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 focused 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(1H)-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(1H)-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).
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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, 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).

![Nexium (Esomeprazole) 1, Sultent (Sunitinib) 2, Ambilify (Aripiprazole) 3, Lipitor (Atorvastatin) 4](image)

**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 and classic reactions such as the Fischer indole, Hantzsch pyridine and Friedlander quinoline 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. 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. 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 is calculated:

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

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)\textsuperscript{9} is reaction mass efficiency (RME) which, unlike atom economy, takes into account the
stoichiometry of reactants being used. RME is calculated:

\[ RME = \frac{\text{Mass of C}}{\text{Mass of A} + \text{Mass of B}} \]

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:

\[ EMY (\%) = \frac{\text{Mass of product} \times 100}{\text{Total mass input}} \]

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.\(^\text{10}\)

\subsection{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.\(^\text{11}\) 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.\(^\text{12}\) To put this into perspective, the estimated global reserves of copper is 626 billion Kg.\(^\text{12}\) 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.\(^\text{13}\) 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.\(^\text{14}\) 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\(^\text{15}\) 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, 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. 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).
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.
Prabhakar et al. synthesised 3,3-disubstituted oxindoles from carboxylic acids 8 by intramolecular formation of the amide bond using DCC (Scheme 1.2). 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 low-temperature reaction steps. From a green metrics perspective this is unfavourable but additionally the R² and R³ 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 9²² 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 disadvantages to this method. Several additives are required for this reaction including 3 equivalents of NaO'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 Hsieh’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.\(^\text{24}\)

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.\(^\text{25}\) A very early example is the Stollé procedure reported in 1914 utilising Friedel-Crafts chemistry to cyclise chloro-anilides 11,\(^\text{26}\) however the use of transition metal catalysis to achieve this feat, e.g. from anilide 12, has now become common practice (Scheme 1.1).\(^\text{20}\)

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.](image)

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 \(\text{Pd(OAc)}_2\), along with several other additives which compromise the reaction mass efficiency.
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(O2Piv)$_2$ and AgF, C–H activation of CH$_3$CN occurs generating Pd$^{IV}$ complex D which undergoes reductive elimination to produce the oxindole product and regenerate palladium complex A.
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, the work of Hartwig illustrates this approach well (Scheme 1.11). 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. In 2012, Bolm reported a transition metal-free variant of Hartwig’s synthesis of oxindoles, by KOtBu promoted intramolecular α-arylation of 2-fluororaniides (Scheme 1.12).

Scheme 1.12 Oxindole synthesis by KOtBu promoted intramolecular α-arylation.

Despite avoiding the use of transition metals, however, there are several drawbacks to this approach. The reaction is effectively an SNAr reaction with fluoride as the leaving group, thus producing halogenated waste. The C–F 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.\textsuperscript{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\textsuperscript{34} (Scheme 1.13).

\textbf{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).\textsuperscript{35}

\textbf{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’.
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”. The key concepts and applications to heterocycle synthesis have been reviewed by Storey and Kwong. This method has been widely implemented in the synthesis of oxindoles. 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 which utilises inexpensive and elementally sustainable FeCl₃ as the catalyst (Scheme 1.16). This method offers high atom economy, utilises an inexpensive catalyst and gives high yields across a wide 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 tBuOOH 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\textsuperscript{40} and Taylor\textsuperscript{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\textsuperscript{19d} offer some advantage over those of Kündig.\textsuperscript{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 and kinetic isotope effect studies which suggested that the formation of the initial radical was not rate limiting. Further evidence was provided by a detailed DFT study by Kündig, 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 (CF₃ 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·H₂O (5 mol%) in refluxing mesitylene without the requirement for base. 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 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\textsuperscript{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).

\begin{center}
\textbf{Scheme 2.1} Synthesis of anilide 40.
\end{center}

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.\textsuperscript{42} Catalysts based on metals other than copper including Fe(acac)\textsubscript{3}, Ni(acac)\textsubscript{2}, Cr(acac)\textsubscript{3} and Co(acac)\textsubscript{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. Neither copper(II) 2-pyrazinecarboxylate (entry 4, Table 2.1) or Cu(NCCH$_3$)$_4$CF$_3$SO$_3$ (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.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Metal Salt (1 eq. unless otherwise stated)</th>
<th>Solvent</th>
<th>Temperature (°C)</th>
<th>Time (hours)</th>
<th>Isolated yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cu(OAc)$_2$·H$_2$O</td>
<td>Mesitylene</td>
<td>165</td>
<td>3</td>
<td>85$^a$</td>
</tr>
<tr>
<td>2</td>
<td>Cu(OAc)$_2$·H$_2$O</td>
<td>Toluene</td>
<td>120</td>
<td>15</td>
<td>85, 83$^a$</td>
</tr>
<tr>
<td>3</td>
<td>Mn(acac)$_3$</td>
<td>Toluene</td>
<td>120</td>
<td>15</td>
<td>56, 19$^a$</td>
</tr>
<tr>
<td>4</td>
<td>Copper(II) 2-pyrazinecarboxylate</td>
<td>Toluene</td>
<td>120</td>
<td>15</td>
<td>46</td>
</tr>
<tr>
<td>5</td>
<td>Cu(NCCH$_3$)$_4$CF$_3$SO$_3$</td>
<td>Toluene</td>
<td>120</td>
<td>15</td>
<td>73</td>
</tr>
<tr>
<td>6</td>
<td>Copper(II) 2-ethylhexanoate</td>
<td>Toluene</td>
<td>120</td>
<td>15</td>
<td>91, 100$^a$</td>
</tr>
<tr>
<td>7</td>
<td>Copper(II) 2-ethylhexanoate</td>
<td>MeCN</td>
<td>120</td>
<td>15</td>
<td>37$^a$</td>
</tr>
<tr>
<td>8</td>
<td>Copper(II) 2-ethylhexanoate</td>
<td>MeCN</td>
<td>120</td>
<td>15</td>
<td>trace$^b$</td>
</tr>
</tbody>
</table>

$^a$ Isolated yield.

$^b$ Trace yield.
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.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Metal Salt</th>
<th>Loading (mol%)</th>
<th>Isolated yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Copper(II) 2-ethylhexanoate</td>
<td>100</td>
<td>91</td>
</tr>
<tr>
<td>2</td>
<td><strong>Copper(II) 2-ethylhexanoate</strong></td>
<td><strong>10</strong></td>
<td><strong>100</strong></td>
</tr>
<tr>
<td>3</td>
<td>Copper(II) 2-ethylhexanoate</td>
<td>1</td>
<td>71&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td>Copper(II) 2-ethylhexanoate</td>
<td>0.1</td>
<td>16&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reactions not gone to completion. <sup>1</sup>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 KOrBu 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.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base (2 eq.)</th>
<th>Solvent</th>
<th>Temperature (°C)</th>
<th>Time (h)</th>
<th>Isolated Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>Toluene</td>
<td>100</td>
<td>40</td>
<td>34</td>
</tr>
<tr>
<td>2</td>
<td>KOtBu</td>
<td>Toluene</td>
<td>100</td>
<td>40</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>NaH</td>
<td>Toluene</td>
<td>100</td>
<td>40</td>
<td>5(^a)</td>
</tr>
<tr>
<td>4</td>
<td>Piperidine</td>
<td>Toluene</td>
<td>100</td>
<td>40</td>
<td>48</td>
</tr>
<tr>
<td>5</td>
<td>DBU</td>
<td>Toluene</td>
<td>100</td>
<td>40</td>
<td>22(^a)</td>
</tr>
<tr>
<td>6</td>
<td>DIPEA</td>
<td>Toluene</td>
<td>100</td>
<td>40</td>
<td>89</td>
</tr>
<tr>
<td>7</td>
<td>-</td>
<td>DIPEA</td>
<td>100</td>
<td>40</td>
<td>43</td>
</tr>
<tr>
<td>8</td>
<td>DIPEA</td>
<td>Toluene</td>
<td>80</td>
<td>40</td>
<td>35</td>
</tr>
</tbody>
</table>

\(^a\) 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 \( \text{41} \) 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.

![Figure 2.1](image)

**Figure 2.1** Investigation into the effect of solvent on oxindole \( \text{41} \) 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 \( \text{41} \) difficult and time-consuming.
Table 2.4 Investigation into the effect of solvent on oxindole 41 formation.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Toluene</td>
<td>40</td>
<td>89</td>
</tr>
<tr>
<td>2</td>
<td>CPME</td>
<td>40</td>
<td>46</td>
</tr>
<tr>
<td>3</td>
<td>PhCF₃</td>
<td>28</td>
<td>73</td>
</tr>
<tr>
<td>4</td>
<td>Tetralin</td>
<td>15</td>
<td>72</td>
</tr>
</tbody>
</table>

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 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
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. 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. 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 (Figure 2.2)

![Figure 2.2 Vasopressin receptor antagonist Satavaptan 6.](image)

Satavaptan (SR121463) is a vasopressin receptor antagonist developed by Sanofi used to treat hyponatremia (Figure 2.2). 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). 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;\textsuperscript{49} the most relevant of which being the work by Liotta.\textsuperscript{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).\textsuperscript{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\textsubscript{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.\textsuperscript{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.\textsuperscript{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**

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

![Scheme 2.8 Modified retrosynthesis of advanced intermediate 50 in the synthesis of Satavaptan.](image)

Acetal 62 was synthesised in 3 steps following the procedure of Brimble (Scheme 2.9). 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.](image)
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 AlMe3 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.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R1</th>
<th>R2</th>
<th>Reagent</th>
<th>Solvent</th>
<th>Temperature (°C)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>Me</td>
<td>DMAP (10 mol%)</td>
<td>Toluene</td>
<td>120</td>
<td>16</td>
<td>71</td>
</tr>
<tr>
<td>2</td>
<td>OEt</td>
<td>Bn</td>
<td>DMAP (10 mol%)</td>
<td>Toluene</td>
<td>120</td>
<td>16</td>
<td>trace</td>
</tr>
<tr>
<td>3</td>
<td>OEt</td>
<td>Bn</td>
<td>DMAP (1 eq.)</td>
<td>Toluene</td>
<td>120</td>
<td>16</td>
<td>trace</td>
</tr>
<tr>
<td>4</td>
<td>OEt</td>
<td>Bn</td>
<td>AlMe3 (3 eq.)</td>
<td>Toluene</td>
<td>120</td>
<td>16</td>
<td>0</td>
</tr>
</tbody>
</table>

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.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent</th>
<th>Solvent</th>
<th>Temperature (°C)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LiOH</td>
<td>EtOH/H₂O</td>
<td>rt → 70</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>KOH</td>
<td>EtOH/H₂O</td>
<td>rt</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>KOTMS</td>
<td>THF</td>
<td>rt</td>
<td>16</td>
<td>0</td>
</tr>
</tbody>
</table>

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 ¹H 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.

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.\textsuperscript{53}

![T3P](image)

**Figure 2.3** Propylphosphonic acid anhydride (T3P)

Using T3P (in EtOAc) at room temperature in toluene gave the desired anilide \textbf{56} in an improved yield of 42\% (entry 3, Table 2.7). Despite aniline \textbf{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.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Eq. Acid</th>
<th>Eq. Aniline</th>
<th>Coupling Reagent</th>
<th>Base</th>
<th>Solvent</th>
<th>Temperature(^\circ)C)</th>
<th>Yield(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>1.2</td>
<td>Mukaiyama’s</td>
<td>NEt(_3)</td>
<td>DCM</td>
<td>rt</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>1.2</td>
<td>1.0</td>
<td>DCC</td>
<td>DMAP</td>
<td>DCM</td>
<td>rt</td>
<td>40</td>
</tr>
<tr>
<td>3</td>
<td>1.2</td>
<td>1.0</td>
<td>T3P (in EtOAc)</td>
<td>DIPEA</td>
<td>Toluene</td>
<td>rt</td>
<td>42</td>
</tr>
<tr>
<td>4</td>
<td>1.2</td>
<td>1.0</td>
<td>T3P (in EtOAc)</td>
<td>DIPEA</td>
<td>Toluene</td>
<td>60</td>
<td>12</td>
</tr>
<tr>
<td>5</td>
<td>1.2</td>
<td>1.0</td>
<td>T3P (in EtOAc)</td>
<td>DIPEA</td>
<td>Toluene</td>
<td>0→rt</td>
<td>38</td>
</tr>
<tr>
<td>6</td>
<td>1.2</td>
<td>1.0</td>
<td>T3P (in EtOAc)</td>
<td>-</td>
<td>Toluene</td>
<td>rt</td>
<td>16</td>
</tr>
<tr>
<td>7</td>
<td>1.2</td>
<td>1.0</td>
<td>T3P (in EtOAc) (\times 4)</td>
<td>DIPEA (\times 4)</td>
<td>Toluene</td>
<td>rt</td>
<td>6</td>
</tr>
<tr>
<td>8</td>
<td>1.2</td>
<td>1.0</td>
<td>T3P (in toluene)</td>
<td>DIPEA</td>
<td>Toluene</td>
<td>rt</td>
<td>46</td>
</tr>
<tr>
<td>9</td>
<td>1.2</td>
<td>1.0</td>
<td>T3P (in THF)</td>
<td>DIPEA</td>
<td>THF</td>
<td>rt</td>
<td>49</td>
</tr>
<tr>
<td>10</td>
<td>1.2</td>
<td>1.0</td>
<td>T3P (in EtOAc)</td>
<td>DIPEA</td>
<td>EtOAc</td>
<td>rt</td>
<td>58</td>
</tr>
<tr>
<td>11</td>
<td>2.0</td>
<td>1.0</td>
<td>T3P (in EtOAc)</td>
<td>DIPEA</td>
<td>EtOAc</td>
<td>rt</td>
<td>75</td>
</tr>
</tbody>
</table>

