 Hz, H-3), 7.18 (2 H, d, *J* = 7.5 Hz, H-1 and H-5), 3.60 (2 H, t, *J* = 5.6 Hz, H-11), 3.26 (3 H, s, H-7), 2.22 (2 H, t, *J* = 6.6 Hz, H-9), 1.83-1.75 (2 H, m, H-10); δ_C (100 MHz, $CDCl_3$):173.7 (C-8), 143.9 (C-6), 129.8 (C-2 and C-

4), 127.9 (C-3), 127.2 (C-1 and C-5), 62.7 (C-11), 37.5 (C-7), 32.0 (C-9), 27.9 (C-10); HRMS [ES$^+$] found MH$^+$, 194.1180. $C_{11}H_{16}NO_2$ requires 194.1176.

Lab book ref. RG235

Data consistent with literature values.[106]

4-(4-Methoxybenzyloxy)-*N*-methyl-*N*-phenylbutanamide (167)[107]

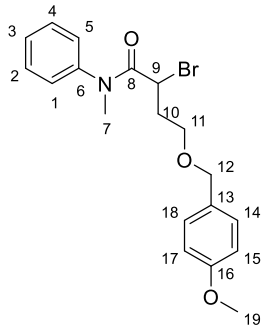


To a stirred solution of 4-(4-hydroxybenzyloxy)-*N*-methyl-*N*-phenylbutanamide **166** (582 mg, 3.01 mmol) in DCM (6.5 mL) was added PMB(HNC)CCl_3 (938 µL, 4.51 mmol) and CSA (69.8 mg, 10 mol%). The reaction mixture was stirred at rt for 21 h. Saturated $NaHCO_3$ (8 mL) was added and the aqueous layer extracted with DCM (3 × 8 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (3:2 hexane/EtOAc) afforded the title compound **167** (595 mg, 1.90 mmol, 63%) as a colourless oil.

Rf: 0.22 (3:2 hexane/EtOAc); ν_{max}/cm^{-1} (neat); 2934, 1657 (C=O), 1596, 1513, 1497, 1385; δ_H (400 MHz, $CDCl_3$): 7.31-7.25 (2 H, m, ArH), 7.25-7.18 (1 H, m, ArH), 7.07-7.02 (4 H, m, ArH), 6.75-6.70 (2 H, m, ArH), 4.23 (2 H, s, H-12), 3.69 (3 H, s, H-19), 3.28 (2 H, t, *J* = 6.1 Hz, H-11), 3.14 (3 H, s, H-7), 2.05 (2 H, t, J = 7.2 Hz, H-9), 1.77 (2 H, quint, *J* = 6.8 Hz, H-10); δ_C (100 MHz, $CDCl_3$):172.7 (C-8), 159.0 (C-16), 144.1 (C-6), 130.6 (C-13), 129.7 (Ar-CH), 129.1 (Ar-CH), 127.7 (Ar-CH), 127.3 (Ar-CH), 113.6 (Ar-CH), 72.2 (C-12), 69.1 (C-11), 55.2 (C-19), 37.3 (C-7), 30.8 (C-9), 25.4 (C-10); HRMS [ES$^+$] found MNa$^+$, 336.1558. $C_{19}H_{23}NNaO_3$ requires 336.1570.

Lab book ref. RG236

2-Bromo-4-(4-methoxybenzyloxy)-*N*-methyl-*N*-phenylbutanamide (131k)[33]



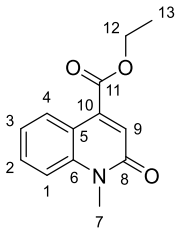
A stirred solution of 4-(4-methoxybenzyloxy)-*N*-methyl-*N*-phenylbutanamide **167** (100 mg, 319 µmol) in THF (1 mL) was cooled to -78 °C. LiHMDS (638 µL, 638 µmol) was added dropwise with stirring continues for a further 15 mins. To the reaction mixture was added dropwise NBS (62 mg, 351 µmol) in THF (0.5 mL) and stirring continued at -78 °C for 2 h. The reaction mixture was quenched with 10 % aqueouse HCl solution (2 mL) the aquesous phase extracted with EtOAc (3 × 2 mL). The organic phases were combined and washed with brine (5 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (4:1 hexane/EtOAc) afforded the title compound **131k** (76 mg, 194 µmol, 61%) as a yellow oil.

R_f: 0.22 (4:1 hexane/EtOAc); ν_{max}/cm^{-1} (neat): 2861, 1664 (C=O), 1595, 1513, 1496, 1389, 1248; δ_H (400 MHz, $CDCl_3$): 7.37-7.29 (3 H, m, ArH), 7.24-7.16 (2 H, m, ArH), 7.11-7.06 (2 H, m, ArH), 6.84-6.81 (2 H, m, ArH), 4.40-4.26 (3 H, m, H-9 and H-12), 3.79 (3 H, s, H-19), 3.46 (2 H, t, *J* = 5.5 Hz, H-11), 3.26 (3 H, s, H-7), 2.44-2.32 (1 H, m, H-10), 2.22-2.10 (1 H, m, H-10); δ_C (100 MHz, $CDCl_3$): 168.9 (C-8), 159.1 (C-16), 142.8 (C-6), 130.2 (C-13), 129.8 (Ar-CH), 129.1 (Ar-CH), 128.3 (Ar-CH), 127.2 (Ar-CH), 113.7 (Ar-CH), 72.5 (C-12), 67.0 (C-11), 55.3 (C-19), 41.5 (C-9), 38.0 (C-7), 35.3 (C-10); HRMS [ES^+] found MNa^+ 414.0670. $C_{19}H_{22}{}^{79}BrNNaO_3$ requires 414.0675.

Lab book ref. RG269

5.8.4 2-Quinolinones

Ethyl 1-methyl-2-oxo-1,2-dihydroquinoline-4-carboxylate (163a)



From ethyl 4-(methyl(phenyl)amino)-4-oxo-2-(phenylsulfonyl)butanoate 164a:

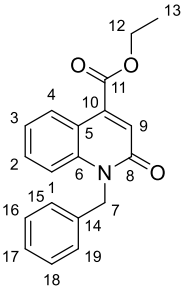
Ethyl 4-(methyl(phenyl)amino)-4-oxo-2-(phenylsulfonyl)butanoate **164a** (100 mg, 266 µmol), copper(II) 2-ethylhexanoate (93.3 mg, 100 mol%) and DIPEA (111 µL, 638 µmol) in mesitylene (8 mL) were subjected to standard procedure C at 165 °C for 18 h. Purification by flash column chromatography (3:2 hexane/EtOAc) afforded the title compound **163a** (59.0 mg, 255 µmol, 96%) as a brown solid.

R_f: 0.19 (3:2 hexane/EtOAc); m.p. 132 °C (Lit[108] 134-135 °C); ν_{max}/cm^{-1} (neat): 2919, 1714 (C=O), 1643 (C=O), 1583, 1454, 1416, 1399, 1334, 1235; δ_H (400 MHz, $CDCl_3$): 8.35 (1 H, dd, *J* = 8.2, 1.1 Hz, H-4), 7.64-7.58 (1 H, m, H-2), 7.41 (1 H, d, *J* = 8.6 Hz, H-1), 7.24-7.18 (1 H, m, H-3), 7.16 (1 H, s, H-9), 4.43 (2 H, d, *J* = 7.1 Hz, H-12), 3.73 (3 H, s, H-7), 1.41 (3 H, t, *J* = 7.1 Hz, H-13); δ_C (100 MHz, $CDCl_3$): 165.3 (C-11), 161.4 (C-8), 140.3 (C-Ar), 138.9 (C-Ar), 131.1 (CH-Ar), 127.1 (CH-Ar), 124.2 (CH-Ar), 122.7 (CH-Ar), 117.5 (C-10), 114.5 (CH-Ar), 62.0 (C-12), 29.8 (C-7), 14.1 (C-13); HRMS [ES^+] found MH^+, 232.0965. $C_{13}H_{14}NO_3$ requires 232.0968.

Data consistent with literature values.[108]

Lab book ref. RG150 and RG185

Ethyl 1-benzyl-2-oxo-1,2-dihydroquinoline-4-carboxylate (163b)



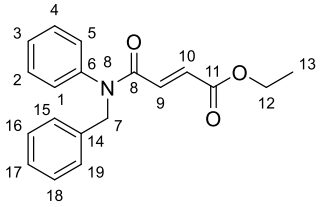
Ethyl 4-(benzyl(phenyl)amino)-4-oxo-2-(phenylsulfonyl)butanoate **164b** (162 mg, 0.359 mmol), copper(II) 2-ethylhexanoate (126 mg, 100 mol%) and DIPEA (150 µL, 0.862 mmol) in mesitylene

(11 mL) were subjected to standard procedure C at 165 °C for 18 h. Purification by flash column chromatography (5:1 hexane/EtOAc) afforded the title compound **163b** (60 mg, 195 µmol, 54%) as a colourless oil and (E)-ethyl 4-(benzyl(phenyl)amino)-4-oxobut-2-enoate **163b'** (19 mg, 61 µmol, 11%) as a yellow oil.

R_f: 0.17 (5:1 hexane/EtOAc); ν_{max}/cm^{-1} (neat): 2978, 1736 (C=O), 1656 (C=O), 1595, 1495, 1449, 1407; δ_H (400 MHz, $CDCl_3$): 8.25 (1 H, d, *J* = 8.2 Hz, H-4), 7.39 (1 H, t, *J* = 8.2 Hz, H-2), 7.28-7.04 (8 H, m, H-1, H-3, H-9 and H-15 to H-19), 5.51 (2 H, s, H-7), 4.40 (2 H, q, *J* = 7.3 Hz, H-12), 1.37 (3 H, t, *J* = 7.3 Hz, H-13); δ_C (100 MHz, $CDCl_3$): 165.3 (C-11), 161.5 (C-8), 139.7 (Ar-C), 139.5 (Ar-C), 135.7 (Ar-C), 131.0 (Ar-CH), 128.7 (Ar-CH), 127.3 (Ar-CH), 127.1 (Ar-CH), 126.5 (Ar-CH), 123.7 (Ar-CH), 122.7 (Ar-CH), 117.7 (Ar-C), 115.5 (Ar-CH), 62.0 (C-12), 46.2 (C-7), 14.2 (C-13); HRMS [ES^+] found MH^+, 308.1282. $C_{19}H_{18}NO_3$ requires 308.1281.

Lab book ref. RG193b-F2

(*E*)-Ethyl 4-(benzyl(phenyl)amino)-4-oxobut-2-enoate (163b')

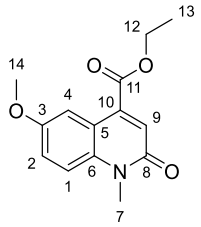


R_f: 0.21 (5:1 hexane/EtOAc); ν_{max}/cm^{-1} (neat): 2980, 1720 (C=O), 1659 (C=O), 1634, 1594, 1494, 1389, 1293, 1160; δ_H (400 MHz, $CDCl_3$): 7.36-7.16 (8 H, m, ArH), 7.01-6.96 (2 H, m, ArH), 6.90 (1 H, d, *J* = 15.3 Hz, H-9), 6.80 (1 H, d, *J* = 15.3 Hz, H-10), 4.98 (2 H, s, H-7), 4.14 (2 H, q, *J* = 7.1 Hz, H-12), 1.23 (3 H, t, *J* = 7.1 Hz, H-13); δ_C (100 MHz, $CDCl_3$): 165.7 (C-11), 164.1 (C-8), 141.1 (C-6), 136.9 (C-14), 134.4 (C-9), 131.6 (C-10), 129.8 (Ar-CH), 128.8 (Ar-CH), 128.6 (Ar-CH), 128.5 (Ar-CH), 128.2 (Ar-CH), 127.7 (Ar-CH), 61.1 (C-12), 53.6 (C-7), 14.2 (C-13); HRMS [ES^+] found MNa^+, 332.1251. $C_{19}H_{19}NNaO_3$ requires 332.1257.

Data consistent with literature values.[109]

Lab book ref. RG193b-F1

Ethyl 6-methoxy-1-methyl-2-oxo-1,2-dihydroquinoline-4-carboxylate (163c)



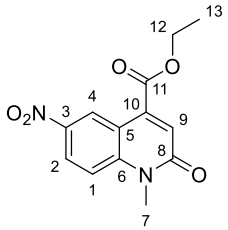
Ethyl 4-((4-methoxyphenyl)(methyl)amino)-4-oxo-2-(phenylsulfonyl)butanoate **164c** (166 mg, 410 µmol), copper(II) 2-ethylhexanoate (144 mg, 100 mol%) and DIPEA (171 µL, 984 µmol) in mesitylene (15 mL) were subjected to standard procedure C at 165 °C for 18 h. Purification by flash column chromatography (1:1 hexane/EtOAc) afforded the title compound **163c** (77 mg, 293 µmol, 71%) as a yellow solid.

R_f: 0.17 (1:1 Petrol/EtOAc); m.p. 99–100 °C (Lit.[110] 105 °C); ν_{max}/cm^{-1} (neat): 1723 (C=O), 1658 (C=O), 1620, 1586, 1563, 1463, 1430; δ_H (400 MHz, $CDCl_3$): 7.97 (1 H, d, *J* = 2.9 Hz, H-4), 7.34 (1 H, d, *J* = 9.3 Hz, H-1), 7.29 (1 H, s, H-9), 7.23 (1 H, dd, *J* = 9.3, 2.9 Hz, H-2), 4.44 (2 H, q, *J* = 7.1 Hz, H-12), 3.87 (3 H, s, H-14), 3.74 (3 H, s, H-7), 1.43 (3 H, t, *J* = 7.1 Hz, H-13); δ_C (100 MHz, $CDCl_3$): 165.4 (C-11), 160.9 (C-8), 155.0 (C-3), 137.6 (C-6), 135.0 (C-5), 125.2 (C-9), 120.1 (C-2), 118.3 (C-10), 115.7 (C-1), 108.8 (C-4), 61.9 (C-12), 55.6 (C-14), 29.9 (C-7), 14.1 (C-13); HRMS [ES^+] found MH^+, 262.1069. $C_{14}H_{16}NO_4$ requires 262.1074.

Data consistent with literature values.[110]

Lab book ref. RG202

Ethyl 1-methyl-6-nitro-2-oxo-1,2-dihydroquinoline-4-carboxylate (163d)

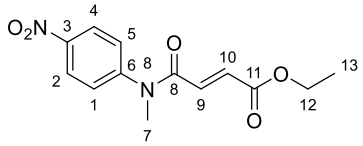


Ethyl 4-(methyl(4-nitrophenyl)amino)-4-oxo-2-(phenylsulfonyl)butanoate **164d** (141 mg, 336 µmol), copper(II) 2-ethylhexanoate (117 mg, 100 mol%) and DIPEA (140 µL, 336 µmol) in mesitylene (10 mL) were subjected to standard procedure C at 165 °C for 18 h. Purification by flash column chromatography (3:2 hexane/EtOAc) afforded the title compound **163d** (21 mg, 76 µmol, 23%) as a yellow solid and alkene **163d'** (32 mg, 115 µmol, 34%) as a brown solid.

R_f: 0.26 (1:1 hexane/EtOAc); m.p. 147–151 °C; ν_{max}/cm^{-1} (neat): 1725 (C=O), 1671 (C=O), 1607, 1524, 1342, 1301; δ_H (400 MHz, $CDCl_3$): 9.44 (1 H, d, *J* = 2.6 Hz, H-4), 8.44 (1 H, dd, *J* = 9.4, 2.6 Hz, H-2), 7.50 (1 H, d, *J* = 9.4 Hz, H-1), 7.40 (1 H, s, H-9), 4.49 (2 H, q, *J* = 7.1 Hz, H-12), 3.80 (3 H, s, H-7), 1.46 (3 H, t, *J* = 7.1 Hz, H-13); δ_C (100 MHz, $CDCl_3$): 171.3 (C-11), 164.2 (C-8), 161.2 (C-Ar), 144.1 (C-Ar), 137.8 (C-Ar), 126.7 (C-9), 125.6 (C-2), 123.8 (C-4), 117.2 (C-Ar), 115.1 (C-1), 62.6 (C-12), 30.4 (C-7), 14.1 (C-13); HRMS [ES^+] found MH^+, 277.0820. $C_{13}H_{13}N_2O_5$ requires 277.0819.

Lab book ref. RG207

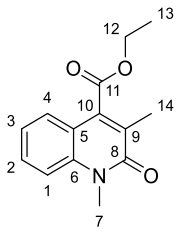
(*E*)-Ethyl 4-(methyl(4-nitrophenyl)amino)-4-oxobut-2-enoate (164d')



R_f: 0.37 (1:1 hexane/EtOAc); ν_{max}/cm^{-1} (neat): 2983, 1720 (C=O), 1665 (C=O), 1592, 1521, 1496, 1341, 1301, 1177; δ_H (400 MHz, $CDCl_3$): 8.30 (2 H, d, *J* = 8.3 Hz, H-2 and H-4), 7.35 (2 H, d, *J* = 8.3 Hz, H-1 and H-5), 6.86 (2 H, s, H-9 and H-10), 4.16 (2 H, q, *J* = 7.3 Hz, H-12), 3.44 (3 H, s, H-7), 1.25 (3 H, t, *J* = 7.3 Hz, H-13); δ_C (100 MHz, $CDCl_3$): 165.2 (C-11), 163.8 (C-8), 148.2 (C-6), 146.2 (C-3), 133.3 (C-9 or C-10), 132.4 (C-9 or C-10), 127.2 (C-1 and C-5), 125.2 (C-2 and C-4), 61.2 (C-12), 37.5 (C-7), 14.0 (C-13); HRMS [ES^+] found MH^+, 279.0971. $C_{13}H_{15}N_2O_5$ requires 279.0975.

Lab book ref. RG207b

Ethyl 1,3-dimethyl-2-oxo-1,2-dihydroquinoline-4-carboxylate (163e)



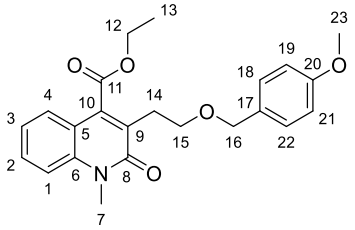
Ethyl 3-methyl-4-(methyl(phenyl)amino)-4-oxo-2-(phenylsulfonyl)butanoate **164e** (167 mg, 429 µmol), copper(II) 2-ethylhexanoate (150 mg, 100 mol%) and DIPEA (179 µL, 1.03 mmol) in mesitylene (12 mL) were subjected to standard procedure C at 165 °C for 18 h. Purification by

flash column chromatography (5:2 hexane/EtOAc) afforded the title compound **163e** (90 mg, 367 µmol, 86%) as an orange solid.