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
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)\(_2\)•H\(_2\)O 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.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>(R^1)</th>
<th>(R^2)</th>
<th>Catalyst (10 mol%)</th>
<th>Solvent</th>
<th>Temperature (°C)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>Aniline isolated (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>Me</td>
<td>Copper(II) 2-ethylhexanoate</td>
<td>Toluene</td>
<td>120</td>
<td>16</td>
<td>83</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>OEt</td>
<td>Bn</td>
<td>Copper(II) 2-ethylhexanoate</td>
<td>Toluene</td>
<td>120</td>
<td>16</td>
<td>34</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>OEt</td>
<td>Bn</td>
<td>(\text{Cu(OAc)}_2\text{•H}_2\text{O})</td>
<td>Mesitylene(^a)</td>
<td>165</td>
<td>0.5</td>
<td>58(^b)</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>OEt</td>
<td>Bn</td>
<td>(\text{Cu(OAc)}_2\text{•H}_2\text{O})</td>
<td>Mesitylene(^a)</td>
<td>165</td>
<td>1</td>
<td>32(^c)</td>
<td>33</td>
</tr>
<tr>
<td>5</td>
<td>OEt</td>
<td>Bn</td>
<td>(\text{Cu(OAc)}_2\text{•H}_2\text{O})</td>
<td>Mesitylene(^a)</td>
<td>165</td>
<td>1</td>
<td>40(^d)</td>
<td>20</td>
</tr>
</tbody>
</table>

\(^a\) dried compressed air bubbled through. \(^b\) 169 \(\mu\)mol 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.

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

![Scheme 2.11 Synthesis of anilide 73.](image)

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. Upon treatment with catalytic Cu(OAc)$_2$\(\cdot\)H$_2$O 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$_2$O. 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.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Temperature (°C)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Toluene</td>
<td>110</td>
<td>66\textsuperscript{a}</td>
</tr>
<tr>
<td>2</td>
<td>PC</td>
<td>110</td>
<td>49</td>
</tr>
<tr>
<td>3</td>
<td>PC</td>
<td>100</td>
<td>73</td>
</tr>
<tr>
<td>4</td>
<td>PC</td>
<td>80</td>
<td>59\textsuperscript{b}</td>
</tr>
<tr>
<td>5</td>
<td>EC</td>
<td>110</td>
<td>72</td>
</tr>
<tr>
<td>6</td>
<td>EC</td>
<td>100</td>
<td>81</td>
</tr>
<tr>
<td>7</td>
<td>EC</td>
<td>80</td>
<td>54</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Reaction carried out by a colleague. \textsuperscript{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)\textsubscript{2}•H\textsubscript{2}O (100 mol%) an improved yield of 62% was observed (Scheme 2.12).

Spirocyclic ketone oxindole 55 was next treated with NaBH\textsubscript{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), quantitative 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.

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 Et₂O 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 CCl₄ 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.

<table>
<thead>
<tr>
<th>Liotta's Synthesis</th>
<th>Our Synthesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall yield = 37%</td>
<td>Overall yield = 2%</td>
</tr>
<tr>
<td>Average yield = 88%</td>
<td>Average yield = 70%</td>
</tr>
<tr>
<td>Overall AE = 20%</td>
<td>Overall AE = 15%</td>
</tr>
<tr>
<td>Average AE = 84%</td>
<td>Average AE = 84%</td>
</tr>
<tr>
<td>Total number of steps = 8</td>
<td>Total number of steps = 10</td>
</tr>
</tbody>
</table>

**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, thus completing the formal synthesis (Scheme 2.16).
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.

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, 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 greatly 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. These couplings are routinely carried out using catalytic Cu(OAc)₂ in the presence of air (Scheme 2.19), a catalyst system we have previously shown is competent in the formation of oxindoles from anilides. 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 oxaly chloride mediated chlorination, followed by exposure to methylamine, yielding the desired amide 77 in 59% yield (Scheme 2.20). Oxaly 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)$_2$·H$_2$O 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.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Copper Salt</th>
<th>Additive</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Atmosphere</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cu(OAc)$_2$·H$_2$O (200 mol%)</td>
<td>-</td>
<td>DCM</td>
<td>rt</td>
<td>Argon</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>Cu(OAc)$_2$·H$_2$O (200 mol%)</td>
<td>-</td>
<td>DCM</td>
<td>45</td>
<td>Argon</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>Cu(OAc)$_2$ (200 mol%)</td>
<td>-</td>
<td>DCM</td>
<td>rt</td>
<td>Argon</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>Cu(OAc)$_2$ (200 mol%)</td>
<td>-</td>
<td>DCM</td>
<td>45</td>
<td>Argon</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>Cu(OAc)$_2$ (200 mol%)</td>
<td>-</td>
<td>MeOH</td>
<td>45</td>
<td>Argon</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>Cu(OAc)$_2$ (200 mol%)</td>
<td>-</td>
<td>Toluene</td>
<td>45</td>
<td>Argon</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>Cu(OAc)$_2$ (100 mol%)</td>
<td>-</td>
<td>DCM</td>
<td>rt</td>
<td>air</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>Cu(OAc)$_2$ (100 mol%)</td>
<td>-</td>
<td>DCM</td>
<td>45</td>
<td>air</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>Cu(OAc)$_2$ (100 mol%)</td>
<td>-</td>
<td>MeOH</td>
<td>45</td>
<td>air</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>Cu(OAc)$_2$ (100 mol%)</td>
<td>-</td>
<td>Toluene</td>
<td>120</td>
<td>air</td>
<td>0</td>
</tr>
<tr>
<td>11</td>
<td>Cu(OAc)$_2$ (100 mol%)</td>
<td>4Å MS</td>
<td>DCM</td>
<td>rt</td>
<td>air</td>
<td>0</td>
</tr>
<tr>
<td>12</td>
<td>Cu(OAc)$_2$ (100 mol%)</td>
<td>4Å MS</td>
<td>DCM</td>
<td>45</td>
<td>air</td>
<td>0</td>
</tr>
<tr>
<td>13</td>
<td>Cu(OAc)$_2$ (100 mol%)</td>
<td>4Å MS</td>
<td>DCM</td>
<td>rt</td>
<td>O$_2$</td>
<td>0</td>
</tr>
<tr>
<td>14</td>
<td>Cu(OAc)$_2$ (100 mol%)</td>
<td>4Å MS</td>
<td>MeOH</td>
<td>rt</td>
<td>O$_2$</td>
<td>0</td>
</tr>
<tr>
<td>15</td>
<td>Cu(OAc)$_2$ (100 mol%)</td>
<td>4Å MS</td>
<td>toluene</td>
<td>rt</td>
<td>O$_2$</td>
<td>0</td>
</tr>
<tr>
<td>16</td>
<td>Cu(OAc)$_2$ (100 mol%)</td>
<td>4Å MS</td>
<td>dioxane</td>
<td>rt</td>
<td>O$_2$</td>
<td>0</td>
</tr>
</tbody>
</table>
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\textsuperscript{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\textsuperscript{59} for N-arylation of amides were employed using catalytic CuI and 2,2,6,6-tetramethylheptane-3,5-dione as ligand and K$_3$PO$_4$ (entry 5, Table 2.12) and phosphazene bases (entry 6, Table 2.12), neither of which gave any reaction. Conditions developed by Buchwald\textsuperscript{58} for N-arylation of amides were next employed utilising diamine ligands. However, both K$_3$PO$_4$ (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\textsubscript{a} 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.\textsuperscript{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.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Copper Salt</th>
<th>Ligand</th>
<th>Base (2 eq.)</th>
<th>Atmosphere</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Copper(II) 2-ethyhexanoate (10 mol%)</td>
<td>-</td>
<td>-</td>
<td>Air</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>Copper(II) 2-ethyhexanoate (10 mol%)</td>
<td>-</td>
<td>-</td>
<td>Argon</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>Copper(II) 2-ethyhexanoate (10 mol%)</td>
<td>-</td>
<td>DIPEA</td>
<td>Air</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>Copper(II) 2-ethyhexanoate (200 mol%)</td>
<td>-</td>
<td>DIPEA</td>
<td>Argon</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>CuI (5 mol%)</td>
<td>(tBuCO)₂CH₂ (20 mol%)</td>
<td>K₃PO₄</td>
<td>Argon</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>CuI (5 mol%)</td>
<td>(tBuCO)₂CH₂ (20 mol%)</td>
<td>Phosphazene&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Argon</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>CuI (5 mol%)</td>
<td>MeNH(CH₂)₂NHMe (20 mol%)</td>
<td>K₃PO₄</td>
<td>Argon</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>CuI (5 mol%)</td>
<td>MeNH(CH₂)₂NHMe (20 mol%)</td>
<td>Phosphazene&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Argon</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>CuI (5 mol%)</td>
<td>MeNH(CH₂)₂NHMe (20 mol%)</td>
<td>KHMDS&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Argon</td>
<td>Trace&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>10</td>
<td>CuI (50 mol%)</td>
<td>MeNH(CH₂)₂NHMe (200 mol%)</td>
<td>KHMDS&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Argon</td>
<td>Trace&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>CuI (50 mol%)</td>
<td>MeNH(CH₂)₂NHMe (200 mol%)</td>
<td>KHMDS&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Argon</td>
<td>6&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>---</td>
<td>-------------</td>
<td>-----------------</td>
<td>-----------------</td>
<td>------</td>
<td>-----</td>
</tr>
</tbody>
</table>

<sup>a</sup> phosphazene base is tert-butylimino-tris(dimethylamino)phosphorane. <sup>b</sup> 2.2 equiv in toluene added by syringe pump over 4 hours. <sup>c</sup> 2.2 eq. KHMDS used. <sup>d</sup> N-methylaniline 71 observed as major product in crude reaction mixture by ¹H 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),<sup>60</sup> but are more commonly employed as useful synthetic intermediates<sup>61</sup> such as in drug synthesis and other applications.<sup>62</sup> A comprehensive review of the thio-amide functionality and its synthetic applications has been published by Jagodinski.<sup>63</sup>

![Thio-oxindole structure](image.png)

**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<sup>64</sup> 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. Tetrahydrothiopyran[2,3-<i>b</i>] indoles are known to have pain-killing activity.<sup>65</sup> 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.
Despite their utility, de novo synthesis of the thio-oxindole core is scarcely reported and generally relies on the sulfonication of preformed oxindole. Functionalisation of thio-oxindoles at the 3-position is usually achieved by deprotonation of thiooxindole by strong base followed by treatment with an electrophile. 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).

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

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

The 3,4-dihydroquinolin-2(1H)-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 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).  

![Figure 3.1](image1.png)

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

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

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

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

3,4-Dihydroquinolin-2(1H)-ones have been synthesised in a multitude of fashions. In a similar approach to oxindole synthesis, 3,4-dihydroquinolin-2(1H)-ones can be prepared by palladium-catalysed intramolecular Heck reactions as shown by Piou et al. 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).
Scheme 3.1 Piou’s approach to the synthesis of 3,4-dihydroquinolin-2(1H)-ones.

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

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

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

Scheme 3.3 Zirconium-catalysed multi-component approach to 3,4-dihydroquinolin-2(1H)-ones.
3.2.2 3,4-Dihydroquinolin-2(1H)-ones by free radical cyclisation

The use of radicals to form 3,4-dihydroquinolin-2(1H)-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(1H)-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. An example that illustrates this well is Zhou’s copper-catalysed approach (Scheme 3.4). The scope is good, the yields are generally excellent and inexpensive Cu₂O is used as the catalyst.