R_f: 0.34 (1:1 hexane/EtOAc); m.p. 68–70 °C; ν_{max}/cm^{-1} (neat): 2982, 1730 (C=O), 1646 (C=O), 1600, 1590, 1464, 1226; δ_H (400 MHz, $CDCl_3$): 7.52 (1 H, t, *J* = 8.5 Hz, H-2), 7.42 (1 H, d, *J* = 8.5 Hz, H-4), 7.34 (1 H, d, *J* = 8.5 Hz, H-1), 7.22 (1 H, t, *J* = 8.5 Hz, H-3), 4.50 (2 H, q, *J* = 7.2 Hz, H-12), 3.74 (3 H, s, H-7), 2.23 (3 H, s, H-14), 1.43 (3 H, t, *J* = 7.2 Hz, H-13); δ_C (100 MHz, $CDCl_3$): 167.0 (C-11), 162.0 (C-8), 139.0 (Ar-C), 138.7 (Ar-C), 130.0 (C-2), 126.9 (Ar-C), 125.5 (C-4), 122.4 (C-3), 117.1 (Ar-C), 114.4 (C-1), 61.9 (C-12), 30.0 (C-7), 14.9 (C-14), 14.2 (C-13); HRMS [ES^+] found MNa^+, 368.0943. $C_{14}H_{15}NNaO_3$ requires 268.0944.

Lab book ref. RG213

Ethyl 3-(2-(4-methoxybenzyloxy)ethyl)-1-methyl-2-oxo-1,2-dihydroquinoline-4-carboxylate (163f)

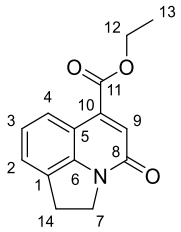


Ethyl 5-(4-methoxybenzyloxy)-3-(methyl(phenyl)carbamoyl)-2-(phenylsulfonyl)pentanoate **164f** (119 mg, 221 µmol), copper(II) 2-ethylhexanoate (77 mg, 100 mol%) and DIPEA (92.0 µL, 529 µmol) in mesitylene (7 mL) were subjected to standard procedure C at 165 °C for 18 h. Purification by flash column chromatography (3:2 hexane/EtOAc) afforded the title compound **163f** (62 mg, 157 µmol, 71%) as an orange oil.

R_f: 0.20 (3:2 hexane/EtOAc); ν_{max}/cm^{-1} (neat): 2935, 1724 (C=O), 1642 (C=O), 1598, 1512, 1462, 1316, 1244; δ_H (400 MHz, $CDCl_3$): 7.57-7.41 (3 H, m, ArH), 7.35-7.26 (1 H, m, ArH), 7.25-7.18 (1 H, m, ArH), 6.88-6.67 (3 H, m, ArH), 4.47-4.41 (3 H, m, CH_2 and CH_2), 3.81-3.65 (5 H, m, H-23, CH_2 and CH_2), 3.46-3.37 (1 H, m, CH_2), 3.27-3.18 (1 H, m, CH_2), 3.00-2.91 (1 H, m, CH_2), 2.63 (3 H, s, H-7), 1.36 (3 H, t, *J* = 7.3 Hz, H-13); δ_C (100 MHz, $CDCl_3$): 170.5 (C-11), 166.9 (C-8), 159.2 (C-20), 140.8 (C-6), 130.5 (Ar-CH), 129.6 (Ar-CH), 129.2 (Ar-CH), 128.3 (Ar-CH), 127.6 (C-17), 126.2 (C-5 or C-9), 122.7 (Ar-CH), 121.2 (C-5 or C-9), 117.4 (C-10), 113.8 (Ar-CH), 72.7 (CH_2), 68.4 (CH_2), 62.2 (CH_2), 55.5 (C-23), 30.2 (CH_2), 26.3 (C-7), 14.4 (C-13); HRMS [ES^+] found MNa^+, 418.1617. $C_{23}H_{25}NNaO_5$ requires 418.1625.

Lab Book Ref. RG282

Ethyl 11-oxo-1-azatricyclo[6.3.1.0^{4,12}]dodeca-4,6,8(12),9-tetraene-9-carboxylate (163h)



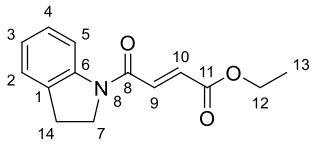
Ethyl 2-(benzenesulfonyl)-4-(2,3-dihydro-1*H*-indol-1-yl)-4-oxobutanoate **164h** (298 mg, 770 µmol), copper(II) 2-ethylhexanoate (270 mg, 100 mol%) and DIPEA (321 µL, 1.85 mmol) in mesitylene (16 mL) were subjected to standard procedure C at 165 °C for 18 h. Purification by flash column chromatography (1:3 hexane/EtOAc) afforded the title compound **163h** (32 mg, 132 µmol, 17%) as an orange oil and alkene **163h'** (87 mg, 355 µmol, 46%) as an orange oil.

R_f: 0.21 (1:3 hexane/EtOAc); ν_{max}/cm^{-1} (neat): 1718 (C=O), 1652 (C=O), 1608, 1469, 1247; δ_H (400 MHz, $CDCl_3$): 8.24 (1 H, d, *J* = 8.0 Hz, H-4), 7.39 (1 H, d, *J* = 8.0 Hz, H-2), 7.35 (1 H, s, H-9), 7.22 (1 H, t, *J* = 8.0 Hz, H-3), 4.49-4.41 (4 H, m, H-7 and H-12), 3.46 (2 H, t, *J* = 8.4, H-14), 1.44 (3 H, t, *J* = 6.9 Hz, H-13); δ_C (100 MHz, $CDCl_3$): 165.1 (C-11), 160.1 (C-8), 143.1 (Ar-C), 137.5 (Ar-C), 130.7 (Ar-C), 127.1 (C-9), 125.8 (C-2), 124.0 (C-3 or C-4), 123.7 (C-3 or C-4), 115.3 (Ar-C), 62.0 (C-12), 47.0 (C-7), 27.3 (C-14), 14.3 (C-13);

HRMS [ES$^+$] found MNa$^+$, 266.0787. $C_{14}H_{13}NNaO_3$ requires 266.0788.

Lab book ref. RG251

Ethyl (2E)-4-(2,3-dihydro-1*H*-indol-1-yl)-4-oxobut-2-enoate (163h')

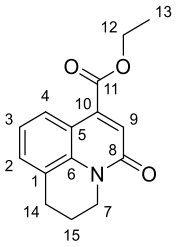


R_f: 0.78 (1:3 hexane/EtOAc); ν_{max}/cm^{-1} (neat): 1716 (C=O), 1649 (C-O), 1482, 1409; δ_H (400 MHz, $CDCl_3$): 8.22 (1 H, d, *J* = 7.6 Hz, H-2), 7.29 (1 H, d, *J* = 15.3 Hz, H-9), 7.18-7.11 (2 H, m, H-3 and H-5), 7.00 (1 H, t, *J* = 7.3 Hz, H-4), 6.90 (1 H, d, *J* = 15.3 Hz, H-10), 4.24-4.13 (4 H, m, H-7 and H-12), 3.17 (2 H, t, *J* = 8.4 Hz, H-14), 1.27 (3 H, t, *J* = 7.3 Hz, H-13); δ_C (100 MHz, $CDCl_3$): 165.7 (C-11), 161.9 (C-8), 142.4 (C-6), 134.6 (C-9), 132.1 (C-10), 131.8 (C-2), 127.7 (C-3 or C-5), 124.7 (C-4 and C-3 or C-5), 117.8 (C-1), 61.3 (C-12), 48.3 (C-7), 28.0 (C-14), 14.2 (C-13); HRMS [ES$^+$] found MH$^+$, 246.1126. $C_{14}H_{16}NO_3$ requires 246.1125.

Data consistent with literature values.[111]

Lab book ref. RG251-alkene

Ethyl 2-oxo-1-azatricyclo[7.3.1^{5,13}]trideca-3,5(13),6,8-tetraene-4-carboxylate (163i)

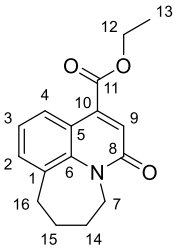


Ethyl 2-(benzenesulfonyl)-4-oxo-4-(1,2,3,4-tetrahydroquinolin-1-yl)butanoate **164i** (230 mg, 574 µmol), copper(II) 2-ethylhexanoate (201 mg, 100 mol%) and DIPEA (240 µL, 1.38 mmol) in mesitylene (12 mL) were subjected to standard procedure C at 165 °C for 18 h. Purification by flash column chromatography (1:1 hexane/EtOAc) afforded the title compound **163i** (80 mg, 311 µmol, 54%) as an orange solid.

R_f: 0.24 (1:1 hexane/EtOAc); m.p. 134–136 °C; ν_{max}/cm^{-1} (neat): 2937, 1718 (C=O), 1641 (C=O), 1582, 1431, 1232, 1066; δ_H (400 MHz, $CDCl_3$): 8.13 (1 H, d, *J* = 8.0 Hz, H-4), 7.32 (d, 1 H, d, *J* = 7.7 Hz, H-2), 7.16 (1 H, t, *J* = 7.7 Hz, H-3), 7.15 (1 H, s, H-9), 4.42 (2 H, q, *J* = 7.1 Hz, H-12), 4.19 (2 H, t, *J* = 6.0 Hz, H-7), 2.98 (2 H, t, *J* = 6.0 Hz, H-14), 2.09 (2 H, quint, *J* = 6.0 Hz, H-15), 1.41 (3 H, t, *J* = 7.1 Hz, H-13); δ_C (100 MHz, $CDCl_3$): 165.5 (C-8), 160.9 (C-11), 138.9 (Ar-C), 137.0 (Ar-C), 130.5 (C-2), 125.0 (C-9), 124.9 (C-3 or C-4), 123.4 (C-3 or C-4), 122.2 (Ar-C), 117.3 (Ar-C), 61.9 (C-12), 42.7 (C-7), 27.9 (C-14), 20.4 (C-15), 14.1 (C-13); HRMS [ES$^+$] found MH$^+$, 258.1125. $C_{15}H_{16}NO_3$ requires 258.1125.