Scheme 3.4 Zhou’s copper-catalysed approach to 3,4-dihydroquinolin-2(1H)-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(1H)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(1H)ones.
A similar method was developed by Chuang utilising Mn(III) to form 3,4-dihydroquinolin-2(1H)-ones (Scheme 3.6).\textsuperscript{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\textsubscript{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(1H)-one 124 is formed.

\begin{center}
\textbf{Scheme 3.6} Proposed mechanism for Chuang’s manganese-mediated approach to the synthesis of 3,4-dihydroquinolin-2(1H)ones.
\end{center}

Nishino and co-workers reported a manganese-mediated approach to the synthesis of 3,4-dihydroquinolin-2(1H)ones which generates radicals and cyclises anilides in a similar fashion to our copper-catalysed approach to oxindoles (Scheme 3.7).\textsuperscript{44a} This method is high-yielding across a range of substrates but the harsh conditions employed (> 3 eq. Mn(OAc)\textsubscript{3} in refluxing AcOH) gave over-oxidation by-products in some cases (methyl groups oxidised to acetoxy groups).
In light of Nishino’s findings, our efforts were focused on the application of our copper-conditions to the synthesis of 3,4-dihydroquinolin-2(1H)-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(1H)-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(1H)-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.
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. 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.

\[
\begin{array}{cccc}
\text{Entry} & \text{Aniline} & \text{Acyl Bromide} & \text{Product} & \text{Yield (\%)} \\
\hline
1 & \begin{array}{c}
\text{Me} \\
133a
\end{array} & \begin{array}{c}
\text{Br} \\
134a
\end{array} & \begin{array}{c}
\text{N} \\
131a \\
\text{Me}
\end{array} & 78 \\
2 & \begin{array}{c}
\text{Bn} \\
133b
\end{array} & \begin{array}{c}
\text{Br} \\
134a
\end{array} & \begin{array}{c}
\text{N} \\
131b \\
\text{Bn}
\end{array} & 68 \\
3 & \begin{array}{c}
\text{Me} \\
133c
\end{array} & \begin{array}{c}
\text{Br} \\
134a
\end{array} & \begin{array}{c}
\text{Me} \\
131c \\
\text{O}
\end{array} & 87 \\
4 & \begin{array}{c}
\text{Me} \\
133d
\end{array} & \begin{array}{c}
\text{Br} \\
134a
\end{array} & \begin{array}{c}
\text{O} \\
131d \\
\text{O}
\end{array} & 48 \\
5 & \begin{array}{c}
\text{Me} \\
133a
\end{array} & \begin{array}{c}
\text{Me} \\
134b
\end{array} & \begin{array}{c}
\text{Me} \\
131e \\
\text{Me}
\end{array} & 99 \\
6 & \begin{array}{c}
\text{Me} \\
133e
\end{array} & \begin{array}{c}
\text{Br} \\
134a
\end{array} & \begin{array}{c}
\text{Me} \\
131f \\
\text{Me}
\end{array} & 81
\end{array}
\]

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.

![Chemical Structure](Image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Anilide</th>
<th>Malonate</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="Image" alt="131a" /></td>
<td><img src="Image" alt="132a" /></td>
<td><img src="Image" alt="130a" /></td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td><img src="Image" alt="131a" /></td>
<td><img src="Image" alt="132b" /></td>
<td><img src="Image" alt="130b" /></td>
<td>71</td>
</tr>
<tr>
<td>3</td>
<td><img src="Image" alt="131b" /></td>
<td><img src="Image" alt="132a" /></td>
<td><img src="Image" alt="130c" /></td>
<td>84</td>
</tr>
<tr>
<td>4</td>
<td><img src="Image" alt="131c" /></td>
<td><img src="Image" alt="132a" /></td>
<td><img src="Image" alt="130d" /></td>
<td>83</td>
</tr>
<tr>
<td>5</td>
<td><img src="Image" alt="131d" /></td>
<td><img src="Image" alt="132a" /></td>
<td><img src="Image" alt="130e" /></td>
<td>74</td>
</tr>
<tr>
<td>6</td>
<td><img src="Image" alt="131e" /></td>
<td><img src="Image" alt="132a" /></td>
<td><img src="Image" alt="130f" /></td>
<td>82</td>
</tr>
<tr>
<td>7</td>
<td><img src="Image" alt="131f" /></td>
<td><img src="Image" alt="132a" /></td>
<td><img src="Image" alt="130g" /></td>
<td>84</td>
</tr>
</tbody>
</table>
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(1H)-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(1H)-ones 129a-f by copper catalysis, and yields reported by Nishino by a manganese-mediated process.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Malonate</th>
<th>Base (2.4 eq.)</th>
<th>Time (h)</th>
<th>Product</th>
<th>Cu(II) Yield</th>
<th>Mn(III) Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>130a</td>
<td>-</td>
<td>24</td>
<td>129a</td>
<td>(46)b</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>130a</td>
<td>DIPEA</td>
<td>15</td>
<td>129a</td>
<td>100</td>
<td>97</td>
</tr>
<tr>
<td>3</td>
<td>130b</td>
<td>DIPEA</td>
<td>2</td>
<td>129b</td>
<td>74</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>DIPEA</td>
<td>15</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>100</td>
<td>93</td>
</tr>
<tr>
<td>---</td>
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<td>---</td>
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<tr>
<td>5</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>DIPEA</td>
<td>15</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>100</td>
<td>97</td>
</tr>
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<td>6</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>DIPEA</td>
<td>15</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>100</td>
<td>92</td>
</tr>
<tr>
<td>7</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>DIPEA</td>
<td>24</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>93</td>
<td>61&lt;sup&gt;d,e&lt;/sup&gt;</td>
</tr>
<tr>
<td>8</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>DIPEA</td>
<td>15</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>0</td>
<td>0&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

* Yields reported by Nishino<sup>44a</sup> employing 3 equivalents of Mn(OAc)₃ in refluxing AcOH for 30 min. * Conversion based on ratio of anilide to product in the <sup>1</sup>H NMR spectrum of the crude reaction mixture. * 165 °C in mesitylene. *<sup>1</sup> 10 equivalents of Mn(OAc)₃ were used in AcOH for 5 h. * Oxidation product 129<sup>f</sup> was also isolated in 28% yield. * Spirolactam 136 was isolated in 85% yield.

When malonate 130<sup>g</sup> 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 135<sup>b</sup> via transition state 135<sup>a</sup> (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 135<sup>b</sup> is then oxidised by Mn(III) to give cationic species 135<sup>c</sup> which upon demethylation of the enol ether either by the AcOH or H₂O gives 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(1H)-ones 129a-f are higher than those observed by Nishino, 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(1H)-one
The synthesis of 3,4-dihydroquinolin-2(1H)-one 129a can be achieved from α-bromo-anilide 131a in a one-pot fashion by sequential addition of diethyl malonate and KOTBu, 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(1H)-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(1H)-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(1H)-one synthesis

Unlike many other procedures, by utilising a homolytic aromatic substitution approach to synthesise 3,4-dihydroquinolin-2(1H)-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(1H)-one synthesis compared to Nishino’s manganese-mediated method, 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. They are also found at the core of numerous natural products (Figure 3.3), and are key synthetic intermediates in the synthesis of 2-amino, 2-alkoxy and 2-amino substituted quinolinones.

![Figure 3.3 Examples of biologically active 2-quinolinones 137-139.](image)

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). 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.](image)

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). 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 leaving group in the starting material.85A 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 moiety, 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.

\[
\begin{array}{c}
\text{H} \\
\text{X} \\
\text{O}
\end{array}
\xrightarrow{\text{Pd(OAc)}_2 (1 \text{ mol\%})}
\begin{array}{c}
\text{R} \\
\text{X} \\
\text{O}
\end{array}
\xrightarrow{\text{TFA/DCM, rt, 0.5-5 h}}
\begin{array}{c}
\text{R} \\
\text{X} \\
\text{O}
\end{array}
\]

\[X = \text{O, NH}\]

\textbf{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).\textsuperscript{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.

\[
\begin{array}{c}
\text{R}^1 \\
\text{R}^2 \\
\text{R}^3 \\
\text{N}
\end{array}
\xrightarrow{\text{Mn(OAc)}_3 (4 \text{ eq.})}
\begin{array}{c}
\text{R}^1 \\
\text{R}^2 \\
\text{R}^3 \\
\text{O}
\end{array}
\xrightarrow{\text{DCE, 70 °C, air, 1-24 h}}
\begin{array}{c}
\text{R}^1 \\
\text{R}^2 \\
\text{R}^3 \\
\text{O}
\end{array}
\]

\[>20 \text{ examples, 53-89\%}\]

\textbf{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 \textbf{154} is formed by oxidation of anilide \textbf{153}, it undergoes a 6-\textit{exo-trig} cyclisation to form radical \textbf{155}. Upon reaction of \textbf{155} with molecular oxygen, \textbf{156} undergoes fragmentation to give 2-quinolinone \textbf{157} and benzaldehyde.
Scheme 3.16 Proposed mechanism for Chuang’s manganese-mediated approach to the synthesis of 2-quinolinones from \(N-[\mathit{(E)}\)-stilben-2-yl]acetamides.

Chuang made an interesting observation during his Mn-mediated synthesis of 3,4-dihydroquinolin-2(1H)-ones\textsuperscript{76a} (Chapter 3.22). It was observed that when the electron withdrawing group is SO\textsubscript{2}Allyl, 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.

<table>
<thead>
<tr>
<th>Entry</th>
<th>$R^1$</th>
<th>EWG</th>
<th>$R$</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td>Ts</td>
<td>4-Cl(C(_6)H(_4))</td>
<td>88</td>
</tr>
<tr>
<td>2</td>
<td>Me</td>
<td>Ts</td>
<td>2,4-Cl(_2)(C(_6)H(_3))</td>
<td>85</td>
</tr>
<tr>
<td>3</td>
<td>Br</td>
<td>Ms</td>
<td>C(_6)H(_5)</td>
<td>65</td>
</tr>
<tr>
<td>4</td>
<td>Me</td>
<td>Ts</td>
<td>Me</td>
<td>62</td>
</tr>
<tr>
<td>5</td>
<td>Me</td>
<td>Ms</td>
<td>OEt</td>
<td>53</td>
</tr>
<tr>
<td>6</td>
<td>H</td>
<td>Ms</td>
<td>OEt</td>
<td>51</td>
</tr>
<tr>
<td>7</td>
<td>Br</td>
<td>Ms</td>
<td>OEt</td>
<td>44</td>
</tr>
<tr>
<td>8</td>
<td>CO(_2)Et</td>
<td>Ms</td>
<td>OEt</td>
<td>42</td>
</tr>
<tr>
<td>9</td>
<td>Cl</td>
<td>Ms</td>
<td>OEt</td>
<td>41</td>
</tr>
</tbody>
</table>

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(1H)-one 161c forms. It is thought β-elimination of $p$-toluensulfinic acid or methanesulfinic acid then occurs to afford the 2-quinolinone 161.
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(1H)-ones were applied to the synthesis of 2-quinolinones with the envisaged route outlined in Scheme 3.19. The required cyclisation precursors \( \text{164} \) were expected to arise from alkylation of \( \alpha \)-bromo anilides \( \text{131} \) which themselves can be readily prepared from anilines \( \text{133} \) and bromoacetyl bromides \( \text{134} \) (Scheme 3.19).

![Scheme 3.18 Suggested mechanism for the formation of 2-quinolinones via cyclisation/sulfone elimination.](image)

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

![Scheme 3.19 Retrosynthesis of 2-quinolinones 163.](image)

**Scheme 3.19** Retrosynthesis of 2-quinolinones \( \text{163} \).
Several α-bromo anilides previously synthesised for the synthesis of 3,4-quinolin-2(1H)-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.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aniline</th>
<th>Acyl Bromide</th>
<th>Product</th>
<th>Yield (%)</th>
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<td>1</td>
<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /></td>
<td><img src="image3.png" alt="Image" /></td>
<td>62</td>
</tr>
<tr>
<td>2</td>
<td><img src="image4.png" alt="Image" /></td>
<td><img src="image5.png" alt="Image" /></td>
<td><img src="image6.png" alt="Image" /></td>
<td>89</td>
</tr>
<tr>
<td>3</td>
<td><img src="image7.png" alt="Image" /></td>
<td><img src="image8.png" alt="Image" /></td>
<td><img src="image9.png" alt="Image" /></td>
<td>88</td>
</tr>
<tr>
<td>4</td>
<td><img src="image10.png" alt="Image" /></td>
<td><img src="image11.png" alt="Image" /></td>
<td><img src="image12.png" alt="Image" /></td>
<td>71</td>
</tr>
</tbody>
</table>

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.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Anilide</th>
<th>Activated Methylene</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="Anilide 131a" /></td>
<td>PhO2S-______CO2Et</td>
<td><img src="image" alt="Product 164a" /></td>
<td>93</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="Anilide 131b" /></td>
<td>PhO2S-______CO2Et</td>
<td><img src="image" alt="Product 164b" /></td>
<td>99</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="Anilide 131c" /></td>
<td>PhO2S-______CO2Et</td>
<td><img src="image" alt="Product 164c" /></td>
<td>71</td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="Anilide 131d" /></td>
<td>PhO2S-______CO2Et</td>
<td><img src="image" alt="Product 164d" /></td>
<td>66</td>
</tr>
<tr>
<td></td>
<td>Chemical Structure 1</td>
<td>Chemical Structure 2</td>
<td>Chemical Structure 3</td>
<td>Percentage</td>
</tr>
<tr>
<td>---</td>
<td>----------------------</td>
<td>----------------------</td>
<td>----------------------</td>
<td>------------</td>
</tr>
<tr>
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<td><img src="image1" alt="Chemical Structure" /></td>
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<tr>
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<td><img src="image11" alt="Chemical Structure" /></td>
<td><img src="image12" alt="Chemical Structure" /></td>
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<td>9</td>
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<tr>
<td>10</td>
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<td><img src="image17" alt="Chemical Structure" /></td>
<td><img src="image18" alt="Chemical Structure" /></td>
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</tr>
<tr>
<td>11</td>
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<td><img src="image20" alt="Chemical Structure" /></td>
<td><img src="image21" alt="Chemical Structure" /></td>
<td>99</td>
</tr>
<tr>
<td>12</td>
<td><img src="image22" alt="Chemical Structure" /></td>
<td><img src="image23" alt="Chemical Structure" /></td>
<td><img src="image24" alt="Chemical Structure" /></td>
<td>57</td>
</tr>
<tr>
<td>13</td>
<td><img src="image25" alt="Chemical Structure" /></td>
<td><img src="image26" alt="Chemical Structure" /></td>
<td><img src="image27" alt="Chemical Structure" /></td>
<td>43</td>
</tr>
</tbody>
</table>
α-Bromo anilide 131k was synthesised in 3 steps (Scheme 3.20). γ-Butyrolactone was opened by N-methylaniline 133a after treatment with AMe₃ 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 SO2Ph 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.