Lab book ref. RG247

Ethyl 3-oxo-5,6,7,8-tetrahydro-3*H*-azepino[3,2,1-ij]quinoline-1-carboxylate (163j)

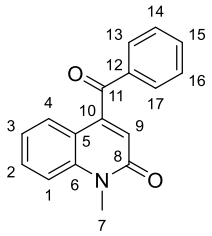


Ethyl 4-oxo-2-(phenylsulfonyl)-4-(2,3,4,5-tetrahydro-1H-benzo[b]azepin-1-yl)butanoate ethyl 4-oxo-2-(phenylsulfonyl)-4-(2,3,4,5-tetrahydro-1*H*-benzo[b]azepin-1-yl)butanoate **164j** (72 mg, 173 µmol), copper(II) 2-ethylhexanoate (60.0 mg, 100 mol%) and DIPEA (72.3 µL, 416 µmol) in mesitylene (5.5 mL) were subjected to standard procedure C at 165 °C for 18 h. Purification by flash column chromatography (13:7 hexane/EtOAc) afforded the title compound **163j** (36 mg, 311 µmol, 77%) as an orange oil.

R_f: 0.22 (13:7 hexane/EtOAc); ν_{max}/cm^{-1} (neat): 2937, 1728 (C=O), 1655 (C=O), 1587, 1448, 1243; δ_H (400 MHz, $CDCl_3$): 8.01 (1 H, d, *J* = 7.6 Hz, H-4), 7.30 (1 H, d, *J* = 7.6 Hz, H-2), 7.12 (1 H, t, *J* = 7.6 Hz), 7.07 (1 H, s, H-9), 4.46-4.38 (4 H, m, H-7 and H-12), 3.17-3.11 (2 H, m, H-16), 2.14-2.05 (2 H, m, H-14 or H-15), 2.02-1.93 (2 H, m, H-14 or H-15), 1.39 (3 H, t, *J* = 7.3 Hz, H-13); δ_C (100 MHz, $CDCl_3$): 165.7 (C-11), 162.4 (C-8), 141.7 (Ar-C), 139.8 (Ar-C), 133.7 (C-2), 130.7 (Ar-C), 124.7 (C-4), 123.4 (C-9), 122.7 (C-3), 118.7 (Ar-C), 61.9 (C-12), 44.8 (C-7), 33.2 (C-14, C-15 or C-16), 25.4 (C-14, C-15 or C-16), 23.8 (C-14, C-15 or C-16), 14.1 (C-14); HRMS [ES^+] found MNa^+, 294.1093. $C_{16}H_{17}NNaO_3$ requires 294.1101.

Lab book ref. RG286

4-Benzoyl-1-methylquinolin-2(1*H*)-one (163k)



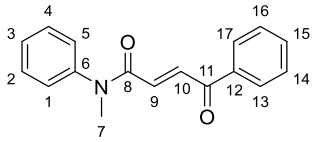
N-methyl-4-oxo-*N*,4-diphenyl-3-(phenylsulfonyl)butanamide **164k** (100 mg, 245 µmol), copper(II) 2-ethylhexanoate (85.9 mg, 100 mol%) and DIPEA (102 µL, 589 µmol) in mesitylene (7 mL) were subjected to standard procedure C at 165 °C for 18 h. Purification by flash column chromatography (13:7 hexane/EtOAc) afforded the title compound **163k** (49 mg, 186 µmol, 76%) as an orange solid and by-product (*E*)-*N*-methyl-4-oxo-*N*,4-diphenylbut-2-enamide **163k'** (14 mg, 52.8 µmol, 22%) as an orange solid.

R_f: 0.19 (13:7 hexane/EtOAc); m.p. 83–85 °C; ν_{max}/cm^{-1} (neat): 1656 (C=O), 1589, 1452, 1250; δ_H (400 MHz, $CDCl_3$): 7.94 (2 H, d, *J* = 8.0 Hz, ArH), 7.67-7.59 (2 H, m, ArH), 7.56-7.44 (4 H, m, ArH), 7.19 (1 H, t, *J* = 8.0 Hz, ArH), 6.72 (1 H, s, H-9), 3.79 (3 H, s, H-7); δ_C (100 MHz, $CDCl_3$): 194.7 (C-11), 161.2 (C-8), 147.2 (Ar-C), 140.3 (Ar-C), 135.7 (Ar-C), 134.5 (Ar-CH), 131.4 (Ar-CH), 130.2 (Ar-CH), 128.8 (Ar-CH), 127.0 (Ar-CH), 122.6 (Ar-CH), 120.5 (C-9), 118.1 (Ar-C), 114.7 (Ar-CH), 29.7 (C-7); HRMS [ES^+] found MNa^+, 286.0833. $C_{17}H_{13}NNaO_2$ requires 286.0838.

Data consistent with literature values.[112]

Lab book ref. RG281-F2

(*E*)-*N*-methyl-4-oxo-*N*,4-diphenylbut-2-enamide (163k')

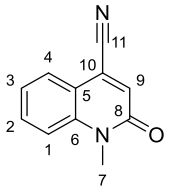


R_f: 0.26 (13:7 hexane/EtOAc); m.p. 65–68 °C; ν_{max}/cm^{-1} (neat): 1644 (C=O), 1594, 1495, 1374, 1306; δ_H (400 MHz, $CDCl_3$): 7.98 (1 H, d, *J* = 15.3 Hz, H-10), 7.98 (2 H, d, *J* = 7.6 Hz, H-13 and H-17), 7.59 (1 H, t, 7.6 Hz, H-15), 7.48 (2 H, t, *J* = 7.6 Hz, H-14 and H-16), 7.45 (2 H, t, *J* = 7.6 Hz, H-2 and H-4), 7.37 (1 H, t, *J* = 7.6 Hz, H-3), 7.20 (2 H, d, *J* = 7.6 Hz, H-1 and H-5), 6.93 (1 H, d, *J* = 15.3 Hz, H-9), 3.44 (3 H, s, H-7); δ_C (100 MHz, $CDCl_3$): 189.8 (C-11), 164.7 (C-8), 142.8 (C-6), 137.0 (C-12), 133.8 (C-10), 133.7 (C-15), 133.4 (C-9), 130.0 (Ar-C), 128.91 (Ar-C), 128.88 (Ar-C), 128.3 (C-13 and C-17), 127.2 (C-1 and C-5), 38.0 (C-4); HRMS [ES^+] found MNa^+, 288.0989. $C_{17}H_{15}NNaO_2$ requires 288.0995.

Data consistent with literature values.[113]

Lab Book Ref. RG281-F1

1-Methyl-2-oxo-1,2-dihydroquinoline-4-carbonitrile (163l)



3-Cyano-*N*-methyl-*N*-phenyl-3-(phenylsulfonyl)propanamide **164l** (76 mg, 231 µmol), copper(II) 2-ethylhexanoate (81.0 mg, 100 mol%) and DIPEA (96.6 µL, 555 µmol) in mesitylene (7 mL) were subjected to standard procedure C at 165 °C for 18 h. Purification by flash column chromatography (3:2 hexane/EtOAc) afforded the title compound **163l** (24 mg, 130 µmol, 56%) as an orange solid.

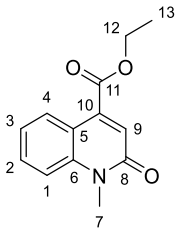
Rf: 0.22 (3:2 hexane/EtOAc); m.p. 127–129 °C (Lit.[114] 165–166 °C); ν_{max}/cm^{-1} (neat): 1659 (C=O), 1593, 1457; δ_H (400 MHz, $CDCl_3$): 7.96 (1 H, dd, *J* = 7.6, 1.5 Hz, H-1), 7.72 (1 H, t, *J* = 8.4 Hz, H-3), 7.46 (1 H, d, *J* = 8.4 Hz, H-4), 7.41 (1 H, t, *J* = 7.6 Hz, H-2), 7.17 (1 H, s, H-9), 3.76 (3 H, s, H-7); δ_C (100 MHz, $CDCl_3$): 159.8 (C-8), 140.0 (C-6), 132.5 (C-3), 128.8 (C-9), 126.8 (C-1), 123.3 (C-2), 122.5 (C-11), 117.6 (C-10), 114.8 (C-4), 114.3 (C-5), 29.8 (C-7); HRMS [ES^+] found MNa^+, 207.0531. $C_{11}H_8N_2NaO$ requires 207.0529.

Data consistent with literature values.[114]

Lab Book Ref. RG284

5.8.5 One-pot synthesis of 2-quinolinones

Ethyl 1-methyl-2-oxo-1,2-dihydroquinoline-4-carboxylate (163a)



*From 2-bromo-N-methyl-N-phenylacetamide **131a**:*

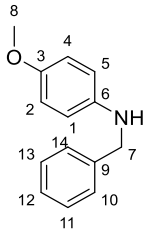
To a stirred solution of ethyl 2-(phenylsulfonyl)acetate **165a** (50 mg, 219 µmol) in mesitylene (2.25 mL) was added KO*t*-Bu (27.0 mg, 241 µmol) and held for 5 min. 2-Bromo-*N*-methyl-*N*-phenylacetamide **131a** (50 mg, 439 µmol) in mesitylene (0.5 mL) was added and stirring continued for 1 h at 60 °C under an atmosphere of air. Copper(II) 2-ethylhexanoate (77 mg, 100 mol%), DIPEA (89 µL, 526 µmol) and mesitylene (1.75 mL) were added to the reaction mixture and stirred at 165 °C for 16 h under an atmosphere of air. The solvent was removed under reduced pressure and EtOAc (10 mL) was added. The solution was washed with 10% HCl solution (8 mL), 10% aqueous NH_4OH solution (8 mL), brine (8 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (3:2 hexane/EtOAc) afforded the title compound **163a** (42 mg, 182 µmol, 83%) as a brown solid.

Data as above.

Lab book ref. RG294

5.9 The first reported total synthesis of the biologically active 2-quinolinones 169 and 170

***N*-Benzyl-4-methoxyaniline (133i)**



To a stirred solution of 4-methoxyaniline **133c** (7.14 g, 58 mmol) in methanol (100 mL) at room temperature was added benzaldehyde (5.93 mL, 58 mmol) over 30 min by syringe-pump. The reaction mixture was heated to reflux and held for 2 min then allowed to cool to room temperature.

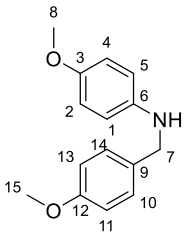
$NaBH_4$ (2.40 g, 63.5 mmol) was added portion-wise over 1 h then the reaction mixture was stirred at room temperature for 2 h. The reaction was quenched with water (100 mL) then the MeOH removed under reduced pressure. The remaining aqueous solution was extracted with EtOAc (3 × 75 mL) and the combined organic fractions concentrated *in vacuo*. Purification by flash column chromatography (9:1 petrol/EtOAc) afforded the title compound **133i** (9.88 g, 43.3 mmol, 75%) as a yellow solid.

R_f: 0.71 (1:1 hexane/EtOAc); m.p. 30–33 °C (Lit.[115] 52 °C); ν_{max}/cm^{-1} (neat); 3414, 2998, 1624, 1510, 1452, 1243, 1233, 1035; δ_H (400 MHz, $CDCl_3$): 7.43-7.36 (4 H, m, H-10, H-11, H-13 and H-14), 7.35-7.28 (1 H, m, H-12), 6.83 (2 H, d, *J* = 8.6 Hz, H-1 and H-5 or H-2 and H-4), 6.63 (2 H, d, *J* = 8.6 Hz, H-1 and H-5 or H-2 and H-4), 4.31 (2 H, s, H-7), 3.86 (1 H, s, N-H), 3.77 (3 H, s, H-8); δ_C (100 MHz, $CDCl_3$): 152.0 (C-3), 142.3 (C-6), 139.6 (C-9), 128.4 (C-10 and C-14 or C-11 and C-13), 127.4, 127.0 (C-12), 114.8 (C-1 and C-5 or C-2 and C-4), 113.9 (C-1 and C-5 or C-2 and C-4), 55.6 (C-8), 49.0 (C-7); HRMS [ES^+] found MH^+, 214.1227. $C_{14}H_{16}NO$ requires 214.1226.

Lab book ref. RG166

Data consistent with literature values.[115]

4-Methoxy-*N*-(4-methoxybenzyl)aniline (133j)



To a stirred solution of 4-methoxyaniline **133c** (2.00 g, 16.2 mmol) in methanol (35 mL) at room temperature was added 4-methoxybenzaldehyde (1.97 mL, 16.2 mmol) over 30 min by syringe-pump. The reaction mixture was heated to reflux and held for 2 min then allowed to cool to room temperature. $NaBH_4$ (1.35 g, 35.8 mmol) was added portion-wise over 1 h then the reaction mixture was stirred at room temperature for 2 h. The reaction was quenched with water (35 mL) then the MeOH removed under reduced pressure. The remaining aqueous solution was extracted with EtOAc (3 × 50 mL) and the combined organic fractions concentrated *in vacuo*. Purification by flash column chromatography (4:1 hexane/EtOAc) afforded the title compound **133j** (3.12 g, 12.8 mmol, 79%) as a colourless crystalline solid.

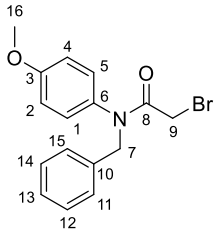
Rf: 0.22 (4:1 hexane/EtOAc); m.p. 100-101 °C (Lit.[116] 94–95 °C); ν_{max}/cm^{-1} (neat); 2958, 2838, 1611, 1517; δ_H (400 MHz, $CDCl_3$): 7.29 (2 H, d, *J* = 8.5 Hz, H-10 and H-14), 6.88 (2 H, d, *J* = 8.5

Hz, H-11 and H-13), 6.78 (2 H, d, *J* = 9.0 Hz, H-1 and H-5 or H-1 and H-4), 6.61 (2 H, d, *J* = 9.0 Hz, H-1 and H-5 or H-1 and H-4), 4.21 (2 H, s, H-7), 3.81 (3 H, s, H-8 or H-15), 3.75 (3 H, s, H-8 or H-15); HRMS [ES$^+$] found MH$^+$, 242.1168. $C_{15}H_{16}NO_2$ requires 242.1176.

Lab book ref. RG263

Data consistent with literature values.[116]

***N*-Benzyl-2-bromo-*N*-(4-methoxyphenyl)acetamide (131l)**

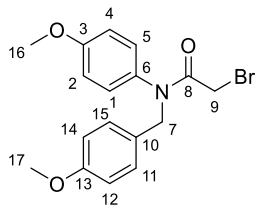


N-benzyl-4-methoxyaniline **133l** (1.28 g, 6.0 mmol), triethylamine (835 µL, 6.0 mmol), DCM (7 mL) and bromoacetyl bromide **134a** (521 µL, 6.0 mmol) in DCM (10 mL) were subjected to general procedure A to afford the title compound **131l** (1.76 g, 5.25 mmol, 88%) as a brown oil.

R_f: 0.37 (1:1 Petrol/EtOAc); ν_{max}/cm^{-1} (neat): 3010, 2934, 2837, 1653 (C=O), 1509, 1434, 1401, 1293, 1251; δ_H (400 MHz, $CDCl_3$): 7.29-7.22 (3 H, m, ArH), 7.20-7.13 (2 H, m, 2 H), 6.94 (2 H, d, *J* = 8.8 Hz, H-1 and H-5), 6.81 (2 H, d, *J* = 8.8 Hz, H-2 and H-4), 4.84 (2 H, s, H-7), 3.79 (3 H, s, H-16), 3.66 (2 H, s, H-9); δ_C (100 MHz, $CDCl_3$): 166.8 (C-8), 159.3 (C-3), 136.5 (C-6 or C-10), 133.6 (Ar-CH), 129.1 (Ar-CH), 128.8 (Ar-CH), 128.3 (Ar-CH), 127.5 (Ar-CH), 114.7 (C-2 and C-4), 55.3 (C-16), 53.7 (C-7), 27.3 (C-9); HRMS [ES$^+$] found MH$^+$ 334.0426. $C_{16}H_{17}{}^{79}BrNO_2$ requires 334.0437.

Lab book ref. RG170

2-Bromo-*N*-(4-methoxybenzyl)-N-(4-methoxyphenyl)acetamide (131m)



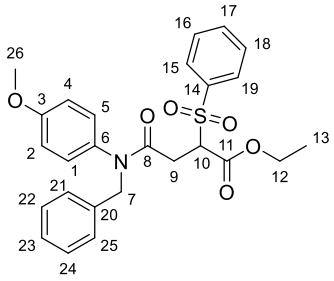
4-Methoxy-*N*-(4-methoxybenzyl)aniline **133j** (2.00 g, 8.22 mmol), triethylamine (1.14 mL, 8.22 mmol), DCM (10 mL) and bromoacetyl bromide **134a** (714 µL, 48.22 mmol) in DCM (14 mL)

were subjected to general procedure A. Purification by flash column chromatography (4:1 hexane/EtOAc) afforded the title compound **131m** (2.64 g, 7.25 mmol, 88%) as a brown oil.

R_f: 0.22 (4:1 hexane/EtOAc); ν_{max}/cm^{-1} (neat): 2934, 1658 (C=O), 1509, 1300, 1247, 1175; δ_H (400 MHz, $CDCl_3$): 7.05 (2 H, d, *J* = 8.5 Hz, ArH), 6.88 (2 H, d, *J* = 8.8 Hz, ArH), 6.78 (2 H, d, *J* = 8.8 Hz, ArH), 6.74 (2 H, d, *J* = 8.5 Hz, ArH), 4.73 (2 H, s, H-7), 3.75 (3 H, s, H-16 or H-17), 3.72 (3H, s, H-16 or H-17), 3.61 (2 H, s, H-9); δ_C (100 MHz, $CDCl_3$): 166.5 (C-8), 159.2 (C-3 or C-13), 158.9 (C-3 or C-13), 133.5 (C-5), 130.2 (Ar-CH), 129.2 (Ar-CH), 128.7 (C-10), 114.6 (Ar-CH), 113.6 (Ar-CH), 55.3 (C-16 or C-17), 55.0 (C-16 or C-17), 53.0 (C-7), 27.5 (C-9); HRMS [ES^+] found MNa^+ 386.0354. $C_{17}H_{18}{}^{79}BrNNaO_3$ requires 386.0362.

Lab book ref. RG264

Ethyl 4-(benzyl(4-methoxyphenyl)amino)-4-oxo-2-(phenylsulfonyl)butanoate (164o)

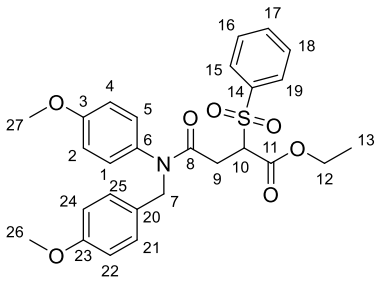


Ethyl 2-(phenylsulfonyl)acetate **165a** (1.36 g, 5.98 mmol) and KO*t*Bu (670 mg, 5.98 mmol) in THF (42 mL) and *N*-benzyl-2-bromo-*N*-(4-methoxyphenyl)acetamide **131l** (1.00 g, 2.99 mmol) in THF (9 mL) were subjected to general procedure B for 4 h. Purification by flash column chromatography (13:7 hexane/EtOAc) afforded the title compound **164o** (1.06 g, 2.20 mmol, 74%) as an orange gum.