![Chemical structures and reaction conditions](image-url)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Sulfone-containing anilide</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image-url" alt="Image" /></td>
<td><img src="image-url" alt="Image" /></td>
<td>84&lt;sup&gt;a&lt;/sup&gt;, 96&lt;sup&gt;b&lt;/sup&gt;, 95&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td><img src="image-url" alt="Image" /></td>
<td><img src="image-url" alt="Image" /></td>
<td>54&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td><img src="image-url" alt="Image" /></td>
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11

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(1H)-ones 168 it is reasonable to assume that the formation of quinolin-2(1H)-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\textsuperscript{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.](image)

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).

![Figure 3.5 Biologically active 2-quinolinone natural products 169 and 170 isolated from oryza sativa.](image)
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 bromoacetyl bromide 134a to afford α-bromo-anilides 131i 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 BBr₃ 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 BBr₃ 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-protentions combined.
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, photopheresis for the treatment of autoimmune diseases and T-cell lymphoma, and in the prevention of organ transplant rejection. Unfortunately many of the furocumarin compounds used in such treatments suffer from toxic side-effects such as genotoxicity, skin erythemas and carcinogenicity.

To reduce furocumarin genotoxicity, derivatives were investigated; among the tested compounds the most active derivative was found to be FQ 140. 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).

![Furocoumarin 171, FQ 140, HOFQ 141]

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. 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 3.24 Synthesis of the 2-quinolinone natural products 169 and 170.
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).
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.
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 163\textit{p} observed and the elimination product alkene 163\textit{p}' 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 163\textit{a} 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(1H)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$_\text{H}$ 7.26 for CHCl$_3$ and δ$_\text{H}$ 2.50 for DMSO were used as a reference for $^1$H NMR and δ$_\text{C}$ 77.0 for CDCl$_3$ and δ$_\text{C}$ 39.5 for $d_6$-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$_2$Cl$_2$ 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 NEt₃ (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 NaHCO₃ (100 mL) then brine (100 mL), dried (MgSO₄), 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.

Rf: 0.29 (1:1 petrol/EtOAc); νmax/cm⁻¹ (neat): 2983, 1736 (C=O), 1659, 1595, 1496, 1381; δH (400 MHz, CDCl₃): 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); δC (100 MHz, CDCl₃): 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. C₁₂H₁₆NO₃ requires 222.1125.

Lab book ref. RG001

Data consistent with literature values.

**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 KOr-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 NH₄Cl (200 mL) was added and the aqueous layer extracted with EtOAc (3 × 200 mL), dried (MgSO₄), 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.
Rf: 0.47 (1:1 petrol/EtOAc); νmax/cm−1 (neat): 2938, 1715 (C=O), 1635 (C=O), 1571, 1473; δH (400 MHz, CDCl3): 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), 3.88 (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); δC (100 MHz, CDCl3): 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. C13H18NO3 requires 236.1281.

Lab book ref. RG002

Data consistent with literature values.

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% NH4OH solution (3 × 8 mL), brine (10 ml), dried (MgSO4), 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.

Rf: 0.21 (4:1 petrol/EtOAc); νmax/cm−1 (neat): 3011, 1729 (C=O), 1689 (C=O), 1567, 1471; δH (400 MHz, CDCl3): 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); δC (100 MHz, CDCl3): 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. C13H16NO3 requires 234.1125.

Lab book ref. RG007

Data consistent with literature values.
**5.3 Application of copper conditions to the formal synthesis of Satavaptan**

**5.3.1 Route 1**

*N-Benzy1-4-ethoxyaniline (44)*[^50]

![Chemical structure of N-Benzy1-4-ethoxyaniline (44)](image)

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. NaBH₄ (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.

Rf: 0.35 (9:1 petrol/EtOAc); m.p: 45-47 °C (Lit.[^50] 44–46 °C); \( \nu_{\text{max}}/\text{cm}^{-1} \) (solid): 3412, 2977, 1511, 1478, 1232, 1049; \( \delta_{\text{H}} \) (400 MHz, CDCl₃): 7.31-7.15 (5 H, m, ArH), 6.70 (2 H, d, \( J = 9.0 \text{ Hz}, \text{H}-2 \) and H-6), 6.52 (2 H, d, \( J = 9.0 \text{ Hz}, \text{H}-3 \) and H-5), 4.20 (2 H, s, H-7), 3.86 (2 H, q, \( J = 7.0 \text{ Hz}, \text{H}-14 \)), 1.29 (3 H, t, \( J = 7.0 \text{ Hz}, \text{H}-15 \)); HRMS [ES⁺] found MH⁺, 228.1375. C₁₅H₁₈NO 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 NaHCO₃ (50 mL) then brine (50 mL), dried (MgSO₄), 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.

Rf: 0.18 (7:3 petrol/EtOAc); νmax/cm⁻¹ (neat): 2981, 1736 (C=O), 1656 (C=O), 1509, 1396, 1326, 1292, 1244, 1151; δH (400 MHz, CDCl₃): 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); δC (100 MHz, CDCl₃): 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. C₂₀H₂₃NNaO₄ 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 K₂CO₃ (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 H₂SO₄ (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 (MgSO₄), filtered and concentrated in vacuo to afford the title compound 58 (3.33 g, 8.09 mmol, 96%) as a pale yellow oil.

Rf: 0.50 (1:1 hexane/EtOAc); νmax/cm⁻¹ (neat): 2981, 1737 (C=O), 1715 (C=O), 1657 (C=O), 1510, 1399, 1292, 1248, 1171; δH (400 MHz, CDCl₃): 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. C₂₄H₃₀N₂O₅ 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 (MgSO₄) 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.

Rf: 0.10 (1:1 petrol/EtOAc); m.p. 61–64 °C; νmax/cm⁻¹ (neat): 2979, 1716 (C=O), 1653-1603 (C=O), 1508, 1396, 1298, 1244, 1187; δH (400 MHz, CDCl₃): 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); δC (100 MHz, CDCl₃): 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_{23}H_{23}NNaO_{4} requires 388.1519.

Lab book ref. RG180-F2 and RG182

\textit{N-Benzyl-2-ethoxy-N-(4-ethoxyphenyl)-4-oxocyclohex-2-enecarboxamide (57a)}

Isolated as a colourless oil. \(R_f: 0.24 \ (1:1 \text{ petrol/EtOAc})\); \(v_{\max }/\text{cm}^{-1} \) (neat): 2981, 2937, 1716 (C=O), 1644 (C=O), 1601, 1509, 1397, 1245, 1188; \(\delta_{\text{H}} \) (400 MHz, CDCl\(_3\)): 7.27-7.14 (5 H, m, ArH), 6.91-6.76 (2 H, m, H-19), 5.30 (1 H, s, H-17), 5.01-4.72 (2 H, m, H-15), 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, \(J = 7.0 \text{ Hz} \), H-15 or H-24), 1.29 (3 H, t, \(J = 7.1 \text{ Hz} \), H-15 or H-24); \(\delta_{\text{C}} \) (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_{25}H_{28}NO_{4} requires 394.2013.

\textbf{Lab book ref. RG180-F1}

\textit{N-Benzyl-N-(4-ethoxyphenyl)-2,4-dioxocyclohexanecarboxamide (57b)}

\textit{From N-benzyl-2-ethoxy-N-(4-ethoxyphenyl)-4-oxocyclohex-2-enecarboxamide (57a)}

To a stirred solution of \textit{N-benzyl-2-ethoxy-N-(4-ethoxyphenyl)-4-oxocyclohex-2-enecarboxamide 57a} (170 mg, 433 \(\mu\)mol) in THF/water (10:1, 3.5 mL) was added 1 M HCl (350 \(\mu\)L) and stirred at room temperature overnight. Upon completion of the reaction the reaction 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 (MgSO₄) 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 K₂CO₃ (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 H₂SO₄ (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 (MgSO₄), 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.

Rf: 0.24 (4:1 petrol/EtOAc); νmax/cm⁻¹ (neat): 2984, 1748 (C=O), 1730 (C=O), 1447, 1370, 1229, 1155, 1028; δH (400 MHz, CDCl₃): 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); δC (100 MHz, CDCl₃): 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. C₁₁H₁₈NaO₅ 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$_2$SO$_4$. 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$_2$O (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); $\nu_{max}$/cm$^{-1}$ (neat): 3389, 2942, 1727 (C=O), 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)**

![Chemical Structure](image)

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.

Rf: 0.19 (1:1 petrol/EtOAc); m.p. 112–114 °C; νmax/cm⁻¹ (solid): 2959, 2887, 1716 (C=O), 1655 (C=O), 1595, 1496, 1387, 1308; δH (400 MHz, CDCl₃): 7.31–7.42 (3 H, m, H₁₃, H₁₄ and H₁₅), 7.20–7.15 (2 H, m, H₁₂ and H₁₆), 3.92–3.79 (4 H, m, H₇ and H₈), 3.23 (3 H, s, H₁₀), 3.16–2.11 (1 H, m, C₅H₂), 2.05–2.95 (1 H, m, CH₂), 1.88–1.79 (1 H, m, CH₂), 1.71–1.61 (1 H, m, CH₂); δC (100 MHz, CDCl₃): 203.2 (C₉), 168.9 (C₆), 143.5 (C₁₁), 129.9 (C₁₃ and C₁₅), 128.2 (C₁₄), 127.2 (C₁₂ and C₁₆), 109.5 (C₂), 64.7 (C₇ and C₈), 53.3 (C₅), 51.2 (C₁), 37.5 (C₁₀), 32.8 (CH₂), 24.0 (CH₂); HRMS [ES⁺] found MNa⁺, 312.1202. C₁₆H₁₉NNaO₄ requires 312.1206.

Lab Book ref. RG149

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

![Chemical Structure](image)

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 ºC 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), H₂O (3 × 30 mL), Brine (30 mL), dried (MgSO₄), 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.
Rf: 0.15 (19:1 hexane/EtOAc); $\nu_{\text{max}}$/cm$^{-1}$ (neat): 2954, 1719 (C=O), 1655 (C=O), 1617 1399, 1297, 1262, 1216; $\delta_{\text{H}}$ (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); $\delta_{\text{C}}$ (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-BenzyI-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); $\nu_{\text{max}}$/cm$^{-1}$ (neat): 2978, 1718 (C=O), 1657 (C=O), 1511, 1401, 1301, 1247; $\delta_H$ (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); $\delta_C$ (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); $\nu_{\text{max}}$/cm$^{-1}$: 2957, 2884, 1716 (C=O), 1121, 1087; $\delta_H$ (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% NH₄OH solution (2 × 2 mL), brine (2 ml), dried (MgSO₄), 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.

R₉: 0.37 (1:1 petrol/EtOAc); ν<sub>max</sub>/cm<sup>-1</sup> (neat): 2928, 1701 (C=O), 1613 (C=O), 1496, 1472, 1350, 1135, 1100; δ<sub>H</sub> (400 MHz, CDCl₃): 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, CH₂), 2.70 (1 H, d, J = 13.9 Hz, H-1), 2.24-2.15 (1 H, m, CH₂), 2.03 (1 H, m, CH₂), 1.92-1.84 (1 H, m, CH₂); δ<sub>C</sub> (100 MHz, CDCl₃): 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 (CH₂), 64.8 (CH₂), 62.3 (C-5), 49.8 (CH₂), 31.6 (CH₂), 30.4 (CH₂), 22.6 (C-10); HRMS [ES<sup>+</sup>] found MNa<sup>+</sup>, 310.1045. C₁₆H₁₇NNaO₄ requires 310.1050.

Lab Book ref. RG151
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)$_2$·H$_2$O (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$_2$O (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$_2$O (5 × 5 mL), 10% aqueous NH$_4$OH 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)$_2$·H$_2$O (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$_4$OH 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); $\nu_{\text{max}}$/cm$^{-1}$ (neat): 2978, 1718 (C=O), 1698 (C=O), 1496, 1455, 1352, 1300; $\delta_H$ (400 MHz, CDCl$_3$): 7.25-7.12 (5 H, m, H$_1$-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); $\delta_C$ (100 MHz,
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 (MgSO₄), filtered and concentrated in vacuo. Purification by flash column chromatography afforded the title compound 73 (108 mg, 440 µmol, 44%) as an orange oil.

Rf: 0.27 (13:7 petrol/EtOAc); νmax/cm⁻¹ (neat): 2930, 1705 (C=O), 1649 (C=O), 1595, 1496, 1381; δH (400 MHz, CDCl₃): 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, CH₂), 2.15-2.06 (1 H, m, CH₂), 2.02-1.73 (5 H, m, CH₂), 1.37-1.10 (3 H, m, CH₃); δC (100 MHz, CDCl₃): 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 (CH₂), 37.4 (C-7), 29.4 (CH₂), 28.4 (CH₂), 28.5 (CH₂), 24.4 (CH₂); HRMS [ES⁺] found MNa⁺, 430.1620. C₂₄H₂₅NNaO₅ requires 430.1625.

Lab book ref. RG246, RG231 and RG222.

**N-Methyl-2-oxo-N-phenycycloheptanecarboxamide (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 (MgSO₄), filtered and concentrated in vacuo. Purification by flash column chromatography afforded the title compound 73 (108 mg, 440 µmol, 44%) as an orange oil.

Rf: 0.27 (13:7 petrol/EtOAc); νmax/cm⁻¹ (neat): 2930, 1705 (C=O), 1649 (C=O), 1595, 1496, 1381; δH (400 MHz, CDCl₃): 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, CH₂), 2.15-2.06 (1 H, m, CH₂), 2.02-1.73 (5 H, m, CH₂), 1.37-1.10 (3 H, m, CH₃); δC (100 MHz, CDCl₃): 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 (CH₂), 37.4 (C-7), 29.4 (CH₂), 28.4 (CH₂), 28.5 (CH₂), 24.4 (CH₂); HRMS [ES⁺] found MNa⁺, 430.1620. C₂₄H₂₅NNaO₅ requires 430.1625.

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)$_2$·H$_2$O (6.3 mg, 100 mol%) in ethylene carbonate (6.5 mL) was stirred at 100 ºC under an atmosphere of air for 24 h. The reaction mixture was removed from heat and allowed to cool for 10 min then H$_2$O (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$_2$O (5 × 10 mL), 10% aqueous NH$_4$OH 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 ºC; $\nu_{max}$/cm$^{-1}$ (solid): 2932, 1719 (C=O), 1693 (C=O), 1608, 1493, 1470, 1346; $\delta$$_H$ (400 MHz, CDCl$_3$): 7.29 (1 H, t, $J$ = 7.6 Hz, H-2), 7.25 (1 H, d, $J$ = 7.6 Hz, H-4), 7.06 (1 H, t, $J$ = 7.6 Hz, H-3), 6.83 (1 H, d, $J$ = 7.6 Hz, H-1), 3.16 (3 H, s, H-7), 3.08-3.01 (1 H, m, CH$_2$), 2.75-2.67 (1 H, m, CH$_2$), 2.35-2.26 (1 H, m, CH$_2$), 2.16-2.07 (1 H, m, CH$_2$), 2.05-1.96 (1 H, m, CH$_2$), 1.93-1.72 (5 H, m, CH$_2$); $\delta$$_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$_3$), 26.3 (C-7), 25.3 (CH$_3$); 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 NaBH₄ (49.5 mg, 1.31 mmol) and stirred for 2 h. The reaction mixture was quenched with NH₄Cl (10 mL) then the aqueous phase was extracted with EtOAc (2 × 10 mL). The combined organic phases were dried (MgSO₄), 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; νmax/cm⁻¹ (solid): 3452 (O–H), 2933, 1698 (C=O), 1597, 1496, 1455, 1442, 1351; δH (400 MHz, CDCl₃): 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); δC (100 MHz, CDCl₃): 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. C₂₄H₂₈NO₅ requires 410.1962.

Lab book ref. RG248
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); $\nu_{\text{max}}$/cm$^{-1}$ (neat): 2979, 1705 (C=O), 1675 (C=O), 1560, 1495, 1453, 1384, 1341; $\delta_H$ (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); $\delta_C$ (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[cyclohexene-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); νmax/cm−1: 3033, 2977, 2928, 1710 (C=O), 1692 (C=O), 1600, 1495, 1477, 1449, 1369, 1345; δH (400 MHz, CDCl3): 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); δC (100 MHz, CDCl3): 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. C22H24NO3 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, H₂O (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 (MgSO₄), filtered and concentrated in vacuo to afford the title compound 86 (6.79 g, 46.5 mmol, 77%) as a colourless oil.

Rf: 0.51 (1:1 petrol/EtOAc); νmax/cm⁻¹ (neat): 3256 (O–H), 1718 (C=O), 1459, 1380, 1181; δH (400 MHz, CDCl₃): 9.26 (1 H, br s, –OH), 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); δC (100 MHz, CDCl₃): 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. C₆H₁₀NaO₄ 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 NH₂Me 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 H₂O (80 mL), extracted with EtOAc (3 × 60 mL), and the combined organics washed with saturated aqueous NaHCO₃ (100 mL), dried (MgSO₄), 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.

Rf: 0.40 (EtOAc); m.p. 69–71 °C; \( \nu_{\text{max}}/\text{cm}^{-1} \) (solid): 3289 (N–H), 2989, 1731 (C=O), 1642 (C=O), 1571, 1369, 1325; \( \delta_{\text{H}} \) (400 MHz, CDCl\(_3\)): 6.62 (1 H, br s, NH), 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); \( \delta_{\text{C}} \) (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\(_{7}\)H\(_{14}\)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)*

![Chemical structure of 41](image)

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 \( \mu \)L, 200 mol%) followed by iodobenzene 88 (111 \( \mu \)L, 1.00 mmol) at room temperature. The stirred solution was heated to 100 °C then KHMDS (0.7 M in toluene, 626 \( \mu \)L, 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 \( \mu \)mol, 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 Lawesson's 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. Et₂O (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.

Rf: 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. C₁₃H₁₄NNaO₂S 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 Lawesson's 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. Et₂O (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.
Rf: 0.20 (9:1 petrol/EtOAc); $\nu_{\text{max}}$/cm$^{-1}$ (neat): 2981, 1742 (C=O), 1492, 1445, 1416, 1074 (C=S); $\delta_h$ (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); $\delta_C$ (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 M$^+$, 328.1368. C$_{19}$H$_{22}$NO$_2$S 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$_4$OH 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.

Rf: 0.23 (5:2 petrol/EtOAc); m.p. 66–67 °C; $\nu_{\text{max}}$/cm$^{-1}$ (solid): 2989, 1736 (C=O), 1466, 1433, 1369, 1101 (C=S); $\delta_h$ (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); $\delta_C$ (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$_2$S 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% NH₄OH solution (2 × 15 mL), brine (15 mL), dried (MgSO₄), 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.

Rf: 0.21 (9:1 petrol/EtOAc); m.p. 76–78 °C; νmax/cm⁻¹ (solid); 2985, 1738 (C=O), 1465, 1386, 1214, 1108 (C=S); δH (400 MHz, CDCl₃): 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); δC (100 MHz, CDCl₃): 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. C₁₉H₂₀NO₂S requires 326.1209.

Lab book ref. RG163c
5.6 General Procedures

**General Procedure A**

![Chemical structure]

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 (MgSO₄) and concentrated *in vacuo* to afford the title compounds.

**General Procedure B**

![Chemical structure]

To a stirred solution of activated methylene compound (1–2 eq.) in THF (~0.26 M) was added KOr-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. NH₄Cl solution), the aqueous extracted (EtOAc), and the combined organics washed (brine), dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by flash column chromatography afforded the title compounds.

**General Procedure C**

![Chemical structure]

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 NH₄OH solution, brine, dried (MgSO₄), 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(1H)-ones

5.7.1 Anilines

**tert-Butyl 2,4-dimethoxyphenylcarbamate**

To a stirred solution of Boc₂O (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**

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 H₂O (20 mL) and the aqueous phase extracted with Et₂O (3 × 30 mL). The ethereal extracts were combined and washed with brine (40 mL), dried (MgSO₄), 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)

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$_2$CO$_3$ 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); $\nu_{max}$/cm$^{-1}$ (neat): 3418 (N–H); $\delta_H$ (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); $\delta_C$ (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$_9$H$_{14}$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); $\nu_{max}$/cm$^{-1}$ (solid): 2997, 2926, 2328, 1622 (C=O), 1570, 1474; $\delta_H$ (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); $\delta_C$ (100 MHz, CDCl$_3$): 166.4 (C-8), 143.0 (C-6), 130.0 (C-1 and C-5), 128.5 (C-3), 130
126.9 (C-2 and C-4), 38.0 (C-7), 26.8 (C-9); HRMS [ES$^+$] found MH$, 228.0019. C$_9$H$_{11}$BrNO requires 228.0019.

Lab book ref. RG046

Data is consistent with literature values.$^{100}$

**N-Benzyl-2-bromo-N-phenylacetamide (131b)**

![Chemical structure](image)

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); $\nu_{max}$/cm$^{-1}$ (solid): 2325, 1634 (C=O), 1567, 1470, 1366, 1176; $\delta_H$ (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); $\delta_C$ (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}$BrNO requires 304.0332.

Lab book ref. RG052

Data is consistent with literature values.$^{101}$

**2-Bromo-N-(4-methoxyphenyl)-N-methylacetamide (131c)**

![Chemical structure](image)

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.
Rf: 0.38 (1:1 petrol/EtOAc); ν\text{max}/\text{cm}^{-1} (neat): 2914, 1638 (C=O), 1489, 1419, 1359, 1281, 1230; δ\text{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\text{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$_{13}$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.

Rf: 0.34 (1:1 petrol/EtOAc); m.p. 84–85 °C (Lit.$^{103}$ 88–89 °C); ν\text{max}/\text{cm}^{-1} (solid): 1654 (C=O), 1587, 1518, 1341, 1104, 866; δ\text{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\text{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$_9$H$_{10}$BrN$_2$O$_3$ 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.
Rf: 0.60 (1:1 petrol/EtOAc); ν\textsubscript{max}/cm\textsuperscript{-1} (neat): 1641 (C=O), 1571, 1368, 1250, 1104; δ\textsubscript{H} (400 MHz, CDCl\textsubscript{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\textsubscript{C} (100 MHz, CDCl\textsubscript{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\textsuperscript{+}] found MH\textsuperscript{+} 242.0172. C\textsubscript{10}H\textsubscript{13}BrNO requires 242.0175.

\textbf{Lab book ref. RG059}

Data is consistent with literature values\textsuperscript{104}

\textbf{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.

Rf: 0.42 (1:1 petrol/EtOAc); ν\textsubscript{max}/cm\textsuperscript{-1} (neat): 1664 (C=O); δ\textsubscript{H} (400 MHz, CDCl\textsubscript{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\textsubscript{C} (100 MHz, CDCl\textsubscript{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\textsuperscript{+}] found MH\textsuperscript{+}, 288.0225. C\textsubscript{11}H\textsubscript{15}BrNO\textsubscript{3} requires 288.0230.

\textbf{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 KOr-Bu (1.61 g, 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 \text{ (1:1 Petrol/EtOAc); } \nu_{\text{max}}/\text{cm}^{-1} \text{ (neat): 2989, 1745 (C=O), 1729 (C=O), 1656 (C=O), 1496, 1391; } \delta_{\text{H}} \text{ (400 MHz, CDCl}_3): 7.44 (2 \text{ H, t, } J = 7.6 \text{ Hz, H-2 and H-4}), 7.35 (1 \text{ H, t, } J = 7.6 \text{ Hz, H-3}), 7.23 (2 \text{ H, d, } J = 7.6 \text{ Hz, H-1 and H-5}), 4.22-4.09 (4 \text{ H, m, H-12 and H-15}), 3.94 (1 \text{ H, t, } J = 7.2 \text{ Hz, H-10}), 3.24 (3 \text{ H, s, H-7}), 2.64 (2 \text{ H, d, } J = 7.2 \text{ Hz, H-9}), 1.23 (6 \text{ H, t, } J = 7.2 \text{ Hz, H-13 and H-16}); \delta_{\text{C}} \text{ (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\textsuperscript+] found MH\textsuperscript{+}, 308.1486. C\textsubscript{16}H\textsubscript{22}NO\textsubscript{5} requires 308.1492.