R_f: 0.22 (13:7 hexane/EtOAc); ν_{max}/cm^{-1} (neat): 1738 (C=O), 1654 (C=O), 1512, 1447, 1408, 1324 (S=O), 1250, 1148 (S=O); δ_H (400 MHz, $CDCl_3$): 7.80 (2 H, dd, *J* = 8.4, 1.2 Hz, H-15 and H-19), 7.66 (1 H, tt, *J* = 7.5, 1.8 Hz, H-17), 7.53 (2 H, t, *J* = 7.4 Hz, H-16 and H-18), 7.27-7.21 (3 H, m, ArH), 7.15-7.12 (2 H, m, ArH), 6.90 (2 H, d, *J* = 9.0 Hz, H-1 and H-5), 6.83 (2 H, d, *J* = 9.0 Hz, H-2 and H-4), 4.84 (1 H, d, *J* = 14.2 Hz, H-7), 4.73 (1 H, d, *J* = 14.2 Hz, H-7), 4.60 (1 H, dd, *J* = 10.6, 4.0 Hz, H-10), 4.13-3.98 (2 H, m, H-12), 3.81 (3 H, s, H-26), 2.95 (1 H, dd, *J* = 16.9, 10.6 Hz, H-9), 2.84 (1 H, dd, *J* = 16.9, 4.0 Hz, H-9), 1.06 (3 H, t, *J* = 7.2 Hz, H-13); δ_C (100 MHz, $CDCl_3$): 168.9 (C-8), 165.4 (C-11), 159.4 (C-3), 138.0 (C-14), 137.0 (C-Ar), 134.3 (C-17), 133.8 (C-Ar), 129.5 (CH-Ar), 129.1 (CH-Ar), 129.0 (CH-Ar), 128.9 (CH-Ar), 128.5 (CH-Ar), 127.6 (CH-Ar), 115.1 (CH-Ar), 67.1 (C-10), 62.4 (C-12), 55.6 (C-26), 53.5 (C-7), 31.0 (C-9), 13.7 (C-13); HRMS [ES^+] found MH^+, 482.1637. $C_{26}H_{28}NO_6S$ requires 482.1632.

Lab book ref. RG187

Ethyl 4-((4-methoxybenzyl)(4-methoxyphenyl)amino)-4-oxo-2-(phenylsulfonyl)butanoate (164p)

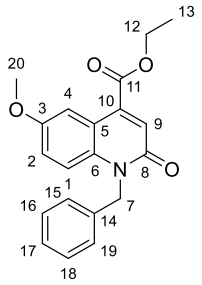


Ethyl 2-(phenylsulfonyl)acetate **165a** (1.00 g, 4.40 mmol) and KO*t*Bu (492 mg, 4.40 mmol) in THF (32 mL) and 2-bromo-*N*-(4-methoxybenzyl)-*N*-(4-methoxyphenyl)acetamide **131m** (800 mg, 2.20 mmol) in THF (6 mL) were subjected to general procedure B for 18 h. Purification by flash column chromatography (3:2 hexane/EtOAc) afforded the title compound **164p** (960 mg, 1.89 mmol, 85%) as an orange gum

R_f: 0.21 (3:2 hexane/EtOAc); ν_{max}/cm^{-1} (neat): 2937, 1738 (C=O), 1654 (C=O), 1512, 1447, 1408, 1323 (S=O), 1248, 1148 (S=O); δ_H (400 MHz, $CDCl_3$): 7.80 (2 H, d, *J* = 7.5 Hz, H-15 and H-19), 7.66 (1 H, t, *J* = 7.5 Hz, H-17), 7.53 (2 H, t, *J* = 7.5 Hz, H-16 and H-18), 7.04 (2 H, d, *J* = 8.6 Hz, H-21 and H-25), 6.89-6.81 (4 H, m, H-1, H-2, H-4 and H-5), 6.76 (2 H, d, *J* = 8.6 Hz, H-22 and H-24), 4.79 (1 H, d, *J* = 14.1 Hz, H-7), 4.66 (1 H, d, *J* = 14.1 Hz, H-7), 4.59 (1 H, dd, *J* = 10.6, 4.0 Hz, H-10), 4.12-3.98 (2 H, m, H-12), 3.82 (3 H, s, H-26 or H-27), 3.77 (3 H, s, H-26 or H-27), 2.93 (1 H, dd, *J* = 16.9, 10.6 Hz, H-9), 2.82 (1 H, dd, *J* = 16.9, 4.0 Hz, H-9), 1.06 (3 H, t, *J* = 7.2 Hz, H-13); δ_C (100 MHz, $CDCl_3$): 168.6 (C-8), 165.3 (C-11), 159.3 (C-3 or C-23), 158.9 (C-3 or C-23), 137.9 (C-14), 134.1 (C-17), 133.6 (Ar-C), 130.1 (Ar-CH), 129.4 (Ar-CH), 129.1 (Ar-C), 129.0 (Ar-CH), 128.8 (Ar-CH), 115.0 (Ar-CH), 113.7 (C-22 and C-24), 66.9 (C-10), 62.2 (C-12), 55.4 (C-26 or C-27), 55.2 (C-26 or C-27), 52.7 (C-7), 31.0 (C-9), 13.6 (C-13); HRMS [ES^+] found MNa^+, 534.1530. $C_{27}H_{29}NNaO_7S$ requires 534.1557.

Lab book ref. RG272

Ethyl 1-benzyl-6-methoxy-2-oxo-1,2-dihydroquinoline-4-carboxylate (163n)

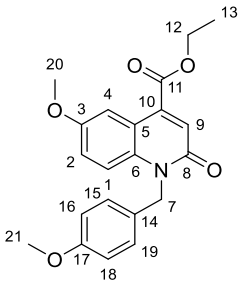


Ethyl 4-(benzyl(4-methoxyphenyl)amino)-4-oxo-2-(phenylsulfonyl)butanoate **164o** (241 mg, 501 µmol), copper(II) 2-ethylhexanoate (175 mg, 100 mol%) and DIPEA (209 µL, 1.20 mmol) in mesitylene (15 mL) were subjected to standard procedure C at 165 °C for 18 h. Purification by flash column chromatography (7:3 hexane/EtOAc) afforded the title compound **163n** (117 mg, 344 µmol, 69%) as an orange solid.

R_f: 0.18 (7:3 hexane/EtOAc); ν_{max}/cm^{-1} (neat): 1723 (C=O), 1655 (C=O), 1617, 1590, 1563, 1496, 1454, 1431; δ_H (400 MHz, $CDCl_3$): 7.91 (1H, d, *J* = 2.8 Hz, H-4), 7.34 (1 H, s, H-9), 7.30-7.13 (6 H, m, ArH), 7.04 (1 H, dd, *J* = 9.3, 2.9 Hz, ArH), 5.54 (2 H, br s, H-7), 4.44 (2 H, q, *J* = 7.1 Hz, H-12), 3.80 (3 H, s, H-20), 1.42 (3 H, t, *J* = 7.1 Hz, H-13); δ_C (100 MHz, $CDCl_3$): 165.3 (C-11), 161.0 (C-8), 154.9 (C-3), 138.2 (C-Ar), 135.8 (C-Ar), 134.2 (C-Ar), 128.7 (CH-Ar), 127.3 (CH-Ar), 126.4 (CH-Ar), 124.8 (C-9), 119.9 (CH-Ar), 118.5 (C-10), 116.5 (CH-Ar), 108.8 (C-4), 61.9 (C-12), 55.5 (C-20), 46.2 (C-7), 14.1 (C-13); HRMS [ES^+] found MNa^+, 360.1211. $C_{20}H_{19}NNaO_4$ requires 360.1206.

Lab book ref. RG189

Ethyl 6-methoxy-1-(4-methoxybenzyl)-2-oxo-1,2-dihydroquinoline-4-carboxylate (163o)

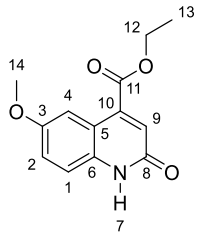


Ethyl 4-((4-methoxybenzyl)(4-methoxyphenyl)amino)-4-oxo-2-(phenylsulfonyl)butanoate **164p** (491 mg, 960 µmol), copper(II) 2-ethylhexanoate (336 mg, 100 mol%) and DIPEA (400 µL, 2.30 mmol) in mesitylene (27 mL) were subjected to standard procedure C at 165 °C for 18 h. Purification by flash column chromatography (7:3 hexane/EtOAc) afforded the title compound **163o** (232 mg, 631 µmol, 66%) as an orange solid.