Lab book ref. RG041 and RG049

Data is consistent with literature values.\textsuperscript{44a}

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

Di-tert-butyl malonate 132b (979 µL, 4.38 mmol) and KOr-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 \text{ (1:1 Petrol/EtOAc); } \nu_{\text{max}}/\text{cm}^{-1} \text{ (neat): 1978, 1742 (C=O), 1724 (C=O), 1660 (C=O), 1597, 1497; } \delta_{\text{H}} \text{ (400 MHz, CDCl}_3): 7.41 (2 \text{ H, t, } J = 7.4 \text{ Hz, H-2 and H-4}), 7.33 (1 \text{ H, t, } J = 7.4 \text{ Hz, H-3)},

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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); δc (100 MHz, CDCl₃): 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. C₂₀H₃₀NO₅ 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 KOtBu (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.

Rf: 0.41 (3:2 Petrol/EtOAc); νmax/cm⁻¹ (neat): 2988, 1746 (C=O), 1727 (C=O), 1654 (C=O), 1397, 1366; δh (400 MHz, CDCl₃): 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); δc (100 MHz, CDCl₃): 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), 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. C₂₂H₂₆NO₅ 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 KOtBu (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.

$\text{R}_f$: 0.39 (1:1 petrol/EtOAc); $\nu_{\text{max}}$/cm$^{-1}$ (neat): 2989, 1739 (C=O), 1728 (C=O), 1655 (C=O), 1510, 1245; $\delta_H$ (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); $\delta_C$ (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.\textsuperscript{44a}

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

Diethyl malonate 132a (1.11 mL, 7.32 mmol) and KOtBu (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 (2:1 Petrol/EtOAc) afforded the title compound 130e (950 mg, 2.70 mmol, 74%) as a yellow oil.

$\text{R}_f$: 0.39 (1:1 petrol/EtOAc); $\nu_{\text{max}}$/cm$^{-1}$ (neat): 2983, 1740 (C=O), 1727 (C=O), 1656 (C=O), 1592, 1520, 1343; $\delta_H$ (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); $\delta_C$ (100 MHz, CDCl$_3$): 169.3 (C-8), 136
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_{2}NaO_{7} requires 375.1163.

Lab book ref. RG071

Data is consistent with literature values.\textsuperscript{44a}

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

Diethyl malonate \textbf{132a} (1.26 mL, 8.26 mmol) and KOtBu (926 mg, 8.26 mmol) in THF (25 mL) and 2-bromo-N-methyl-N-phenylpropanamide \textbf{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 \textbf{130f} (1.10 g, 3.44 mmol, 82%) as a colourless oil.

Rf: 0.60 (1:1 Petrol/EtOAc); \nu_{\text{max}}/\text{cm}^{-1} \text{ (neat): 2983, 1747 (C=O), 1729 (C=O), 1652 (C=O), 1595, 1496, 1391, 1367; } \delta_{\text{H}} (400 MHz, CDCl\textsubscript{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), 1.95 (3 H, d, J = 7.0 Hz, H-17); \delta_{\text{C}} (100 MHz, CDCl\textsubscript{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.\textsuperscript{44a}
Diethyl 2-(2-((2,4-dimethoxyphenyl)(methyl)amino)-2-oxoethyl)malonate (130g)

Diethyl malonate 132a (1.05 mL, 6.94 mmol) and KOtBu (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.

Rf: 0.38 (1:1 Petrol/EtOAc); νmax/cm⁻¹ (neat): 1982, 1742 (C=O), 1730 (C=O), 1658 (C=O), 1512;

δH (400 MHz, CDCl3):
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), 1.71-1.20 (6 H, m, H-13 and H-16);

δC (100 MHz, CDCl3):
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. C18H26N2O7 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(1H)-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 ºC 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.

Rf: 0.23 (10:3 Petrol/EtOAc); m.p. 80–81 °C (Lit.\textsuperscript{44a} 86–87 °C); \(v_{\text{max}}/\text{cm}^{-1}\) (solid): 2983, 2934, 1729 (C=O), 1658 (C=O), 1367, 1224; \(\delta\)\textsubscript{H} (400 MHz, CDCl\textsubscript{3}): 7.35 (1 H, ddd, \(J = 8.0, 7.2, 1.6 \text{ Hz}\, H-2), 7.28 (1 H, dd, \(J = 8.0, 1.6 \text{ Hz}\, H-4), 7.09 (1 H, td, \(J = 7.6, 1.2 \text{ Hz}\, H-3), 7.01 (1 H, dd, \(J = 8.0, 1.2 \text{ 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); \(\delta\)\textsubscript{C} (100 MHz, CDCl\textsubscript{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\textsuperscript{+}] found MH\textsuperscript{+}, 306.1336. C\textsubscript{16}H\textsubscript{20}NO\textsubscript{5} requires 306.1336.

Lab book ref. RG043/RG047

Data is consistent with literature values.\textsuperscript{44a}

\textbf{Di-\textit{tert}-butyl 1-methyl-2-oxo-2,3-dihydroquinoline-4,4(1H)-dicarboxylate (129b)}

Di-\textit{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.

Rf: 0.58 (1:1 petrol/EtOAc); m.p. 69–71 °C; \(v_{\text{max}}/\text{cm}^{-1}\) (solid): 2978, 1728 (C=O), 1686 (C=O), 1448, 1368, 1285, 1248, 1146; \(\delta\)\textsubscript{H} (400 MHz, CDCl\textsubscript{3}): 7.39 (1 H, dd, \(J = 7.7, 1.5 \text{ Hz}\, H-4), 7.34 (1 H, ddd, \(J = 8.1, 7.5, 1.5 \text{ Hz}\, H-2), 7.10 (1 H, td, \(J = 7.6, 1.2 \text{ Hz}\, H-3), 7.01 (1 H, dd, \(J = 8.2, 1.0 \text{ 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); \(\delta\)\textsubscript{C} (100 MHz, CDCl\textsubscript{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\textsuperscript{+}] found MNa\textsuperscript{+}, 384.1788. C\textsubscript{20}H\textsubscript{27}NNaO\textsubscript{5} requires 384.1781.

Lab book ref. RG160e
Diethyl 1-benzyl-2-oxo-2,3-dihydroquinoline-4,4(1H)-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.

Rf: 0.50 (1:1 petrol/EtOAc); m.p. 80–81 °C (Lit.44a 96–97 °C); νmax/cm⁻¹ (solid): 2977, 1757 (C=O), 1724 (C=O), 1678 (C=O), 1381, 1268; δH (400 MHz, CDCl₃): 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); δC (100 MHz, CDCl₃): 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. C₂₂H₂₅NNaO₅ 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(1H)-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.
Rf: 0.38 (1:1 petrol/EtOAc); ν_max/cm⁻¹: 2989, 1730 (C=O), 1675 (C=O), 1506, 1367, 1268, 1231; δH (400 MHz, CDCl₃): 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); δC (100 MHz, CDCl₃): 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. C₁₇H₂₁N₆O₆ requires 358.1261.

Lab book ref. RG072

Data is consistent with literature values.⁴⁴a

Diethyl 1-methyl-6-nitro-2,3-dihydroquinoline-4,4(1H)-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.

Rf: 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; δH (400 MHz, CDCl₃): 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); δC (100 MHz, CDCl₃): 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), 59.8 (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⁺, 373.1000. C₁₆H₁₈N₂O₇ 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(1H)-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, CDCl₃): 7.53 (1 H, dd, J = 7.6, 1.2 Hz, H-4), 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, CDCl₃): 169.4 (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. C₁₇H₂₁N₂NaO₅ 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(1H)-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 KOtBu (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 (182 µL, 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)

![Chemical structure](image)

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); $\nu_{\text{max}}$/cm$^{-1}$ (neat): 1650 (C=O), 1593, 1494, 1377, 1118; $\delta_h$ (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); $\delta_c$ (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$_{14}$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

Rf: 0.52 (1:1 Petrol/EtOAc); m.p. 96–98 °C; νmax/cm⁻¹ (neat): 2949, 1664 (C=O), 1598, 1481, 1461, 1410, 1347; δH (400 MHz, CDCl₃): 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-7), 3.92 (2 H, s, H-9); δC (100 MHz, CDCl₃): 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. C₁₀H₁₀BrNNaO requires 261.9838.

Lab book ref. RG237

Data is consistent with literature values.⁷⁸a

2-Bromo-1-(3,4-dihydroquinolin-1(2H)-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.

Rf: 0.52 (1:1 hexane/EtOAc); νmax/cm⁻¹ (neat): 2948, 1654 (C=O), 1581, 1491, 1458, 1428, 1389; δH (400 MHz, CDCl₃): 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); δC (100 MHz, CDCl₃): 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. C₁₁H₁₂BrNNaO requires 275.9994.

Lab book ref. RG238

Data consistent with literature values.⁷⁸b
2-Bromo-1-(2,3,4,5-tetrahydro-1H-benzo[b]azepin-1-yl)ethanone (131j)

2,3,4,5-Tetrahydro-1H-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.

Rf: 0.21 (4:1 hexane/EtOAc); m.p. 93-95 °C; νmax/cm\(^{-1}\) (neat): 2938, 1654 (C=O), 1492, 1440, 1399, 1311; δH (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\(_2\)); δC (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-(phenylsulfonfyl)butanoate (164a)

Ethyl 2-(phenylsulfonfyl)acetate 165a (2.00 g, 8.76 mmol) and KOtBu (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.

Rf: 0.25 (1:1 hexane/EtOAc); m.p. 120–123 °C; νmax/cm\(^{-1}\) (neat): 2936, 1736 (C=O), 1649 (C=O), 1595, 1497, 1449, 1309 (S=O), 1226, 1145 (S=O); δH (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, ArH), 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); δC (100 MHz, CDCl₃): 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. C₁₉H₂₁N₂NaO₅S 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 KOtBu (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.

Rf: 0.18 (7:3 hexane/EtOAc); νmax/cm⁻¹ (neat): 1736 (C=O), 1651 (C=O), 1595, 1494, 1407, 1322 (S=O), 1146 (S=O); δH (400 MHz, CDCl₃): 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), 7.36-7.39 (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); δC (100 MHz, CDCl₃): 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. C₂₅H₂₅N₂NaO₅S 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 KOtBu (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.

Rf: 0.12 (55:45 hexane/EtOAc); νmax/cm⁻¹ (neat): 1738 (C=O), 1655 (C=O), 1512, 1448, 1392, 1323 (S=O), 1249, 1148 (S=O); δH (400 MHz, CDCl₃): 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); δC (100 MHz, CDCl₃): 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. C₂₀H₂₃NNaO₆S requires 428.1139.

Lab book ref. RG195

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

Ethyl 2-(phenylsulfonyl)acetate 165a (399 mg, 1.75 mmol) and KOtBu (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.
Rf: 0.19 (1:1 Petrol/EtOAc); νmax/cm⁻¹ (neat): 1737 (C=O), 1663 (C=O), 1593, 1522, 1496, 1448, 1342 (S=O), 1148 (S=O); δH (400 MHz, CDCl₃): 8.31 (2 H, d, J = 8.3 Hz, H-2 and H-4), 7.83 (2 H, 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); δC (100 MHz, CDCl₃): 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), 129.1 (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. C₁₉H₂₀N₂NaO₇S 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 KOrBu (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.

Rf: 0.23 (1:1 Petrol/EtOAc); νmax/cm⁻¹ (neat): 2983, 1732 (C=O), 1651 (C=O), 1595, 1495, 1448, 1392, 1323 (S=O), 1144 (S=O); δH (400 MHz, CDCl₃): 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); δC (100 MHz, CDCl₃): 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_{2}NaO_{3}S requires 412.1189.

Lab book ref. RG208c

**Ethyl 5-(4-methoxybenzyl)oxy)-3-(methyl(phenyl)carbamoyl)-2-(phenylsulfonyl)pentanoate (164f)**

![Chemical structure of 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-methoxybenzyl)oxy)-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.

Rf: 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), 7.40-7.32 (5 H, m, ArH), 7.32-7.27 (2 H, s), 7.14-7.10 (4 H, m, ArH), 7.10-6.87 (5 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), 4.39-4.22 (6 H, m, ArH), 4.04-3.82 (5 H, m), 3.83-3.11 (8 H, m), 2.26 (2 H, s), 1.08 (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_{7}S 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 KOtBu (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.

Rf: 0.15 (9:1 hexane/EtOAc); νmax/cm⁻¹ (neat): 1741 (C=O), 1655 (C=O), 1496, 1448, 1325 (S=O), 1309, 1151 (S=O); δH (400 MHz, CDCl₃): 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); δC (100 MHz, CDCl₃): 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. C₂₅H₂₆NO₅S 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 KOrBu (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.

Rf: 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); δH (400 MHz, CDCl3): 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, m, H-9 and H-20), 1.03 (3 H, t, J = 7.1 Hz, H-13); δC (100 MHz, CDCl3): 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_{5}S requires 388.1213.

Lab book ref. RG240

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

Ethyl 2-(phenylsulfonyl)acetate 165a (381 mg, 1.67 mmol) and KOrBu (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.
Rf: 0.23 (13:7 hexane/EtOAc); νmax/cm⁻¹ (neat): 2942, 1737 (C=O), 1650 (C=O), 1492, 1400, 1323 (S=O), 1240, 1147 (S=O); δH (400 MHz, CDCl₃): 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); δC (100 MHz, CDCl₃): 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. C₂₁H₂₄NO₅S requires 402.1370.

Lab book ref. RG241

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

Ethyl 2-(phenylsulfonyl)acetate 165a (204 mg, 896 µmol) and KOrBu (100 mg, 896 µmol) in THF (5 mL) and 2-bromo-1-(2,3,4,5-tetrahydro-1H-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.

Rf: 0.22 (3:2 hexane/EtOAc); νmax/cm⁻¹ (neat): 2938, 1737 (C=O), 1650 (C=O), 1408, 1400, 1322 (S=O), 1145 (S=O); δH (400 MHz, CDCl₃): 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 CH₂), 4.13-3.96 (2 H, m, H-10 and CH₂), 3.24-3.02 (1 H, m, CH₂), 2.89-2.76 (1 H, m, CH₂), 2.73 (3 H, m, CH₂ and CH₂), 2.01-1.69 (3 H, m, CH₂ and CH₂), 1.41-1.27 (1 H, m, CH₂), 1.08-1.02 (3 H, m, H-13); δC (100 MHz, CDCl₃): 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 (CH₂), 47.65 (CH₂), 34.4 (CH₂), 34.2 (CH₂), 31.1 (CH₂), 31.0 (CH₂), 29.0 (CH₂), 28.96 (CH₂), 26.4 (CH₂), 13.7 (C-13) (nb. 13C spectra contains mixture of rotamers so assignment was problematic); HRMS [ES⁺] found MH⁺, 438.1349. C₂₂H₂₅NNaO₅S requires 438.1346.

Lab book ref. RG283
**N-Methyl-4-oxo-N,4-diphenyl-3-(phenylsulfonyl)butanamide (164k)**

![Chemical Structure](image)

1-Phenyl-2-(phenylsulfonyl)ethanone **165b** (274 mg, 1.05 mmol) and KOrBu (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.

Rf: 0.22 (4:1 hexane/EtOAc); \(\nu_{\text{max}}/\text{cm}^{-1}\) (neat): 3061, 1681 (C=O), 1654 (C=O), 1596, 1496, 1448, 1377, 1310 (S=O), 1150 (S=O); \(\delta_{\text{H}}\) (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); \(\delta_{\text{C}}\) (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\(_4\)S requires 430.1083.

Lab book ref. RG280b

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

![Chemical Structure](image)

2-(Phenylsulfonyl)acetonitrile **165c** (191 mg, 1.05 mmol) and KOrBu (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.

Rf: 0.24 (4:1 hexane/EtOAc); \(\nu_{\text{max}}/\text{cm}^{-1}\) (neat): 2925, 1656 (C=O), 1596, 1496, 1333 (S=O), 1157 (S=O); \(\delta_{\text{H}}\) (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 (100 MHz, CDCl₃): 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. C₁₇H₁₇N₂O₃S 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 KOtBu (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.

Rf: 0.23 (7:3 hexane/EtOAc); m.p. 112–114 °C; νmax/cm⁻¹ (neat): 1655 (C=O), 1596, 1497, 1448, 1392, 1331 (S=O), 1156 (S=O), 1079; δH (400 MHz, CDCl₃): 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); δC (100 MHz, CDCl₃): 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. C₂₂H₁₇NNaO₃S₂ requires 466.0753.

Lab book ref. RG172-F3
(E)-N-Methyl-N-phenyl-3-(phenylsulfonyl)acrylamide (164\textsuperscript{m'})

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\end{array}
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R\textsubscript{f}: 0.21 (3:2 hexane/EtOAc); m.p. 85–87 °C; \( \nu_{\text{max}}/\text{cm}^{-1} \) (neat): 3032, 1701 (C=O), 1650, 1612, 1493, 1466, 1377, 1310 (S=O), 1146 (S=O); \( \delta_{\text{H}} \) (400 MHz, CDCl\textsubscript{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);

\( \delta_{\text{C}} \) (100 MHz, CDCl\textsubscript{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\textsuperscript{+}] found MNa\textsuperscript{+}, 324.0654. C\textsubscript{16}H\textsubscript{15}NNaO\textsubscript{3}S requires 324.0665.

Lab book ref. RG172-F2

5.8.3 Intermediates

4-(4-Hydroxybenzyloxy)-N-methyl-N-phenylbutanamide (166)\textsuperscript{106}

To a stirred solution of AlCl\textsubscript{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 \( \gamma \)-butyrolactone (384 \mu L, 5.00 mmol) was added in one portion. The reaction mixture was stirred at rt for 1 h before being quenched with H\textsubscript{2}O (10 mL). The aqueous phase was extracted with DCE (2 \times 10 mL) and the combined organic layers were washed with brine (10 mL), dried (MgSO\textsubscript{4}), filtered and concentrated \textit{in vacuo}. Purification by flash column chromatography (EtOAc) afforded the title compound 166 (582 mg, 3.01 mmol, 60\%) as a colourless oil.

R\textsubscript{f}: 0.21 (EtOAc); \( \nu_{\text{max}}/\text{cm}^{-1} \) (neat): 3418 (O–H), 2934, 1635 (C=O), 1595, 1422, 1390; \( \delta_{\text{H}} \) (400 MHz, CDCl\textsubscript{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); \( \delta_{\text{C}} \) (100 MHz, CDCl\textsubscript{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\(_{10}\)H\(_{16}\)NO\(_2\) requires 194.1176.

Lab book ref. RG235

Data consistent with literature values.\(^{106}\)

4-(4-Methoxybenzylloxy)-N-methyl-N-phenylbutanamide (167)\(^{107}\)

To a stirred solution of 4-(4-hydroxybenzylloxy)-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 \times 8 mL). The combined organic extracts were washed with brine (10 mL), dried (MgSO\(_4\)), filtered and concentrated \textit{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.

\(\text{Rf: 0.22 (3:2 hexane/EtOAc); } \nu_{\text{max}}/\text{cm}^{-1} \text{ (neat): } 2934, 1657 \text{ (C=O), } 1596, 1513, 1497, 1385; \delta_{\text{H}} \text{ (400 MHz, CDCl}_3\text{): 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 \text{ Hz, H-11), 3.14 (3 H, s, H-7), 2.05 (2 H, t, } J = 7.2 \text{ Hz, H-9), 1.77 (2 H, quint, } J = 6.8 \text{ Hz, H-10); } \delta_{\text{C}} \text{ (100 MHz, CDCl}_3\text{): 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\(^+\)] \text{ found MNa}^+, 336.1558. C\(_{19}\)H\(_{23}\)NNaO\(_3\) requires 336.1570.\)

Lab book ref. RG236
2-Bromo-4-(4-methoxybenzoyloxy)-N-methyl-N-phenylbutanamide (131k)\textsuperscript{33}

A stirred solution of 4-(4-methoxybenzoyloxy)-N-methyl-N-phenylbutanamide 167 (100 mg, 319 \(\mu\)mol) in THF (1 mL) was cooled to -78 °C. LiHMDS (638 \(\mu\)L, 638 \(\mu\)mol) was added dropwise with stirring continues for a further 15 mins. To the reaction mixture was added dropwise NBS (62 mg, 351 \(\mu\)mol) in THF (0.5 mL) and stirring continued at -78 °C for 2 h. The reaction mixture was quenched with 10 % aqueous HCl solution (2 mL) the aqueous phase extracted with EtOAc (3 \(\times\) 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 \(\mu\)mol, 61%) as a yellow oil.

R\(_f\): 0.22 (4:1 hexane/EtOAc); \(\nu\)\(_{\text{max}}\)/cm\(^{-1}\) (neat): 2861, 1664 (C=O), 1595, 1513, 1496, 1389, 1248; \(\delta\)\(_H\) (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); \(\delta\)\(_C\) (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.

Rf: 0.19 (3:2 hexane/EtOAc); m.p. 132 °C (Lit108 134-135 °C); νmax/cm⁻¹ (neat): 2919, 1714 (C=O), 1643 (C=O), 1583, 1454, 1416, 1399, 1334, 1235; δH (400 MHz, CDCl₃): 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); δC (100 MHz, CDCl₃): 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. C₁₃H₁₄NO₃ 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.

Rf: 0.17 (5:1 hexane/EtOAc); νmax/cm⁻¹ (neat): 2978, 1736 (C=O), 1656 (C=O), 1595, 1495, 1449, 1407; δH (400 MHz, CDCl₃): 8.25 (1 H, d, J = 8.2 Hz, H₄), 7.39 (1 H, t, J = 8.2 Hz, H₂), 7.28-7.04 (8 H, m, H₁, H₃, H₉ and H₁₅ to H₁₉), 5.51 (2 H, s, H₇), 4.40 (2 H, q, J = 7.3 Hz, H₁₂), 1.37 (3 H, t, J = 7.3 Hz, H₁₃);

δC (100 MHz, CDCl₃): 165.3 (C₁₁), 161.5 (C₈), 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), 60.0 (C₁₂), 46.2 (C-7), 14.2 (C-13); HRMS [ES⁺] found MH⁺, 308.1282. C₁₉H₁₈NO₃ requires 308.1281.

Lab book ref. RG193b-F2

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

Rf: 0.21 (5:1 hexane/EtOAc); νmax/cm⁻¹ (neat): 2980, 1720 (C=O), 1659 (C=O), 1634, 1594, 1494, 1389, 1293, 1160; δH (400 MHz, CDCl₃): 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, H₉), 6.80 (1 H, d, J = 15.3 Hz, H₁₀), 4.98 (2 H, s, H-7), 4.14 (2 H, q, J = 7.1 Hz, H₁₂), 1.23 (3 H, t, J = 7.1 Hz, H₁₃); δC (100 MHz, CDCl₃): 165.7 (C₁₁), 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 (C₁₂), 53.6 (C-7), 14.2 (C-13); HRMS [ES⁺] found MNa⁺, 332.1251. C₁₉H₁₉NNaO₃ 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.

Rf: 0.17 (1:1 Petrol/EtOAc); m.p. 99–100 °C (Lit. 105 °C); \( \nu_{\max}/\text{cm}^{-1} \) (neat): 1723 (C=O), 1658 (C=O), 1620, 1586, 1563, 1463, 1430; \( \delta_{\text{H}} \) (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), 7.23 (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); \( \delta_{\text{C}} \) (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.
Rf: 0.26 (1:1 hexane/EtOAc); m.p. 147–151 °C; νmax/cm⁻¹ (neat): 1725 (C=O), 1671 (C=O), 1607, 1524, 1342, 1301; δH (400 MHz, CDCl₃): 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); δC (100 MHz, CDCl₃): 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), 117.2 (C-1), 62.6 (C-12), 30.4 (C-7), 14.1 (C-13); HRMS [ES⁺] found MH⁺, 277.0820. C₁₃H₁₃N₂O₅ requires 277.0819.

Lab book ref. RG207

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

Rf: 0.37 (1:1 hexane/EtOAc); νmax/cm⁻¹ (neat): 2983, 1720 (C=O), 1665 (C=O), 1592, 1521, 1496, 1341, 1301, 1177; δH (400 MHz, CDCl₃): 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); δC (100 MHz, CDCl₃): 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. C₁₃H₁₅N₂O₅ 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.

Rf: 0.34 (1:1 hexane/EtOAc); m.p. 68–70 °C; \( \nu_{\text{max}} / \text{cm}^{-1} \) (neat): 2982, 1730 (C=O), 1646 (C=O), 1600, 1590, 1464, 1226; \( \delta_H \) (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); \( \delta_C \) (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-methoxybenzyl)oxy)ethyl)-1-methyl-2-oxo-1,2-dihydroquinoline-4-carboxylate (163f)**

Rf: 0.20 (3:2 hexane/EtOAc); \( \nu_{\text{max}} / \text{cm}^{-1} \) (neat): 2935, 1724 (C=O), 1642 (C=O), 1598, 1512, 1462, 1316, 1244; \( \delta_H \) (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\(_3\)), 3.81-3.65 (5 H, m, H-23, CH\(_2\) and CH\(_3\)), 3.46-3.37 (1 H, m, CH\(_2\)), 3.27-3.18 (1 H, m, CH\(_3\)), 3.00-2.91 (1 H, m, CH\(_3\)), 2.63 (3 H, s, H-7), 1.36 (3 H, t, J = 7.3 Hz, H-13); \( \delta_C \) (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\(_3\)), 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-1H-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.

Rf: 0.21 (1:3 hexane/EtOAc); \( \nu_{\text{max}}/\text{cm}^{-1} \) (neat): 1718 (C=O), 1652 (C=O), 1608, 1469, 1247; \( \delta_{\text{H}} \) (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, \( J = 8.4 \) Hz, H-14), 1.44 (3 H, t, \( J = 6.9 \) Hz, H-13); \( \delta_{\text{C}} \) (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-1H-indol-1-yl)-4-oxobut-2-enoate (163h')

Rf: 0.78 (1:3 hexane/EtOAc); \( \nu_{\text{max}}/\text{cm}^{-1} \) (neat): 1716 (C=O), 1649 (C=O), 1482, 1409; \( \delta_{\text{H}} \) (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 (3 H, t, \( J = 8.4 \) Hz, H-14), 1.27 (3 H, t, \( J = 7.3 \) Hz, H-13); \( \delta_{\text{C}} \) (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.