R_f: 0.19 (7:3 hexane/EtOAc); m.p. 84–86 °C; ν_{max}/cm^{-1} (neat): 2937, 1725 (C=O), 1656 (C=O), 1513, 1431, 1247; δ_H (400 MHz, $CDCl_3$): 7.91 (1 H, d, 2.9 Hz, H-4), 7.33 (1 H, s, H-9), 7.25 (1 H, d, *J* = 9.5 Hz, H-1), 7.11 (2 H, d, *J* = 8.7 Hz, H-15 and H-19 or H-16 and H-18), 7.07 (1 H, dd, *J* = 9.5, 2.9 Hz, H-2), 6.80 (2 H, d, *J* = 8.7 Hz, H-15 and H-19 or H-16 and H-18), 5.48 (2 H, s, H-7), 4.44 (2 H, q, *J* = 7.1 Hz, H-12), 3.82 (3 H, s, H-20 or H-21), 3.73 (3 H, s, H-20 or H-21), 1.43 (3 H, t, *J* = 7.1 Hz, H-13); δ_C (100 MHz, $CDCl_3$): 165.4 (C-11), 161.0 (C-8), 158.8 (C-14), 154.9 (C-17), 138.2 (C-3 or C-5), 134.3 (C-3 or C-5), 127.9 (C-6), 127.8 (C-15 and C-19 or C-16 and C-18), 125.0 (C-9), 120.0 (C-2), 118.6 (C-10), 116.6 (C-1), 114.2 (C-15 and C-19 or C-16 and C-18), 108.8 (C-4), 62.0 (C-12), 55.6 (C-20 or C-21), 55.2 (C-20 or C-21), 45.7 (C-7), 14.1 (C-13); HRMS [ES^+] found MNa^+, 390.1301. $C_{21}H_{21}NNaO_5$ requires 390.1312.

Lab book ref. RG273

Ethyl 6-methoxy-2-oxo-1,2-dihydroquinoline-4-carboxylate (169)



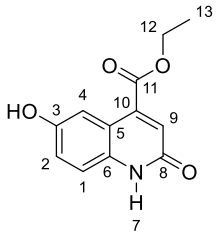
Ethyl 6-methoxy-1-(4-methoxybenzyl)-2-oxo-1,2-dihydroquinoline-4-carboxylate **163o** (100 mg, 272 µmol) in TFA (2 mL) was stirred at 85 °C for 18 h. The reaction mixture was added dropwise to cold saturated $NaHCO_3$ solution (20 mL) then extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (20 mL) and concentrated *in vacuo*. Purification by flash column chromatography (3:1 hexane/EtOAc) afforded the title compound **169** (55 mg, 0.22 mmol, 82%) as a yellow solid.

R_f: 0.27 (1:3 hexane/EtOAc); m.p. 140–143 °C (Lit.[80c] 183–186 °C); ν_{max}/cm^{-1} (neat): 2991, 1726 (C=O), 1681 (C=O), 1623, 1503, 1448, 1234; δ_H (400 MHz, d_6-DMSO): 12.04 (1 H, s, N-H), 7.60 (1 H, d, *J* = 2.6 Hz, H-4), 7.31 (1 H, d, *J* = 8.9 Hz, H-1), 7.24 (1 H, dd, *J* = 8.9, 2.6 Hz, H-2), 6.92 (1 H, s, H-9), 4.38 (2 H, q, *J* = 6.9 Hz, H-12), 3.33 (3 H, s, H-14), 1.35 (3 H, t, *J* = 6.9 Hz, H-13); δ_C (100 MHz, d_6-DMSO): 165.6 (C-11), 160.9 (C-8), 154.9 (C-3), 139.8 (C-6), 134.6 (C-5), 125.4 (C-9), 120.8 (C-2), 117.8 (C-1), 116.6 (C-10), 108.0 (C-4), 62.4 (C-12), 55.9 (C-14), 14.5 (C-13); HRMS [ES^+] found MNa^+, 270.0743. $C_{13}H_{13}NNaO_4$ requires 270.0737.

Lab Book Ref: RG275b

Data consistent with literature values[80c]

Ethyl 6-hydroxy-2-oxo-1,2-dihydroquinoline-4-carboxylate (170)[117]



*From ethyl 6-methoxy-2-oxo-1,2-dihydroquinoline-4-carboxylate **169**:*

To a stirred solution of ethyl 6-methoxy-2-oxo-1,2-dihydroquinoline-4-carboxylate **169** (28 mg, 113 µmol) in DCM (1.13 mL) at -78 °C was added BBr_3 (1 M solution in DCM, 340 µL, 340 µmol). The solution was allowed to warm to room temperature and stirred for 16 h. The reaction mixture was quenched with brine (5 mL) and extracted with EtOAc (3 × 5 mL). The combined organic extracts were washed with brine (5 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography afforded the title compound **170** (25 mg, 107 µmol, 95%) as a colourless solid.

Lab Book Ref: RG291c

*From ethyl 6-methoxy-1-(4-methoxybenzyl)-2-oxo-1,2-dihydroquinoline-4-carboxylate (**163o**):*

To a stirred solution of ethyl 6-methoxy-1-(4-methoxybenzyl)-2-oxo-1,2-dihydroquinoline-4-carboxylate **163o** (37 mg, 101 µmol) in DCM (1.01 mL) at -78 °C was added BBr_3 (1 M solution in DCM, 605 µL, 605 µmol). The solution was allowed to warm to room temperature and stirred for 16 h. The reaction mixture was quenched with brine (5 mL) and extracted with EtOAc (3 × 5 mL). The combined organic extracts were washed with brine (5 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography afforded the title compound **170** (15 mg, 64.4 µmol, 64%) as a colourless solid.

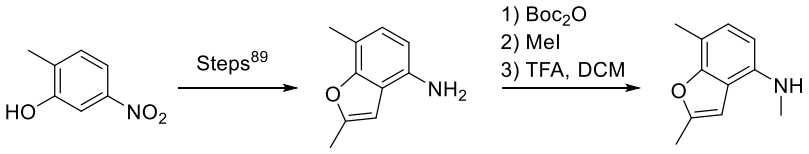
R_f: 0.22 (19:1 hexane/EtOAc); m.p. > 200 °C; ν_{max}/cm^{-1} (neat): 3289 (O-H), 1712 (C=O), 1654 (C=O), 1615, 1423, 1254; δ_H (400 MHz, d_6-DMSO): 11.93 (1 H, s, N-H), 9.54 (1 H, s, O-H), 7.46 (1 H, d, *J* = 2.6 Hz, H-4), 7.22 (1 H, d, *J* = 8.9 Hz, H-1), 7.06 (1 H, dd, *J* = 8.9, 2.6 Hz, H-2), 6.85 (1 H, s, H-9), 4.36 (2 H, q, *J* = 6.9 Hz, H-12), 1.34 (3 H, t, *J* = 6.9 Hz, H-13); δ_C (100 MHz, d_6-DMSO): 166.1 (C-11), 161.1 (C-8), 153.4 (C-3), 140.2 (C-6), 133.7 (C-5), 125.0 (C-9), 121.6 (C-2), 117.8 (C-1), 117.2 (C-10), 110.4 (C-4), 62.7 (C-12), 14.8 (C-13); HRMS [ES^+] found MNa^+, 256.0577. $C_{12}H_{11}NNaO_4$ requires 256.0580.

Lab Book Ref: RG291a

Data consistent with literature values.[80c]

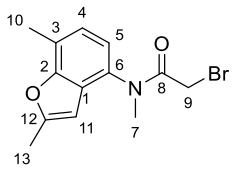
5.10 Application of copper conditions to the total synthesis of HOFQ

N,2,7-Trimethylbenzofuran-4-amine (154)



The title compound was synthesised by a colleague. The multi-step synthesis of 2,7-dimethylbenzofuran-4-amine **153** was carried out according to the procedure reported by Rodighiero *et al.*[93] This was then converted to title compound **154** by the same procedure as 2,4-dimethoxy-*N*-methylaniline **133e** was synthesised from 2,4-dimethoxy aniline as described previously.

2-Bromo-*N*-(2,7-dimethylbenzofuran-4-yl)-*N*-methylacetamide (131n)

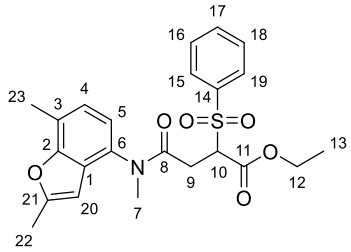


N,2,7-Trimethylbenzofuran-4-amine **133k** (1.13 g, 6.42 mmol), triethylamine (971 µL, 6.98 mmol), DCM (7 mL) and bromoacetyl bromide (607 µL, 6.98 mmol) in DCM (10 mL) were subjected to general procedure A. Purification by flash column chromatography (3:2 hexane/EtOAc) afforded the title compound **131n** (1.670 g, 5.64 mmol, 88%) as a colourless solid.

R_f: 0.21 (3:2 hexane/EtOAc); m.p. 64–66 °C; ν_{max}/cm^{-1} (neat): 3107, 2917, 1672 (C=O), 1505, 1371, 1186; δ_H (400 MHz, $CDCl_3$): 7.02 (1 H, d, *J* = 7.8 Hz, H-4 or H-5), 6.98 (1 H, d, *J* = 7.8 Hz, H-4 or H-5), 6.31 (1 H, s, H-11), 3.66-3.64 (2 H, m, H-9), 3.31 (3 H, s, H-7), 2.51 (3 H, s, H-10 or H-13), 2,48 (3 H, s, H-10 or H-13); δ_C (100 MHz, $CDCl_3$): 166.9 (C-8), 156.8 (C-12), 154.3 (C-2), 131.9 (C-6), 125.9 (C-1), 124.5 (C-4 or C-5), 121.7 (C-3), 121.1 (C-4 or C-5), 100.1 (C-11), 37.3 (C-7), 27.1 (C-9), 14.8 (C-10 or C-13), 14.1 (C-10 or C-13); HRMS [ES^+] found MH^+ 296.0281. $C_{13}H_{15}{}^{79}BrNO_2$ requires 296.0281.