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)

![Chemical structure](image)

Ethyl 2-(benzenesulfonyl)-4-oxo-4-(1,2,3,4-tetrahydroquinolin-1-yl)butanoate 164i (230 mg, 574 \(\mu\)mol), copper(II) 2-ethylhexanoate (201 mg, 100 mol%) and DIPEA (240 \(\mu\)L, 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 \(\mu\)mol, 54%) as an orange solid.

\(R_f\): 0.24 (1:1 hexane/EtOAc); m.p. 134–136 °C; \(\nu_{max}/cm^{-1}\) (neat): 2937, 1718 (C=O), 1641 (C=O), 1582, 1431, 1232, 1066; \(\delta_H\) (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); \(\delta_C\) (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\(_{16}\)N\(_2\)O\(_3\) requires 258.1125.

Lab book ref. RG247

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

![Chemical structure](image)

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-1H-benzo[b]azepin-1-yl)butanoate 164j (72 mg, 173 \(\mu\)mol), copper(II) 2-ethylhexanoate (60.0 mg, 100 mol%) and DIPEA (72.3 \(\mu\)L, 416 \(\mu\)mol) 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 \(\mu\)mol, 77%) as an orange oil.
Rf: 0.22 (13:7 hexane/EtOAc); \( \nu_{\text{max}} \)/cm\(^{-1}\) (neat): 2937, 1728 (C=O), 1655 (C=O), 1587, 1448, 1243; \( \delta \)\(^H\) (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);
\( \delta \)\(^C\) (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(1H)-one (163k)

N-methyl-4-oxo-N,4-diphenyl-3-(phenylsulfonyl)butanamide 164k (100 mg, 245 \( \mu \)mol), copper(II) 2-ethylhexanoate (85.9 mg, 100 mol\%) and DIPEA (102 \( \mu \)L, 589 \( \mu \)mol) 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 \( \mu \)mol, 76\%) as an orange solid and by-product (E)-N-methyl-4-oxo-N,4-diphenylbut-2-enamide 163k’ (14 mg, 52.8 \( \mu \)mol, 22\%) as an orange solid.

Rf: 0.19 (13:7 hexane/EtOAc); m.p. 83–85 °C; \( \nu_{\text{max}} \)/cm\(^{-1}\) (neat): 1656 (C=O), 1589, 1452, 1250; \( \delta \)\(^H\) (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); \( \delta \)\(^C\) (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

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\(^{112}\) Data consistent with literature values.
(E)-N-methyl-4-oxo-N,4-diphenylbut-2-enamide (163k’)

Rf: 0.26 (13:7 hexane/EtOAc); m.p. 65–68 °C; ν\textsubscript{max}/cm\textsuperscript{-1} (neat): 1644 (C=O), 1594, 1495, 1374, 1306; δ\textsubscript{H} (400 MHz, CDCl\textsubscript{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\textsubscript{C} (100 MHz, CDCl\textsubscript{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\textsuperscript{+}] found MNa\textsuperscript{+}, 288.0989. C\textsubscript{17}H\textsubscript{15}NNaO\textsubscript{2} requires 288.0995.

Data consistent with literature values.\textsuperscript{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.\textsuperscript{114} 165–166 °C); ν\textsubscript{max}/cm\textsuperscript{-1} (neat): 1659 (C=O), 1593, 1457; δ\textsubscript{H} (400 MHz, CDCl\textsubscript{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\textsubscript{C} (100 MHz, CDCl\textsubscript{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\textsuperscript{+}] found MNa\textsuperscript{+}, 207.0531. C\textsubscript{11}H\textsubscript{8}N\textsubscript{2}NaO requires 207.0529.

Data consistent with literature values.\textsuperscript{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 KOr-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 NH₄OH solution (8 mL), brine (8 mL), dried (MgSO₄), 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.
NaBH₄ (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.

Rf: 0.71 (1:1 hexane/EtOAc); m.p. 30–33 °C (Lit.¹¹⁵ 52 °C); νmax/cm⁻¹ (neat); 3414, 2998, 1624, 1510, 1452, 1243, 1233, 1035; δH (400 MHz, CDCl₃): 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); δC (100 MHz, CDCl₃): 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. C₁₄H₁₆NO 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. NaBH₄ (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); νmax/cm⁻¹ (neat); 2958, 2838, 1611, 1517; δH (400 MHz, CDCl₃): 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_{13}H_{16}NO_{2} requires 242.1176.

Lab book ref. RG263

Data consistent with literature values.\textsuperscript{116}

\textbf{N-Benzyl-2-bromo-N-(4-methoxyphenyl)acetamide (131l)}

\begin{center}
\includegraphics[width=0.2\textwidth]{structure131l.png}
\end{center}

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\textsubscript{f}: 0.37 (1:1 Petrol/EtOAc); \nu\textsubscript{max}/cm\textsuperscript{-1} (neat): 3010, 2934, 2837, 1653 (C=O), 1509, 1434, 1401, 1293, 1251; \delta\textsubscript{H} (400 MHz, CDCl\textsubscript{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); \delta\textsubscript{C} (100 MHz, CDCl\textsubscript{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\textsubscript{16}H\textsubscript{17}BrNO\textsubscript{2} requires 334.0437.

Lab book ref. RG170

\textbf{2-Bromo-N-(4-methoxybenzyl)-N-(4-methoxyphenyl)acetamide (131m)}

\begin{center}
\includegraphics[width=0.2\textwidth]{structure131m.png}
\end{center}

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.

Rf: 0.22 (4:1 hexane/EtOAc); νmax/cm⁻¹ (neat): 2934, 1658 (C=O), 1509, 1300, 1247, 1175; δH (400 MHz, CDCl₃): 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); δC (100 MHz, CDCl₃): 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. C₁₇H₁₈NO₇NaO₃ 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 KOrBu (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.

Rf: 0.22 (13:7 hexane/EtOAc); νmax/cm⁻¹ (neat): 1738 (C=O), 1654 (C=O), 1512, 1447, 1408, 1324 (S=O), 1250, 1148 (S=O); δH (400 MHz, CDCl₃): 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); δC (100 MHz, CDCl₃): 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. C₂₆H₂₇NO₆S 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 KOtBu (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

Rf: 0.21 (3:2 hexane/EtOAc); ν\text{max}/\text{cm}^{-1} (neat): 2937, 1738 (C=O), 1654 (C=O), 1512, 1447, 1408, 1323 (S=O), 1248, 1148 (S=O); δH (400 MHz, CDCl\textsubscript{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); δC (100 MHz, CDCl\textsubscript{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\textsuperscript{+}] found MNa\textsuperscript{+}, 534.1530. C\textsubscript{27}H\textsubscript{29}NNaO\textsubscript{7}S 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.

Rf: 0.18 (7:3 hexane/EtOAc); \( \nu_{\text{max}} / \text{cm}^{-1} \) (neat): 1723 (C=O), 1655 (C=O), 1617, 1590, 1563, 1496, 1454, 1431; \( \delta_{\text{H}} \) (400 MHz, CDCl3): 7.91 (1 H, 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); \( \delta_{\text{C}} \) (100 MHz, CDCl3): 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\textsuperscript{+}] found MNa\textsuperscript{+}, 360.1211. C\textsubscript{20}H\textsubscript{19}N\textsubscript{2}O\textsubscript{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.
Rf: 0.19 (7:3 hexane/EtOAc); m.p. 84–86 °C; νmax/cm−1 (neat): 2937, 1728, 1656 (C=O), 1513, 1431, 1247; δH (400 MHz, CDCl3): 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); δC (100 MHz, CDCl3): 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. C21H21NNaO5 requires 390.1312.

Lab book ref. RG273

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

![Ethyl 6-methoxy-2-oxo-1,2-dihydroquinoline-4-carboxylate](image)

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 NaHCO3 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.

Rf: 0.27 (1:3 hexane/EtOAc); m.p. 140–143 °C (Lit.80c 183–186 °C); νmax/cm−1 (neat): 2991, 1726 (C=O), 1681 (C=O), 1623, 1503, 1448, 1234; δH (400 MHz, d6-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); δC (100 MHz, d6-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), 45.7 (C-7), 14.1 (C-13); HRMS [ES+] found MNa+, 270.0743. C13H13NNaO4 requires 270.0737.

Lab Book Ref: RG275b

Data consistent with literature values80c
Ethyl 6-hydroxy-2-oxo-1,2-dihydroquinoline-4-carboxylate (170)\textsuperscript{117}

![Ethyl 6-hydroxy-2-oxo-1,2-dihydroquinoline-4-carboxylate](image)

*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\textsubscript{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\textsubscript{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\textsubscript{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\textsubscript{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\textsubscript{f}: 0.22 (19:1 hexane/EtOAc); m.p. > 200 °C; v\textsubscript{max}/cm\textsuperscript{-1} (neat): 3289 (O-H), 1712 (C=O), 1654 (C=O), 1615, 1423, 1254; δ\textsubscript{H} (400 MHz, d\textsubscript{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\textsubscript{C} (100 MHz, d\textsubscript{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\textsuperscript{+}] found MNa\textsuperscript{+}, 256.0577. C\textsubscript{12}H\textsubscript{11}NNaO\textsubscript{4} requires 256.0580.

Lab Book Ref: RG291a

Data consistent with literature values.\textsuperscript{80c}

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5.10 Application of copper conditions to the total synthesis of HOFQ

\[N,2,7\text{-Trimethylbenzofuran-4-amine} \ (154)\]

The title compound was synthesised by a colleague. The multi-step synthesis of \(2,7\text{-dimethylbenzofuran-4-amine} \ (153)\) was carried out according to the procedure reported by Rodighiero et al.\(^9\) This was then converted to title compound \(154\) by the same procedure as \(2,4\text{-dimethoxy-N-methylaniline} \ (133e)\) was synthesised from \(2,4\text{-dimethoxy aniline}\) as described previously.

\[2\text{-Bromo-N-(2,7-dimethylbenzofuran-4-yl)-N-methylacetamide} \ (131n)\]

\(N,2,7\text{-Trimethylbenzofuran-4-amine} \ (133k)\) (1.13 g, 6.42 mmol), triethylamine (971 \(\mu\)L, 6.98 mmol), DCM (7 mL) and bromoacetyl bromide (607 \(\mu\)L, 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 \ \text{hexane/EtOAc}); \ \text{m.p.} \ 64–66 \ ^\circ\text{C}; \ \nu_{\text{max}}/\text{cm}^{-1} \ (\text{neat}): 3107, 2917, 1672 (C=O), 1505, 1371, 1186; \ \delta_H \ (400 \text{MHz, CDCl}_3) \ : 7.02 (1 \ H, d, J = 7.8 \text{ Hz, H-4 or H-5}), 6.98 (1 \ H, d, J = 7.8 \text{ 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); \ \delta_C \ (100 \text{ 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); \ \text{HRMS [ES]+} \ \text{found} \ MH^+ \ 296.0281. \ \text{C}_{13}H_{15}^{79}\text{BrNO}_2 \ \text{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 KOtBu (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.

RF: 0.35 (1:1 hexane/EtOAc); \( \nu_{\text{max}}/\text{cm}^{-1} \) (neat): 2925, 1738 (C=O), 1658 (C=O), 1324 (S=O), 1188, 1148 (S=O); \( \delta_{\text{H}} \) (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); \( \delta_{\text{C}} \) (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\(_{36}\)NO\(_6\)S 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.

Rf: 0.22 (1:1 hexane/EtOAc); $\nu_{\text{max}}$/cm$^{-1}$ (neat): 2924, 1726 (C=O), 1652 (C=O), 1590, 1236; $\delta$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); $\delta$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’)

Rf: 0.61 (1:1 hexane/EtOAc); $\nu_{\text{max}}$/cm$^{-1}$ (neat): 2927, 1720 (C=O), 1661 (C=O), 1508, 1369, 1293; $\delta$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); $\delta$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

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References

3. (a) Heterocycles - an international journal for reviews and communications in heterocyclic chemistry; (b) Chemistry of Heterocyclic Compounds - A journal dedicated to the fundamental aspects, physical and chemical properties, synthesis, structure and reactivity of heterocyclic compounds.
10. Innovative Medicines Initiative (IMI) - Europe's largest public-private initiative aiming to speed up the development of better and safer medicines for patients.
13. Prices taken from sigmaaldrich.com on 25/06/2016 quoted 25 g of Cu(OAc)2 for £37.90, whereas 25 g of Pd(OAc)2 was £668.00.


111. Goldfarb, D. S. Method using lifespan-altering compounds for altering the lifespan of eukaryotic organisms, and screening for such compounds. 2009.