Lab book ref. RG296

Ethyl 4-((2,7-dimethylbenzofuran-4-yl)(methyl)amino)-4-oxo-2-(phenylsulfonyl)butanoate (134q)

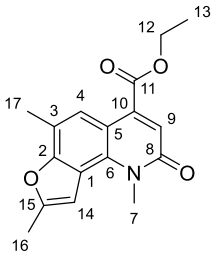


Ethyl 2-(phenylsulfonyl)acetate **165a** (578 mg, 2.54 mmol) and KO*t*Bu (303 mg, 2.70 mmol) in THF (20 mL) and 2-bromo-*N*-(2,7-dimethylbenzofuran-4-yl)-*N*-methylacetamide **131n** (500 mg, 1.69 mmol) in THF (7.5 mL) were subjected to general procedure B for 18 h. Purification by flash column chromatography (7:3 hexane/EtOAc) afforded the title compound **134q** (678 mg, 1.53 μmol, 90%) as a colourless gum.

R_f: 0.35 (1:1 hexane/EtOAc); ν_{max}/cm^{-1} (neat): 2925, 1738 (C=O), 1658 (C=O), 1324 (S=O), 1188, 1148 (S=O); δ_H (400 MHz, $CDCl_3$): 7.72 (2 H, d, *J* = 7.8 Hz, H-15 and H-19), 7.62 (1 H, t, *J* = 7.8 Hz, H-17), 7.47 (2 H, t, *J* = 7.8 Hz, H-16 and H-18), 7.01 (1 H, d, *J* = 7.8 Hz, H-4 or H-5), 6.96-6.89 (1 H, m, H-4 or H-5), 6.27 (1 H, s, H-20), 4.54-4.47 (1 H, m, H-10), 4.12-3.96 (2 H, m, H-12), 3.23 (3 H, s, H-7), 3.10-3.61 (2 H, m, H-9), 2.52 (3 H, s, H-22 or H-23), 2.46 (3 H, s, H-22 or H-23), 1.04 (3 H, t, *J* = 7.15 Hz, H-13); δ_C (100 MHz, $CDCl_3$): 168.7 (C-8), 165.2 (C-11), 156.6 (C-21), 154.3 (C-2), 137.6 (C-14), 134.0 (C-17), 131.6 (C-6), 128.8 (C-15 and C-19 or C-16 and C-18), 128.7 (C-15 and C-19 or C-16 and C-18), 126.0 (C-1), 124.7 (C-4 or C-5), 121.4 (C-3), 121.2 (C-4 or C-5), 100.0 (C-20), 66.7 (C-10), 62.1 (C-12), 36.7 (C-7), 30.6 (C-9), 14.8 (C-22 or C-23), 14.1 (C-22 or C-23), 13.6 (C-13); HRMS [ES^+] found MH^+, 444.1479. $C_{23}H_{26}NO_6S$ requires 444.1475.

Lab book ref. RG297

Ethyl 1,6,8-trimethyl-2-oxo-1,2dihydrofuro[2,3-*h*]quinoline-4-carboxylate (163p)

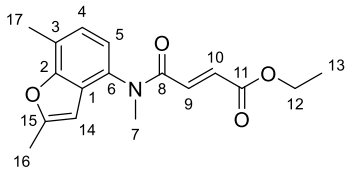


Ethyl 4-((2,7-dimethylbenzofuran-4-yl)(methyl)amino)-4-oxo-2-(phenylsulfonyl)butanoate **134q** (270 mg, 609 µmol), copper(II) 2-ethylhexanoate (416 mg, 200 mol%) and DIPEA (254 µL, 1.46 mmol µmol) in mesitylene (18 mL) were subjected to standard procedure C at 165 °C for 18 h. Purification by flash column chromatography (13:7 hexane/EtOAc) afforded the title compound **163p** (52 mg, 174 µmol, 29%) as an orange oil and (*E*)-ethyl 4-((2,7-dimethylbenzofuran-4-yl)(methyl)amino)-4-oxobut-2-enoate **163p'** (66 mg, 285 µmol, 36%) as an orange oil.

R_f: 0.22 (1:1 hexane/EtOAc); ν_{max}/cm^{-1} (neat): 2924, 1726 (C=O), 1652 (C=O), 1590, 1236; δ_H (400 MHz, $CDCl_3$): 7.86 (1 H, s, H-9), 7.06 (1 H, s, H-4), 6.91 (1 H, s, H-14), 4.46 (2 H, q, 7.3 Hz, H-12), 4.03 (3 H, s, H-12), 2.53 (6 H, s, H-16 and H-17), 1.44 (3 H, *J* = 7.3 Hz, H-13); δ_C (100 MHz, $CDCl_3$): 166.4 (C-11), 162.0 (C-8), 155.9 (C-2), 154.6 (C-15), 140.4 (C-6), 134.4 (C-10), 125.0 (C-1), 122.5 (C-9), 120.4 (C-4), 117.8 (C-5), 113.0 (C-3), 104.5 (C-14), 62.2 (C-12) 33.5 (C-7), 15.2 (C-16 or C-17), 14.4 (C-13), 14.1 (C-16 or C-17); HRMS [ES^+] found MNa^+, 322.1043. $C_{17}H_{17}NNaO_4$ requires 322.1050.

Lab Book Ref: RG299-F4 and RG298-F4

(*E*)-Ethyl 4-((2,7-dimethylbenzofuran-4-yl)(methyl)amino)-4-oxobut-2-enoate (163p')



R_f: 0.61 (1:1 hexane/EtOAc); ν_{max}/cm^{-1} (neat): 2927, 1720 (C=O), 1661 (C=O), 1508, 1369, 1293; δ_H (400 MHz, $CDCl_3$): 7.00 (1 H, d, *J* = 7.6 Hz, H-5), 6.86 (1 H, d, *J* = 7.6 Hz, H-4), 6.86 (1 H, d, *J* = 15.3 Hz, H-9), 7.68 (1 H, d, *J* = 15.3 Hz, H-10), 6.24 (1 H, s, H-14), 4.12 (2 H, q, *J* = 7.3 Hz, H-12), 3.38 (3 H, s, H-7), 2.51 (3 H, s, H-16 or H-17), 2.46 (3 H, s, H-16 or H-17), 1.21 (3 H, t, *J* = 7.3 Hz, H-13); δ_C (100 MHz, $CDCl_3$): 165.6 (C-11), 164.3 (C-8), 156.6 (C-2), 154.2 (C-15), 134.2 (C-10) 131.5 (C-3), 130.8 (C-6), 125.9 (C-1), 124.7 (C-9), 124.5 (C-5), 121.3 (C-4), 100.1 (C-14), 60.8 (C-12) 36.9 (C-7), 14.8 (C-16 or C-17), 14.1 (C-16 or C-17), 13.9 (C-13); HRMS [ES^+] found MNa^+, 324.1208. $C_{17}H_{19}NNaO_4$ requires 324.1212.

Lab Book Ref: RG299-F2 and RG298-F2

Abbreviations

acac	acetylacetonate
ADH	antidiuretic hormone
Ar	aryl
br	broad
Bu	butyl
bz	benzoyl
Cat.	catalyst
CN	cyano
COSY	correlation spectroscopy
CPME	cyclopentyl methyl ether
CSA	camphor sulfonic acid
Cy	cyclohexyl
δ	chemical shift
d	doublet
dba	*E*,*E*-dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0] undec-7-ene
DCC	*N,N'*-dicyclohexylcarbodiimide
DCE	dichloroethane
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEPT	distortionless enhancement by polarisation transfer
DFT	density functional theory
DIPEA	*N*,*N*-diisopropylethylamine
DMA	*N*,*N*-dimethylacetamide
DMAP	*N*,*N*-dimethylaminopyridine
DME	*N*,*N*-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
Boc	*t*-butyloxycarbonyl
e^-	electron
EC	ethylene carbonate
edathamil	ethylenediaminetetraacetic acid copper(II) disodium salt
EDTA	ethylenediaminetetraacetic acid
ee	enantiomeric excess
EnCat	encapsulated catalyst
eq.	equivalent(s)
ESI	electrospray ionisation

Et-glycol	ethylene glycol
ether	diethyl ether
Et	ethyl
EWG	electron-withdrawing group
FGI	functional group interconversion
h	hour(s)
HMBC	heteronuclear multiple bond correlation
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum coherence
i	iso
IR	infrared
J	coupling constant (Hz)
KHMDS	potassium bis(trimethylsilyl)amide
LiHMDS	lithium bis(trimethylsilyl)amide
m	multiplet
MAP	methylaminopropyl
Me	methyl
mesityl.	mesitylene
min	minute(s)
m.p.	melting point
Ms	mesyl
MS	molecular sieves
NBS	*N*-bromosuccinimide
NHC	*N*-heterocyclic carbene
NMP	*N*-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
[O]	oxidation
Pc	2-pyrazinecarboxylate
PC	propylene carbonate
petrol	petroleum ether 40–60 °C
Ph	phenyl
Phosphazene	*tert*-butylimino-tris(diethylamino)phosphorane
PMB	4-methoxybenzyl ether
PMP	1,2,2,6,6-pentamethylpiperidine
ppm	parts per million
Pr	propyl
p-TSA	*para*-toluene sulfonic acid
q	quartet

[R]	reduction
RDS	rate determining step
R_f	retention factor
RME	reaction mass efficiency
rt	room temperature
s	singlet
sat.	saturated
t	triplet
t	tertiary
TBACl	tetrabutylammonium chloride
TBHP	*tert*-butyl hydroperoxide
TBPB	*tert*-butyl peroxybenzoate
TCA	trichloroacetic acid
tetralin	1,2,3,4-tetrahydronaphthalene
Tf	triflate
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	tetramethylsilyl
trig	trigonal
Ts	tosyl
T3P	propane phosphonic acid anhydride
UV	ultraviolet

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